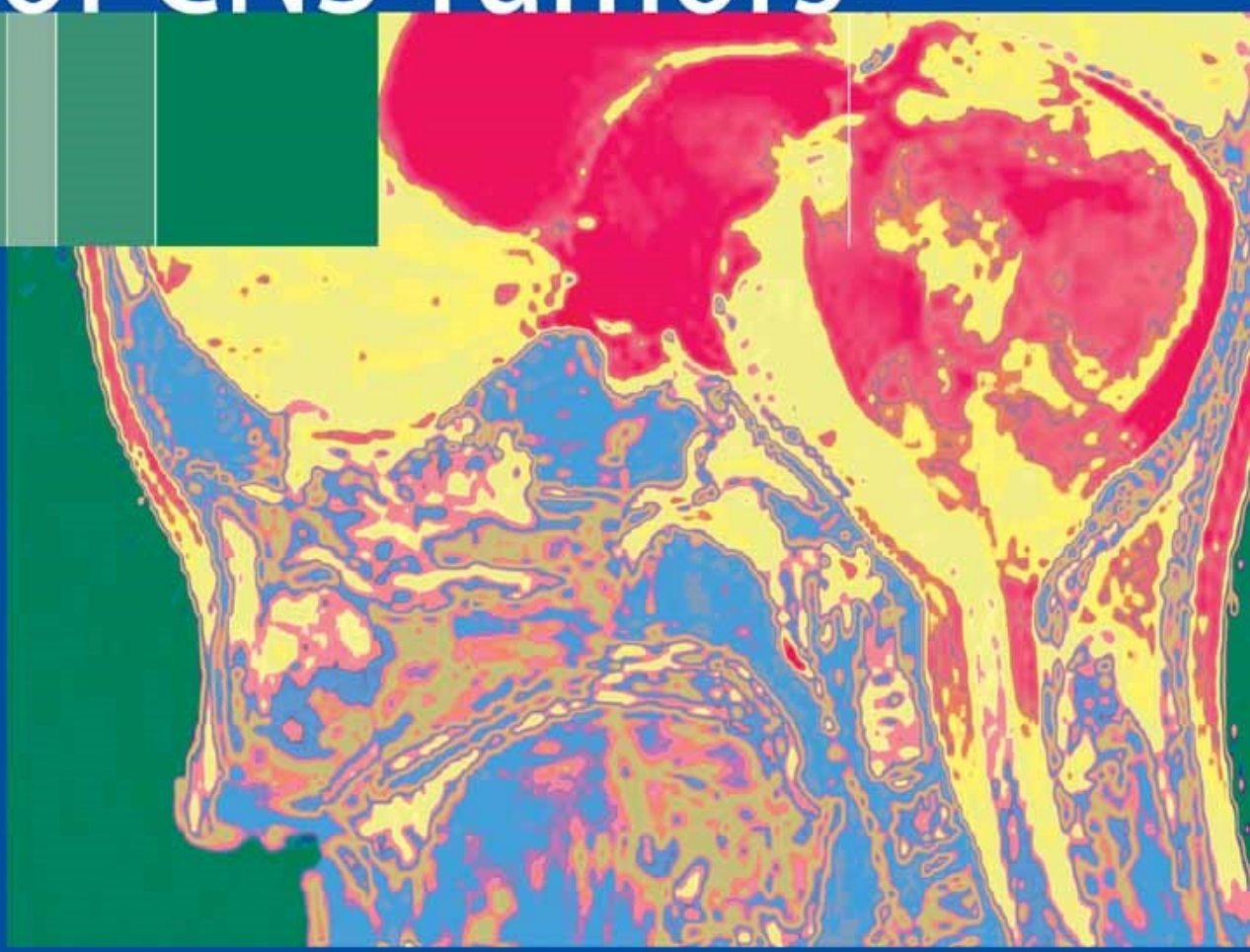
J. C. Tonn
M. Westphal
J. T. Rutka
S. A. Grossman
Editors

Neuro-Oncology of CNS Tumors



Springer

J.-C. Tonn (Ed.)
M. Westphal (Ed.)
J. T. Rutka (Ed.)
S. A. Grossman (Ed.)

Neuro-Oncology of CNS Tumors

J.-C. Tonn (Ed.)
M. Westphal (Ed.)
J. T. Rutka (Ed.)
S. A. Grossman (Ed.)

Neuro-Oncology of CNS Tumors

With 260 Figures and 60 Tables

Springer

Jörg-Christian Tonn, MD
(e-mail:
Joerg.Christian.Tonn@med.uni-muenchen.de)
Department of Neurosurgery,
Klinikum Großhadern,
Marchioninistrasse 15,
81377 Munich, Germany

Stuart A. Grossman
(e-mail: grossman@jhmi.edu)
Johns Hopkins Oncology Center
Neuro-Oncology,
Cancer Bldg G-93
1650 Orleans St., Baltimore, MD 21231, USA

James T. Rutka, MD
(e-mail: james.rutka@sickkids.ca)
Division of Neurosurgery
The University of Toronto
The Hospital for Sick Children, Suite 1504
555 University Avenue, Toronto, Ontario,
M5G 1X8, Canada

Manfred Westphal, MD
(e-mail: westphal@uke.uni-hamburg.de)
Neurochirurgische Klinik
Universitätskrankenhaus Eppendorf
Martinistrasse 52
20246 Hamburg, Germany

ISBN-10 3-540-25833-7
ISBN-13 978-3-540-25833-7

Library of Congress Control Number: 2005925618

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer-Verlag. Violations are liable for prosecution under the German Copyright Law.

Springer is a part of Springer Science+Business Media
springeronline.com

© Springer-Verlag Berlin Heidelberg 2006
Printed in Germany

Springer
Berlin Heidelberg New York

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publishers cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Editor: Dr. Ute Heilmann, Heidelberg
Desk Editor: Meike Stoeck, Heidelberg
Typesetting: Satz-Druck-Service, Leimen
Printing and Binding: Stürtz, Würzburg

Printed on acid-free paper
21/3150Re 5 4 3 2 1 0

Preface

Knowledge about the etiology and diagnosis as well as treatment concepts of neuro-oncologic diseases is rapidly growing.

This turnover of knowledge makes it difficult for the physician engaged in the treatment to keep up to date with current therapies. This book sets out to close the gap and pursues several innovative concepts.

As a comprehensive text on neuro-oncology, its chapters are interconnected, but at the same time some chapters or subdivisions are so thoroughly assembled that the whole volume gives the impression of several books combined into one. Neuropathology is treated in an extensive and clearly structured section. The interested reader finds for each tumor entity the latest well-referenced consensus regarding histologic and molecular pathology. Through this "book-in-the-book" concept, information on neuropathology is readily at hand in a concise form and without overloading the single chapters.

Pediatric neuro-oncology differs in many entities from tumors in adult patients; also, certain tumors of the CNS are typically or mainly found only in the child. Therefore, pediatric neuro-oncology was granted its own, book-like section. Tumor entities that are treated differently in children and adults are included both in the pediatric neuro-oncology section and in the general section. Entities which typically occur only in the child and adolescent are found in the pediatric section in order to avoid redundancies.

Chapters in this book are divided according to practical clinical needs. On the one hand, tumor location was selected as the ordering principle for several chapters (i.e. skull base tumors, hypophyseal adenoma, orbital tumors, spinal tumors or tumors of the peripheral nerves). On the other hand, division according to histology or tumor type was chosen where this appeared clinically appropriate (astrocytic tumors, lymphomas, hemangioblastomas, etc.). A chapter on general care concludes the book.

In order to facilitate orientation on the part of the reader, all chapters (with the exception of neuropathology) adhere to a uniform scheme, intended to be pragmatic for the clinician. This should simplify use of the book in everyday clinical practice.

All contributions have been written by excellent international professionals, renowned specialists in their field. Medicine today is nurtured by dialogue; therefore, the editors would appreciate constructive critique and suggestions for improvements, as well as positive reactions. We wish the book to become a topical and practical daily reference for all those interested in neuro-oncology.

This work could not have been accomplished without the exceptional commitment of many persons. In particular, Ms. Ilona Anders (University of Munich, LMU) and Ms. Meike Stoeck (Springer) were of invaluable assistance in editing and professionally coordinating the book, not to forget the superb cooperation in terms of format and layout of the volume. The editors deeply acknowledge their assistance and all other contributions that helped generate this book.

J.-C. Tonn, M. Westphal,
J.T. Rutka, S.A. Grossman

Contents

Part I
Cranial Neuro-Oncology
Organised by Jörg-Christian Tonn and Manfred Westphal

Chapter 1
Pathology and Classification of Tumors of the Nervous System 3
Guido Reifenberger, Ingmar Blümcke, Torsten Pietsch, Werner Paulus

Chapter 2
Tumors of the Skull 73
Roland Goldbrunner

Chapter 3
Meningiomas and Meningeal Tumors 81
Manfred Westphal, Katrin Lamszus, Jörg-Christian Tonn

Chapter 4
Low-Grade Astrocytoma 103
G. Evren Keles, Tarik Tihan, Eric Burton, Mitchel S. Berger

Chapter 5
Interstitial Radiosurgery in Low-Grade Gliomas 119
Friedrich W. Kreth, Jan H. Mehrkens

Chapter 6
High-Grade Astrocytoma / Glioblastoma .. 127
Jon D. Weingart, Matthew J. McGirt, Henry Brem

Chapter 7
Oligodendroglioma 139
Michael Weller

Chapter 8
Ependymomas and Ventricular Tumors ... 145
Manfred Westphal

Chapter 9
Adult Tumors of Pediatric Origin 159
(Medulloblastomas-PNETs, Craniopharyngiomas, Ependymomas-Ependymoblastomas)
Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

Chapter 10
Glioneuronal Tumors 167
Johannes Schramm, Rudolf Kristof

Chapter 11
Inactive Adenomas 181
John A. Jane Jr, Aaron S. Dumont, Jason P. Sheehan, Edward R. Laws Jr.

Chapter 12
Functioning Adenomas 189
Dieter K. Lüdecke, Takumi Abe, Jörg Flitsch, Stephan Petersen, Wolfgang Saeger

Chapter 13
Tumors of the Pineal Region 207
Yutaka Sawamura, Nicolas de Tribolet

Chapter 14
Tumors of the Cranial Nerves 217
Berndt Wowra, Jörg-Christian Tonn

Chapter 15
Hemangioblastoma and Von Hippel-Lindau Disease 235
Juha E. Jääskeläinen, Mika Niemelä

Chapter 16
Tumors of the Skull Base 243
Kadir Erkmen, Ossama Al-Mefty, Badih Adada

Chapter 17
Orbital Tumors 269
Christoph Hintschich, Geoff Rose

Chapter 18
Primary CNS Lymphoma 291
Uwe Schlegel, Fred H. Hochberg

Chapter 19
Brain Metastasis 303
Zeena Dorai, Raymond Sawaya, W.K. Alfred Yung

Part II
Pediatric Neuro-Oncology
Organised by James T. Rutka

Chapter 20
Neurocutaneous Syndromes 327
Paul Kongkham, James T. Rutka

Chapter 21
Supratentorial Hemispheric Low Grade Gliomas in Children 345
Paul Chumas, Atul Tyagi

Chapter 22
Optic Gliomas 353
Ian F. Pollack, Regina I. Jakacki

Chapter 23
Thalamic Gliomas 363
Christian Sainte-Rose, Darach W. Crimmins, Jacques Grill

Chapter 24
Midbrain Gliomas 377
Leland Albright

Chapter 25
Supratentorial High-Grade Gliomas 385
Rene O. Sanchez-Mejia, Anu Banerjee, Nalin Gupta

Chapter 26
Ganglioglioma 393
Concezio Di Rocco, Gianpiero Tamburrini

Chapter 27
Cerebellar Astrocytomas 401
John C. Wellons III

Chapter 28
Diffuse Intrinsic Pontine Gliomas 407
Milind Ronghe, Eric Bouffet

Chapter 29
Dorsally Exophytic Brainstem Gliomas 415
Ian D. Kamaly-Asl, James M. Drake

Chapter 30
Cervicomedullary Gliomas 421
Alexa L. Reeves, Richard G. Ellenbogen

Chapter 31
Desmoplastic Infantile Gangliogliomas 431
Jeffrey P. Blount

Chapter 32
Pleomorphic Xanthoastrocytoma 437
Jean-Pierre Farmer, P. Daniel McNeely

Chapter 33
Hypothalamic Hamartoma 443
Jeffrey V. Rosenfeld, A. Simon Harvey

Chapter 34
Ependymomas 453
Nicholas Wetjen, Corey Raffel

Chapter 35
Medulloblastoma 461
Michael D. Taylor

Chapter 36
Supratentorial Primitive Neuroectodermal Tumors 471
Shahid Gul, Paul Steinbok

Chapter 37
Dysembryoplastic Neuroectodermal Tumors 479
Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

Chapter 38
Meningiomas 485
Abhaya V. Kulkarni, Patrick McDonald

Chapter 39
Pineal Region Tumors in Children 491
Anna J. Janss, Timothy Mapstone

Chapter 40
Pituitary Tumors in Children 499
Aaron S. Dumont, Jay Jagannathan, John A. Jane Jr

Chapter 41
Craniopharyngiomas 505
Rémy van Effenterre, Anne-Laure Boch

Chapter 42
Intracranial Germ Cell Tumors 517
Kyu-Chang Wang, Seung-Ki Kim, Sung-Hye Park, In-One Kim, Byung-Kyu Cho

Chapter 43
Choroid Plexus Tumors 529
Paul Kongkham, James T. Rutka

Chapter 44
Malignant Rhabdoid Tumors of the CNS ... 539
Michael R. Carter

Chapter 45
Langerhans Cell Histiocytosis 547
Clare Gallagher, Walter J. Hader

Chapter 46
Tumors of the Skull Base in Children 555
Eve C. Tsai, Gregy Hawryluk, James T. Rutka

Chapter 47
Calvarial Tumors in Children 567
Ganesh Rao, John R.W. Kestle

Chapter 48
Epidural Spinal Tumors in Children 575
Colin Kazina, Patrick McDonald

Chapter 49
Spinal Column Tumors 583
William E. Whitehead, Anna Illner

Chapter 50
Pediatric Spinal Intradural Extramedullary Tumors 599
Peter Dirks

Chapter 51
Intramedullary Spinal Tumors in Children .. 603
John S. Myseros

Chapter 52
Peripheral Nerve Tumors in Children 611
W. Bradley Jacobs, Rajiv Midha

Part III
Spinal Neuro-Oncology
Organised by Jörg-Christian Tonn

Chapter 53
Intramedullary Tumors 619
Manfred Westphal

Chapter 54
Intradural Extramedullary Tumors 635
Roland Goldbrunner

Chapter 55
Epidural Tumors and Metastases 645
Carlos A. Bagley, Ziya L. Gokaslan

Part IV
Peripheral Nerve Tumors
Organised by Abhijit Guha

Chapter 56
Peripheral Nerve Tumors 665
Joseph Wiley, Asis Kumar Bhattacharyya, Gelareh Zadeh, Patrick Shannon, Abhijit Guha

Part V
Systemic and General Aspects of Neuro-Oncology

Chapter 57
General Care of Patients with Cancer Involving the Central Nervous System 687
Stuart A. Grossman

Subject Index 697

Contributors

Takumi Abe, MD
Department of Neurosurgery, Showa University School of Medicine, 1–5-8 Hatanodai, Shinagawa-ku, Tokyo 1428666, Japan

Badih Adada, MD
University of Arkansas, 4301 W. Markham St; Slot 507, Little Rock, AR 72205–7101, USA

A. Leland Albright, MD
(e-mail: leland.albright@chp.edu)
Department of Neurosurgery, Children's Hospital of Pittsburgh, 3705 Fifth Ave., Pittsburgh, PA 15213, USA

Ossama Al-Mefty, MD
(e-mail: almeftyossama@exchange.uams.edu)
University of Arkansas, 4301 W. Markham St; Slot 507, Little Rock, AR 72205–7101, USA

Carlos A. Bagley, MD
Department of Neurosurgery, Meyer Building 7–109, John Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287–7713, USA

Anu Banerjee, MD
Department of Neurologic Surgery and Pediatrics, University of California, San Francisco, CA 94143–0112, USA

Mitchel S. Berger, MD
(e-mail: bergerm@neurosurg.ucsf.edu)
Department of Neurological Surgery, University of California San Francisco, 505 Parnassus Ave, M-787, San Francisco, CA 94143–0112, USA

Asis Kumar Bhattacharyya, MS
Department of Neurosurgery, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada

Jeffrey P. Blount, MD
(e-mail: jeffrey.blount@ccc.uab.edu)
Children's Hospital of Alabama, 1600 7th Avenue, S., ACC 400, Birmingham, AL 35233, USA

Ingmar Blümcke, MD
Department of Neuropathology, Friedrich-Alexander-University, Krankenhausstrasse 8–10, 91054 Erlangen, Germany

Anne-Laure Boch, MD
Department de Neurosurgery, Group Hospitalier Pitie-Salpetriere, 91, 105 Boulevard de l'Hôpital, 75013 Paris, France

Eric Bouffet, MD
(e-mail: eric.bouffet@sickkids.ca)
The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Henry Brem, MD
(e-mail: hbrem@jhmi.edu)
Department of Neurosurgery, Johns Hopkins University School of Medicine, 600 N Wolfe St. Meyer 7–113, Baltimore, MD 21287, USA

Eric Burton, MD
Department of Neurological Surgery, University of California San Francisco, Box 0372, 400 Parnassus Ave, UC Clinics A808, San Francisco, CA. 94143–0372, USA

Michael R. Carter, BM
(e-mail: mjkd@ukonline.co.uk)
Department of Neurosurgery, Frenchay Hospital, Frenchay Park Road, Bristol, BS16 1LE, UK

Byung-Kyu Cho, MD, PhD
Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110–744, Korea

Paul Chumas, MD
(e-mail: p.chumas@leeds.ac.uk)
Department of Neurosurgery, The General Infirmary at Leeds, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK

Darach Crimmins, FRCSI
(e-mail: dcrimmins@ireland.com)
Consultant Paediatric Neurosurgeon
Department of Neurosurgery, Leeds General Infirmary, Leeds LS1 3EX, UK

Concezio Di Rocco, MD
(e-mail: cdirocco@rm.unicatt.it)
Institute of Neurosurgery, Catholic University Medical School, Policlinico Gemelli, Largo Gemelli 8, 00168 Rome, Italy

Peter Dirks, MD PhD
(e-mail: peter.dirks@sickkids.ca)
Division of Neurosurgery, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada,

Zeena Dorai, MD
Department of Neurosurgery, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

James M. Drake, MD
(e-mail: james.drake@sickkids.ca)
The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Aaron S. Dumont, MD
(e-mail: asd2f@virginia.edu)
Department of Neurosurgery, Box 800212, University of Virginia Health System, Charlottesville, VA 22903, USA

Rèmy van Effenterre, MD
(e-mail: remy.van-effenterre@psl.ap-hop-paris.fr)
Department of Neurosurgery, Group Hospitalier Pitie-Salpetriere, 91, 105 boulevard de l'Hôpital, 75013 Paris, France

Richard G. Ellenbogen, MD
(e-mail: rich.ellenbogen@seattlechildrens.org)
Department of Neurological Surgery, University of Washington School of Medicine, 700 9th Avenue, Seattle, WA 98104, USA

Kadir Erkmen, MD
University of Arkansas, 4301 W. Markham St; Slot 507, Little Rock, AR 72205–7101, USA

Jean-Pierre Farmer, MDCM
(e-mail: jean-pierre.farmer@mcgill.ca)
Department of Surgery, Montreal Children's Hospital, 8C1–2300 rue Tupper, Montréal, Québec, H3H 1P3, Canada

Jörg Flitsch, MD
Neurochirurgische Klinik, Universitätskrankenhaus Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

Clare Gallagher, MD, PhD
(e-mail: claregallagher1@shaw.ca)
University of Calgary, Alberta's Childrens Hospital, 1820 Richmond Rd SW, Calgary, Alberta, T2T 5C7, Canada

Ziya L. Gokaslan, MD
(e-mail: zgokasl1@jhmi.edu)
Department of Neurosurgery, Meyer Building 7–109, John Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287–7713, USA

Roland Goldbrunner, MD
(e-mail: roland.goldbrunner@med.uni-muenchen.de)
Department of Neurosurgery, Klinikum Großhadern, Marchioninistrasse 15, 81377 Munich, Germany

Jacques Grill, MD, PhD
(e-mail: grill@igr.fr)
Institut Gustave-Roussy, Villejuif, 94805, France

Abhijit Guha, MD
(e-mail: abhijit.guha@uhn.on.ca)
Department of Neurosurgery, 2–415 McLaughlin Pavilion, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada

Shahid Gul, MD
Department of Surgery, British Columbias's, Children's Hospital, 4480 Oak Street, Vancouver, B.C. V6H 3V4, Canada

Nalin Gupta, MD, PhD
(e-mail: guptan@neurosurg.ucsf.edu)
Department of Neurological Surgery and Pediatrics, University of California, San Francisco, CA 94143–0112, USA

Stuart A. Grossman
(e-mail: grossman@jhmi.edu)
Johns Hopkins Oncology Center, Neuro-Oncology, Cancer Bldg G-93, 1650 Orleans St., Baltimore, MD 21231, USA

Walter J. Hader, MD
(e-mail: walter.hader@calgaryhealthregion.ca)
University of Calgary, Alberta's Childrens Hospital, 1820 Richmond Rd SW, Calgary, Alberta, T2T 5C7, Canada

A. Simon Harvey, MD
Children's Epilepsy Program, Department of Neurology, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia

Gregy Hawryluk, MD
Division of Neurosurgery, The University of Toronto, The Hospital for Sick Children, Suite 1504, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Christoph Hintschich
(e-mail: christoph.hintschich@ak-i.med.uni-muenchen.de)
Augenklinik, Klinikum der Universität München Innenstadt, Mathildenstrasse 8, 80336 Munich, Germany

Fred H. Hochberg
(e-mail: hochberg.fred@mgh.harvard.edu)
Massachusetts General Hospital, Brain Tumor/Oncology Center, 100 Blossom Street, COX 315, Boston, MA 02114–2617, USA

Anna Illner, MD
Department of Pediatric Neurosurgy, James Whitcomb Riley Hospital for Children, One Children's Square, Indianapolis, IN 46202–5200, USA

W. Bradley Jacobs, MD
The University of Toronto, The Hospital for Sick Children, Suite 1504, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Juha E. Jääskeläinen, MD, PhD
(e-mail: juha.e.jaaskelainen@kuh.fi)
Department of Neurosurgery, Kuopio University Hospital, PL 1777, Kuopio 70211, Finland

Jay Jagannathan, MD
Department of Neurosurgery, University of Virginia Health System, Box 800212, Charlottesville, VA 22908–0711, USA

Regina I. Jakacki
(e-mail: jakacki@chplink.chp.edu)
Department of Pediatric Neurosurgery, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213, USA

John A. Jane, Jr. MD
(e-mail: jaj2k@virginia.edu)
Department of Neurosurgery, University of Virginia Health System, Box 800212, Charlottesville, VA 22908–0711, USA

Anna J. Janss, MD, PhD
Department of Pediatrics, Emory University, 2040 Ridgewood Drive NE, Atlanta, GA 30322, USA

Ian D. Kamaly-Asl, MD
The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Colin Kazina, MD
Division of Neurosurgery, Children's Hospital of Winnipeg, GB126–820 Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada

G. Evren Keles, MD
(e-mail: kelese@neurosurg.ucsf.edu)
Department of Neurological Surgery, University of California San Francisco, 505 Parnassus Ave, M-787, San Francisco, CA 94143–0112, USA

John R.W. Kestle, MD
(e-mail: john.kestle@hsc.utah.edu)
Department of Neurosurgery, University of Utah School of Medicine, 100 North Medical Drive, Salt Lake City, UT 84113, USA

In-One Kim, MD, PhD
Department of Diagnostic Radiology, Seoul National University Children's Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110–744, Korea

Seung-Ki Kim, MD, PhD
Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110–744, Korea

Paul Kongkham, MD
(e-mail: paul.kongkham@utoronto.ca)
Division of Neurosurgery, The University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada

Friedrich W. Kreth, MD
(e-mail: Friedrich-Wilhelm.Kreth@med.uni-muenchen.de)
Department of Neurosurgery, Klinikum Großhadern, Ludwig-Maximilians-University Munich, Marchioninistrasse 15, 81377 Munich, Germany

Rudolf Kristof, MD
Neurochirurgische Klinik, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund Freud-Strasse 25, 53127 Bonn, Germany

Abhaya V. Kulkarni, MD, PhD
(e-mail: abhaya.kulkarni@sickkids.ca)
Division of Neurosurgery, The University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Katrin Lamszus, MD
Neurochirurgische Klinik, Universitätskrankenhaus Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Edward R. Laws Jr., MD
(e-mail: ek5g@virginia.edu)
Department of Neurosurgery, Box 800212, University of Virginia Health System, Charlottesville, VA 22903, USA

Dieter K. Lüdecke, MD
(e-mail: luedecke@uke.uni-hamburg.de)
Neurochirurgische Klinik, Universitätskrankenhaus Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Timothy Mapstone, MD
(e-mail: timothy_mapstone@emory.org)
Emory University, 1365 Clifton Road, NE, Atlanta, GA 30322, USA

Patrick McDonald, MD
Division of Neurosurgery, Children's Hospital of Winnipeg, GB126–820 Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada

Matthew J. McGirt, MD
Department of Neurology, Johns Hopkins University School of Medicine, 600 N Wolfe St. Meyer 7–113, Baltimore, MD 21287, USA

P. Daniel McNeely
(e-mail: dmcneely@dal.ca)
Department of Surgery, Montreal Children's Hospital, 8C1–2300 rue Tupper, Montréal, Québec, H3H 1P3, Canada

Jan H. Mehrkens, MD
Department of Neurosurgery, Klinikum Großhadern, Ludwig-Maximilians-University Munich, Marchioninistrasse 15, 81377 Munich, Germany

Rajiv Midha, MD
(e-mail: rajmidha@ucalgary.ca)
Department of Clinical Neurosciences, University of Calgary, Foothills Medical Center, 1403–29 Street NW, Calgary, Alberta T2N 2T9, Canada

John S. Myseros, MD
(e-mail: john.myseros@cchmc.org)
Division of Pediatric Neurosurgery, Cincinnati Children's Hospital, 3333 Burnet Avenue, Cincinnati, OH 45229–3039, USA

Mika Niemelä, MD, PhD
Department of Neurosurgery, Helsinki University Hospital, Topeliuksenkatu 5, Helsinki 00029, Finland

Sung-Hye Park, MD, PhD
Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110–799, Korea

Werner Paulus, MD
Department of Neuropathology, Westfälische-Wilhelms-University, Domagkstrasse 19, 48149 Münster, Germany

Aurelia Peraud, MD
(e-mail: aurelia.peraud@med.uni-muenchen.de)
Department of Neurosurgery, Klinikum Großhadern, Marchioninistrasse 15, 81377 Munich, Germany

Stephan Petersen, MD
Department of Endocrinology, University Clinic, Hufelandstrasse 55, 45122 Essen, Germany

Torsten Pietsch, MD
Department of Neuropathology, University of Bonn Medical Center, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany

Ian F. Pollack, MD
(e-mail: ian.pollack@chp.edu)
Department of Pediatric Neurosurgery, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213, USA

Corey Raffel, MD, PhD
(e-mail: raffel.corey@mayo.edu)
Department of Neurological Surgery Go8 S, Mayo Clinic, 200 First St. SW, Rochester, MN 55902, USA

Ganesh Rao, MD
Department of Neurosurgery, University of Utah School of Medicine, 30 N 1900 East, Salt Lake City, Utah 84132, USA

Alexa L. Reeves, MD
(e-mail: alexal@u.washington.edu)
3230 Eastlake Ave. #410, Seattle, WA 98102, USA

Guido Reifenberger, MD
(e-mail: reifenberger@med.uni-duesseldorf.de)
Department of Neuropathology, Heinrich-Heine-University, Moorenstrasse 5, 40225 Düsseldorf, Germany

Milind Ronghe, MD
Schiehallion Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow, G3 8SJ, UK

Geoff Rose
(e-mail: geoff.rose@breathemail.net)
Moorfields Eye Hospital, City Road, London EC1V 2PD, UK

Jeffrey V. Rosenfeld, MD
Department of Neurosurgery, Alfred Hospital, Prahran, Victoria 3181, Australia

James T. Rutka, MD
(e-mail: james.rutka@sickkids.ca)
Division of Neurosurgery, The University of Toronto, The Hospital for Sick Children, Suite 1504, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Wolfgang Saeger, MD
Department of Pathology, Marienkrankenhaus, Alfredstrasse 9, 22087 Hamburg, Germany

Christian Sainte-Rose, MD
(e-mail: christian.sainte-rose@nck.ap-hop-paris.fr)
L'Hopital Enfants Malades, 149, rue de Sèvres, 75743 Paris Cedex 15, France

Rene O. Sanchez-Mejia, MD
Department of Neurological Surgery and Pediatrics, University of California, San Francisco, CA 94143–0112, USA

Yutaka Sawamura, MD, PhD
(e-mail: ysawamu@med.hokudai.ac.jp)
Department of Neurosurgery, Hokkaido University Hospital, North-15, West-7, Kita-ku, Sapporo 060–8638, Japan

Raymond Sawaya, MD
(e-mail: rsawaya@mdanderson.org)
Department of Neurosurgery, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

Uwe Schlegel
(e-mail: uwe.schlegel@uni-bonn.de)
Neurologische Klinik und Poliklinik der Universität Bonn, Siegmund Freud Strasse 25, 53105 Bonn, Germany

Johannes Schramm, MD
(e-mail: johannes.schramm@ukb.uni-bonn.de)
Neurochirurgische Klinik, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund Freud-Strasse 25, 53127 Bonn, Germany

Patrick Shannon, MD
Department of Pathology, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada

Jason P. Sheehan, MD
(e-mail: jps2f@virginia.edu)
Department of Neurosurgery, Box 800212, University of Virginia Health System, Charlottesville, VA 22903, USA

Paul Steinbok, MC
(e-mail: psteinbok@cw.bc.ca)
Department of Surgery, British Columbias's, Children's Hospital, 4480 Oak Street, Vancouver, B.C. V6H 3V4, Canada

Gianpiero Tamburrini, MD
(e-mail: gianpiero.tamburrini@rm.unicatt.it)
Institute of Neurosurgery, Section of Pediatric Neurosurgery, Catholic University Medical School, Policlinico Gemelli, Largo Gemelli 8, 00168 Rome, Italy

Michael D. Taylor, MD, PhD
(e-mail: mdtaylor@sickkids.on.ca)
The University of Toronto, The Hospital for Sick Children, Suite 1504, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Tarik Tihan, MD, PhD
University of California San Francisco, Neuropathology Unit, HSW 408 (Box 0511), 513 Parnassus Avenue, San Francisco, CA 94143–0511, USA

Jörg-Christian Tonn, MD
(e-mail: Joerg.Christian.Tonn@med.uni-muenchen.de)
Department of Neurosurgery, Klinikum Großhadern, Marchioninistrasse 15, 81377 Munich, Germany

Nicolas de Tribolet, MD
(e-mail: nicolas.detribolet@hcupe.ch)
Department of Neurosurgery, De L'HCUG, Rue Micheli du Crest 24, Geneva 1211, Switzerland

Eve C. Tsai, MD
Division of Neurosurgery, The University of Toronto, The Hospital for Sick Children, Suite 1504, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

Atul Tyagi, MD
Department of Neurosurgery, The General Infirmary at Leeds, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK

Kyu-Chang Wang, MD, PhD
(e-mail: kcwang@snu.ac.kr)
Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110–744, Korea

Jon D. Weingart, MD
Department of Neurosurgery, Johns Hopkins University School of Medicine, 600 N Wolfe St. Meyer 7–113, Baltimore, MD 21287, USA

Michael Weller, MD
(e-mail: michael.weller@uni-tuebingen.de)
Molecular Neuro-Oncology, University of Tübingen, Hoppe-Seyler-Strasse 3, 72076 Tübingen, Germany

John C. Wellons, III, MD
(e-mail: jay.wellons@ccc.uab.edu)
Section of Pediatric Neurosurgery, Children's Hospital of Alabama, 1600 7th Avenue, S., ACC 400, Birmingham, AL 35233, USA

Manfred Westphal, MD
(e-mail: westphal@uke.uni-hamburg.de)
Neurochirurgische Klinik, Universitätskrankenhaus Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Nicholas Wetjen, MD
(e-mail: wetjen.nicholas@mayo.edu)
Department of Neurological Surgery Go8 S, Mayo Clinic, 200 First St. SW, Rochester, MN 55902, USA

William E. Whitehead, MD
(e-mail: wwhiteheadmd@yahoo.com)
Department of Pediatric Neurosurgy, James Whitcomb Riley Hospital for Children, One Children's Square, Indianapolis, IN 46202–5200, USA

Jospeh Wiley
Arthur & Sonia Labatts Brain Tumor Centre, Hospital for Sick Children's, Toronto, Ontario, M5G 1X8, Canada

Berndt Wowra, MD
(e-mail: Berndt.Wowra@cyber-knife.de)
Cyberknife Zentrum, Max-Lebsche Platz 31, 81377 Munich, Germany

W.K. Alfred Yung, MD
(e-mail: yung@mdanderson.org)
Department of Neurooncology, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

Gelareh Zadeh, MD, PhD
Arthur & Sonia Labatts Brain Tumor Centre, Hospital for Sick Children's, Toronto, Ontario, M5G 1X8, Canada

Cranial Neuro-Oncology I

Organised by Jörg-Christian Tonn and Manfred Westphal

1 **Pathology and Classification of Tumors of the Nervous System – 3**
Guido Reifenberger, Ingmar Blümcke, Torsten Pietsch, Werner Paulus

2 **Tumors of the Skull – 73**
Roland Goldbrunner

3 **Meningiomas and Meningeal Tumors – 81**
Manfred Westphal, Katrin Lamszus, Jörg-Christian Tonn

4 **Low-Grade Astrocytoma – 103**
G. Evren Keles, Tarik Tihan, Eric Burton, Mitchel S. Berger

5 **Interstitial Radiosurgery in Low-Grade Gliomas – 119**
Friedrich W. Kreth, Jan H. Mehrkens

6 **High-Grade Astrocytoma / Glioblastoma – 127**
Jon D. Weingart, Matthew J. McGirt, Henry Brem

7 **Oligodendroglioma – 139**
Michael Weller

8 **Ependymomas and Ventricular Tumors – 145**
Manfred Westphal

9 **Adult Tumors of Pediatric Origin – 159**
(Medulloblastomas-PNETs, Craniopharyngiomas, Ependymomas-Ependymoblastomas)
Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

10 **Glioneuronal Tumors – 167**
Johannes Schramm, Rudolf Kristof

11 **Inactive Adenomas – 181**
John A. Jane Jr, Aaron S. Dumont, Jason P. Sheehan, Edward R. Laws Jr.

12 **Functioning Adenomas – 189**
Dieter K. Lüdecke, Takumi Abe, Jörg Flitsch, Stephan Petersen, Wolfgang Saeger

13 **Tumors of the Pineal Region – 207**
Yutaka Sawamura, Nicolas de Tribolet

14 **Tumors of the Cranial Nerves – 217**
Berndt Wowra, Jörg-Christian Tonn

15 **Hemangioblastoma and Von Hippel-Lindau Disease – 235**
Juha E. Jääskeläinen, Mika Niemelä

16 **Tumors of the Skull Base – 243**
Kadir Erkmen, Ossama Al-Mefty, Badih Adada

17 **Orbital Tumors – 269**
Christoph Hintschich, Geoff Rose

18 **Primary CNS Lymphoma – 291**
Uwe Schlegel, Fred H. Hochberg

19 **Brain Metastasis – 303**
Zeena Dorai, Raymond Sawaya, W.K. Alfred Yung

Pathology and Classification of Tumors of the Nervous System

1

Guido Reifenberger, Ingmar Blümcke,
Torsten Pietsch, Werner Paulus

Introduction – 5
Classification of Tumors of the Nervous System
Immunohistochemistry in Brain Tumor Classification
Contribution of Molecular Genetics to Brain Tumor Classification

Astrocytic Tumors – 11
Diffuse Astrocytoma (WHO Grade II)
Anaplastic Astrocytoma (WHO Grade III)
Glioblastoma (WHO Grade IV)
Pilocytic Astrocytoma (WHO Grade I)
Pleomorphic Xanthoastrocytoma (WHO Grade II)

Oligodendroglial Tumors and Mixed Gliomas – 21
Oligodendroglioma (WHO Grade II)
Anaplastic Oligodendroglioma (WHO Grade III)
Oligoastrocytoma (WHO Grade II)
Anaplastic Oligoastrocytoma (WHO Grade III)

Ependymal Tumors – 25
Ependymoma (WHO Grade II)
Anaplastic Ependymoma (WHO Grade III)
Myxopapillary Ependymoma (WHO Grade I)
Subependymoma (WHO Grade I)

Choroid Plexus Tumors – 26
Choroid Plexus Papilloma (WHO Grade I)
Choroid Plexus Carcinoma (WHO Grade III)
Atypical choroid plexus papilloma (WHO Grade II)

Neuroepithelial Tumors of Uncertain Origin – 29
Astroblastoma
Chordoid Glioma of the Third Ventricle (WHO Grade II)
Gliomatosis cerebri (WHO Grade III)

Neuronal and Mixed Neuronal-Glial Tumors – 31
Gangliocytoma and Ganglioglioma (WHO Grade I)
Desmoplastic Infantile Astrocytoma/Ganglioglioma (WHO Grade I)
Dysembryoplastic Neuroepithelial Tumor (WHO Grade I)
Central Neurocytoma (WHO Grade II)
Cerebellar Liponeurocytoma (WHO Grade II)
Paraganglioma (WHO Grade I)

Pineal Parenchymal Tumors – 36
Pineocytoma (WHO Grade II)
Pineoblastoma (WHO Grade IV)
Pineal Parenchymal Tumor of Intermediate Differentiation (WHO Grade III)

Embryonal Tumors – 37
Ependymoblastoma (WHO Grade IV)
Medulloblastoma (WHO Grade IV)
Supratentorial Primitive Neuroectodermal Tumor (WHO Grade IV)
Medulloepithelioma (WHO Grade IV)
Atypical Teratoid/Rhabdoid Tumor (WHO Grade IV)

Tumors of Cranial and Peripheral Nerves – 41
Schwannoma (WHO Grade I)
Neurofibroma (WHO Grade I)
Perineurioma (WHO Grade I)
Malignant Peripheral Nerve Sheath Tumor (MPNST)

Meningeal Tumors – 46
Meningiomas
Mesenchymal, Non-meningothelial Tumors
Solitary Fibrous Tumor
Hemangiopericytoma
Melanocytic Lesions

Tumors of the Hematopoietic and Lymphoid System – 53
Primary Central Nervous System Lymphoma (PCSNL)
Histiocytic Lesions Affecting the CNS and Its Coverings
Langerhans Cell Histiocytosis
Non-Langerhans Cell Histiocytoses

Germ-Cell Tumors of the CNS – 55

Familial Tumor Syndromes – 57
Subependymal Giant Cell Astrocytoma (WHO Grade I)
Capillary Hemangioblastoma (WHO Grade I)
Dysplastic Gangliocytoma of the Cerebellum (WHO Grade I)

Tumors of the Sellar Region – 61
Craniopharyngioma (WHO Grade I)
Pituitary Adenoma
Granular Cell Tumor of the Neurohypophysis (WHO Grade I)

Metastatic Tumors of the CNS – 63

Emerging New CNS Tumor Entities and Variants – 64

References – 66

Introduction

Classification of Tumors of the Nervous System

Rudolph Virchow (1821–1902), the founder of cellular pathology, already separated the gliomas from the 'psammomas', the 'melanomas' and other 'sarcomas' of the nervous system in 1864/65 (Virchow 1864/65). However, it was not before 1926 that Bailey and Cushing developed the first systematic classification scheme for gliomas and introduced the concept of brain tumor grading (Bailey and Cushing 1926). The first World Health Organization (WHO) classification of tumors of the nervous system was published in 1979 (Zülch 1979), followed by revisions in 1993 (Kleihues et al. 1993) and 2000 (Kleihues and Cavenee 2000). All WHO classifications, including the latest version of 2000 (Table 1), followed the histogenetic principle originally proposed by Bailey and Cushing (1926). Based on morphologic and immunohistochemical features, each tumor entity is classified according to its presumed cell of origin. Although commonly used, this concept is challenged by the fact that the actual cell of origin is unknown for most brain tumors. Furthermore, experimental evidence from mouse models suggests that gliomas, for example, are more likely to arise from glial precursor cells than from terminally differentiated astrocytes or oligodendrocytes (Shih and Holland 2004). Nevertheless, histologic classification according to the WHO criteria allows for a meaningful separation of biologically and clinically distinct brain tumor entities that is unsurpassed by any other diagnostic approach so far. Thus, the morphologic classification of brain tumors is and will remain the diagnostic 'gold standard' in neuro-oncology.

In addition to tumor typing, the WHO classification comprises a histologic grading according to a four-tiered scheme ranging from WHO grade I (benign) to WHO grade IV (malignant) (Table 2). The WHO grading is not equivalent to the histologic tumor grading commonly used in other fields of surgical pathology, but rather reflects an estimate of a tumor's malignancy and the patient's prognosis (Kleihues et al. 2002). In general, WHO grade I lesions include tumors with a minimal proliferative potential and the possibility of cure following surgical resection alone. Typical examples are pilocytic astrocytomas, subependymomas, myxopapillary ependymomas of the cauda equina, a variety of neuronal and mixed neuronal/glial tumors, schwannomas, and most meningiomas. Tumors of WHO grade II are those with low mitotic activity but a tendency for recurrence. Diffuse astrocytomas, oligodendrogliomas, oligoastrocytomas and ependymomas are classic examples of WHO grade II tumors. WHO grade III is reserved for neoplasms with histologic evidence of anaplasia, generally in the form of increased mitotic activity, increased cellularity, nuclear pleomorphism, and cellular anaplasia. WHO grade IV is assigned to mitotically active and necrosis-prone highly malignant neoplasms that are typically associated with a rapid pre- and postoperative evolution of the disease. These include glioblastoma and the various forms of embryonal tumors.

To introduce the pathology and genetics of tumors of the nervous system, this chapter will closely adhere to the WHO classification of 2000 (Kleihues and Cavenee 2000). This classification scheme is being used around the world, which thereby facilitates comparison of clinical and experimental brain tumor studies from different countries. However, neuropathology and molecular neuro-oncology are rapidly evolving, so that updates concerning novel tumor entities as well as recent progress in brain tumor genetics were incorporated into the chapter where appropriate.

Immunohistochemistry in Brain Tumor Classification

Immunohistochemical staining for the expression of specific differentiation markers as well as proliferation-associated antigens has greatly facilitated the morphologic classification of brain tumors. Table 3 provides a list of diagnostically helpful antigens that are commonly used for the differential diagnosis of different tumor entities or the assessment of proliferative activity. In the routine diagnostic setting, immunohistochemistry for these antigens is usually performed on formalin-fixed paraffin sections using peroxidase- or alkaline phosphatase-based detection systems. Thereby, important differential diagnostic problems that are difficult or even impossible to solve by conventional stainings can be clarified. For example, the challenging differential diagnosis of malignant small, round and blue cell tumors can usually be solved by immunohistochemistry. In case of a metastasis of an unknown primary, several organ-specific markers are now available that help to identify the organ site and type of the primary tumor. Immunohistochemistry has also been instrumental for the reclassification of certain entities, e.g., the so-called 'monstrocellular sarcoma' (Zülch 1979) as giant-cell glioblastoma, and the identification of novel tumor entities, e.g., the chordoid glioma of the third ventricle. However, there are a number of issues that cannot be solved by immunohistochemical stainings, such as the differential diagnosis of mixed gliomas (oligoastrocytomas), which still suffers from considerable subjectivity and interobserver varia-

Table 1. WHO classification of tumors of the nervous system (Kleihues and Cavenee 2000)

Tumors of neuroepithelial tissue		Neuroblastic tumors	
Astrocytic tumors		Olfactory neuroblastoma (Esthesioneuroblastoma)	
Diffuse astrocytoma		Olfactory neuroepithelioma	
Variants	Fibrillary astrocytoma	Neuroblastoma of the adrenal gland and sympathetic nervous system	
	Protoplasmic astrocytoma	Pineal parenchymal tumors	
	Gemistocytic astrocytoma	Pineocytoma	
Anaplastic astrocytoma		Pineoblastoma	
Glioblastoma		Pineal parenchymal tumor of intermediate differentiation	
Variants	Giant cell glioblastoma	Embryonal tumors	
	Gliosarcoma	Medulloepithelioma	
Pilocytic astrocytoma		Ependymoblastoma	
Pleomorphic xanthoastrocytoma		Medulloblastoma	
Subependymal giant cell astrocytoma		*Variants*	Desmoplastic medulloblastoma
			Large cell medulloblastoma
			Medullomyoblastoma
			Melanotic medulloblastoma
Oligodendroglial tumors		Supratentorial primitive neuroectodermal tumor (PNET)	
Oligodendroglioma		*Variants*	Neuroblastoma
			Ganglioneuroblastoma
Anaplastic oligodendroglioma		Atypical teratoid / rhabdoid tumor	
Mixed gliomas		Tumors of peripheral nerves	
Oligoastrocytoma		Schwannoma (neurinoma, neurilemmoma)	
Anaplastic oligoastrocytoma		*Variants*	Cellular schwannoma
			Plexiform schwannoma
			Melanotic schwannoma
Ependymal tumors		Neurofibroma	
Ependymoma		*Variant*	Plexiform neurofibroma

Table 1. (Continue)

Tumors of neuroepithelial tissue		Neuroblastic tumors	
Variants	Cellular ependymoma Papillary ependymoma Clear-cell ependymoma Tanycytic ependymoma		
Anaplastic ependymoma		Perineurioma	
		Variants	Intraneural perineurioma Soft-tissue perineurioma
Myxopapillary ependymoma			
Subependymoma		Malignant peripheral nerve sheath tumor (MPNST)	
Choroid plexus tumors		*Variants*	Epithelioid MPNST Glandular MPNST Malignant triton tumor Melanotic MPNST Melanotic psammomatous MPNST
Choroid plexus papilloma			
Choroid plexus carcinoma			
Glial tumors of uncertain origin			
Astroblastoma			
Gliomatosis cerebri			
Chordoid glioma of the third ventricle			
Neuronal and mixed neuronal-glial tumors Gangliocytoma			
Dysplastic ganglio-cytoma of the cerebellum			
Desmoplastic infantile astrocytoma/ganglioglioma			
Dysembryoplastic neuro-epithelial tumor			
Ganglioglioma			
Anaplastic ganglioglioma			
Central neurocytoma			
Cerebellar liponeurocytoma			

▼

Table 1. (Continue)

Tumors of neuroepithelial tissue		Neuroblastic tumors	
Paraganglioma of the filum terminale			
Tumors of the meninges		Primary melanocytic lesions	
Tumors of meningothelial cells		Diffuse melanocytosis	
Meningioma		Melanocytoma	
Variants	Meningothelial meningioma Fibroblastic (fibrous) meningioma Transitional meningioma Psammomatous meningioma Angiomatous meningioma Microcystic meningioma Secretory meningioma Lymphoplasmacyte-rich meningioma Metaplastic meningioma		
all WHO grade I			
Clear-cell meningioma		Malignant melanoma	
Chordoid meningioma		Meningeal melanomatosis	
Atypical meningioma		Tumors of uncertain histogenesis	
Papillary meningioma		Capillary hemangioblastoma	
Rhabdoid meningioma		Lymphomas and hematopoietic tumors	
Anaplastic meningioma		Malignant lymphomas	
Mesenchymal, non-meningothelial tumors		Plasmacytoma	
Lipoma		Granulocytic sarcoma (chloroma)	
Angiolipoma		Germ-cell tumors	
Hibernoma		Germinoma	
Liposarcoma (intracranial)		Embryonal carcinoma	
Solitary fibrous tumor		Yolk sac tumor	
Fibrosarcoma		Choriocarcinoma	
Malignant fibrous		Teratoma	▼

Table 1. (Continue)

Tumors of neuroepithelial tissue		Neuroblastic tumors	
histiocytoma (MFH)		*Variants*	Mature teratoma Immature teratoma Teratoma with malignant transformation
Leiomyoma		Mixed germ-cell tumors	
Leiomyosarcoma		Tumors of the sellar region	
Rhabdomyoma		Craniopharyngioma *Variants*	 Adamantinomatous Papillary
Rhabdomyosarcoma		Granular-cell tumor	
Chondroma		Metastatic tumors	
Chondrosarcoma			
Osteoma			
Osteosarcoma			
Osteochondroma			
Hemangioma			
Epithelioid hemangioendothelioma			
Hemangiopericytoma			
Angiosarcoma			
Kaposi sarcoma			

bility because specific immunohistochemical markers for neoplastic astrocytes or oligodendrocytes are lacking. In addition, most of the available differentiation antigens are expressed in both neoplastic and non-neoplastic cells, i.e., do not allow for a reliable distinction between neoplastic and reactive lesions. For example, GFAP immunoreactivity is found in normal and reactive astrocytes as well as in astrocytic tumor cells.

To facilitate the histologic assessment of a tumor's malignancy grade, immunohistochemistry for the proliferation-associated antigen Ki-67 using the MIB1 antibody has become common practice. Although there is no doubt that the MIB1 index does provide diagnostically useful information in several circumstances, the fact that staining results and evaluation methods are quite variable in different laboratories, together with the considerable overlap of MIB1 positivity in tumors of different WHO grades, has so far precluded the definition of diagnostic cut-off values. Therefore, the WHO classification has not included MIB1 staining as a diagnostic criterion for the classification or grading of most tumor entities, with the meningiomas being a notable exception (see chapter 11).

In the future, immunohistochemical analyses will certainly become even more important in brain tumor diagnostics, as novel cell- and/or tumor-type specific markers are being developed. In addition, the advent of targeted therapies directed against certain proteins that are aberrantly activated or overexpressed by tumor cells requires specific immunohistochemical analyses to demonstrate expression of the target proteins before therapy is initiated. Prominent examples from general oncology include the demonstration of Her2/Erbb2 overexpres-

Table 2. WHO grading of tumors of the nervous system

Tumor group	Tumor entity	Grade I	Grade II	Grade III	Grade IV
Astrocytic tumors	Pilocytic astrocytoma	o			
	Diffuse astrocytoma		o		
	Anaplastic astrocytoma			o	
	Glioblastoma				o
	Pleomorphic xanthoastrocytoma		o		
	Subependymal giant-cell astrocytoma	o			
Oligodendroglial tumors	Oligodendroglioma		o		
	Anaplastic oligodendroglioma			o	
Mixed gliomas	Oligoastrocytoma		o		
	Anaplastic oligoastrocytoma			o	
Ependymal tumors	Myxopapillary ependymoma	o			
	Subependymoma	o			
	Ependymoma		o		
	Anaplastic ependymoma			o	
Choroid plexus tumors	Choroid plexus papilloma	o			
	Choroid plexus carcinoma			o	
Neuronal and mixed neuronal-glial tumors	Ganglioglioma	o	(o)		
	Anaplastic ganglioglioma			o	
	Dysembryopl. neuroepithelial tumor	o			
	Desmoplastic infantile ganglioglioma	o			
	Central neurocytoma		o		
	Cerebellar liponeurocytoma		o		
	Paraganglioma of the filum terminale	o			
Pineal parenchymal tumors	Pineocytoma		o		
	Pineoblastoma				o
Embryonal tumors	Medulloblastoma				o
	Medulloepithelioma				o
	Supratentorial PNET				o
	Neuroblastoma				o
	Ependymoblastoma				o
	Atypical teratoid/rhabdoid tumor				o
Tumors of peripheral nerves	Schwannoma	o			
	Neurofibroma	o			
	MPNST			o	o
	Perineurioma	o			
Tumors of the meninges	Meningioma	o			
	Atypical meningioma		o		
	Clear-cell meningioma		o		
	Chordoid meningioma		o		
	Anaplastic meningioma			o	
	Papillary meningioma			o	
	Rhabdoid meningioma			o	

▼

Table 2. (Continued)

Tumor group	Tumor entity	Grade I	Grade II	Grade III	Grade IV
Others	Gliomatosis cerebri			o	
	Chordoid glioma of the third ventricle		o		
	Hemangiopericytoma		o	o	
	Capillary hemangioblastoma	o			

sion in breast carcinomas and cKit overexpression in gastrointestinal stromal tumors. In neuro-oncology, immunohistochemical assessment of such target proteins is likely to become of diagnostic importance as well, e.g. the immunohistochemical demonstration of the epidermal growth factor receptor as a target for the molecular therapy of malignant gliomas (Rich and Bigner 2004).

Contribution of Molecular Genetics to Brain Tumor Classification

Knowledge of the molecular pathogenesis of primary brain tumors is rapidly advancing, and numerous genetic and epigenetic alterations have been identified in the different tumor types. At present, however, genetic analysis has not yet gained a significant impact on the classification, prognostic assessment and therapeutic management of most tumor entities. Nevertheless, there are some notable exceptions. In oligodendroglial tumors, for example, the allelic status on chromosome arms 1p and 19q has been closely linked to the prognosis and response to therapy (Reifenberger and Louis 2003). Therefore, molecular testing of oligodendroglial tumors for 1p and 19q deletions is now routinely applied at several centers around the world to identify those tumors that are most likely to respond to adjuvant therapy. Testing for 1p/19q loss and *EGFR* amplification may also help to solve the histologically difficult differential diagnosis between anaplastic oligodendroglioma and small-cell glioblastoma (Burger et al. 2001). Potential indications for molecular tests in diagnostic neuro-oncology are listed in Table 4. Among these, testing for *MGMT* promoter methylation in malignant gliomas of WHO grade III and IV has recently gained considerable attention. *MGMT* encodes the DNA repair enzyme O^6-methylguanine DNA methyltransferase, also known as O^6-alkylguanine DNA alkyltransferase, which removes mutagenic alkyl-adducts from the O^6-position of guanine and thereby causes resistance to those alkylating drugs that are commonly used for glioma treatment, i.e., nitrosourea compounds and temozolomide. Several studies on malignant glioma patients treated with nitrosourea derivatives or temozolomide have reported *MGMT* promoter hypermethylation as an independent marker of response to chemotherapy and survival (Esteller et al. 2000; Hegi et al. 2004; Paz et al. 2004).

Taken together, there is growing evidence that molecular markers may not only help in certain differential diagnostic problems but may also improve the prediction of an individual patient's response to therapy and outcome. In the near future, it will be important to systematically evaluate the emerging molecular markers by their incorporation into controlled prospective clinical trials. In addition, novel techniques such as microarray-based comparative genomic hybridization and mRNA expression profiling allow for the simultaneous analysis of multiple genes in a single experiment, which opens up promising perspectives for molecular diagnostics. In fact, initial data suggest that the classification of malignant gliomas by microarray-based expression profiling correlates better with the clinical outcome than histologic classification (Nutt et al. 2003; Freije et al. 2004). Despite these optimistic findings, however, current molecular analyses cannot replace the established morphologic brain tumor classification and grading according to the WHO classification of tumors of the nervous system.

Astrocytic Tumors

Astrocytic gliomas are the most common primary brain tumors and account for about 60% of all glial neoplasms. The WHO classification distinguishes two major categories: 1. The more common group of diffusely infiltrating astrocytomas (diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma), and 2. the less common group of astrocytic neoplasms with a more circumscribed growth (pilocytic astrocytoma and pleomorphic xanthoastrocytoma). Tumors of the latter group preferentially develop in children and young adults, grow slowly, have a limited potential for malignant progression, and can be cured by tumor resection. In contrast, the diffusely infiltrating astrocytic tumors predominantly af-

fect adult patients, have an inherent tendency for local recurrence and malignant progression, and usually cannot be cured by neurosurgery, radiotherapy, and chemotherapy.

Diffuse Astrocytoma (WHO Grade II)

Definition. A well-differentiated, slowly growing astrocytic glioma with diffuse infiltration into the adjacent brain tissue.

Incidence and Age Distribution. Diffuse astrocytomas account for approximately 5% of all primary CNS tumors and 10–15% of the astrocytic gliomas. They develop preferentially in young adults (age peak: 30–40 years) but may occur at any age.

Macroscopy and Localization. Diffuse astrocytomas predominantly grow in the cerebral hemispheres. Other localizations are rare, except for the brain stem in children. Macroscopically, diffuse astrocytomas are ill-defined, gray to yellow, usually soft lesions in the white and/or gray matter. They enlarge pre-existing structures and blur normal anatomical boundaries (Fig. 6a). Cystic changes are common. The tumors may infiltrate to contralateral structures via the corpus callosum.

Histopathology. Microscopy shows a well differentiated astrocytic tumor of low to moderate cellularity and infiltrative growth into the adjacent brain parenchyma. Microcystic degeneration is a common feature. The mitotic activity is low. Necrosis and microvascular proliferation are absent. Three histologic subtypes are distinguished. The *fibrillary astrocytoma* (Fig. 7a) is the most common variant and composed of multipolar neoplastic astrocytes with scant cytoplasm and fine cell processes that build a fiber-rich glial matrix. The less common *gemistocytic astrocytoma* (Fig. 7b) is characterized by gemistocytic astrocytes, i.e., tumor cells with an enlarged eosinophilic cytoplasm, eccentric nuclei and stout processes. To make the diagnosis, at least 20% of the tumor cells should demonstrate the gemistocytic phenotype. The third variant, the *protoplasmic astrocytoma*, is rare and composed of tumor cells with eosinophilic cytoplasm and few, flaccid processes embedded in a microcystic or mucoid matrix (Fig. 7c). The tumor cell processes in protoplasmic astrocytomas contain only small amounts of glial filaments.

Grading. Diffuse astrocytomas correspond to WHO grade II. However, these tumors have an inherent tendency for recurrence and spontaneous progression to anaplastic astrocytoma or secondary glioblastoma. Histologic signs of progression, such as increased cellularity and mitotic activity, may develop focally. Therefore, selection of biopsy site and tissue sampling are important issues. Gemistocytic astrocytomas have been associated with a higher tendency to progression and less favorable prognosis. In contrast, a subset of WHO grade II astrocytomas in patients with long-standing epilepsy have a lower likelihood for recurrence and a more favorable survival (Schramm et al. 2004).

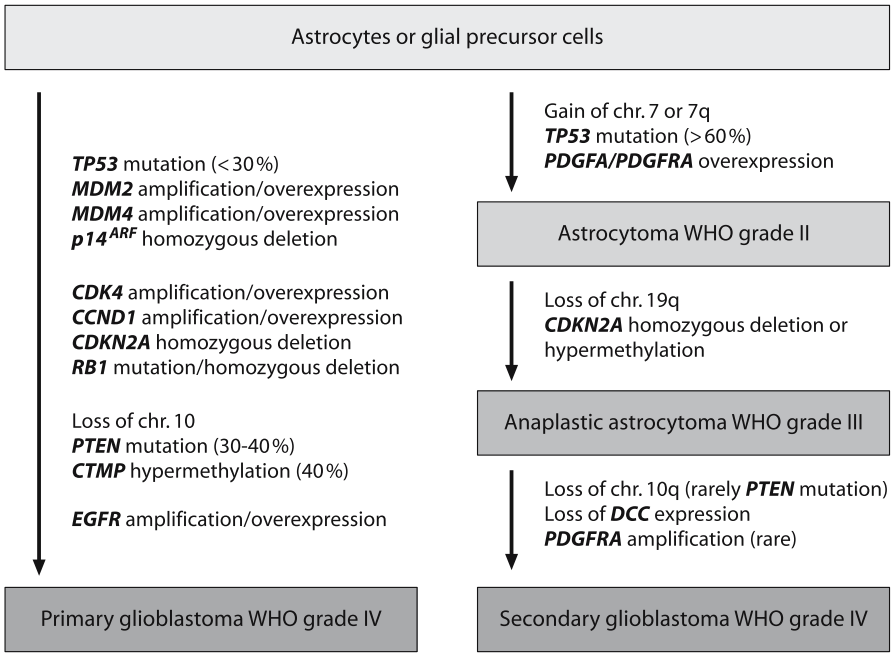


Fig. 1. Schematic representation of molecular aberrations frequently detected in the different types of diffusely infiltrating astrocytic gliomas (modified according to Reifenberger and Collins 2004)

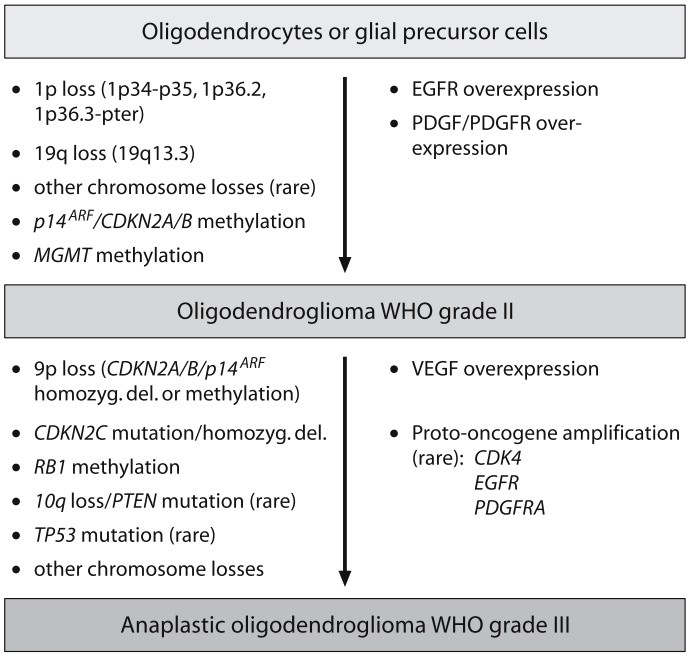


Fig. 2. Schematic representation of molecular aberrations associated with the initiation and progression of oligodendroglial tumors (modified according to Reifenberger and Louis 2003). The most common early chromosomal changes in WHO grade II oligodendrogliomas are losses on 1p and 19q. Promoter methylation of the *p14*^{ARF}, *CDKN2 A* and/or *CDKN2B* genes on 9p21, as well as the *MGMT* gene on 10q25 is also frequent. Oligodendrogliomas often demonstrate overexpression of the epidermal growth factor receptor (EGFR) as well as platelet-derived growth factors and receptors (PDGF and PDGFR). Anaplastic oligodendrogliomas are characterized by progression-associated genetic changes, such as homozygous deletions affecting the cell-cycle regulatory genes *CDKN2 A*, *CDKN2B* or *CDKN2 C*, mutations in the *PTEN* gene and/or allelic loss on the long arm of chromosome 10. *TP53* mutations are restricted to a low fraction of cases. Anaplastic oligodendrogliomas frequently demonstrate overexpression of vascular endothelial growth factor (VEGF). Amplification of proto-oncogenes is rare

Immunohistochemistry. Diffuse astrocytomas stain positive for glial fibrillary acidic protein (GFAP) and protein S-100. GFAP immunoreactivity is strong in the gemistocytic and fibrillar variants, whereas protoplasmic astrocytomas are only weakly positive. Immunostaining for the p53 tumor suppressor protein shows widespread nuclear immunoreactivity in about 60% of the cases. The Ki-67 (MIB1) labeling index is low (<5%).

Differential Diagnosis. Histologic distinction between diffuse astrocytoma and reactive astrogliosis is important. Immunohistochemistry for p53 can sometimes be helpful by demonstrating nuclear p53 accumulation in astrocytic tumor cells. However, negative p53 staining does not exclude a diffuse astrocytoma, and the presence of just individual p53-positive cells needs to be interpreted with caution. The differential diagnosis towards pilocytic astrocytoma may be difficult when only small biopsy specimens are available. Anaplastic astrocytoma differs from diffuse astrocytoma by the presence of histologic features of anaplasia, in particular increased mitotic activity.

Molecular Pathology (Fig. 1). The most common karyotypic abnormality is trisomy/polysomy 7. Molecular cytogenetic analyses found gains of chromosome 7 or 7q in more than 50% of the cases (Reifenberger and Collins 2004; Ichimura et al. 2004). Losses of chromosomes 22q, 13q, 10p, 6, and the sex chromosomes are somewhat less frequent. Mutations in the *TP53* tumor suppressor gene at 17p13 and loss of heterozygosity on 17p are present in approximately 50–60% of all diffuse astrocytomas and up to 80% of the gemistocytic tumors. A subset of the diffuse astrocytomas without *TP53* mutation shows promoter methylation of the *p14*^{ARF} gene (Nakamura et al. 2001). Increased expression of the platelet-derived growth factor receptor alpha (PDGFRA) and its ligand PDGFα is also common, preferentially in tumors with LOH on 17p (Hermansson et al. 1996). Potential molecular markers of malignant progression include allelic losses on chromosomes 6 and 19q (Miyakawa et al. 2000; von Deimling et al. 1994).

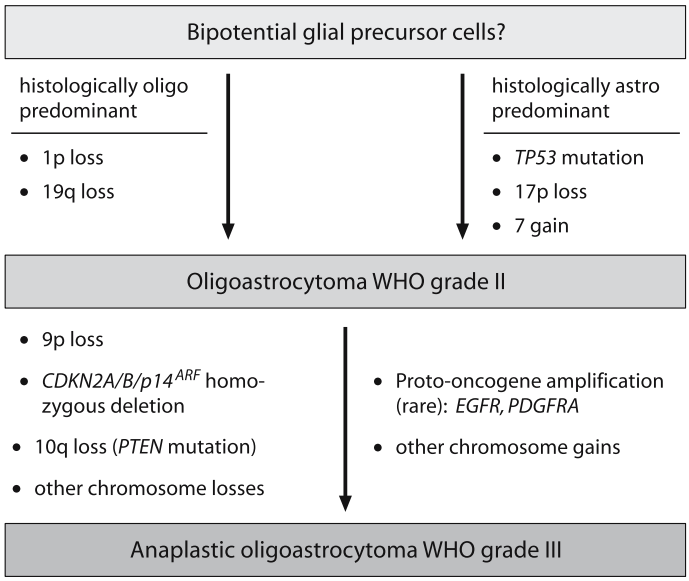


Fig. 3. Schematic representation of molecular aberrations frequently associated with the initiation and progression of oligoastrocytomas (modified from Reifenberger and Louis 2003). Oligoastrocytomas with 1p/19q loss tend to be histologically oligodendroglioma-predominant, whereas oligoastrocytomas with 17p loss and/or *TP53* mutation are more often astrocytoma-predominant. Progression to anaplastic oligoastrocytoma seems to be associated with similar genetic changes as in other gliomas, such as loss of 9p and homozygous deletion of *CDKN2 A*, *p14*^{ARF} and *CDKN2B*, as well as loss of 10q and *PTEN* mutation. Amplification of proto-oncogenes is restricted to a low fraction of anaplastic oligoastrocytomas

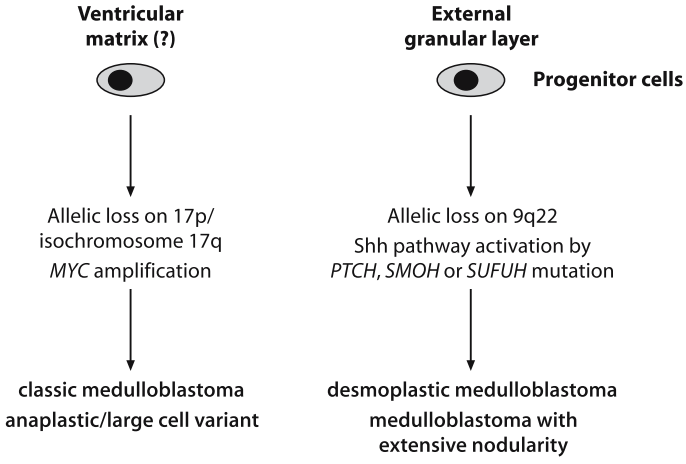


Fig. 4. Putative histogenesis and genetics of different medulloblastoma variants. The classic variant is characterized by frequent alterations of chromosome 17, while the desmoplastic subtype shows frequent activation of the sonic hedgehog signaling pathway. Desmoplastic medulloblastomas are thought to derive from external granule cell precursors. In contrast, the cellular origin of classic medulloblastomas, which are mostly located in the midline, is still under discussion but may be ventricular matrix cells. There seems to be a continuum from the classic to the anaplastic variant, with the latter frequently displaying *MYC* gene amplification. Medulloblastoma with extensive nodularity represents a rare variant of medulloblastoma that occurs in young children and is associated with a favorable prognosis

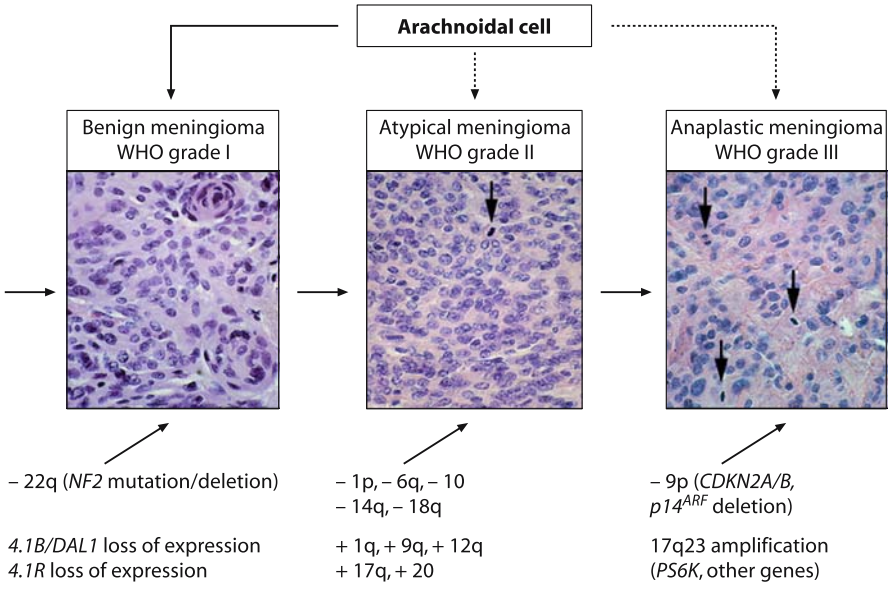


Fig. 5. Schematic representation of molecular aberrations associated with the initiation and progression of meningiomas (modified from Perry et al. 2004). Meningiomas are assumed to arise from either the arachnoidal cells or an earlier meningothelial progenitor cell. Progression from benign meningioma to atypical to anaplastic meningioma has been well documented. However, de novo development of atypical and anaplastic meningiomas is more common (dotted lines). Genetic and chromosomal alterations most commonly involved in tumor initiation and the different steps of progression are listed. Arrows in the histologic pictures indicate mitotic figures

Anaplastic Astrocytoma (WHO Grade III)

Definition. A diffusely infiltrating astrocytic glioma with increased cellularity, cytologic atypia and prominent mitotic activity.

Incidence and Age Distribution. Anaplastic astrocytomas account for approximately 10–25% of the astrocytic gliomas. The incidence peaks between 40–45 years.

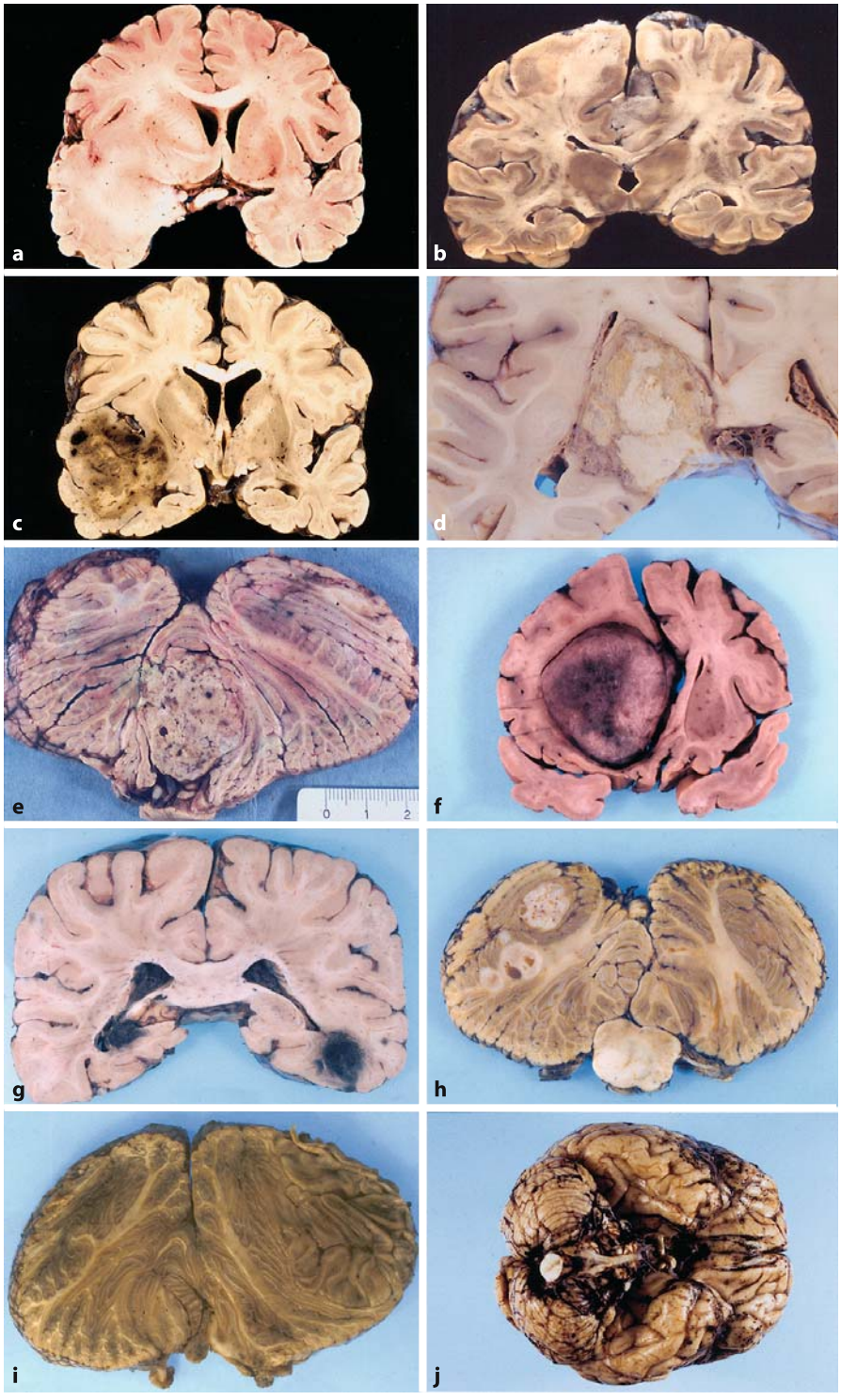
Macroscopy and Localization. Anaplastic astrocytomas are preferentially located in the cerebral hemispheres. In children and young adults, the brain stem and thalamus are also typical sites. Macroscopically, anaplastic astrocytomas are expanding lesions with perifocal edema. The distinction from normal brain tissue may be easier than in diffuse astrocytomas, but the borders are similarly ill-defined.

Histopathology. Microscopically, anaplastic astrocytomas are characterized by signs of focal or diffuse anaplasia, such as increased cellularity, nuclear atypia, and prominent mitotic activity (Fig. 7d). The histologic hallmarks of glioblastoma (microvascular proliferation and necrosis) are missing, but anaplastic astrocytomas tend to progress to secondary glioblastoma.

Immunohistochemistry. Anaplastic astrocytomas are positive for GFAP and protein S-100. Nuclear p53 staining is found in about 60% of the cases. Staining for Ki-67 (MIB1) usually shows nuclear positivity in more than 5% of the tumor cells.

Molecular Pathology (Fig. 1). Similar to the diffuse astrocytomas, anaplastic astrocytomas frequently show gains of chromosome 7, *TP53* mutation and PDGFRA/PDGFα overexpression (Reifenberger and Collins 2004; Ichimura et al. 2004). Alternative to *TP53* mutation, subsets of anaplastic astrocytomas show loss of $p14^{ARF}$ expression, either due to homozygous deletion or to promoter hypermethylation, or MDM 2 amplification. Thus, the majority of anaplastic astrocytomas carry genetic alterations that deregulate p53 function. The *CDKN2 A* and *CDKN2B* genes on 9p21 are deleted or hypermethylated in about 20–25% of the cases. These genes code for negative regulators of G1/S-phase progression ($p16^{INK4a}$ and $p15^{INK4b}$) that inhibit the activity of the cyclin-dependent kinases Cdk4 or Cdk6 (Reifenberger and Collins 2004; Ichimura et al. 2004). Subsets of tumors without *CDKN2 A* or *CDKN2B* alterations were found to have amplified the *CDK4* gene or carry mutations in the retinoblastoma gene (*RB1*) (Reifenberger and Collins 2004; Ichimura et al. 2004). Taken together, at least one-third of the tumors has

gene alterations affecting the pRb1-dependent cell cycle control. In contrast to glioblastomas, mutation of the *PTEN* gene on 10q23 is rare. When present, the prognosis is usually as poor as for glioblastomas (Smith et al. 2001). Additional chromosomal deletions in anaplastic astrocytomas have been mapped to chromosomes 6, 11p, 14q, 19q, and 22q, with the respective tumor suppressor genes not yet known.



Glioblastoma (WHO Grade IV)

Definition. The most malignant astrocytic glioma, histologically characterized by high cellularity, marked cellular pleomorphism, nuclear atypia, brisk mitotic activity, microvascular proliferation and necrosis.

Incidence and Age Distribution. Glioblastomas are the most common primary brain tumors. They account for 10–15% of all intracranial tumors and 50–60% of the astrocytic gliomas. The annual incidence is approximately 2–3 new cases per 100,000 population. Glioblastomas may develop at any age, but adult patients are most commonly affected (peak incidence: 50–70 years).

Macroscopy and Localization. The vast majority of glioblastomas develop in the cerebral hemispheres. Tumor spread into the basal ganglia or the contralateral hemisphere is not uncommon. The brain stem is a rare location, found particularly in children. Glioblastomas of the cerebellum and spinal cord are very rare. Macroscopically, glioblastomas are largely necrotic masses with a peripheral zone of fleshy gray tumor tissue (Fig. 6c,d). Intratumoral hemorrhages are frequent. The surrounding brain tissue usually shows a marked edema.

Histopathology. Glioblastomas are cellular, highly anaplastic tumors, which may be composed of cells with various morphologies, including fibrillar and gemistocytic cells, fusiform cells, small anaplastic cells, and multinuclear giant cells. Nuclear atypia is usually marked, and mitotic activity, including atypical forms, is prominent (Fig. 7e). The presence of microvascular proliferation and/or necrosis is essential for the diagnosis. Microvascular proliferation often results in glomerulus- or garland-like capillary structures (Fig. 7f). Vascular thrombosis is common. In addition to large ischemic necroses, which are macroscopically visible and appear as the nonenhancing central part of the tumor on neuroimaging, glioblastomas typically demonstrate small, often multiple, irregularly shaped, band-like or serpiginous foci of necrosis that are surrounded by pseudopalisading cells (Fig. 7 g).

Glioblastoma Variants. The WHO classification distinguishes two histologic glioblastoma variants from the classic glioblastoma, i.e., *giant-cell glioblastoma* and *gliosarcoma*.

Giant-cell glioblastoma is characterized by numerous pleomorphic, multinucleated giant cells that may be extremely bizarre and reach sizes up to 500 µm (Fig. 7h). Some giant-cell glioblastomas demonstrate a collagen and reticulin fiber-rich matrix. Lymphocytic infiltration may be prominent. Giant-cell glioblastomas often show a more circumscribed growth that may contribute to the somewhat better prognosis reported for this variant. Morphologic features reminiscent of giant-cell glioblastoma may develop following irradiation of an ordinary glioblastoma. Such cases should not be diagnosed as giant-cell glioblastoma.

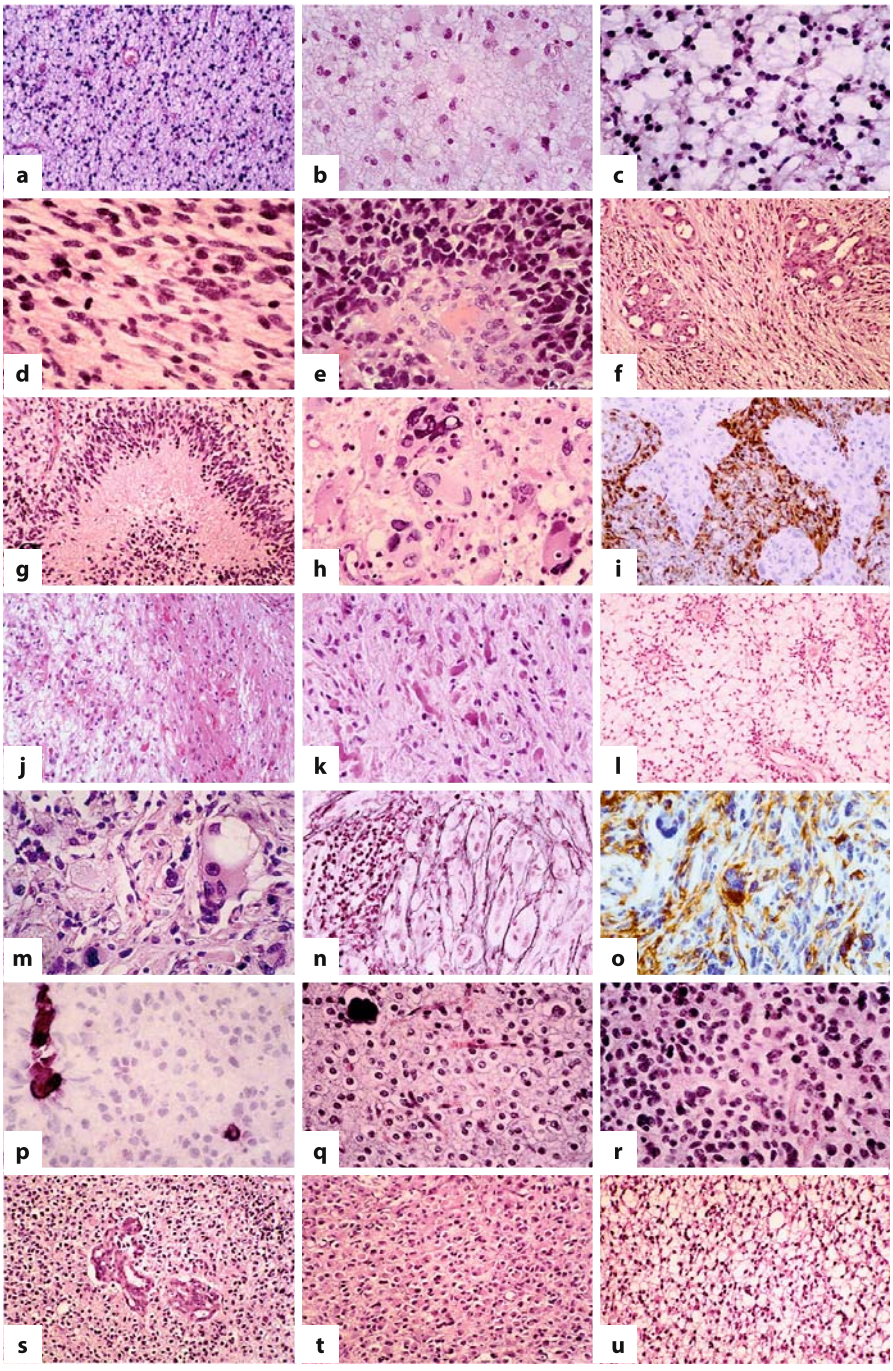
Gliosarcomas are characterized by a biphasic tissue pattern with areas displaying phenotypic features of glioma and sarcoma (Fig. 7i). The glial component shows the histologic features of glioblastoma and is immunohistochemically positive for GFAP. The sarcomatous tumor parts are rich in reticulin fibers and composed of GFAP-negative spindle cells, thus resembling the morphologic appearance of fibrosarcoma. Occasional cases may show evidence of chondroid, osseous, or myogenic differentiation. Epithelial metaplasia has also been reported.

In addition to the two WHO-recognized glioblastoma variants, other less common variants may be distinguished. These include a small subset of otherwise typical glioblastomas that show morphological features associated with oligodendroglial differentiation. Such cases can be classified as *glioblastoma with oligodendroglial component*. However, the diagnostic criteria for these tumors are poorly defined, thus allowing for a high degree of subjectivity in their differential diagnosis towards anaplastic oligoastrocy-

Fig. 6. Macroscopic appearance of selected types of primary and metastatic brain tumors. **a** Diffuse astrocytoma in the left temporal lobe. Note a diffuse mass lesion in the white matter without any distinct borders and blurring of the border between gray and white matter. **b** Oligodendroglioma involving the corpus callosum and cingulated gyrus on the right side. The tumor lacks any clear-cut borders and grows into the cortical gray matter. **c** Glioblastoma in the left temporal lobe with a heterogeneous cut surface demonstrating areas of necrosis and intratumoral hemorrhages. **d** Larger magnification of a glioblastoma showing large necroses in the tumor center. **e** Ependymoma in the fourth ventricle with complete obstruction of the ventricular lumen. Note that the tumor appears well-demarcated from the surrounding cerebellar tissue. **f** Intraventricular meningioma in the left lateral ventricle. **g** Two distinct melanoma metastases in the brain. **h** Multiple metastases of a bronchial adenocarcinoma in the cerebellum and brain stem. **i** Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease). Note enlargement of the cerebellar folia in the right hemisphere. **j** Diffuse leptomeningeal melanocytosis

toma and ordinary glioblastoma. Nevertheless, glioblastomas with an oligodendroglial component may be associated with a somewhat better prognosis and a higher likelihood of a favorable response to adjuvant treatment as compared with ordinary glioblastomas (Kraus et al. 2001; He et al. 2001).

Another histologic variant, *the small-cell glioblastoma*, is composed of a monomorphic population of small anaplastic cells with sparse cytoplasm and round or carrot-shaped hyperchromatic nuclei (Burger et al. 2001). Histologically, this variant may be mistaken for a highly anaplastic oligodendroglioma or a primitive neuroectodermal tumor. Genetically, EGFR amplification and losses on chromosome 10 are common, while combined losses on 1p and 19q are absent. The so-called *small-cell astrocytoma* is a recently described related variant that shares this genetic profile and behaves like a glioblastoma, but lacks endothelial hyperplasia and necrosis (Perry et al. 2004).



Further uncommon variants of glioblastoma include *granular cell glioblastoma*, which consist of glioma cells with foamy granular cytoplasm, *heavily lipidized glioblastoma*, and *glioblastoma with epithelial metaplasia*, i.e., glioblastomas characterized by areas of epithelial differentiation, including immunohistochemical positivity for cytokeratins.

Primary and Secondary Glioblastoma. Most glioblastomas develop rapidly in a *de novo* manner with a short clinical history and without evidence of a previous lesion of lower malignancy. These tumors are called *primary glioblastomas*. Less commonly, glioblastomas develop by progression from a pre-existing lower grade glioma. These cases are designated as *secondary glioblastomas*. Morphologically, primary and secondary glioblastomas cannot be distinguished. Clinically, secondary glioblastomas mostly occur in younger patients below the age of 45 years, while primary glioblastomas account for the vast majority of glioblastomas in older patients. The prognosis of primary and secondary glioblastomas seems to be equally poor when adjusted for patient age (Ohgaki et al. 2004).

Immunohistochemistry. Similar to the other astrocytic tumors, glioblastomas are positive for GFAP and protein S-100. However, there may be marked intratumoral heterogeneity in immunoreactivity, with fibrillary and gemistocytic tumor cells often being positive and small anaplastic cells frequently being negative. Multinucleated giant cells are variably GFAP and S-100 positive. Strong nuclear p53 immunoreactivity can be detected in 30–40% of all glioblastomas, with giant-cell glioblastomas and secondary glioblastomas being p53 positive in up to 80% of the cases. Strong expression of the epidermal growth factor receptor (EGFR) is found in about 60% of primary glioblastomas but is rare in secondary glioblastomas. The MIB1 labeling index is usually high (>10%) but often shows marked regional heterogeneity.

Differential Diagnosis. The presence of microvascular proliferation and/or necrosis distinguishes glioblastomas from anaplastic astrocytomas. The differential diagnosis towards anaplastic oligodendroglioma and anaplastic oligoastrocytoma is more difficult and associated with considerable interobserver variability. Molecular testing may be helpful in certain instances, such as the differential diagnosis between small-cell astrocytoma/glioblastoma and anaplastic oligodendroglioma (Reifenberger and Louis 2003; Perry et al. 2004).

Molecular Pathology (Fig. 1). Molecular genetic analyses have shown that the pattern of genetic aberrations differs between primary and secondary glioblastomas (Ohgaki et al. 2004). Primary glioblastomas more frequently demonstrate *EGFR* amplification, homozygous deletion of *CDKN2 A* and $p14^{ARF}$, *CDK4* amplification, *MDM 2* or *MDM 4* amplification, *RB1* mutation/homozygous deletion, monosomy 10 and *PTEN* mutation (Reifenberger and Collins 2004). *TP53* mutations are found in approximately 30% of primary glioblastomas but more than 60%

Fig. 7. Histology of different types of gliomas. **a–c** Diffuse astrocytomas of WHO grade II (H&E). Shown are typical examples of fibrillary (**a**), gemistocytic (**b**), and protoplasmic (**c**) astrocytoma variants. **d** Anaplastic astrocytoma of WHO grade III (H&E). Note increased cellularity, nuclear pleomorphisms, and mitotic activity. **e** Glioblastoma (WHO grade IV). Highly cellular, pleomorphic glioma with mitotic activity and a pathological tumor vessel (H&E). **f** Microvascular proliferation with formation of glomeruloid capillary tufts in a glioblastoma (H&E). **g** Typical necrosis with perinecrotic pseudopalisading in a glioblastoma (H&E). **h** Giant-cell glioblastoma (WHO grade IV) with numerous multinucleated giant cells (H&E). **i** Gliosarcoma (WHO grade IV). Note the biphasic pattern caused by GFAP-positive glial tumor areas and GFAP-negative sarcomatous tissue (GFAP). **j** Pilocytic astrocytoma (WHO grade I) showing a typical biphasic architecture with compact areas of bipolar (piloid) tumor cells and microcystic areas of multipolar tumor cells (H&E). **k** Numerous Rosenthal fibers in a pilocytic astrocytoma (H&E). The Rosenthal fibers appear as homogeneous, brightly eosinophilic, corkscrew-shaped structures. **l** Monomorphous pilomyxoid astrocytoma with perivascular tumor cell arrangements and myxoid degeneration of the tumor matrix (H&E). **m** Pleomorphic xanthoastrocytoma (WHO grade II) characterized by pleomorphic tumor cells with cytoplasmic vacuolization (H&E). **n** Pericellular reticulin network and lymphocytic infiltrates in a pleomorphic xanthoastrocytoma (Gomori stain for reticulin). **o** Strong expression of CD34 in a pleomorphic xanthoastrocytoma. **p** Oligodendroglioma (WHO grade II). This frozen section shows a monomorphic, moderately cellular glioma with calcifications. The oligodendroglioma-typical honeycomb artifact (q) is not seen on frozen sections (H&E). **q** Oligodendroglioma (WHO grade II). On paraffin sections, oligodendrogliomas demonstrate the characteristic honeycomb appearance of tumor cells (H&E). **r** Anaplastic oligodendroglioma (WHO grade III). A cellular oligodendroglial tumor with anaplastic features including nuclear pleomorphism and mitotic activity. **s–u** Anaplastic oligoastrocytoma (WHO grade III). The pictures show different areas from the same tumor, demonstrating oligodendroglial differentiation with vascular proliferation (**s**), numerous so-called minigemistocytes (**t**), and fibrillary astrocytic differentiation (**u**)

of secondary glioblastomas. In the latter, *TP53* mutations cluster at codons 248 and 273 (Ohgaki et al. 2004). *EGFR*, *MDM 2*, or *MDM 4* amplification as well as *PTEN* mutation are rare, and allelic losses on chromosome 10 are frequently confined to markers on 10q. Allelic losses on 19q and 13q, promoter hypermethylation of the *RB1* gene, and overexpression of *PDGFRA* are more common in secondary glioblastomas. Taken together, primary and secondary glioblastomas carry different genetic alterations. However, the genetic alterations in both glioblastoma types target the same oncogenic pathways, namely the p53, pRb1, Pten/Pi3 k/Akt, and mitogen-activated protein kinase pathways (Reifenberger and Collins 2004).

TP53 mutations are detected in up to 80% of *giant-cell glioblastomas*, while *PTEN* mutations are found at similar frequency (approximately 30%) as in primary glioblastomas. *EGFR* amplification and homozygous deletions of *CDKN2 A* and $p14^{ARF}$ are rare. *Gliosarcomas* show similar genetic changes to primary glioblastomas, except for less common *EGFR* amplification. Gliomatous and sarcomatous areas invariably share common genetic aberrations, which strongly argues for a monoclonal origin of both components (Reis et al. 2000; Actor et al. 2002).

Pilocytic Astrocytoma (WHO Grade I)

Definition. A slowly growing, well-circumscribed, and frequently cystic astrocytoma of children and young adults. Histologic characteristics include a biphasic growth pattern of loose and compact tissue, Rosenthal fibers, and eosinophilic granular bodies.

Incidence and Age Distribution. Pilocytic astrocytomas account for approximately 6% of all intracranial tumors. Children and young adults are preferentially affected. Pilocytic astrocytomas are the most common primary brain tumors in pediatric patients. Patients with neurofibromatosis type 1 (NF1) have an increased risk for pilocytic astrocytomas, in particular optic nerve gliomas. However, the vast majority of pilocytic astrocytomas are sporadic tumors occurring in patients without an inherited tumor syndrome.

Macroscopy and Localization. More than 80% of pilocytic astrocytomas are cerebellar tumors. Other typical sites include the optic nerve and optic chiasm ('optic glioma'), hypothalamus, thalamus, basal ganglia, brain stem, and spinal cord. Rare cases may originate in the cerebral hemispheres. Macroscopically, pilocytic astrocytomas are soft, gray, frequently cystic lesions that are well-circumscribed. However, local involvement of the pia mater is not uncommon.

Histopathology. Pilocytic astrocytomas are characterized by low to moderate cellularity and a biphasic architecture, consisting of compact areas with bipolar (piloid) tumor cells and microcystic areas with multipolar tumor cells (Fig. 7j). An important diagnostic feature, albeit not unique to these tumors, is the presence of Rosenthal fibers and eosinophilic granular bodies (Fig. 7k). Capillary proliferation, degenerative cellular pleomorphism, foci of non-palisading necrosis, and occasional mitoses are still consistent with this diagnosis. However, high mitotic activity and palisading necrosis indicate that the tumor behaves more aggressively. Such rare cases are classified as *anaplastic pilocytic astrocytoma*.

A novel histologic variant is the so-called *pilomyxoid astrocytoma* (Tihan et al. 1999). These tumors are characterized by a monomorphic population of bipolar neoplastic astrocytes in a myxoid matrix. The tumor cells form characteristic pseudorosette-like angiocentric architectures (Fig. 7l). In contrast to ordinary pilocytic astrocytomas, Rosenthal fibers are often missing. Pilomyxoid astrocytomas are predominantly found in the optic chiasms/hypothalamus region of children and are clinically associated with a higher risk of local recurrence and CSF seeding (Tihan et al. 1999). More recently, histologically similar tumors have been reported in the spinal cord (Komotar et al. 2005).

Immunohistochemistry. Pilocytic astrocytomas are positive for GFAP and protein S-100. Immunostaining for p53 remains negative or restricted to individual cells. Except for the rare anaplastic variants, MIB1 labeling is low (<5%).

Differential Diagnosis. The most important differential diagnosis is piloid gliosis, which may be found as a reaction to slowly growing tumors, such as craniopharyngioma or capillary hemangioblastoma, vascular malformations, as well as other chronic CNS lesions. In the spinal cord, tanycytic ependymoma is a rare differential diagnosis. Gangliogliomas are a common clinical differential diagnosis in long-standing, well-circumscribed lesions of the temporal lobe. However, the histologic demonstration of neoplastic ganglion cells clearly separates ganglioglioma from pilocytic astrocytomas.

Molecular Pathology. Investigation of pilocytic astrocytomas by comparative genomic hybridization (CGH) analysis revealed chromosomal imbalances in less than 20% of cases, with a gain of 9q34.1-qter being the most common change (Sanoudou et al. 2000). Pilocytic astrocytomas in NF1 patients frequently carry allelic losses on 17q11.2, the *NF1* gene locus. This aberration is rare in sporadic tumors (Kluwe et al. 2001). In contrast to the diffuse astrocytomas,

most pilocytic astrocytomas do not demonstrate allelic losses on 17p and mutations in the *TP53* gene.

Pleomorphic Xanthoastrocytoma (WHO Grade II)

Definition. A well-circumscribed, slowly growing astrocytic glioma with a superficial (meningocerebral) location and usually favorable prognosis. Histologic characteristics include pronounced cellular pleomorphism, xanthomatous tumor cells, perivascular lymphocytes, a reticulin network around single or grouped cells, and eosinophilic granular bodies.

Incidence and Age Distribution. Pleomorphic xanthoastrocytomas are rare (<1% of the astrocytic tumors). Children and young adults are primarily affected. A long-standing history of seizures is common.

Macroscopy and Localization. Pleomorphic xanthoastrocytomas are well-circumscribed, often cystic tumors that grow superficially in the cerebral cortex and extend into the adjacent leptomeninges. The temporal lobe is most commonly affected. Individual cases have been reported in the cerebellum, spinal cord, or retina.

Histopathology. Microscopically, pleomorphic xanthoastrocytomas are relatively compact and well-circumscribed tumors growing in the cerebral cortex and invading the meninges. A fascicular growth pattern is commonly seen. Histologic hallmarks include the presence of pleomorphic, sometimes bizarre and multinucleated giant cells, lipidized astrocytic tumor cells, eosinophilic protein droplets, often prominent perivascular lymphocytic infiltrates, and a variably dense pericellular/perilobular network of reticulin fibers (Fig. 7m,n). The adjacent cortex frequently shows dysplastic features. Rare histologic variants include tumors with angiomatous, epithelioid, or gangliocytic components.

Pleomorphic xanthoastrocytoma is a WHO grade II glioma and associated with a relatively favorable prognosis, as indicated by a 10-year survival rate of >70% (Giannini et al. 1999). For lesions with 5 or more mitoses per 10 high power fields and/or areas of necrosis, the WHO classification suggests using the term *pleomorphic xanthoastrocytoma with anaplastic features.* The WHO grade of these rare tumors has not yet been defined. Because their prognosis is better than that for anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV) (Giannini et al. 1999), the WHO classification no longer recommends classifying these tumors as anaplastic pleomorphic xanthoastrocytoma (WHO grade III).

Immunohistochemistry. GFAP immunoreactivity is generally present but may be highly variable. S-100 staining is usually strong. Nuclear p53 staining is usually absent or restricted to a few cells. A subset of pleomorphic xanthoastrocytomas, including the rare tumors with a ganglion cell component, additionally stains for neuronal markers, such as neurofilaments and synaptophysin (Giannini et al. 2002). Another interesting feature of pleomorphic xanthoastrocytomas is their frequent expression of CD34 (Fig. 7o), which is seen in tumor cells and dysplastic cells in the adjacent cortex (Reifenberger et al. 2003). MIB1 labeling is low (<5%) in pleomorphic xanthoastrocytomas of WHO grade II.

Differential Diagnosis. Their superficial location, preferential occurrence in young patients, and typical histologic features distinguish pleomorphic xanthoastrocytomas from high-grade diffuse astrocytic gliomas. Occasionally, the differential diagnosis between pleomorphic xanthoastrocytoma with anaplastic features and giant-cell glioblastoma may be difficult. Histologically, the absence of lipidized tumor cells and eosinophilic granular bodies as well as the presence of atypical mitoses, microvascular proliferation, and pseudopalisading necroses argue in favor of a giant-cell glioblastoma. Furthermore, widespread nuclear p53 staining is common in giant-cell glioblastoma but rare in pleomorphic xanthoastrocytoma. On the other end of the spectrum, pleomorphic xanthoastrocytoma needs to be distinguished from pilocytic astrocytoma and ganglioglioma.

Molecular Pathology. Genetic alterations frequently found in diffuse astrocytic gliomas, such as alterations of the *EGFR*, *CDK4*, *MDM 2*, *CDKN2 A*, and $p14^{ARF}$ genes, are rare or absent in pleomorphic xanthoastrocytomas (Kaulich et al. 2002). *TP53* mutations are present in <10% of the cases. Microsatellite analysis revealed recurrent losses on chromosome 9, while other chromosomes, including 1p, 10, 17, 19q, and 22q, showed either no or rare losses (Kaulich et al. 2002). Thus, the genetic aberrations in pleomorphic xanthoastrocytomas clearly differ from those associated with diffusely infiltrating astrocytic and oligodendroglial gliomas.

Oligodendroglial Tumors and Mixed Gliomas

Oligodendroglioma (WHO Grade II)

Definition. A diffusely infiltrating glioma composed of neoplastic cells morphologically resembling oligodendroglia.

Incidence and Age Distribution. The annual incidence of oligodendroglial tumors (including anaplastic forms) is approximately 0.3 per 100,000 individuals. About 10–15% of all gliomas are oligodendroglial tumors. The incidence peaks in the fifth decade, although children may also be affected.

Macroscopy and Localization. Most oligodendrogliomas arise in the cerebral hemispheres. The frontal lobe is the most common location. The tumor mass is typically located in the white matter, but extension into the cerebral cortex is common. Rarely, oligodendrogliomas develop in the cerebellum, brain stem, or spinal cord. Macroscopically, the tumors appear as rather well-defined soft masses of grayish-pink color (Fig. 6b). Calcifications are frequently found. Areas of mucoid degeneration, cystic changes, and intratumoral hemorrhages are not unusual.

Histopathology. Oligodendrogliomas are moderately cellular, diffusely infiltrating gliomas composed of isomorphic cells with round, hyperchromatic nuclei. Nodular areas of increased cellularity may be encountered that are not indicative of anaplasia as long as mitotic activity is low. After formalin fixation and embedding in paraffin, oligodendroglial tumor cells suffer from artifactual swelling that results in clear cells with central spherical nuclei and well-defined cell borders, the so-called honeycomb appearance (Fig. 7q). This diagnostically useful artifact is absent in smear preparations and frozen sections (Fig. 7p), thus making a definite intraoperative diagnosis difficult. Oligodendrogliomas may contain small gemistocytic cells that are GFAP positive (so-called mini- or microgemistocytes). Tumors consisting largely of signet-ring cells or eosinophilic granular cells are very rare. Microcalcifications in the tumor tissue and/or the surrounding brain are common. Other degenerative features include extracellular mucin deposition and microcyst formation. Oligodendrogliomas demonstrate a typical vascularization pattern that consists of a dense network of branching capillaries resembling the pattern of chicken-wire. Infiltration of the cortex is frequent in oligodendrogliomas, with tumor cells forming so-called secondary structures, such as perineuronal satellitosis, perivascular aggregations, and subpial accumulations.

Immunohistochemistry. Oligodendrogliomas are consistently positive for S-100, CD57, MAP2, Olig1, and Olig2. However, none of these markers is truly specific for oligodendrogliomas. GFAP-positive minigemistocytes and so-called gliofibrillary oligodendrocytes are frequently found. Synaptophysin usually labels the residual cortical neuropil that is infiltrated by oligodendroglioma cells, while the neoplastic cells themselves are usually negative. However, recent data indicated that a small subset of oligodendrogliomas, including mostly cases with combined losses of 1p and 19q, may show neurocytic differentiation with expression of synaptophysin and formation of Homer Wright-like and perivascular rosettes (Perry et al. 2002). Most oligodendrogliomas lack nuclear p53 staining. The MIB1 index is usually low (<5%).

Differential Diagnosis. Oligodendrogliomas need to be distinguished from macrophage-rich reactive lesions (demyelinating diseases or cerebral infarcts) as well as several other tumor types that may present with clear cells, such as clear-cell ependymoma, neurocytoma, dysembryoplastic neuroepithelial tumor (DNT), clear-cell meningioma, and metastatic clear-cell carcinoma. Immunohistochemical analysis usually helps to separate these different entities.

Molecular Pathology (Fig. 2). Allelic losses on chromosome arms 1p and 19q are found in up to 80% of oligodendrogliomas (Reifenberger and Louis 2003). The majority of cases show large deletions resulting in the loss of one copy of both chromosome arms. So far, the oligodendroglioma suppressor genes on 1p and 19q are not known, but several candidate gene regions have been delineated (Reifenberger and Louis 2003; Felsberg et al. 2004). Deletions affecting chromosomes 4, 6, 11p, 14, and 22q are also found in oligodendrogliomas but are less common than 1p/19q losses. In contrast to diffuse astrocytomas, losses on 17p and *TP53* gene mutations are rare. Interestingly, *TP53* mutation is mutually exclusive to loss of heterozygosity on 1p and 19q. However, oligodendrogliomas with 1p/19q losses frequently show promoter hypermethylation of the $p14^{ARF}$ gene, which may alter p53-dependent growth regulation (Wolter et al. 2001). About half of the oligodendrogliomas overexpress epidermal growth factor receptors in the absence of *EGFR* gene amplification. In addition, most tumors demonstrate a co-expression of platelet-derived growth factors and their receptors, suggesting that auto- or paracrine growth stimulation plays a role in their pathogenesis.

Anaplastic Oligodendroglioma (WHO Grade III)

Definition. An oligodendroglioma with focal or diffuse histologic features of anaplasia.

Incidence and Age Distribution. Anaplastic oligodendrogliomas account for approximately half of the oligodendroglial tumors. The incidence peaks between 45–50 years.

Macroscopy and Localization. Anaplastic oligodendrogliomas are usually hemispheric tumors with a preference for the frontal lobe, followed by the temporal lobe. In contrast to WHO grade II oligodendrogliomas, necrotic areas may be seen.

Histopathology. Anaplastic oligodendrogliomas are diffusely infiltrating cellular oligodendrogliomas with signs of anaplasia, including obvious mitotic activity (Fig. 7r), microvascular proliferation, and necrosis with or without pseudopalisading. The typical honeycomb cells and the vascular pattern of oligodendrogliomas are still recognizable. Microcalcifications may also be seen. Gliofibrillary oligodendrocytes and minigemistocytes are common. Some cases may show marked cellular pleomorphism including multinucleated giant cells.

Immunohistochemistry. The immunohistochemical profile is similar to WHO grade II oligodendrogliomas. However, GFAP-positive cells are more common, and proliferative activity is increased as indicated by MIB1 indices surpassing 5%.

Differential Diagnosis. The diagnosis of most cases is straight-forward. In a fraction of cases, the differential diagnosis versus anaplastic oligoastrocytoma is problematic and associated with a considerable degree of interobserver variability. The distinction of highly cellular and poorly differentiated anaplastic oligodendrogliomas from malignant small-cell astrocytic neoplasms may be facilitated by molecular genetic analysis (see above).

Molecular Pathology (Fig. 2). Combined losses of 1p and 19q are found in 60–70% of anaplastic oligodendrogliomas (Reifenberger and Louis 2003). Homozygous deletions of the *CDKN2 A* gene (9p21) are detectable in about one-third of cases. *CDKN2 A* deletion is more common in anaplastic oligodendrogliomas with intact 1p and 19q, but may also be seen in tumors with 1p/19q loss. The adjacent $p14^{ARF}$ and *CDKN2B* genes are commonly deleted as well. *PTEN* mutations are restricted to less than 10% of anaplastic oligodendrogliomas and preferentially found in tumors without 1p/19q loss. Several other chromosomes (chromosomes 4, 6, 7, 11, 13q, 15, 18, and 22q) are gained or lost at more than random frequency in anaplastic oligodendrogliomas. In contrast to glioblastomas, amplification of proto-oncogenes is rare (<10% of the cases).

Clinical significance of genetic alterations. Following the original study by Cairncross et al. (1998), several independent studies have confirmed combined deletions of 1p and 19q as an independent marker of a favorable response to radiation and chemotherapy, as well as longer survival (for review, see Reifenberger and Louis 2003; Fallon et al. 2004; Felsberg et al. 2004). In contrast, homozygous deletion of *CDKN2 A* and mutation of *PTEN* represent molecular alterations associated with a poor survival of oligodendroglioma patients (Reifenberger and Louis 2003). More recently, 8q gain was reported to be strongly associated with a poor outcome (Kitange et al. 2004). Concerning the diagnostic application of molecular testing, analysis for 1p/19q losses, either using microsatellite polymorphism or FISH-based techniques, appears to be useful in the following settings: (1) after the diagnosis of an anaplastic oligodendroglial tumor; (2) after the diagnosis of a low-grade (WHO grade II) oligodendroglioma or oligoastrocytoma; and (3) for a small-cell malignant glioma in which the differential diagnosis is anaplastic oligodendroglioma or small-cell astrocytoma/glioblastoma (Reifenberger and Louis 2003). In addition, therapeutic trials on malignant gliomas nowadays should consider including molecular testing of the tumors in order to prevent unrecognized molecular heterogeneity obscuring a truly effective new therapy (Betensky et al. 2002).

Oligoastrocytoma (WHO Grade II)

Definition. A diffusely infiltrating glioma composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumor cells in oligodendroglioma or diffuse astrocytoma of WHO grade II. The oligodendroglial and astroglial components may either be diffusely intermingled or separated into distinct areas.

Incidence and Age Distribution. Mixed gliomas (oligoastrocytomas and anaplastic oligoastrocytomas) are estimated to account for about 5% of all gliomas. However, because the histologic criteria for these tumors are highly variable, this figure must be interpreted with caution. Oligoastrocytomas preferentially develop in adults between 35 and 45 years of age.

Macroscopy and Localization. The vast majority of oligoastrocytomas arise in the cerebral hemispheres, with the frontal lobe being the most common localization. The macroscopy picture is similar to that of oligodendrogliomas.

Histopathology. Oligoastrocytomas are diffusely infiltrating gliomas of moderate cellularity and low mitotic activity. Microcalcifications and microcystic degeneration are commonly seen. Necrosis and vascular endothelial proliferation are absent. The tumor consists of at least two distinct cell populations showing either astrocytic or oligodendroglial phe-

notypes, respectively. Some tumors demonstrate regionally distinct areas of oligodendroglial and astrocytic differentiation ('compact variant'). In others, both populations are intimately admixed ('diffuse variant'). Neoplastic cells with ambiguous (transitional) phenotypes that are difficult to assign to either the astrocytic or the oligodendroglial lineage may also be found in these tumors. Subdivision into oligodendroglioma-predominant, astrocytoma-predominant, and tumors with approximately equal oligodendroglial and astroglial components has been suggested, but the clinical significance of this histologic subclassification is unclear.

Immunohistochemistry. A specific marker that reliably distinguishes between astrocytic and oligodendroglial components is still lacking. However, GFAP immunoreactivity is usually strong in the astroglial and more variable in the oligodendroglial component. Approximately one-third of the oligoastrocytomas demonstrate nuclear p53 accumulation. The MIB1 index is low (<5%).

Differential Diagnosis. Oligoastrocytomas differ from pure oligodendrogliomas and astrocytomas by the presence of two morphologically distinct cell populations with oligodendroglial or astrocytic phenotypes, respectively. An admixture of GFAP-positive minigemistocytes and gliofibrillary oligodendrocytes with typical oligodendroglial cells is not sufficient to shift a diagnosis from oligodendroglioma to oligoastrocytoma. Only tumors with a fibrillary, protoplasmic, or classic gemistocytic astroglial component in addition to the oligodendroglial cells should be diagnosed as oligoastrocytoma.

Molecular Pathology (Fig. 3). Approximately 30–50% of the oligoastrocytomas show allelic losses on 1p and 19q. Loss of heterozygosity on 17p and/or *TP53* mutation can be detected in one-third of cases, with *TP53* mutation being mutually exclusive to 1p/19q deletion (Reifenberger and Louis 2003). Histologically, oligoastrocytomas with 1p/19q loss are frequently oligodendroglioma predominant, whereas oligoastrocytomas with TP53 mutations are more often astrocytoma predominant (Maintz et al. 1997). In addition, 1p/19q deletions have been detected less commonly than *TP53* mutation in oligoastrocytomas of the temporal lobe, whereas oligoastrocytomas in other locations more frequently demonstrated 1p/19q losses than *TP53* mutation (Müller et al. 2002). However, the correlation between 1p/19q losses and tumor location was not corroborated in a more recent study on a smaller number of cases (Felsberg et al. 2004). Separate molecular analyses of microdissected oligodendroglial and astrocytic tumor parts show common genetic alterations in most instances, indicating a monoclonal origin of both components (Kraus et al. 1995; Dong et al. 2002).

Anaplastic Oligoastrocytoma (WHO Grade III)

Definition. An oligoastrocytoma with focal or diffuse histologic features of anaplasia.

Incidence and Age Distribution. Anaplastic oligoastrocytomas are most common in the fifth decade.

Macroscopy and Localization. Anaplastic oligoastrocytomas are predominantly hemispheric tumors with a preference for the frontal lobes, followed by the temporal lobes. The macroscopic appearance is similar to other malignant astrocytic or oligodendroglial tumors.

Histopathology. Microscopy shows a diffusely infiltrating oligoastrocytoma with focal or diffuse histologic signs of anaplasia, such as high cellularity, nuclear atypia, cellular pleomorphism, obvious mitotic activity, and microvascular proliferation (Fig. 7s–u). Necrosis may also be present. Most commonly, the astrocytic and oligodendroglial components both demonstrate anaplastic features. In some cases, however, anaplasia may be focal and restricted to either component.

Immunohistochemistry. The immunohistochemical profile is similar to WHO grade II oligoastrocytomas, except for a higher MIB1 index (usually >5%).

Differential Diagnosis. The most important differential diagnoses are anaplastic oligodendroglioma, anaplastic astrocytoma, and glioblastoma. Among these, the distinction from anaplastic astrocytoma poses no problem when a definite oligodendroglioma component is identified. The separation from anaplastic oligodendroglioma may be more challenging because some anaplastic oligodendrogliomas show considerable cellular pleomorphism, including tumor cells with transitional phenotypes ranging from minigemistocytes to frank gemistocytes. Most difficult is the differential diagnosis between anaplastic oligoastrocytoma and glioblastoma, since oligodendroglioma-like regions may be present in a small fraction of otherwise typical glioblastomas (so-called 'glioblastoma with oligodendroglial component'). As definite histologic criteria for the separation of anaplastic oligoastrocytomas and glioblastomas with oligodendroglial component are missing, this differential diagnosis is associated with a high degree of subjectivity and interobserver vari-

ability. It is hoped that molecular markers may help to stratify such patients with morphologically ambiguous malignant gliomas into clinically meaningful subgroups.

Molecular Pathology (Fig. 3). Combined deletions of 1p and 19q are present in up to 50% of the anaplastic oligoastrocytomas. *TP53* mutations are found in one-third of the cases, predominantly those that lack 1p/19q losses. Progression-associated changes include losses on 9p and homozygous deletion of *CDKN2 A*, as well as losses on chromosomes 10, 11p, and 13q. Amplification of proto-oncogenes, e.g. *EGFR* or *PDGFRA*, may be present but is less common than in primary glioblastomas.

Ependymal Tumors

Definition. Glial tumors with histologic features of ependymal differentiation, including perivascular pseudorosettes and true ependymal rosettes.

Incidence and Age Distribution. Ependymal tumors represent 5% of CNS tumors in adults, 10% in children under 15 years of age, and 30% in children under 3 years of age. They are the most common glial tumor of the spinal cord (50%). Subependymoma and myxopapillary ependymoma are tumors of adults.

Macroscopy and Localization. Ependymomas typically arise along the ventricular system (Fig. 6e), including the central canal of the spinal cord. In the brain, infratentorial ependymomas are more common in children. In adults, the frequency of infratentorial versus supratentorial ependymomas is approximately equal. Subependymomas are usually attached to the wall of the fourth or the lateral ventricles. The vast majority of myxopapillary ependymomas are located in the conus/cauda region. Ependymal tumors may occasionally grow without relation to the ventricles or even outside of the brain.

Ependymoma (WHO Grade II)

Histopathology. Diagnostic hallmarks are pseudorosettes, i.e., perivascular tumor cells extending radial, fibrillary processes towards the vessel wall, and true ependymal rosettes, i.e., canals and tubuli composed of a single layer of cuboidal tumor cells (Fig. 8c). Cellular density is moderate, and mitoses are rare, while necroses may occur. Compared with diffuse astrocytomas, ependymomas are usually well delineated from the brain. The WHO classification lists four histologic variants of ependymoma. *Cellular ependymoma* is characterized by high cellular density in the absence of increased mitotic activity. *Papillary ependymoma* shows marked disintegration of areas remote to vessels, leading to a pseudopapillary pattern (Fig. 8d). *Clear-cell ependymoma* is largely composed of tumor cells with non-stained (clear or 'white' in H&E), round cytoplasm. *Tanycytic ependymoma* features fascicles of spindle cells with elongated processes (Fig. 8e).

Immunohistochemistry. Tumor cells are positive for GFAP, preferentially around blood vessels. Upon staining for epithelial membrane antigen (EMA), most ependymomas exhibit a characteristic dot-like perinuclear positivity, while ring-like staining pattern and linear labeling of luminal surfaces are less common. Ki-67/MIB1 labeling index is usually <4%.

Differential Diagnosis. In the vast majority of cases, the histologic diagnosis is easy and straightforward, while the variants commonly pose problems. Papillary ependymoma has to be differentiated from other types of papillary tumors, including choroid plexus papilloma, astroblastoma, papillary meningioma, pineocytoma, or even papillary carcinoma. Clear-cell ependymoma closely resembles neurocytoma and oligodendroglioma, and the diagnosis may be difficult and requires application of immunohistochemistry for various neuronal and glial antigens. Tanycytic ependymoma is one of the most difficult and uncertain diagnoses in surgical neuropathology, because unequivocal criteria are missing and the similarity to astrocytoma is striking; proponents of the electron microscope stress the usefulness of ultrastructural examination in these cases.

Molecular Pathology. The most common numerical chromosomal change is loss of chromosome 22 in 30–60% of cases. Additional losses involve 6q, 10q, 11q, 1p, 14q, and 13, while gains may involve 1q and 7 (Rickert and Paulus 2004). The responsible tumor suppressor gene on chromosome 22 remains to be determined, since *NF2* is mutated in only a subgroup of tumors, most of them being of spinal location, and *hSNF5/INI1* mutations are absent. *CDKN2 A* deletions, *TP53* mutations, and amplifications of *CDK4* and *EGFR*, which are commonly encountered in astrocytomas, are usually absent in ependymomas, although hypermethylation of *CDKN2 A*, *CDKN2B*, and $p14^{ARF}$ has been reported (Rousseau et al. 2003).

Anaplastic Ependymoma (WHO Grade III)

Histopathology. The most important criterion for anaplasia and differentiation from WHO grade II ependymoma is high mitotic activity (usually more

than 4 mitoses per 10 HPF), while high cellular density, microvascular proliferation, and pseudopalisading necrosis are also typically encountered. Pseudorosettes are less prominent, and ependymal rosettes are commonly missing.

Immunohistochemistry. The expression pattern of GFAP and EMA corresponds to that of grade II ependymoma, but is often less pronounced. MIB1 index exceeds 4% and may be higher than 20%.

Differential Diagnosis. Compared with anaplastic ependymoma, malignant astrocytic gliomas are more invasive, more diffusely positive for GFAP, and lack dots and rings upon immunohistochemistry for EMA. *Ependymoblastoma* is an extremely rare embryonal tumor resembling medulloblastoma, but containing multi-layered rosettes of mitotically active tumor cells around small, round lumina ('ependymoblastic' rosettes). Unfortunately, ependymoblastoma has previously been admixed with anaplastic ependymoma, but it clearly represents a distinct entity.

Molecular Pathology. No genetic aberrations typical for anaplastic ependymoma have been described. Genetic progression models as developed for astrocytic and oligodendroglial tumors have not been elaborated so far.

Myxopapillary Ependymoma (WHO Grade I)

Histopathology. As the name suggests, salient features include marked myxoid and pseudopapillary degeneration due to deposition of mucinous extracellular material by tumor cells (Fig. 8b). Other typical features include perivascular pseudorosettes and vascular hyalinosis.

Immunohistochemistry. Tumor cells are consistently GFAP positive, while most cases do not show the EMA staining pattern typical for ependymoma. Ki-67/MIB1 index is usually less than 3%, although higher values may occur without necessarily being related to recurrence or the very rare extraspinal metastases.

Differential Diagnosis. Knowledge of a conus/cauda location provides a high suspicion of the diagnosis. Differential diagnostic considerations may occasionally include chordoma, chondroid tumors, adenoid cystic carcinoma, and mucinous adenocarcinoma, but in those less unequivocal cases, immunostaining for GFAP is helpful. More commonly, the question arises of whether the myxoid and pseudopapillary features of an ependymal tumor are pronounced enough to justify the diagnosis of myxopapillary ependymoma.

Molecular Pathology. Remarkably, myxopapillary ependymomas harbor the highest number of numerical chromosomal aberrations among ependymal tumors (gains of chromosome 9 and 18 being the most common), and they commonly show aneuploidy or tetraploidy. As with other ependymal tumors, consistent mutations have not been identified. The NF2 gene is intact.

Subependymoma (WHO Grade I)

Histopathology. A tumor of low cellular density, with clustering of tumor cell nuclei against a microcystic, fibrillary background (Fig. 8a). Perivascular pseudorosettes are indistinct. Mitoses and necrosis are absent. Nuclear pleomorphism, calcification, and hemorrhage are degenerative features. Vessels may undergo hyalinosis, but endothelial hyperplasia is usually absent.

Immunohistochemistry. Tumor cells express GFAP. Ki-67/MIB1 index is less than 1.5%.

Differential Diagnosis. Taking the intraventricular localization into consideration, there is virtually no differential diagnosis. Some tumors focally comprise areas corresponding to ependymoma, but this is without clinical implication.

Molecular Pathology. The few genetic studies performed so far analyzed the *hSNF5/INI1*, *NF2*, and *PTEN* genes but did not find any aberrations.

Choroid Plexus Tumors

Definition. Intraventricular neuroectodermal tumors with a papillary pattern resembling non-neoplastic choroid plexus.

Incidence and Age Distribution. Choroid plexus tumors account for 0.5% of all CNS tumors, 2.5% of CNS tumors in children under 15 years of age, and 13% in children under 1 year of age. More than 85% of choroid plexus tumors are papillomas (WHO grade I), while atypical tumors (WHO grade II) and choroid plexus carcinomas (WHO grade III) are less common.

Macroscopy and Localization. Tumors arise from the choroid plexus of the lateral ventricles (50%), the third ventricle (5%), the fourth ventricle (40%), or from more than one ventricle (5%). Primary

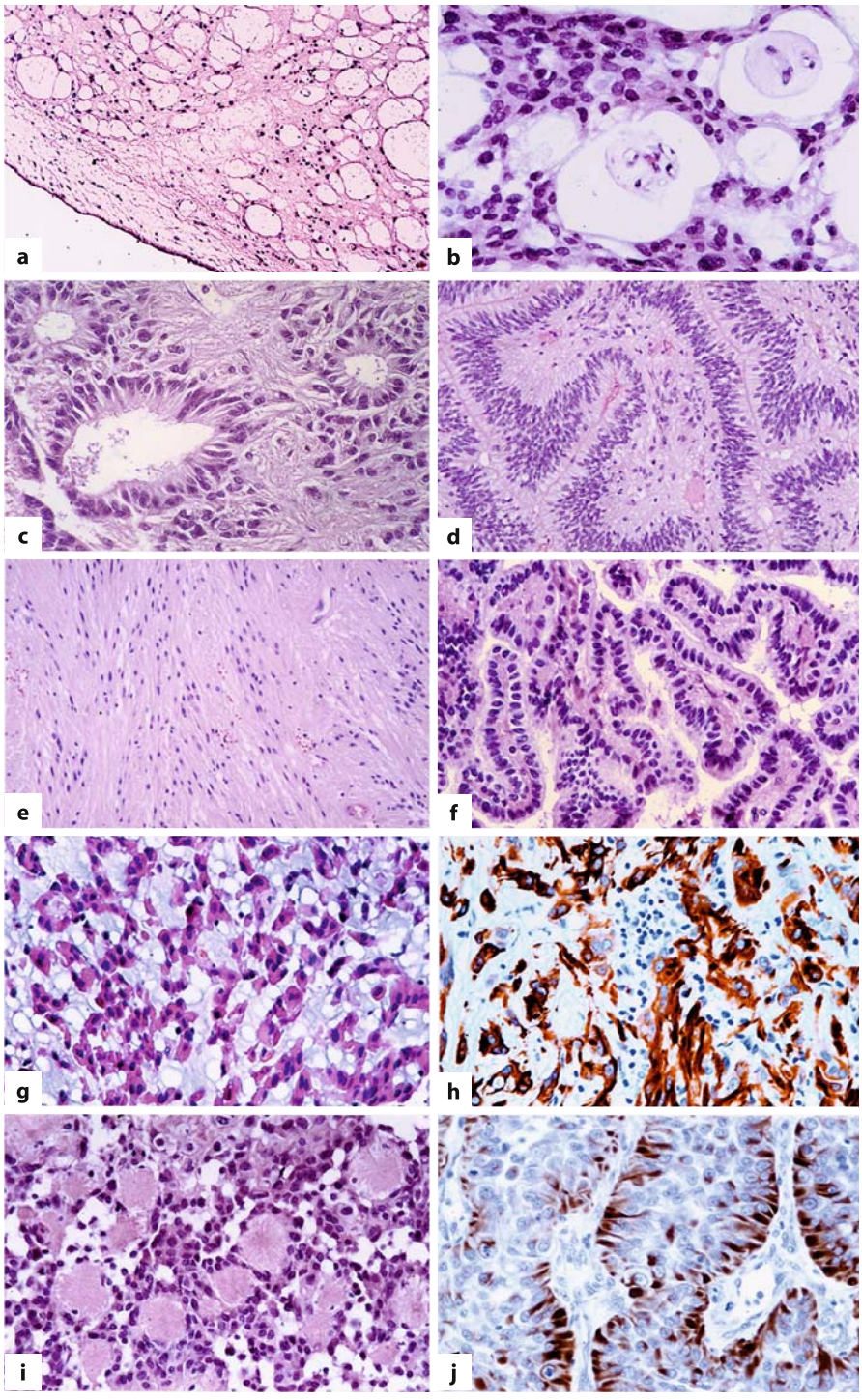


Fig. 8. Histology of ependymal tumors, choroid plexus tumors, and neuroepithelial tumors of uncertain origin. **a** Subependymoma (WHO grade I). Shown is a subependymal tumor of low cellularity with numerous microcysts (H&E). **b** Myxopapillary ependymoma (WHO grade I). Note ependymal tumor cells around hyalinized vessels with perivascular mucin deposition (H&E). **c** Ependymoma (WHO grade II). Formation of typical ependymal canals (H&E). **d** Papillary ependymoma (WHO grade II) (H&E). **e** Tanycytic ependymoma (WHO grade II) composed of elongated tumor cells (H&E). **f** Choroid plexus papilloma (WHO grade I) (H&E). **g** Chordoid glioma of the third ventricle (WHO grade II) with eosinophilic cells forming chordoma-like cords in a strongly mucinous matrix (H&E). **h** The same tumor shows strong immunoreactivity for GFAP. **i** Astroblastoma with glial tumor cells forming astroblastic pseudorosettes around hyalinized blood vessels (H&E). **j** GFAP staining of this tumor highlights perivascular astroblastic cells

manifestation in the cerebellopontine angle is rare. Tumors of the lateral ventricles occur predominantly in children, and 60% manifest in the first decade of life. The age distribution is relatively even in tumors of the fourth ventricle. Macroscopically, the floating cauliflower-like appearance imposed by the papillary structure is characteristic.

Choroid Plexus Papilloma (WHO Grade I)

Histopathology. The histologic appearance closely resembles non-neoplastic choroid plexus. Fibrovascular cores are lined by a single layer of columnar, cuboidal, or flattened epithelial cells (Fig. 8f). Nuclei are usually monomorphic, and mitoses are rare (less than 1 mitosis per 20 HPF). A variety of degenerative features are common and include nuclear polymorphism, calcification, stromal edema, and accumulation of macrophages.

Immunohistochemistry. Currently, there is no specific marker for choroid plexus epithelial cells. However, the expression pattern using routinely employed antibodies is diagnostically useful and includes invariable positivity for cytokeratins and vimentin, as well as immunoreactivity for epithelial membrane antigen, S-100 protein, and transthyretin in the vast majority of cases. GFAP may be focally positive. The MIB1 index is <5% (mean: 2%).

Differential Diagnosis. In cases where only tiny surgical specimens are available, the problem may arise regarding whether the tissue represents non-neoplastic choroid plexus adjacent to the (unavailable) pathologic lesion rather than a tumor. Choroid plexus papilloma usually shows a higher cellular density, more frequently flattened epithelial cells, and more irregularities with respect to the lining and nuclear morphology. In contrast to choroid plexus tumors, papillary ependymoma exhibits perivascular pseudorosettes, widespread positivity for GFAP, and a dot-like staining pattern for EMA. For exclusion of highly differentiated papillary carcinoma metastases, immunohistochemistry for antigens expressed by lung, thyroid, colon, and other carcinomas (thyroglobulin, thyroid transcription factor-1, CEA) can be useful.

Molecular Pathology. Comparative genomic hybridization revealed that more than 90% of choroid plexus papillomas show numerical chromosomal aberrations, including +7q (65%), +5q (62%), +7p (59%), +5p (56%), +9p (50%), +9q (41%), +12p, +12q (38%), and +8q (35%) as well as –10q (56%), –10p, and –22q (47%) (Rickert and Paulus 2004). *TP53* and *hSNF5/INI1* mutations are absent.

Choroid Plexus Carcinoma (WHO Grade III)

Histopathology. This choroid plexus tumor shows frank signs of malignancy, such as brisk mitotic activity, high cellular density, high nucleus:cytoplasm ratio, and necroses. Indistinct papillary structure with sheets of tumor cells, nuclear pleomorphism, and diffuse brain invasion are common.

Immunohistochemistry. Like their benign counterparts, choroid plexus carcinomas typically express cytokeratins, vimentin, and S-100 protein and occasionally GFAP. They are negative for lung and thyroid carcinoma markers (see above), and most tumors stain with the anti-epithelial antibodies HEA125 and BerEP4, which do not stain most metastases. Ki-67/MIB1 index of choroid plexus carcinoma is higher than 5% (mean: 15%).

Differential Diagnosis. In children, choroid plexus carcinoma is one of the most difficult diagnoses, in particular in dedifferentiated cases where the papillary pattern has been lost. Atypical teratoid tumor/rhabdoid tumor can in principle be excluded on the basis of its immunohistochemical expression profile, although recent data suggest a genetic, morphologic, and possibly nosologic relationship between the two tumor entities (Gessi et al. 2003). Immunohistochemistry for germ-cell antigens (PLAP, alpha-fetoprotein, β-HCG) is useful for excluding papillary germ-cell tumors. Metastatic carcinoma can closely mimic choroid plexus carcinoma, but hardly ever occurs in infancy. In contrast, malignant papillary epithelial tumors in old patients virtually never are choroid plexus carcinomas, even if located around the ventricles, and usually represent metastatic carcinomas.

Molecular Pathology. Almost all choroid plexus carcinomas carry numerical chromosomal changes, including +12p, +12q, +20p (60%), +1, +4q, +20q (53%), +4p (47%), +8q, +14q (40%), +7q, +9p, +21 (33%) as well as –22q (73%), –5q (40%), –5p, and –18q (33%) (Rickert and Paulus 2004). Choroid plexus carcinoma may occur in the setting of germ line inactivations of *TP53* (Li-Fraumeni syndrome) and *hSNF5/INI1* (rhabdoid predisposition syndrome). In sporadic tumors, mutations were identified in *hSNF5/INI1* but not in *TP53*.

Atypical Choroid Plexus Papilloma (WHO Grade II)

Tumors not corresponding to the prototypical features of either choroid plexus papilloma or choroid plexus carcinoma are not uncommon. These include

tumors with one or two of the following features: moderately elevated mitotic activity, indistinct papillary pattern, necrosis, and diffuse brain invasion. Clinical and prognostic correlations of such atypical choroid plexus papillomas are unknown so far, and they have not yet been included in the WHO classification. In analogy to atypical meningiomas (see below), atypical choroid plexus tumors may be considered as corresponding to WHO grade II, and patients should be followed up at regular intervals.

Neuroepithelial Tumors of Uncertain Origin

The WHO classification lists three rare entities among the neuroepithelial tumors of uncertain origin, namely astroblastoma, chordoid glioma of the third ventricle, and gliomatosis cerebri. All three entities are of glial origin, hence they might as well be grouped together as 'other gliomas'. In fact, some authors consider chordoid glioma of the third ventricle as a special type of ependymal tumor originating from modified ependymal cells of the subcommissural organ (Cenacchi and Giangaspero 2004). In addition, molecular findings suggested that many cases of gliomatosis cerebri are genetically related to the diffuse astrocytic gliomas (Herrlinger et al. 2002).

Astroblastoma

Definition. A well-circumscribed glioma with prominent formation of distinctive perivascular pseudorosettes ('astroblastic pseudorosettes'), which are characterized by a single layer of GFAP-positive epithelioid tumor cells sending broad, non-tapering processes towards a central blood vessel. Vascular thickening and hyalinization are a second characteristic histologic feature.

Incidence and Age Distribution. Astroblastomas are extremely rare tumors. Precise data on their incidence are not available. Young adults and children are preferentially affected.

Macroscopy and Localization. Astroblastomas may be found throughout the CNS, with the cerebral hemispheres being the most common site. The tumors are often superficially located and macroscopically appear as well-circumscribed, solid, or cystic mass lesions. Areas of necrosis may be discernible.

Histopathology. The histologic hallmark consists in the formation of a distinctive type of perivascular pseudorosette, the astroblastic pseudorosette. In contrast to ependymal pseudorosettes, astroblastic pseudorosettes are formed by a single layer of tumor cells with eosinophilic, epithelioid cytoplasm and broad, non-tapering processes radiating towards a central vessel (Fig. 8i). Artificial tissue shrinkage may give rise to the formation of pseudopapillae. A second characteristic histologic feature of astroblastomas is the presence of prominent vascular hyalinization and tissue fibrosis. Dystrophic calcifications may also be found.

Grading. Astroblastomas are not assigned to a definite WHO grade in the present WHO classification. However, histologic subdivision into low-grade (well-differentiated) and high-grade (malignant) lesions has been suggested (Thiessen et al. 1998; Brat et al. 2000). High-grade lesions show increased cellularity and cellular atypia, high mitotic activity, microvascular proliferation, as well as necrosis with pseudopalisading (Brat et al. 2000). The prognosis appears to be favorable for patients with completely resected, well-differentiated astroblastomas. In contrast, high-grade lesions frequently recur after resection, thus arguing in favor of adjuvant therapy.

Immunohistochemistry. Astroblastomas are strongly immunoreactive for GFAP (Fig. 8j), S-100 protein, and vimentin. Focal staining for EMA is also common. The MIB1 index varies greatly with high-grade lesions demonstrating markedly increased levels.

Differential Diagnosis. Astroblastomas need to be distinguished from diffuse astrocytic gliomas, ependymomas, and papillary meningiomas. Astroblastic differentiation with pseudorosette formation may occasionally be seen in diffuse astrocytic gliomas, including some glioblastomas, but is generally restricted to focal areas. In addition, the diffuse astrocytic gliomas are characterized by diffusely infiltrative growth, which is in contrast to the well-demarcated growth of astroblastomas. The differential diagnosis towards ependymoma relies on the absence of astroblastic pseudorosettes and the presence of ependymal pseudorosettes as well as true ependymal rosettes in ependymomas. Papillary meningioma, which may be a differential diagnosis in superficially located astroblastomas, usually contains areas of conventional meningioma and shows stronger expression of EMA.

Molecular Pathology. A CGH study of seven astroblastomas revealed gains of chromosome arm 20q and chromosome 19 as the most frequent chromosomal alterations (Brat et al. 2000). Recurrent losses were found on 9q, 10, and the X-chromosome. These data indicate that the genetic alterations in astroblastomas differ from those typically found in diffuse astrocytic, oligodendroglial, or ependymal tumors.

Chordoid Glioma of the Third Ventricle (WHO Grade II)

Definition. A well-circumscribed glioma in the third ventricle characterized by chordoma-like histologic features.

Incidence and Age Distribution. Chordoid gliomas are rare tumors that manifest in adults. Women are more commonly affected than men.

Macroscopy and Localization. The tumors are located in the anterior part of the third ventricle and may extend to the suprasellar region. Macroscopically, chordoid gliomas are well-circumscribed, solid tumors that adhere to the ventricular wall and may cause obstructive hydrocephalus.

Histopathology. Chordoid gliomas are moderately cellular and characterized by clusters and cords of epithelioid tumor cells with prominent eosinophilic cytoplasm, relatively uniform nuclei, and inconspicuous nucleoli (Fig. 8g). The tumor cells are embedded in an alcianophilic, mucinous, and sometimes vacuolated matrix. Lympho-plasmacellular infiltrates are a regular feature. Mitotic activity is low, and signs of anaplasia are absent. The tumors are well demarcated from the surrounding brain tissue, which shows reactive astrogliosis, often with Rosenthal fibers.

Immunohistochemistry. The immunohistochemical profile consists of strong positivity for GFAP (Fig. 8h), vimentin, and CD34, as well as variable expression of S-100, EMA, and cytokeratins. Synaptophysin is negative, and nuclear accumulation of p53 is absent. The MIB1 index is low (<5%).

Differential Diagnosis. The most important differential diagnoses are chordoid meningioma and chordoma. Chordoid meningiomas usually show at least focal areas with characteristic meningeal features, such as whorl formation and psammoma bodies, and are positive for EMA but negative for GFAP and CD34. Chordomas stain strongly positive for cytokeratins and lack immunoreactivity for GFAP and CD34. In addition, chordomas contain physaliphorous cells, which are not seen in chordoid gliomas.

Molecular Pathology. A CGH study of four chordoid gliomas did not identify any chromosomal imbalances (Reifenberger et al. 1999). Genetic alterations of *TP53*, *CDKN2 A*, *EGFR*, *CDK4*, and *MDM 2* were also absent, indicating that chordoid gliomas are genetically distinct from the common types of gliomas and meningiomas.

Gliomatosis Cerebri (WHO Grade III)

Definition. An extensively infiltrating, diffuse glioma involving three or more cerebral lobes.

General Comment. The question of whether gliomatosis cerebri constitutes a distinct tumor entity or just represents a glioma with unusually extensive infiltrative properties is not resolved. The diagnosis is established by the combination of histology (showing a diffusely infiltrating glioma) and radiologic features (showing extensive tumor growth with involvement of three or more cerebral lobes).

Incidence and Age Distribution. Gliomatosis cerebri is a rare lesion that may be found in any age group but preferentially develops in adults (age peak: 40–50 years).

Macroscopy and Localization. By definition, gliomatosis cerebri is characterized by extensive tumor infiltration of the brain involving three or more cerebral lobes. Bilateral tumor spread via the corpus callosum is common, as is involvement of the basal ganglia. Extension into infratentorial structures and even the spinal cord may occur. Depending on the presence or absence of a circumscribed tumor mass, two types of gliomatosis cerebri are distinguished in the WHO classification. Type I is the classic form with diffuse tumor growth and widespread involvement of large parts of the CNS. Type II is characterized by the presence of a focal mass lesion, usually a high-grade glioma, in addition to the diffusely infiltrating areas of gliomatosis. Type I lesions may develop into type II lesions.

Histopathology. Histologic specimens show an infiltrating glioma composed of monomorphic, often elongated tumor cells that grow diffusely in the brain parenchyma. In most instances, tumor cells demonstrate astrocytic features while cases of oligodendroglial gliomatosis are documented as well. Tumor cells infiltrating the cortex frequently form secondary structures, such as perineuronal satellitosis as well as perivascular and subpial aggregates. Mitotic activity is variable from case to case. Type I lesions of gliomatosis cerebri often lack marked microvascular proliferation and necrosis. In type II lesions, biopsy specimens from the focal mass show histologic features similar to the common types of diffuse gliomas, most frequently anaplastic astrocytoma or even glioblastoma.

Grading. Grading of gliomatosis cerebri is difficult due to the diffusely infiltrating growth with a sometimes very low density of infiltrating glioma cells. Nevertheless, most cases of gliomatosis cerebri show

a malignant behavior and are associated with a poor prognosis. Therefore, the WHO classification recommends WHO grade III for most cases of gliomatosis cerebri.

Immunohistochemistry. Immunoreactivity for GFAP and S-100 may be variably in the tumor cells, while reactive astrocytes are generally stained. About half of the cases show nuclear p53 immunoreactivity. MIB1 levels are highly variable, with some cases showing a low labeling fraction (<1%) while others are highly proliferative.

Differential Diagnosis. Gliomatosis cerebri is distinguished from the other more common types of diffusely infiltrative gliomas by neuroradiologic demonstration of widespread tumor growth involving three or more cerebral lobes. Sometimes, biopsy specimens may be of rather low cellularity, making the differential diagnosis from reactive gliosis difficult. The so-called *microgliomatosis*, a lesion consisting of diffusely infiltrating, rod-shaped microglial cells expressing macrophage markers like CD68 and RCA1, is an extremely rare differential diagnosis (Hulette 1996).

Molecular Pathology. *TP53* mutations were detected in between 11% (2/18 tumors; Mawrin et al. 2003) and 43% (3/7 tumors; Herrlinger et al. 2002) of cases. Individual tumors may show *PTEN* mutation and *EGFR* amplification (Herrlinger et al. 2002). Thus, the genetic alterations detected in gliomatosis cerebri are similar to those typically found in diffuse astrocytic gliomas.

Neuronal and Mixed Neuronal–Glial Tumors

This comprises a quite heterogeneous group of tumors showing neuronal or biphasic neuronal-glial differentiation. These include ganglioglioma/gangliocytoma, dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos), desmoplastic infantile astrocytoma/ganglioglioma, dysembryoblastic neuroepithelial tumor (DNT), central neurocytoma, cerebellar liponeurocytoma, and paraganglioma. Except for rare cases of anaplastic ganglioglioma (WHO grade III), most neuronal and mixed neuronal-glial tumors are slowly growing tumors corresponding to WHO grades I or II. Clinically, intractable focal seizures are a frequent symptom of supratentorial neuronal or mixed neuronal-glial tumors, with ganglioglioma being the most common tumor type found in patients operated on for chronic epilepsy.

Incidence and Age Distribution. Neuronal and mixed neuronal-glial tumors represent less than 2% of all CNS neoplasms. Children and young adults are most frequently affected, except for central neurocytoma, cerebellar liponeurocytoma, dysplastic gangliocytoma of the cerebellum, and paraganglioma, which predominately manifest in adult patients.

Macroscopy and Localization. Neuronal or mixed neuronal-glial tumors may originate at all sites of the CNS. However, the preferred localization of gangliogliomas and DNTs is the temporal lobe. Central neurocytomas are typically located within the supratentorial ventricles close to the foramen of Monro. Dysplastic gangliocytoma of the cerebellum and cerebellar liponeurocytomas are infratentorial lesions. Desmoplastic infantile astrocytomas/gangliogliomas are often very large lesions involving the cerebral cortex and the meninges. Paragangliomas are most common in the cauda equina region. Rare examples of intracranial paraganglioma are usually extensions from jugulotympanic tumors.

Gangliocytoma and Ganglioglioma (WHO Grade I)

Definition. Slowly growing, benign, neuroepithelial tumors either consisting entirely of neuronal cells (gangliocytoma) or, more commonly, of neuronal and glial cells (ganglioglioma).

Histopathology. Gangliocytomas are homogeneously composed of a neuronal cell population with ganglion cell differentiation (Fig. 9a,b). Gangliogliomas are biphasic tumors consisting of dysplastic, sometimes binucleate neurons with condensed Nissl substance along the cell membrane and irregular anatomical orientation, as well as neoplastic glial cells (Fig. 9c,d). The glial component most commonly shows astrocytic differentiation, but oligodendroglial cells may also be found. The fraction of neuronal and glial cells varies from tumor to tumor. Additional histopathological features often observed are calcification, lymphocytic infiltrates, eosinophilic granular or hyaline bodies, areas with stromal reticulin network, as well as microcysts. Some tumors are densely vascularized and may mimic cavernomas. Subarachnoidal tumor spread is common in superficially located lesions. Recently found rare variants of glioneuronal tumors with papillary architecture or rosetted neuropil islands are described in chapter 17.

Immunohistochemistry. Immunohistochemical reactions are important to establish the diagnosis. Almost 80% of the gangliogliomas are CD34 positive

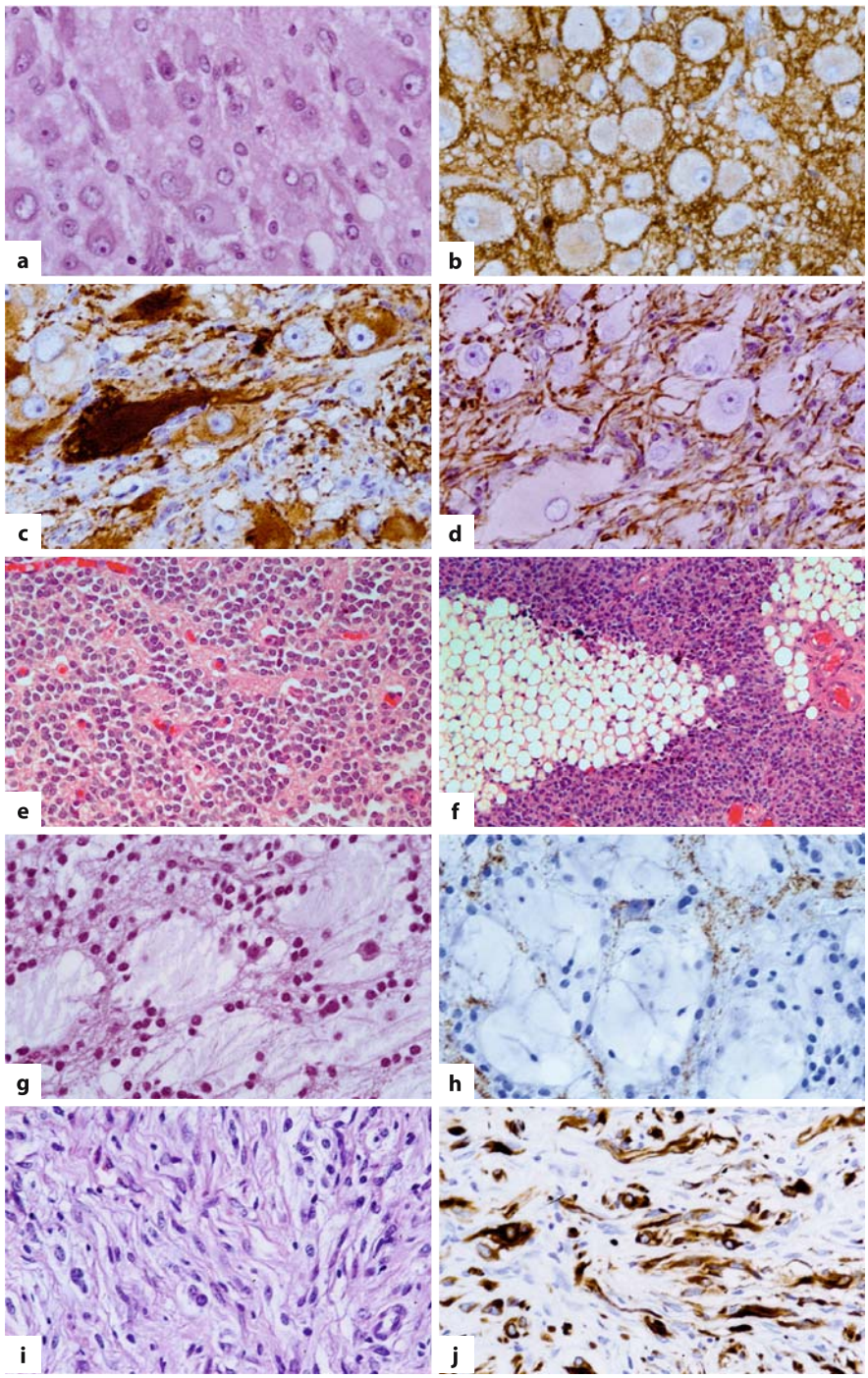


Fig. 9. Histology of selected neuronal and mixed glioneuronal neoplasms. **a,b** Gangliocytoma (WHO grade I). H&E stain (**a**) shows a tumor composed of ganglion cells that are strongly positive for synaptophysin (**b**). **c,d** Ganglioglioma (WHO grade I) is a mixed tumor composed of dysplastic ganglion cells expressing synaptophysin (**c**) and a neoplastic glial component that stains for GFAP (**d**). **e** Central neurocytoma (WHO grade II). Note an isomorphic tumor composed of oligodendroglia-like neurocytic cells and neuropil islands (H&E). **f** Cerebellar liponeurocytoma (WHO grade II). These rare neoplasms are characterized by neurocytic tumor cells and areas of lipomatous differentiation (H&E). **g,h** Dysembryoplastic neuroepithelial tumor (WHO grade I). H&E stain (**g**) shows an area composed of small, oligodendroglia-like cells and individual neurons floating in a myxoid matrix. Staining for synaptophysin shows positivity for a floating neuron (**h**). **i,j** Desmoplastic infantile astrocytoma (WHO grade I). On H&E, the tumors are characterized by spindle-shaped astrocytic cells in a desmoplastic matrix (**i**). Immunostaining for GFAP highlights the astrocytic tumor cells (**j**)

(Blümcke and Wiestler 2002). Immunoreactivity may be found along the cell membrane of glial and neuronal cells, either within the bulk tumor mass or in small clusters in adjacent cortical regions. Dysplastic neurons accumulate neurofilament proteins and/or demonstrate a perisomatic rim of enhanced synaptophysin staining ('corona') (Fig. 9b). The glial tumor cells express S-100 protein and often GFAP (Fig. 9d), whereas glial MAP2 staining and strong nuclear p53 accumulation are usually absent. The MIB1 index is typically less than 1%. If the glial cell component demonstrates increased MIB1 activity, atypical or anaplastic variants of gangliogliomas should be considered (see below).

Grading. In a large series of 184 patients with supratentorial gangliogliomas and a median follow-up of 8 years, tumor recurrence occurred in only 3% of the cases (Luyken et al. 2004). However, malignant progression (2%) and death (1%) were occasionally encountered. Tumor location within the temporal lobe, complete surgical resection, history of longstanding epilepsy, and histopathological classification according to WHO grade I are associated with a favorable prognosis. The same study suggested that increases in cellularity, nuclear pleomorphism, and proliferative activity (MIB1>5%) of the glial component are indicative of WHO grade II. A markedly increased MIB1 index of more than 10% and the presence of necrosis were regarded as signs of progression to anaplastic ganglioglioma (WHO grade III) (Luyken et al. 2004).

Differential Diagnosis. Most importantly, gangliogliomas need to be distinguished from diffuse astrocytomas and oligodendrogliomas with entrapped residual neurons. Immunohistochemical staining for CD34, MAP2, and p53 may help in this respect. Another differential diagnosis is pilocytic astrocytoma, which differs by the absence of a dysplastic neuronal component. Lack of specific glio-neuronal elements (see below) and the characteristic immunohistochemical profile help to separate ganglioglioma from dysembryoplastic neuroepithelial tumor (DNT). The desmoplastic infantile ganglioglioma differs from ordinary ganglioglioma by its age restriction, massive growth, dural attachment, and marked desmoplasia (see below). Extraventricular neurocytic neoplasms with ganglion cell differentiation, so-called ganglioneurocytomas or ganglioglioneurocytomas, are extremely rare lesions (see below). In gangliogliomas with a markedly pleomorphic glial component, the differential diagnosis of pleomorphic xanthoastrocytoma may arise, in particular since several cases of pleomorphic xanthoastrocytoma with a ganglion cell component have been reported. Gangliocytomas primarily need to be distinguished from cortical dysplasias, which may be quite difficult in small surgical specimens. In cerebellar gangliocytomas, Lhermitte-Duclos disease is the major differential diagnosis.

Molecular Pathology. The molecular genetics of gangliogliomas is poorly understood. Gene alterations typically found in diffuse gliomas, e.g., *TP53* mutation, are generally absent. Preliminary data suggest that aberrations in neurodevelopmentally important signaling cascades may play a role. For example, rare polymorphisms in genes associated with the tuberin/insulin-like growth factor receptor pathway seem to be more common in ganglioglioma patients (Blümcke and Wiestler 2002). In addition, decreased expression of members of the reelin signaling cascade has been reported (Becker et al. 2002; Kam et al. 2004). Molecular analysis of microdissected glial and neuronal cells supports a dysontogenic origin from a glioneuronal precursor lesion with clonal proliferation of a neoplastic glial cell component (Becker et al. 2001).

Desmoplastic Infantile Astrocytoma/Ganglioglioma (WHO Grade I)

Definition. A benign neuroepithelial tumor that develops in the first two years of life and is composed of astrocytes (desmoplastic infantile astrocytoma) or astrocytes and neurons (desmoplastic infantile ganglioglioma) embedded in a markedly desmoplastic stroma.

Macroscopy and Localization. Desmoplastic infantile astrocytomas/gangliogliomas are usually large, superficially located, supratentorial lesions with dural attachment. Cyst formation is common. The tumors may occupy large parts of a cerebral hemisphere and cause macrocephaly and increased intracranial pressure.

Histopathology. The histologic picture is characterized by small astrocytes with elongated nuclei in a reticulin and collagen fiber-rich desmoplastic stroma (Fig. 9i). In the ganglioglioma variant, intermingled ganglion cells are additionally present. Some tumors contain mitotically active cellular areas resembling a primitive neuroectodermal tumor or a high-grade glioma. Microvascular proliferation and necrosis may occur but do not appear to be invariably associated with malignant behavior.

Immunohistochemistry. The neoplastic astrocytes are positive for GFAP (Fig. 9j) and S-100 while neuronal cells, when present, express synaptophysin and neurofilaments.

Differential Diagnosis. The young patient age, the superficial tumor localization with dural attachment, as well as the markedly desmoplastic stroma are diagnostic features that allow the distinction from ordinary ganglioglioma as well as malignant gliomas, such as glioblastoma or gliosarcoma. The demonstration of immunohistochemical positivity for GFAP excludes fibrous lesions like meningeal fibromatosis, solitary fibrous tumor, or fibrous histiocytoma.

Molecular Pathology. Desmoplastic infantile astrocytomas/gangliogliomas showed only a few genomic imbalances on CGH analysis and lacked *TP53* mutations as well as allelic losses on chromosomes 10 and 17 (Louis et al. 1992; Kros et al. 2002). Although limited to analyses of only a low number of cases, these data indicate a different genetic profile compared with diffuse astrocytic gliomas.

Dysembryoplastic Neuroepithelial Tumor (WHO Grade I)

Definition. Benign, intracortical, multinodular glioneuronal tumors composed of monomorphic oligodendrocyte-like cells in a mucinous matrix. Characteristic histologic features are the formation of glioneuronal elements and the presence of floating neurons.

Macroscopy and Localization. The vast majority of dysembryoplastic neuroepithelial tumors (DNTs) are supratentorial lesions, with the temporal cortex being most commonly involved. The majority of DNT patients present with a history of chronic epilepsy. The macroscopic picture may vary but typically shows a multinodular, intracortical lesion of soft gelatinous consistency that expands the cortex. Extension of tumor tissue into the subcortical white matter may occur. Erosion of the inner table of the overlying skull is not infrequent.

Histopathology. Microscopy shows a moderately cellular, multinodular lesion within the cortex that consists of isomorphic oligodendroglia-like cells within a mucinous matrix (Fig. 9g). Mitotic activity is generally low. Microvascular proliferation may be present but is not indicative of anaplasia. Formation of so-called 'specific glio-neuronal elements', which consist of vertical columns of neurites sheathed by oligodendroglia-like cells, and the presence of cortical ganglion cells floating in mucin, the so-called 'floating neurons' (Fig. 9g,h), are characteristic diagnostic features. However, DNTs may display various additional histologic features, ranging from areas of cortical dysplasia to tumor parts resembling pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, or ganglioglioma. While the detection of dysplastic neurons in the vicinity of the tumor is regarded as a component of its dysontogenic origin (and not as 'dual pathology'), the latter variants are classified as a 'complex form' of DNT. DNT corresponds to WHO grade I, with the prognosis being generally favorable even after partial resection. The complex variants behave similarly benignly (Nolan et al. 2004).

Immunohistochemistry. The small oligodendroglia-like cells are strongly positive for S-100 but negative for GFAP and CD34. Floating neurons are positive for neurofilament protein and synaptophysin (Fig. 9h). The MIB1 index is generally low.

Differential Diagnosis. The major differential diagnosis is oligodendroglioma. The demonstration of predominantly intracortical and multinodular growth, specific glio-neuronal elements, and floating neurons strongly argues for DNT. The neuropathologist should be aware of the existence of complex forms of DNT to avoid misclassification of such lesions as pilocytic astrocytoma, diffuse astrocytoma, or oligodendroglioma.

Molecular Pathology. In contrast to oligodendrogliomas, DNTs do not show loss of heterozygosity on 1p and 19q (Fujisawa et al. 2002). *TP53* mutations are also absent. Most DNTs are sporadic lesions, but rare instances of familial occurrence have been reported (Hasselblatt et al., 2004).

Central Neurocytoma (WHO Grade II)

Definition. An intraventricular tumor composed of isomorphic neurocytic cells and typically located in the region of the foramen of Monro.

Macroscopy and Localization. 'Central' refers to the tumors' deep midline location in the ventricles close to the foramen of Monro. The tumors are commonly attached to the septum pellucidum and extend into the lateral and/or third ventricles. Macroscopically, central neurocytomas are solid or partly cystic lesions that are well demarcated from the brain parenchyma. Calcifications may be seen.

Histopathology. The tumor is composed of small, uniformly shaped, oligodendroglia-like neurocytic cells embedded in a finely fibrillar matrix (Fig. 9e). Nuclei-free neuropil islands and microcalcifications are common features. Rare tumors demonstrate ganglion cell differentiation ('*ganglioneurocytomas*'). Mitotic activity is usually low. However, a small fraction of central neurocytomas may show obvious mi-

totic activity and a correspondingly elevated MIB1 index. Such tumors have been designated as '*atypical neurocytomas*' and carry a higher risk of local recurrence (Soylemezoglu et al. 1997).

Immunohistochemistry. Immunohistochemistry for synaptophysin is used to demonstrate neurocytic differentiation of the tumor cells. Rarely, focal expression of GFAP may be seen. The MIB1 index is usually low (<5%), except for the rare 'atypical' variants.

Differential Diagnosis. On H&E, central neurocytoma can mimic oligodendroglioma, (clear-cell) ependymoma, or dysembryoplastic neuroepithelial tumor. Expression of synaptophysin excludes these differential diagnoses. Pineocytoma is distinguished by its location and the characteristic rosettes. Extraventricular (parenchymal) neurocytomas are discussed in chapter 17.

Molecular Pathology. No specific genetic changes have been associated with central neurocytomas so far. In contrast to the majority of oligodendrogliomas, central neurocytomas lack combined losses on 1p and 19q (Tong et al. 2000).

Cerebellar Liponeurocytoma (WHO Grade II)

Definition. A very rare cerebellar tumor of adults, histologically characterized by isomorphic neurocytic cells and focal lipomatous differentiation.

Histopathology. Microscopically, cerebellar liponeurocytomas are cellular tumors composed of uniform neurocytic cells with round, isomorphic nuclei as well as local accumulations of lipidized tumor cells resembling adipocytes (Fig. 9f). Mitotic activity is low.

Immunohistochemistry. The neurocytic tumor cells are positive for synaptophysin. Expression of GFAP may be seen in a small fraction of tumor cells. The MIB1 index is generally low.

Differential Diagnosis. Manifestation in adults, lack of anaplastic features, and the presence of focal lipomatous differentiation separate cerebellar liponeurocytoma from the medulloblastomas. Immunohistochemical staining for synaptophysin helps to distinguish oligodendroglial and ependymal tumors. Rare cases of cerebellar neurocytoma without lipomatous change (Enam et al. 1997) have been reported. On the other hand, lipomatous change may be seen in rare instances of central neurocytoma (George and Scheithauer 2001), indicating a close relationship between the neurocytic tumors in different locations. Concerning the prognosis, most reported cerebellar liponeurocytomas showed a favorable clinical outcome, but occasional cases may take an aggressive course (Jenkinson et al. 2003).

Molecular Pathology. Molecular investigation of 20 cerebellar liponeurocytomas revealed *TP53* mutation in 20% of cases (Horstmann et al. 2004). In contrast, medulloblastoma-associated alterations, such as isochromosome 17q or mutations in *PTCH*, *APC*, or *CNNTB1*, are absent. Cluster analysis of mRNA expression profiles grouped cerebellar liponeurocytomas close to central neurocytomas but apart from medulloblastomas (Horstmann et al. 2004)

Paraganglioma (WHO Grade I)

Definition. A well-demarcated, usually encapsulated and slowly growing tumor composed of uniform neuroendocrine cells (chief cells) forming nests or lobules ('Zellballen') that are surrounded by sustentacular cells.

Macroscopy and Localization. Paragangliomas are thought to originate from specialized neural crest cells in the autonomic ganglia. In the CNS, the vast majority of paragangliomas are located in the filum terminale/cauda equina region, where they grow as intradural tumors attached to the filum terminale and/or caudal nerve roots. Paragangliomas of the head and neck typically originate from the glomus jugulare (jugulotympanic paragangliomas) or the glomus caroticum. Intracranial paragangliomas are rare and usually extend from jugulotympanic lesions. Macroscopically, paragangliomas are encapsulated, soft, and vessel-rich tumors. Cystic areas may be present.

Histopathology. Microscopy shows a cellular neuroendocrine tumor composed of uniform, so-called 'chief' cells growing in a characteristic 'Zellballen' architecture (Fig. 11i). So-called 'sustentacular cells' are spindle cells located at the margins of the Zellballen. Focal ganglion cell differentiation is detectable in up to 50% of the cauda equina tumors ('gangliocytic variant') (Fig. 11j). Paragangliomas are densely vascularized and often contain microcystic areas. Formation of perivascular pseudorosette-like structure mimicking ependymal pseudorosettes can occur. Scattered mitotic figures and foci of hemorrhagic necrosis may be present but are not indicative of malignancy.

Immunohistochemistry. Immunohistochemical stainings confirm the neuroendocrine nature of

this tumor by demonstrating strong expression of chromogranin A and synaptophysin in the chief cells. Most paragangliomas of the cauda equina are additionally positive for vimentin and cytokeratins. The sustentacular cells react with antibodies against S-100 protein and partially GFAP. In addition, S-100 may be variably expressed by chief cells.

Differential Diagnosis. The major clinical differential diagnoses are ependymoma, schwannoma, and meningioma. These entities can easily be distinguished by histology and immunohistochemistry. Occasionally, a metastasis from an extra-axial neuroendocrine tumor needs to be excluded.

Molecular Pathology. The genetic alterations in sporadic paragangliomas, including the cauda equina tumors, are still poorly known. Familial paragangliomas of the head and neck are frequently caused by germline mutations in the mitochondrial complex II genes *SDHB*, *SDHC*, or *SDHD* (Koch et al. 2002). A subset of patients with apparently sporadic paragangliomas, including rare instances of spinal paragangliomas, also carry germline mutations in these genes (Masuoka et al. 2001). Paragangliomas occur at increased frequency in patients with multiple endocrine neoplasia (MEN) types 2 A and 2B, as well as von Hippel-Lindau disease.

Pineal Parenchymal Tumors

Pineocytoma (WHO Grade II)

Definition. A well-circumscribed and slowly growing pineal parenchymal neoplasm composed of uniform cells resembling pineocytes.

Incidence and Age Distribution. Pineocytomas are rare intracranial neoplasms representing approximately 0.1% of all intracranial tumors. They do not show a specific predilection for an age group or gender. Young adults are affected with the highest frequency.

Macroscopy and Localization. Pineocytomas are well-circumscribed, homogeneous tumors of the pineal region with gray-brown color. They may contain degenerative changes such as cystic alterations or hemorrhages.

Histopathology. Pineocytomas show moderate cellularity and are composed of isomorphic cells with round nuclei characterized by a granular chromatin and low mitotic activity. The cells form larger, solid nodules. A characteristic feature is the formation of relatively large, sometimes confluent 'pineocytomatous' rosettes. According to the WHO classification, pineocytomas correspond to WHO grade II. Jouvet et al. (2000) proposed an alternative grading system for pineal parenchymal tumors, which consists of four distinct grades, with pineocytomas corresponding to grade I.

Immunohistochemistry. A strong expression of synaptophysin can be demonstrated. Some tumors show photoreceptor-like differentiation with expression of retinal S-antigen and/or rhodopsin.

Differential Diagnosis. The differential diagnosis includes other pineal parenchymal tumors (pineoblastomas, pineal parenchymal tumors of intermediate differentiation), but these can be separated by determining the proliferative activity, which is generally low in pineocytomas. Ependymomas do not express synaptophysin but are characterized by glial markers and EMA reactivity. If the biopsy material is limited, the distinction between pineocytoma and normal pineal tissue may be difficult although the lobulation pattern is different and proliferative activity is absent in normal pineal tissue. With a cystic lesion, a pineal cyst needs to be distinguished from a cystic pineocytoma.

Molecular Pathology. Only a few cases have been studied by cytogenetics or molecular genetics. Rickert et al. (2001) reported on a CGH analysis of three cases of pineocytomas that did not show any gains or losses of chromosomal material.

Pineoblastoma (WHO Grade IV)

Definition. Pineoblastomas are highly malignant, primitive, neuroectodermal tumors of the pineal gland composed of densely packed, small, round tumor cells.

Incidence and Age Distribution. These tumors can arise at any age but most frequently occur in children. They represent approximately 45% of all pineal parenchymal tumors.

Macroscopy and Localization. Pineoblastomas are usually soft and poorly demarcated tumors of the pineal region. Hemorrhagic and necrotic areas may be present. Some tumors show craniospinal dissemination.

Histopathology. Pineoblastomas are composed of densely packed, small, undifferentiated cells with scant cytoplasm and round or irregularly shaped nuclei (Fig. 10a). The cells resemble those in other primitive neuroectodermal tumors. The chromatin is usually dense; mitotic figures are frequent. Homer-

Wright (neuroblastic) rosettes can be seen, but 'pineocytomatous' larger rosettes are usually absent.

Immunohistochemistry. Similar to pineocytomas, pineoblastomas frequently express synaptophysin (Fig. 10b). Some tumors show expression of retinal S-antigen. Rare tumors contain areas with features and immunohistochemical markers of melanocytic, myogenic, or mesenchymal differentiation.

Differential Diagnosis. The differential diagnosis includes other small, round, blue-cell tumors metastatic to the pineal region as well as primitive neuroectodermal tumors of other regions that can seed to or infiltrate into the pineal region.

Molecular Pathology. So far, no consistent molecular alterations have been described for pineoblastomas. Only a few cases were studied by CGH (Rickert et al. 2001). Three cases showed recurrent losses on chromosome 22. Other studies uncovered increased expression of the *MYC* oncogene but no amplification in a pineoblastoma cell line (Kees et al. 1998). Although most pineoblastomas occur sporadically, the incidence is higher in patients carrying an *RB1* germline mutation. Occasional patients with familial retinoblastoma may additionally develop a pineoblastoma ('trilateral retinoblastoma'). However, *RB1* mutations have not been detected in sporadic pineoblastomas.

Pineal Parenchymal Tumor of Intermediate Differentiation (WHO Grade III)

These tumors represent only 10% of all pineal parenchymal lesions and show moderate to high cellularity. Pineocytomatous rosettes are absent, but the signs of anaplasia and proliferation are not as prominent as in pineoblastomas. A histopathological and clinical study of 39 patients showed a high variability in the clinical course, which was correlated to certain histopathological parameters, so that two distinct prognostic subgroups of this rare entity were proposed to exist (Jouvet et al. 2000).

Embryonal Tumors

Embryonal tumors represent a heterogeneous group of highly malignant tumors composed of immature cells resembling neural progenitor cells during embryonal development of the nervous system. These tumors most frequently occur in the pediatric age group. Despite rapid proliferation, some tumor cells show the potency to differentiate along various neuroectodermal or other lineages.

Ependymoblastoma (WHO Grade IV)

Definition. A highly malignant, primitive, neuroepithelial tumor of young children histologically characterized by multilayered 'ependymoblastic' rosettes.

Incidence and Age Distribution. The tumor is very rare and occurs in neonates and young children.

Macroscopy and Localization. Ependymoblastomas show relatively distinct tumor margins. The tumors are frequently inhomogeneous with the formation of intratumoral cysts. Most tumors are located supratentorially and are usually related to the ventricles. t, other locations have been described. Leptomeningeal seeding is common.

Histopathology. Ependymoblastomas display features of other primitive neuroectodermal tumors. They are composed of densely packed, small, round, blue cells with high mitotic activity. The distinctive histologic feature is the presence of multi-layered rosettes with highly proliferating cells arranged around a lumen (Fig. 10g,h).

Immunohistochemistry. Ependymoblastomas have been demonstrated to express S-100 protein, vimentin, and GFAP at variable levels. Extensive neuronal differentiation is uncommon.

Differential Diagnosis. The major differential diagnosis includes primitive neuroectodermal tumor (PNET) and anaplastic ependymoma. Cerebral PNETs or medulloblastomas of the cerebellum often contain Homer-Wright rosettes but not the multi-layered 'ependymoblastic' rosettes. Ependymomas display perivascular pseudorosettes and true ependymal rosettes, but no ependymoblastic rosettes.

Medulloblastoma (WHO Grade IV)

Definition. A malignant embryonal tumor of the cerebellum mainly occurring in children.

Incidence and Age Distribution. Medulloblastomas represent the most frequent malignant brain tumor in childhood. The incidence is approximately 5 cases/1 million children. The incidence peaks at the age of 7 years, but infants and young adults may also be affected by this malignant tumor. Approximately 65% of the patients are male.

Macroscopy and Localization. The macroscopic finding vary considerably. Many tumors are soft. Others, in particular desmoplastic variants, may present as firm tumors. Some medulloblastomas show calci-

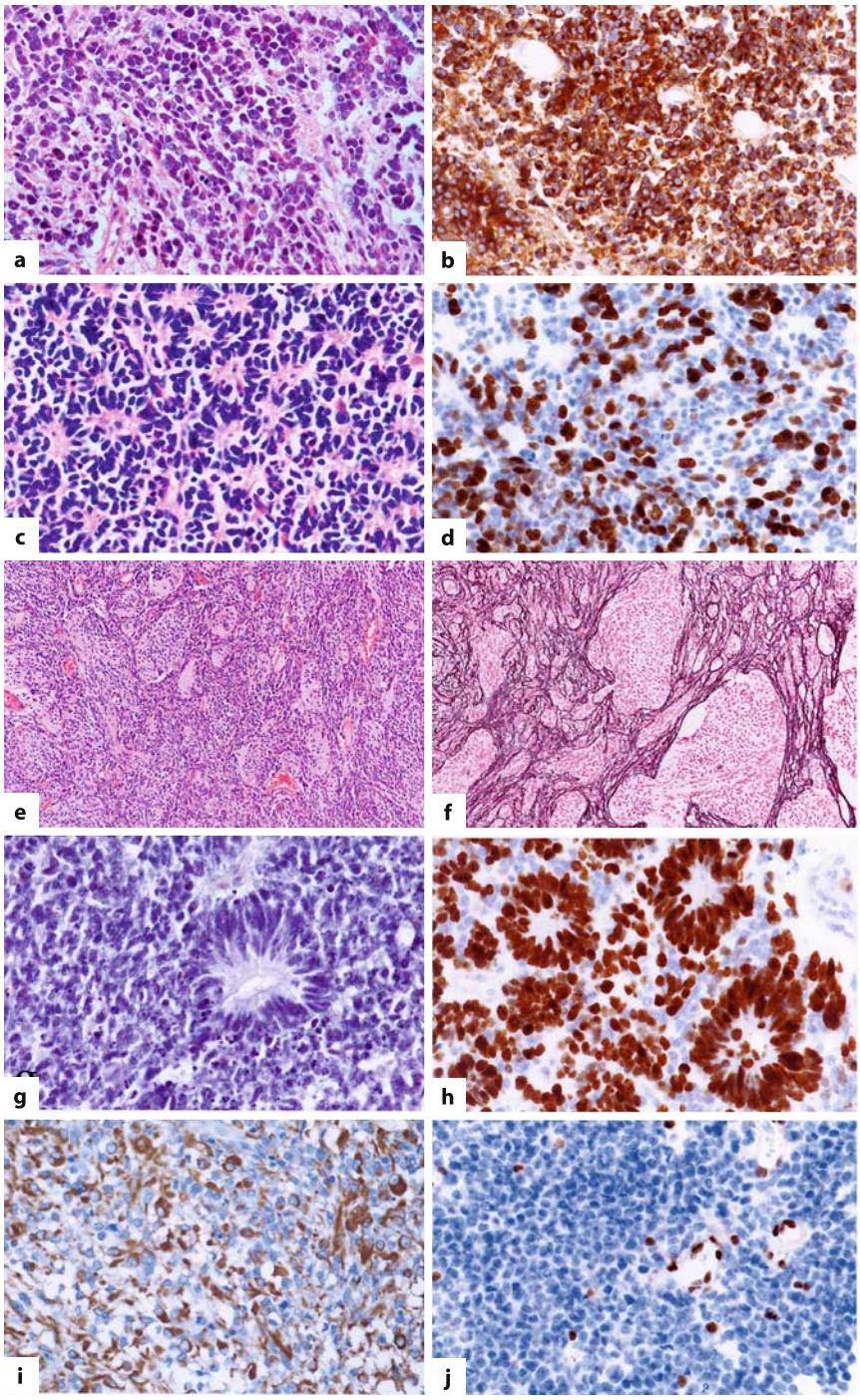


Fig. 10. Histology of pineal parenchymal and embryonal tumors of the CNS. **a,b** Pineoblastoma (WHO grade IV). H&E picture (**a**) shows a cellular tumor composed of poorly differentiated neuroepithelial cells. The tumor cells are strongly positive for synaptophysin (**b**). **c,d** Medulloblastoma (WHO grade IV). Shown is an H&E-stained section of a classic medulloblastoma with formation of multiple neuroblastic (Homer-Wright) rosettes (**c**). Proliferative activity determined by MIB1 expression is generally high in medulloblastomas (**d**). **e,f** Desmoplastic medulloblastoma (WHO grade IV). This medulloblastoma variant is characterized by a biphasic pattern consisting of reticulin-rich, highly proliferative desmoplastic areas and reticulin-free pale island showing neuronal differentiation (**e** H&E; **f** reticulin stain). **g,h** Ependymoblastoma (WHO grade IV). The characteristic histologic feature of this rare embryonal tumor is the formation of multilayered, highly proliferative rosettes, the so-called ependymoblastic rosettes (**g** GFAP; **h** MIB1). **i,j** Atypical teratoid/rhabdoid tumor (WHO grade IV) with expression of vimentin in rhabdoid tumor cells (**i**) and loss of INI1 immunoreactivity (**j**). Note that only vascular cells show nuclear expression of INI1 (**j**)

fication. The extent of infiltration into adjacent brain structures as well as the tendency to seed along the CSF pathways is also highly variable. At the time of diagnosis, metastatic disease is seen in approximately 30% of the patients. Most medulloblastomas are located in the midline/cerebellar vermis. Desmoplastic medulloblastomas are more commonly located in the cerebellar hemispheres.

Histopathology. Medulloblastomas are composed of densely packed, small, round tumor cells with scant cytoplasm, round or carrot-shaped nucleus, and condensed chromatin. Several histologic variants can be distinguished. The most frequent *classic variant* shows a solid growth pattern with or without the formation of Homer-Wright rosettes (Fig. 10c). The tumor cells may be arranged in files ('Indian files'). The mitotic activity is elevated to varying extents. Nuclear and cellular anaplasia shows a continuum from low nuclear variance to a severely anaplastic phenotype. The latter seems to correlate with an unfavorable clinical course, suggesting a potential clinical usefulness in the histologic grading of medulloblastomas (Eberhardt et al. 2002). Approximately 25% of medulloblastomas correspond to the *desmoplastic* (*nodular*) variant. These tumors are characterized by a biphasic architecture consisting in densely cellular and reticulin-rich (desmoplastic) areas and less cellular, reticulin-free islands (so-called pale islands) (Fig. 10e,f). Mitotic activity is highest in the desmoplastic areas. A less common subtype is the *large-cell* (*anaplastic*) *medulloblastoma*, which is characterized by anaplastic tumor cells of somewhat larger cell size with eosinophilic cytoplasm, enlarged pleomorphic nuclei and prominent nucleoli. Mitoses and apoptotic figures are abundant, and large areas of necrosis are commonly present. Clinically, this variant is associated with a very aggressive behavior and poor outcome. A rare variant occurring in young children during the first years of life is the *medulloblastoma* with *extensive nodularity*. These tumors show large nodules with advanced neurocytic differentiation and smaller areas resembling desmoplastic medulloblastomas. The prognosis after surgery and chemotherapy appears to be favorable (Giangaspero et al. 1999). While large cell/anaplastic medulloblastoma shows overlapping features with classic medulloblastoma, medulloblastoma with extensive nodularity is more closely related to desmoplastic medulloblastoma. Extremely rare medulloblastoma variants showing tumor cells with melanocytic differentiation or a striated muscle component are referred to as *melanotic medulloblastoma* and *medullomyoblastoma*, respectively.

Immunohistochemistry. Medulloblastomas consistently express neural markers such as neuron-specific enolase, MAP2, and NCAM. The MIB1 index is usually high (Fig. 10d). Synaptophysin immunoreactivity is detected in the vast majority of cases. In desmoplastic medulloblastomas, synaptophysin expression is particularly prominent in the pale islands. GFAP-positive tumor cells are restricted to a small subset of medulloblastomas. The reticulin-rich areas of desmoplastic medulloblastomas may contain neoplastic cells with GFAP expression. These areas also stain with antibodies against the low-affinity nerve growth factor receptor p75. The large islands of medulloblastomas with extensive nodularity are strongly stained for synaptophysin and the neuronal marker NeuN, reflecting an advanced neurocytic or granule cell differentiation. Myogenic markers are positive in the striated muscle component of medullomyoblastomas.

Differential Diagnosis. The differential diagnosis includes various other malignant CNS tumors, such as anaplastic ependymoma, atypical teratoid/rhabdoid tumor as well as small-cell glioblastoma. On the other end of the spectrum, medulloblastoma needs to be distinguished from cerebellar neurocytoma/liponeurocytoma and dysembryoplastic neuroepithelial tumors. In adult patients, cerebellar metastases from other small, round, blue-cell tumors, e.g., small-cell carcinoma, need to be considered in the differential diagnosis.

Molecular Pathology. The most frequent genetic alteration in classic and large-cell (anaplastic) medulloblastomas is the loss of chromosome arm 17p, which is found in more than 50% of the cases and often associated with a gain of 17q, i.e., formation of isochromosome 17q. Target genes on 17p that have been implicated in medulloblastoma pathogenesis are the *REN* (*KCTD11*) and *HIC1* genes. While *REN* encodes a hedgehog suppressor that inhibits medulloblastoma growth *in vitro* (Di Marcotullio et al. 2004), *HIC-1* encodes a tumor suppressor gene that is silenced by *de novo* promoter methylation in more than 80% of medulloblastomas (Waha et al. 2003). Approximately 10% of medulloblastomas, in particular tumors of the large-cell anaplastic variant, show an amplification of the *MYC* or *NMYC* oncogenes (Aldosari et al. 2002; Eberhart et al. 2002). Both *MYC* or *MYCN* amplification and large-cell anaplastic phenotype have been associated with a poor outcome.

Desmoplastic medulloblastomas often lack 17p losses but carry other genetic alterations, including frequent mutations in the tumor suppressor gene *PTCH* on the long arm of chromosome 9. *PTCH* encodes a receptor component of the sonic hedgehog developmental control pathway which controls precursor cell proliferation in cerebellar development.

Inactivating mutations in the signal components *PTCH* or *SUFUH* or activating mutations in *SMOH* contribute to the pathogenesis of medulloblastomas by overactivation of the pathway most frequently seen in the desmoplastic subtype (Pietsch et al. 1997; Reifenberger et al. 1998; Taylor et al. 2002). In addition, alterations of genes involved in the *WNT* and *NOTCH* developmental control pathways have been found in subsets of medulloblastomas (Zurawel et al. 1998; Eberhart et al. 2000; Koch et al. 2001; Dahmen et al. 2001). The importance of the sonic hedgehog and WNT signaling pathways in medulloblastoma pathogenesis is further supported by the increased incidence of these tumors in patients with germline mutations in *PTCH* (Gorlin syndrome) or *APC* (Turcot syndrome).

Taken together, clinicopathological data and genetic findings indicate that medulloblastoma is not a single disease entity but may be subdivided into at least two entities with different histogenesis, genetic events involved in transformation, expression pattern and different clinical behavior (Bühren et al. 2000; Pomeroy et al. 2002, Pietsch et al. 2004) (Fig. 4).

Supratentorial Primitive Neuroectodermal Tumor (WHO Grade IV)

Definition. A malignant embryonal tumor located in the cerebral hemispheres or suprasellar region and histologically composed of immature neuroepithelial cells with the capacity of differentiation into various neural cell lineages.

Incidence and Age Distribution. Supratentorial PNETs are rare tumors that are far less common than cerebellar medulloblastomas. The tumors occur mainly in children of pre-school or school age. Boys are affected more frequently than girls.

Macroscopy and Localization. Most supratentorial PNETs are of soft consistency unless a desmoplastic reaction has been induced by superficial growth. The tumors may contain areas of hemorrhage and/or necrosis. The degree of demarcation against the adjacent brain varies. By definition, these tumors are found in supratentorial locations, most commonly the cerebral hemispheres and suprasellar region.

Histopathology. The histology of supratentorial PNET closely resembles that of classic medulloblastoma, i.e., the tumor is mainly composed of densely packed, small, undifferentiated or poorly differentiated, neuroepithelial cells with high proliferative activity. Formation of Homer-Wright or Flexner-Wintersteiner rosettes may be seen. Occasional tumors may show advanced neuronal differentiation and thus resemble neuroblastoma or ganglioneuroblastoma. Supratentorial PNETs with melanotic cells are rare.

Immunohistochemistry. Immunohistochemical analysis often uncovers at least a subset of tumor cells with expression of markers indicating differentiation towards neuronal, glial, or other lineages. Similar to medulloblastomas, most supratentorial PNETs demonstrated at least a focal expression of neuronal markers, such as synaptophysin or neurofilaments.

Differential Diagnosis. The differential diagnosis includes small-cell glioblastoma, anaplastic ependymoma, ependymoblastoma, atypical teratoid/rhabdoid tumor, and other highly proliferative, small-cell neoplasms. The differential diagnosis between small-cell glioblastoma/anaplastic astrocytoma and supratentorial PNET may sometimes be difficult. Immunohistochemical evidence for neuronal differentiation argues in favor of a PNET.

Molecular Pathology. Although the histology and immunophenotype are similar in PNETs and medulloblastomas, chromosome 17 alterations or mutations of components of the sonic hedgehog pathway are uncommon in supratentorial PNETs, which carry a variety of other genetic abnormalities (Burnett et al. 1997; Russo et al. 1999; Kraus et al. 2002).

Medulloepithelioma (WHO Grade IV)

Definition. An extremely rare, highly malignant, embryonal tumor of childhood characterized by immature neural tumor cells growing in tubulopapillary formations that resemble the embryonic neural tube.

Incidence and Age Distribution. Medulloepithelioma is an extremely rare CNS tumor that either manifests as a congenital neoplasm or develops during the first 5 years of life.

Macroscopy and Localization. The tumor most frequently arises in the cerebral hemispheres but can affect almost all CNS structures, including the eye. Medulloepitheliomas are usually bulky tumors that are well-demarcated from the adjacent brain. Cysts, hemorrhages, and necrotic areas may be macroscopically visible. Some tumors disseminate in the subarachnoid space.

Histopathology. Medulloepitheliomas are characterized by the formation of pseudostratified neu-

roepitheliomatous structures resembling the primitive neural tube. The neoplastic neuroepithelium is arranged in tubular, papillary, or trabecular formations with an external limiting basal membrane. The rapidly dividing cells are of cuboid, sometimes elongated shape. The nuclei are oval and have a coarse chromatin structure. Mitotic figures tend to be located near the luminal surface. In other areas, the tumor cells are often densely packed. These areas may show evidence of divergent lines of differentiation, including an advanced neuronal differentiation. Ependymoblastomatous rosettes can also occur.

Immunohistochemistry. The medulloepitheliomatous component is positive for nestin and vimentin. Focal expression of cytokeratin or EMA has been described. In contrast, GFAP, S-100 protein, and NSE immunoreactivity is absent. In other areas, various differentiation lineages may be detected by immunohistochemistry, including tumor cells with neuronal (synaptophysin and neurofilament positivity) and glial (GFAP positivity) differentiation.

Differential Diagnosis. The differential diagnoses include choroid plexus carcinoma, PNET/medulloblastoma, anaplastic ependymoma, and ependymoblastoma. These entities, however, do not contain the characteristic 'medulloepitheliomatous' component. Another differential diagnosis is immature teratoma, which additionally contains tissues from the other germ layers.

Atypical Teratoid/Rhabdoid Tumor (WHO Grade IV)

Definition. A highly malignant, embryonal CNS tumor containing rhabdoid cells with or without primitive neuroectodermal tumor-like areas and/or tumor cells showing epithelial, mesenchymal, glial, or neuronal differentiation. The tumors are molecularly characterized by mutations in the *INI-1* gene.

Incidence and Age Distribution. Atypical teratoid/rhabdoid tumor (AT/RT) accounts for approximately 2% of brain tumors in patients less than 18 years old. Most tumors occur in the first 3 years of life or are already present at birth. Adults are only exceptionally affected.

Macroscopy and Localization. Macroscopically, these often bulky tumors are soft and pink or white in color. The degree of demarcation from the surrounding brain tissue varies. The tumors may contain hemorrhagic or necrotic areas. Growth and seeding in the leptomeninx is frequently seen already at the time of diagnosis. AT/RTs can arise in any CNS area. However, the highest incidence is found in the posterior fossa, especially the cerebello-pontine angle, followed by supratentorial locations.

Histopathology. AT/RTs are characterized by typical rhabdoid cells with eosinophilic, frequently homogenously stained cytoplasm and an eccentric nucleus with vesicular chromatin structure and prominent nucleolus. Mitotic figures are abundant. In addition to these characteristic rhabdoid cells, AT/RTs often contain areas showing differentiation along glial, epithelial, mesenchymal, and other lineages, i.e., may mimic the appearance of a malignant glioma, carcinoma, or sarcoma, respectively. Furthermore, PNET-like areas composed of small, undifferentiated cells are not infrequent.

Immunohistochemistry. Immunohistochemical studies are very helpful to establish the diagnosis of AT/RT, especially in cases with only rare rhabdoid cells and/or undifferentiated areas. Rhabdoid cells strongly express vimentin (Fig. 10i). EMA reactivity is also found in most tumors. Reflecting their variable differentiation potential, neoplastic cells with immunoreactivity for cytokeratins, smooth muscle actin, desmin, GFAP, and/or synaptophysin may be detected in variable amounts. Recently, Judkins et al. (2004) demonstrated that AT/RTs lack expression of the *INI-1* gene product (Fig. 10j), which is ubiquitously expressed in normal tissues and other tumors. This tool is very helpful in the analysis of small specimens lacking typical rhabdoid cells.

Differential Diagnosis. AT/RT needs to be distinguished from medulloblastoma/PNET, glioblastoma, or choroid plexus carcinoma. Application of a panel of antibodies and cytogenetic evaluation help to circumvent diagnostic difficulties caused by the lack of a significant rhabdoid cell component and potentially misleading differentiation.

Molecular Pathology. FISH analysis demonstrates that 90% of AT/RTs show monosomy 22 and/or deletions of the *INI-1* locus at 22q11.2. The *INI-1* gene is inactivated by mutations or homozygous deletion in almost all AT/RTs, similar to rhabdoid tumors of the kidney (Biegel et al. 2002). Ini-1 is a component of the SWI/SNF chromatin remodeling complex regulating transcription. Few patients carry *de novo* germline mutations in *INI-1*.

Tumors of Cranial and Peripheral Nerves

Tumors of the peripheral nervous system include a large variety of different entities. This chapter will focus on the most important ones, namely *schwan-*

noma, *neurofibroma*, *perineurioma*, and *malignant peripheral nerve sheath tumor* (MPNST). For the discussion of other, less common tumor types, such as granular cell tumor, nerve sheath myxoma, neurothekeoma, and ganglioneuroma, the reader is referred to the respective chapters in more comprehensive textbooks (e.g., Scheithauer et al. 1999; Burger et al. 2002). An important clinical issue of peripheral nervous system tumors is their frequent association with hereditary tumor syndromes, in particular the neurofibromatoses. Patients diagnosed with multiple peripheral nerve sheath tumors or certain tumor entities, e.g., plexiform neurofibroma, should be checked for further clinical features of an underlying hereditary disorder.

Schwannoma (WHO Grade I)

Definition. A benign, usually encapsulated, peripheral nerve sheath tumor composed of neoplastic Schwann cells.

Incidence and Age Distribution. Schwannomas (synonyms: neurinoma, neurilemmoma) account for about 8–10% of intracranial and 25–30% of spinal tumors. They may develop at any age, with a peak of incidence between the 4th and 6th decades. Women are affected twice as often as men. Patients with neurofibromatosis type 2 (NF2) often have multiple schwannomas, with bilateral vestibular schwannomas being pathognomonic for this disorder.

Macroscopy and Localization. Schwannomas are usually encapsulated, globular to multinodular masses associated with a nerve or nerve root. Mucosal and visceral schwannomas, including the rare intraparenchymal CNS tumors, lack encapsulation and obvious association with a parent nerve. On the cut surface, schwannomas are light tan to yellow, frequently cystic, and partially hemorrhagic. The vast majority of intracranial schwannomas develop from the vestibular nerve (Fig. 11a). Tumors of the trigeminal or facial nerve are far less common. Primary intracerebral, intraventricular, or intramedullary schwannomas are very rare. Spinal schwannomas can originate from any nerve root, with the dorsal (sensory) roots being more commonly affected than the ventral roots. The majority of spinal schwannomas are intradural lesions. However, some tumors extend through the intervertebral foramen and form so-called *dumbbell* or *hourglass schwannomas*.

Histopathology. Schwannomas typically show two distinct histologic patterns designated as *Antoni A* and *B*, respectively. Antoni A areas are characterized by spindle-shaped Schwann cells with elongated nuclei arranged in streams and nuclear palisades known as *Verocay bodies* (Fig. 11b). For unknown reasons, Verocay bodies are more common in peripheral and spinal tumors than vestibular tumors. The Antoni B pattern refers to loosely textured, less cellular, and often lipidized tumor areas that are thought to result from a degenerative process. In Antoni B areas, the neoplastic Schwann cells commonly demonstrate more rounded nuclei and stellate processes. Foamy histiocytes may be prominent. Vascular hyalinization is another characteristic feature of schwannomas. In addition, areas with cystic degeneration and intratumoral hemorrhages are frequently encountered. Marked nuclear pleomorphism, including the presence of bizarre nuclei, is a prominent degenerative feature in the so-called '*ancient schwannomas*'. Occasional mitotic figures may be present in schwannomas but are not indicative of malignancy. The Gomori reveals a dense network of curly reticulin fibers in the tumor tissue, in particular in the Antoni A areas.

Three histologic variants are listed in the WHO classification: *cellular schwannoma*, *plexiform schwannoma*, and *melanotic schwannoma*. *Cellular schwannoma* refers to hypercellular tumors with low to moderate mitotic activity and an exclusive or predominant Antoni A growth pattern. Verocay bodies are absent. Cellular schwannomas are benign tumors that need to be distinguished from malignant peripheral nerve sheath tumors. However, the risk of recurrence after incomplete resection is higher than with conventional schwannoma. *Plexiform schwannomas* are characterized by a multinodular or plexiform growth pattern and most commonly involve dermal or subcutaneous nerves. Most cases are sporadic solitary lesions. In contrast to plexiform neurofibromas, plexiform schwannomas are not associated with neurofibromatosis type 1 (NF1). However, plexiform schwannomas may be more common in a recently separated third form of neurofibromatosis, i.e., *schwannomatosis*. *Melanotic schwannomas* are characterized by tumor cells containing melanosomes. Two forms can be distinguished, melanotic schwannoma with and without psammoma bodies. Most non-psammomatous tumors affect spinal nerves, whereas psammomatous variants are also found in visceral organs. About half of the psammomatous melanotic schwannomas occur in patients with *Carney complex*. Other clinical manifestations of this rare, autosomal-dominantly inherited disorder include facial lentigines, cardiac myxoma, endocrine hyperfunction (Cushing syndrome), and Sertoli cell tumors. About 10% of melanotic schwannomas show histologic signs of anaplasia and behave clinically malignant.

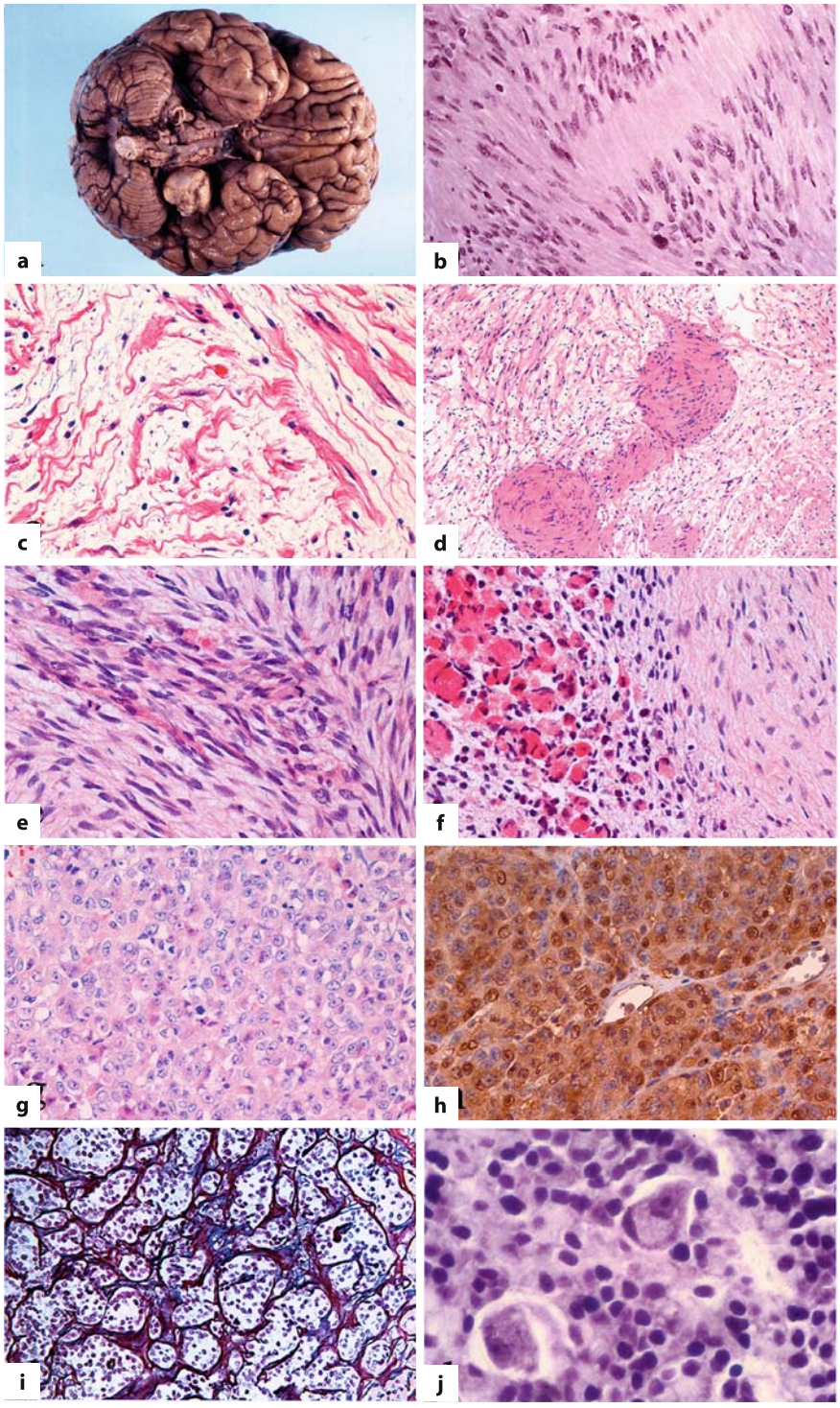


Fig. 11. Macroscopic and histologic characteristics of selected tumors of the peripheral and autonomic nervous system. **a** Autopsy finding of a vestibular schwannoma in the right cerebello-pontine angle. **b** Schwannoma (WHO grade I) with typical formation of palisades (*Verocay bodies*) (H&E). **c** Neurofibroma (WHO grade I). Note spindle cells and collagen bundles in a myxoid matrix (H&E). **d** Plexiform neurofibroma with formation of schwannoma-like nodules (H&E). **e** Malignant peripheral nerve sheath tumor (MPNST) with fascicular growth and high mitotic activity (H&E). **f** MPNST with rhabdomyoblastic differentiation (malignant triton tumor) (H&E). **g,h** Epithelioid MPNST composed of epithelioid tumor cells with prominent nucleoli (g, H&E) and strong expression of S-100 (**h**). **i** Paraganglioma of the cauda equina (WHO grade I) with characteristic `zellballen' architecture (reticulin stain). **j** Gangliocytic differentiation in a paraganglioma (H&E)

Immunohistochemistry. The neoplastic Schwann cells are strongly positive for S-100 and vimentin. Antibodies against collagen IV or laminin stain the pericellular basal lamina. Focal GFAP immunoreactivity may be observed. Melanotic schwannomas can react with antibodies against melan A or HMB-45.

Differential Diagnosis. The diagnosis of a conventional schwannoma showing the Antoni A and B patterns, Verocay bodies, and strong S-100 expression is straightforward. Occasionally, the distinction from localized intraneural neurofibroma may be difficult. Neurofibromas containing Schwannoma-like nodules are sometimes encountered, in particular in patients with NF1. Plexiform schwannomas must not be confused with plexiform neurofibromas, which are usually larger and more deeply situated lesions closely associated with NF1. Cellular schwannomas need to be distinguished from malignant peripheral nerve sheath tumors (MPNST) by the absence of marked features of anaplasia and uniform S-100 expression. The principal differential diagnosis of melanotic schwannoma includes melanocytic tumors, such as melanocytoma and malignant melanoma.

Molecular Pathology. The majority of sporadic schwannomas carry somatic mutations in the *NF2* tumor suppressor gene at 22q12, frequently combined with loss of heterozygosity on chromosome 22 (Jacoby et al. 1994; Twist et al. 1994). Germline *NF2* mutations underlie the development of often multiple schwannomas in NF2 patients (Rouleau et al. 1993; Trofatter et al. 1993). CGH analyses confirmed 22q loss as the most frequent chromosomal imbalance in schwannomas, while other chromosomes, including 9q, 17, and 19, are far less commonly altered (Koga et al. 2002; Warren et al. 2003).

Neurofibroma (WHO Grade I)

Definition. A benign peripheral nerve sheath tumor composed of neoplastic Schwann cells, perineural-like cells and fibroblasts located in a collagen fiber-rich and mucinous matrix.

Incidence and Age Distribution. Neurofibromas are common tumors that are found at all ages without any gender preference.

Macroscopy and Localization. Most neurofibromas present as solitary, slowly growing, circumscribed but not encapsulated cutaneous nodules. These *localized cutaneous neurofibromas* are distinguished from several other variants. *Diffuse cutaneous neurofibroma* are large, ill-defined, plaque-like lesions in the dermis and subcutis. *Localized intraneural neurofibroma* typically presents as fusiform swelling of a spinal or peripheral nerve. *Plexiform neurofibromas* are elongated, multinodular lesions involving multiple fascicles of a large nerve or multiple trunks of a nerve plexus. Their macroscopic appearance is frequently referred to as corresponding to a 'bag of worms'. With very rare exceptions, plexiform neurofibromas are pathognomonic of NF1. Similarly, *massive soft-tissue neurofibromas* ('elephantiasis neuromatosa') are huge lesions closely associated with NF1 and leading to localized gigantism of certain regions of the body, such as the shoulder, pelvic girdle, or a limb. *Visceral neurofibromas* affect inner organs, most commonly the gastrointestinal tract. Interestingly, neurofibromas of the cranial nerves are extremely rare. Solitary neurofibromas are mostly sporadic tumors, whereas multiple neurofibromas, e.g., multiple diffuse or localized cutaneous tumors or multiple localized intraneural tumors of the spinal roots, are frequently associated with NF1. Plexiform neurofibromas and intraneural neurofibromas of major nerves are associated with an increased risk of progression towards MPNST.

Histopathology. In contrast to schwannomas, neurofibromas consist of a mixture of different cell types including neoplastic Schwann cells, perineural-like cells and fibroblasts. Mast cells are also commonly seen. The different cells are typically embedded in an alcianophilic myxoid matrix containing thick collagen fibers (Fig. 11c). The latter often resemble the picture of 'shredded carrots'. Mitotic figures are rare. The tumors lack encapsulation and may diffusely infiltrate into the surrounding soft tissue. Intraneural lesions infiltrate along existing axons, which often remain visible within the tumor tissue. Tumors originating from spinal roots frequently infiltrate into the adjacent ganglia. Formation of tactile structures (Wagner-Meissner-like or Pacinian-like corpuscles) is occasionally seen. Tumors with degenerative nuclear atypia may be referred to as '*atypical neurofibroma*', while '*cellular neurofibromas*' show increased cellularity but no definite features of malignancy. Rare cases of plexiform neurofibroma may contain intratumoral nodules resembling schwannoma tissue (Fig. 11d).

Immunohistochemistry. The neoplastic Schwann cells in neurofibromas are positive for S-100 protein.

Differential Diagnosis. Schwannoma is the principal differential diagnosis of localized intraneural neurofibroma. Large neurofibromas of major nerves as well as plexiform variants should be carefully screened for the presence of anaplastic features.

Perineurioma differs from neurofibroma by lack of S-100 expression and positivity for EMA.

Molecular Pathology. Neurofibromas are caused either by somatic (sporadic tumors) or by germline (NF1-associated tumors) mutations in the NF1 tumor suppressor gene. Among the different cell types in neurofibromas, the Schwann cells are the neoplastic cells that show biallelic *NF1* inactivation (Serra et al. 2000).

Perineurioma (WHO Grade I)

Definition. A benign peripheral nerve sheath tumor composed of neoplastic perineural cells. Two principal types are distinguished, namely *intraneural perineurioma* and *soft-tissue perineurioma*.

Incidence and Age Distribution. Perineuriomas are very rare tumors that account for less than 1% of all peripheral nerve neoplasms. Intraneural perineuriomas (formerly considered as hypertrophic neuropathy) predominantly affect adolescents and young adults without any gender preference. Soft-tissue perineuriomas are more common in female patients and preferentially occur in adults.

Macroscopy and Localization. Intraneural perineuriomas present as cylindrical nerve enlargement, typically affecting peripheral nerves of an extremity. In contrast, soft-tissue perineuriomas are not associated with a nerve and most commonly present as small, solitary, unencapsulated, subcutaneous, nodular lesions of the leg or hand.

Histopathology. Intraneural perineurioma is microscopically characterized by perineural cells that form concentric, multilayered whorls around central nerve fibers ('pseudo-onion bulbs'). Soft-tissue perineuriomas consist of spindle-shaped perineural cells forming fascicles, storiform patterns and/or loose whorls in a collagen-rich matrix. Markedly sclerotic areas may be seen. Mitotic activity is generally low, and necroses are absent.

Immunohistochemistry. Perineuriomas are positive for EMA but negative for S-100. Thus, immunohistochemistry clearly distinguishes these tumors from Schwann cell neoplasms.

Molecular Pathology. Perineuriomas commonly demonstrate monosomy of chromosome 22.

Malignant Peripheral Nerve Sheath Tumor (MPNST)

Definition. A malignant tumor arising from a peripheral nerve and/or composed of tumor cells showing variable peripheral nerve sheath differentiation.

Incidence and Age Distribution. MPNSTs are estimated to account for less than 5% of all malignant soft-tissue tumors. Young and middle-aged adults (3rd–6th decade of life) are primarily affected. More than half of the MPNSTs develop in NF1 patients, often from pre-existing neurofibromas of major nerves and/or of the plexiform type.

Macroscopy and Localization. Most MPNSTs arise from medium or large nerves, with the sciatic nerve being most often affected. As stated above, development from a precursor lesion, such as a plexiform neurofibroma, is also frequent, in particular in NF1. Less commonly, MPNST presents as a soft-tissue mass not associated with a recognizable nerve. Macroscopically, MPNST usually appears as a large, fusiform or globoid, pseudoencapsulated tumor with a firm, gray, or tan cut surface. Hemorrhagic and necrotic areas are often present.

Histopathology. The histology of MPNST is highly variable. The classic picture refers to a densely cellular spindle-cell tumor often showing a fibrosarcoma-like fascicular growth pattern (Fig. 11e). Most tumor cells have elongated, hyperchromatic nuclei with tapered ends and a bipolar, faintly eosinophilic cytoplasm. Mitotic activity is usually brisk, and necroses with or without pseudopalisading are commonly seen. MPNSTs invade not only the parent nerve but also grow invasively into the surrounding soft tissue. The following histologic variants are distinguished in the WHO classification: *epithelioid MPNST, glandular MPNST, melanotic MPNST*, and *MPNST with rhabdomyoblastic differentiation* (so-called *malignant Triton tumor*). The epithelioid variant is composed of malignant epithelioid cells and accounts for approximately 5% of all MPNSTs (Fig. 11g,h). Epithelioid MPNSTs are not associated with NF1. The glandular variant is characterized by the presence of epithelial glands, often with mucin production. The characteristic feature of a malignant Triton tumor is areas of rhabdomyosarcomatous differentiation (Fig. 11f). Both glandular MPNST and malignant Triton tumor are associated with NF1. Occasional cases of MPNST may show formation of bone or cartilage or demonstrate areas of both mesenchymal and epithelial differentiation (*pluridirectional MPNST*).

Immunohistochemistry. Vimentin is strongly expressed in MPNST but is of limited diagnostic help. Expression of protein S-100 is found in half of the MPNSTs and, when present, often restricted to only a fraction of tumor cells. In contrast to benign Schwann cell tumors, nuclear accumulation of p53 is commonly seen in MPNST. Occasional tumors may show EMA immunoreactivity, indicating cells with perineural differentiation. Epithelial elements in glandular MPNST are positive for cytokeratins and EMA. Rhabdomyoblastic cells in malignant Triton tumors react with antibodies against muscle antigens, such as desmin and MyoD. Expression of melanocytic antigens (HMB-45, melan A) may be seen in melanotic MPNST. The fraction of MIB1-positive tumor cells is generally high.

Differential Diagnosis. MPNST needs to be distinguished from benign Schwann cell tumors, in particular from the cellular variants of schwannoma and neurofibroma. To identify focal progression towards MPNST in predisposing lesions such as plexiform neurofibroma, careful sampling is an important issue. Furthermore, malignant melanoma as well as several malignant soft-tissue tumors, such as fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, and epithelioid sarcoma, have to be considered in the differential diagnosis. The distinction of these entities from MPNST often requires a detailed immunohistochemical analysis as well as the consideration of important clinical parameters, e.g., location of the tumor, relationship to a peripheral nerve, and presence of clinical features indicative of NF1.

Molecular Pathology. In addition to *NF1* gene inactivation, MPNSTs frequently show mutations in the *TP53* gene, homozygous deletion of *CDKN2 A*, and/or *EGFR* overexpression (Carroll and Stonecypher 2004). CGH analysis has identified several chromosomal regions that demonstrate frequent gains (e.g., 17q24-q25, 7p11-p13, 5p15, 8q22-q24, and 12q21-q24) or losses (e.g., 13q14-q22 and 1p) in MPNSTs (Mechtersheimer et al. 1999).

Meningeal Tumors

Meningiomas

Definition. Meningiomas are tumors composed of neoplastic meningothelial (arachnoidal) cells. Most meningiomas are slowly growing, benign tumors that are attached to the dura mater. Less commonly, meningiomas show atypical or anaplastic histologic features that are associated with an increased likelihood for recurrence and/or aggressive behavior.

Incidence and Age Distribution. Meningiomas are the second most common group of primary CNS tumors after the gliomas. The annual incidence is estimated as approximately 6 per 100,000 population. The tumors preferentially develop in elderly patients (age peak: 50–70 years). Women are more commonly affected than men. Most meningiomas are sporadic tumors. Patients with neurofibromatosis type 2 (NF2) have a significantly increased risk of meningioma, often resulting in the development of multiple meningiomas. Familial meningioma in the absence of NF2 is rare.

Macroscopy and Localization. Most meningiomas arise in the intracranial cavity, followed by spinal and intraorbital locations. Typical sites of intracranial meningiomas are the cerebral convexity and falx cerebri, olfactory groove, sphenoid or petrous ridges, parasellar region, optic nerve sheath, tentorium cerebelli, and posterior fossa. Intraventricular meningiomas are rare tumors thought to arise from meningothelial cells located in the choroid plexus or tela choroidea (Fig. 6f). Macroscopically, most meningiomas are solid, well-demarcated, often firm tumors that are broadly attached to the dura. The cut-surface frequently appears lobulated. Benign meningiomas compress and displace, but do not usually invade the adjacent brain tissue. In contrast, even benign meningiomas commonly invade the dura, including the dural sinuses. Tumor growth into the skull is not infrequent, with some tumors invading through the skull into the adjacent extracranial soft tissues. Reactive hyperostosis of the skull involved by a meningioma is a typical finding. *Meningioma en plaque* describes a carpet-like flat meningioma, most often found over the sphenoid wing.

Histopathology. The histologic appearance of meningiomas is highly variable. The WHO classification includes 9 different histologic variants associated with benign clinical behavior (meningiomas of WHO grade I) and 6 histologic variants associated with a greater risk for recurrence and/or aggressive clinical behavior (meningiomas of WHO grade II or III) (Table 5). Circa 85–90% of all meningiomas belong to the first group of benign tumors corresponding to WHO grade I, with meningothelial, fibrous/fibroblastic, and transitional variants being most common. Atypical meningiomas are the most frequent meningiomas of WHO grade II, which account for approximately 10% of all meningiomas. Malignant meningiomas of WHO grade III (anaplastic, papillary, and rhabdoid meningiomas) are relatively rare tumors (2–3% of all meningiomas).

Benign Meningiomas of WHO Grade I. This group of tumors consists of 9 different histologic variants.

In general, benign meningiomas show low mitotic activity (<4 mitoses per 10 high power fields) and do not fulfill the other histologic criteria indicative of atypical or anaplastic meningiomas (see below). *Meningothelial meningioma* is composed of uniform tumor cells closely resembling normal arachnoid cap cells (Fig. 12a). The tumor cells show a syncytial growth in sheets and lobules surrounded by thin stromal septa. Nuclei are rounded to oval and may contain eosinophilic cytoplasmic invagination (pseudoinclusions). Nuclei with central clearing (hole nuclei) are also common. Whorl formations and occasional psammoma bodies may be seen but are less common compared with transitional and psammomatous variants, respectively. The *fibrous (fibroblastic) meningioma* is characterized by fibroblast-like spindle cells growing in a collagen and reticulin fiber-rich matrix (Fig. 12b). A vaguely fascicular growth pattern is frequently seen, while whorls and psammoma bodies are rare. The *transitional (mixed) meningioma* shows both meningothelial and fibroblastic features. Whorl formation is often very prominent in this variant (Fig. 12c). *Psammomatous meningiomas* are characterized by the presence of abundant psammoma bodies. In some tumors, the psammoma bodies become confluent and form areas of calcification, occasionally leading to rock-hard lesions. The psammomatous variant is particularly common among meningiomas arising in the thoracic spinal region of women. *Angiomatous meningioma* refers to meningiomas showing excessive vascularization by small- to medium-sized, often hyalinized blood vessels with only interspersed meningothelial tumor cells (Fig. 12 f). *Microcystic meningioma* is composed of bi- and multipolar cells lying in a mucinous matrix characterized by prominent microcystic degeneration (Fig. 12d). Occasionally, the tumor cells may be quite pleomorphic. Cytoplasmic vacuolation may also be seen. The *secretory meningioma* shows focal epithelial differentiation with deposition of glycogen-rich, strongly PAS-positive droplets (Fig. 12e). These so-called 'pseudo-psammoma bodies' are surrounded by tumor cells expressing epithelial antigens, such as cytokeratins and carcinoembryonic antigen (CEA). A clinically important feature associated with secretory meningiomas is the induction of a marked peritumoral edema in the adjacent brain tissue. *Lymphoplasmacyte-rich meningioma* is a rare variant showing extensive inflammatory infiltrates and formation of Russell bodies. Recognition of the actual meningioma tissue may be difficult in some of these lesions. *Metaplastic meningioma* refers to tumors showing areas of differentiation towards adipose tissue, cartilage, or bone. The WHO classification also lists meningiomas with prominent xanthomatous or myxoid change under this subtype.

Table 5. WHO classification and grading of meningiomas

Meningiomas with low risk of recurrence and/or aggressive growth	
Meningothelial meningioma	WHO grade I
Fibrous/fibroblastic meningioma	WHO grade I
Transitional (mixed) meningioma	WHO grade I
Psammomatous meningioma	WHO grade I
Angiomatous meningioma	WHO grade I
Microcystic meningioma	WHO grade I
Secretory meningioma	WHO grade I
Lymphoplasmacyte-rich meningioma	WHO grade I
Metaplastic meningioma	WHO grade I
Meningiomas with greater risk of recurrence and/or aggressive growth	
Atypical meningioma	WHO grade II
Clear-cell meningioma (intracranial)	WHO grade II
Chordoid meningioma	WHO grade II
Rhabdoid meningioma	WHO grade III
Papillary meningioma	WHO grade III
Anaplastic (malignant) meningioma	WHO grade III
Meningiomas of any subtype or grade with high proliferation index and/or brain invasion	

Meningiomas of WHO Grade II. Three histologic meningioma variants are known to be associated with an increased likelihood for local recurrence after operative resection. *Atypical meningioma* (Fig. 12 g) is the most common representative of WHO grade II meningioma and defined by an increased mitotic count (4 or more mitoses per 10 high power fields) or 3 or more of the following histologic criteria: (1) increased cellularity, (2) presence of small-cells with high nuclear/cytoplasmic ratios, (3) prominent nucleoli, (4) uninterrupted patternless or sheet-like growth, and (5) foci of spontaneous necrosis. Meningiomas with brain invasion but no other features of atypia or anaplasia are thought to behave similarly to atypical meningiomas and thus correspond to WHO grade II. *Chordoid meningioma* is a rare meningioma subtype characterized by areas histologically resembling chordoma, i.e., consisting of cords and clusters of eosinophilic, sometimes vacuolated cells in a basophilic myxoid matrix (Fig. 12h). In contrast to chordoma, chordoid meningioma lacks typical physaliphorous cells and usually contains areas showing meningeal features, such as whorl formation or psammoma bodies. Clear-cell meningioma is another rare variant composed of

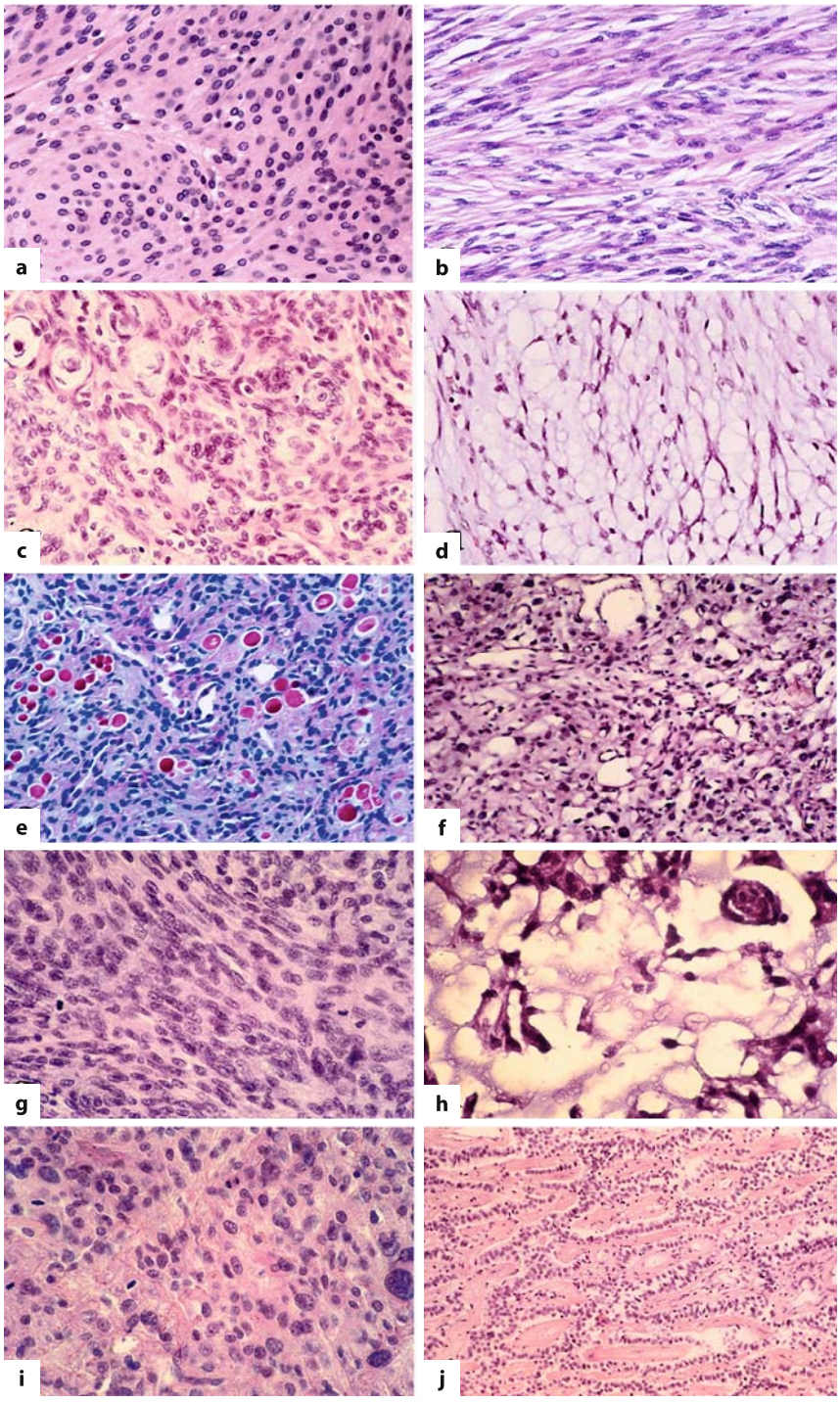


Fig. 12. Histology of selected meningioma variants. **a–f** Benign meningiomas (WHO grade I) corresponding to meningothelial (**a**), fibrous (**b**), transitional (**c**), microcystic (**d**), secretory (**e**), and angiomatous (**f**) variants (**a–d**, **f** H&E; **e** PAS). Note syncytial growth of meningothelial cells (**a**), fascicular growth of fibroblast-like spindle cells (**b**), formation of multiple meningeal whorls (**c**), prominent microcystic degeneration (**d**), production of PAS-positive pseudopsammoma bodies (**e**), and numerous densely packed blood vessels (**e**). **g** Atypical meningioma (WHO grade II) with increased mitotic activity (H&E). **h** Chordoid meningioma (WHO grade II) showing chordoma-like growth of tumor cells in a myxoid matrix (H&E). In contrast to chordoma, meningeal whorl formation can usually be recognized in chordoid meningioma. **i** Anaplastic meningioma (WHO grade III) with cellular anaplasia and numerous mitotic figures (H&E). **j** Papillary meningioma (WHO grade III) demonstrating a pseudopapillary growth pattern (H&E)

glycogen-rich, PAS-positive cells showing a clear cytoplasm on H&E-stained paraffin sections. The tumors typically lack the classic features of meningioma and are preferentially found in the cauda equina region and the cerebellopontine angle.

Meningiomas of WHO Grade III. This group of tumors includes three histologic variants that show aggressive clinical behavior with locally invasive and destructive growth and the potential of metastasis formation. The prognosis is usually unfavorable, as indicated by a mean overall survival of less than two years for patients with anaplastic meningiomas. *Anaplastic meningioma* (Fig. 12i) is histologically characterized by signs of frank malignancy, including a high mitotic count (20 or more mitoses per 10 high power fields) or an obviously malignant morphology resembling sarcoma, carcinoma, or malignant melanoma. Brain invasion is frequently present. However, brain invasion alone is not sufficient for the diagnosis of anaplastic meningioma. *Rhabdoid meningioma* is an uncommon variant that is predominantly composed of so-called rhabdoid cells, i.e., tumor cells with rounded, eosinophilic cytoplasm and an eccentric nucleus. Mitotic activity is usually high in these tumors, and other histologic features of malignancy, such as necroses, are present. The prognostic significance of focal rhabdoid differentiation in an otherwise ordinary meningioma without other signs of malignancy is questionable. A third variant of WHO grade III meningioma, the *papillary meningioma*, is also very rare and seems to occur more commonly in children. Histology shows a cellular meningeal tumor with prominent formation of perivascular pseudorosette-like structures and pseudopapillae (Fig. 12j).

Immunohistochemistry. Meningiomas are generally positive for vimentin and EMA, although EMA expression may sometimes be focal or patchy. Secretory meningiomas show additional expression of cytokeratins and CEA, typically restricted to cells adjacent to pseudo-psammoma bodies. Immunoreactivity for S-100 or CD34 is seen in some cases but generally less widespread and weaker than with schwannomas and solitary fibrous tumors, respectively. More than half of the benign meningiomas express progesterone receptors, while estrogen receptors are rarely detectable. The MIB1 index is generally low (<5%) in benign meningiomas. In contrast, atypical meningiomas usually show increased MIB1 labeling of more than 5%, while anaplastic meningiomas are generally characterized by very high MIB1 expression. However, whether or not elevated MIB1 indices represent an independent prognostic variable in meningiomas that should be used for tumor grading is debated. Therefore, the MIB1 index has not been accepted as a grading criterion in the WHO classification. However, it is recognized that a high proliferation index should be considered as an indicator of a greater likelihood of recurrence and/or aggressive behavior (Table 5).

Differential Diagnosis. The differential diagnosis of meningiomas is rather complex and, depending on the histologic subtype of meningioma, includes a spectrum of different types of benign and malignant neoplasms. For example, fibrous meningiomas need to be distinguished from other spindle-cell tumors, such as schwannoma, solitary fibrous tumor, or smooth muscle tumors. Immunohistochemistry for EMA, S-100, CD34, and smooth muscle actin (SMA) helps to separate these entities. Immunohistochemistry for EMA also allows us to distinguish meningioma from meningeal hemangiopericytoma (see below). The differential diagnosis of chordoid meningioma primarily includes chordoma and chordoid glioma of the third ventricle. Chordomas strongly stain for cytokeratins, while chordoid gliomas are positive for GFAP and CD34. Microcystic meningiomas may be confused with astrocytic gliomas, in particular on frozen section, but are GFAP negative. Clear-cell meningioma lacks immunoreactivity for cytokeratins and thereby differs from metastatic clear-cell carcinoma. Papillary meningiomas usually lack GFAP expression. In contrast, papillary ependymoma and astroblastoma, two important differential diagnoses, are GFAP positive. In occasional cases of lymphoplasmacyte-rich meningioma, the meningeal tumor cells may be difficult to find, hence the differential diagnosis of an inflammatory pseudotumor may arise. On the other hand, plasmacytoma needs to be excluded by demonstrating polyclonal expression of kappa and lambda light chains. Anaplastic meningioma may mimic metastatic carcinoma, sarcoma, or melanoma. Again, thorough immunohistochemical analysis may be necessary to separate these entities.

Molecular Pathology. Meningioma was the first solid neoplasm shown to carry a characteristic cytogenetic alteration, namely monosomy 22. Subsequent studies revealed the *NF2* gene as the primary target on 22q, whose mutation and/or deletion constitutes that most common early event in meningiomas. *NF2* alterations are particularly common in fibroblastic and transitional meningiomas (up to 80% of the cases) but less common in meningothelial meningiomas (approximately 30%). The *NF2* gene product (merlin/schwannomin) belongs to the protein 4.1 family. Recent studies have shown loss of expression of other protein 4.1 molecules in subsets of meningiomas, including protein 4.1B (DAL-1) and protein 4.1R (Perry et al. 2004). The respective genes map to

chromosomal arms frequently deleted in meningiomas (18p and 1p, respectively), but intragenic mutations seem to be rare.

A number of genomic alterations are associated with meningioma progression and atypical or anaplastic histology (Fig. 5), including losses of chromosome arms 1p, 6q, 9p, 10, 14q, and 18q, as well as gains/amplifications on 1q, 9q, 12q, 15q, 17q, and 20q (Perry et al. 2004; Lamszus 2004). The relevant candidate genes on these chromosomes are largely unknown so far. About two-thirds of anaplastic meningiomas demonstrate homozygous deletion, mutation, or promoter hypermethylation of the *CDKN2 A* ($p16^{INK4a}$), $p14^{ARF}$, and *CDKN2B* ($p15^{INK4b}$) tumor suppressor genes on 9p21 (Boström et al. 2001). *CDKN2 A* deletion has been associated with poorer survival in patients with anaplastic meningiomas (Perry et al. 2002). Amplification of genes on 17q23, including the ribosomal protein S6 kinase gene (*RPS6KB1*), is seen in a minor fraction of anaplastic meningiomas (Perry et al. 2004).

Mesenchymal, Non-meningothelial Tumors

This group of tumors consists of a heterogeneous mixture of benign and malignant mesenchymal neoplasms that arise in the meninges or, less commonly, in the CNS parenchyma or choroid plexus. The WHO classification lists different types of lipomatous, fibrous, myogenic, osteocartilaginous, and vascular neoplasms under this category (Table 1). The histologic features of the individual mesenchymal tumor entities correspond to their respective counterparts arising in soft tissues or bone, respectively. For a detailed description of the individual entities, the reader is referred to the WHO classification and the comprehensive textbook by Weiss and Goldblum (2001). Here, we will only address two entities that are important in the differential diagnosis for meningiomas, i.e., *solitary fibrous tumor* and *hemangiopericytoma*.

Solitary Fibrous Tumor

Definition. A usually benign, collagen-rich, spindle-cell tumor with strong immunoreactivity for CD34.

Incidence and Age Distribution. Meningeal solitary fibrous tumors (SFTs) are rare neoplasms of adults.

Macroscopy and Localization. SFT presents as a well-circumscribed, dura-based tumor that cannot be macroscopically distinguished from a meningioma. Most tumors are located intracranially, but spinal, orbital, and paranasal examples are also known. Some SFTs may invade into the adjacent CNS tissue or nerve roots.

Histopathology. Histologically, meningeal SFTs correspond to SFTs in other locations outside the CNS. The tumors are composed of elongated to spindle-shaped cells growing in fascicles in a collagen fiber-rich matrix. Cellular regions often alternate with fibrotic, paucicellular regions. In contrast to meningiomas, whorls and psammoma bodies are absent. Mitotic activity is usually low. However, occasional cases with elevated mitotic rate and histologic features of malignancy have been reported (Tihan et al. 2003).

Immunohistochemistry. SFTs are strongly positive for vimentin and CD34 but lack expression of EMA and S-100.

Differential Diagnosis. SFT needs to be distinguished from fibrous meningioma and meningeal hemangiopericytoma, respectively.

Molecular Pathology. CGH analysis of three meningeal SFTs showed losses involving 3p21-p26 in all 3 cases (Martin et al. 2002). Other imbalances were found on several other chromosomes but generally restricted to individual tumors. Losses on 22q were not detected.

Hemangiopericytoma

Definition. A highly cellular and densely vascularized tumor arising in the meninges. The histologic appearance corresponds to hemangiopericytoma arising in the soft tissues.

Incidence and Age Distribution. Hemangiopericytomas are about 50 times less common than meningiomas. The patient age at diagnosis is lower than with meningiomas, with a peak incidence in the 4th–6th decades. Men are more commonly affected than women.

Macroscopy and Localization. Most hemangiopericytomas are solitary tumors attached to the intracranial or spinal dura. Macroscopically, the tumors are well-demarcated, solid, and firm lesions. The cut surface may appear somewhat lobulated, and numerous vessels as well as intratumoral hemorrhage may be visible.

Histopathology. Light microscopy shows a highly cellular tumor composed of relatively uniform, small, pericyte-like cells with oval nuclei and inconspicuous nucleoli. Mitotic activity is usually low to moder-

ate. The tumor tissue is richly vascularized and contains characteristic slit-like or staghorn-like sinusoidal vessels. The reticulin stain reveals a dense pericellular network of reticulin fibers. Less cellular areas of fibrosis are often present. According to the WHO classification, hemangiopericytomas may correspond to WHO grade II or III. However, the criteria for grading these tumors are not well defined. Increased mitotic activity (5 or more mitoses per 10 high-power fields), high cellularity, nuclear pleomorphism, and the presence of necrotic areas appear to be associated with decreased survival and are indicative of a WHO grade III lesion.

Immunohistochemistry. The dense tumor vascularization is nicely demonstrated by staining for endothelial antigens such as CD31 or factor VIII (von Willebrand). The tumor cells are generally positive for vimentin. Immunoreactivity for EMA is either negative or restricted to focal staining. The majority of hemangiopericytomas show widespread immunostaining for CD99 and Bcl2 (Rajaram et al. 2004). Focal or patchy staining for CD34 is often seen. MIB1 staining is highly variable.

Differential Diagnosis. The principal differential diagnoses include meningioma and solitary fibrous tumor, which are immunohistochemically distinguishable by the strong expression of EMA and CD34, respectively. Strong expression of cytokeratins suggests metastatic carcinoma rather than hemangiopericytoma.

Molecular Pathology. Data on the molecular genetics of hemangiopericytomas are limited (Rajaram et al. 2004). The tumors differ from meningiomas by the absence of *NF2* mutations and chromosome 22 deletions. Homozygous *CDKN2 A* deletion has been detected in about 25% of the cases (Ono et al. 1996). CGH analysis did not reveal any conclusive genomic copy number changes (Miettinen et al. 1997).

Melanocytic Lesions

Definition. A spectrum of benign to malignant melanocytic tumors arising from leptomeningeal melanocytes. Three major lesions are distinguished: (1) *diffuse melanocytosis*, (2) *meningeal melanocytoma*, and (3) *malignant melanoma*.

Incidence and Age Distribution. Primary melanocytic tumors of the meninges are rare neoplasms. *Diffuse melanocytosis* is most common in pediatric patients and may be combined with giant and/or numerous congenital cutaneous nevi (*neurocutaneous melanosis*). Congenital nevus of Ota may also be associated. *Melanocytoma* and *malignant melanoma* may manifest at any age but are preferentially found in adults.

Macroscopy and Localization. Diffuse melanocytosis causes a diffuse thickening and black discoloration of large parts of the intracranial and spinal leptomeninges (Fig. 6j). Melanocytomas are usually solitary, circumscribed tumors attached to the dura mater. Preferential locations of melanocytoma and primary meningeal melanoma include regions where leptomeningeal melanocytes are physiologically present at highest density, such as the base of the brain and posterior fossa, as well as the upper cervical cord.

Histopathology. *Diffuse melanocytosis* is histologically characterized by a diffuse proliferation of uniform melanocytic cells in the leptomeninges. Tumor cells often spread along vessels in the Virchow-Robin spaces. Mitotic activity is low. However, focal progression to malignant melanoma may occur. The morphology of tumor cells in *meningeal melanocytoma* is quite variable, ranging from epithelioid cells growing in a nested pattern to spindle cells forming fascicular architectures. Melanin pigmentation is also variable, with some tumors being heavily melanotic (Fig. 13a) and others containing large amelanotic areas. Nucleoli are usually prominent, but mitotic activity is low. Histologic features of anaplasia are absent. Primary *malignant melanomas* of the meninges histologically resemble melanomas in other locations. In contrast to melanocytomas, the tumors show obvious features of malignancy, including marked cellular and nuclear pleomorphism, high mitotic activity, areas of necrosis and intratumoral hemorrhage, as well as invasion into CNS tissue. *Meningeal melanomatosis* refers to a secondary diffuse subarachnoid tumor spread of a malignant melanoma. Meningeal melanocytic tumors of intermediate grade, i.e. tumors showing transitional features between melanocytoma and melanoma, have been reported (Brat et al. 1999). In addition, occasional melanocytomas may show progression to malignant melanoma on recurrence.

Immunohistochemistry. Melanocytic lesions stain strongly for vimentin and protein S-100. In addition, immunoreactivity for melanocytic markers such as melan A and HMB-45 is usually present. The MIB1 index is low in melanocytoma and diffuse melanocytosis but high in malignant melanoma.

Differential Diagnosis. Melanocytoma is distinguished from primary or metastatic malignant melanoma by its low mitotic activity and the absence of other histologic signs of anaplasia. The differen-

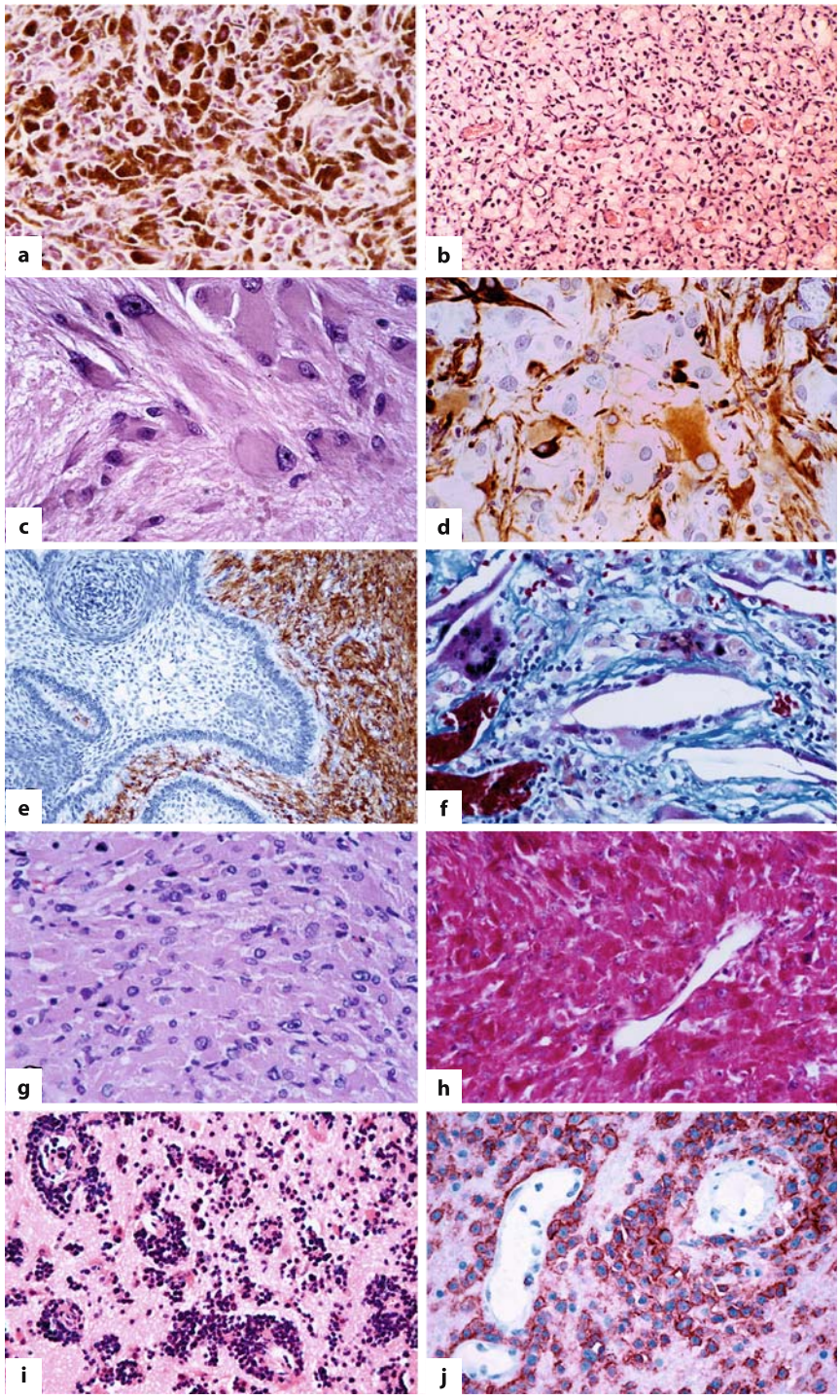


Fig. 13. Histology of selected other types of CNS tumors. **a** Meningeal melanocytoma composed of isomorphic melanocytic cells with abundant melanin pigmentation (H&E). **b** Capillary hemangioblastoma (WHO grade I). On H&E, these tumors are characterized by vacuolated stromal cells located in a dense network of capillary vessels (H&E). **c** Subependymal giant-cell astrocytoma (WHO grade I). Histology shows a moderately cellular tumor composed of astrocytic cells with abundant eosinophilic cytoplasm and enlarged ganglion cell-like nuclei (H&E). **d** Variable expression of GFAP in a subependymal giant-cell astrocytoma. **e** Adamantinous craniopharyngioma (WHO grade I) pushing towards the adjacent brain tissue, which shows a strongly GFAP-positive reactive gliosis (*right side*). The actual craniopharyngioma tissue (*left side*) is GFAP negative. **f** Xanthogranuloma of the sellar region. This lesion is characterized by a chronic inflammatory reaction with foreign-body giant ▶

tial diagnosis between melanocytoma and melanotic schwannoma relies on the presence of areas with typical schwannoma features and a dense pericellular reticulin network in the latter tumors. Histology and immunohistochemistry cannot reliably distinguish between a primary meningeal melanoma and a melanoma metastasis.

Tumors of the Hematopoietic and Lymphoid System

The nervous system may be affected by a variety of lymphoid and hematopoietic tumors. This chapter will specifically focus on malignant lymphomas manifesting primarily in the CNS as well as a number of less common histiocytic lesions that may affect the CNS and its coverings. In addition to primary CNS lymphomas, systemic lymphomas and leukemias may secondarily involve the nervous system by metastatic spread or continuous growth from adjacent structures. These secondary tumor manifestations prefer the dura and meninges, while intraparenchymal CNS seeding from systemic lymphomas or leukemias is rare.

Primary Central Nervous System Lymphoma (PCNSL)

Definition. PCNSLs are extranodal, malignant lymphomas arising in the CNS without any lymphoma manifestation in other organs at the time of diagnosis. The vast majority of PCNSLs are highly malignant B-cell lymphomas while primary T-cell lymphomas are rare.

Incidence and Age Distribution. PCNSLs are estimated to account for 2–6% of all primary intracranial neoplasms. Several studies have reported an increasing incidence of PCNSLs over the past few decades. The incidence of sporadic PCNSLs in immunocompetent patients reaches a peak in the 6th and 7th decade. PCNSLs arising in immunodeficient patients more commonly affect younger individuals.

Macroscopy and Localization. The majority of PCNSLs present as supratentorial, homogenously contrast-enhancing lesions located in the deep white matter that often abut the ventricular walls. Multiple intracerebral lesions are commonly seen. The macroscopic appearance of PCNSL is highly variable, ranging from rather well-circumscribed masses to diffusely growing lesions with indistinct borders. Areas of necrosis are more common in AIDS-associated PCNSLs than in sporadic tumors.

Histopathology. The vast majority of PCNSLs (>95%) are highly malignant non-Hodgkin lymphomas of B-cell type, morphologically corresponding to *diffuse large B-cell lymphomas* according to the WHO classification of tumors of hematopoietic and lymphoid tumors (Gatter and Warnke 2001). Rare cases corresponding to *Burkitt's lymphoma*, *large-cell anaplastic lymphoma* (Ki-1 lymphoma) or *T-cell lymphoma* have also been reported. Primary intracerebral *Hodgkin lymphoma* is a rarity. *Intravascular lymphomatosis* represents a rare form of mostly B-cell lymphomas characterized by largely intravascular tumor growth, often with predominant involvement of cerebral vessels. *Primary low-grade B-cell lymphoma of the dura* is a rare meningial tumor showing histologic and biologic similarities to the mucosa-associated lymphoid tissue-type (MALT) lymphoma.

Typical PCNSLs are highly cellular tumors composed of lymphoid blasts with enlarged nuclei and often prominent nucleoli. The tumor cells grow in perivascular cuffs and solid sheets blending into a diffuse infiltration of the adjacent brain parenchyma. Mitotic activity is high. Reactive changes are common, including marked reactive astrogliosis and sometimes prominent infiltrates consisting of small T-cells.

PCNSL is usually diagnosed by means of stereotactic biopsy. Preoperative corticosteroid treatment should be avoided because the tumor cells rapidly undergo apoptosis after treatment. Thus, biopsies taken after corticosteroid treatment may remain diagnostically inconclusive because the tumor cells have disappeared, leaving only reactive infiltrates consisting of macrophages and small T-cells remaining.

About one-third of PCNSLs show tumor cell dissemination into the cerebrospinal fluid (CSF). Thus, cytologic and immunocytochemical investigation of CSF may help to establish the diagnosis.

cells, hemorrhages, and cholesterol clefts (Masson trichrome stain). **g,h** Granular cell tumor of the neurohypophysis (WHO grade I). The H&E stain (**g**) shows a moderately cellular neuroepithelial tumor composed of isomorphic cells with somewhat granular cytoplasm. The tumor cells are strongly PAS positive (**h**). **i,j** Primary intracerebral malignant non-Hodgkin lymphoma (PCNSL). On H&E (**i**), the tumor shows angiocentric growth within the brain parenchyma. Immunohistochemically, PCNSL are usually positive for the B-cell marker CD20 (**j**)

Immunohistochemistry. The vast majority of PCNSLs are positive for B-cell markers, such as CD20, while expression of the T-cell markers (CD3) is restricted to small reactive T-cells. Proliferative activity is high, with MIB1 indices often exceeding 50%. PCNSLs arising in immunocompromised patients are frequently positive for Epstein-Barr virus (EBV) antigens. In contrast, sporadic tumors rarely stain positive for EBV.

Differential Diagnosis. Immunohistochemical analysis allows for the distinction of PCNSLs from malignant gliomas and other malignant tumors, such as small-cell carcinomas and malignant melanomas. In cases treated with corticosteroids, the differential diagnosis of infarction or demyelinating disease may sometimes be difficult. PCNSLs arising in immunosuppressed patients need to be distinguished from opportunistic infections, such as toxoplasmosis or progressive multifocal leukoencephalopathy. Metastatic spread of systemic lymphomas usually involves the leptomeninges, dura, and/or epidural space, while intraparenchymal CNS metastases from systemic lymphomas are uncommon.

Molecular Pathology. Molecular analyses have revealed that most PCNSLs are derived from highly mutated germinal center B-cells homing to the CNS. The tumor cells show a preferential usage of the immunoglobulin V4–34 gene segment and are targeted by aberrant somatic hypermutation (Montesinos-Rongen et al. 1999, 2004). Homozygous deletion or promoter hypermethylation of *CDKN2 A* is frequent, while *TP53* mutations are rare (Cobbers et al. 1998). Both sporadic and AIDS-associated tumors often show *BCL6* mutations (Larocca et al. 1998). Furthermore, PCNSLs frequently demonstrate deletions on the long arm of chromosome 6, which appear to be associated with a shorter survival (Rickert et al. 1999; Nakamura et al. 2003).

Histiocytic Lesions Affecting the CNS and Its Coverings

Definition. A heterogeneous group of lesions composed of histiocytic cells, including Langerhans cell histiocytosis and various forms of non-Langerhans cell histiocytoses.

Incidence and Age Distribution. The majority of histiocytic lesions involving the CNS and its coverings are rare and preferentially occur in children and young adults. An exception is the so-called xanthogranuloma of the choroid plexus, which is a common incidental finding at autopsy but usually remains asymptomatic during the patient's lifetime. Erdheim-Chester disease is a rare non-Langerhans cell histiocytosis that preferentially manifests in adults.

Langerhans Cell Histiocytosis

Macroscopy and Localization. Langerhans cell histiocytosis (LCH) comprises a spectrum of diseases ranging from solitary benign lesions to a disseminated disease with visceral involvement and poor outcome. Most commonly, LCH presents in the form of solitary or multifocal osteolytic lesions of the skull (*eosinophilic granuloma*). *Hand-Schüller-Christian disease* refers to multifocal LCH involving bones and the hypothalamus. *Abt-Letterer Siwe disease* is a multifocal LCH involving lymph nodes, skin, and viscera. The most common intracranial location of LCH is the hypothalamus and infundibulum, often resulting in the development of diabetes insipidus. Rarely, LCH presents with lesions in the cerebral hemispheres, choroid plexus or brain stem. Macroscopically, eosinophilic granuloma appears as an osteolytic, soft, gray-tan to yellow lesion that extends through the skull bone.

Histopathology. LCH lesions are composed of a mixture of different cell types, including large, pleomorphic histiocytes (Langerhans cells) with folded and indented nuclei. These are accompanied by a reactive inflammatory infiltrate consisting of eosinophils, lymphocytes, and plasma cells. Foamy macrophages are also commonly present. Occasional multinucleated giant cells may also be observed. Long-standing and regressing eosinophilic granulomas may be largely fibrotic.

Immunohistochemistry. The Langerhans cells are positive for vimentin, S-100, and CD1a.

Differential Diagnosis. The differential diagnosis includes the various forms of non-Langerhans cell histiocytoses (see below) as well as other xanthomatous or xanthogranulomatous lesions. Occasional cases of eosinophilic granuloma may be heavily infiltrated by polymorphonuclear leukocytes, thereby raising the differential diagnosis of acute osteomyelitis.

Molecular Pathology. LCH is thought to be caused by an uncontrolled clonal proliferation of immature dendritic cells with Langerhans cell characteristics (Laman et al. 2003). Various chromosomal imbalances have been detected by CGH analysis of LCH lesions in the bone, but no consistent genetic defect has been identified (Murakami et al. 2002).

Non-Langerhans Cell Histiocytoses

The non-LCH comprise a heterogeneous group of lesions showing macrophage but no Langerhans cell differentiation. The WHO classification lists the following entities under this category that may present with CNS involvement: *Rosai-Dorfmann disease, Erdheim-Chester disease, familial hemophagocytic lymphohistiocytosis, juvenile xanthogranuloma, xanthoma disseminatum*, and *choroid plexus xanthogranuloma. Rosai-Dorfmann disease* typically presents as an intracranial, dural-based mass mimicking a meningioma. The prognosis is good after resection. The classic clinical features of the disease, i.e., cervical lymphadenopathy, fever, and weight loss, are present in only a subset of the patients with intracranial lesions. *Erdheim-Chester disease* develops preferentially in adults and can involve multiple organs. Intracranial lesions are most commonly located in the cerebellum, the pituitary region, and the meninges. Spinal and orbital manifestations are also known. *Familial hemophagocytic lymphohistiocytosis* is a rare autosomal recessive disorder characterized by excessive immune activation. Aberrantly activated T-lymphocytes and macrophages infiltrate multiple organs including the CNS, resulting in a rapidly progressive multisystem disorder of early infancy. Without treatment (bone marrow transplantation), median survival is in the range of only 2 months. The disease is caused by germline mutations in different genes, including perforin 1 (PRF1) on 10q22 (Stepp et al. 1999) and *MUNC13–4* on 17q25 (Feldmann et al. 2003). *Juvenile xanthogranuloma* usually presents as a solitary skin nodule in children, but visceral involvement may occur, including the brain and meninges, even in the absence of any cutaneous manifestation (Boström et al. 2000). *Xanthoma disseminatum* refers to lesions composed of lipidized (xanthomatous) histiocytes and is associated with generalized hyperlipidemia. Intracranial lesions are preferentially located in the pituitary/hypothalamic region or associated with the dura mater. *Choroid plexus xanthogranuloma* are intraventricular lesions, most commonly located in the lateral ventricles, which may rarely become symptomatic by obstructing CSF flow. Microscopy shows a granulomatous lesion composed of foamy macrophages, chronic inflammatory infiltrates, cholesterol clefts, and foreign-body giant cells. In contrast, *choroid plexus xanthoma* consists only of foamy macrophages.

Germ-Cell Tumors of the CNS

Definition. Tumors arising in the central nervous system that are homologous to germ-cell tumors in the gonads or in extragonadal sites outside the CNS.

The histologic classification of CNS germ-cell tumors follows the classification of gonadal germ-cell neoplasms, with the following entities being distinguished: *germinoma, embryonal carcinoma, endodermal sinus tumor (yolk sac tumor), choriocarcinoma, mature teratoma, immature teratoma, teratoma with malignant transformation* and *mixed germ-cell tumor.*

Incidence and Age Distribution. In western countries, CNS germ-cell tumors account for less than 0.5% of all primary brain tumors. In Asia, their incidence is markedly higher. For example, germ-cell tumors account for up to 3% of all primary intracranial tumors in Japan. CNS germ-cell tumors most frequently develop in children and young adults, with an incidence peak between 10–12 years of age. Overall, males are approximately twice as often affected as females. Germinoma accounts for up to 50% of all germ-cell tumors in the pineal region and thus is the most common type of intracranial germ-cell tumor.

Macroscopy and Localization. Germ-cell tumors preferentially develop in midline structures of the CNS, with more than 80% of the cases arising in the pineal and third ventricular region. Other sites include the suprasellar region, basal ganglia, thalamus, cerebral hemispheres, and spinal cord. Multifocal tumors often involve both the pineal and suprasellar regions. The macroscopic appearance depends on the type of germ-cell tumor.

Histopathology. The typical histologic features of the various germ-cell tumor types can be summarized as follows:

- *Germinomas* are the CNS homologues to testicular seminomas and ovarian dysgerminomas, respectively. They are typically composed of two cell populations, large neoplastic cells and small reactive lymphocytes. The large tumor cells are relatively uniform, round cells with large vesicular nuclei, prominent nucleoli and pale, often vacuolated, glycogen-rich (PAS-positive) cytoplasm. Mitoses are frequent while necroses are uncommon. The tumor tissue is traversed by fibrous septa that are densely infiltrated by reactive lymphocytes, mostly T-cells. Some germinomas demonstrate a prominent granulomatous inflammation, in which the actual germinoma cells may be difficult to identify. Occasionally, syncytiotrophoblastic giant cells are present in otherwise typical germinomas.
- *Yolk sac tumors* (synonym: *endodermal sinus tumors*) are highly malignant germ-cell tumors composed of primitive epithelial cells in a myxoid matrix. Formation of so-called *Schiller-Duval bodies* is a characteristic finding. These are small

glomeruloid or papillae-like structures formed by small vessels covered with epithelium and projecting into epithelium-lined channels resembling endodermal sinuses. The presence of eosinophilic hyaline bodies that are PAS positive and strongly react with antibodies against alpha-fetoprotein is another diagnostically important feature of yolk sac tumors.

- *Embryonal carcinomas* consist of large, cuboidal to columnar epithelial cells that grow in sheets or cords and may form abortive papillae or gland-like structures. The tumor cell nuclei are enlarged and contain prominent nucleoli. Mitotic activity is high and areas of coagulation necrosis are common. Formation of so-called embryoid bodies showing early embryonic or extraembryonic differentiation is occasionally seen.
- *Choriocarcinomas* are highly malignant tumors that demonstrate extra-embryonic differentiation as evidenced by the presence of malignant cytotrophoblastic cells and syncytiotrophoblastic giant cells. Choriocarcinomas often show large areas of hemorrhagic necrosis and are prone to intratumoral bleedings.
- *Teratomas* are germ-cell tumors that contain areas corresponding to endodermal, mesodermal and ectodermal differentiation. Mature teratomas are benign tumors with low or absent mitotic activity that are composed of fully differentiated tissues derived from all three germ layers, including most commonly skin and brain tissue (ectodermal derivatives), cartilage, bone, fat and muscle (mesodermal derivatives), and cystic structures lined by enteric or respiratory epithelia (endodermal derivatives). More frequent among the CNS germ-cell tumors are *immature teratomas*, which are characterized by the presence of incompletely differentiated, embryonic or fetal tissues. Most commonly observed are hypercellular stromal areas resembling immature mesenchyme as well as highly cellular primitive neuroectodermal tissue, often with formation of neuroepithelial rosettes or canals. *Teratoma with malignant transformation* refers to a teratoma that gives rise to the development of a malignant cancer of somatic type, most commonly a sarcoma, such as rhabdomyosarcoma or not otherwise specified sarcoma, and less commonly a squamous cell carcinoma or an adenocarcinoma.
- *Mixed germ-cell tumors* are composed of more than one of the different entities listed above. Such mixed tumors are not uncommon among the CNS germ-cell neoplasms. Since both sensitivity to therapy and prognosis differ markedly between the different germ-cell tumor entities, it is important to identify mixed lesions. In particular, pure germinomas show a markedly better outcome as compared to germinomas containing a malignant non-germinomatous tumor component. When intracranial germ-cell tumors are diagnosed by means of stereotactic biopsy, one has to be aware of the risk of missing small non-germinomatous areas in a germinoma, or small malignant areas in an otherwise well-differentiated teratoma.

Immunohistochemistry. Germinomas are positive for placental alkaline phosphatase (PLAP). However, PLAP positivity may also be seen in other malignant germ-cell tumors, such as embryonal carcinoma and, less consistently, yolk sac tumor and choriocarcinoma. Germinomas also demonstrate frequent overexpression of c-kit. Focal or patchy immunoreactivity for cytokeratins is not infrequent in intracranial germinomas. Syncytiotrophoblastic giant cells are characterized by expression of beta-HCG. Yolk sac tumors are positive for alpha-fetoprotein and cytokeratins. Useful diagnostic markers for embryonal carcinomas include cytokeratins, PLAP, CD30 and OCT4 (POU5F1). Choriocarcinomas are also positive for cytokeratins and express beta-HCG and human placental lactogen.

Differential Diagnosis. Germ-cell tumors of the pineal region need to be distinguished from pineal parenchymal neoplasms. Histologically, this distinction is usually no problem. The distinction of malignant germ-cell tumors as well as the identification of mixed variants requires immunohistochemical analyses as detailed above. Similarly, immunohistochemistry allows for the distinction of embryonal carcinomas and choriocarcinomas from metastases of somatic carcinomas.

Molecular Pathology. Gains of hypomethylated, active X chromosomes have been detected in the vast majority of intracranial germ-cell tumors, regardless of histologic subtype, while gains of 12p, including formation of isochromosome 12p, and losses on 13q were found to be restricted to subsets of the cases (Okada et al. 2002). One study reported on frequent homozygous deletion of the *CDKN2 A/p14^{ARF}* locus in intracranial germ-cell tumors (Iwato et al. 2000a), while another paper did not confirm this finding (Okada et al. 2002). *TP53* mutation or *MDM 2* amplification have been detected in small fractions of intracranial germ-cell neoplasms (Iwato et al. 2000b). More recent studies identified frequent mutations in the proto-oncogene *c-KIT* in testicular seminomas and intracranial germinomas (Kemmer et al. 2004; Sakuma et al. 2004). The corresponding gene product is overexpressed in most germinomas and thus can serve as a diagnostic marker as well as a potential therapeutic target.

Familial Tumor Syndromes

The majority of tumors of the nervous system are sporadic lesions that arise in patients without an obvious hereditary predisposition to cancer. However, there are a number of familial tumor syndromes that are associated with a markedly increased risk of nervous system tumors. The most prominent examples are: *neurofibromatosis type 1* (NF1) and *neurofibromatosis type 2* (NF2), *tuberous sclerosis, von Hippel-Lindau syndrome, Li-Fraumeni syndrome, Cowden syndrome, Turcot syndrome* and *nevoid basal cell carcinoma syndrome (Gorlin syndrome)*. The genes responsible for each of these syndromes have been identified and characterized during the past decade. The fact that most of these diseases may present with characteristic manifestations outside the nervous system, in particular skin abnormalities, is of major clinical relevance because the presence of such signs and symptoms helps to identify patients with hereditary cancer predisposition, which of course is of paramount importance concerning aspects of prevention and genetic counseling. Table 6 provides an overview of the responsible genes, the associated CNS and PNS lesions, as well as other characteristic clinical features of the major familial tumor syndromes involving the nervous system. A detailed account of the pathogenetic and clinicopathologic characteristics of each syndrome is beyond the scope of this chapter, and the interested reader is referred to the WHO classification (Kleihues et al. 2000) and a more recent review article (Melean et al. 2004). Here, we will specifically focus on three tumor entities, namely *subependymal giant- cell astrocytoma, capillary hemangioblastoma,* and *dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos),* which are associated with tuberous sclerosis, von Hippel-Lindau syndrome, and Cowden syndrome, respectively.

Subependymal Giant-Cell Astrocytoma (WHO Grade I)

Definition. A benign, well-demarcated tumor consisting of large, astrocytic tumor cells with ganglioid features. Subependymal giant-cell astrocytomas (SEGAs) typically arise in the ventricular wall of the lateral ventricles near the foramen of Monro. SEGAs are closely associated with tuberous sclerosis, although occasional cases may occur in the absence of clinical and radiologic features of the syndrome.

Incidence and Age Distribution. SEGAs most commonly manifest in the first two decades of life. It is estimated that approximately 6% to 16% of patients with tuberous sclerosis develop SEGAs.

Macroscopy and Localization. The tumors are located in the wall of the lateral ventricles, typically in the region of the foramen of Monro. Hydrocephalus caused by blockade of the foramen of Monro is a common feature. Macroscopically, SEGAs are discrete intraventricular masses that frequently contain areas with calcifications. The tumors are well vascularized, and spontaneous intratumoral hemorrhage is not infrequent.

Histopathology. SEGAs are circumscribed, moderately cellular tumors composed of pleomorphic, large, astrocytic cells having abundant glassy eosinophilic cytoplasm and round ganglioid nuclei with distinct nucleoli (Fig. 13c). In addition, somewhat smaller spindle cells growing in streams are commonly encountered. Multinucleated cells may be present, but true giant cells are rare. Formation of perivascular pseudorosettes mimicking ependymal pseudorosettes is sometimes seen. Calcification is common. Mitotic activity is usually low. However, some cases show increased mitotic activity, but this does not appear to be associated with malignant behavior. Similarly, the occasional presence of necrotic areas does not imply malignant behavior.

Immunohistochemistry. The tumor cells show variable expression of glial (GFAP, S-100) and/or neuronal markers (synaptophysin, neurofilaments) (Fig. 13d). The MIB1 index is usually low (<5%).

Differential Diagnosis. Due to their distinctive morphologic and immunohistochemical features, the differential diagnosis of SEGA is limited. The tumors primarily need to be distinguished from diffuse astrocytic gliomas, in particular gemistocytic astrocytomas and giant-cell glioblastomas. Patients diagnosed with a SEGA should be clinically checked for the presence of other manifestations of tuberous sclerosis, if not already known to have the syndrome.

Molecular Pathology. SEGAs are characterized by biallelic inactivation of either the *TSC1* or the *TSC2* tumor suppressor gene (Chan et al. 2004). Inactivation of these tuberous sclerosis genes leads to aberrant activation of signaling via the mTOR kinase, which in turn represents an interesting novel target for specific pharmacologic inhibition. Chromosomal imbalances detectable by CGH are rare or absent in SEGAs (Rickert and Paulus 2002).

Capillary Hemangioblastoma (WHO Grade I)

Definition. A benign tumor of uncertain histogenesis composed of so-called stromal cells and a dense capillary network.

Table 6. Familial tumor syndromes of the nervous system

Syndrome	Gene	Chromosome	CNS manifestations	Skin lesions	Lesions in other organs	Nervous system tumors
Tuberous sclerosis complex	*TSC1* *TSC2*	9q34 16p13	Cortical tubers, subependymal nodules, white matter hamartomas, epilepsy, mental retardation	Facial angiofibroma (adenoma sebaceum), shagreen patch, forehead plaque, peri- & subungual fibromas	Cardial rhabdomyoma, renal angiomyolipoma, renal cysts, liver hamartoma, retinal hamartoma, hypopigmented iris spot	Subependymal giant-cell astrocytoma
Neurofibromatosis type 1	*NF1*	17q11	Tumors (see there), aqueduct stenosis, epilepsy, learning deficits	Neurofibromas, café-au-lait spots, axillary/inguinal freckling	Osseous malformations, Lisch nodules, pheochromocytoma, juvenile CML, rhabdomyosarcoma	Neurofibromas, plexiform neurofibroma, MPNST, malignant triton tumor, optic glioma, pilocytic astrocytoma, less commonly diffuse astrocytoma
Neurofibromatosis type 2	*NF2*	22q12	Glial microhamartomas, cerebral calcifications, meningioangiomatosis, spinal schwannosis	No	Posterior lens opacities, retinal hamartomas	Bilateral vestibular schwannoma, spinal root schwannoma, meningiomas, spinal ependymoma, astrocytoma
von Hippel-Lindau syndrome	*VHL*	3p25	Hemangioblastomas	No	Renal cell carcinoma, pheochromocytoma, endolymphatic sac, tumor, pancreatic cysts, kidney cysts	Hemangioblastoma (cerebellar, retinal, brain stem, spinal or multiple)
Cowden syndrome	*PTEN*	10q23	Megalencephaly, gray matter heterotopias	Multiple trichilemmomas, fibromas	Colon polyps, breast & thyroid carcinomas	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos)
Gorlin syndrome (nevoid basal cell carcinoma syndrome)	*PTCH*	9q31	Intracranial (dural), calcifications, dysgenesis of corpus callosum	Multiple basal cell carcinomas, palmar & plantar pits, epidermal cysts	Odontogenic keratocysts, keletal malformations, sovarian fibroma	Desmoplastic medulloblastoma

▼

Table 6. (Continued)

Syndrome	Gene	Chromosome	CNS manifestations	Skin lesions	Lesions in other organs	Nervous system tumors
Turcot syndrome	*APC*	5q21	Tumors (see there)	-	Multiple colon polyps, colon carcinoma	Mostly medulloblastoma
	HMLH1[a] *HPSM2*[a]	3p21 7p22	Tumors (see there)	Café-au-lait spots	Colon carcinoma	Mostly glioblastoma
Li-Fraumeni syndrome	*TP53*	17p13	Tumors (see there)	-	Breast carcinoma, sarcomas, leukemias, other cancers	Astrocytic glioma, PNETs/ medulloblastoma, choroid plexus carcinoma

[a] DNA mismatch repair genes

Incidence and Age Distribution. Capillary hemangioblastomas account for less than 2% of all intracranial neoplasms. The tumors usually manifest in adults, with a peak incidence between the third and fifth decade. Approximately 25%–30% of capillary hemangioblastoma patients have von Hippel-Lindau (VHL) syndrome, with tumors in VHL patients more commonly arising before the age of 30 years. Because of the association with VHL syndrome, it is recommended that all capillary hemangioblastoma patients should be screened for clinical and radiological features of this syndrome. In addition, it has been suggested that genetic testing for *VHL* gene mutation should be offered to capillary hemangioblastoma patients who are younger than 50 years (Hes et al. 2000).

Macroscopy and Localization. The vast majority of capillary hemangioblastomas (>85% of the cases) are located in the cerebellum. Other less common sites include the brain stem and spinal cord. Supratentorial hemangioblastomas are rare. The combination of retinal and cerebellar hemangioblastomas is a characteristic feature of VHL syndrome. Multiple hemangioblastomas located at various sites in the CNS may also be found in this syndrome. Macroscopically, capillary hemangioblastomas typically present as a well-demarcated, large cyst with a densely vascularized, red or yellow tumor nodule attached to the cyst wall.

Histopathology. Microscopically, hemangioblastomas are composed of two principal components: a dense network of vascular channels, mostly capillaries, and so-called stromal or interstitial cells, which represent the actual tumor cells (Fig. 13b). They are characterized by a relatively large, often lipidized (vacuolated) cytoplasm. Nuclear pleomorphism may be prominent, but mitoses are rare or absent. Mast cells are commonly observed, and some tumors may demonstrate foci of intratumoral erythropoiesis. Cystic degeneration is commonly seen, as are areas of fibrosis. The brain parenchyma adjacent to the tumor often shows marked reactive gliosis. Depending on the abundance of stromal cells, cellular and reticular histologic variants may be distinguished.

Immunohistochemistry. The stromal cells are positive for S-100, neuron-specific enolase, and vimentin but negative for cytokeratins and EMA. In addition, EGFR and its ligand TGF-α are strongly coexpressed by the stromal cells. Focal staining for erythropoietin may be observed in some cases. The dense vasculature is highlighted by staining for endothelial markers such as CD31 or CD34. The MIB1 index is generally low.

Differential Diagnosis. On frozen sections, capillary hemangioblastoma may sometimes be difficult to distinguish from a glioma. In addition, the cerebellar tissue adjacent to a capillary hemangioblastoma may demonstrate a marked pilocytic gliosis, which should not be mistaken for a pilocytic astrocytoma. The cellular variant of hemangioblastoma needs to be distinguished from a clear-cell carcinoma metastasis. Immunoreactivity for cytokeratins and EMA indicates a carcinoma metastasis and excludes capillary hemangioblastoma.

Molecular Pathology. Germline mutations in the *VHL* gene have been detected in the vast majority of hereditary (VHL-associated) capillary hemangioblastomas (Glasker et al. 2001). Somatic *VHL* mutations were found in about one-third of sporadic cases (Oberstrass et al. 1996; Lee et al. 1998; Glasker et al. 2001). Interestingly, VHL gene alterations are restricted to the stromal cells, supporting the hypothesis that these cells are the neoplastic elements in capillary hemangioblastomas (Lee et al. 1998). Loss of VHL protein function in the stromal cells leads to stabilization of hypoxia-inducible factors (HIFs) and constitutive upregulation of HIF-regulated genes, including the genes for vascular endothelial growth factor (VEGF) and erythropoietin (Krieg et al. 1998). The receptors for VEGF, i.e., VEGFR-1 and VEGFR-2, are expressed on the capillary endothelial cells, suggesting that angiogenesis and cyst formation in hemangioblastomas are stimulated via a paracrine mechanism (Wizigmann-Voos et al. 1995). Other genetic alterations detected in capillary hemangioblastomas include losses on chromosome arms 6q and 22q (Lemeta et al. 2004; Beckner et al. 2004).

Dysplastic Gangliocytoma of the Cerebellum (WHO Grade I)

Definition. Dysplastic gangliocytoma of the cerebellum (synonym: Lhermitte-Duclos disease, LDD) is a benign mass lesion of the cerebellum leading to a massive enlargement of the affected cerebellar folia. Histologically, the lesion is composed of large dysplastic ganglion cells replacing and expanding the internal granular layer.

Incidence and Age Distribution. LDD is a rare disease that can be familial or, more commonly, sporadic. Most patients present in the second or third decade of life with cerebellar symptoms and/or signs of increased intracranial pressure due to obstructive hydrocephalus.

Macroscopy and Localization. The lesion is usually confined to one cerebellar hemisphere which shows

a diffuse hypertrophy with thickened cerebellar folia (Fig. 6i).

Histopathology. Histology reveals a diffuse replacement of the internal granule cells by enlarged dysplastic neurons resembling small ganglion cells. Thereby, the layer's thickness increases up to several-fold. The Purkinje cell layer may also be affected and replaced by the dysplastic neurons. In addition, abnormal bundles of myelinated fibers extend from the internal granule cell layer to the molecular layer. Thus, the affected folia show a very distinctive morphology referred to as 'inverted cerebellar cortex'. Calcifications may be present within the lesion.

Immunohistochemistry. The dysplastic neurons are positive for neuronal markers (synaptophysin, neurofilaments) and usually show complete or partial loss of Pten expression accompanied by elevated phosphorylated Akt (Zhou et al. 2003).

Differential Diagnosis. Dysplastic gangliocytoma of the cerebellum differs from a conventional ganglion cell tumor by its confinement to the internal granule cell layer.

Molecular Pathology. Patients with LDD often show additional features of Cowden syndrome, which is caused by germline mutations in the *PTEN* gene. Accordingly, the vast majority of LDD patients also carry *PTEN* germline mutations (Zhou et al. 2003). Thus, LDD patients should be counseled similarly to patients with Cowden disease.

Tumors of the Sellar Region

Craniopharyngioma (WHO Grade I)

Definition. A benign epithelial tumor of the sellar region related to Rathke's pouch, occurring in two clinically, genetically, and pathologically distinct forms: adamantinomatous and papillary.

Incidence and Age Distribution. Craniopharyngioma represents 3% of all intracranial tumors and 5–10% of pediatric intracranial tumors. Adamantinomatous craniopharyngioma occurs in all age groups, while the papillary form is virtually restricted to adults.

Macroscopy and Localization. Adamantinomatous craniopharyngioma is most commonly localized in the suprasellar region (95%), with most tumors comprising an additional intrasellar component. A purely intrasellar location is found in only 5% of cases. Papillary craniopharyngioma typically involves the third ventricle. Only the adamantinomatous form is frequently cystic and calcified.

Histopathology. *Adamantinomatous craniopharyngioma* (Fig. 13e) resembles odontogenic tumors, particularly calcifying odontogenic cyst and ameloblastoma. A basal layer of palisading cuboidal tumor cells merges with stratified epithelial cells arranged in a reticular pattern. Cuboidal cells form tubuli and larger cysts. The upper layers of the epithelium undergo keratinization, typically with recognizable cell borders, and calcification. Cholesterol clefts may occur, but they are more typical of xanthogranuloma of the sellar region. *Papillary craniopharyngioma* shows multilayered squamous epithelial cells covering fibrovascular cores. Infiltration of neutrophilic granulocytes among epithelial cells is common, whereas keratinization and calcification are absent.

Immunohistochemistry. Given the distinct histologic appearance, immunostaining is not required for making the diagnosis of craniopharyngioma. Like all epithelial tumors, they are positive for cytokeratins. In line with their odontogenic appearance, adamantinomatous but not papillary tumors express enamel proteins (amelogenin, enamelin, enamelysin). MIB1 proliferation indices are relatively high for a benign tumor with a mean of 9%, but they are not strictly related to recurrence.

Differential Diagnosis. *Xanthogranuloma of the sellar region* (Fig. 13f) is to be differentiated from craniopharyngioma. These lesions, histologically composed of cholesterol clefts, xanthoma cells, chronic inflammatory cells, necroses, hemosiderin deposits, and occasionally a few epithelial cells, are typically intrasellar masses of young adults.

Molecular Pathology. Numerical chromosomal changes have been found in a minority of adamantinomatous craniopharyngiomas, while the papillary tumors studied so far showed a normal karyotype. Most adamantinomatous craniopharyngiomas contain mutations in the β-catenin gene (*CNNTB1*) that lead to overexpression of β-catenin (Kato et al. 2004).

Pituitary Adenoma

Definition. Benign epithelial tumors derived from secretory cells of the adenohypophysis, which are classified according to their immunohistochemical expression pattern of hormones.

General comment. Pituitary adenomas were included in the 1979 and 1993 editions but not in the 2000 edition of the WHO classification of tumors of the

nervous system. However, since pituitary adenomas are among the most common brain tumors encountered by neuropathologists, their most important pathologic features will be briefly summarized here.

Incidence and Age Distribution. In autopsy and MRI series, pituitary adenomas occur in up to 25% of the general population, the vast majority being asymptomatic. Symptomatic tumors are much rarer and account for approximately 10% of surgically resected intracranial tumors. They usually occur in adults, with only 5% being diagnosed before the age of 20 years.

Macroscopy and Localization. Based on tumor size and amount of local invasion, pituitary adenomas are classified into four grades. Grade I includes microadenomas (<10 mm diameter) within the pituitary, grade II includes intrapituitary tumors with a diameter of 10 mm or more, grade III shows local extension with erosion of the osseous sella, and grade IV involves extrasellar structures such as the cavernous sinus or the hypothalamus.

Histopathology. Tumor cells usually show a monomorphic, round or oval nucleus, and well-delineated cytoplasm. The tinctorial properties of the cytoplasm no longer represent the basis for histologic classification, but typically they are to some degree correlated with immunohistochemistry in that eosinophilic cells often express hGH, basophilic cells often express ACTH, and 'chromophobic' cells may express prolactin, gonadotrophins, or no routinely detectable hormone. Mitotic figures are rare. Common histologic patterns include small-cell nests surrounded by capillaries, trabecules, pseudopapillae, or perivascular pseudorosettes. Some histologic features are typical for but not specific to certain immunohistochemical subtypes. Invasion of the meninges is common and does not reflect increased aggressiveness.

Immunohistochemistry. Tumor cells express neuronal and neuroendocrine antigens such as chromogranin and synaptophysin. The expression of hormones of the pituitary gland forms the basis of adenoma subtyping. Gonadotroph adenomas are positive for FSH and/or LH, corticotroph adenomas for ACTH, thyrotroph adenomas for TSH, lactotroph adenomas for prolactin, and somatotroph adenomas for hGH (STH). Adenomas expressing both hGH and prolactin have previously been classified into acidophilic stem-cell adenoma, mammosomatotroph adenoma, and mixed somatotroph/lactotroph adenoma based on electron microscopy, but this has been largely abandoned given the lack of clinical relevance. Plurihormonal adenomas express various combinations of hormones. All of these adenoma types may be associated with endocrine manifestations (clinically functioning), or they may be non-functioning. Null cell adenomas are negative for all of these hormones and clinically non-functioning. A subtype of null cell adenoma is oncocytoma, being composed of cells with an abundance of mitochondria which can be immunohistochemically verified by using anti-mitochondrial antibodies. There is no generally accepted minimum percentage of positive tumor cells required for classification, although 10% immunopositive cells has most often been suggested.

Differential Diagnosis. *Pituitary carcinoma* is exceedingly rare and defined as adenoma undergoing metastasis, implying that the diagnosis cannot be made on the basis of a surgical specimen derived from the sellar region. It often but not necessarily exhibits anaplastic histologic features, such as numerous mitoses, high cellular density, cellular pleomorphism, necrosis, and diffuse brain invasion. *Pituitary hyperplasia* represents an increased number of secretory cells in response to a physiological or pathological stimulus; it is histologically characterized by the lack of the typical lobulation of the normal adenohypophysis. Various cysts, most commonly Rathke's cleft cyst and colloid cyst of the intermediate lobe, and *inflammatory lesions*, most commonly lymphocytic hypophysitis and granulomatous hypophysitis, may present as mass lesions. Finally, a wide variety of tumors that are histogenetically unrelated to the pituitary gland may occasionally arise in the sellar region.

Molecular Pathology. The molecular pathogenesis of pituitary adenomas, i.e., involvement of mutations and hypothalamic hormone stimulation, remains largely unknown to date. The only mutations identified in a significant proportion of tumors, and particularly in somatotroph adenomas (40%), occur in the Gsα gene (*GNAS1*), causing constitutive activation of the cAMP pathway. Several tumor suppressor genes such as *CDKN2 A* are downregulated, presumably due to hypermethylation of the promoter (Levy and Lightman 2003). Germline mutations of the MEN1 tumor suppressor gene are responsible for MEN type 1, which in 10–50% comprises pituitary adenoma, whereas sporadic pituitary adenomas show *MEN1* mutations in only 2% of cases (Wrocklage et al. 2002).

Granular Cell Tumor of the Neurohypophysis (WHO Grade I)

Definition. A tumor of the sellar region composed of polygonal granular cells that are strongly PAS

positive. The tumors are thought to arise from specialized neuroglial cells (pituicytes) of the neurohypophysis or infundibulum. However, a possible histogenetic relationship with pituicytoma (see chapter 17) is not yet resolved.

Incidence and Age Distribution. Granular tumors are rare lesions that manifest in adults.

Macroscopy and Localization. The tumor presents as an intrasellar and/or suprasellar, well-circumscribed mass lesion with a granular, gray to yellow cut surface.

Histopathology. Granular cell tumors are composed of polygonal or elongated cells with small nuclei and abundant, granular, strongly PAS-positive cytoplasm (Fig. 13g,h). Ultrastructural studies show that the cytoplasmic granularity and PAS positivity are due to a dense accumulation of lysosomes. Mitotic activity is low or absent. Perivascular lymphocytic cuffs are often seen.

Immunohistochemistry. Granular cell tumors are positive for vimentin and S-100. Expression of GFAP is variable. The MIB1 index is low (<5%).

Differential Diagnosis. Granular tumors of the neurohypophysis or infundibulum need to be differentiated from pituitary adenomas and other more common lesions of the sellar region.

Metastatic Tumors of the CNS

Definition. Malignant tumors involving the CNS and/or its coverings that originate from but are discontinuous with primary cancers in other organs.

Incidence and Age Distribution. Altogether, metastatic tumors are the most common tumors of the CNS. Their overall annual incidence is estimated to range between 4–11 per 100,000 population. The incidence markedly increases with age, i.e., metastatic lesions are rare in children and young adults but common in old patients (>40 cases per 100,000 population over 65 years). Autopsy series reported intracranial metastases in 24% and spinal metastases in 5% of all cancer patients.

Origin. Metastatic tumors reach the CNS and/or its coverings by hematogenous spread of tumor cells from malignant neoplasms in other organs. Tumors that most commonly metastasize to the brain are carcinomas of the lung (in particular, bronchial adenocarcinomas and small-cell carcinomas), which account for approximately 50% of all CNS metastases, followed by carcinomas of the breast, malignant melanomas, and renal carcinomas. In at least 10% of the patients operated on for metastatic brain tumors, the corresponding primary tumor is unknown at the time of brain surgery. Diffuse infiltration of the leptomeninges (*leptomeningial carcinomatosis/leptomeningial blastomatosis*) is most commonly seen in patients suffering from leukemia or lymphoma, melanoma, and carcinomas of the breast, lung, or gastrointestinal tract.

Macroscopy and Localization. The vast majority of CNS metastases are located within the brain parenchyma itself, most commonly at the cortical/subcortical border in the cerebral hemispheres and in the cerebellum (Fig. 6g,h). Dural metastases often compress rather than infiltrate the adjacent brain and may be macroscopically mistaken for meningiomas. Spinal metastases are most commonly located in the epidural space and frequently extend from metastatic lesions in the vertebral bodies. Spinal intramedullary metastases are rare. Leptomeningeal tumor spread may be found in patients with or without intraparenchymal metastases. Macroscopically, intracerebral metastases are either solitary or multiple, usually well-demarcated lesions surrounded by edematous brain tissue. The tumor's cut surface is inhomogeneous, with gray, white, or tan areas of vital tumor tissue, hemorrhagic zones, as well as frequently large areas of necrosis. Intratumoral bleeding is particularly common in metastases from renal cell carcinoma, choriocarcinoma, and malignant melanoma. Dural metastases may present as nodular or plaque-like lesions. Leptomeningeal carcinomatosis may lead to circumscribed or diffuse thickening of the meninges.

Histopathology. The histologic appearance and immunohistochemical profile of metastatic lesions in the CNS usually correspond to those of the respective primary tumor. However, many metastases of carcinomas are histologically poorly differentiated. Therefore, histology often does not allow for a firm conclusion regarding the site of the respective primary tumor. In contrast to malignant gliomas and primary CNS lymphomas, carcinoma metastases typically show histologically well-defined borders towards the adjacent brain tissue. However, metastases of small-cell carcinomas and malignant melanomas may also demonstrate an infiltrative growth. Areas of necrosis are usually present and may be quite large in CNS metastases, with vital tumor tissue often restricted to perivascular tumor cuffs within the necrotic zones. The brain parenchyma adjacent to a metastasis is characterized by edema, reactive gliosis, and sometimes microvascular proliferation. In

addition, reactive lymphocytic infiltrates may be seen at the tumor border and around blood vessels.

Immunohistochemistry. Immunohistochemical stainings are important to separate different types of metastatic lesions from each other as well as from primary brain tumors. In case of a metastasis from an unknown primary tumor, immunohistochemistry may help to identify the site of the corresponding primary tumor. Carcinoma metastases are generally positive for epithelial antigens such as cytokeratins and EMA. A specific expression pattern of cytokeratin subtypes may help to distinguish carcinomas of different types and origin, e.g., adenocarcinoma and squamous cell carcinoma. Neuroendocrine carcinomas are revealed by their expression of synaptophysin and chromogranin A. When positive, organ-specific markers such as thyroid transcription factor 1 (thyroid and bronchial carcinomas), prostate-specific antigen (prostate carcinoma), HepPar (hepatocellular carcinoma), and thyroglobulin (thyroid carcinoma) are indicative of tumor origin. Expression of estrogen and/or progesterone receptors may help to identify a metastatic breast carcinoma. Metastases from malignant germ-cell tumors are also characterized by expression of specific marker proteins, e.g., placenta-like alkaline phosphatase (PLAP), alpha-fetoprotein (AFP), and beta human chorionic gonadotropin (beta-HCG). Melanoma metastases are characterized by positivity for S-100, vimentin, and melanocytic markers (HMB-45, melan A). Malignant lymphomas, either primary or metastatic, are immunohistochemically characterized by their positivity for lymphocytic markers. The MIB1 index in metastatic tumors is usually high.

Differential Diagnosis. The differential diagnosis of metastases in the cerebral hemispheres primarily includes malignant glioma and primary CNS lymphoma. Dural metastases need to be distinguished from malignant meningiomas. Among cerebellar metastases, small-cell carcinomas must be separated from medulloblastomas, while clear-cell carcinoma metastases may mimic capillary hemangioblastoma. Because metastatic papillary adenocarcinomas are primarily tumors of adults, the differential diagnosis of choroid plexus carcinoma, which is mostly present in young children, rarely arises. In case of a pineal tumor, the recently identified papillary tumor of the pineal region needs to be distinguished from a metastatic adenocarcinoma.

Molecular Pathology. Metastatic tumors in the CNS are highly malignant neoplasms with grossly rearranged karyotypes. A CGH study revealed multiple chromosomal losses, gains and amplifications in these tumors, with the average of genomic aberrations detected per tumor ranging from 39.6 in breast carcinoma metastases, 35.6 in lung carcinoma metastases, 28.6 in melanoma metastases, 28.2 in colon carcinoma metastases, to 25.8 in renal carcinoma metastases (Petersen et al. 2000). Genomic imbalances that were most commonly detected in CNS metastases included gains on 17q24-q25, 8q24, 20q13, 1q23, and 7p12 as well as losses on 4q22, 4q26, 5q21, and 9p21 (Petersen et al. 2000). According to these authors, gains on 17q24-q25 appeared to be particularly common in brain metastases compared with metastases in other organs. However, several other chromosomal regions as well as a number of candidate genes have been reported to contribute to the formation of metastases in the CNS and other organs (for recent reviews, see Puduvalli 2001; Fidler 2003; Pantel and Brakenhoff 2004).

Emerging New CNS Tumor Entities and Variants

A number of novel tumor entities and new histologic variants of established tumor entities have been reported since the publication of the latest WHO classification in the year 2000. A list of tumor entities and variants that are likely to be discussed as candidates for inclusion into the next edition of the WHO classification is provided in Table 7. This brief chapter will only mention some of the most important features of these tumors. For a more detailed account, the reader is referred to the recent review article by Cenacchi and Giangaspero (2004).

New Variants of Neuronal and Mixed Neuronal–Glial Tumors. Although the existence of extraventricular tumors resembling central neurocytoma is already mentioned in the WHO classification, *extraventricular (parenchymal) neurocytoma* was not formally listed as a distinct variant of neurocytic tumor. However, several recent studies have delineated the typical clinico-pathologic features of extraventricular neurocytoma. Although the histology of these lesions is closely related to that of central neurocytoma, astrocytic and/or ganglionic differentiation is more common. Although most tumors show a good prognosis after complete resection, about one-third recurs, with 'atypical' histologic features (high proliferative activity, vascular proliferation, necrosis), subtotal resection and older age being associated with a higher likelihood of recurrence (Brat et al. 2001). The so-called *papillary glioneuronal tumors* (Komori et al. 1998) are hemispheric, contrast-enhancing, cystic mass lesions that are histologically characterized by the formation of pseudopapillary structures consisting of hyalinized blood vessels surrounded by astrocytic cells. Sheets of synaptophysin-

positive cells, morphologically ranging from neurocytes to ganglion cells, are located between the pseudopapillae. Mitotic activity is low, and the prognosis appears to be favorable after total resection. Another distinctive glioneuronal tumor type, the *glioneuronal tumor with neuropil-like islands or rosetted glioneuronal tumor*, consists of a diffuse astrocytic glioma of WHO grade II or III containing sharply delimited neuropil-like islands that are synaptophysin positive and rimmed in a rosette-like fashion by sometimes quite pleomorphic neurocytic and/or neuronal cells (Teo et al. 1999). Both the astrocytic and neurocytic/neuronal populations show proliferative activity. The biological behavior and clinical prognosis correspond to ordinary diffuse or anaplastic astrocytomas. More recently, rare cases of *oligodendroglioma with neurocytic differentiation* have been reported (Perry et al. 2002). These tumors are diffusely growing oligodendrogliomas that contain areas of neurocytic/neuronal differentiation, as indicated by the presence of well-formed Homer Wright-like and perivascular rosettes, immunohistochemical expression of neuronal markers, and ultrastructural features of neuronal differentiation. FISH analyses revealed that combined losses on 1p and 19q were similarly common as in ordinary oligodendrogliomas (Perry et al. 2002). Diagnostically, the rare oligodendroglioma with neurocytic differentiation needs to be distinguished from ordinary oligodendrogliomas that infiltrate into the cerebral gray matter.

The *rosette-forming glioneuronal tumor of the fourth ventricle* (Komori et al. 2002) and the *DNT-like tumor of the septum pellucidum and caudate nucleus areas* (Cervera-Pierot et al. 1997; Baisden et al. 2001) are morphologically distinctive tumor types related to DNTs that seem to be restricted to specific locations. The former lesions are single or multicentric, focally enhancing masses involving the aqueduct, fourth ventricle, and cerebellar vermis. Hydrocephalus is a common feature. Histology shows a benign tumor consisting of two distinct components, a neurocytic component with formation of neurocytic and/or perivascular pseudorosettes and an astrocytic component resembling pilocytic astrocytoma (Komori et al. 2002). The DNT-like tumor of the septum pellucidum and caudate nucleus areas often presents with symptoms of increased intracranial pressure due to obstructive hydrocephalus rather than epileptic seizures. The histology resembles that of cortical DNTs with oligodendrocyte-like cells in a mucinous matrix, floating neurons, and the formation of specific glioneuronal elements. The biological behavior is indolent.

Other New Tumor Entities and Variants. *Pituicytoma* has been reported as a distinctive, low-grade glioma that may arise from so-called pituicytes, i.e., specialized glial cells of the posterior lobe and the stalk of the pituitary gland (Brat et al. 2000). Other authors suggested a possible origin from specialized stromal folliculo-stellate cells of the adenohypophysis (Cenacchi et al. 2001). Pituicytomas are slowly growing tumors of the sellar and suprasellar regions that occur in adult patients and are associated with a favorable prognosis following total resection. Histologically, pituicytomas consist of sheets and fascicles of spindle cells with oval-to-elongated nuclei and pinpoint nucleoli. Mitotic activity is low. In contrast to pilocytic astrocytomas, Rosenthal fibers and eosinophilic granular bodies are absent. Immunohistochemistry shows strong staining for vimentin and S-100. GFAP expression is variable and may be negative. Neuronal markers are negative.

Papillary tumor of the pineal region is a recently delineated clinicopathologic entity that typically presents in adult patients as a large, well-circumscribed mass lesion in the pineal region (Jouvet al. 2003). Histology shows a cellular tumor with epithelial-like growth pattern and papillary areas composed of large, columnar or cuboidal cells, often with clear cytoplasm and nuclei located at the basal pole. Formation of true rosettes is a common feature. Immunohistochemically, the tumor cells express cytokeratins, S-100 protein, and vimentin. Staining for EMA and GFAP is weak and/or focal. Based on ultrastruc-

Table 7. New tumor entities and variants not yet included in the WHO classification

Extraventricular (parenchymal) neurocytoma
Papillary glioneuronal tumor
Glioneuronal tumor with neuropil-like islands (rosetted glioneuronal tumor)
Oligodendroglioma with neurocytic differentiation
Rosette-forming glioneuronal tumor of the fourth ventricle
DNT-like tumor of the septum pellucidum and caudate nucleus areas
Pilomyxoid astrocytoma
Lipoastrocytoma
Granular cell astrocytoma
Papillary tumor of the pineal region
Pituicytoma
Embryonal tumor with abundant neuropil and true rosettes

tural features, it is speculated that these papillary tumors of the pineal region may be derived from specialized ependymocytes of the so-called subcommissural organ (Jouvet et al. 2003). The differential diagnosis primarily includes papillary ependymoma, a choroid plexus tumor, and a metastatic papillary carcinoma.

The *pilomyxoid astrocytoma* has been identified as a rare variant of pilocytic astrocytoma that is associated with a less favorable outcome (Tihan et al. 1999). The morphologic features of this variant are described above (see chapter 2.4).

Granular cell astrocytoma is a rare variant of infiltrative astrocytoma that contains a prominent component of granular cells, which are large, round cells packed with eosinophilic, PAS-positive granules (Brat et al. 2002). Occasional tumors may almost entirely consist of such atypical granular cells. Lymphocytic infiltrates are often present. By WHO criteria, granular cell astrocytomas may correspond to WHO grade II, III, or IV, respectively. The clinical course is rapidly progressive and fatal in most cases. Molecular genetic investigation showed a high incidence of genetic alterations typically found in high-grade astrocytic tumors, in particular losses on chromosome arms 9p and 10q, but no specific genetic alterations that would distinguish granular cell astrocytomas from other diffuse astrocytic gliomas (Castellano-Sanchez et al. 2003). Thus, these neoplasms represent a morphologic variant of diffuse astrocytoma but do not appear to constitute an entity on their own.

Giangaspero et al. (2002) reported about two children with cerebral astrocytic gliomas showing extensive lipomatous change of the tumor cells. The authors proposed that these cerebral *lipoastrocytomas* may represent a rare variant of pediatric low-grade astrocytoma that is distinct from pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and diffuse astrocytoma.

A rare embryonal tumor variant that combines features of ependymoblastoma and neuroblastoma has been reported and designated as *embryonal tumor with abundant neuropil and true rosettes* (Eberhart et al. 2000). These tumors develop in the first three years of life and may originate in supratentorial as well as infratentorial locations. Histologically, the tumors are biphasic lesions composed of densely cellular regions and virtually anuclear regions of fibrillary neuropil containing true rosettes that resemble those typically seen in ependymoblastomas. Other rosettes of Flexner-Winterstein type or occasionally Homer-Wright type may also be present. Mitoses and apoptoses are common, while large areas of necrosis are absent. The clinical behavior corresponds to other malignant embryonal tumors of the CNS.

References

Actor B, Cobbers JM, Buschges R, Wolter M, Knobbe CB, Lichter P, Reifenberger G, Weber RG. Comprehensive analysis of genomic alterations in gliosarcoma and its two tissue components. Genes Chromosomes Cancer 2002; 34(4):416–27.

Aldosari N, Bigner SH, Burger PC, Becker L, Kepner JL, Friedman HS, McLendon RE. *MYCC* and *MYCN* oncogene amplification in medulloblastoma. A fluorescence in situ hybridization study on paraffin sections from the Children's Oncology Group. Arch Pathol Lab Med 2002; 126(5):540–4.

Bailey P, Cushing H. A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. J.B. Lippincott Co., Philadelphia, 1926.

Baisden BL, Brat DJ, Melhem ER, Rosenblum MK, King AP, Burger PC. Dysembryoplastic neuroepithelial tumor-like neoplasm of the septum pellucidum: a lesion often misdiagnosed as glioma: report of 10 cases. Am J Surg Pathol 2001; 25(4):494–9.

Becker AJ, Lobach M, Klein H, Normann S, Nothen MM, von Deimling A, Mizuguchi M, Elger CE, Schramm J, Wiestler OD, Blumcke I. Mutational analysis of *TSC1* and *TSC2* genes in gangliogliomas. Neuropathol Appl Neurobiol 2001; 27(2):105–14.

Becker AJ, Klein H, Baden T, Aigner L, Normann S, Elger CE, Schramm J, Wiestler OD, Blumcke I. Mutational and expression analysis of the reelin pathway components CDK5 and doublecortin in gangliogliomas. Acta Neuropathol (Berl) 2002; 104(4):403–8.

Beckner ME, Sasatomi E, Swalsky PA, Hamilton RL, Pollack IF, Finkelstein SD. Loss of heterozygosity reveals non-VHL allelic loss in hemangioblastomas at 22q13. Hum Pathol 2004; 35(9):1105–11.

Betensky RA, Louis DN, Cairncross JG. Influence of unrecognized molecular heterogeneity on randomized clinical trials. J Clin Oncol. 2002; 20(10):2495–9.

Biegel JA, Tan L, Zhang F, Wainwright L, Russo P, Rorke LB. Alterations of the hSNF5/INI1 gene in central nervous system atypical teratoid/rhabdoid tumors and renal and extrarenal rhabdoid tumors. Clin Cancer Res 2002; 8(11):3461–7.

Blümcke I, Wiestler OD. Gangliogliomas: an intriguing tumor entity associated with focal epilepsies. J Neuropathol Exp Neurol 2002; 61(7):575–84.

Boström J, Janssen G, Messing-Junger M, Felsberg JU, Neuen-Jacob E, Engelbrecht V, Lenard HG, Bock WJ, Reifenberger G. Multiple intracranial juvenile xanthogranulomas. Case report. J Neurosurg 2000; 93(2):335–41.

Boström J, Meyer-Puttlitz B, Wolter M, Blaschke B, Weber RG, Lichter P, Ichimura K, Collins VP, Reifenberger G. Alterations of the tumor suppressor genes *CDKN2 A* ($p16^{INK4\alpha}$), $p14^{ARF}$, *CDKN2B* ($p15^{INK4b}$), and *CDKN2 C* ($p18^{INK4c}$) in atypical and anaplastic meningiomas. Am J Pathol 2001; 159(2):661–9.

Brat DJ, Giannini C, Scheithauer BW, Burger PC. Primary melanocytic neoplasms of the central nervous systems. Am J Surg Pathol 1999; 23(7):745–54.

Brat DJ, Hirose Y, Cohen KJ, Feuerstein BG, Burger PC. Astroblastoma: clinicopathologic features and chromosomal abnormalities defined by comparative genomic hybridization. Brain Pathol 2000; 10(3):342–52.

Brat DJ, Scheithauer BW, Eberhart CG, Burger PC. Extraventricular neurocytomas: pathologic features and clinical outcome. Am J Surg Pathol 2001; 25(10):1252–60.

Brat DJ, Scheithauer BW, Medina-Flores R, Rosenblum MK, Burger PC. Infiltrative astrocytomas with granular cell features (granular cell astrocytomas): a study of histopathologic features, grading, and outcome. Am J Surg Pathol 2002; 26(6):750–7.

Brat DJ, Scheithauer BW, Staugaitis SM, Holtzman RN, Morgello S, Burger PC. Pituicytoma: a distinctive low-grade glioma of the neurohypophysis. Am J Surg Pathol 2000; 24(3):362–8.

Bühren J, Christoph AH, Buslei R, Albrecht S, Wiestler OD, Pietsch T. Expression of the neurotrophin receptor p75NTR in medulloblastomas is correlated with distinct histological and clinical features: evidence for a medulloblastoma subtype derived from the external granule cell layer. J Neuropathol Exp Neurol 2000; 59(3):229–40.

Burger PC, Pearl DK, Aldape K, Yates AJ, Scheithauer BW, Passe SM, Jenkins RB, James CD. Samll cell architecture–a histological equivalent of *EGFR* amplification in glioblastoma multiforme? J Neuropathol Exp Neurol 2001; 60(11):1099–104.

Burger PC, Scheithauer BW, Vogel SE. Surgical pathology of the nervous system and its coverings. 4th edition. Churchill Livingston, New York, Edinburg, London, Philadelphia, 2002:579–648.

Burnett ME, White EC, Sih S, von Haken MS, Cogen PH. Chromosome arm 17p deletion analysis reveals molecular genetic heterogeneity in supratentorial and infratentorial primitive neuroectodermal tumors of the central nervous system. Cancer Genet Cytogenet 1997; 97(1):25–31.

Carroll SL, Stonecypher MS. Tumor suppressor mutations and growth factor signaling in the pathogenesis of NF1-associated peripheral nerve sheath tumors. I. The role of tumor suppressor mutations. J Neuropathol Exp Neurol 2004; 63(11):1115–23.

Castellano-Sanchez AA, Ohgaki H, Yokoo H, Scheithauer BW, Burger PC, Hamilton RL, Finkelstein SD, Brat DJ. Granular cell astrocytomas show a high frequency of allelic loss but are not a genetically defined subset. Brain Pathol 2003; 13(2):185–94.

Cenacchi G, Giangaspero F. Emerging tumor entities and variants of CNS neoplasms. J Neuropathol Exp Neurol 2004; 63(3):185–92.

Cenacchi G, Giovenali P, Castrioto C, Giangaspero F. Pituicytoma: ultrastructural evidence of a possible origin from folliculo-stellate cells of the adenohypophysis. Ultrastruct Pathol 2001; 25(4):309–12.

Cervera-Pierot P, Varlet P, Chodkiewicz JP, Daumas-Duport C. Dysembryoplastic neuroepithelial tumors located in the caudate nucleus area: report of four cases. Neurosurgery 1997; 40(5):1065–9.

Chan JA, Zhang H, Roberts PS, Jozwiak S, Wieslawa G, Lewin-Kowalik J, Kotulska K, Kwiatkowski DJ. Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: biallelic inactivation of *TSC1* or *TSC2* leads to mTOR activation. J Neuropathol Exp Neurol 2004; 63(12):1236–42.

Cobbers JM, Wolter M, Reifenberger J, Ring GU, Jessen F, An HX, Niederacher D, Schmidt EE, Ichimura K, Floeth F, Kirsch L, Borchard F, Louis DN, Collins VP, Reifenberger G. Frequent inactivation of *CDKN2 A* and rare mutation of *TP53* in PCNSL. Brain Pathol 1998; 8(2):263–76.

Dahmen RP, Koch A, Denkhaus D, Tonn J.C., Sorensen N, Berthold F, Behrens J, Birchmeier W, Wiestler OD, Pietsch T. Deletions of *AXIN1*, a component of the WNT/wingless pathway, in sporadic medulloblastomas. Cancer Res 2001; 61(19):7039–43.

Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER Jr, Vedrenne C. Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery 1988; 23(5):545–56.

Di Marcotullio L, Ferretti E, De Smaele E, Argenti B, Mincione C, Zazzeroni F, Gallo R, Masuelli L, Napolitano M, Maroder M, Modesti A, Giangaspero F, Screpanti I, Alesse E, Gulino A. REN(KCTD11) is a suppressor of Hedgehog signaling and is deleted in human medulloblastoma. Proc Natl Acad Sci USA 2004; 101(29):10833–8.

Dong ZQ, Pang JC, Tong CY, Zhou LF, Ng HK. Clonality of oligoastrocytomas. Hum Pathol 2002; 33(5):528–35.

Eberhart CG, Brat DJ, Cohen KJ, Burger PC. Pediatric neuroblastic brain tumors containing abundant neuropil and true rosettes. Pediatr Dev Pathol 2000; 3(4):346–52.

Eberhart CG, Kepner JL, Goldthwaite PT, Kun LE, Duffner PK, Friedman HS, Strother DR, Burger PC. Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. Cancer 2002; 94(2):552–60.

Eberhart CG, Kratz JE, Schuster A, Goldthwaite P, Cohen KJ, Perlman EJ, Burger PC. Comparative genomic hybridization detects an increased number of chromosomal alterations in large cell/anaplastic medulloblastomas. Brain Pathol 2002; 12(1):36–44.

Eberhart CG, Tihan T, Burger PC. Nuclear localization and mutation of beta-catenin in medulloblastomas. J Neuropathol Exp Neurol 2000; 59(4):333–7.

Enam SA, Rosenblum ML, Ho KL. Neurocytoma in the cerebellum. Case report. J Neurosurg 1997; 87(1):100–2.

Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG. Inactivation of the DNA-repair gene *MGMT* and the clinical response of gliomas to alkylating agents. N Engl J Med 2000; 343(19):1350–4.

Feldmann J, Callebaut I, Raposo G, Certain S, Bacq D, Dumont C, Lambert N, Ouachee-Chardin M, Chedeville G, Tamary H, Minard-Colin V, Vilmer E, Blanche S, Le Deist F, Fischer A, de Saint Basile G. Munc13–4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). Cell 2003; 115(4):461–73.

Felsberg J, Erkwoh A, Sabel MC, Kirsch L, Fimmers R, Blaschke B, Schlegel U, Schramm J, Wiestler OD, Reifenberger G. Oligodendroglial tumors: refinement of candidate regions on chromosome arm 1p and correlation of 1p/19q status with survival. Brain Pathol 2004; 14(2):121–30.

Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003; 3(6):453–8.

Freije WA, Castro-Vargas FE, Fang Z, Horvath S, Cloughesy T, Liau LM, Mischel PS, Nelson SF. Gene expression profiling of gliomas strongly predicts survival. Cancer Res 2004; 64(18):6503–10.

Fallon KB, Palmer CA, Roth KA, Nabors LB, Wang W, Carpenter M, Banerjee R, Forsyth P, Rich K, Perry A. Prognostic value of 1p, 19q, 9p, 10q, and EGFR-FISH analyses in recurrent oligodendrogliomas. J Neuropathol Exp Neurol 2004; 63(4):314–22.

Fujisawa H, Marukawa K, Hasegawa M, Tohma Y, Hayashi Y, Uchiyama N, Tachibana O, Yamashita J. Genetic differences between neurocytoma and dysembryoplastic neuroepithelial tumor and oligodendroglial tumors. J Neurosurg 2002; 97(6):1350–5.

Gatter KC, Warnke RA. Diffuse large B-cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology and Genetics. Tumors of Hematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumors. IARC Press, Lyon, France, 2001:171–174.

Gessi M, Giangaspero F, Pietsch T. Atypical teratoid/rhabdoid tumors and choroid plexus tumors: when genetics ‚surprise' pathology. Brain Pathol 2003; 13(3):409–14.

George DH, Scheithauer BW. Central liponeurocytoma. Am J Surg Pathol 2001; 25(12):1551–5.

Giannini C, Scheithauer BW, Burger PC, Brat DJ, Wollan PC, Lach B, O'Neill BP. Pleomorphic xanthoastrocytoma: what do we really know about it? Cancer 1999; 85(9):2033–45.

Giannini C, Scheithauer BW, Lopes MB, Hirose T, Kros JM, VandenBerg SR. Immunophenotype of pleomorphic xanthoastrocytoma. Am J Surg Pathol 2002; 26(4):479–85.

Giangaspero F, Kaulich K, Cenacchi G, Cerasoli S, Lerch KD, Breu H, Reuter T, Reifenberger G. Lipoastrocytoma: a rare low-grade astrocytoma variant of pediatric age. Acta Neuropathol (Berl) 2002; 103(2):152–6.

Giangaspero F, Perilongo G, Fondelli MP, Brisigotti M, Carollo C, Burnelli R, Burger PC, Garre ML. Medulloblastoma with extensive nodularity: a variant with favorable prognosis. J Neurosurg 1999; 91(6):971–7.

Glasker S, Bender BU, Apel TW, van Velthoven V, Mulligan LM, Zentner J, Neumann HP. Reconsideration of biallelic inactivation of the VHL tumor suppressor gene in hemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry 2001; 70(5):644–8.

He J, Mokhtari K, Sanson M, Marie Y, Kujas M, Huguet S, Leuraud P, Capelle L, Delattre JY, Poirier J, Hoang-Xuan K. Glioblastomas with an oligodendroglial component: a pathological and molecular study. J Neuropathol Exp Neurol 2001; 60(9):863–71.

Hegi ME, Diserens AC, Godard S, Dietrich PY, Regli L, Ostermann S, Otten P, Van Melle G, de Tribolet N, Stupp R. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. Clin Cancer Res 2004; 10(6):1871–4.

Herrlinger U, Felsberg J, Kuker W, Bornemann A, Plasswilm L, Knobbe CB, Strik H, Wick W, Meyermann R, Dichgans J, Bamberg M, Reifenberger G, Weller M. Gliomatosis cerebri: molecular pathology and clinical course. Ann Neurol 2002; 52(4):390–9.

Hermanson M, Funa K, Koopmann J, Maintz D, Waha A, Westermark B, Heldin CH, Wiestler OD, Louis DN, von Deimling A, Nister M. Association of loss of heterozygosity on chromosome 17p with high platelet-derived growth factor alpha receptor expression in human malignant gliomas. Cancer Res 1996; 56(1):164–71.

Hes FJ, McKee S, Taphoorn MJ, Rehal P, van Der Luijt RB, McMahon R, van Der Smagt JJ, Dow D, Zewald RA, Whittaker J, Lips CJ, MacDonald F, Pearson PL, Maher ER. Cryptic von Hippel-Lindau disease: germline mutations in patients with hemangioblastoma only. J Med Genet 2000; 37(12):939–43.

Horstmann S, Perry A, Reifenberger G, Giangaspero F, Huang H, Hara A, Masuoka J, Rainov NG, Bergmann M, Heppner FL, Brandner S, Chimelli L, Montagna N, Jackson T, Davis DG, Markesbery WR, Ellison DW, Weller RO, Taddei GL, Conti R, Del Bigio MR, Gonzalez-Campora R, Radhakrishnan VV, Soylemezoglu F, Uro-Coste E, Qian J, Kleihues P, Ohgaki H. Genetic and expression profiles of cerebellar liponeurocytomas. Brain Pathol 2004; 14(3):281–9.

Ichimura K, Ohgaki H, Kleihues P, Collins VP. Molecular pathogenesis of astrocytic tumors. J Neuro-Oncol 2004; 70 (2):137–160.

Iwato M, Tachibana O, Tohma Y, Arakawa Y, Nitta H, Hasegawa M, Yamashita J, Hayashi Y. Alterations of the INK4a/ARF locus in human intracranial germ cell tumors. Cancer Res 2000; 60(8):2113–5.

Iwato M, Tachibana O, Tohma Y, Nitta H, Hayashi Y, Yamashita J. Molecular analysis for p53 and mdm2 in intracranial germ cell tumors. Acta Neuropathol (Berl) 2000; 99(1):21–5.

Jacoby LB, MacCollin M, Louis DN, Mohney T, Rubio MP, Pulaski K, Trofatter JA, Kley N, Seizinger B, Ramesh V, et al. Exon scanning for mutation of the NF2 gene in schwannomas. Hum Mol Genet 1994; 3(3):413–9.

Jenkinson MD, Bosma JJ, Du Plessis D, Ohgaki H, Kleihues P, Warnke P, Rainov NG. Cerebellar liponeurocytoma with an unusually aggressive clinical course: case report. Neurosurgery 2003; 53(6):1425–7.

Jouvet A, Fauchon F, Liberski P, Saint-Pierre G, Didier-Bazes M, Heitzmann A, Delisle MB, Biassette HA, Vincent S, Mikol J, Streichenberger N, Ahboucha S, Brisson C, Belin MF, Fevre-Montange M. Papillary tumor of the pineal region. Am J Surg Pathol 2003; 27(4):505–12.

Jouvet A, Saint-Pierre G, Fauchon F, Privat K, Bouffet E, Ruchoux MM, Chauveinc L, Fevre-Montange M. Pineal parenchymal tumors: a correlation of histological features with prognosis in 66 cases. Brain Pathol 2000; 10(1):49–60.

Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol 2004; 28(5):644–50.

Kam R, Chen J, Blümcke I, Normann S, Fassunke J, Elger CE, Schramm J, Wiestler OD, Becker AJ. The reelin pathway components disabled-1 and p35 in gangliogliomas–a mutation and expression analysis. Neuropathol Appl Neurobiol 2004; 30(3):225–32.

Kato K, Nakatani Y, Kanno H, Inayama Y, Ijiri R, Nagahara N, Miyake T, Tanaka M, Ito Y, Aida N, Tachibana K, Sekido K, Tanaka Y. Possible linkage between specific histological structures and aberrant reactivation of the Wnt pathway in adamantinomatous craniopharyngioma. J Pathol 2004; 203(3):814–21.

Kaulich K, Blaschke B, Numann A, von Deimling A, Wiestler OD, Weber RG, Reifenberger G. Genetic alterations commonly found in diffusely infiltrating cerebral gliomas are rare or absent in pleomorphic xanthoastrocytomas. J Neuropathol Exp Neurol 2002; 61(12):1092–9.

Kees UR, Spagnolo D, Hallam LA, Ford J, Ranford PR, Baker DL, Callen DF, Biegel JA. A new pineoblastoma cell line, PER-480, with der(10)t(10;17), der(16)t(1;16), and enhanced *MYC* expression in the absence of gene amplification. Cancer Genet Cytogenet 1998; 100(2):159–64.

Kemmer K, Corless CL, Fletcher JA, McGreevey L, Haley A, Griffith D, Cummings OW, Wait C, Town A, Heinrich MC. KIT mutations are common in testicular seminomas. Am J Pathol 2004; 164(1):305–13.

Kitange G, Misra A, Law M, Passe S, Kollmeyer TM, Maurer M, Ballman K, Feuerstein BG, Jenkins RB. Chromosomal imbalances detected by array comparative genomic hybridization in human oligodendrogliomas and mixed oligoastrocytomas. Genes Chromosomes Cancer 2005; 42(1):68–77.

Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumors of the central nervous system. 2nd edition. International histological classification of tumors. Springer-Verlag, Berlin – Heidelberg – New York – Tokyo, 1993.

Kleihues P, Cavenee WK. Pathology and genetics of tumors of the nervous system. World Health Organisation Classification of Tumors. IARCPress, Lyon, 2000.

Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 2002; 61(3):215–25.

Kluwe L, Hagel C, Tatagiba M, Thomas S, Stavrou D, Ostertag H, von Deimling A, Mautner VF. Loss of NF1 alleles distinguish sporadic from NF1-associated pilocytic astrocytomas. J Neuropathol Exp Neurol 2001; 60(9):917–20.

Koch A, Waha A, Tonn J.C., Sorensen N, Berthold F, Wolter M, Reifenberger J, Hartmann W, Friedl W, Reifenberger G, Wiestler OD, Pietsch T. Somatic mutations of WNT/wingless signaling pathway components in primitive neuroectodermal tumors. Int J Cancer 2001; 93(3):445–9.

Koch CA, Vortmeyer AO, Zhuang Z, Brouwers FM, Pacak K. New insights into the genetics of familial chromaffin cell tumors. Ann N Y Acad Sci 2002; 970:11–28.

Koga T, Iwasaki H, Ishiguro M, Matsuzaki A, Kikuchi M. Frequent genomic imbalances in chromosomes 17, 19, and 22q in peripheral nerve sheath tumors detected by comparative genomic hybridization analysis. J Pathol 2002; 197(1):98–107.

Komori T, Scheithauer BW, Anthony DC, Rosenblum MK, McLendon RE, Scott RM, Okazaki H, Kobayashi M. Papillary glioneuronal tumor: a new variant of mixed neuronal-glial neoplasm. Am J Surg Pathol 1998; 22(10):1171–83.

Komori T, Scheithauer BW, Hirose T. A rosette-forming glioneuronal tumor of the fourth ventricle: infratentorial form of dysembryoplastic neuroepithelial tumor? Am J Surg Pathol 2002; 26(5):582–91.

Komotar RJ, Carson BS, Rao C, Chaffee S, Goldthwaite PT, Tihan T. Pilomyxoid astrocytoma of the spinal cord: report of three cases. Neurosurgery 2005; 56(1):191.

Kraus JA, Felsberg J, Tonn J.C., Reifenberger G, Pietsch T. Molecular genetic analysis of the *TP53, PTEN, CDKN2 A, EGFR, CDK4* and *MDM 2* tumor-associated genes in supratentorial primitive neuroectodermal tumors and glioblastomas of childhood. Neuropathol Appl Neurobiol 2002; 28(4):325–33.

Kraus JA, Koopmann J, Kaskel P, Maintz D, Brandner S, Schramm J, Louis DN, Wiestler OD, von Deimling A. Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. J Neuropathol Exp Neurol 1995; 54(1):91–5.

Kraus JA, Lamszus K, Glesmann N, Beck M, Wolter M, Sabel M, Krex D, Klockgether T, Reifenberger G, Schlegel U. Molecular genetic alterations in glioblastomas with oligodendroglial component. Acta Neuropathol (Berl) 2001; 101(4):311–20.

Kros JM, Delwel EJ, de Jong TH, Tanghe HL, van Run PR, Vissers K, Alers JC. Desmoplastic infantile astrocytoma and ganglioglioma: a search for genomic characteristics. Acta Neuropathol (Berl) 2002; 104(2):144–8.

Laman JD, Leenen PJ, Annels NE, Hogendoorn PC, Egeler RM. Langerhans-cell histiocytosis 'insight into DC biology'. Trends Immunol 2003; 24(4):190–6.

Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol 2004; 63(4):275–86.

Larocca LM, Capello D, Rinelli A, Nori S, Antinori A, Gloghini A, Cingolani A, Migliazza A, Saglio G, Cammilleri-Broet S, Raphael M, Carbone A, Gaidano G. The molecular and phenotypic profile of primary central nervous system lymphoma identifies distinct categories of the disease and is consistent with histogenetic derivation from germinal center-related B cells. Blood 1998; 92(3):1011–9.

Lee JY, Dong SM, Park WS, Yoo NJ, Kim CS, Jang JJ, Chi JG, Zbar B, Lubensky IA, Linehan WM, Vortmeyer AO, Zhuang Z. Loss of heterozygosity and somatic mutations of the VHL tumor suppressor gene in sporadic cerebellar hemangioblastomas. Cancer Res 1998; 58(3):504–8.

Lemeta S, Pylkkanen L, Sainio M, Niemela M, Saarikoski S, Husgafvel-Pursiainen K, Bohling T. Loss of heterozygosity at 6q is frequent and concurrent with 3p loss in sporad-

ic and familial capillary hemangioblastomas. J Neuropathol Exp Neurol 2004; 63(10):1072–9.

Levy A, Lightman S. Molecular defects in the pathogenesis of pituitary tumors. Front Neuroendocrinol 2003; 24(2):94–127.

Louis DN, von Deimling A, Dickersin GR, Dooling EC, Seizinger BR. Desmoplastic cerebral astrocytomas of infancy: a histopathologic, immunohistochemical, ultrastructural, and molecular genetic study. Hum Pathol 1992; 23(12):1402–9.

Luyken C, Blümcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer 2004; 101(1):146–55.

Maintz D, Fiedler K, Koopmann J, Rollbrocker B, Nechev S, Lenartz D, Stangl AP, Louis DN, Schramm J, Wiestler OD, von Deimling A. Molecular genetic evidence for subtypes of oligoastrocytomas. J Neuropathol Exp Neurol 1997; 56(10):1098–104.

Martin AJ, Summersgill BM, Fisher C, Shipley JM, Dean AF. Chromosomal imbalances in meningeal solitary fibrous tumors. Cancer Genet Cytogenet 2002; 135(2):160–4.

Masuoka J, Brandner S, Paulus W, Soffer D, Vital A, Chimelli L, Jouvet A, Yonekawa Y, Kleihues P, Ohgaki H. Germline SDHD mutation in paraganglioma of the spinal cord. Oncogene 2001; 20(36):5084–6.

Mawrin C, Kirches E, Schneider-Stock R, Scherlach C, Vorwerk C, Von Deimling A, Van Landeghem F, Meyermann R, Bornemann A, Muller A, Romeike B, Stoltenburg-Didinger G, Wickboldt J, Pilz P, Dietzmann K. Analysis of *TP53* and *PTEN* in gliomatosis cerebri. Acta Neuropathol (Berl) 2003; 105(6):529–36.

Mechtersheimer G, Otano-Joos M, Ohl S, Benner A, Lehnert T, Willeke F, Möller P, Otto HF, Lichter P, Joos S. Analysis of chromosomal imbalances in sporadic and NF1-associated peripheral nerve sheath tumors by comparative genomic hybridization. Genes Chromosomes Cancer 1999; 25(4):362–9.

Melean G, Sestini R, Ammannati F, Papi L. Genetic insights into familial tumors of the nervous system. Am J Med Genet C Semin Med Genet 2004; 129(1):74–84.

Miettinen MM, el-Rifai W, Sarlomo-Rikala M, Andersson LC, Knuutila S. Tumor size-related DNA copy number changes occur in solitary fibrous tumors but not in hemangiopericytomas. Mod Pathol 1997; 10(12):1194–200.

Miyakawa A, Ichimura K, Schmidt EE, Varmeh-Ziaie S, Collins VP. Multiple deleted regions on the long arm of chromosome 6 in astrocytic tumors. Br J Cancer 2000; 82(3):543–9.

Möllemann M, Wolter M, Felsberg J, Collins VP, Reifenberger G. Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. Int J Cancer 2005; 113(3):379–85.

Montesinos-Rongen M, Küppers R, Schluter D, Spieker T, Van Roost D, Schaller C, Reifenberger G, Wiestler OD, Deckert-Schluter M. Primary central nervous system lymphomas are derived from germinal-center B cells and show a preferential usage of the V4–34 gene segment. Am J Pathol 1999; 155(6):2077–86.

Montesinos-Rongen M, Van Roost D, Schaller C, Wiestler OD, Deckert M. Primary diffuse large B-cell lymphomas of the central nervous system are targeted by aberrant somatic hypermutation. Blood 2004; 103(5):1869–75.

Mueller W, Hartmann C, Hoffmann A, Lanksch W, Kiwit J, Tonn J.C., Veelken J, Schramm J, Weller M, Wiestler OD, Louis DN, von Deimling A. Genetic signature of oligoastrocytomas correlates with tumor location and denotes distinct molecular subsets. Am J Pathol 2002; 161(1):313–9.

Murakami I, Gogusev J, Fournet JC, Glorion C, Jaubert F. Detection of molecular cytogenetic aberrations in langerhans cell histiocytosis of bone. Hum Pathol 2002; 33(5):555–60.

Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, Ishida E, Konishi N. Novel tumor suppressor loci on 6q22–23 in primary central nervous system lymphomas. Cancer Res 2003; 63(4):737–41.

Nakamura M, Watanabe T, Klangby U, Asker C, Wiman K, Yonekawa Y, Kleihues P, Ohgaki H. *p14^{ARF}* deletion and methylation in genetic pathways to glioblastomas. Brain Pathol 2001; 11(2):159–68.

Nolan MA, Sakuta R, Chuang N, Otsubo H, Rutka JT, Snead OC 3rd, Hawkins CE, Weiss SK. Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. Neurology. 2004; 62(12):2270–6.

Nutt CL, Mani DR, Betensky RA, Tamayo P, Cairncross JG, Ladd C, Pohl U, Hartmann C, McLaughlin ME, Batchelor TT, Black PM, von Deimling A, Pomeroy SL, Golub TR, Louis DN. Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. Cancer Res 2003; 63(7):1602–7.

Oberstrass J, Reifenberger G, Reifenberger J, Wechsler W, Collins VP. Mutation of the von Hippel-Lindau tumor suppressor gene in capillary hemangioblastomas of the central nervous system. J Pathol 1996; 179(2):151–6.

Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, Burkhard C, Schuler D, Probst-Hensch NM, Maiorka PC, Baeza N, Pisani P, Yonekawa Y, Yasargil MG, Lutolf UM, Kleihues P. Genetic pathways to glioblastoma: a population-based study. Cancer Res 2004; 64(19):6892–9.

Okada Y, Nishikawa R, Matsutani M, Louis DN. Hypomethylated X chromosome gain and rare isochromosome 12p in diverse intracranial germ cell tumors. J Neuropathol Exp Neurol 2002; 61(6):531–8.

Ono Y, Ueki K, Joseph JT, Louis DN. Homozygous deletions of the *CDKN2/p16* gene in dural hemangiopericytomas. Acta Neuropathol (Berl) 1996; 91(3):221–5.

Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. Nat Rev Cancer 2004; 4(6):448–56.

Paz MF, Yaya-Tur R, Rojas-Marcos I, Reynes G, Pollan M, Aguirre-Cruz L, Garcia-Lopez JL, Piquer J, Safont MJ, Balana C, Sanchez-Cespedes M, Garcia-Villanueva M, Arribas L, Esteller M. CpG island hypermethylation of the DNA repair enzyme methyltransferase predicts response to temozolomide in primary gliomas. Clin Cancer Res 2004; 10(15):4933–8.

Perry A, Aldape KD, George DH, Burger PC. Small cell astrocytoma: an aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. Cancer 2004; 101(10):2318–26.

Perry A, Banerjee R, Lohse CM, Kleinschmidt-DeMasters BK, Scheithauer BW. A role for chromosome 9p21 deletions in the malignant progression of meningiomas and the prognosis of anaplastic meningiomas. Brain Pathol 2002; 12(2):183–90.

Perry A, Gutmann DH, Reifenberger G. Molecular pathogenesis of meningiomas. J Neuro-Oncol 2004; 70(2): 183–202.

Perry A, Scheithauer BW, Macaulay RJ, Raffel C, Roth KA, Kros JM. Oligodendrogliomas with neurocytic differentiation. A report of 4 cases with diagnostic and histogenetic implications. J Neuropathol Exp Neurol 2002; 61(11):947–55.

Petersen I, Hidalgo A, Petersen S, Schluns K, Schewe C, Pacyna-Gengelbach M, Goeze A, Krebber B, Knosel T, Kaufmann O, Szymas J, von Deimling A. Chromosomal imbalances in brain metastases of solid tumors. Brain Pathol 2000; 10(3):395–401.

Pietsch T, Waha A, Koch A, Kraus J, Albrecht S, Tonn J.C., Sörensen N, Berthold F, Henk B, Schmandt N, Wolf HK, von Deimling A, Wainwright B, Chenevix-Trench G, Wiestler OD, Wicking C. Medulloblastomas of the desmoplastic variant carry mutations of the human homologue of Drosophila patched. Cancer Res 1997; 57(11):2085–8.

Pietsch T, Taylor MD, Rutka JT. Molecular pathogenesis of childhood brain tumors. J Neurooncol 2004; 70(2):203–15.

Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, Kim JY, Goumnerova LC, Black PM, Lau C, Allen JC, Zagzag D, Olson JM, Curran T, Wetmore C, Biegel JA, Poggio T, Mukherjee S, Rifkin R, Califano A, Stolovitzky G, Louis DN, Mesirov JP, Lander ES, Golub TR. Prediction of central nervous system embryonal tumor outcome based on gene expression. Nature 2002; 415(6870):436–42.

Puduvalli VK. Brain metastases: biology and the role of the brain microenvironment. Curr Oncol Rep 2001; 3(6):467–75.

Rajaram V, Brat DJ, Perry A. Anaplastic meningioma versus meningeal hemangiopericytoma: immunohistochemical and genetic markers. Hum Pathol 2004; 35(11):1413–8.

Reifenberger G, Collins VP. Pathology and molecular genetics of astrocytic gliomas. J Mol Med 2004; 82(10):656–70.

Reifenberger G, Kaulich K, Wiestler OD, Blümcke I. Expression of the CD34 antigen in pleomorphic xanthoastrocytomas. Acta Neuropathol (Berl) 2003; 105(4):358–64.

Reifenberger G, Louis DN. Oligodendroglioma: toward molecular definitions in diagnostic neuro-oncology. J Neuropathol Exp Neurol 2003; 62(2):111–26.

Reifenberger G, Weber T, Weber RG, Wolter M, Brandis A, Kuchelmeister K, Pilz P, Reusche E, Lichter P, Wiestler OD. Chordoid glioma of the third ventricle: immunohistochemical and molecular genetic characterization of a novel tumor entity. Brain Pathol 1999; 9(4):617–26.

Reifenberger J, Wolter M, Weber RG, Megahed M, Ruzicka T, Lichter P, Reifenberger G. Missense mutations in SMOH in sporadic basal cell carcinomas of the skin and primitive neuroectodermal tumors of the central nervous system. Cancer Res 1998; 58(9):1798–803

Reis RM, Konu-Lebleblicioglu D, Lopes JM, Kleihues P, Ohgaki H. Genetic profile of gliosarcomas. Am J Pathol 2000; 156(2):425–32.

Rich JN, Bigner DD. Development of novel targeted therapies in the treatment of malignant glioma. Nat Rev Drug Discov 2004; 3(5):430–46.

Rickert CH, Dockhorn-Dworniczak B, Simon R, Paulus W. Chromosomal imbalances in primary lymphomas of the central nervous system. Am J Pathol 1999; 155(5):1445–51.

Rickert CH, Simon R, Bergmann M, Dockhorn-Dworniczak B, Paulus W. Comparative genomic hybridization in pineal parenchymal tumors. Genes Chromosomes Cancer 2001; 30(1):99–104.

Rickert CH, Paulus W. No chromosomal imbalances detected by comparative genomic hybridisation in subependymal giant cell astrocytomas. Acta Neuropathol (Berl) 2002; 104(2):206–8.

Rickert CH, Paulus W. Comparative genomic hybridization in central and peripheral nervous system tumors of childhood and adolescence. J Neuropathol Exp Neurol 2004; 63(5):399–417.

Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C, Plougastel B, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 1993; 363(6429):515–21.

Rousseau E, Ruchoux MM, Scaravilli F, Chapon F, Vinchon M, De Smet C, Godfraind C, Vikkula M. *CDKN2 A, CDKN2B* and $p14^{ARF}$ are frequently and differentially methylated in ependymal tumors. Neuropathol Appl Neurobiol 2003; 29(6):574–83.

Russo C, Pellarin M, Tingby O, Bollen AW, Lamborn KR, Mohapatra G, Collins VP, Feuerstein BG. Comparative genomic hybridization in patients with supratentorial and infratentorial primitive neuroectodermal tumors. Cancer 1999; 86(2):331–9.

Sakuma Y, Sakurai S, Oguni S, Satoh M, Hironaka M, Saito K. *c-kit* gene mutations in intracranial germinomas. Cancer Sci 2004; 95(9):716–20.

Sanoudou D, Tingby O, Ferguson-Smith MA, Collins VP, Coleman N. Analysis of pilocytic astrocytoma by comparative genomic hybridization. Br J Cancer 2000; 82(6):1218–22.

Scheithauer BW, Woodruff JM, Erlandson RA. Tumors of the peripheral nervous system. Atlas of Tumor Pathology. Third series. Fascicle 24. Armed Forces Institute of Pathology, Washington, D.C., 1997.

Schramm J, Luyken C, Urbach H, Fimmers R, Blümcke I. Evidence for a clinically distinct new subtype of grade II astrocytomas in patients with long-term epilepsy. Neurosurgery 2004; 55(2):340–7.

Serra E, Rosenbaum T, Winner U, Aledo R, Ars E, Estivill X, Lenard HG, Lazaro C. Schwann cells harbor the somatic *NF1* mutation in neurofibromas: evidence of two different Schwann cell subpopulations. Hum Mol Genet 2000; 9(20):3055–64.

Shih AH, Holland EC. Developmental neurobiology and the origin of brain tumors. J Neuro-Oncol 2004; 70(2): 125–135.

Smith JS, Tachibana I, Passe SM, Huntley BK, Borell TJ, Iturria N, O'Fallon JR, Schaefer PL, Scheithauer BW, James CD, Buckner JC, Jenkins RB. *PTEN* mutation, *EGFR* amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme. J Natl Cancer Inst 2001; 93(16):1246–56.

Soylemezoglu F, Scheithauer BW, Esteve J, Kleihues P. Atypical central neurocytoma. J Neuropathol Exp Neurol 1997; 56(5):551–6.

Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, Mathew PA, Henter JI, Bennett M, Fischer A, de Saint Basile G, Kumar V. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science 1999; 286(5446):1957–9.

Taylor MD, Liu L, Raffel C, Hui CC, Mainprize TG, Zhang X, Agatep R, Chiappa S, Gao L, Lowrance A, Hao A, Goldstein AM, Stavrou T, Scherer SW, DuraWT, Wainwright B, Squire JA, Rutka JT, Hogg D. Mutations in *SUFU* predispose to medulloblastoma. Nat Genet 2002; 31(3):306–10.

Teo JG, Gultekin SH, Bilsky M, Gutin P, Rosenblum MK. A distinctive glioneuronal tumor of the adult cerebrum with neuropil-like (including 'rosetted') islands: report of 4 cases. Am J Surg Pathol 1999; 23(5):502–10.

Thiessen B, Finlay J, Kulkarni R, Rosenblum MK. Astroblastoma: does histology predict biologic behavior? J Neurooncol 1998; 40(1):59–65.

Tihan T, Fisher PG, Kepner JL, Godfraind C, McComb RD, Goldthwaite PT, Burger PC. Pediatric astrocytomas with monomorphous pilomyxoid features and a less favorable outcome. J Neuropathol Exp Neurol 1999; 58(10):1061–8.

Tihan T, Viglione M, Rosenblum MK, Olivi A, Burger PC. Solitary fibrous tumors in the central nervous system. A clinicopathologic review of 18 cases and comparison to meningeal hemangiopericytomas. Arch Pathol Lab Med 2003; 127(4):432–9.

Tong CY, Ng HK, Pang JC, Hu J, Hui AB, Poon WS. Central neurocytomas are genetically distinct from oligodendrogliomas and neuroblastomas. Histopathology 2000; 37(2):160–5.

Trofatter JA, MacCollin MM, Rutter JL, Murrell JR, Duyao MP, Parry DM, Eldridge R, Kley N, Menon AG, Pulaski K, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell 1993; 72(5):791–800.

Twist EC, Ruttledge MH, Rousseau M, Sanson M, Papi L, Merel P, Delattre O, Thomas G, Rouleau GA. The neurofibromatosis type 2 gene is inactivated in schwannomas. Hum Mol Genet 1994; 3(1):147–51.

Virchow R. Die krankhaften Geschwülste. Achtzehnte Vorlesung: Psammome, Melanome, Gliome. Verlag von August Hirschwald, Berlin, 1864/65:106–169.

von Deimling A, Bender B, Jahnke R, Waha A, Kraus J, Albrecht S, Wellenreuther R, Fassbender F, Nagel J, Menon AG, et al. Loci associated with malignant progression in astrocytomas: a candidate on chromosome 19q. Cancer Res 1994; 54(6):1397–401.

Waha A, Waha A, Koch A, Meyer-Puttlitz B, Weggen S, Sörensen N, Tonn J.C., Albrecht S, Goodyer CG, Berthold F, Wiestler OD, Pietsch T. Epigenetic silencing of the *HIC-1* gene in human medulloblastomas. J Neuropathol Exp Neurol 2003; 62(11):1192–201.

Warren C, James LA, Ramsden RT, Wallace A, Baser ME, Varley JM, Evans DG. Identification of recurrent regions of chromosome loss and gain in vestibular schwannomas using comparative genomic hybridisation. J Med Genet 2003; 40(11):802–6.

Weiss SW, Goldblum JR, eds. Enzinger and Weiss's Soft Tissue Tumors. 4th edition. Mosby, St. Louis, 2001.

Wizigmann-Voos S, Breier G, Risau W, Plate KH. Up-regulation of vascular endothelial growth factor and its receptors in von Hippel-Lindau disease-associated and sporadic hemangioblastomas. Cancer Res 1995; 55(6):1358–64.

Wolter M, Reifenberger J, Blaschke B, Ichimura K, Schmidt EE, Collins VP, Reifenberger G. Oligodendroglial tumors frequently demonstrate hypermethylation of the *CDKN2 A (MTS1, p16^{INK4a}), p14ARF,* and *CDKN2B (MTS2, p15^{INK4b})* tumor suppressor genes. J Neuropathol Exp Neurol 2001; 60(12):1170–80.

Wrocklage C, Gold H, Hackl W, Buchfelder M, Fahlbusch R, Paulus W. Increased menin expression in sporadic pituitary adenomas. Clin Endocrinol (Oxf) 2002; 56(5):589–94.

Zhou XP, Marsh DJ, Morrison CD, Chaudhury AR, Maxwell M, Reifenberger G, Eng C. Germline inactivation of *PTEN* and dysregulation of the phosphoinositol-3-kinase/Akt pathway cause human Lhermitte-Duclos disease in adults. Am J Hum Genet 2003; 73(5):1191–8.

Zülch KJ. Histological typing of tumors of the central nervous system. International histological classification of tumors, no. 21, World Health Organization, Geneva, 1979.

Zurawel RH, Chiappa SA, Allen C, Raffel C. Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res 1998; 58(5):896–9.

Tumors of the Skull

2

Roland Goldbrunner

Epidemiology – 74

Symptoms and Clinical Signs – 74

Diagnostics – 74
Synopsis

Staging and Classification – 74
Synopsis
Tumors of Bony Origin
Tumors of Cartilaginous Origin
Tumors of Histiocytotic Origin
Fibrous Dysplasia

Treatment – 77
Synopsis
Surgery
Radiotherapy
Chemotherapy/Medical Therapy

Prognosis/Quality of Life – 78

Follow-Up/Specific Problems and Measures – 78

Future Perspectives – 78

References – 78

Epidemiology

Skull tumors comprise a wide variety of entities, ranging from chronic inflammatory diseases to primary and secondary neoplasms. There are no valid data about the incidence of skull tumors in general, but the epidemiology of single entities has been assessed:

Osteoma is the most common diagnosis in benign skull neoplasms [20] and may be accompanied by Gardner's syndrome [2]. In most series, the second most common finding in benign calvarian tumors is hemangioma [8]. Benign osteoblastoma represents about 1% of all bone tumors, and a craniofacial localization is found in 15% of all osteoblastomas [2]. The most common malignant skull tumors are osteogenic sarcoma and chondrosarcoma. The former – in general – is the second most common primary malignant bone tumor after plasmocytoma. Osteogenic sarcoma occurs in all ages with a peak within the first two decades; 85% of osteogenic sarcoma arises before the age of 30 [22]. The main cranial locations are maxilla and mandible, while manifestation in the calvaria is less common. In contrast, cranial chondrosarcoma arises preferentially at the skull base, accounting for 6% of all skull base tumors [10]. The highest incidence is in the second decade; however, chondrosarcomas may be found at any age.

Symptoms and Clinical Signs

Most entities can be found in any cranial bone; therefore, the clinical presentation varies according to the site of tumor origin. Tumors involving the paranasal sinuses may present with frontal headache and recurrent sinusitis. Intracranial extension of large skull tumors can cause epidural compression and symptoms of elevated intracranial pressure like headache and nausea. Tumors of the skull base may present with cranial nerve symptoms like diplopia, visual or hearing loss, olfactory sensations, or impaired swallowing function. However, the most common symptom is a painless, slowly growing epicranial mass, which may vary widely regarding size and velocity of growth. Localized pain is a typical symptom for benign osteoid osteoma, aneurysmal bone cyst, or all types of rapidly growing malignant tumors.

Diagnostics

Synopsis

Simple calvarian tumors are sufficiently diagnosed by CT. The modern assessment of skull base tumors or complex calvarian tumors is multimodal: MRI is mandatory to evaluate soft-tissue structures, and CT for visualizing bone alterations. In some cases, there are indications for angiography or radionuclide scans.

The basic method for diagnostics in skull tumors is still CT. It is superior to MRI in assessing the bony structures and can display bone destruction as well as bone formation or intratumoral calcification in a proper way. Similar information may also be provided by plain skull X-ray films, if the tumor is localized at the calvaria. Altogether, CT may be sufficient for the diagnosis of small calvarian tumors without intracranial growth. MRI including T2-weighted images and contrast-enhanced T1-weighted images is important for the investigation of tumors at the skull base, where CT diagnosis of soft-tissue structures is impaired by artifacts. Involvement of cranial nerves, which are surrounded by CSF during their intradural extension, are best visualized by constructive interference in steady-state (CISS) sequences. Additionally, in case of intracranial growth of skull tumors, MRI provides more valuable information about the involvement of intracranial structures. MRI angiography may be helpful if the venous sinuses or arterial structures at the skull base are involved. Sometimes the classic invasive angiography may be indicated, particularly in cases where interventional procedures like embolization are discussed. Radionuclide scans using technetium 99 (^{99m}Tc) may provide additional information in diffusely growing lesions like fibrous dysplasia [23].

Staging and Classification

Synopsis

There is a wide variety of histopathological diagnoses in tumors of the skull. These neoplasms comprise tumors of bony, cartilaginous, fibrous, histiocytic, or hematological origin. In several types of skull tumors, the tissue of origin is still a matter of debate among pathologists. This chapter does not intend to provide a complete list of any tumorous disorder of the cranium but will concentrate on the most common and best characterized entities.

Tumors of Bony Origin

Osteomas are the most common primary tumors in the craniofacial bones. Skull osteomas are slowly growing, benign entities usually arising from the tabula externa and growing outward. Therefore, intracranial extension is rare. Two distinct subtypes can be differentiated histopathologically: the compact

('ivory') and the spongy osteoma, with the former being the more common variety. The compact osteoma consists of dense lamellar bone, whereas the spongy osteoma is characterized by a trabecular architecture with a peripheral bony margin.

Osteoid osteoma is another benign lesion, which is common in the skeleton in general but is found extremely rarely within the skull. It consists of a well-defined osteolytic nidus, comprised of osteoid matrix, bony trabeculae, and vessels. The nidus is surrounded by dense cortical sclerosis [8].

Osteoblastoma is a rare, benign entity with strong histopathological similarities to osteoid osteoma. Therefore, it has also been termed 'giant osteoid osteoma'. Compared with osteoid osteoma, osteoblastomas are usually larger and possess more fibrous stroma, many multinucleated giant cells, extravasated blood, and less osteoid. Local recurrence after subtotal excision as well as malignant transformation have been reported; therefore, complete excision should be preferred to curettage of the nidus [12].

Osteogenic sarcoma is a highly malignant tumor occurring before the age of 30 in 85% and after the age of 60 in 10% of patients. It is the second most common bone tumor after multiple myeloma. Involvement of craniofacial bones is seen more often in elderly patients, growth within the skull accounts for less than 1% of all osteogenic sarcomas. These tumors may grow in an osteolytic or osteoblastic pattern. The histological diagnosis is based on the identification of a malignant spindle-cell stroma which produces osteoid or immature bone. Fibroblastic, chondroblastic, and osteoblastic subtypes of osteogenic sarcoma can be distinguished, but these types do not correspond with the prognosis. In elderly patients, more than half of all osteogenic sarcomas arise secondary to fibrous dysplasia or Paget's disease [8]. Previous radiation therapy or occurrence of retinoblastoma is also a known risk factor for secondary osteosarcoma. The 500-fold increased risk of developing an osteogenic sarcoma for retinoblastoma patients might be due to a common mutation of the retinoblastoma tumor suppressor gene, which is observed in a variety of malignancies [18].

Tumors of Cartilaginous Origin

Benign, well-circumscribed *chondromas* and locally aggressive *chondroblastomas* are very rare tumors of the skull. There are only 59 cases of temporal chondroblastomas, which is the typical localization of this entity, reported in the literature [5]. Both entities may expand the cortex of the bone and typically show intralesional calcifications, which may display a pathognomonic 'chicken wire' arrangement in chondroblastomas.

Chondrosarcoma is the third most common malignant tumor of bone, following multiple myeloma and osteogenic sarcoma. Patients with cranial manifestations of chondrosarcoma are usually younger (peak second decade) than patients with extracranial manifestations (peak fourth decade). Some 80% of cranial chondrosarcomas arise in the skull base, representing 6% of all skull base tumors [10]. Two subtypes can be differentiated histologically, the myxochondrosarcoma and the mesenchymal (dedifferentiated) chondrosarcoma. The former is characterized histopathologically by a myxomatous stroma and cystic degeneration, the latter by absence of cartilage lobules and presence of spindle-cell sarcomatous areas. Mesenchymal chondrosarcoma seems to have a poorer prognosis than myxochondrosarcoma; the former subtype representing 80% of recurrent chondrosarcomas after surgical resection [7]. Other prognostic factors are cellularity and nuclear atypia, stage, and presence of metastases [14].

Tumors of Histiocytotic Origin

One of the most common benign lesions found in the calvaria is *eosinophilic granuloma*. It is a proliferative disease of Langerhans-type histiocytes and may be one manifestation of histiocytosis X. Eosinophilic granuloma may present as a single lesion or as part of the Hand-Schüller-Christian syndrome, which is characterized by the triad of diabetes insipidus, exophthalmos, and bony lesions, located in the skull. Eosinophilic granuloma in general may involve any bone, but the skull is the most commonly affected site. Some 34% of patients with eosinophilic granuloma are younger than 4 years of age, 74% are younger than 20 years [8]. The radiological appearance is an osteolytic lesion without peripheral sclerosis (Fig. 1). Small eosinophilic granulomas may shrink or even disappear after local injection of corticosteroids, which therefore should be the first choice of therapy. If resection is performed, brownish masses are found, which may contain cysts or hemorrhagic fluid. Histiocytes are also involved in locally aggressive or malignant tumors like *giant-cell tumor* of the bone, *Ewing's sarcoma*, or *malignant fibrous histiocytoma*. However, skull manifestations of these entities are extremely uncommon. Thus, these tumors represent very rare differential diagnoses of skull tumors.

Fibrous Dysplasia

Fibrous dysplasia is characterized by the presence of woven bone which has not transformed to lamellar bone during normal evolutionary development. The

etiology of fibrous dysplasia has not been explored yet; it occurs spontaneously, and there is no evidence for Mendelian inheritance. A mutation of the G(s) alpha subunit and activation of *c-fos* and other proto-oncogenes have been observed, representing possible etiologic mechanisms [15]. Fibrous dysplasia occurs in the monostotic form or polyostotic form involving multiple bone sites. Of all patients with fibrous dysplasia, 3% has McCune-Albright syndrome, which is characterized by precocious puberty, hyperpigmented maculae, and polyostotic fibrous dysplasia. The typical histological appearance of fibrous dysplasia is anvil-shaped trabeculae of woven bone surrounded by swirls of abundant fibrous tissue. The radiological appearance may be cystic, sclerotic, or mixed. The cystic form is usually present in the calvaria with thinned and bulged outer table and a thickened, but preserved inner table. The sclerotic form is typical for fibrous dysplasia of the skull base, mostly present in the anterior and middle fossa, ignoring any suture lines. The mixed form, which is also called 'pagetoid' form, is found in patients older than 30 years of age, whereas the other forms are observed in younger individuals. Therefore, the pagetoid form is considered a natural progression of the cystic and sclerotic form. Patients with fibrous dysplasia are considered to have a 400-fold increased risk of developing malignant bone tumors, with osteogenic sarcoma being the most common entity in this patient population [4]. *Paget's disease* is an important differential diagnosis to fibrous dysplasia. Paget's disease is a premalignant condition with increased bone resorption and bone formation [11]. Woven bone replaces lamellar bone in contrast to fibrous dysplasia where not even lamellar bone develops. Paget's disease occurs in elderly patients, and malignant transformation into osteogenic sarcoma (50%), fibrosarcoma (30%), chondrosarcoma (16%), or other malignancies occurs in about 2% of patients [8].

Miscellaneous

Besides tumors of well-defined, bony, chondroid, or histiocytic origin, there is a variety of tumors arising from connective tissue or poorly differentiated mesenchymal structures. Tumors arising from vascular structures are found in the calvaria as well, like the most common malignant neoplasm of the bone in adults, plasmocytoma.

Plasmocytoma, also known as multiple myeloma, may involve any bone, but the vertebral bodies, ribs, pelvic bones, and the skull are most frequently involved. Plasmocytoma usually produces multiple osteolytic lesions which may be pathognomonic on skull X-ray. These lesions are highly vascularized, with the blood supply derived from scalp arteries. Solitary plasmocytoma of the skull is an extremely rare lesion representing a single mass of plasma cells without any sign of systemic disease.

Hemangioma is the second most common skull tumor – after osteoma – in several series comprising 10% of benign skull neoplasms [6, 19]. The incidence of calvarian hemangioma is increasing with age, with a peak between the fourth and sixth decade. Two distinct subtypes are differentiated: the more common sessile hemangioma, which causes an expansion of the diploe and represents a well-demarcated, lytic lesion; and the globular type, which arises from the skull base and acts like a space-occupying lesion. Remnants of the bony trabecular structure are usually seen in hemangioma, but the pathognomonic bony 'sunburst' striations occur in only 10–15% of hemangiomas. Hemangiomas are classified according to their vessel size, with cavernous hemangiomas being the most common entity within the skull. Important differential diagnoses for hemangioma are giant-cell tumor and – in particular – *aneurysmal bone cyst*. The latter entity is characterized by a multiloculated, painful swelling and a thin-walled bone cyst filled with unclotted blood.

One of the most common neoplasms within the skull is *intraosseous meningioma*, which usually grows in an osteoplastic pattern and arises within

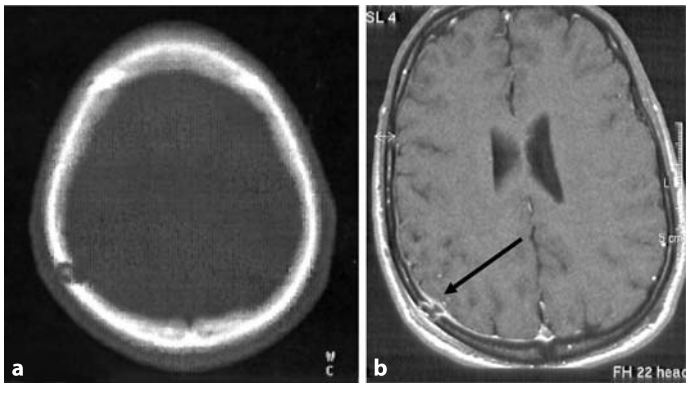


Fig. 1. a CT scan of a parietal eosinophilic granuloma showing a small, osteolytic lesion without any space-occupying effect or any sclerotic reaction. **b** T1-weighted MRI of the same patient showing slight contrast enhancement around the lesion (arrow)

the anterior fossa. This entity is described in detail elsewhere in this textbook.

An important differential diagnosis to any primary bone tumor is *metastatic carcinoma*. These lesions, derived from breast, prostate, ovarian, or many other types of cancer, may arise in any bone and have to be treated within a comprehensive treatment concept (Fig. 2).

Treatment

Synopsis

Total surgical resection is the standard treatment for benign and most malignant tumors of the skull. Radiation and chemotherapy may be indicated as adjuvant options in case of metastatic or incompletely resected tumors. Local injection of corticosteroids should be considered in the case of small eosinophilic granuloma.

Surgery

The standard treatment for benign skull tumors or tumors of unknown etiology is total surgical resection. Most calvarian tumors are palpable, and therefore, a straight skin incision above the tumor can be made depending on the size of the tumor. In small, nonpalpable tumors, neuronavigation or marking of the lesion during CT scanning may be useful to ensure a minimal approach. If a complete resection is accomplished, the bone defect should be covered by cranioplasty, e.g., by artificial polymers. Skull base tumors still represent a major surgical challenge in many cases. Even locally aggressive or malignant tumors like chondrosarcomas may be cured by total excision [14]. Therefore, transfrontal, transsphenoidal, midfacial, pterional, or transzygomatic approaches to the anterior skull base may be used for en bloc resection of these tumors. The risk of cranial nerve impairment or even sacrifice of one carotid artery to enable complete removal has to be discussed with the patient before the procedure (please see chapter about skull base tumors). In large skull base neoplasms or bone-forming conditions like fibrous dysplasia, decompression of single cranial nerves may be indicated to improve or prevent nerve dysfunctions like visual loss or trigeminal neuralgia [3, 16].

Fig. 2. CT scan of a skull metastasis from ovarian cancer. This mass lesion has been growing for more than 6 months in parallel to systemic bone metastases. The tumor displays a sharp demarcation towards the brain, significant perifocal edema, and no evidence of intratumoral sclerosis

Radiotherapy

The vast majority of skull tumors is cured by surgery alone. However, radiotherapy may be indicated in malignant tumors of the skull after incomplete resection. In large skull base tumors, commonly chondrosarcomas, which often are nonresectable despite sophisticated skull base approaches, a combined treatment regime consisting of surgery and radiation may be the therapy of choice. In premalignant bone-forming conditions like Paget's disease or fibrous dysplasia, radiation is even contraindicated, since radiation increases the risk of secondary malignancies [13].

Chemotherapy/Medical Therapy

There are only a few indications for chemotherapy within the treatment of skull tumors. High-dose chemotherapeutic regimes combined with autologous stem-cell transplantation and, currently, anti-angiogenic therapy is the standard treatment for plasmocytoma. Metastatic malignancies primarily located at the skull, like osteogenic sarcoma or Ewing's sarcoma, also have to be treated by chemotherapy within a multimodality concept. Medical treatment is required in conditions with increased bone turnover like fibrous dysplasia, and – even more – Paget's disease. Second- or third-generation bisphosphonates have been shown to effectively inhibit bone turnover in these conditions [11]. However, the majority of tumors of the skull in general is successfully treated by surgical resection and does not need any adjunctive therapy.

Prognosis/Quality of life

The prognosis of skull base tumors is defined by the tumor entity. All benign, totally removed tumors have an excellent prognosis. The same is true for locally aggressive or malignant nonmetastatic tumors which have been resected completely. In metastatic tumors, the prognosis depends on the systemic control of the disease. Quality of life may be impaired by the degree of resection, particularly in the frontal or skull base area. Cranial nerve dysfunction may lead to a significant worsening in the quality of life. Cosmetic alterations due to large bone defects should be avoided by adequate plastic techniques, e.g., polymer plastic in calvarian defects or autologous bone grafts in skull base surgery.

Follow-Up/Specific Problems and Measures

If a benign tumor of the skull is excised completely, as documented by postoperative imaging, no further follow-up is mandatory. However, an intense local and systemic follow-up has to be performed in possibly metastatic or incomplete resected malignant skull tumors. In incompletely resected chondrosarcomas, MRI and CT are recommended every 6 months; highly malignant tumors like osteogenic sarcoma need local checks every 3 months for the first 2 years, followed by further checks twice a year.

Future Perspectives

Modern skull base surgery has already provided the chance to cure even complex processes by total resection or to improve local control of these lesions. Improving imaging modalities based on MRI, CT, or radionuclide scans will allow better demarcation of skull base processes. Implementation of this imaging information in modern neuronavigation systems will provide the basis for more extensive curative surgical approaches. On the other hand, future developments in radiation protocols based on proton beam or carbon ion techniques may enhance the chance of local control of nonresectable neoplasms [17]. Sparing functional structures like cranial nerves by a sharp delineation of the radiation target will be extremely important in radiotherapeutic treatment of these patients. Therefore, LINAC or Gamma Knife-based radiosurgery is also a rapidly developing field in the therapy of skull base tumors [9]. Highly vascular skull base tumors may be treated with increasing frequency by interventional neuroradiology employing different embolization techniques [21]. Currently, these procedures are performed preoperatively to decrease blood loss; however, many tumors may be completely controlled by these techniques alone [1].

References

1. Bendszus M, Martin-Schrader I, Schlake HP, Solymosi L. Embolisation of intracranial meningiomas without subsequent surgery. Neuroradiology 2003; 45:451–455.
2. Bilkay U, Erdem O, Ozek C, Helvaci E, Kilic K, Ertan Y, Gurler T. Benign osteoma with Gardner syndrome: review of the literature and report of a case. J Craniofac Surg 2004; 15:506–509.
3. Chen YR, Breidahl A, Chang CN. Optic nerve decompression in fibrous dysplasia: indications, efficacy, and safety. Plast Reconstr Surg 1997; 99:22–30.
4. Chen YR Noordhoff MS. Treatment of craniomaxillofacial fibrous dysplasia: how early and how extensive? Plast Reconstr Surg 1990; 86:835–842.
5. Gaudet EL Jr, Nuss DW, Johnson DH Jr, Miranne LS Jr. Chondroblastoma of the temporal bone involving the temporomandibular joint, mandibular condyle, and middle cranial fossa: case report and review of the literature. Cranio 2004; 22:160–168.
6. Hamilton HB, Voorhies RM. Tumors of the skull. In: Wilkins RH, Rengechary SS, eds. Neurosurgery. New York, McGraw-Hill, 2004:1503–1528.
7. Hassounah M, Al Mefty O, Akhtar M, Jinkins JR, Fox JL. Primary cranial and intracranial chondrosarcoma. A survey. Acta Neurochir (Wien) 1985; 78:123–132.
8. Huvos AG. Bone Tumors: Diagnosis, Treatment and Prognosis. Philadelphia, Saunders, 1991.
9. Jawahar A, Jawahar LL, Nanda A, Sharp CD, Warren A, Elrod JW, Jennings M, Alexander JS, Minagar A. Stereotactic radiosurgery using the Leksell Gamma Knife: current trends and future directives. Front Biosci 2004; 9:932–938.
10. Kveton JF, Brackmann DE, Glasscock ME III, House WF, Hitselberger WE. Chondrosarcoma of the skull base. Otolaryngol Head Neck Surg 1986; 94:23–32.
11. Langston AL, Ralston SH. Management of Paget's disease of bone. Rheumatology (Oxford) 2004; 43:955–959.
12. Low Y, Foo CL, Seow WT. Childhood temporal bone osteoblastoma: a case report. J Pediatr Surg 2000; 35:1127–1129.
13. Mortensen A, Bojsen-Moller M, Rasmussen P. Fibrous dysplasia of the skull with acromegaly and sarcomatous transformation. Two cases with a review of the literature. J Neurooncol 1989; 7:25–29.
14. Neff B, Sataloff RT, Storey L, Hawkshaw M, Spiegel JR. Chondrosarcoma of the skull base. Laryngoscope 2002; 112:134–139.
15. Parekh SG, Donthineni-Rao R, Ricchetti E, Lackman RD. Fibrous dysplasia. J Am Acad Orthop Surg 2004; 12:305–313.
16. Ricalde P, Horswell BB. Craniofacial fibrous dysplasia of the fronto-orbital region: a case series and literature review. J Oral Maxillofac Surg 2001; 59:157–167.

17. Schulz-Ertner D, Nikoghosyan A, Thilmann C, Haberer T, Jakel O, Karger C, Kraft G, Wannenmacher M, Debus J. Results of carbon ion radiotherapy in 152 patients. Int J Radiat Oncol Biol Phys 2004; 58:631–640.
18. Shen WP, Young RF, Walter BN, Choi BH, Smith M, Katz J. Molecular analysis of a myxoid chondrosarcoma with rearrangements of chromosomes 10 and 22. Cancer Genet Cytogenet 1990; 45:207–215.
19. Thomas JE, Baker HL Jr. Assessment of roentgenographic lucencies of the skull: a systematic approach. Neurology 1975; 25:99–106.
20. Tucker WS, Nasser-Sharif FJ. Benign skull lesions. Can J Surg 1997; 40:449–455.
21. Turowski B, Zanella FE. Interventional neuroradiology of the head and neck. Neuroimaging Clin N Am 2003; 13:619–645.
22. Vege DS, Borges AM, Aggrawal K, Balasubramaniam G, Parikh DM, Bhaser B. Osteosarcoma of the craniofacial bones. A clinico-pathological study. J Craniomaxillofac Surg 1991; 19:90–93.
23. Zhibin Y, Quanyong L, Libo C, Jun Z, Hankui L, Jifang Z, Ruisen Z. The role of radionuclide bone scintigraphy in fibrous dysplasia of bone. Clin Nucl Med 2004; 29:177–180.

Meningiomas and Meningeal Tumors

3

Manfred Westphal, Katrin Lamszus, Jörg-Christian Tonn

Definition – 82

Epidemiology – 82

Molecular Genetics – 82

Etiology and Prevention – 83

Signs and Symptoms – 83

Staging and Classification – 85

Diagnostic Procedures – 86

Therapy – 88
Surgery

Prognosis – 93

Follow-Up – 95

Future Perspectives – 95

Other Meningeal Tumors – 98

References – 99

Definition

Meningiomas are tumors arising from the arachnoidal coverings of the brain [35]. They are responsible for the vast majority of meningeal tumors and occur anywhere on the brain surface including the skull base and rarely also in the ventricular system.

Other than meningiomas, hemangiopericytomas and meningeal sarcomas belong to the group of intrinsic meningeal tumors [35]. As with every other tissue, metastases and lymphoma can also occur in the meninges.

Epidemiology

Epidemiological data for most tumors of the central nervous system are difficult to obtain as cancer registries tend to be regional or at best national as in the Scandinavian countries [12]. A comprehensive source is the CBTRUS (2002) statistical report published by the Central Brain Tumor Registry of the USA.

Meningiomas show a rising incidence with age. In unselected autopsy series, 2.7% of the male and 6.2% of the female population over the age of 80 have meningiomas which up to that point were undiscovered. The reported incidence is variable between different investigations, but disregarding the changing proportions from the growing incidence of cerebral metastases with better oncological therapies, one can assume that meningiomas are responsible for about 15% of all male intracranial tumors and 30% of the female ones. Not considering the autopsy cases, the numbers which are reported on a population basis vary between 1.6 and 5.5 per 100,000. CBTRUS reports an incidence of 4.03 per 100,000 person-years, resulting in 28.7% of all tumors of the central nervous system. As a rule, the tumors are reported to be 1.5 to 3 times more frequent in women. In the 1995 to 1999 period, the rate given by CBTRUS is 2.66 for men and 5.19 for women. Peak incidence is the sixth decade in life (median age at diagnosis at CBTRUS is 65 years). Pediatric meningiomas are very rare, with 2% of all tumors occurring in that population [40].

There does not seem to be any association with race or any geographical preference which cannot be explained with access to medical care or pattern of reporting.

An unselected 10-year series from the University Department of Neurosurgery in Hamburg reflects these demographics with a female/male ratio of 507:172 (2.9:1) (Table 1).

Molecular Genetics

The majority of patients who suffer from neurofibromatosis type 2 (NF2) develop meningiomas [31, 33, 45]. In sporadic meningiomas, *NF2* gene mutations are detectable in up to 60%, and thus repre-

Table 1. Meningiomas in an unselected departmental series (n=679 cases, 1992 to 2001; Emami et al., unpublished results)

Location	*n*	Histology[a]	*n*	Age	*n*
Convexity	291				
Skull base	153				
Posterior fossa/tentorium	93				
Orbit	28				
Ventricular	5				
		Meningiotheliomatous	250		
		Fibrillary	142		
		Transitional	163		
				0–30 years	35
				31–50 years	190
				51–70 years	361
				71–90 years	93

[a] The three most frequent histological subtypes

sent the most frequent gene alteration. The *NF2* tumor suppressor gene is located on chromosome arm 22q, and mutations in one allele are typically associated with either monosomy 22 or large deletions involving the other allele. Absent or strongly reduced immunoreactivity of the NF2 gene product merlin (schwannomin) has also been demonstrated in meningiomas. Merlin belongs to the 4.1 family of structural proteins that link the cytoskeleton to proteins of the cytoplasmic membrane. Recently, another member of this family, the *4.1B/DAL-1* protein, was implicated in meningioma pathogenesis. The *4.1B/DAL-1* expression is lost in 70–80% of meningiomas. No mutations were detected in the 4.1B/DAL-1 gene, which is located on chromosome arm 18p. However, loss of heterozygosity (LOH) involving the 4.1B/DAL-1 region on 18p was identified in 70% of meningiomas [30].

Inactivation of the *NF2* and *4.1B/DAL-1* genes occurs with approximately equal frequency in benign (WHO grade I, see also chapter on meningioma grading), atypical (WHO grade II), and anaplastic (WHO grade III) meningiomas, suggesting that both represent relatively early events in tumorigenesis. In contrast, several other genetic alterations have been identified more frequently in the more malignant tumor forms and are therefore believed to be associated with meningioma progression [55]. In the approximate order of their frequency, these alterations are allelic losses on chromosome arms 1p, 14q, 10q, 9p, and 17q. However, with the exception of the *CDKN2A, p14*^{ARF}, and *CDKN2B* genes on 9p which display alterations in the majority of malignant meningiomas, no other tumor suppressor genes could be consistently identified as altered in meningiomas.

Etiology and Prevention

Meningiomas should be considered spontaneous tumors. Very early on, they were found to be associated with a complete or partial loss of chromosome 22, but that has so far not provided any clues about the origin of these tumors. The only established association is with ionizing radiation and that has been obtained from the large series of immigrants into Palestine in the early 1950s who were regularly irradiated for tinea capitis and then had a much higher incidence of meningiomas than normal with a delay of about 35 years [46]. Likewise, the follow-up of citizens from Hiroshima and Nagasaki who were exposed to the atomic blasts has shown that in this population there was a higher incidence of meningiomas with a very similar delay [41]. The doses producing meningioma with this long delay are to be considered rather low as high doses of therapeutic radiation for neoplasm produces meningiomas with a shorter delay (around 5 years [50]) or rather induces anaplastic gliomas. The indications for the role of diagnostic exposure to radiation are most likely limited to specific dental procedures [34].

As meningiomas occur most frequently in postmenopausal women [51] and are known to have high levels of steroid hormone receptors, attempts have been made for a long time to establish a relationship between steroid hormones and the growth of meningiomas [20, 22]. The only vague association comes from the observation that in some cases, meningiomas which had gone undetected became symptomatic during pregnancy [54] (Fig. 1) and even grew so rapidly that they spontaneously hemorrhaged (personal observation). In that context, there is an ongoing debate about whether women who are known to have a meningioma or have had a meningioma removed should be on hormonal replacement therapy. As no study has yet been done in which the use of steroid replacement has been evaluated in a randomized, controlled, prospective fashion in these patients and likely never will be, the management of these patients will remain in the hands of individual physicians who will have to closely observe the patient and decide what is best.

Signs and Symptoms

There are no typical signs or symptoms which are unequivocally specific for meningiomas. The clinical symptomatology is basically determined by the location of the lesion, its size and impact on its immediate surroundings. For clinical purposes, meningiomas are subspecified according to their site of origin, and this classification allows the description of the most frequent signs associated with the typical locations (Table 2).

The direct symptoms also depend very much on the size of the tumor and its growth rate. Large tumors which have grown over many years may have produced very few symptoms because the surrounding brain had a chance to adapt while slowly becoming displaced (Fig. 2). In cases of caudal skull base meningiomas, this may lead to extreme brain-stem compression without almost any symptoms (Fig. 3). As meningiomas also differ in their respect for the arachnoidal boundary – independent of size – the tumors are usually bigger, the less the brain shows any reaction to the tumor. Seizures are more frequent in the typical ictogenic regions, particularly when lesions extend exophytically into the temporomesial region or the perirolandic area.

There are many ways for meningiomas to affect the brain also indirectly and produce symptoms. Meningiomas at the tentorial edge, be they supra- or infratentorial, can lead to compression of the CSF

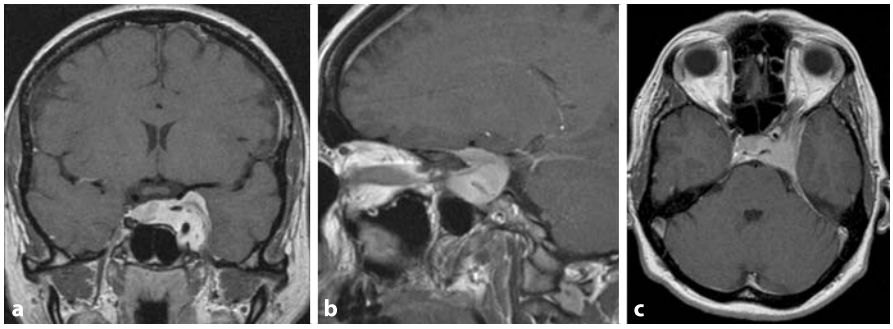


Fig. 1. Cavernous sinus meningioma of a 30-year-old woman which caused transient visual problems in the left eye during two pregnancies. Despite extension into the sellar lumen, there is no endocrine dysfunction. The tumor has been biopsied and is under observation with the option of radiotherapy in case of progressive symptoms

Table 2. Symptoms of meningiomas according to location

Location	Typical symptoms
Convexity	
frontal	Affective disorders;
parietal	Seizures; motor or sensory disorder, hemiparesis
temporal	Speech disorders, memory impairment
Parasagittal	Seizures; motor or sensory disturbance
Olfactory meningioma	Loss of olfaction; affective disorders; loss of activity
Tuberculum sellae meningioma	Visual field or visual acuity loss
Clinoid process meningioma	Visual field or visual acuity loss
Cavernous sinus meningioma	Diplopia facial pain or numbness; ocular venous congestion
Optic sheath meningioma	Loss of vision
Orbital meningioma	Exophthalmos
Sphenoid wing meningioma medial	Loss of vision, diplopia psychomotor seizures; schizoaffective disorders
lateral	Seizures; speech problems
Tentorial meningioma	Hydrocephalus, seizures, visual field loss; ataxia
Cerebellar meningioma	Ataxia, vertigo, hydrocephalus
Foramen magnum meningioma	Hydrocephalus, symptoms of dorsal, lateral or ventral brain-stem compression
Cerebellopontine angle meningioma	Unilateral cranial nerve dysfunction
Petroclival or clivus meningioma	Unilateral or bilateral cranial nerve dysfunction and symptoms of ventral brain-stem compression
Ventricular meningioma	Partial hydrocephalus

pathways and thus result in occlusive hydrocephalus, as can large meningiomas in the posterior fossa (Fig. 4). Meningiomas which produce an extraordinary amount of edema (frequently of the secretory type [7]) cause an indirect mass effect exceeding their own mass several-fold and can cause drowsiness and even loss of consciousness up to the extreme of herniation (Fig. 5). Meningiomas occluding a major sinus such as the falcine meningiomas or parasagittal meningiomas or those of the torcular or transverse sinus can cause venous congestion and generalized edema to the extreme of chronic intracranial hypertension with papilloedema and impairment of visual acuity (Fig. 6). An edema-like change in signal intensity on MRI can remain for many years and is frequently seen even after complete resection of a meningioma (Fig. 6).

It is a general rule that the risk of surgical treatment of a meningioma can be very well assessed when there are edema and neurological symptoms. When these symptoms disappear with appropriate treatment with steroids (see below), surgery will be much less risky than when the symptoms persist despite edema resolution.

Staging and Classification

As described in the chapter on histopathology of CNS tumors, meningiomas are graded according to the WHO grading system into well-differentiated meningiomas (WHO grade I), atypical meningiomas (WHO grade II), and anaplastic meningiomas (WHO grade III) [13]. In addition, there are several subtypes of which two by themselves are equivalent to a higher grade [35]. Due to serially acquired genetic aberrations, progression from a lower grade to the next higher grade is possible [31] (Fig. 7), and that is also accompanied by increasing production of angiogenic factors [32] and the late incidence of metastasis in the situation of anaplastic meningioma [24].

There is no clinical staging for the extent of the disease or the aggressiveness of the tumor, but there is for the resection (see below). The significance of the histological grading is related to the decision-making for adjuvant therapies (see below) and the follow-up regimen. In general, there is a correlation of the grades with survival but only when the tumors

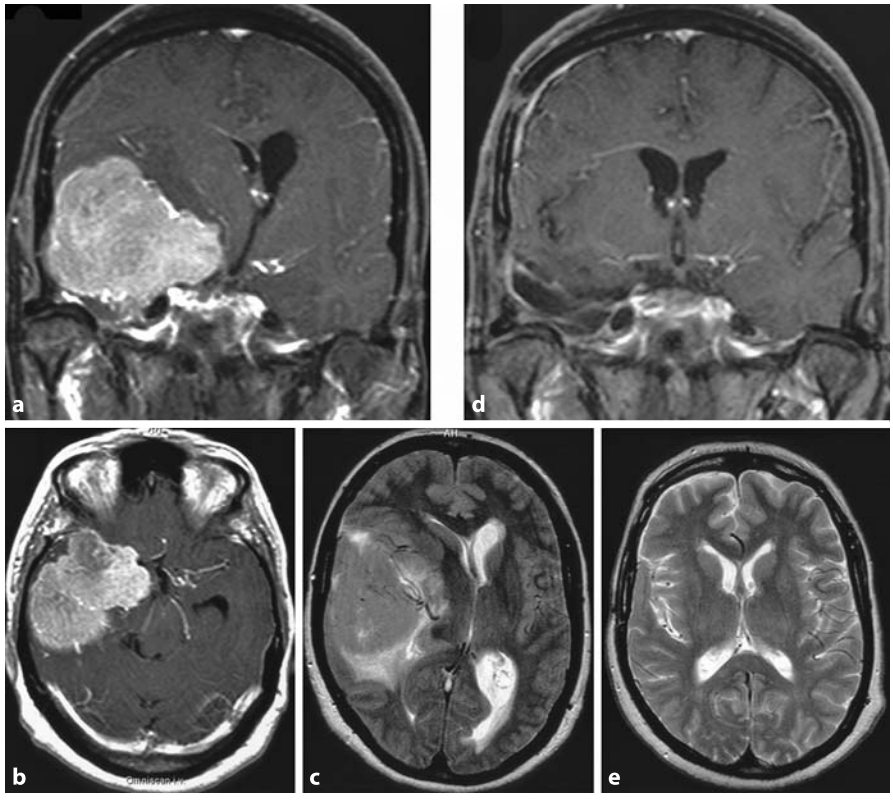


Fig. 2. Large temporal meningioma with impressive midline shift but no specific symptoms. The diagnosis was made after lack of concentration and inability to complete simple tasks in daily life led to cranial imaging. Despite the appearance of encased large vessels, the tumor was completely removed without any deficits (**d, e**). The minimal perilesional edema was reflected by a good dissection plane over most of the tumor surface

are in comparable locations and similar extents of resection can be achieved. On the other hand, there is a much better prognosis for a completely resected atypical meningioma (WHO grade II) of the convexities compared with a non-resectable meningioma grade WHO I of the skull base (Fig. 8).

Diagnostic Procedures

Many meningiomas are found incidentally due to unrelated complaints such as a dizzy spell, a transient ischemic attack, uncharacteristic headache,

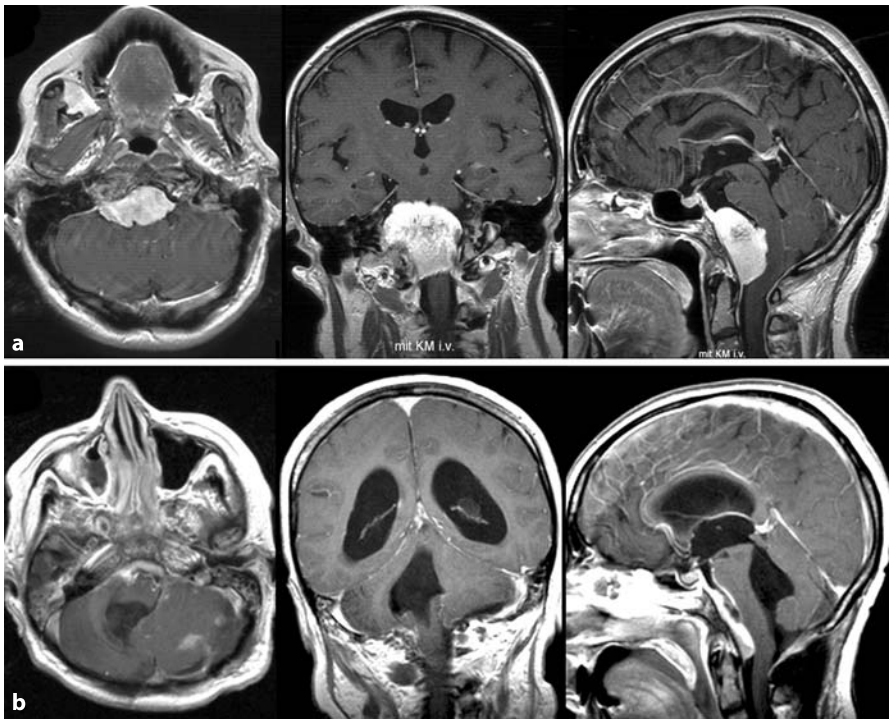


Fig. 3. Large meningioma of the clivus extending mostly into the right CP angle. The removal required approaches from both sides because of encasement of the caudal cranial nerves on both sides. The dura of the clivus was completely invaded and was left in place after extensive coagulation. The course has been stable with no indication of growth of the possible extradural tumor layer seen at the level of the foramen magnum (*bottom right*). Postoperatively, the patient developed a malresorptive hydrocephalus which required shunting

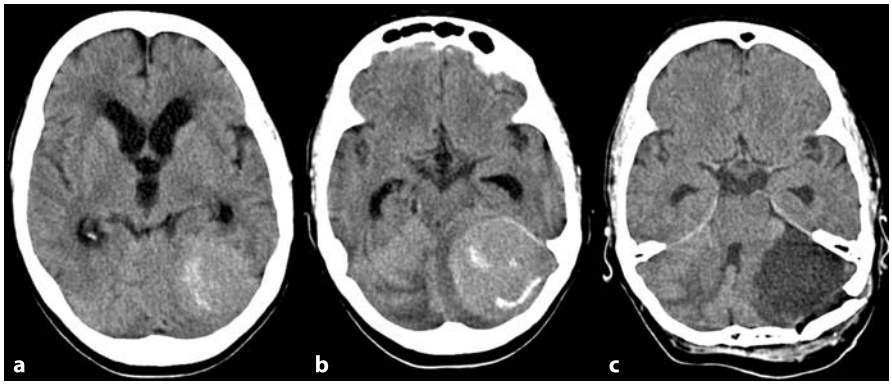


Fig. 4. CT of a large meningioma in the posterior fossa which has led over months to occlusive hydrocephalus, resulting in distended temporal horns and periventricular capping over the frontal part of the lateral ventricles. A few days after removal, the fourth ventricle is again visible, and the temporal distension is slowly regressing

or because an MRI has been performed after a minor trauma (Fig. 9). Otherwise, any of the symptoms summarized in Table 2 may have specifically led to some kind of neuroimaging.

Computed Tomography (CT). CT shows meningiomas usually as well-described mass lesions with uniform contrast enhancement located at the surface of the brain, either at the convexity or the base of the skull. A non-enhanced scan must be obtained in the first place because it may show extensive calcification which is mostly associated with very slow growth and thus only relative indications for therapy. Especially with fronto-orbital tumors, it is important to have thin sections and a series of bone windows because that defines the borders of infiltration and resection, if not even resectability. CT is the optimal modality to assess intraosseous components of frontobasal skull base meningiomas (Fig. 10) or to detect primary intraosseous meningiomas (Fig. 11).

Magnetic Resonance Imaging (MRI). MRI is now the major modality for the diagnosis of meningiomas, especially as many lesions have some skull base component or extensions into compartments which are not as well visualized or differentiated on CT. Again, the mass of the tumor will show homogeneous contrast enhancement, but also tail-like extensions in the meninges will be seen (the so-called meningeal tail sign (Fig. 12) and infiltration of neighboring structures. Petroclival meningiomas, for example, can be assessed anatomically for their complex extension towards the optic canal and into the cerebellopontine angle (Fig. 13). The carotid artery which is regularly encased by petroclival meningiomas can be judged for its width and shape and patency. When considerable narrowing is present, a 'time to peak' analysis after gadolinium application comparing the timing of gadolinium arrival in the two hemispheres already allows some estimate of hemodynamic relevance and indication for bypass surgery (Fig. 14). Frontobasal meningiomas are occasionally not much more than a thin layer of contrast enhancement, and that is especially true for optic sheath meningiomas which will be missed on any study other than thin-sliced MRI with special attention to all three planes (Fig. 15). When close to a sinus or originating from a sinus wall, extension of the tumor into the sinus or patency of the sinus can be seen on T2-weighted images and MR-angiography (Fig. 16).

The extent of edema is shown equally well on CT and MRI. The major differential diagnosis is a solid metastatic lesion because the age groups with the peak incidence overlap. Clues to decide for meningioma include the extent of dural involvement and especially a reaction of the bone like hyperostosis (Fig. 17). Meningiomas may also occur in multiple locations in the same patient (Fig. 18), but multiplicity is much more common in metastasis, and for three metastatic lesions it would be very unusual to have all of them on the surface of the brain. Metastases also tend to be cystic from necrosis after a certain size. In tumors over 1 cm2, MR spectroscopy is an additional tool which shows a characteristic spectrum of metabolites which can provide an increasingly reliable estimate of the nature of the lesion [16]. Diagnostic pitfalls are the rare cystic meningiomas which resemble a pilocytic astrocytoma or a cystic metastasis (Fig. 5).

Angiography. This diagnostic tool is only used to answer specific questions related to the surgical strategy and has no use in the diagnosis itself. It is indicated to answer the question of patency of si-

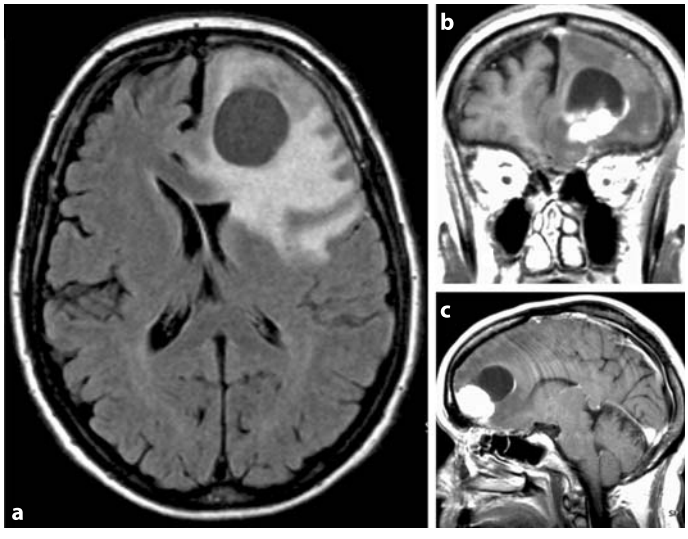


Fig. 5. MRI of a patient with a massive edema resulting from a meningioma of the secretory type. As seen on the T2 images, the amount of space occupation is mostly due to the edema and not so much to the mass effect of the tumor

nuses, collateralizations, and the hemodynamic relevance of a stenosis within a sinus. It provides a good overview of the vascularization (Fig. 19) and in some cases will provide an opportunity for preoperative embolization, especially when there is a major blood supply from tentorial or mastoidal meningeal arteries which during surgery will be caught only later during the procedure.

Therapy

Surgery

Therapy of meningiomas is generally surgical [2, 3]. Especially for the skull base locations, over the last decade it has become more interdisciplinary [19] with additional treatment opportunities for radio-

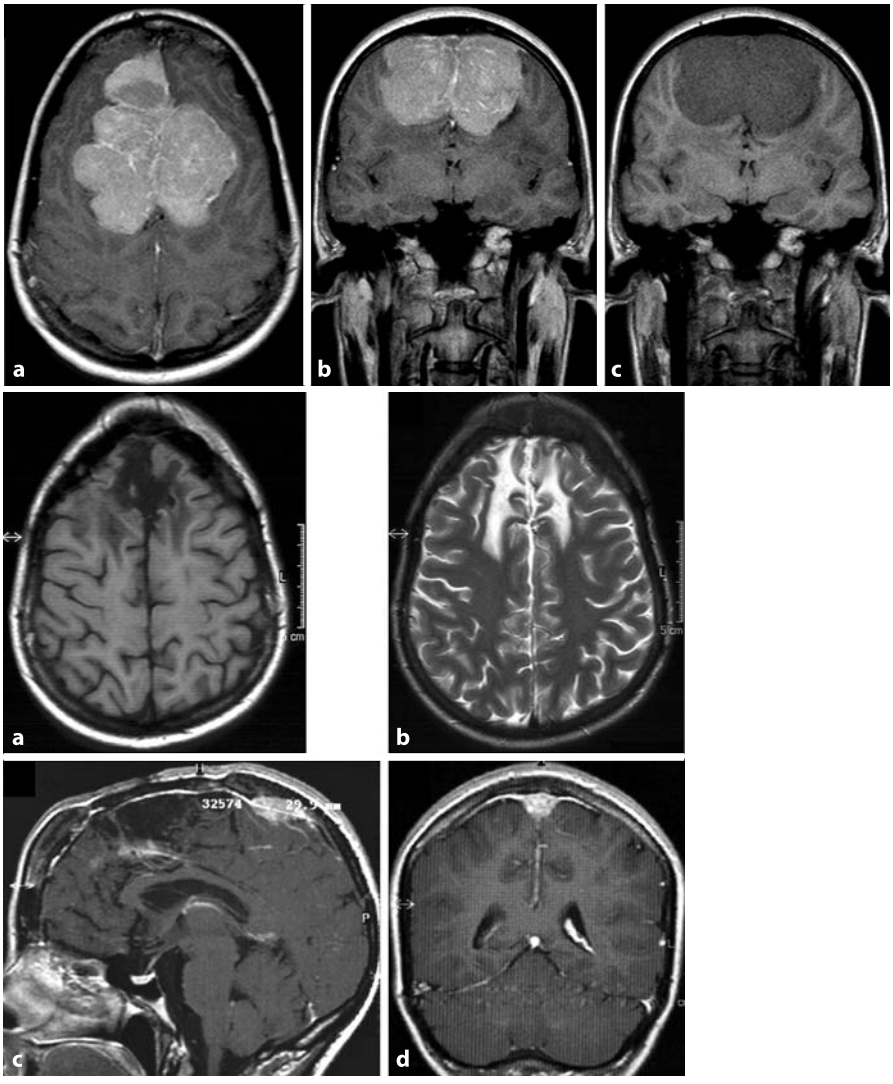


Fig. 6. a Very sharply demarcated bilateral falx meningioma of a 28-year-old woman who had papilledema and developed optic nerve atrophy from constant pressure. The sinus was removed in its occluded parts. **b** The edema which was present only in the most central aspects around the tumor was still present 5 years after follow-up (*top*), at which time a recurrence was also seen in the distal part of the sagittal sinus (*bottom*). This is asymptomatic and will be observed until a sufficiently large tumor has developed to warrant another operation and sufficient collaterals have formed so that the segment can be removed without congestive sequelae

therapists and neuroradiologists involving their improved tools [26]. The refinement of microsurgical approaches offers a resection option, at least partial, for almost all locations of meningiomas [2, 3]. Again, regarding the symptoms, there are differences in the surgical management according to the location.

The most important question is whether a meningioma needs to be treated at all or can be left to observation, keeping in mind that many lesions are found accidentally. Especially with incidental, calcified meningiomas in the elderly, a repeated imaging within 6 months or even a year is justified, and when no increase in size is seen, the lesion can be left to observation. Tumors may even change their growth characteristics over time. A tumor may recur, or a residual may slowly grow with advancing age and then slow down and remain constant for many years (Fig. 20).

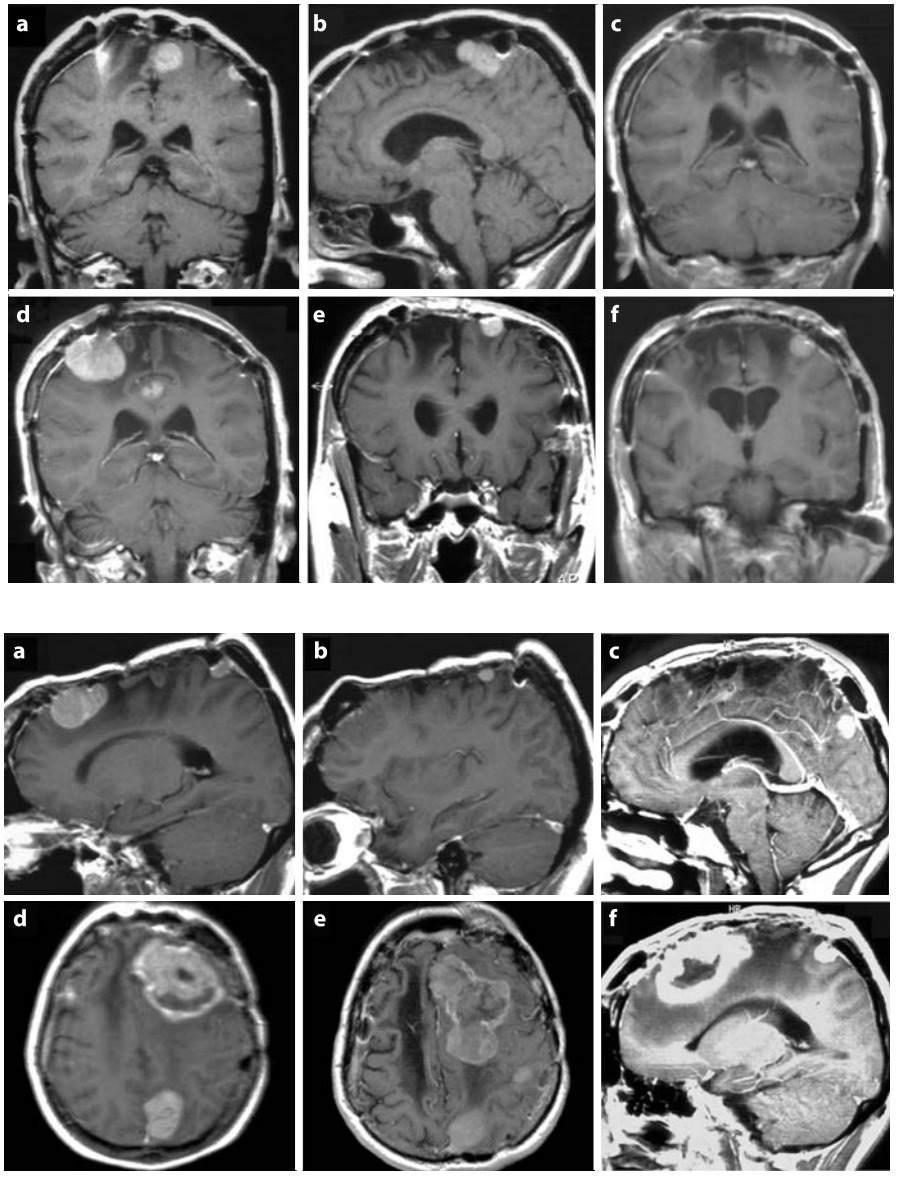


Fig. 7. a Progressive dedifferentiation of a meningioma which was originally operated on in 1978. Altogether six operations with increasingly difficult wound conditions followed for recurrences occurring at increasingly shorter intervals. This was correlated to accumulation of additional genetic alterations. **b** After removal, a cranioplasty flap had become necessary, and the patient received radiosurgical treatment (top); the lesions expanded with the development of a steroid dependence (middle). With further progression and severe disability (bottom); the patient declined any further treatment in 2003, after 25 years of struggle with a clinically aggressive meningioma

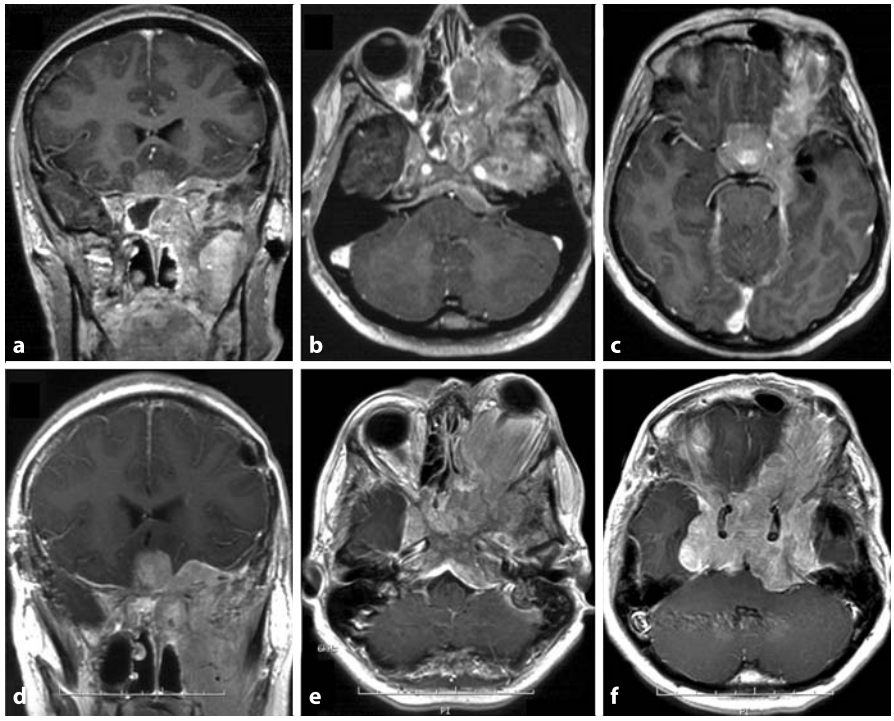


Fig. 8. Surgically not manageable, extensive fibrillary meningioma WHO I of the skull base which was partially decompressed twice to save vision in the right eye. The tumor is rapidly progressive, and radiosurgery, bromocriptine, antiprogesterone and hydroxyurea treatments failed

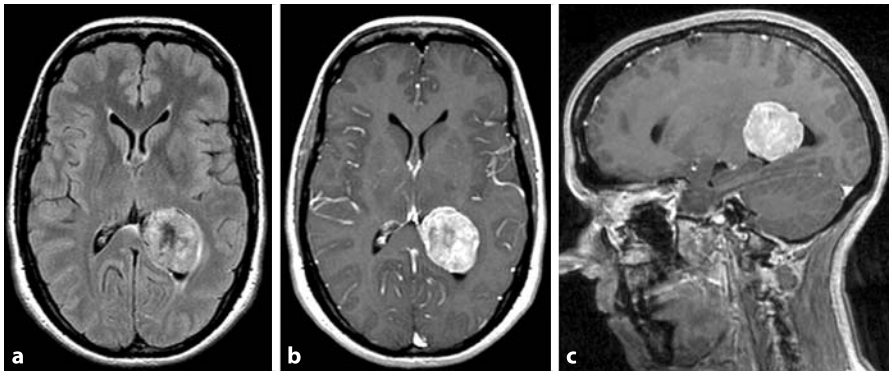


Fig. 9. A ventricular meningioma which was diagnosed because of intermittent headache which is completely nonreactive in the brain. The intact, not-invaded ependymal surface allowed for unrestricted CSF passage so that not even a partial hydrocephalus had developed

The classical, typical meningioma of the convexity or lateral sphenoid wing is resected along with its origin, as would meningiomas of the falx or the frontal skull base. Excision of the dura should be performed to the extent that the preoperative imaging showed any enhancement (meningeal tail sign). In most cases there will be sufficient periosteum to substitute for the resected dura. If not, artificial materials exist which may be used instead. When the bone appears to be affected, it could be drilled out at the suspicious site, and if it is completely infiltrated, it has to be replaced as well. Thus, in some cases reconstruction is more laborious than the resection itself, especially in fronto-orbital meningiomas or olfactory groove meningiomas where it may be necessary to close a bony destruction of the frontal skull base with split bone and periosteum [8].

Involvement of sinuses poses a specific problem. When the frontal part of the sagittal sinus is involved or a transverse sinus which has become hemodynamically irrelevant and is compensated by the other side, it can be sacrificed for the sake of a radical resection as there are good collaterals. If the sagittal sinus in its parietal aspect or the confluens or a dominant transverse sinus is involved and still patent and infiltrated to an extent which is beyond what

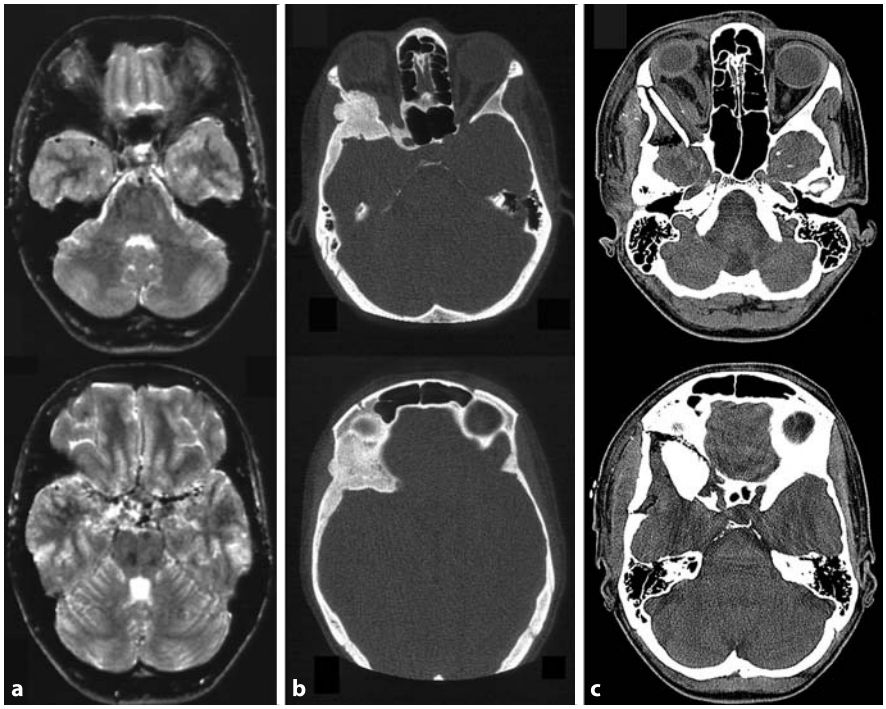


Fig. 10. Osseous meningioma of the lateral sphenoid wing, completely taking up the lateral wall of the orbit. No soft-tissue components are present. Removal requires extensive drilling of the bone and decompression of the optic canal. The bone is reconstructed with methyl-methylacrylate providing an orbital roof *(right bottom)* and a lateral wall *(right top)*

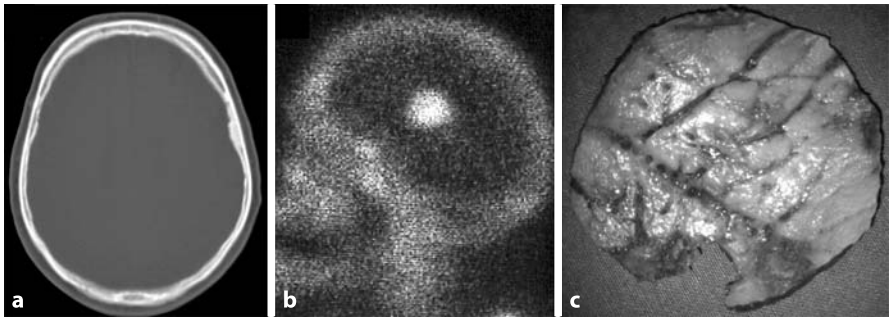


Fig. 11. Primary intraosseous meningioma which was found because of a staging for prostate carcinoma involving whole skeletal scintigraphy. The only sign of the tumor was a slight thickening of the bone and a changed bone structure. The tumor itself could be seen as pale sclerotic bone. The dura underneath the tumor was completely free of tumor and unreactive. There was no indication of any metastatic involvement

can be easily patched during surgery, the wall and any intrasinusoidal part should be left. It can be irradiated or left to grow on slowly, occluding the sinus while forming collaterals, which usually happens over years and as a rule goes unnoticed. Then the whole residual can be removed in one block. There are papers about sinus repair, but the rates of complication exceed that of this 'wait and see' and 'second look' approach [48]. Reports about focal irradiation have not yet been published, but it is to be expected that this will lead to some better local control, either arresting the tumor or leading to a longer delay until the sinus is closed.

The use of preoperative embolization has not become standard [5, 42]. Although many meningiomas would lend themselves to this approach, it is an unnecessary risk for the patient because for most tumors, the surgical approach to the lesion already involves extensive devascularization and achieves the same result as embolization. Fibrin glue and particles have been used mostly as embolic materials, and this leads to necrosis in the tumor which can make histopathological classification more difficult. Also, there may be swelling with ensuing neurological deficits, necessitating more urgent surgical intervention than anticipated. The indication for preop-

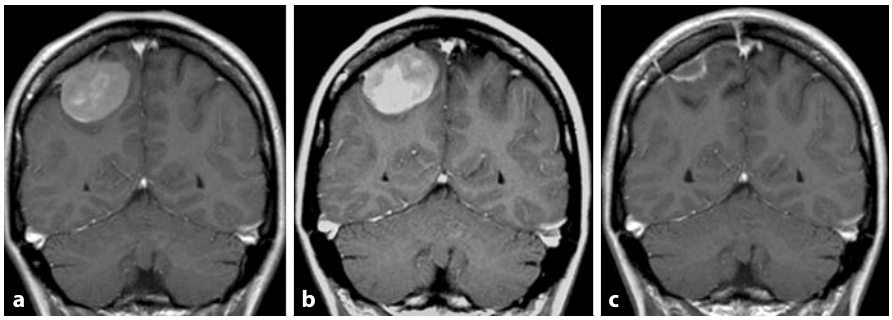


Fig. 12. Typical convexity meningioma with the broad dural attachment which extends further than the tumor (meningeal tail sign). Removal of the tumor (*right*) should include all the infiltrated zone which is to be replaced with periosteum

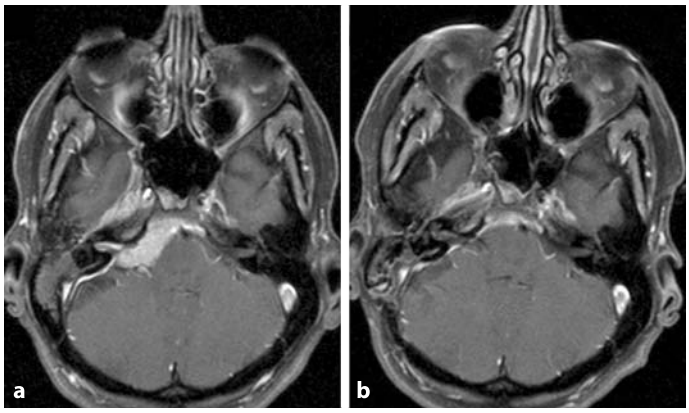


Fig. 13. Extensive, non-resectable meningioma of the clivus, CP angle, cavernous sinus, sellar lumen, and jugular foramen with extracranial extension (partially not shown). Removal of the intracranial parts to decompress the brainstem and free the cranial nerves together with coagulation of the clival and posterior petrosal dura was performed, and the whole residual has been irradiated by fractionated stereotactic radiation.

erative embolization should be very strict and limited to cases where there is a clear surgical advantage or a situation in which blood transfusions are anticipated but cannot be done for medical or non-medical reasons [43].

There are several tumor locations where the treatment paradigms over the last few years have changed, and the extensive skull base approaches with bypass surgery and cranial nerve interpositions have been abandoned in favor of a radiosurgical treatment component (Fig. 21). It is now common to approach large skull base meningiomas which involve the cavernous sinus as a whole or in part opportunistically. That applies to petroclival meningiomas and some lesions of the clivus and cerebellopontine angle. Any exophytic parts will be aggressively removed, and the tumor reduced to the part containing encased cranial nerves and blood vessels which will be left. That part can then be treated with conformal fractionated radiation or radiosurgery with any of the available radiosurgical tools (Fig. 22) [19].

Another specific situation occurs in optic sheath meningiomas (Fig. 23) [39].These meningiomas are usually very difficult to treat and pose a major dilemma. In an attempt to stabilize the disease temporarily, surgery is limited to decompression of the optic nerve canal and splitting of the sheath as much as the tumor infiltration allows. Attempts at resection almost always result in severe immediate deterioration of vision. With decompression only, visual loss will develop gradually and may be postponed for a long time. There are reports about radiosurgery, and they show that in the majority of cases stable disease can be secured, although long-term results over several decades are not available yet [4]. Whatever therapy is selected, care should be taken that it is administered only to patients with progressive disease because the course can be stable without treatment for many years [15].

Radiosurgery as a primary modality is reserved for cases in which surgical manipulation is associated with presently unacceptable morbidity and the likelihood of only subradical resection. As with the meningiomas which have a radiosurgical component in the interdisciplinary strategy, locations are mostly at the skull base, with true intracavernous meningiomas forming the largest group, but also locations in the cerebellopontine angle and the perisellar region. In addition to location, age, comorbidities, and general status of health have to be included into the decision-making (Fig. 24). The results of larger series show that disease control can be achieved in the

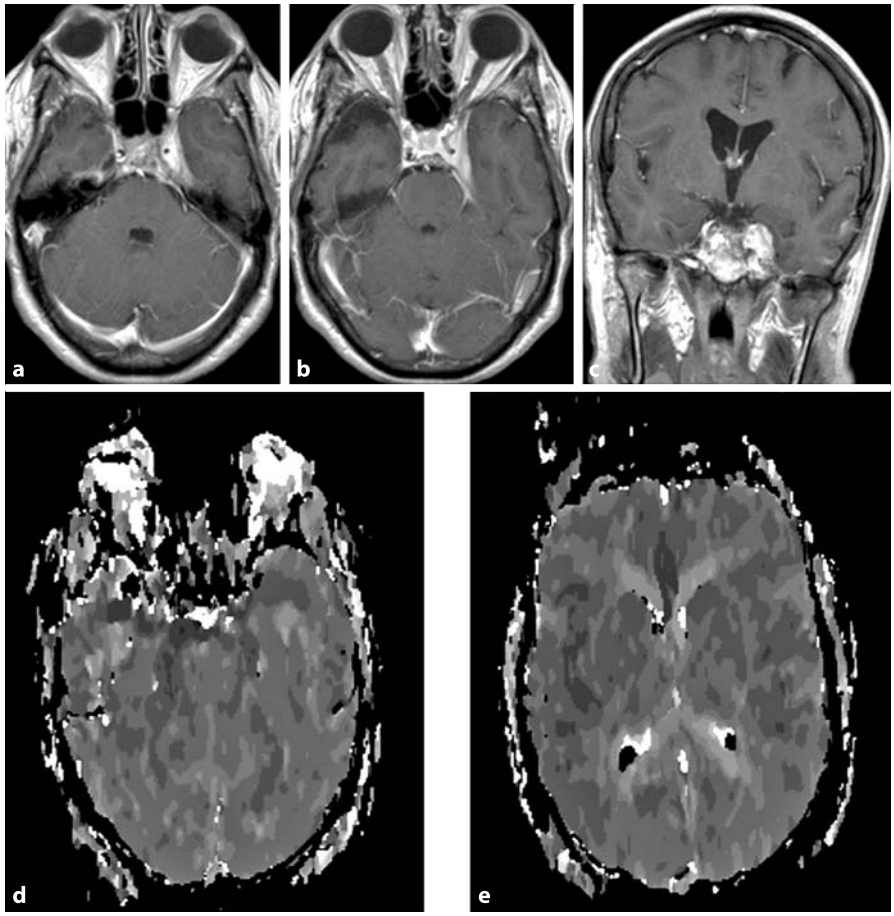


Fig. 14. Very compact meningioma of the anterior part of the cavernous sinus with significant narrowing of the left carotid but no symptoms of ischemia. In these situations, further progression of the tumor or the sequelae of radiosurgery may lead to 'silent' occlusion of the carotid in case of sufficient collateralization. To assess the risk, a very easy screening method is the so-called 'time to peak' measurement of the gadolinium distribution in both hemispheres in perfusion-weighted MRI (*right*). If the peaks are reached simultaneously, there is no hemodynamic relevance of the stenosis, and bypass surgery is not indicated

majority of cases with no or only minimal morbidity. Total remissions, however, are rare, which is to be expected when the induction of fibrous changes and stable disease is the major goal in these rather slowly proliferating lesions [26].

Chemotherapy has almost no role in the treatment of meningiomas. Even with anaplastic meningiomas, there is only limited experience and limited efficacy with the classical chemotherapeutic agents [10, 11, 28]. Hope has for a long time rested on new discoveries regarding the cell biology of meningiomas and the possibility to develop targeted approaches. But neither the presence of progesterone receptors nor the presence of dopamine receptors [9] has led to therapeutic opportunities despite phase II clinical trials [18]. The only option with some limited efficacy comes from drawing an analogy to chronic lymphatic leukemia, which also is a slowly proliferating disorder. Hydroxyurea which is effective in that disorder has shown a therapeutic effect also in some patients [36, 38], but a large, randomized, prospective, phase III trial is still unavailable.

Prognosis

The prognosis of meningiomas depends on their grade and their location. It can only be determined in the individual patient from regular follow-up. It has been difficult to find prognostic parameters based on histological markers except for grade and subtype. All other markers do not seem to have prognostic relevance. Based on the resection, the completeness of removal has been classified and basically distinguishes between a radical resection including the origin (Simpson grade 1), resection with coagulation of the origin

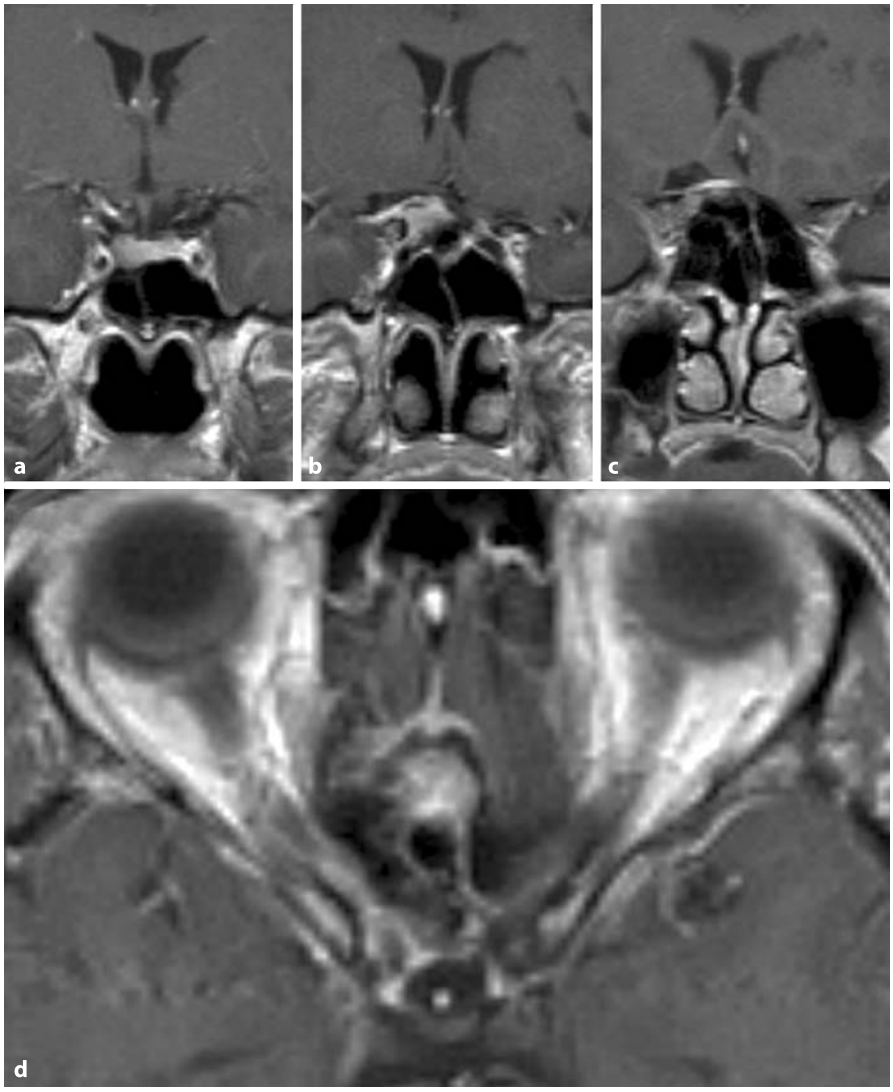


Fig. 15. Very small meningioma of the optic nerve which has led to visual impairment. Only in the coronal view can one see the enhancement which is minimal in the other planes. The only option is decompression of the optic canal

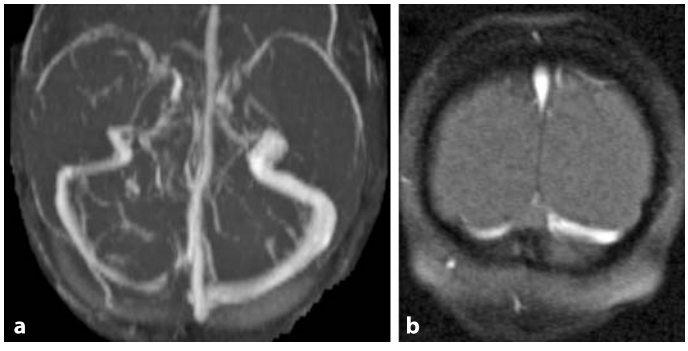


Fig. 16. Intrasinusoidal residual of an infratentorial meningioma involving the torcular area. This tumor is seen best as a 'negative' impression on MRI and was not removed because the sinus still carried significant amounts of blood. This tumor is under observation following a single-dose radiosurgical procedure

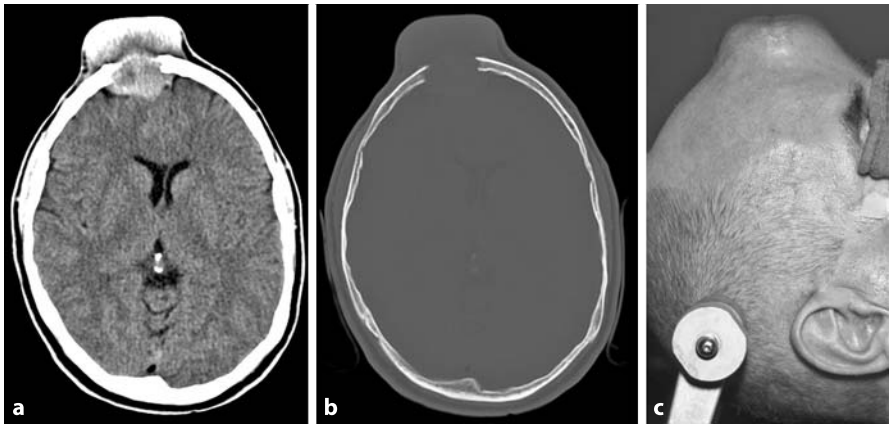


Fig. 17. Meningioma which has grown through the bone and can be seen extracranially as a deformity of the skull

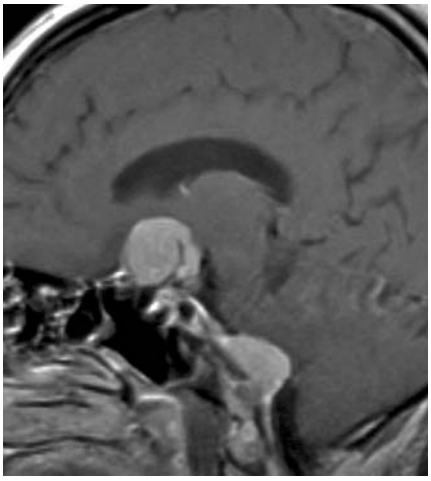


Fig. 18. Multiple meningiomas of a patient who was seen because of visual problems in the right eye as a result of a suprasellar meningioma. The MRI revealed a second, unconnected lesion in the right CP-angle which was removed in a separate session

(Simpson grade 2), partial resection (Simpson grade 3), and a mere biopsy (Simpson grade 4) [47].

Evidently there is a better prognosis with more radical resection but that may need to be revisited with the now widespread use of radiotherapeutic techniques for residual tumors. As a rule of thumb, one can expect permanent cure of a convexity meningioma grade WHO I or II which is fully resected in over 90% of the cases. Skull base meningiomas will recur in 50% of cases even when completely reduced to their site of origin.

Anaplastic meningiomas have a poor prognosis and will eventually even metastasize.

Follow-Up

Patients with resected meningiomas need to be followed up regularly after treatment, and that process may require interdisciplinary cooperation. At first, follow-ups with imaging should be conducted at 6 months or 1 year and later 2 years. MRI is generally the best modality, but in cases of bone involvement at the skull base, CT may need to be done as well. Because imaging changes may be subtle in some patients, other monitoring modalities may need to be included like regular ophthalmological assessment or audiograms when the tumor is in the area of the respective compromised cranial nerves, and recurrence/progression impairing their function is feared.

Only when there is no evidence for any activity of the disease after 10 years can patients be taken off regular follow-up. Bearing in mind that tumors may alter their growth characteristics over the years, patients can be advised that not each indication of new tumor activity needs to be treated right away because it may not cause any symptoms and might be safely watched for some time. On the other hand, it must be pointed out that exactly due to the usually slowly growing nature, regular follow-up is important because symptoms from a recurrent or progressing lesion may arise only late, and then optimal therapeutic opportunities may have been missed. There are no blood tests which would allow monitoring of tumor activity.

Future Perspectives

Optimal definition of the treatment modalities in an interdisciplinary setting and evaluation of that concept in larger series with meticulous follow-up will make the treatment of meningiomas safer and more efficacious on a much more individualized basis.

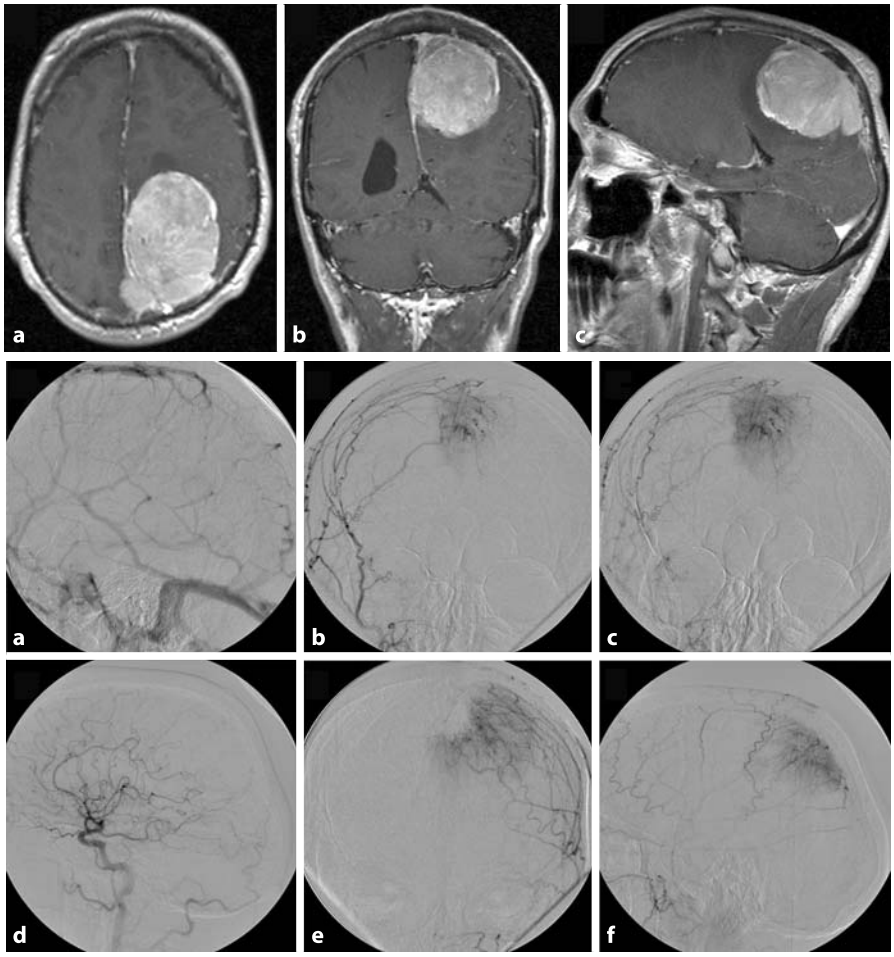


Fig. 19. a,b Large meningioma of the falx which had occluded the sinus and resulted in pronounced edema which was the cause of the neurological deficit and which completely resolved within a week of surgery. Vascularisation is exclusively via the external carotid artery and is completely eliminated when performing dural circumcision as the first step in surgery. Consequently, this tumor was an avascular mass during the removal without preoperative embolization

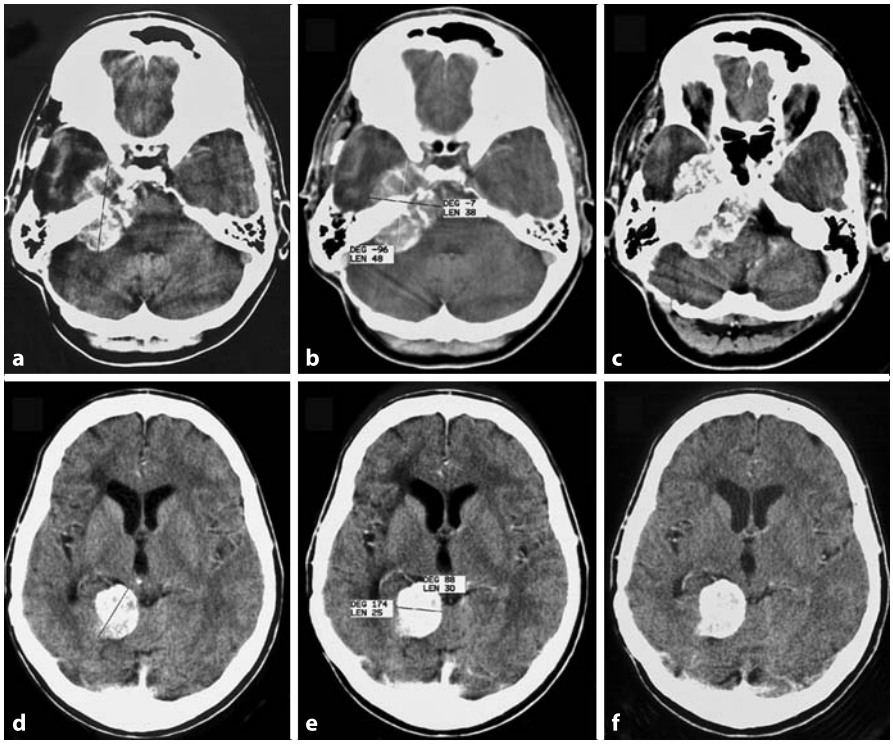


Fig. 20. Residuals of a meningioma which was operated on 10 years before the first CT scan seen in this follow-up. The patient felt no symptoms at the time and had other health problems which resulted in the decision to remain in follow-up without any surgical therapy. Further follow-up showed that after 5 years there is almost no further growth, and the patient is in stable condition without neurological deficits

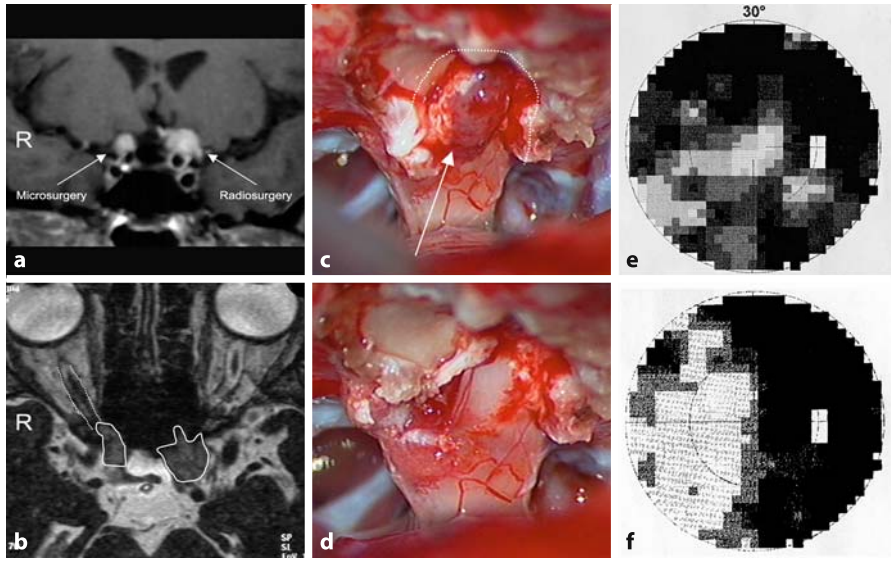


Fig. 21. Recurrent parasellar meningioma, blindness in the left eye, rapid deterioration of vision and visual field on the right side. Tumor extension (*solid line*) into right optic canal adjacent to optic nerve (*dotted line*). **b** Plan to surgically remove tumor in optic canal because of high risk of radiosurgery for the optic nerve (**a**). Intra-operative situation before (**c**) and after (**d**) tumor removal. Visual field prior to (**e**) and 1 week after (**f**) surgery

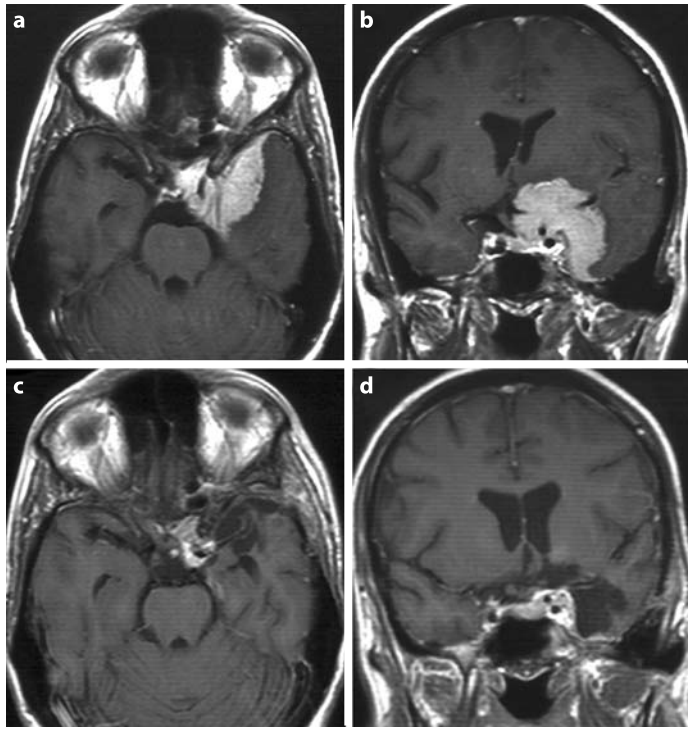


Fig. 22. Exophytic meningioma of the anterior clinoid process extending into the cavernous sinus and around the optic canal. Small residuals of the tumor were left, and at the first sign of progressive growth (*bottom right*) fractionated stereotactic surgery was indicated

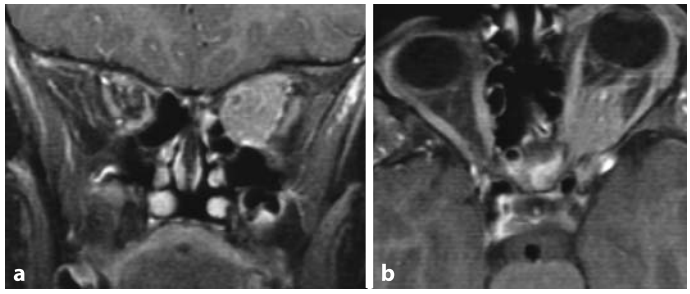


Fig. 23. Biopsy-proven meningioma of the optic nerve in a young boy, which upon inspection proved to be inseparable from the nerve and thus could not be removed without risking blindness which in this case was not yet present. Should the eye lose sight at some point, a complete resection might be attempted with the risk that the eyeball may degenerate completely when disconnected from the nerve

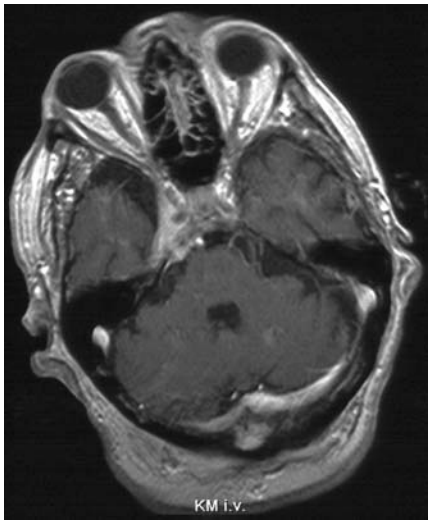


Fig. 24. Primarily radiated meningioma of the cavernous sinus in an otherwise severely disabled patient. Such cases are the domain of primary radiotherapeutic interventions

Given the absence of any pharmacological treatment option and lack of perspective of such in the near future, therapy will be based for a long time on surgery and radiation.

Other Meningeal Tumors

Haemangiopericytoma comprises about 2% of meningeal tumors [21]. They tend to occur at a younger age than meningiomas, with a peak incidence in the fourth and fifth decades. Also, there appears to be a slight prevalence for the male sex. By WHO grading, they are allocated to grades II and III, but the parameters distinguishing the two still need to be fully validated. The genetic alterations are different from meningioma, with alterations of chromosome 22 absent. Most alterations are found on chromosomes 12q13 and 6p21.

As for clinical signs and symptoms, there is no difference between meningiomas and hemangiopericytomas. The neuroradiological features are slightly different from meningiomas. The tumors tend to cause lytic lesions in bone and do not grow through the bone like the meningiomas, which with rare exceptions either cause hyperostosis or just distend the bone without completely destroying it. The tumors are highly vascularized and upon angiography show a wealth of pathological vessels [37]. In contrast to meningiomas, calcifications are rare.

The treatment of haemangiopericytoma is more complex than that of the average meningioma. The tumors should be removed as completely as possible, and then there is a consensus that the region needs to be irradiated [1] because otherwise the rate of recurrence is 91% [53]. Also, these tumors have a tendency to metastasize, primarily into bone [49]. No chemotherapeutic regimen has emerged as an effective standard [14]. Corresponding to the aggressiveness of the disease, patients need to be followed closely, especially to detect metastases. The high rate of recurrence and metastases are the cause of mortality, and despite aggressive treatment, up to 60% of the patients may have succumbed to the disease within 15 years [53].

Dural lymphomas present as contrast-enhancing lesions with an extension like a subdural hematoma, like a nodular meningioma with a dural tail, like an en-plaque meningioma, or just as dural hypertrophy. Primary dural lymphomas are rare and not to be mistaken for primary CNS lymphoma (see Schlegel, this volume). They are mostly of the MALT type [17, 44], although other kinds and regular Hodgkin's disease have been reported [23]. They seem to have a better prognosis than PCNSL and respond well

to cranial radiation [6]. Many of the reported dural lymphomas were unexpected, and therefore some were resected like en-plaque meningiomas. Cranial radiation is to be recommended even after resection but certainly after biopsy.

Dural metastases. Metastatic disease to the brain is seen with increasing frequency, but in comparison to the parenchymal or leptomeningeal variants, purely dural involvement is rare and is detected most frequently in the context of suspected meningioma [29, 52]. Whereas in intracranial disease, a metastasis is more readily suspected because of imaging characteristics and has a known primary in about 80% [56], the diagnosis of a dural metastasis is made much more frequently when the primary tumor is still unknown [52]. This can be partially explained by the fact that dural metastases may occur with any type of cancer but show a spectrum which is different from intracranial disease. A large combined surgical and autopsy series showed a surprisingly broad spectrum including the expected high numbers of breast cancer as the primary, but an even higher number of underlying prostate cancer and also such primaries as larynx, gall bladder and stomach, which otherwise rarely metastasize to the brain [25].

When purely dural and resembling a meningioma, the differential diagnosis is close to impossible without a tissue diagnosis because the neuroradiological techniques may not provide sufficient parameters for differentiation [27]. The tumors may be dural with a flat spread, nodular, or show a combination of subdural-dural-skull extension. Depending on the context of the patient's overall status, there may be an indication for resection, especially when the differential diagnosis towards meningioma cannot be made without histology, and there is no known primary. As the spectrum of histological origins is very heterogeneous, there are no published series about the role of radiotherapy or chemotherapy as there are for leptomeningeal metastatic disease. How to proceed after histological verification of a dural metastasis will depend on the established treatment paradigms for the primary tumor and has to be determined in an interdisciplinary tumor board.

References

1. Alen JF, Lobato RD, Gomez PA, Boto GR, Lagares A, Ramos A, Ricoy JR. Intracranial hemangiopericytoma: study of 12 cases. Acta Neurochir (Wien) 2001; 143:575–586.
2. Al-Mefti O. Meningiomas. New York, Raven Press, 1991.
3. Al-Mefti O. Operative Atlas of Meningioma. Philadelphia, Lippincott-Raven, 1998.
4. Becker G, Jeremic B, Pitz S, Buchgeister M, Wilhelm H, Schiefer U, Paulsen F, Zrenner E, Bamberg M. Stereotactic fractionated radiotherapy in patients with optic nerve sheath meningioma. Int J Radiat Oncol Biol Phys 2002; 54:1422–1429.
5. Bendszus M, Rao G, Burger R, Schaller C, Scheinemann K, Warmuth-Metz M, Hofmann E, Schramm J, Roosen K, Solymosi L. Is there a benefit of preoperative meningioma embolization? Neurosurgery 2000; 47:1306–1311; discussion 1311–1302.
6. Beriwal S, Hou JS, Miyamoto C, Garcia-Young JA. Primary dural low grade BCL-2 negative follicular lymphoma: a case report. J Neurooncol 2003; 61:23–25.
7. Buhl R, Hugo HH, Mehdorn HM. Brain oedema in secretory meningiomas. J Clin Neurosci 2001; 8 Suppl 1:S19–S21.
8. Bull WJ, Vandevender D, Cimino VG. Reconstruction of defects of the cranial base. Techniques in Neurosurgery 2003; 9:106–112.
9. Carroll RS, Schrell UM, Zhang J, Dashner K, Nomikos P, Fahlbusch R, Black PM. Dopamine D1, dopamine D2, and prolactin receptor messenger ribonucleic acid expression by the polymerase chain reaction in human meningiomas. Neurosurgery 1996; 38:367–375.
10. Chamberlain MC. Meningiomas. Curr Treat Options Neurol 2001; 3:67–76.
11. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. Neurology 2004; 62:1210–1212.
12. Christensen HC, Kosteljanetz M, Johansen C. Incidences of gliomas and meningiomas in Denmark, 1943 to 1997. Neurosurgery 2003; 52:1327–1333; discussion 1333–1324.
13. Collins VP. Brain tumours: classification and genes. J Neurol Neurosurg Psychiatry 2004; 75 Suppl 2:Sii2–S11.
14. Ecker RD, Marsh WR, Pollock BE, Kurtkaya-Yapicier O, McClelland R, Scheithauer BW, Buckner JC. Hemangiopericytoma in the central nervous system: treatment, pathological features, and long-term follow up in 38 patients. J Neurosurg 2003; 98:1182–1187.
15. Egan RA, Lessell S. A contribution to the natural history of optic nerve sheath meningiomas. Arch Ophthalmol 2002; 120:1505–1508.
16. Fountas KN, Kapsalaki EZ, Gotsis SD, Kapsalakis JZ, Smisson HF 3rd, Johnston KW, Robinson JS Jr, Papadakis N. In vivo proton magnetic resonance spectroscopy of brain tumors. Stereotact Funct Neurosurg 2000; 74:83–94.
17. Goetz P, Lafuente J, Revesz T, Galloway M, Dogan A, Kitchen N. Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue of the dura mimicking the presentation of an acute subdural hematoma. Case report and review of the literature. J Neurosurg 2002; 96:611–614.
18. Grunberg SM. Role of antiprogestational therapy for meningiomas. Hum Reprod 1994; 9 Suppl 1:S202–S207.
19. Hart DJ, Gianotta SL. Complex cranial base meningioma: Combined management. Techniques in Neurosurgery 2003; 9:86–92.
20. Hsu DW, Efird JT, Hedley-Whyte ET. Progesterone and estrogen receptors in meningiomas: prognostic considerations. J Neurosurg 1997; 86:113–120.

21. Jääskeläinen J, Louis DN, Paulus W, Haltia M. Haemangiopericytoma. In: Kleihues P, Cavanee WK, eds. Tumors of the Central Nervous System : Pathology and Genetics. Lyon, IARC Press, 2000.
22. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Sex steroid hormone exposures and risk for meningioma. J Neurosurg 2003; 99:848–853.
23. Johnson MD, Kinney MC, Scheithauer BW, Briley RJ, Hamilton K, McPherson WF, Barton JH Jr. Primary intracerebral Hodgkin's disease mimicking meningioma: case report. Neurosurgery 2000; 47:454–456; discussion 456–457.
24. Kaminski JM, Movsas B, King E, Yang C, Kronz JD, Alli PM, Williams J, Brem H. Metastatic meningioma to the lung with multiple pleural metastases. Am J Clin Oncol 2001; 24:579–582.
25. Kleinschmidt-DeMasters BK. Dural metastases. A retrospective surgical and autopsy series. Arch Pathol Lab Med 2001; 125:880–887.
26. Kondziolka D, Nathoo N, Flickinger JC, Niranjan A, Maitz AH, Lunsford LD. Long-term results after radiosurgery for benign intracranial tumors. Neurosurgery 2003; 53:815–821; discussion 821–812.
27. Kremer S, Grand S, Remy C, Pasquier B, Benabid AL, Bracard S, Le Bas JF. Contribution of dynamic contrast MR imaging to the differentiation between dural metastasis and meningioma. Neuroradiology 2004; 46:642–648.
28. Kyritsis AP. Chemotherapy for meningiomas. J Neurooncol 1996; 29:269–272.
29. Laidlaw JD, Kumar A, Chan A. Dural metastases mimicking meningioma. Case report and review of the literature. J Clin Neurosci 2004; 11:780–783.
30. Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol 2004; 63:275–286.
31. Lamszus K, Kluwe L, Matschke J, Meissner H, Laas R, Westphal M. Allelic losses at 1p, 9q, 10q, 14q, and 22q in the progression of aggressive meningiomas and undifferentiated meningeal sarcomas. Cancer Genet Cytogenet 1999; 110:103–110.
32. Lamszus K, Lengler U, Schmidt NO, Stavrou D, Ergun S, Westphal M. Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. Neurosurgery 2000; 46:938–947; discussion 947–938.
33. Lamszus K, Vahldiek F, Mautner VF, Schichor C, Tonn J.C., Stavrou D, Fillbrandt R, Westphal M, Kluwe L. Allelic losses in neurofibromatosis 2-associated meningiomas. J Neuropathol Exp Neurol 2000; 59:504–512.
34. Longstreth WT Jr, Phillips LE, Drangsholt M, Koepsell TD, Custer BS, Gehrels JA, van Belle G. Dental X-rays and the risk of intracranial meningioma: a population-based case-control study. Cancer 2004; 100:1026–1034.
35. Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ. Meningiomas. In: Kleihues P, Cavanee WK, eds. Tumours of the Nervous System. Pathology and Genetics. Lyon, IARC Press, 2000.
36. Loven D, Hardoff R, Sever ZB, Steinmetz AP, Gornish M, Rappaport ZH, Fenig E, Ram Z, Sulkes A. Non-resectable slow-growing meningiomas treated by hydroxyurea. J Neurooncol 2004; 67:221–226.
37. Marc JA, Takei Y, Schechter MM, Hoffman JC. Intracranial hemangiopericytomas. Angiography, pathology and differential diagnosis. Am J Roentgenol Radium Ther Nucl Med 1975; 125:823–832.
38. Mason WP, Gentili F, Macdonald DR, Hariharan S, Cruz CR, Abrey LE. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. J Neurosurg 2002; 97:341–346.
39. Newman SA. Optic nerve sheath meningiomas. Techniques in Neurosurgery 2003; 9:64–77.
40. Perry A, Dehner LP. Meningeal tumors of childhood and infancy. An update and literature review. Brain Pathol 2003; 13:386–408.
41. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, Tokunaga M, Tokuoka S, Mabuchi K. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst 2002; 94:1555–1563.
42. Probst EN, Grzyska U, Westphal M, Zeumer H. Preoperative embolization of intracranial meningiomas with a fibrin glue preparation. AJNR Am J Neuroradiol 1999; 20:1695–1702.
43. Rosen CL, Ammerman JM, Sekhar LN, Bank WO. Outcome analysis of preoperative embolization in cranial base surgery. Acta Neurochir (Wien) 2002; 144:1157–1164.
44. Rottnek M, Strauchen J, Moore F, Morgello S. Primary dural mucosa-associated lymphoid tissue-type lymphoma: case report and review of the literature. J Neurooncol 2004; 68:19–23.
45. Ruttledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, Delattre O, Thomas G, Nordenskjold M, Collins VP, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat Genet 1994; 6:180–184.
46. Sadetzki S, Modan B, Chetrit A, Freedman L. An iatrogenic epidemic of benign meningioma. Am J Epidemiol 2000; 151:266–272.
47. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957; 20:22–29.
48. Sindou M. Meningiomas invading the sagittal or transverse sinuses, resection with venous reconstruction. J Clin Neurosci 2001; 8 Suppl 1:S8–S11.
49. Soyuer S, Chang EL, Selek U, McCutcheon IE, Maor MH. Intracranial meningeal hemangiopericytoma: the role of radiotherapy: report of 29 cases and review of the literature. Cancer 2004; 100:1491–1497.
50. Strojan P, Popovic M, Jereb B. Secondary intracranial meningiomas after high-dose cranial irradiation: report of five cases and review of the literature. Int J Radiat Oncol Biol Phys 2000; 48:65–73.
51. Swensen R, Kirsch W. Brain neoplasms in women: a review. Clin Obstet Gynecol 2002; 45:904–927.

52. Tagle P, Villanueva P, Torrealba G, Huete I. Intracranial metastasis or meningioma? An uncommon clinical diagnostic dilemma. Surg Neurol 2002; 58:241–245.
53. Vuorinen V, Sallinen P, Haapasalo H, Visakorpi T, Kallio M, Jaaskelainen J. Outcome of 31 intracranial haemangiopericytomas: poor predictive value of cell proliferation indices. Acta Neurochir (Wien) 1996; 138:1399–1408.
54. Wan WL, Geller JL, Feldon SE, Sadun AA. Visual loss caused by rapidly progressive intracranial meningiomas during pregnancy. Ophthalmology 1990; 97:18–21.
55. Weber RG, Bostrom J, Wolter M, Baudis M, Collins VP, Reifenberger G, Lichter P. Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. Proc Natl Acad Sci USA 1997; 94:14719–14724.
56. Westphal M, Heese O, de Wit M: Intracranial metastases: therapeutic options. Ann Oncol 2003; 14 Suppl 3:Siii4–S10.

Low-Grade Astrocytoma 4

G. Evren Keles, Tarik Tihan,
Eric Burton, Mitchel S. Berger

Pathology – 104
Intraoperative Evaluation
Macroscopic Features
Microscopic Features
Granular Cell Astrocytoma
Gemistocytic Astrocytoma
Immunohistochemical Features
Ultrastructural Features

Clinical Characteristics – 107

Treatment and Outcome – 108
Surgery
Radiation Therapy
Chemotherapy

Conclusion – 113

References – 114

Low-grade astrocytomas reviewed in this chapter are grade 2 tumors according to the World Health Organization (WHO) classification [42], and correspond to grade 1 and 2 tumors of the Kernohan grading system [41] and to grade 2 tumors of the St Anne/Mayo classification [17]. They include fibrillary, protoplasmic, and gemistocytic astrocytomas [42]. In the literature, these histological entities are usually grouped together and referred to as 'low-grade gliomas'. Although this terminology is helpful in differentiating these tumors from higher grade gliomas which have a significantly different prognosis, grouping all histological subtypes together results in a heterogeneous group of tumors with different natural histories and therefore provides limited prognostic information. Various grading systems further complicate the overall picture.

Approximately 50% of newly diagnosed brain tumors are primary brain tumors of glial origin. Astrocytomas represent 26.6% of all newly diagnosed glial primary brain tumors [53]. This corresponds to 1500 to 1800 new cases of low-grade gliomas diagnosed in North America each year [18, 53]. Age-specific data show that low-grade astrocytomas constitute 15% of brain tumors in adults and 25% of brain tumors in children [26].

The etiology of low-grade gliomas is unknown. Except for patients with one of the phakomatoses, it has not been documented that genetic predisposition plays a role in the development of these tumors. There is no indication in the literature that low-grade gliomas are more prevalent in a specific ethnic or national group.

The only molecular genetic alteration consistently observed in otherwise healthy patients with low-grade astrocytomas is mutation of p53 [30]. The p53 gene is located at chromosomal location 17p13.1, and this site is often deleted in astrocytomas. The remaining copy of p53 is usually inactivated through a subtle mutation. The end product of this gene is a nuclear DNA-binding phosphoprotein that has transcriptional activity which is essential in the regulation of apoptosis and cell cycle progression. It has been shown that loss of normal p53 function promotes the accelerated growth and malignant differentiation of astrocytes [8, 103]. Astrocytomas are the only type of brain tumor to have significant p53 mutation rates. Some 50–60% of grade 2 and grade 3 astrocytomas exhibit p53 mutations, suggesting that this tumor suppressor gene inactivation is an early lesion among gene alterations associated with the development of malignant gliomas [98]. While some glioblastomas exhibit p53 mutations, a significant subset of them do not and instead have amplification of the epidermal growth factor receptor (EGFR) gene, suggesting that they arise from different genetic pathways. Other recurrent alterations observed in adult low-grade astrocytomas are gain of chromosome 7 and double-minute chromosomes. Losses of chromosomes 10, 13, 15, 20, and 22 and structural rearrangements involving chromosomes 4, 11, 12, 13, 16, 18, and 21 are observed in isolated patients [76].

Pathology

In recent years, the critical progress in our understanding of gliomas has led to the distinction between circumscribed and infiltrating types of astrocytoma. Circumscribed and infiltrating astrocytomas display distinct characteristics in their morphological, clinical, radiological, and genetic features [20]. The current nosology of brain tumors considers infiltrating astrocytomas as diffuse and progressive gliomas that gradually accumulate more aggressive histological and molecular features [43]. The 'infiltrating astrocytoma' without additional qualifiers is a WHO grade II neoplasm, even though the term can be used to identify all astrocytomas from grade II to IV [42]. WHO grade II astrocytoma is synonymous with low-grade infiltrating astrocytoma (LGIA). 'Astrocytoma, NOS' (not otherwise specified) is a highly vague and confusing term that should not be considered as a specific diagnostic entity. 'Well-differentiated astrocytoma' is another vague term that should be avoided as a final diagnostic category.

Intraoperative Evaluation

The fundamental purpose of the intraoperative evaluation or the 'frozen section' is to provide information for the surgeon which is needed to complete the surgical procedure. As in all cases submitted for intraoperative evaluation, a few critical steps facilitate the proper interpretation of infiltrating astrocytomas. The first step is the issue of sample adequacy and the studies needed for adequate interpretation of cytological and architectural detail. We believe the standard hematoxylin-eosin stain is sufficient for such an evaluation and should be adhered to until better and more detailed alternatives are discovered. Secondly, it is imperative to obtain intraoperative smears that provide the best venue for accurate interpretation of the cytological detail. Finally, intraoperative evaluation should never be considered as a substitute for a final diagnosis, and an adequate sample should always be saved for permanent sections. The pathologist should clearly communicate to the neurosurgeon that frozen sections always have the potential to require additional tissue. Frozen section requests made after completion of the surgical procedure are superfluous, or where additional tissue will not be available.

Frozen sections are particularly challenging for LGIA since there is a great tendency for the tissue to exhibit marked freezing artifact, often in the form of clear spaces and vacuoles. In addition, frozen sectioning greatly distorts the nuclear size and shape. It is also difficult to estimate the degree of cellularity and the relation of the cells to each other. Vacuolar artifacts may be difficult to distinguish from microcysts that are often filled with a faintly basophilic material. In most of these problems, the intraoperative smear proves to be an invaluable aid to the interpretation.

Grading of infiltrating astrocytomas during intraoperative evaluation is a nagging problem in surgical neuropathology. Particularly with the advent of more sophisticated treatment options that require intraoperative decisions, there is an increasing pressure for at least a tentative grading of the pathology material. The problem is often resolved if the surgical pathologist can 'unequivocally' identify the highest grade, but in the case of LGIA, it is best to evaluate histological features in the light of clinical and radiological evidence. For a more effective and appropriate evaluation of the intraoperative samples from LGIA, a visit to the operating room and a discussion with the neurosurgeon are invaluable.

Interpretation of tissue previously utilized for a frozen section should also be done with great caution and with the understanding that artifacts in nuclear size and shape can cause misinterpretations. Post-frozen samples can mislead the interpreter to diagnose gliosis as glioma and cause misinterpretations about the grade and type of the tumors.

MacroscopicFeatures

The external appearance of LGIA largely depends on the extent of cortical involvement, in other words, the involvement of superficial structures. There may be little or no external abnormality in tumors that are seated deep within the cerebral hemisphere. In tumors involving the cortex, the gyri appear edematous, expanded, and slightly discolored. The infiltrative astrocytomas almost imperceptively blend with the brain parenchyma, and the boundaries are often difficult to define. In surgical and autopsy material, LGIAs cause gray-dusky discoloration of the white matter with a focal cystic appearance, and soft to gelatinous consistency. The cysts may be large enough to be noticed during surgery but are often small, and can be seen after examination of the cut surface of the pathology specimen. The outlines of the anatomical structures are typically effaced, and the boundary between the white matter and cortex becomes indistinct. In the brain stem, LGIA can expand the pons and medulla and fill the cerebellopontine angle or interpeduncular fossa. These tumors can also distort the fourth ventricle and encase the basilar artery.

Microscopic Features

An astrocytoma is traditionally described as a tumor resembling normal astrocytic cells [12]. However, there is variability concerning the microscopic attributes of an astrocyte, and hence what an astrocytoma should look like microscopically. Nevertheless, the morphological features of cells recognized as fibrillary or protoplasmic astrocytes constitute the standards for defining an astrocytoma.

Typically, LGIA is hypercellular by a factor of two or more when compared with normal white matter. Recognizing the hypercellularity and the disruption of the architecture are the first clues to the diagnosis. Occasionally, the cell density may only minimally exceed that of normal white matter. In such cases, a correct diagnosis depends on the accurate interpretation of the cytological features.

The microscopic nature of infiltrating astrocytomas is evident in their ability to penetrate the brain parenchyma and permeate among glia, neuronal cells, and axonal segments.

The infiltrating astrocytomas have substantial nuclear hyperchromasia and pleomorphism. The nuclei often display striking irregularities with invaginations, sharp edges, and irregular contours. The chromatin is much coarser than that of normal astrocytes. Most astrocytic nuclei do not exhibit prominent nucleoli, or the nucleoli are rather indistinct within a markedly condensed chromatin. The size and shape of tumor nucleoli are quite variable among tumors as well as within a single specimen. Tumor cells occasionally display a fibrillary, eosinophilic cytoplasm. In paucicellular areas, the cytoplasm appears even more indistinct, and it may not be easy to associate the nuclei with the background fibrillarity.

Perinuclear haloes or the so-called fried-egg appearance of the cytoplasm can be seen in astrocytomas and do not necessarily imply an oligodendroglial component. Nevertheless, the prominence of such cells always raises the differential issue of oligodendroglioma or the dubious category of oligoastrocytoma.

The most common pattern for infiltrating astrocytoma is the microcystic pattern, which is a reliable indicator of an infiltrating low-grade glioma since it rarely occurs in reactive conditions. However, the microcystic pattern is not specific to LGIA and can also be observed in oligodendrogliomas and glioneuronal tumors.

A rare pediatric type of infiltrating astrocytoma with a unique histological pattern has been termed bipolar angiocentric astrocytoma [96]. It is still not

clear whether this pattern represents a unique entity or a morphological variant of LGIA.

LGIAs display secondary structures such as perineuronal satellitosis, subpial or leptomeningeal spread. Although these features are helpful in defining a low-grade glial neoplasm, they are neither specific nor common in LGIA. Mineralizations (either as amorphous or concentric forms) can be seen in association with LGIA. These mineralizations often occur within the gray matter and are more typical of an oligodendroglioma than astrocytoma.

Chondroid metaplasia or chondroid pattern is an extremely rare but striking finding in LGIA. The production of cartilage by neoplastic astrocytes may be related to their ability to secrete basement membrane material and other forms of mucopolysaccharides, which may become condensed to form a chondroid ground substance [40]. The chondroid cells in these metaplastic regions are also GFAP-positive [40].

The histological definition of LGIA practically excludes the presence of mitoses [43]. The significance of a solitary mitosis in a fairly well sampled tumor is still controversial. A recent study found a trend for a better prognosis for infiltrating astrocytomas with a single mitotic figure compared with frankly anaplastic astrocytomas. However, this trend could not be substantiated in multivariate analyses [67]. Nevertheless, it has been suggested that a single mitotic figure in a resection specimen may not impact the prognosis significantly, and some authors accept the presence of a solitary mitosis in a well-sampled grade II astrocytoma [12]. In such cases, it is even more critical to be aware of the radiological, surgical, and clinical findings to interpret the biopsy better. In our opinion, it is not appropriate to view the microscopic features in isolation from the clinical and radiological data.

Neither the presence of necrosis nor of vascular proliferation is acceptable in LGIA. Nevertheless, it is rarely possible that LGIA might show focal necrosis due to vascular compression and ischemia. A rare LGIA that was inadvertently or deliberately subjected to radiation treatment can also present with necrosis. Accurate clinical information and knowledge of the biopsy site are often helpful to avoid overgrading such lesions.

Granular Cell Astrocytoma

Granular cell astrocytoma is a unique and rare form of infiltrating astrocytoma that has been recently described [9, 14]. This neoplasm is described as an infiltrating glioma that contains individual large, round cells or sheets of them packed with eosinophilic, PAS-positive granules. Most granular cell astrocytomas contain lymphocytic infiltrates, either perivascular or admixed with neoplastic cells, and often there is a transition to typical infiltrating astrocytoma. Granular cell astrocytomas can be grade II, but most reported cases are higher grade neoplasms [9].

Gemistocytic Astrocytoma

Some LGIAs primarily consist of plump cells with abundant eosinophilic, hyaline cytoplasm and an asymmetric array of short processes. These tumors are designated as 'gemistocytic astrocytomas'. Gemistocytic astrocytomas rarely occur in pure form and often coexist with the classical infiltrating astrocytoma pattern. Perivascular lymphocytic infiltrates, occasionally creating germinal centers, are common and typical for these neoplasms. Gemistocytic astrocytomas possess brightly eosinophilic bodies resembling the Rosenthal fibers in their highly fibrillary cytoplasm. However, typical Rosenthal fibers are not seen in these tumors. Gemistocytic astrocytomas also contain a second population of small astrocytic cells with hyperchromatic nuclei, mitoses, and a higher MIB-1 labeling index than the gemistocytic cell population. They are believed to represent the main proliferating element of this variant of astrocytoma [99]. Krouwer et al. [46] suggest that the presence of at least 20% gemistocytes in a glial neoplasm is a poor prognostic sign, irrespective of the pathological background. These authors also propose that gemistocytic astrocytomas be classified with anaplastic astrocytomas and treated accordingly [46]. The current WHO classification does not provide an automatic designation of grade III for gemistocytic astrocytomas [43]. Currently, there is little doubt that gemistocytic cells in infiltrating astrocytomas are neoplastic rather than reactive. The frequency of p53 mutations is significantly higher (approximately twofold) in gemistocytic astrocytomas than in other astrocytoma subtypes [44]. Further studies on the cytogenetics of gemistocytes confirm that the gemistocytic cells in most infiltrating astrocytomas are neoplastic [45].

A critical issue for gemistocytic astrocytomas is their distinction from oligodendrogliomas that typically contain plump cells known as 'minigemistocytes'. The 'minigemistocyte' has an eccentric, spherical, GFAP-positive cytoplasm, and GFAP staining can be even more pronounced than with typical astrocytic cells. True gemistocytes seen in astrocytomas are larger, more eosinophilic, and have less distinct cytoplasm with short processes. In contrast to the minigemistocyte, GFAP-positivity is confined to the periphery of the gemistocyte, while the central portion of the perikarya is weakly positive. There is a considerable overlap in the appearance of gemisto-

cytes and minigemistocytes, and neither is absolutely diagnostic of any specific entity.

Immunohistochemical Features

In essence, the diagnosis of LGIA is primarily done on routine H&E stains, and immunohistochemical stains can hardly make up for a poorly sampled specimen. Nevertheless, a number of immunohistochemical stains are useful adjuncts in the interpretation of LGIA. The commonly used antibodies for neurofilament protein (NF) aid in defining axons within the specimen and confirm the infiltrative nature of the tumor. Even though astrocytomas and astrocytes are strongly positive for GFAP, this antibody is often unhelpful in determining the type and the grade of the neoplasm since the cells of many astrocytomas have little cytoplasm. In addition, the strongest GFAP-positivity is seen in reactive rather than neoplastic astrocytes. The gemistocytic cells are often weakly positive for GFAP, and the staining is usually located in the periphery of the cytoplasm. In contrast, minigemistocytes of oligodendroglioma are strongly GFAP-positive. Staining for MIB-1 (Ki-67 antibody) is usually less than 2%, and a neoplasm with higher than 5% MIB-1 labeling should raise suspicions of a higher grade neoplasm. Despite extensive studies on the Ki-67 labeling index and its relation to grade and survival, changing the grade of the lesion based on the MIB-1 labeling index is not justified in the current WHO classification [51, 91]. A significant percentage of LGIAs are immunoreactive for p53 [16]. This is particularly predominant in gemistocytic astrocytomas [97, 99].

Ultrastructural Features

The ultrastructural examination of a LGIA is not undertaken for diagnostic purposes, and only to explain an unusual histological feature. The fine structure of the astrocytic cell bodies and the processes are fundamentally similar to those of normal or developing astrocytes. The nuclei often display marked chromatin condensation and irregularities. The astrocytomas differ in their less developed cell junctions and poorly formed peripheral processes. The processes often consist of small microvilli or pseudopod-like protrusions. The cytoplasm of astrocytoma cells often contains little or no intermediate filaments, except in areas with increased cellularity [27]. The cytoplasm of gemistocytes is typically loaded with organelles and is sparse in intermediate filaments The granular cell astrocytomas contain partially membrane-bound, dense bodies compatible with secondary lysosomes. The granular cells also contain intermediate filaments corresponding to GFAP [59], supporting their glial origin.

Clinical Characteristics

It is important to obtain the past history and a physical examination, together with a thorough neurological examination preoperatively, for relevant details and information regarding the patient's general medical condition. Currently, with the help of better health care systems and advanced diagnostic technology, patients are diagnosed at an earlier stage of the disease. In a modern series, approximately half of the patients present with a seizure disorder, and half of the patients with a low-grade glioma appear neurologically intact [80].

The median age of patients with low-grade astrocytomas is approximately 35 years which is considerably lower than that of patients with higher grade gliomas. There is a biphasic age distribution with two peak incidences at 6–12 years and 26–46 years. Most studies have shown that males constitute between 55% and 65% of patients with low-grade astrocytomas [26]. This corresponds to a sex ratio of male-to-female incidence rates of approximately 1.5 [93]. The frontal lobe is the most common location, followed by the temporal and parietal lobes [105]. Low-grade astrocytomas may be lobar and relatively well-circumscribed or deep and diffusely infiltrating.

The most common presenting feature for patients with low-grade astrocytomas is seizures. One half to two-thirds of patients with low-grade gliomas present with seizures. Approximately 50% of the patients have headaches. In larger series and community-based studies, the presence of a brain tumor was detected in 8–30% of patients who presented with partial seizures, with age increasing the risk of epilepsy being caused by a tumor [37, 54, 102]. Together with gangliogliomas, the tumors reviewed in this chapter constitute gliomas that are most commonly associated with intractable epilepsy [37]. This fact is attributed to the characteristics of the tumor's growth pattern, with a higher seizure incidence being associated with relatively slowly growing tumors. In Penfield's series including 230 astrocytomas, low-grade gliomas were associated with epilepsy twice as frequently as glioblastomas [65]. The clinical course of 48% of 209 patients with hemispheric astrocytomas presented by Gonzales and Elvidge [24] was complicated by seizures.

Headache, lethargy, and personality change may be caused by the general increase in intracranial pressure. Papilledema may be present. Focal neurological deficits due to direct tumor infiltration or local pressure depend on the location of the lesion. Depending on the location of the low-grade glioma,

disinhibition, irritability, impaired judgment, abulia, apathy, motor and sensory loss, dysphasia, aphasia, anosognosia may be present. Tumors involving the parieto-occipital area may cause visual agnosias.

MRI and CT are the two neuroradiological tools that provide valuable diagnostic information. The diagnostic procedure of choice, however, is MRI due to its higher sensitivity in differentiating tumor tissue from normal brain. Although low-grade astrocytomas are often not associated with a significant mass effect, a mass effect upon the surrounding ventricular structures and cortical sulci is common, and in some cases a considerable mass effect may be seen in patients without a neurological deficit due to the slow-growth characteristics of these tumors. The typical CT image is a non-enhancing isodense or hypodense mass. Calcification may be detected in 15–20% of cases, and mild to moderate inhomogeneous contrast enhancement can be seen in up to 40% of all cases [78]. Cystic changes are not rare. On MRI, T1-weighted images reveal a isointense to hypointense non-enhancing mass which is hyperintense on T2-weighted images. Enhancement, when it occurs, is generally faint. In an earlier study, contrast enhancement was found to have no prognostic effect for patients with low-grade gliomas [87]. In contrast, more recent studies showed that enhancement has a negative effect on the time to progression and overall outcome [55, 69].

An adjunct to conventional neuroimaging techniques is magnetic resonance spectroscopy (MRS), which can be obtained during the same MR examination with little additional time. This technique allows the detection of metabolite levels in and around tumors, thereby providing metabolic data in addition to morphological imaging. Additional functional information may be obtained preoperatively with functional MRI and magnetic source imaging (MSI). This information integrated with the anatomical information obtained from conventional MRI and intraoperative stimulation mapping data can allow for more precise and complete resection of the tumor and enable the surgeon to minimize morbidity when operating in functionally eloquent brain areas [4].

Treatment and Outcome

Treatment options for diffuse astrocytomas at the time of initial diagnosis include observation, surgery in the form of biopsy or resection, and radiotherapy. The efficiency of chemotherapy is also being studied, mostly for recurrent tumors.

Surgery

The extent of the surgical resection and its timing are still controversial in the management of diffuse astrocytomas, mainly due to a lack of conclusive studies addressing these issues. In the literature, there are reports questioning the value of immediate treatment when an imaging study suggests a low-grade glioma [75]. Although there is no class 1 evidence in favor of early intervention, there is also no study showing an outcome benefit for patients when treatment is deferred. Furthermore, there are several potential risks that the patients would be exposed to by delaying surgery, including the risk of malignant degeneration, probability of developing irreversible neurological deficit, and a more persistent seizure disorder refractory to medical treatment.

Dedifferentiation or malignant transformation is a well-described phenomenon observed in low-grade gliomas. In the literature, 13–86% of tumors initially diagnosed as low grade recur at a higher histological grade [5, 47, 55, 58, 61, 69, 89, 94, 100]. Similar to its broad range of incidence, the time to malignant differentiation is also variable, ranging from 28 to 60 months [5, 55, 75, 81, 94]. However, the factors resulting in the change to a malignant phenotype remain unclear. In a recent study investigating the relationship between anaplastic transformation and the patient's age, a strong inverse relationship was found between the age at initial diagnosis and time to progression to a higher grade glioma [81]. The effect of treatment on malignant transformation is controversial. In Recht et al.'s [75] series, 58% of patients who did not initially undergo biopsy and treatment of a suspected low-grade glioma after diagnostic imaging studies eventually required surgery at a median interval of 29 months, and 50% of the tumors then showed anaplastic features. Although a higher incidence of malignant transformation at the time of operation and shorter time to tumor progression were observed compared with those in patients who were initially operated upon, the authors stated that no difference was observed in terms of survival [75]. The opposite was found in a series of 53 hemispheric low-grade gliomas volumetrically analyzed regarding recurrence patterns [5]. The risk of recurrence, either as low grade or at a higher histological grade, was minimized when less residual tumor volume was present postoperatively. The residual tumor volume was found to be more important than the percentage of resection in predicting the histological phenotype of recurrence. In addition, time to tumor progression was longer with more extensive resections associated with a smaller volume of residual tumor [5]. Additional studies evaluating the role of residual tumor volume on survival provided inconclusive results [48, 57].

The surgical treatment of diffuse astrocytomas consists of several different approaches depending on the patient's clinical condition and the surgeon's preferences. The surgical intervention may range from a simple stereotactic biopsy to obtain a tissue diagnosis to an extensive resection coupled with seizure surgery in patients with diffuse astrocytomas associated with intractable epilepsy. Surgical intervention is the essential treatment modality in the management of low-grade gliomas, and the main goals are histological diagnosis and reducing the tumor bulk in order to decrease intracranial pressure, improve neurological deficit, prevent malignant dedifferentiation, and obtain seizure control.

Stereotactic techniques or frameless methods, i.e., neuronavigation, have a lower morbidity and mortality, i.e., 1.2–6.4% [1, 7], than open surgical approaches; however, with the exception of computer-assisted stereotactic resections, they only serve the aim of obtaining a tissue diagnosis. Therefore, the use of stereotactic biopsy is limited to a subgroup of patients harboring suspected low-grade glial tumors depending on the characteristics of the lesion, e.g., depth, small size, multiplicity, diffuseness, or the patient's clinical condition. An incorrect pathological diagnosis is not uncommon for tumors of glial origin, and the misdiagnosis usually consists of misinterpreting a high-grade tumor as a low-grade glioma. Although the incidence of this problem varies in different series, it may be significantly reduced by serial sampling along the entire radius of the lesion and beyond. Close collaboration with an experienced neuropathologist is essential for the diagnostic efficiency of stereotactic biopsies. There are no randomized studies examining the prognostic effect of stereotactic biopsy followed by radiation therapy for the initial management of patients with diffuse astrocytomas. Retrospective, non-randomized studies including selected patients do not show any substantial benefit in terms of overall survival for patients who receive a biopsy followed by radiotherapy when compared with those patients who receive conventional surgical resections [52, 69, 85, 86].

Computer-assisted stereotactic resections are helpful for tumor resection in certain locations that are technically challenging and associated with high morbidity rates. This technique, by providing images of lesions in triplanar format and by accurately referencing the data to either a stereotactic frame or the patient's surface anatomy, permits the neurosurgeon to plan precisely an approach that minimizes injury to critical neural structures. As an example, perioperative mortality for radical resection of gliomas in and around the thalamus now approaches zero with modern techniques [90]. Unnecessary brain resection and retraction are also minimized.

Contemporary neurosurgical methods, including ultrasonography [6, 39], functional mapping [36], frameless navigational resection devices, and intraoperative imaging techniques [104], enable the neurosurgeon to achieve more extensive resections with less morbidity. Intraoperative stimulation mapping of cortical and subcortical tissue in and around a tumor will identify functional tissue, and its preservation will minimize the risk of permanent postoperative deficit. It has been shown that resection of tumors located near or within functional brain areas may not be safe even if the surgeon remains within the boundaries of the macroscopically obvious tumor. In addition to its use to determine functional cortical sites, stimulation mapping is the only available method that provides reliable identification of descending subcortical motor, sensory, and language tracts. Hemispheric gliomas located within or adjacent to functional areas, such as the Rolandic cortex, supplementary motor area, corona radiata, internal capsule, and uncinate fasciculus, constitute the major indications for intraoperative motor mapping. Due to the tendency of infiltrative gliomas to invade underlying white matter tracts, it is important to identify both cortical motor sites and their descending pathways. Regardless of the gross appearance and consistency of the tumor, functional tissue may also reside within the mass itself and must be identified with stimulation mapping before definitive resection.

Cortical language localization, through object-naming and reading, is variable in each individual and does not follow any reproducible pattern across the population. The traditional concept regarding the cortical representation of language function involves an anterior language site, Broca's area (posterior part of the inferior frontal gyrus), and a posterior site, Wernicke's area (perisylvian in the temporoparietal cortex). This concept was challenged by some early studies in which electrical cortical stimulation was used. In addition, dominant temporal-lobe resections guided by standard neurosurgical landmarks – that is, restricting the temporal lobe resections to within 4 cm of the temporal tip and limiting the removal of the superior temporal gyrus – have been associated with permanent postoperative language deficits. A negative stimulation mapping may not provide the necessary security to proceed confidently with the resection. Therefore, it is essential to document where language is located, as well as where it is not located, if feasible. This is also the reason for having a generous exposure, not only to maximize the extent of resection but also to minimize the possibility of obtaining negative data. It has been shown that the distance of the resection margin from the nearest language site is the most important factor in determining recovery from preoperative language

deficits, the duration of postoperative language deficits, and whether the postoperative language deficits are permanent. Significantly fewer permanent language deficits occur if the distance of the resection margin from the nearest language site is >1 cm.

Reviewing the four prospective, randomized studies currently available for diffuse astrocytomas in adult patients, age, histology, and tumor size appear to be generally accepted prognostic factors influencing the outcome [19, 34, 71, 83]. The prognostic effect of the surgical intervention is controversial, however [38]. The majority of low-grade gliomas seen in adults are located in the cerebral hemispheres, and their natural history is significantly different than their pediatric counterparts. The trend in the literature, unfortunately, has been to include all low-grade gliomas into the series regardless of the age group and location, making the data difficult to interpret. A review of the literature from 1970 to 2000 shows that in recent years, i.e., 1990s, there was a noticeable increase in the number of studies that support more extensive resections along with a decrease in the number of reports showing no difference in terms of outcome [2, 3, 19, 29, 31, 33, 35, 47, 48, 50, 56, 57, 60, 61, 66, 68–70, 74, 77, 79, 82, 84, 85, 86, 88, 89, 92, 101]. All of these studies are non-randomized except for two [19, 35], and in all studies, the extent of resection was determined by non-volumetric methods, mostly depending on the surgeon's intraoperative estimate.

Studies with a distinct subgroup of patients who had a macroscopically gross total resection of their tumor [2, 29, 47, 56, 57, 60, 61, 66, 68–70, 74, 79, 85, 89, 101] found a statistically significant effect of the extent of surgery on survival. Results of studies in which gross total resections were combined with less than total resections [3, 19, 31, 33, 35, 48, 50, 77, 82, 86, 88, 92] were also consistent with an improved survival observed in patients with a higher degree of resection. Although longer 5-year survival rates were observed for patients who undergo a more extensive resection, the difference of survival benefit was less pronounced compared with those patients who received a gross total resection. However, there was no indication that more extensive resections were associated with a less favorable outcome.

There are few studies that simultaneously excluded pediatric patients and pilocytic and gemistocytic histologies, which have a significantly different prognosis, and included more than 75 patients [48, 68, 74, 89, 92]. Despite the fact that these 5 studies are all retrospective and non-matched, they are the most homogeneous series that are available in the literature regarding patient population and histologic characteristics. The prognostic effect of extent of resection was found to be statistically significant in univariate analysis in every study. In multivariate analysis, however, the extent of resection was a significant independent factor in 4 of these 5 series [48, 68, 89, 92].

Within the last few years since 2001, five new studies have addressed the issue of extent of resection for diffuse astrocytomas as it relates to outcome. Two of these studies [71, 83] are prospective and randomized, and although they were not designed to evaluate the extent of resection specifically, both had this parameter as a variable in their statistical analysis. The volume assessments, however, were not volumetric. In both studies, extent of resection was found to be a statistically significant predictor of outcome in univariate analysis, but not in multivariate statistics [71, 83]. The results of these studies will be discussed further later in this chapter. In the remaining 3 retrospective studies, the extent of resection had a significant prognostic impact for low-grade tumors [28, 32, 49].

The surgical management of patients with low-grade gliomas and seizures is controversial. Surgical options include focal excision of the tumor alone, radical tumor resection without electrocorticography, and a radical resection with seizure foci mapping. In patients with low-grade gliomas who are under complete seizure control preoperatively or those who have an occasional seizure on medication, seizure control with or without the need for postoperative anticonvulsants is often achieved only with radical tumor resection.

Radiation Therapy

Radiation therapy is one option for the treatment of patients with low-grade glioma. Other options include postoperative observation or chemotherapy. The role of radiation has been controversial for many decades, with physician and patient bias supporting the decision to treat once the diagnosis is made, or to defer therapy until further tumor progression or symptoms occur, prompting the need for intervention. Retrospective, single-institution reviews seemed to suggest a benefit for the use of radiation therapy at the time of the initial diagnosis. Fortunately, over the past few years, a number of prospective clinical trials have been reported which should be helpful as guidelines for treatment decision.

In general, treatment is reserved for patients with symptomatic residual disease despite optimal surgical resection or for patients who are felt to have high-risk features. Further studies are needed to fully define 'high-risk' features, but the current hypothesis is that patients over the age of 40 with residual disease represent a subset of cases in which earlier intervention may be warranted. These recommendations are based upon three prospective studies done over the last 10 years [34, 35, 83]. The studies were designed

to address two specific questions: Is there a radiation dose that might improve survival, and does early intervention with radiation improve the outcome compared with observation. A fourth study was also conducted which sought to evaluate the survival impact of chemotherapy in addition to radiation [19].

The European Organization for Research and Treatment of Cancer (EORTC) conducted two prospective studies in adults with low-grade glioma, which included astrocytoma, oligodendroglioma, and mixed oligoastrocytoma [34, 35]. EORTC protocol 22845 randomized 311 patients to postoperative observation versus postoperative radiation (54 Gy), while EORTC 22844 randomized 379 patients to high-dose (59.4 Gy) versus low-dose (45 Gy) radiation. The two studies were conducted simultaneously, with similar eligibility and stratification factors. No survival benefit was seen with high-dose radiation compared with low-dose radiation, and perhaps more importantly, no survival benefit was seen when radiation was used postoperatively compared with patients who were followed by observation alone. The 5-year overall survival rate for observation was 66% compared with 63% after radiation with 54 Gy, 58% for low-dose radiation of 45 Gy, and 59% for 59.4 Gy. There was no difference in the 5-year progression-free survival rate when comparing the low-dose (47%) versus higher-dose radiation (50%). However, there was an improvement in the 5-year progression-free survival in patients randomized to radiation (44%) compared with patients who were observed (37%). The conclusions from these two large prospective studies support the notion that a survival benefit does not exist when radiation is used in the initial treatment of adults with low-grade glioma, although there does appear to be a difference in progression-free survival.

The Southwest Oncology Group (SWOG) conducted a small, prospective, randomized study of radiation alone (55 Gy) versus radiation plus adjuvant chemotherapy using the single agent lomustine (CCNU) [19]. This study included adult patients with subtotally resected or biopsied astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. Only 60 patients were randomized. There appeared to be a trend toward better median survival with chemotherapy (7.4 years) compared with radiation alone (4.45 years), but the 10-year survival rate was 40% for radiation alone compared with radiation plus CCNU (20%). Thus, this study also suggests that more therapy is not necessarily better.

Finally, the North Central Cancer Treatment Group (NCCTG) along with the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Group conducted a large phase-3 study in adult patients with newly diagnosed low-grade glioma (astrocytoma, oligodendroglioma, and oligoastrocytoma), randomizing patients to high-dose (64.8 Gy) versus low-dose (50.4 Gy) radiation [83]. As with the EORTC 22844 trial, no survival benefit was seen with the higher dose of radiation. There appeared to be a higher incidence of neurotoxicity at 5 years with the higher dose strategy (10% rate) than the lower dose radiation (2% rate). The 5-year overall survival rate was 72% and 65% with low-dose radiation and higher dose radiation, respectively. Important negative prognostic factors included age >40 years, tumor size larger than 5 cm, and astrocytoma histology. Extent of resection was an important prognostic factor in the EORTC 22844 study.

RTOG recently completed accrual to a large, randomized, phase-3 study comparing radiation alone versus radiation plus adjuvant chemotherapy using procarbazine, CCNU, and vincristine (PCV) in patients with high-risk features, which they defined as age >40 years or any age with less than a gross-total resection. Patients aged less than 40 years with a gross-total resection were followed by observation. The results of this study have not been analyzed but will be of interest, and will hopefully add further information about prognostic subgroups and the impact of the combination of radiation and chemotherapy. Other randomized studies are ongoing in the EORTC as well. These new studies will be of great interest not only for the outcomes data, but also for the results of tissue correlation studies that will compare biologic factors in the outcomes analysis. Molecular pathology and genetic characterization of tumors will hopefully become as important as age, histology, and extent of resection as prognostic factors. The goal of these studies will ultimately allow specific stratification of patients towards treatment more likely to improve survival with minimal risk.

Radiation frequently will be necessary in patients with low-grade glioma. Older, newly diagnosed patients with larger tumors or any patient with symptomatic lesions should be considered for radiation. The alternative approach is to use chemotherapy in an attempt to defer the need for radiation (see below). In general, radiation is given to a dose of 50–54 Gy, in 1.8 to 2.0 Gy fractions, to a focal field with 2-cm margins. Whole brain radiation is rarely indicated and can cause significant neuro-cognitive deficits over time. This is especially relevant in older patients who appear to have less tolerance to radiation-associated injury. Younger patients, who may live for decades, are also at greater risk for late radiation effects. The volume of brain irradiated, total dose given, as well as tumor location may play a role in the development of late radiation effects. Unfortunately, there are limited prospective data concerning the scope and degree of neurotoxicity in long-term survivors treated with radiation. Improved techniques now exist for radiation treatment planning which

make it possible to limit normal brain exposure to higher dose radiation, and hopefully these advances will minimize the potentially negative impact of radiation-associated injury.

With the results thus far presented in the literature, a practical approach to the patient with low-grade glioma would be to consider prognostic factors and make specific recommendations based upon age, extent of resection, tumor location, and presence of symptoms related to the residual disease. One could strongly consider the option of observation, particularly in the setting of a younger patient with a gross-total resection of disease. Observation of the older patient with gross-total resection is also an option, although the risk of earlier progression may be higher compared with younger patients. More frequent scanning may be indicated in this setting. Younger patients (age <40 years) with partially resected disease, who are without significant symptoms, could also be given the option of observation as well, as no survival benefit has been demonstrated with early intervention using radiation. This is not to state categorically that radiation is not indicated, as there may appear to be some benefit in progression-free survival. Some patients and physicians may feel that the potential to defer growth is an appropriate reason to choose radiation early. In this setting, the risks of radiation need to be weighed against this non-survival benefit. Smaller lesions in non-eloquent areas of the brain would seem to offer less long-term risk, and thus may be a situation where radiation would be a reasonable approach. Younger patients with symptomatic disease, despite optimal surgery, could be given the option of radiation or perhaps chemotherapy and, as noted previously, should consider enrollment into clinical trials. Older patients with residual disease with or without symptoms appear to represent the highest-risk group for early progression and should be considered for treatment. Whenever possible, enrollment into clinical studies should be encouraged, given the uncertainty of specific therapies on survival outcomes within patient subgroups.

Chemotherapy

Management options for adults with low-grade astrocytomas (LGA) include observation, surgery, radiation, or chemotherapy, but there is no well-established standard approach. Patients who have undergone a complete radiographic resection of their tumor are often followed with surveillance MRI scans and treated upon progression. Patients who have undergone subtotal resections have been treated with radiation therapy in the past. However, there is now a trend to avoid up-front radiation based on an EORTC study that suggests there is no survival benefit [34]. Adjuvant chemotherapy after radiation has not typically been given. However, RTOG is conducting a study that addresses the question of a possible benefit with this approach. In this trial, patients over 40 or those with incompletely resected low-grade tumors will receive radiation with or without procarbazine, CCNU, and vincristine (PCV).

The role of chemotherapy in adult patients with LGA has not been extensively investigated. This section will focus on the use of chemotherapy in the treatment of adults with LGA and the relevant clinical studies that have been completed or are presently being conducted.

In the available literature describing the use of chemotherapy for low-grade gliomas in adults, there are differences in trial methodology that can confound an interpretation of the results. Most studies are retrospective and have a mixture of low-grade histologies included in them. Patients may also have had different prior therapies before receiving chemotherapy, i.e., radiation. Chemotherapy in adults with LGA has most commonly been used as a salvage treatment for post-radiotherapy progression [10, 13, 22]. However, in many instances, it is not clear that the tumor has remained low grade at progression since tissue confirmation has not been obtained. Up-front chemotherapy has been used primarily to treat children in order to avoid the potential long-term deleterious effects of radiation [21, 72].

To date, there has only been a single published, randomized trial to assess the role of chemotherapy in patients with low-grade astrocytomas. SWOG conducted a prospectively randomized study to evaluate the addition of CCNU to radiation therapy for the treatment of low-grade gliomas. This study included grade I or II astrocytomas that were pilocytic astrocytomas, gemistocytic astrocytomas, mildly anaplastic astrocytomas, mixed gliomas, oligodendrogliomas, and gangliogliomas [19]. Fifty-four patients were randomized after incomplete resection to receive radiation or radiation in combination with CCNU. There was no statistically significant difference in survival time seen between the two groups. The median survival for patients who received radiation alone was 4.5 years, and for patients who received irradiation plus CCNU, the median survival was 7.4 years (p=0.7). Other clinical factors that impacted survival in this study were age, functional status, and extent of resection.

Temozolomide, an oral alkylating agent, is now being investigated in several trials for patients with progressive low-grade gliomas. In a study published by Quinn et al., temozolomide was administered at 200 mg/m^2 daily for 5 consecutive days to 46 patients with progressive low-grade gliomas [73]. Histologic types included in this cohort were astrocytoma, oli-

godendroglioma, mixed glioma, and pilocytic astrocytoma. Some 35% of the patients had astrocytomas. The median period of follow-up was 11.2 months. Some 15% of the patients had undergone prior radiation and 22%, prior chemotherapy. The objective response rate for all histologic types was 61%, with an additional 35% having stable disease. The median progression-free survival was 22 months. In the 16 patients with astrocytomas, the overall objective response rate was 69% (31%, 5/16 complete response and 38%, 6/16 partial response). Of the astrocytoma patients 25% (4/16) had stable disease for an overall response rate of 94%.

Pace et al. have also looked at temozolomide in patients with progressive low-grade gliomas [62]. Forty-three patients were enrolled in this study. Tumor types included grade II astrocytomas, oligodendrogliomas, and mixed gliomas. Patients began therapy at the time of documented radiographic progression. Thirty patients had previously received radiation. Sixteen patients had already been treated with PCV chemotherapy. Temozolomide was administered at 200 mg/m^2 daily for 5 consecutive days. They observed 4 complete responses and 16 partial responses for an objective response rate of 47%. Seventeen patients had stable disease, making the overall response rate 86%. Median length of response was 10 months. Progression-free survival at 12 months was 39.6%.

Viviers et al. assessed the efficacy of temozolomide in patients with stable or progressive low-grade gliomas [95]. Patients in this study had no antitumor therapy other than resection. Twenty-five patients were enrolled (18 grade II astrocytoma and 7 oligodendroglioma). All patients had radiographic residual disease at study entry. Of the 12 patients who received a minimum of 6 cycles, an overall objective response rate of 67% was seen.

Based on these studies, it is apparent that temozolomide is an effective therapy for patients with recurrent or progressive low-grade gliomas. This raises the question of a role for this agent in patients with newly diagnosed low-grade gliomas. Currently, a single-institution phase-II investigation is being conducted at UCSF that will address this question. In this study, newly diagnosed patients will be treated with temozolomide as the primary therapy after an incomplete resection. The goals of this study are to determine the efficacy by radiographic response criteria and time until disease progression.

Other chemotherapy regimens that have been investigated in adults are carboplatin and PCV. Christina et al. treated 22 patients with progressive low-grade gliomas using carboplatin[15]. Carboplatin was given at 560 mg/m2 every 4 weeks. The maximum response was stable disease in 12 patients (55%). The 3-year progression-free survival was 20%. Median follow-up was 28 months. Carboplatin in combination with vincristine has been used often to treat children with low-grade gliomas [63, 64].

The reported data using the PCV regimen have predominantly involved patients with low-grade oligodendroglioma and oligoastrocytoma, which is outside the focus of this review [11].

The best management for adult patients with low-grade gliomas has not been defined. And the only clear role for chemotherapy in adults with LGA is in the setting of postradiation progression. In those patients with gross totally resected tumors, it is advisable to just observe after surgery, reserving further therapy until tumor progression. At the time of progression, both radiation and chemotherapy may be considered. Investigations also show that chemotherapy can be used effectively in some patients with progressive tumors that have not been previously treated. Postoperative high-risk patients (those over 40 and those with significant residual disease) having stable tumors may also receive radiation or chemotherapy. There is an emerging trend to forgo or delay radiation and use chemotherapy in this setting. The efficacy of this approach is currently being evaluated in a single-institution phase-II trial using temozolomide.

Conclusion

Despite a better prognosis when compared with higher grade glial tumors, low-grade glioma patients have a median survival of 5–10 years and a 10-year survival rate which ranges from 5% to 50% [19, 23, 25, 31, 48, 55, 68, 69, 86, 94]. Some 50–75% of the patients will eventually die of their disease. Within the last 10 years, several studies analyzing the prognostic impact of tumor resection on outcome have revealed lower recurrence rates and improved overall survival with radical resection. Moreover, aggressive resection minimizes the chances of misdiagnosis as a result of sampling error and also relieves symptomatic mass effect, obstructive hydrocephalus, and neurologic deficit. Our standard practice is radical resection whenever feasible. This approach requires precise delineation of both the tumor margins and functional regions of involved and adjacent brain. A combination of methods, including intraoperative navigation techniques, intraoperative ultrasonography, cortical and subcortical functional mapping may be used to minimize the incidence of morbidity. Adjuvant postoperative therapy is usually not required in the treatment of localized, low-grade gliomas resected with minimal or no residual tumor volume. The patient is followed with sequential imaging, and recurrence is treated with another operation and irradiation, chemotherapy, or both. Overall, the management of low-grade gliomas is still controversial, and

practice parameters are ill-defined. This is caused by our limited knowledge regarding the natural history of this entity, and lack of high-quality evidence supporting various treatment options.

References

1. Apuzzo MLJ, Chandrasoma PT, Cohen D, et al. Computed imaging stereotaxy: experience and perspective related to 500 procedures applied to brain masses. Neurosurgery 1987; 20:930–937
2. Bahary JP, Villemure JG, Choi S, et al. Low-grade pure and mixed cerebral astrocytomas treated in the CT scan era. J Neurooncol 1996; 27:173–177
3. Bauman G, Lote K, Larson D, et al. Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis. Int J Radiat Oncol Biol Phys 1999; 45:923–929
4. Berger MS, Ghatan S, Haglund MM, et al. Low grade gliomas associated with intractable epilepsy: Seizure outcome utilizing electrocorticography during tumor resection. J Neurosurg 1993; 79:62–69
5. Berger MS, Deliganis AV, Dobbins J, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer 1994; 74:1784–1791
6. Berger MS, Keles GE. Intraoperative image update by interface with ultrasound. In: Germano IM, ed. Advanced Techniques in Image-Guided Brain and Spine Surgery. Thieme Medical Publishers, New York, 2002:141–145
7. Bernstein M, Parrent AG. Complications of CT-guided stereotactic biopsy of intra-axial brain lesions. J Neurosurg 1994; 81:165–168
8. Bogler O, Huang HJ, Cavenee WK. Loss of wild-type p53 bestows a growth advantage on primary cortical astrocytes and facilitates their in vitro transformation. Cancer Res 1995; 55:2746–2751
9. Brat DJ, Scheithauer BW, Medina-Flores R, Rosenblum MK, Burger PC. Infiltrative astrocytomas with granular cell features (granular cell astrocytomas): a study of histopathologic features, grading, and outcome. Am J Surg Pathol 2002; 26:750–7
10. Buckner JC, Brown LD, Kugler JW, et al. Phase II evaluation of recombinant interferon alpha and BCNU in recurrent glioma. J Neurosurg 1995; 82(3):430–5
11. Buckner JC, Gesme D Jr, O'Fallon JR. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol 2003; 21(2):251–5
12. Burger PC, Scheithauer BW. Armed Forces Institute of Pathology (U.S.), Pathology. UAfRaEi. Tumors of the central nervous system. Washington, D.C.: Armed Forces Institute of Pathology 1994:452
13. Cairncross G, Macdonald D, Ludwin S, et al. Chemotherapy for anaplastic oligodendroglioma. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1994; 12(10):2013–21
14. Castellano-Sanchez AA, Ohgaki H, Yokoo H et al. Granular cell astrocytomas show a high frequency of allelic loss but are not a genetically defined subset. Brain Pathol 2003; 13:185–94
15. Christina M, Cavazos SG, James Herndon II, Sandra Tourt-Uhlig, Moghrabi A, Rich JN, Quinn JA, Reardon D, Friedman AH, Friedman HS. A Phase II Study of Low-Dose Carboplatin (CBDCA) Chemotherapy in Adults with Progressive Low-Grade Gliomas. Proc Am Soc Clin Oncol 2001
16. Cunningham JM, Kimmel DW, Scheithauer BW, O'Fallon JR, Novotny PJ, Jenkins RB. Analysis of proliferation markers and p53 expression in gliomas of astrocytic origin: relationships and prognostic value. J Neurosurg 1997; 86:121–30
17. Daumas-Duport C, Scheithauer BW, O'Fallon J, Kelly P. Grading of astrocytomas: a simple and reproducible method. Cancer 1988; 62:2152–2165
18. Davis FG, Malinski N, Haenszel W, et al. Primary brain tumor incidence rates in four United States regions, 1985–1989: a pilot study. Neuroepidemiology 1996; 15:103–112
19. Eyre HJ, Crowley JJ, Townsend JJ, et al. A randomized trial of radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study. J Neurosurg 1993; 78:909–914
20. Fisher PG, Breiter SN, Carson BS et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000; 89:1569–76
21. Gajjar A, Heideman RL, Kovnar EH, et al. Response of pediatric low grade gliomas to chemotherapy. Pediatr Neurosurg 1993; 19(3):113–8; discussion 119–20
22. Galanis E, Buckner JC, Burch PA, et al. Phase II trial of nitrogen mustard, vincristine, and procarbazine in patients with recurrent glioma: North Central Cancer Treatment Group results. J Clin Oncol 1998; 16(9):2953–8
23. Gannett DE, Wisbeck WM, Silbergeld DL, Berger MS. The role of postoperative irradiation in the treatment of oligodendroglioma. Int J Radiat Oncol Biol Phys 1994; 30:567–573
24. Gonzales D, Elvidge AR. On the occurrence of epilepsy caused by astrocytoma of the cerebral hemispheres. J Neurosurg 1962; 19:470–482
25. Guidelines and Outcomes Committee of the AANS. Practice parameters in adults with suspected or known supratentorial nonoptic pathway low-grade glioma. Neurosurgical Focus 1998; 4(6):Article 10
26. Guthrie BL, Laws ER. Supratentorial low-grade gliomas. Neurosurg Clin North Am 1990; 1:37–48
27. Hang Z, Wei Y, Liao W. [A comparison between astrocytoma cells and the developing astrocytes in human embryo brain by electron microscopy]. Zhonghua Bing Li Xue Za Zhi 1995; 24:65–8
28. Hanzely Z, Polgar C, Fodor J, Brucher JM, Vitanovics D, Mangel LC, Afra D. Role of early radiotherapy in the treatment of supratentorial WHO Grade II astrocytomas:

long-term results of 97 patients. J Neurooncol 2003; 63(3):305–12
29. Ito S, Chandler KL, Prados MD, et al. Proliferative potential and prognostic evaluation of low-grade astrocytomas. J Neurooncol 1994; 19:1–9
30. James CD, Carlbom E, Nordenskjold M, et al. Mitotic recombination of chromosome 17 in astrocytomas. Proc Natl Acad Sci USA 1989; 86:2858–2862
31. Janny P, Cure H, Mohr M, et al. Low grade supratentorial astrocytomas. Management and prognostic factors. Cancer 1994; 73:1937–1945
32. Jeremic B, Milicic B, Grujicic D, Samardzic M, Antunovic V, Dagovic A, Aleksandrovic J, Stojanovic M. Hyperfractionated radiation therapy for incompletely resected supratentorial low-grade glioma: a 10-year update of a phase II study. Int J Radiat Oncol Biol Phys 2003; 57(2):465–71
33. Jeremic B, Shibamoto Y, Grujicic D, et al. Hyperfractionated radiation therapy for incompletely resected supratentorial low-grade glioma. A phase II study. Radiotherapy and Oncology 1998; 49:49–54
34. Karim ABMF, Afra D, Cornu P, Bleehan N, Schraub S, De Witte O, Darcel F, Stenning S, Pierart M, van Glabbeke M. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council Study BR04: an interim analysis. Int J Radiat Oncol Biol Phys 2002; 52: 316–324
35. Karim ABMF, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 1996; 36:549–556
36. Keles GE, Berger MS. Functional Mapping. In: Bernstein M, Berger MS, eds. Neuro-Oncology Essentials. Thieme Medical Publishers, New York, 2000:130–134
37. Keles GE, Berger MS. Epilepsy associated with brain tumors. In: Kaye AH, Laws ER, eds. Brain Tumors: An Encyclopedic Approach, 2nd edition, Churchill Livingstone (Harcourt Publishers Ltd), London 2001:273–279
38. Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 2001; 95:735–745
39. Keles GE, Lamborn KR, Berger MS. Coregistration accuracy and detection of brain shift using intraoperative sononavigation during resection of hemispheric tumors. Neurosurgery 2003; 53:556–62
40. Kepes JJ, Rubinstein LJ, Chiang H. The role of astrocytes in the formation of cartilage in gliomas. An immunohistochemical study of four cases. Am J Pathol 1984; 117:471–83
41. Kernohan JW, Mabon RF, Svien HJ, Adson AW. A simplified classification of the gliomas. Proc Staff Meet Mayo Clin 1949; 24:71–75
42. Kleihues P, Burger PC, Scheithauer, BW. The new WHO classification of brain tumours. Brain Pathol 1993; 3: 255–68
43. Kleihues P, Cavenee WKe. Pathology and Genetics of Tumours of the Nervous System. World Health Organization Classification of Tumours. Lyon: IARC Press; 2000
44. Kosel S, Scheithauer BW, Graeber MB. Genotype-phenotype correlation in gemistocytic astrocytomas. Neurosurgery 2001; 48:187–94
45. Kros JM, Waarsenburg N, Hayes DP, Hop WC, van Dekken H. Cytogenetic analysis of gemistocytic cells in gliomas. J Neuropathol Exp Neurol 2000; 59:679–86
46. Krouwer HG, Davis RL, Silver P, Prados M. Gemistocytic astrocytomas: a reappraisal. J Neurosurg 1991; 74:399–406
47. Laws ER, Taylor WF, Clifton MB, Okazaki H. Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. J Neurosurg 1984; 61:665–673
48. Leighton C, Fisher B, Bauman G, Depiero S, Stitt L, Macdonald D, Cairncross G. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol 1997; 15:1294–1301
49. Lo SS, Hall WA, Cho KH, Orner J, Lee CK, Dusenbery KE. Radiation dose response for supratentorial low-grade glioma–institutional experience and literature review. J Neurol Sci 2003; 214:43–8
50. Lote K, Egeland T, Hager B, et al. Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. J Clin Oncol 1997; 15:3129–3140
51. Louis DN. The p53 gene and protein in human brain tumors. J Neuropathol Exp Neurol 1994; 53:11–21
52. Lunsford LD, Somaza S, Kondziolka D, Flickenger JC. Survival after stereotactic biopsy and radiation of cerebral non-neoplastic, non-pilocytic astrocytoma. J Neurosurg 1995; 82:523–529
53. Mahaley MS, Mettlin C, Narajan N. National survey of patterns of care for brain-tumor patients. J Neurosurg 1989; 28:659–665
54. Manford M, Hart YM, Sander JWAS, et al. National General Practice Study of Epilepsy (NGPSE): Partial seizure patterns in a general population. Neurology 1992; 42:1911–1917
55. McCormack BM, Miller DC, Budzilovich GN, Voorhees GJ, Ransohoff J. Treatment and survival of low-grade astrocytoma in adults 1977–1988. Neurosurgery 1992; 31:636–642
56. Medberry III CA, Straus KL, Steinberg SM, et al. Low-grade astrocytomas: treatment results and prognostic variables. Int J Radiat Oncol Biol Phys 1988; 15:837–841
57. Miralbell R, Balart J, Matias-Guiu X, Molet J, Ariza A, Craven-Bartle J. Radiotherapy for supratentorial low-grade gliomas: results and prognostic factors with special focus on tumour volume parameters. Radiotherapy and Oncology 1993; 27:112–116
58. Muller W, Afra D, Schroder R. Supratentorial recurrences of gliomas: Morphological studies in relation to time intervals with astrocytomas. Acta Neurochir 1977; 37:75–91
59. Nakamura T, Hirato J, Hotchi M, Kyoshima K, Nakamura Y. Astrocytoma with granular cell tumor-like chang-

es. Report of a case with histochemical and ultrastructural characterization of granular cells. Acta Pathol Jpn 1990; 40:206–11

60. Nicolato A, Gerosa MA, Fina P, et al. Prognostic factors in low-grade supratentorial astrocytomas: a uni-multivariate statistical analysis in 76 surgically treated adult patients. Surg Neurol 1995; 44:208–223
61. North CA, North RB, Epstein JA, Piantadosi S, Wharam MD. Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. Cancer 1990; 66:6–14
62. Pace A, Maschio M, Carosi MA, et al. Temozolomide chemotherapy for progressive low grade glioma. Proc Am Soc Clin Oncol 2003; z:107
63. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 1993; 11(5):850–6
64. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 1997; 86(5):747–54
65. Penfield W, Erickson TC, Tarlov IM. Relation of intracranial tumors and symptomatic epilepsy. Arch Neurol Psychiatry 1940; 44:300–315
66. Peraud A, Ansari H, Bise K, Reulen HJ. Clinical outcome of supratentorial astrocytoma WHO Grade II. Acta Neurochir 1998; 140:1213–1222
67. Perry A, Jenkins RB, O'Fallon JR, et al. Clinicopathologic study of 85 similarly treated patients with anaplastic astrocytic tumors. An analysis of DNA content (ploidy), cellular proliferation, and p53 expression. Cancer 1999; 86:672–83
68. Philippon JH, Clemenceau SH, Fauchon FH, Foncin JF. Supratentorial low-grade astrocytomas in adults. Neurosurgery 1993; 32:554–559
69. Piepmeier JM. Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. J Neurosurg 1987; 67:177–181
70. Piepmeier J, Christopher S, Spencer D, et al. Variations in the natural history and survival of patients with supratentorial low-grade astrocytomas. Neurosurgery 1996; 38:872–879
71. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, Afra D, Cornu P, Bolla M, Vecht C, Karim AB. European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group; European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group: Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002; 20:2076–84
72. Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA. Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neurooncol 1997; 32(3):235–41
73. Quinn JA, Reardon DA, Friedman AH, et al. Phase II trial of temozolomide in patients with progressive low-grade glioma. J Clin Oncol 2003; 21:646–651
74. Rajan B, Pickuth D, Ashley S, Traish D, Monro P, Elyan S, Brada M. The management of histologically unverified presumed cerebral gliomas with radiotherapy. Int J Radiat Oncol Biol Phys 1993; 28:405–413
75. Recht LD, Lew R, Smith TW. Suspected low-grade glioma: Is deferring therapy safe? Ann Neurol 1992; 31:431–436
76. Rey JA, Bello MJ. Cytogenetics. In: Berger MS, Wilson CB, eds. The Gliomas. WB Saunders, Philadelphia, 1999:25–37
77. Rudoler S, Corn BW, Werner-Wasik M, et al. Patterns of tumor progression after radiotherapy for low-grade gliomas. Am J Clin Oncol 1998; 21:23–27
78. Salcman M. The natural history of low grade gliomas. In: Benign Cerebral Gliomas, Apuzzo MLJ, eds. AANS Publications, Park Ridge, Il, 1995:213–229
79. Scerrati M, Roselli R, Iacoangeli M, et al. Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery. J Neurol Neurosurg Psychiatry 1996; 61:291–296
80. Schuurman PR, Troost D, Verbeeten B Jr, Bosch DA. 5-year survival and clinical prognostic factors in progressive supratentorial diffuse 'low grade' astrocytoma: a retrospective analysis of 46 cases. Acta Neurochir 1997; 139:2–7
81. Shafqat S, Hedley-White ET, Henson JW. Age-dependent rate of anaplastic transformation in low-grade astrocytoma. Neurology 1999; 52:867–869
82. Shaw EG, Daumas-Duport C, Scheithauer BW, et al. Radiation therapy in the management of low-grade supratentorial astrocytomas. J Neurosurg 1989; 70:853–861
83. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dianpoli R, Nelson D, Earle J, Jones C, Cascino T, Nichols D, Ivnik R, Hellman R, Curran W, Abrams R. Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002; 20: 2267–2276
84. Shaw EG, Scheithauer BW, Gilbertson DT, et al. Postoperative radiotherapy of supratentorial low-grade gliomas. Int J Radiat Oncol Biol Phys 1989; 16:663–668
85. Shaw EG, Scheithauer BW, O'Fallon JR, Davis DH. Mixed oligoastrocytomas: a survival and prognostic factor analysis. Neurosurgery 1994; 34:577–582
86. Shibamoto Y, Kitakabu Y, Takahashi M, et al. Supratentorial low-grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. Cancer 1993; 72:190–195
87. Silverman C, Marks JE. Prognostic significance of contrast enhancement in low-grade astrocytomas of the adult cerebrum. Radiology 1981; 139:211–213
88. Singer JM. Supratentorial low grade gliomas in adults. A retrospective analysis of 43 cases treated with surgery and radiotherapy. European Journal of Surgical Oncology 1995; 21:198–200
89. Soffietti R, Chio A, Giordana MT, Vasario E, Schiffer D. Prognostic factors in well-differentiated cerebral astrocytomas in the adult. Neurosurgery 1989; 24:686–692
90. Souweidane NM, Hoffman HJ. Current treatment of thalamic gliomas in children. J Neurooncol 1996; 28:157–166

91. Tihan T, Davis R, Elowitz E, DiCostanzo D, Moll U. Practical value of Ki-67 and p53 labeling indexes in stereotactic biopsies of diffuse and pilocytic astrocytomas. Arch Pathol Lab Med 2000; 124:108–13
92. van Veelen MLC, Avezaat CJJ, Kros JM, van Putten W, Vecht C. Supratentorial low grade astrocytoma: prognostic factors, dedifferentiation, and the issue of early versus late surgery. J Neurol Neurosurg Psychiatry 1998; 64:581–587
93. Velema JP, Walker AM. The age curve of nervous system tumor incidence in adults: common shape but changing levels by sex, race and geographical location. Int J Epidemiol 1987; 16:177–183
94. Vertosick FT, Selker RG, Arena VC. Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. Neurosurgery 1991; 28:496–501
95. Viviers L, Hines F, Britton J, et al. A Phase II Trial of Primary Chemotherapy with Temozolomide in Patients with Low-Grade Cerebral Gliomas. Proc Am Soc Clin Oncol z 200
96. Wang M, Tihan T, Rojiani AM, Bodhireddy S, Burger PC. Angiocentric bipolar astrocytoma: a distinctive infiltrating astrocytoma of children. J Neuropathol Exp Neurol 2002; 61:475
97. Watanabe K, Peraud A, Gratas C, Wakai S, Kleihues P, Ohgaki H. p53 and PTEN gene mutations in gemistocytic astrocytomas. Acta Neuropathol (Berl) 1998; 95:559–64
98. Watanabe K, Sato K, Biernat W, et al. Incidence and timing of p53 mutations during astrocytoma progression in patients with multiple biopsies. Clinical Cancer Research 1997; 3:523–530
99. Watanabe K, Tachibana O, Yonekawa Y, Kleihues P, Ohgaki H. Role of gemistocytes in astrocytoma progression. Lab Invest 1997; 76:277–84
100. Weingart J, Olivi A, Brem H. Supratentorial low-grade astrocytomas in adults. Neurosurg Q 1991; 1:141–159
101. Whitton AC, Bloom HJG. Low grade glioma of the cerebral hemispheres in adults: a retrospective analysis of 88 cases. Int J Radiat Oncol Biol Phys 1990; 18:783–786
102. Wyke BD. The cortical control of movement: A contribution to the surgical physiology of seizures. Epilepsia 1959; 1:4–35
103. Yahamada AM, Bruner JM, Donehower LA, et al. Astrocytes derived from p53-deficient mice provide a multistep in vitro model for development of malignant gliomas. Mol Cell Biol 1995; 15:4249–4259
104. Zakhary R, Keles GE, Berger MS. Intraoperative imaging techniques in the treatment of brain tumors. Currt Opin Oncol 1999; 11:152–156
105. Zulch KJ. Brain tumors: their biology and pathology. 3rd edition. Springer-Verlag, Berlin 1986:210–213

Interstitial Radiosurgery in Low-Grade Gliomas

5

Friedrich W. Kreth, Jan H. Mehrkens

Background and Indication – 120

Rationale for Interstitial Irradiation/Radiophysics/Radiobiology – 120

Role of Stereotactic Biopsy – 121

Technique, Implants, and Dosimetry – 121

Follow-Up – 123

Results – 123
WHO Grade II Gliomas
WHO Grade I Gliomas

Complications – 123
Perioperative Morbidity
Radiogenic Complications

Combined Approach – 124

Summary – 125

References – 125

Background and Indication

The management of patients with low-grade gliomas remains a challenge. The natural course of the disease varies considerably and is highly influenced by treatment-independent factors such as age, pretreatment performance score, tumor volume, contrast-enhancement on CT/MRI, and tumor histology [10] (Fig. 1). Young patients with small, nonenhancing tumors, excellent performance score, and oligodendroglial differentiation usually have favorable outcome scores (5-year survival rate in the range of 85%). The prognosis, however, dramatically decreases in the case of two or more unfavorable prognostic factors (5-year survival rates in the range of 10–40%). Given the strong impact of treatment-independent factors, it is not surprising that treatment effects are difficult to assess for patients with WHO grade II glioma. This problem has recently been highlighted by the results of three prospective randomized studies [4, 5, 19]: Neither early external beam radiation (after tumor resection or stereotactic biopsy) nor tumor dose escalation from 45 Gy to 59.4 Gy resulted in better survival rates. However, patients treated with higher tumor doses experienced more side-effects of the therapy in terms of the quality of life paradigm. Therefore, risk minimization must be the paramount aim in any treatment modality considered. Bearing this in mind, the growing interest in less invasive and more individualized (tailor-made) therapeutic approaches is not surprising. Over the last few years, stereotactic treatment modalities (i.e., interstitial radiosurgery and stereotactic radiotherapy) as well as chemotherapeutic regimens (for oligoastrocytomas and oligodendrogliomas) have gained in importance.

Taking into account all the facts and factors mentioned above, interstitial radiosurgery might offer an adequate, alternative, minimally invasive treatment modality for the subgroup of patients with a Karnofsky Performance Score ≥70, harboring a well-circumscribed, low-grade glioma with a given tumor diameter (≤ 3.5 cm). These selection criteria apply to de novo gliomas as well as to recurrences or residual tumor after microsurgical resection. The true minimally invasive character and low-risk profile of this treatment concept is explained by the stereotactic technique itself, the radiophysics of the implanted source, and the radiobiology of the procedure.

Rationale for Interstitial Irradiation/Radiophysics/Radiobiology

The concept of interstitial radiosurgery (brachytherapy) was introduced as early as 1914 and has been refined and used ever since [1], with Fritz Mundinger being one of the pioneers [16, 17]. The method requires the permanent or temporary implantation of one or more radioactive sources in the form of seeds (iodine-125) or wire pieces (iridium-192) directly into the target volume. Tumor volume and target volume are ideally identical. Since the first introduction of radioactive material into cerebral gliomas by Mundinger in 1953, his group had already gained extensive experience with more than 213

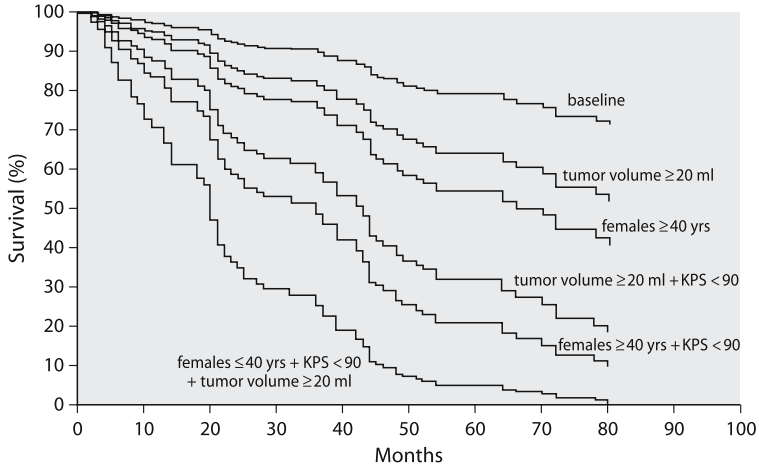


Fig. 1. Graph showing the estimated influence of different patterns of prognostic factors on survival rates for 197 patients with WHO grade II astrocytomas/oligoastrocytomas as obtained from the Cox model. The baseline plot represents men and young women (<40 years) with a Karnofsky performance status (KPS) ≥90, and a tumor volume <20 ml. The strong influence of pretreatment factors is demonstrated. Patients with only one unfavorable factor had a relatively favorable outcome (reprinted from [10])

iridium-192 implants into cerebral gliomas by 1978 [16]. The half-life of iridium-192 is 74.2 days. The isotope emits gamma-rays ranging in energy from 300 to 610 keV. The specific dose-rate factor used for dosimetry is 4.55 cGy/h and mCi at 1 cm in tissue. Iodine-125 has a slightly shorter half-life of 60.2 days and a much lower photon energy spectrum, ranging from 27 to 35 keV. The specific dose-rate constant is 1.32 cGy/h and mCi at 1 cm in tissue. The dose decrease from center to periphery is more rapid with I-125 than with Ir-192 [17]. Due to the more favorable radiobiological properties, exclusively I-125 in the form of seeds has been used for implantation by the 'Freiburg Group' (and the authors) since 1979 [8, 9, 10, 14, 17, 18].

The therapeutic approach of an I-125 implant fulfills one major definition of radiosurgery as given by Larson [13], i.e., the application of a highly focused necrotizing dose to a well-defined target volume with maximal sparing of the surrounding nonpathological tissue (intentional radionecrosis). This is realized by the physical advantage of an accurate dose distribution, a steep dose decrease from the center to the periphery, and the favorable biologically effective dose for the late responding tissue at the outer rim of the tumor (due to continuous low-dose rate radiation). For a detailed review, see Kreth et al. [9].

Role of Stereotactic Biopsy

It is important to stress that diagnostic imaging is not sufficient for the planning of a rational individualized treatment strategy in patients harboring WHO grade I and II gliomas, since the 'typical' imaging features do not consistently predict the histological diagnosis (e.g., problem of undergrading) and clinical behavior of 'astrocytoma' [7, 15]. Therefore, frame-based (MRI or CT guided) stereotactic biopsy is a prerequisite for individualized treatment strategies and should be performed in all patients who present with imaging features that suggest a primary brain tumor. With an exact histopathological diagnosis being crucial, we believe that performing extensive serial biopsies and having the pathologist on site in the OR for rapid smear preparation should be considered the 'gold standard' in stereotactic biopsy (diagnostic accuracy of the stereotactic biopsy in the series of Muacevic and Kreth: 96.8% [15]).

Technique, Implants, and Dosimetry

A detailed description of the stereotactic technique of biopsy and implantation has been given in several reports by Kreth et al. [8, 9]. We are using the Riechert-Mundinger stereotactic device originally developed in 1956 and modified by Mundinger and Birg to be computer-compatible. All stereotactic operations are usually performed under local anesthesia (children under the age of 16 are operated on under general anesthesia). In contrast to what was published in previous reports [8, 16, 17], implantation is usually not performed in the same operation as the biopsy for histopathological diagnosis anymore. This staged approach allows for a better counseling of the patient and more individualized approach (due exact WHO diagnosis, e.g., oligodendroglioma-component, LOH-analysis, etc.).

Interstitial irradiation was initially considered to be indicated for patients with a circumscribed tumor with a maximum diameter of 5 cm [8, 9, 10] and a clinically (defined as drop of KPS and/r increasing seizure frequency) or radiographically documented progress of the disease. Due to the results of risk-analyses performed in the course of the last decade (see 'complications' [9, 14]), the treatment is now limited to small circumscribed tumors with a diameter not larger than 3.5 cm.

Iodine-125 seeds can be used for permanent or temporary implants, and exclusively low activity iodine-125 seeds (<20 mCi) should be implanted. Due to the fact that experimental data had shown an increased risk of prolonged edema for permanent implants [3], the mode of implantation was changed, and we have used solely temporary implants since 1985. Permanent iodine-125 seeds were designed to deliver a total dose of 100 Gy to the tumor at a dose rate in the range of 3 cGy/h within the first 3 months (half-life of iodine-125: 59 days). Temporary implants are nowadays selected to deliver a total dose of 50–60 Gy to the tumor margin at a dose rate of approximately 10 cGy/h. After the iodine-125 seed (length 4.3 mm) contained in the tip of a Teflon catheter has been stereotactically implanted, the catheter is cut to the appropriate length and is secured epidurally at the burrhole with a hemoclip. Figure 2 shows an example of lateral intraoperative X-ray control after the implantation of two I-125 seeds. The skin is then closed and re-opened for seed-removal after 20–30 days (local anesthesia, no stereotactic equipment needed). A hospital stay of no longer than 3 days is required for the implantation procedure. The low rate of local external irradiation emitted by the implant(s) is checked by the physicist before the patient leaves the OR.

The prerequisite for an interstitial implant is that the treatment volume matches the tumor volume. Usually, one to four seeds (isocenters) are used in order to achieve a conformal interstitial irradiation of the tumor volume. The basis for exact interstitial radiosurgery is a tri-planar treatment planning using stereotactic CT and MRI (PET) and an adequately equipped workstation. A MRI (T2-weighted image)-

based dosimetry is usually performed using Krishnaswamy's dose-rate tables for dose calculation at any point of interest [11]. The isodoses are calculated by a computer program specially adapted for this purpose [e.g., Target or i-plan stereotaxy (Brainlab)]. The tumor reference dose is calculated to the outer rim of the tumor as defined by (contrast-enhanced) MRI (usually T2-weighted) (and PET). An example containing isodose distribution for temporary implants is given in Fig. 3.

Steroids should be administered routinely on the day of implantation and for 3 days postoperatively at a daily decreasing dose of 24, 12, 8, and 4 mg dexamethasone, respectively.

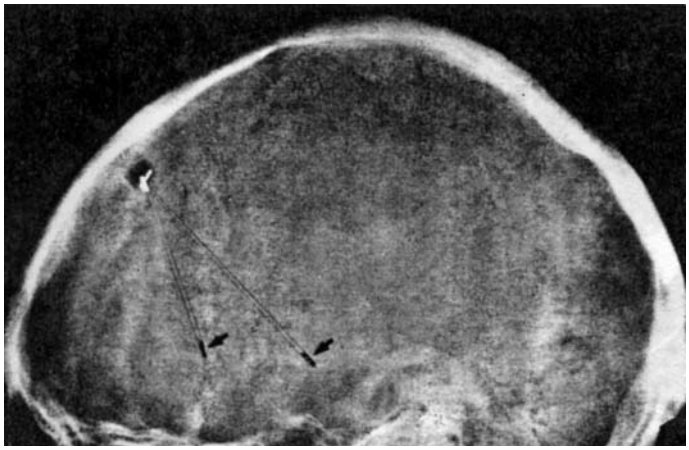


Fig. 2. Lateral intraoperative X-ray after the implantation of two I-125 seeds contained in the tip of a Teflon catheter

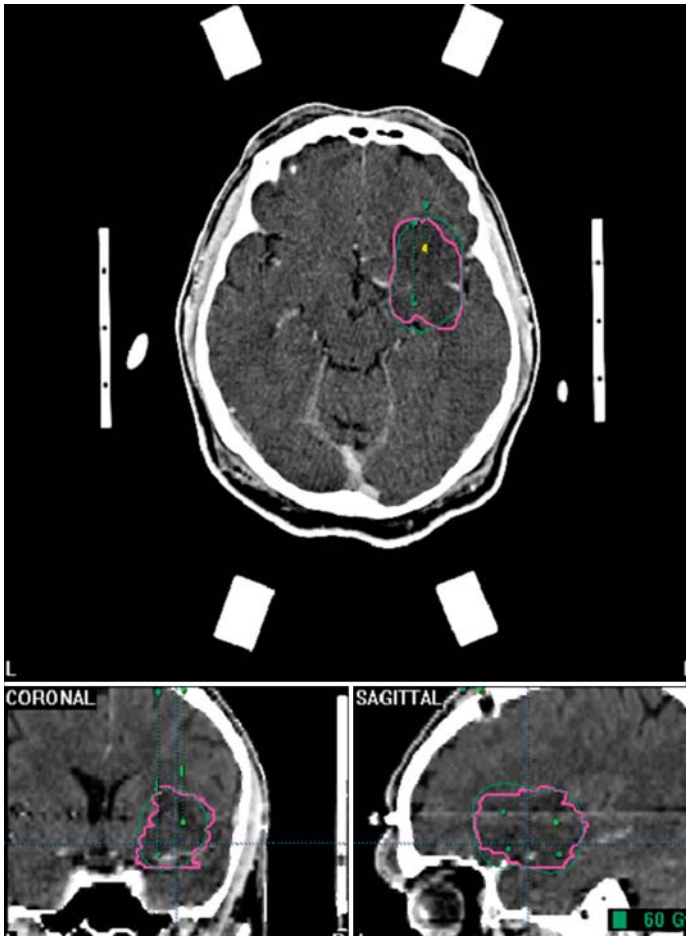


Fig. 3. Representative example for treatment planning in a large right-sided astrocytoma of the insula of Reil. Tumor volume (as defined by the *pink line*) was 31.6 ml. Four temporary iodine-125 seeds (activity 10 mCi) were stereotactically implanted in the rostral and caudal areas of the tumor (seed position indicated by the *green intratumoral points*). The *green line* represents the reference dose of 60 Gy. The dose rate was 7.5 cGy/h

Follow-Up

First clinical and neuroradiological (MRI, T1/T2 with/without contrast) follow-up should be performed 3 months postoperatively. After that, 6-month intervals are sufficient.

Results

WHO Grade II Gliomas

The results after interstitial radiosurgery of WHO grade II low-grade gliomas with respect to overall and progression-free survival are comparable to those after microsurgical resection and/or percutaneous radiotherapy: A meta-analysis (unpublished data, performed by us) including 10 studies from the CT era (of at least 50 patients) with different therapeutic approaches (surgery alone, surgery and radiotherapy, radiotherapy alone, primary interstitial radiosurgery) showed the 5-year and 10-year survival rates to be in the range of 55–70% (61% after interstitial radiosurgery [8]) and 40–53% (51% after interstitial radiosurgery [8]), respectively. There is no statistically significant difference between the different therapeutic approaches. As an example, Fig. 4 shows the survival curves after primary interstitial radiosurgery [8] and after surgery and radiotherapy [4] (EORTC study 22844).

The technique is suitable for supratentorial (lobar) and as well as for deep-seated, e.g., brain-stem, gliomas as already shown by Mundinger et al. in a long-term analysis as early as 1991 [17]. It was shown that patients with non-lobar tumors do not fare worse than patients with a lobar tumor location after primary interstitial radiosurgery. I-125-implantation very often is performed in low-grade gliomas with complex and/or eloquent locations. This can be done with the same low-risk profile as in noneloquent or less complex areas.[9, 10].

WHO Grade I Gliomas

The treatment results of pilocytic astrocytomas must not be confused with those of WHO grade II gliomas. Patients with pilocytic astrocytomas represent a separate entity with a significantly younger age and a higher frequency of non-lobar tumor location [8].

In a series of 45 hypothalamic pilocytic astrocytomas (as part of a large series of 97 pilocytic and 358 WHO grade II glioma), Kreth et al. [8] showed the treatment modality to be associated with low risk and high efficacy in this tumor entity. The 5- and 10-year survival rates for all 97 patients with pilocytic astrocytomas in that series were 84.9% and 83%, respectively. An example of a young patient with a large chiasmatic tumor before and 6 months after primary interstitial radiosurgery is given in Fig. 5.

Complications

Perioperative Morbidity

In the hands of an experienced stereotactic neurosurgeon, the directly surgery-related risk (e.g., symptomatic hemorrhage) is in the range of 1% [9, 10, 15]. Stereotactic procedures of any kind should only be performed in specialized centers.

Radiogenic Complications

Typical imaging changes on the follow-up MRI/CT scan can usually be detected in over 80% of the patients after interstitial radiosurgery: Due to the distortion of the blood-brain barrier, an enhanced ring

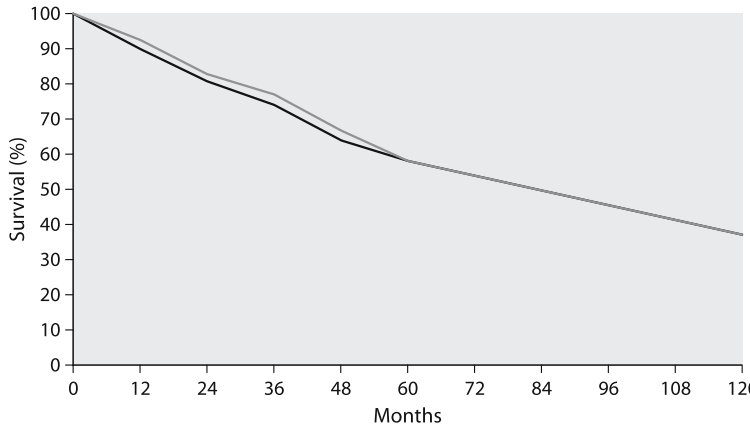


Fig. 4. Graph showing the survival after primary interstitial radiosurgery [8] as the *pink plot* and after surgery and radiotherapy [4] (EORTC study 22844) as the *red plot*

formation can be observed that develops gradually from the center to the periphery of the treatment volume and resolves completely over time (see Fig. 6). In a small percentage of patients, these imaging changes can be progressive, with subsequent increased edema and mass effect associated with clinical deterioration. Those patients with transient symptoms (commonly headache) can usually be rapidly stabilized with steroids (dexamethasone, dose range between 2 and 12 mg per day) within 4 weeks. Very rarely, radiation necrosis that cannot be controlled with steroids might occur, making surgical decompression necessary [9, 10, 14]. The estimated rate of radiogenic complications within the first 2 years in a series of 515 patients by Kreth et al.[9] was 7.5%, and no long-term complications were observed beyond this time interval (Fig. 7).

It was shown that these complications are mostly generated within the treatment volume and are strongly correlated to the tumor volume. Accordingly, the volume has been shown to be the most important risk factor, i.e., beyond a cut-off of 3.5 cm in tumor diameter (tumor volume 22.4 ml), an exponential increase of radiogenic complications can be observed. As a consequence of the results of the risk analysis performed by Kreth et al. [9], the indication for low-risk interstitial irradiation of low-grade gliomas should be limited to small, circumscribed tumors with a diameter not larger than 3.5 cm.

Neither a re-implantation nor additional external beam radiation in case of tumor progression significantly increases the risk of radiogenic complications [8, 9, 10, 14]. Thus, interstitial irradiation does not limit treatment options for the future in the case of tumor recurrence or tumor progression.

Combined Approach

Given the limitations of both microsurgery and interstitial irradiation (high complication rate with radical tumor resection, high incidence of radiogenic

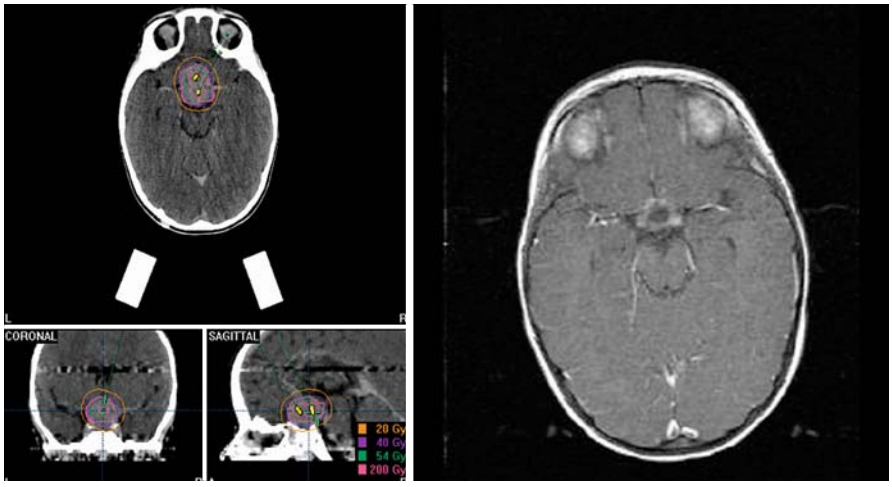


Fig. 5. Example for treatment planning (*left*) and result (*right*) in a large midline (chiasmatic) pilocytic astrocytoma. Tumor volume is defined by the *outer pink line*. Two temporary iodine-125 seeds (activity 10 mCi) were stereotactically implanted. (seed position indicated by the *yellow intratumoral markers*). The *green line* represents the reference dose of 54 Gy. The *inner pink line* represents the 200-Gy isodose. The steep characteristic dose decrease from the high-dose center to the periphery (note the orange 20 Gy isodose) becomes very obvious

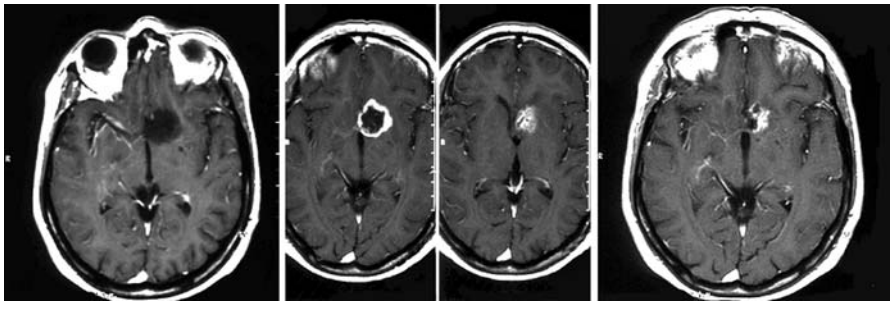


Fig. 6. Example documenting the typical imaging changes after interstitial radiosurgery (*left* pre-op, *middle* 3 months, *right* 6 months)

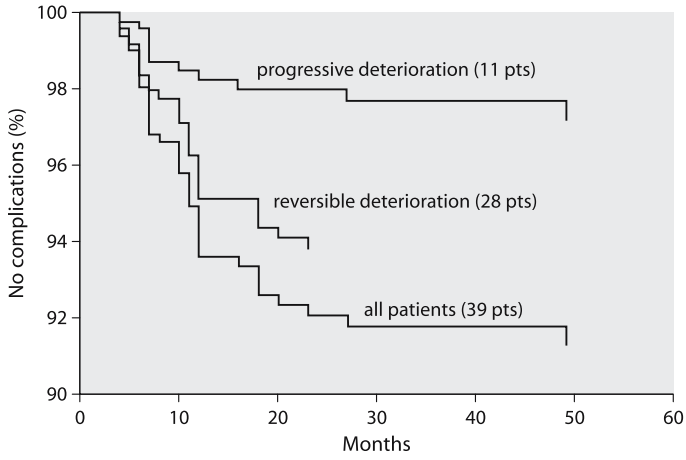


Fig. 7. Graph showing the rate of radiogenic complications after primary interstitial radiosurgery as function of time. The rate of complication was 7.5% (reversible and progressive complications). Reprinted from Kreth et al. 1997 *Radiotherapy and Oncology* [9]

complications after interstitial irradiation of large tumor volumes), a combination of these highly localized treatment modalities seems to be attractive for patients with large, circumscribed tumors. Primary microsurgical resection of easily accessible parts of the tumor could be performed, leaving the residual part for I-125 seed implantation. This combined approach might very well spare the patient from the increased risk of suffering a neurological deficit due to attempted radical resection as well as the increased risk for a radiogenic complication linked to interstitial irradiation of tumors with diameters >3.5 cm [14].

Summary

1. Interstitial irradiation offers a safe and minimally invasive treatment option with low peri/postoperative morbidity and mortality for a selected group of patients with circumscribed WHO grade I and II gliomas with a tumor diameter ≤3.5 cm. There is a steep increase of the risk beyond this limit.
2. A hospital stay of no longer than 3 days after which patients return to their everyday life activities; the small area of shaved skin, the lack of loss of hair and skin affection as observed with external beam radiation, add to the minimal invasiveness of this technique.
3. The results after interstitial radiosurgery of low-grade gliomas with respect to overall and progression-free survival are comparable to those after microsurgical resection or primary percutaneous radiotherapy.
4. Interstitial irradiation is associated with a low risk of long-term side-effects, and additional external beam radiation (in case of tumor progression) does not significantly increase the risk of radiogenic complications.
5. In patients harboring large low-grade gliomas, a less aggressive microsurgical approach combined with minimally invasive interstitial irradiation might overcome the limitations of both microsurgery and interstitial irradiation. This approach needs further evaluation to improve the risk/benefit ratio in a prospective study.

References

1. Bernstein M, Gutin PH. Interstitial irradiation of brain tumors: A review. Neurosurgery 1981; 6:741–750.
2. Brenner DJ, Martel MK, Hall EJ. Fractionated regimes for stereotactic radiotherapy of recurrent tumors in the brain. Int J Radiat Oncol Biol Phys 1991; 21: 819–824.
3. Groothuis DR, Wright DC, Ostertag CB. The effect of 125 I interstitial radiotherapy on blood-brain barrier function in normal canine brain. J Neurosurg 1987; 67:895–902.
4. Karim ABMF, Maat B, Hatlevoll R, Menten J, Rutten EHJM, Thomas DGT, Mascarenhas F, Horiot JC, Parvinen LM, van Reijn M, Jager JJ, Fabrini MG, van Alphen AM, Hamers HP, Gaspar L, Noordman E, Pierart M, Glabbeke M. A randomized trial on dose response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 1996; 36: 549–556.
5. Karim AB, Afra D, Cornu P, Bleehan N, Schraub S, De Witte O, Darcel F, Stenning S, Pierart M, Van Glabbeke M. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. Int J Radiat Oncol Biol Phys 2002; 52:316–324.
6. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod M, ed. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949:1991–205.

7. Kondziolka, D, Lunsford LD, Martinez AJ. Unreliability of contemporary neurodiagnostic imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma. J Neurosurg 1993; 79:533–536.
8. Kreth FW, Faist M, Warnke PC, Rossner R, Volk B, Ostertag CB. Interstitial radiosurgery of low-grade gliomas. J Neurosurg 1995; 82:418–429.
9. Kreth FW, Faist M, Rossner R, Birg W, Volk B, Ostertag CB. The risk of interstitial radiotherapy of low-grade gliomas. Radiother Oncol 1997; 43:253–260.
10. Kreth FW, Faist M, Rossner R, Volk B, Ostertag CB. Supratentorial World Health Organization Grade 2 Astrocytomas and Oligoastrocytomas: A New pattern of Prognostic Factors. Cancer 1997; 79: 370–379.
11. Krishnaswamy V. Dose distribution around an 125I seed source in tissue. Radiology 1978; 126:489–491.
12. Lapierre NJ. Brachytherapy. In: Bernstein M, Berger MS, eds. Neuro-Oncology: The Essentials. Thieme Medical Publishers, Inc., New York, 2000:200.
13. Larsson B. Radiobiological fundamentals in radiosurgery. In: Steiner L, ed. Radiosurgery: Baseline and Trends. Raven Press, New York, 1992:3–14.
14. Mehrkens JH, Kreth FW, Muacevic A, Ostertag CB. Long term course of WHO grade II astrocytomas of the Insula of Reil after I-125 interstitial irradiation. Journal of Neurology 2004; in press.
15. Muacevic A, Kreth FW. Significance of stereotactic biopsy for the management of WHO grade II supratentorial glioma. Nervenarzt 2003; 74:350–354.
16. Mundinger F, Birg W, Ostertag CB. Treatment of small cerebral gliomas with CT-aided stereotaxic Curietherapy. Neuroradiology 1978; 16:564–567.
17. Mundinger F, Braus DF, Krauss JK, Birg W. Long.term outcome of 89 low-grade brain-stem gliomas after interstitial radiation therapy. J Neurosurg 1991; 75:740–746.
18. Ostertag CB. Interstitial Radiosurgery of Brain Tumors. In: Gildenberg PL, Tasker RR, eds. Textbook of Stereotactic and Functional Neurosurgery. McGraw-Hill, New York, 1998:589–598.
19. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, Nelson D, Earle J, Jones C, Cascino T, Nichols D, Ivnik R, Hellman R, Curran W, Abrams R. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002; 20:2267–2276.

High-Grade Astrocytoma/Glioblastoma

6

Jon D. Weingart, Matthew J. McGirt, Henry Brem

Epidemiology – 128

Symptoms and Clinical Signs – 128

Diagnostics – 129
Synopsis
Body

Grading and Classification – 131
Synopsis
Body

Treatment – 133
Synopsis

Body – 134
Surgery
Radiotherapy
Chemotherapy
Recurrent Tumors

Prognosis/Quality of Life – 136

Follow-Up/Specific Problems and Measures – 137

Future Perspectives – 137

References – 138

Disclosure: Under separate licensing agreements between the Johns Hopkins University and Guilford Pharmaceuticals, Inc. and the Johns Hopkins University and Angiotech Pharmaceuticals, Inc., Dr. Brem is entitled to a share of the royalty received by the University on sales of products described in this work. Dr. Brem owns Guilford Pharmaceuticals, Inc. stock, which is subject to certain restrictions under University policy. Dr. Brem also is a paid consultant to Guilford Pharmaceuticals, Inc. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Epidemiology

Malignant astrocytomas, glioblastoma multiforme (WHO grade IV), and anaplastic astrocytoma (WHO grade III), remain the most common primary cerebral neoplasms in adults. These highly invasive tumors have a strong predilection for cerebral hemispheres. Glioblastoma multiforme (GBM) comprises 80% of malignant gliomas. While malignant astrocytomas comprise only 2% of all adult tumors at a rate of 5 cases per 100,000 adults per year, their malignant nature makes them the fourth greatest cause of cancer death [1]. Malignant astrocytomas are associated with a slight male to female preference (1.6:1.0). The peak age at onset for GBM is in the sixth or seventh decade, whereas anaplastic astrocytoma (AA) usually presents in the fourth or fifth decade. GBM (0.2/100,000 per year) and AA (0.5/100,000 per year) rarely occur in children less than 14 years of age. While malignant astrocytomas occur less commonly in African-Americans, no national differences in incidence have been consistently demonstrated after racial and age correction. Recent evidence suggests that the incidence of GBM and AA have doubled over the past decade. While the significance of this observation is unclear, many believe this to be a result of the increased use of MRI and CT.

To date, malignant astrocytoma is not believed to be a familial disease. However, an increased incidence has been observed in multiple syndromes. Patients with Turcot's syndrome, familial colonic polyposis with frequent colon cancer, may develop malignant astrocytoma more frequently [2]. Low-grade astrocytomas occurring at higher frequencies in patients with tuberous sclerosis and neurofibromatosis type 1 and 2 may progress to malignant glioma. Patients with an autonomic-dominant inheritance of a germline mutation of Tp53, Li-Fraumeni syndrome, are predisposed to developing tumors of the breast, soft tissues, bone, blood, adrenal cortex, and brain, including malignant astrocytomas. Nevertheless, a clear genetic predisposition to malignant astrocytoma has yet to be found.

Symptoms and Clinical Signs

The symptomatic presentation of malignant astrocytomas can be divided into two, often coexistent categories: nonspecific symptoms of elevated intracranial pressure (ICP) and site-specific symptoms due to the location of tumor. Nonspecific symptoms include headache, drowsiness, visual obscurations, nausea, vomiting, nuchal rigidity, papilledema, and occasionally 6th nerve palsy. Site-specific symptoms vary by tumor location and include motor, sensory, visual, language, and speech disturbances. Hearing and gait abnormalities may also be seen. The rate of symptom onset, extent of nonspecific symptoms, and localization of site-specific symptoms can provide important information regarding the aggressiveness, location, and extent of disease.

The most common nonspecific symptom associated with malignant astrocytomas is headache, occurring in 77% of patients, and is the initial symptom in 40% of patients with malignant glioma. Headaches resulting from malignant astrocytomas are often intermittent, deep, pressure-like, and are typically worse in the morning and improve throughout the day or with physical activity. Headache on awakening is thought to result from mild hypercapnia during sleep, resulting in cerebral vasodilation and transiently elevated ICP. The headache is most often nonlocalizing, but traction against meningeal structures may localize the pain to the side of the tumor.

Drowsiness is also frequently seen in patients with malignant astrocytomas, reflecting increased ICP. A depressed level of consciousness is seen at diagnosis in 40% of patients with malignant glioma and is a warning sign that the ICP may be nearing a critical level. Psychomotor retardation is the most common mental status change associated with malignant astrocytomas. Lack of persistence in routine tasks, faulty insight, emotional liability, forgetfulness, indifference to social practices, and blunted affect can be seen. Patients may also sleep for longer periods, often napping during the day. Frank confusion and dementia occur with more advanced disease and often accompany site-specific symptoms.

Both generalized major motor seizures and various focal seizures are observed in 29% of patients with malignant astrocytomas and occur less frequently in malignant astrocytomas versus all other glioma types (54%). A new onset seizure in a patient over 40 years of age should be considered indicative of a brain tumor until proven otherwise. Temporal lobe lesions often give rise to partial simple or complex (temporal lobe) seizures resembling petit mal attacks and may be associated with olfactory hallucinations, disorders of visual or auditory perception, or episodes of déjà vu. Epileptic progression

from one body part to another, typical of Jacksonian lesions, may suggest a lesion of the motor or sensory cortex.

Site-specific symptoms are location dependent and a result of either irritation or destruction of functional brain. Tumors in silent brain areas produce symptoms by extension of edema into functional areas, which can be ameliorated by corticosteroids. An improvement in symptoms with steroids often predicts a more durable improvement with surgical debulking and subsequent decrease in regional ICP. Direct invasion of tumor into eloquent brain often results in loss of function and is most often irreversible. Focal neurological findings, especially motor weakness, are more frequently seen with malignant astrocytomas than low-grade gliomas. Some 42% and 14% of patients with GBM present with some degree of hemiparesis or hemianesthesia, respectively. Temporal lobe and motor cortex lesions have a higher incidence of seizures. Apathy, memory loss, and personality disturbances occur more often with frontal and temporal lobe lesions. Frontoparietal lesions are often associated with hemiparesis and sensory loss. Sensory changes typically include paresthesias, anesthesia, and dysesthesias. Parietal lesions more typically result in proprioceptive loss, decreased two-point discrimination, and astereognosis. Dominant posterior inferior frontal lobe or posterior parietotemporal lesions may result in an expressive or receptive dysphasia, respectively, that progresses to aphasia. While gait disturbances and ataxia are most often due to posterior fossa pathology, gait disturbances of apraxia can be seen with frontal lobe lesions. Bifrontal lesions can cause urinary incontinence [3].

Diagnostics

Synopsis

While radiographic assessment may be highly suggestive of malignant glioma, diagnosis and subsequent treatment planning still depend on tissue sampling in all cases. CT and MRI exquisitely define normal and pathological intracranial tissues. CT offers superior imaging of acute blood, intraglioma calcium, and bone, while MRI allows multiplanar assessment of volumetric size and tumor extension into adjacent tissues. On MRI, GBM classically presents with a central area of T1 hypointensity, representing necrosis, surrounded by a gadolinium-enhancing ring, representing active tumor (Fig. 1). Infiltrating tumor and marked edema are often present and visualized by T2 hyperintensity. The degree of enhancement, necrosis, hemorrhage, and associated edema is usually less prominent for AA (Fig. 2) [4]. While these radiographic characteristics are strongly suggestive of malignant astrocytoma, metastatic tumors, lymphomas, abscesses, and occasionally demyelinating diseases can have a similar appearance (Fig. 3). The advent of MR spectroscopy may now allow noninvasive differentiation in many of these problematic cases. Nevertheless, the diagnosis remains dependent on tissue sampling in all cases (Fig. 4) [3].

Body

A diagnosis of malignant gliomas should be obtained by integrating clinical, radiological, and histopathological findings in all cases. While clinical presentation and radiological tumor characteristics allow a focused differential diagnosis, the definitive diagnosis remains dependent on tissue histology. High-grade gliomas must be differentiated from low-grade astrocytomas, metastases, primary CNS lymphomas, abscess, and multiple sclerosis plaques. The surgical procedure and its timing are based on the likely diagnosis, which is derived primarily from the radiographic appearance.

The radiographic appearance of a high-grade glioma is typically an irregular, heterogeneous lesion that is poorly marginated from normal brain on noncontrasted CT or MRI (Fig. 1). Active malignant glioma cells appear hyperdense on CT, hyperintense on T1-weighted MRI, and enhance with contrast administration. Irregular ring enhancement (active tumor) typically surrounds areas of low or abnormal signal (necrotic tissue, proteinaceous fluid, and old blood). These nonenhancing areas of necrosis within the tumor reflect malignant behavior and rapid growth. Infiltration through white matter bundles such as the

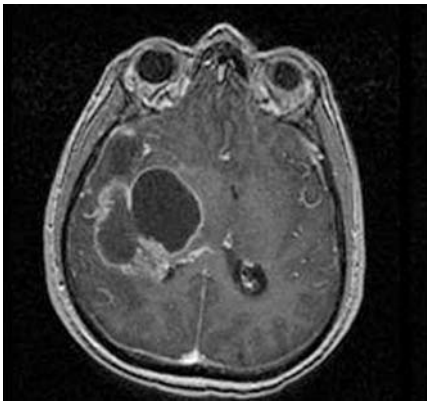


Fig. 1. Contrast-enhanced, T1-weighted MRI demonstrating classic radiographic signs of a GBM. A central area of low attenuation (necrosis) with multifocal and rim enhancement (active tumor) can be seen infiltrating the corpus callosum and is associated with mass effect and diffuse edema

corpus callosum or into the ependyma or subarachnoid spaces is also suggestive of an aggressive astrocytoma, most typically GBM. GBM are also commonly associated with prominent mass effect and edema. T2-weighted hyperintensity corresponds to both edema and infiltrating nonenhancing glioma that usually extends diffusely into the adjacent brain.

While these radiographic characteristics are strongly suggestive of malignant astrocytoma, lymphoma, metastatic tumors, and abscesses often cannot be differentiated from GBM on CT or MRI alone.

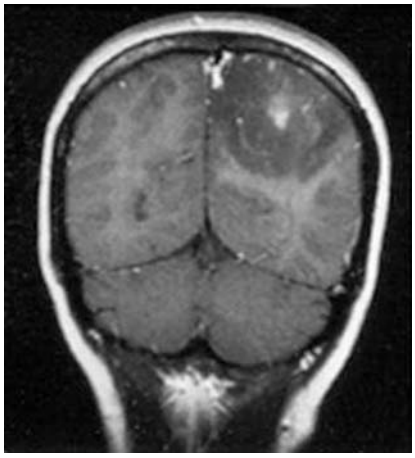


Fig. 2. Contrast-enhanced, T1-weighted MRI of an anaplastic astrocytoma (AA). A low attenuation lesion with minimal enhancement on T1-weighted MRI with minimal to moderate edema on T2-weighted MRI is suggestive of AA. (Printed with permission from [4])

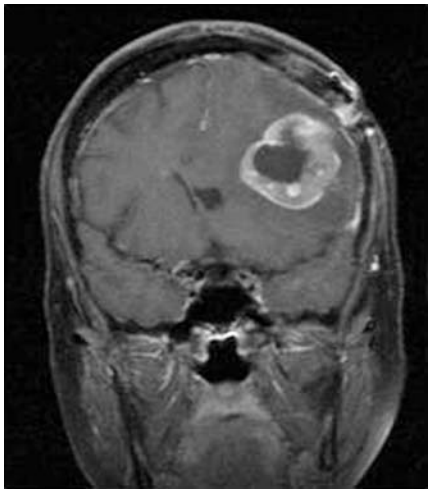


Fig. 3. Coronal contrast-enhanced, T1-weighted MRI of a patient with a ring-enhancing left frontal lesion with mass effect and surrounding edema. Histopathological diagnosis was lymphoma

However, subtle differences do exist. Despite having a central area of nonenhancement similar to GBM, metastases are more often round, well marginated, and have excessive edema relative to their size. Furthermore, metastases may be multiple, whereas GBM is usually a single lesion. Like GBM and metastasis, abscesses may have marked surrounding edema, mass effect, and intense enhancement. Abscesses are usually rounded with a smooth, thin-walled, enhancing rim with a nonenhancing center. The rim is characteristically hypointense on T2-weighted images. Compared with GBM, the enhancing wall is usually thinner; however, multiloculated abscesses may closely mimic a GBM with an irregular pattern. Although clinical correlation may strongly suggest a diagnosis in these difficult cases, biopsy and histological analysis are often needed to definitively differentiate these three lesions.

The characteristics of anaplastic astrocytomas (AA or grade 3 glioma) is radiographically more variable than GBM. Noncontrasted CT and MRI may resemble low-grade gliomas, but mass effect with AA is usually greater with more tumor heterogeneity. In contrast to GBM, the distribution of enhancement with AA is usually homogenous. Areas of necrosis are not present, and the degree of brain edema is variable.

Demyelinating diseases can present as a solitary mass with peripheral enhancement. Although a mass effect can be seen, there is often no mass effect or less than would be expected based on the size of the enhancement. Other differentiating features include minimal surrounding brain edema and minimal symptoms. When presented with this clinical scenario, additional tests such as MR spectroscopy are appropriate (Fig. 4) [3]. High-dose steroids will often result in resolution of the mass in as little as 1–3 weeks.

MR spectroscopy has become increasingly utilized to differentiate malignant astrocytomas from non-neoplastic lesions such as radiation necrosis, abscess, or demyelinating lesions. MR spectroscopy measures choline (marker of membrane turnover), creatine and phosphocreatine (components of the energy pool); glutamate and glutamine (excitatory neurotransmitters); N-acetyl aspartate (NAA, marker of neuronal health); lactate (marker of anaerobic metabolism); and myoinositol (a sugar phosphate). MR spectroscopy divides the image into voxels of interest. The composition within individual voxels can then be compared between the lesion of interest and normal brain. MR spectroscopy demonstrating elevated choline in relation to NAA or creatine suggests neoplasm, whereas the absence of elevated choline in a background of other lipids and lactate would suggest a non-glioma lesion (Fig. 4) [3]. MR spectroscopy may also be useful in differentiating the grade or

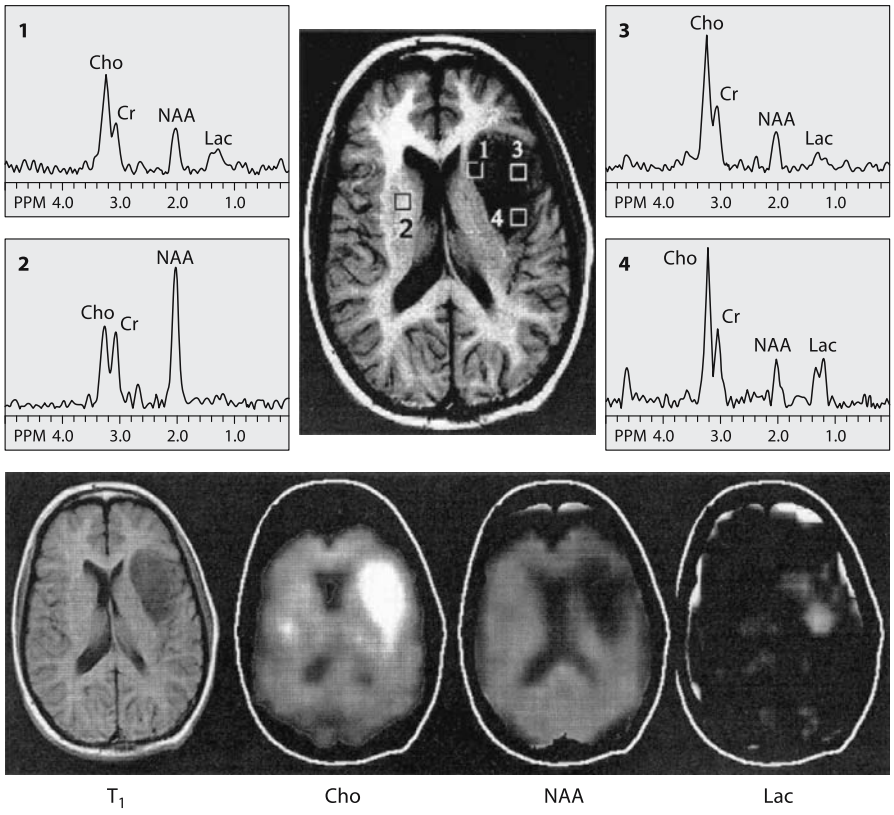


Fig. 4. MR spectroscopy of a glioblastoma. *Upper panel* Single pixel spectrographs (*1–4*) corresponding to regions sampled within tumor (regions *1, 3* and *4*) and contralateral normal brain (region *2*). Normal brain (region *2*) contains high *N*-acetylaspartate (*NAA*) relative to choline (*Cho*) and creatine (*Cr*) and no lactate (*Lac*). All regions with tumor show elevated choline, elevated lactate, and diminished *N*-acetylaspartate relative to creatine. *Lower panel* MR spectroscopic imaging of the same tumor depicting diffusely elevated choline, diffusely diminished *N*-acetylaspartate, and multifocally elevated lactate within tumor. (Printed with permission from [3])

aggressiveness of glioma. While a moderate choline elevation in the setting of modest NAA depression without increased lactate suggests low-grade glioma, marked elevation of choline, marked depression of NAA, and increased lactate strongly suggest malignant glioma. Nonetheless, almost all cases require tissue sampling. This can be done with a stereotactic biopsy or during an open resection. If there is concern that the abnormality may represent multiple sclerosis and a MR spectroscopy study is consistent with this, then repeat MRI scanning in 4–6 weeks is prudent.

Grading and Classification

Synopsis

Several grading systems have been formulated which rely solely on cytological and histological characteristics. Currently, the World Health Organization system is the most widely used and differentiates three grades of astrocytomas: WHO grade 2 (low-grade astrocytoma), WHO grade 3 (anaplastic astrocytomas), and WHO grade 4 (glioblastoma multiforme). WHO grade 3 (AA) and WHO grade 4 (GBM) are considered malignant or high-grade gliomas. The spectrum from grade 2 to grade 4 is characterized by increased cellularity and pleomorphism, higher mitotic rate, and the presence of vascular proliferation and necrosis. The finding of vascular proliferation and necrosis is required for the diagnosis of grade 4 (Fig. 5) [5].

Body

Neoplasms arising from an astrocytic lineage form a large and heterogeneous group that can be divided into two groups of gliomas: fibrillary gliomas (astrocytoma, AA, GBM) and another more diverse group with distinct clinicopathological features (juvenile

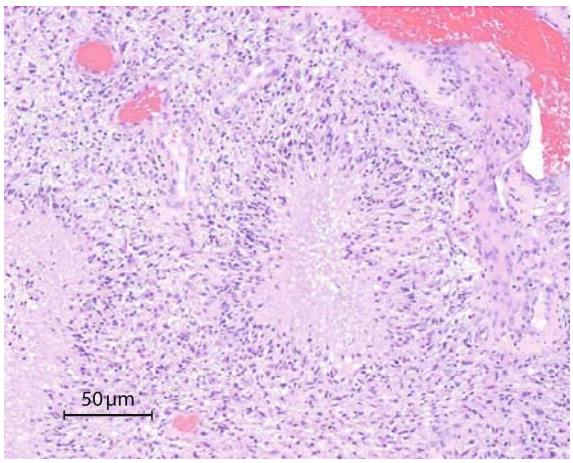


Fig. 5. Histopathology of glioblastoma multiforme (GBM) demonstrating classic features of GBM: palisading neoplastic cells around a zone of necrosis with vascular proliferation adjacent to the necrotic core

pilocytic astrocytoma, pleomorphic xanthrocytoma, and subependymal giant-cell astrocytoma). Current pathological classification systems rely solely on histological characteristics. Gliomas rarely metastasize beyond the CNS, and therefore, the tumor size, nodal status, and metastasis system used for systemic cancers is not applicable.

Fibrillary astrocytomas represent 80% of all astrocytic tumors. These tumors exist along a spectrum of well-differentiated tumors to highly anaplastic tumors. Several grading systems have been proposed and used in order to classify astrocytomas along this continuous spectrum. The WHO classification is the most widely accepted system. In this system, fibrillary astrocytomas are graded as 2, 3, or 4. These numbers correlate with the old modified Ringertz system of astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. In the literature and in practice, these terms are synonymous with each other, i.e., grade 2 = astrocytoma, grade 3 = anaplastic astrocytoma, and grade 4 = glioblastoma multiforme. In the WHO system, pilocytic astrocytomas are grade 1 lesions. However, they are not part of the continuum of fibrillary astrocytomas as they do not progress to a grade 2, 3, or 4.

The progression from grade 2 to 4 is characterized by increased cellularity, increased cellular atypia, increased mitotic index, and finally the appearance of vascular proliferation and necrosis. In general, necrosis is necessary for the diagnosis of a grade 4 lesion. The natural history of the fibrillary astrocytomas is for the lower grade lesions to progress to the grade 4 lesion (Fig. 6). The prognosis for the patient is directly related to the tumor grade at diagnosis, with median survivals of 8–10 years for grade 2, 2–3 years for grade 3, and 50 weeks for grade 4.

The MRI radiologic appearance of the tumor correlates well with the histopathology. Understanding this relationship is important in planning surgical intervention and in understanding the neurologic sequelae of surgery. Grade 2 lesions are usually isodense or hypodense on T1-weighted images and hyper-intense on T2 weighted images. The histopathology demonstrates a slight increase in cellularity, minimal atypia, and few if any mitoses. The Grade 2 lesion is characterized as brain with infiltrated tumor cells. As this brain may retain neurologic function, plans to remove the tumor must be weighed against the risk of the potential neurologic compromise.

The high-grade astrocytomas, grades 3 and 4, are characterized by the presence of gadolinium enhancement on MRI (Figs. 1, 2). The grade 4 tumor usually has a central area that does not enhance, which represents necrotic tumor tissue. Although both grades 3 and 4 have surrounding edema, this finding is more prominent in the grade 4 tumor. Histopathologically, the enhancing portion of the tumor seen on MRI represents pure tumor with no intervening brain. There is high cellularity, marked nuclear pleomorphism, mitoses, and necrosis. It is this enhancing portion of the tumor that is removed at surgical resection or is biopsied at stereotactic biopsy. The histopathology can vary in different regions of the tumor, which necessitates generous sampling at the time of surgery or biopsy. For stereotactic biopsies, sampling error is a real concern and mandates close communication between the pathologist and the surgeon to maximize the chance of an accurate diagnosis.

An important pathologic issue with high-grade gliomas is the tissue diagnosis of recurrent tumor. Treatment, including radiation and local chemotherapy, can alter the histopathology, making interpretation very difficult. In particular, the effects of treatment result in necrosis and changes in cellular morphology. Therefore, at the time of a second surgical procedure, progressive or recurrent tumor requires the presence of viable tumor cells being examined by the pathologist.

The degree of surgical resection of a primary brain tumor is an important prognostic factor in predicting the outcome of the disease. It is therefore important to obtain a contrast-enhanced scan within 48 h so that an accurate assessment of the residual tumor can be made. Delayed scans are confounding because artifactual enhancement (secondary to surgery or radiation on local implants) may obscure the actual tumor that needs to respond to adjuvant therapy.

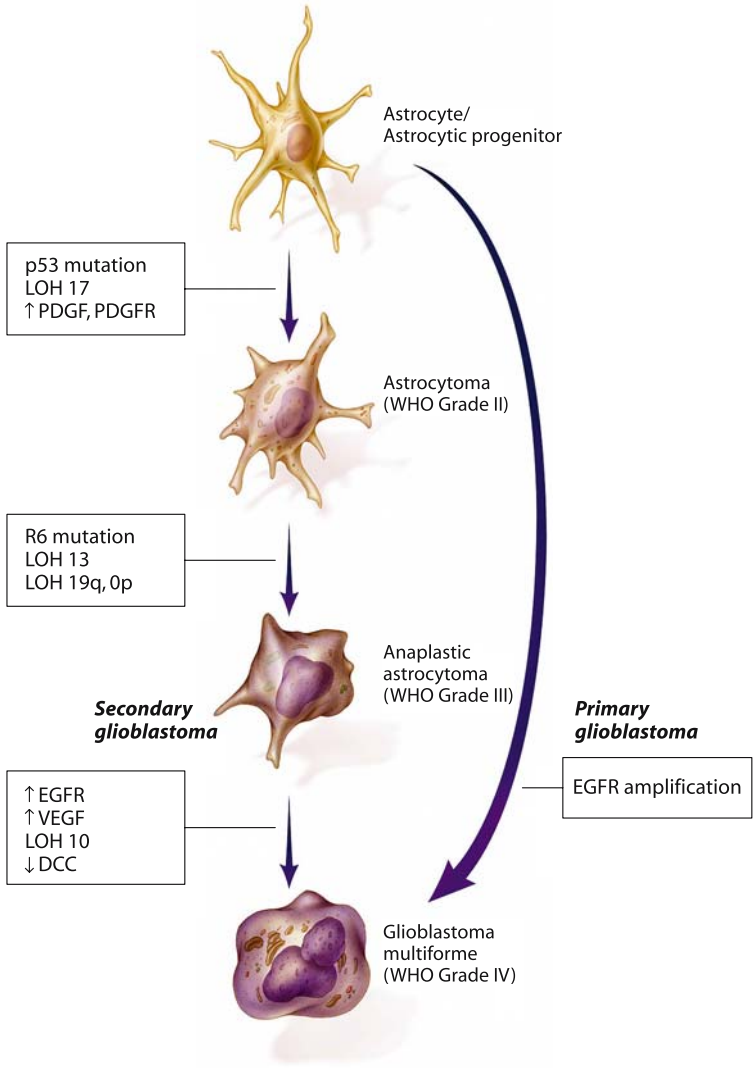


Fig. 6. Development and progression of astrocytic brain tumors. Malignant brain tumors can arise in one of two ways. Astrocytes can undergo genetic changes accompanied by upregulation of certain receptors, such as the platelet-derived growth factor (PDGF), endothelial growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF). These progressive changes culminate in the formation of a glioblastoma. Alternatively, most primary glioblastomas arise de novo, without the need for gradual progression from an astrocytoma to a high-grade astrocytoma to a glioblastoma multiforme. (Illustration by Ian Suk, Johns Hopkins University)

Treatment

Synopsis

Patients with AA or GBM undergo surgery, either a stereotactic biopsy or a tumor resection. The goal of surgery is to establish the diagnosis and remove the enhancing portion of the tumor. The decision for a resection versus a stereotactic biopsy is based on the location of the tumor and its MRI appearance. A treatment option at the time of surgery is the implantation of chemotherapy (BCNU), in the form of impregnated polymer wafers (Gliadel) [6]. Following surgery, patients are treated with fractionated radiation therapy, often with temozolomide given concurrently. Temozolomide is then continued after the radiation therapy for up to 6 months [7].

The majority of tumor recurrences are local, occurring within 2 cm of the original enhancing tumor. Treatment options include repeat surgery with or without local chemotherapy (Gliadel) (Fig. 7), standard chemotherapy regimens, brachytherapy with the Gliasite balloon (Fig. 8), or some combination. Whereas treatment at the time of initial presentation tends to be fairly consistent from patient to patient, treatment at the time of recurrence needs to be individualized based on the patient's disease status, performance status, and the tumor anatomy. Investigational treatments begin to play a role in the care of these patients at the time of tumor recurrence.

Body

Surgery

The role of surgery in the treatment of high-grade astrocytoma has often been debated. Historically, the value of surgery was in establishing the diagnosis and decreasing the size of the tumor mass by resection. As novel treatments have been developed, surgery has become important in the delivery of these treatments, such as Gliadel Wafers, Gliasite balloon, and convection-enhanced delivery via intratumoral catheters.

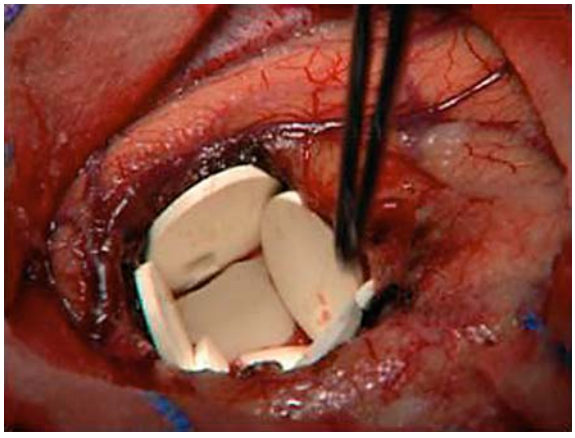


Fig. 7. Intraoperative view of a recurrent GBM resection cavity lined with biodegradable BCNU wafers

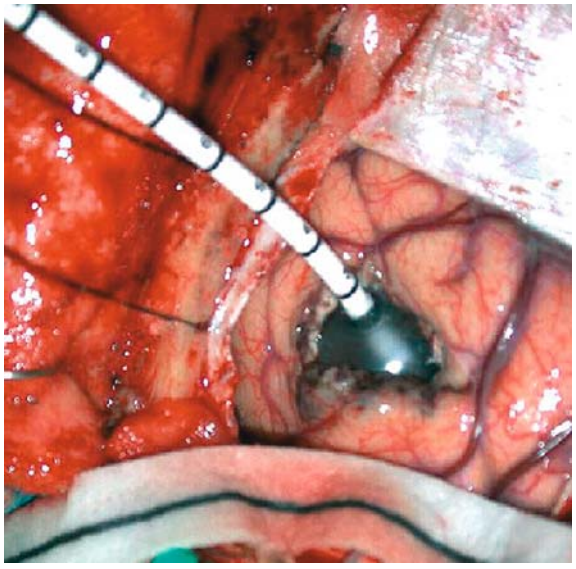


Fig. 8. Intraoperative photograph demonstrating Gliasite balloon within the resection cavity

The basic goals of surgery are tissue diagnosis, mass reduction, and tumor resection. Although the impact of resection on survival has been difficult to demonstrate in controlled trials, anecdotal experience strongly supports the value of resection. Quality of life is certainly enhanced by resection in patients with increased ICP, mass effect, and brain edema. In the majority of patients, resection does not result in increased neurologic deficits due to the cytoarchitecture of the tumor. The enhancing portion of a high-grade glioma represents tumor cells without intervening brain. Therefore, the removal of this portion of the tumor can be carried out safely even in eloquent brain regions. The improved neuroimaging, intraoperative navigation techniques, intraoperative MRI, preoperative and intraoperative functional mapping allow for better tumor resections with less neurologic morbidity.

In certain cases, tumor resection is not beneficial to the patient. Typically, tumors located primarily in the basal ganglia, thalamus, or corpus callosum are biopsied only. Lesions centered in the corpus callosum will sometimes have a large extension into one hemisphere, and resection may be beneficial in these circumstances to decrease the mass effect. In patients with diffuse infiltrating tumors characterized by T2-weighted signal change only which involve large areas of a hemisphere, biopsy is the procedure of choice. Deeper brain lesions are biopsied using CT- or MRI-guided stereotactic techniques. Open biopsy is appropriate for diffuse tumors located in the subcortical white matter. As sampling error and failure to obtain diagnostic tissue are risks of stereotactic biopsies, good communication with the pathologist during the procedure is important in maximizing an accurate diagnosis.

Adjuvant treatment can be initiated at the time of surgical resection with the implantation of Gliadel wafers. Gliadel wafers, a polymer-based drug delivery system that provides sustained local release of BCNU, has been evaluated in three randomized, prospective, placebo-controlled phase III trials [6, 9, 10]. Gliadel was approved in 1996 for use in patients with recurrent GBM. This approval was based on a phase III prospective, randomized, placebo-controlled trial conducted in 222 patients at 27 centers. Results showed a median posttreatment survival of 31 weeks for patients treated with BCNU-polymer versus 23 weeks for blank polymer (hazard ratio 6.67, p=0.006). In the subgroup of patients with glioblastoma, the 6-month survival was increased 60% in the BCNU-polymer group (64% vs 44%, p=0.02). There were no clinically significant adverse effects attributable to the BCNU-loaded polymers [9].

To evaluate whether the treatment was effective as initial therapy in combination with radiation therapy, Valtonen et al. reported a prospective, randomized,

placebo-controlled study of BCNU polymers or placebo as part of initial treatment, followed by standard radiotherapy. Thirty-two patients were enrolled in the study and equally divided between the groups, and all completed the study. All placebo patients had glioblastomas. Median survival was 58.1 weeks for the Gliadel group, versus 39.9 weeks for placebo (hazard ratio 0.27, p=0.012). When considering only the 27 patients with glioblastomas, median survival was 53.5 weeks with Gliadel and 39.9 weeks with placebo (hazard ratio 0.28, p=0.008). Moreover, of six patients alive at 2 years, five were in the Gliadel group (31% 2-year survival vs 6% for the control group), and four of them had glioblastomas. At 3 years, 25% of patients in the Gliadel group were alive compared with 1 of 16 in the control patients. Westphal et al. [6] carried out a 340-patient, randomized, prospective trial using Gliadel as the initial therapy. They reported a median survival of 13.9 months vs. 11.6 months for those patients treated with surgery and radiation (hazard ratio 0.73, p<0.05). At 3 years, 9.2% of patients with Gliadel were alive compared with 1.7% of controls. A meta-analysis of the GBM population of the Westphal and Valtonen study showed a significant improvement in survival for GBM patients (hazard ratio 0.75, p=0.034).

These studies strongly suggest that Gliadel is safe and effective as an initial therapy. Based on the cumulative evidence above, Gliadel was approved for use as the initial treatment in the USA by the FDA on February 25, 2003, and in Europe in 2004.

Radiotherapy

Radiation therapy is a critical component of the treatment plan for patients diagnosed with high-grade astrocytomas. Attempts to alter radiation schedules, change fraction size, or increase the dose have not resulted in added benefit. Recently, clinical trials have demonstrated a survival benefit by combining Temozolomide with radiation therapy [8]. Other new approaches to enhance and expand the role of radiation include brachytherapy with the Gliasite balloon, stereotactic radiosurgery, a second course of radiation, and the use of radiation sensitizers.

Fractionated radiotherapy has been shown to extend survival in multiple randomized trials. The treatment regimen involves 30–33 treatments at 180–200 rads/treatment for a total dose of 5400–6000 rads. Patients with a very poor prognosis can be treated in a more rapid fashion in order to complete the course of radiation more quickly. This treatment regimen involves 300 rads/day in 17 treatments. Patients are treated with 10 treatments over 2 weeks. The last 7 treatments are given after a week off. In a retrospective study looking at 219 patients treated in this way, outcomes were as expected when the patients were assigned to six prognostic groups identified in a recursive partitioning analysis by the RTOG. These findings suggested that this shortened regimen results in a similar survival to the standard regimens [11].

Concomitant temozolomide and radiotherapy have recently been shown to be superior to radiation alone. A randomized phase III trial reported a significant improvement in the progression-free survival and overall survival in patients diagnosed with GBM. The study enrolled 573 patients from 85 centers. Patients treated with both temozolomide and radiation had an increased median survival of 15 months compared with 12 months with radiation only. Furthermore, the 2-year survival was 26% in patients treated with both temozolomide and radiation and 8% in patients treated with radiation only. These findings have now resulted in temozolomide being used in combination with radiation therapy as the initial treatment regimen for most patients diagnosed with glioblastoma [8].

Stereotactic radiosurgery has been utilized to increase or to boost the dose to a portion of the radiation field in the newly diagnosed patient. In the recurrent tumor setting, this modality is being employed to treat focal-enhancing recurrences. However, there is no study that has demonstrated a statistically significant benefit in terms of tumor control or increased survival.

Intracavitary brachytherapy using the Gliasite balloon is a novel approach to delivering additional radiation to the brain surrounding a tumor cavity (Fig. 8). Approved by the FDA as a device to be used in this fashion, the Gliasite balloon is being used in both recurrent and newly diagnosed settings. The balloon is sized and implanted at the time of resection. Several weeks later, an ^{125}I solution is injected into the balloon via an attached port. The radiation material and the balloon are removed 4–5 days later [12]. A study of 24 recurrent GBM patients treated in this way had a median survival after Gliasite brachytherapy of 9 months.

Finally, a second course of radiation for patients with recurrent tumors is offered to some patients. The rationale is that the expected survival even with a treatment benefit from the second course of radiation is not long enough if patients suffer the morbidity of additional radiation on normal brain function.

Chemotherapy

In the past, most patients were treated with systemic chemotherapy at the time of tumor recurrence or following radiation as part of the patient's primary ad-

juvant treatment. For GBM, this occurred in the absence of any statistically significant benefit in any individual, controlled clinical trials. For AA, the combination of procarbazine, CCNU, and vincristine was found to be beneficial in several noncontrolled studies. Recently, when this combination was evaluated in a randomized, controlled fashion in patients with high-grade gliomas who were treated with the chemotherapy regimen following radiation compared with patients treated with radiation alone, no significant difference in survival was demonstrated for patients with AA or GBM.

Recent trials have focused on temozolomide, an oral alkylating agent, at the time of recurrence and at initial treatment for patients with GBM and AA. In 162 patients with refractory, recurrent AA who had failed a nitrosourea procarbazine combination, temozolomide treatment resulted in a 9% complete response rate and a 13% partial response rate. When tested in patients with recurrent GBM in a phase II study compared with procarbazine, the median progression-free survival was 12 weeks with a progression-free survival at 6 months of 21%. Based on these findings, temozolomide has been approved for use in patients with recurrent AA who have failed a nitrosourea procarbazine regimen [7].

The recent phase III trial showing the benefit of combining temozolomide and radiation will result in many patients receiving temozolomide as their initial treatment [8]. For this reason, the majority of patients will have already received temozolomide at the time of recurrence. Chemotherapy options for these patients will include a variety of agents such as BCNU, procarbazine, CPT-11, and cisplatin, which have been used in this patient population but have not been shown to be statistically beneficial in controlled trials. Other options for patients include participation in investigational chemotherapy and immunotherapy trials.

Recurrent Tumors

The clinical problem of tumor recurrence arises in virtually all patients with this diagnosis. As patients are followed every 2–3 months with serial MRI scans, tumor progression is often documented before symptoms appear. As the intensity of treatment has increased, in particular local treatments, differentiating tumor recurrence vs treatment effect or treatment necrosis has become an important and difficult diagnostic dilemma. This is most problematic when the MRI change is increased enhancement around the original tumor cavity in the absence of mass effect. Although MRI spectroscopy and PET scans have been employed to differentiate tumor from treatment effect, these have not been found to be completely reliable. Often tissue obtained via stereotactic biopsy or open biopsy/resection is necessary. Given the problem of sampling error with stereotactic biopsy, open biopsy/resection is often preferred.

For patients with focal recurrences, surgical resection is an option. Additional treatment can be administered locally at the time of resection or systemically following surgery. Local treatments administered at the time of surgery include implantation of Gliadel wafers or brachytherapy using the Gliasite balloon. Systemic chemotherapy is an option with or without surgical resection. Initial drug options include temozolomide or BCNU. A number of other single agents such as procarbazine, CPT-11, or carboplatin have been used with only anecdotal reports of treatment response.

Prognosis/Quality of Life

The overall prognosis for patients with high-grade gliomas remains poor. For GBM, surgical resection following radiation therapy results in median survival of 50 weeks. Recent advances, Gliadel and temozolomide, have resulted in extending the median survival, but neither offer long-term control for most patients. Age and Karnofsky Performance Scores (KPS) are the factors that have the strongest association with survival.

Patients with high KPS at presentation, in general, continue with high KPS throughout surgery and radiation treatment. Dexamethasone is used, perioperatively and during radiation, to counteract the symptoms that arise from the brain edema associated with high-grade gliomas. Typical doses are 4–8 mg of dexamethasone four times a day. Doses as high as 20 mg every 4 h can be used on patients with high ICP due to brain edema. In these circumstances, dexamethasone has a profound effect on reducing patient symptoms and improving the quality of life. Following surgery and radiation therapy, dexamethasone should be tapered, as over time the side-effects secondary to the steroids begin to detract from quality of life.

Recurrences occur primarily locally in the region of the original site of the presentation. This recurrence pattern has resulted in new approaches, such as Gliadel and convection-enhanced delivery, directed locally at the tumor site. Common patterns of spread include white matter tracts, in particular the corpus callosum. As local tumor control improves, distant recurrences are now developing. Because of the almost 100% recurrence rate, close radiological follow-up every 2 months is essential in the management of these patients in terms of treatment decisions and prognosis counseling. In addition to the enhancing portion of the tumor, attention should also focus on

the signal change on flair and T2-weighted images, as changes seen on these MRI sequences can also represent progressive disease.

Follow-Up/Specific Problems and Measures

An important management issue in patients with high-grade gliomas is the interpretation of the follow-up images after surgery and radiation therapy. With the intensification of therapy with these patients, MRI changes can be related to the treatment itself and not to tumor progression. For the first 3 months following radiation therapy, increased enhancement is often seen on follow-up images. Similar changes are now being seen 3 months to 1 year after treatment. Differentiating tumor verses treatment effect is critical as patients may receive unnecessary treatment, and furthermore, apparent benefits of some treatment may be overstated.

There are no diagnostic studies which differentiate recurrence versus treatment effect in a consistent manner. Clues on imaging studies include an enhancement pattern which surrounds the original tumor site and lacks nodularity. Often there is minimal or no mass effect associated with changes caused by treatment effect. Surrounding brain edema can be minimal or quite significant and will respond to steroids if present. MRI spectroscopy and PET scanning can be employed and may be helpful in suggesting recurrence versus treatment effect. In patients where treatment effect is suspected and the symptoms are minimal, increased steroids and repeating the MRI scan in 4–6 weeks are appropriate. Obtaining tissue is the gold standard, and this is recommended in cases where the risk of surgery is acceptable, and the outcome will alter treatment. Because of the difficulty in identifying active tumor in these cases, open surgery with adequate tissue sampling is superior to stereotactic biopsy. If treatment effect is found at surgery, additional antitumor treatment would not be appropriate. Hyperbaric oxygen and steroids are used in this scenario.

The use of local chemotherapy with Gliadel implanted at the time of surgery at initial diagnosis and recurrence has increased with its approval by the FDA. Up to 8 wafers are placed along the walls of the tumor cavity with Surgicel used to cover them. The Surgicel should overlap onto the cortex and intervening white matter in order to hold the wafers in place. Irrigation fluid can be used to fill up the cavity, although this is not required. A water-type dual closure is absolute as infections in the setting of Gliadel is closely associated with CSF leaks. The use of fibrin glue and dural grafts are encouraged when necessary.

Ideal patients for Gliadel use are those with solitary lesions where a near gross total resection of the enhancing tissue is possible. Patients with significant amounts of gross tumor left at the end of surgery can have significant problems with brain edema as tumor cells die due to the local release of BCNU. Patients with tumor in the corpus callosum or distant from the resection cavity are not ideal candidates. Placement of Gliadel in the setting of a ventricular opening is permitted. If the surgeon has concerns about migration of the polymer into the ventricular system, then the polymer should not be used. Exposure of the ventricular cerebrospinal fluid to the BCNU released by the polymer does not result in BCNU toxicity.

Postoperatively, patients should be maintained on steroids for several weeks and may initially need higher doses than usual. The wafers can be seen on MRI images, hyperdense on T1-weighted images and dark on T2-weighted images. The hydrophobic component of the wafer can take months to absorb and can be seen on reoperation. There is no BCNU in this polymer remnant. The interpretation of posttreatment imaging is critical as there is a local treatment effect. Within the first 3 months, there is often increased enhancement around the margin of the tumor cavity. This enhancement can at times appear quite significant and suggest progressive tumor. In these circumstances, serial imaging is helpful in differentiating progressive tumor versus treatment effect. Changes related to the Gliadel will diminish over time. Air within the tumor cavity can also be seen for a number of weeks after treatment. In the initial experience, there was a concern that this represented infection, and the patients were explored. However, no infection was found in these cases. Therefore, when air is found within the tumor cavity, close follow-up and correlation with other clinical signs should be used to guide treatment decisions. Finally, the rim of enhancement around the cavity can persist indefinitely in some patients. Although it is not clear what this represents, observation with serial MRI scans is all that is necessary. Additional treatment should be withheld until the enhancement pattern increases.

Future Perspectives

Significant advances in imaging and surgical techniques have allowed for more rapid precision diagnosis and initial therapy of high-grade astrocytomas. Advances in radiation and chemotherapy have led to newer and better methods of treating these patients with less morbidity. However, in the future there will need to be greater attention to predicting the response to individualized therapies and to over-

coming the tumors' resistance mechanisms. For example, the MGMT gene can be identified and is associated with increased responsiveness to alkylating agents [14]. Studies are underway to see if blocking resistance enzymes by agents such as O^6-benzylguanine will further enhance the benefit of newly approved treatments using Gliadel and temozolomide [15]. Combination therapies will likely improve the outcomes [16].

In the future, it is conceivable that we will first sample the tumor, evaluate its sensitivity and genetic characteristics, and then design the most individually appropriate therapy. Future advances in antiangiogenesis therapy and immunotherapy will likely improve the outcome for these patients. The current approach of offering patients the best possible therapies together with entering patients into new innovative clinical trials will likely lead to further advances in this field.

References

1. Davis F, et al. Survival rates in patients with primary malignant brain tumors stratified by patients age and tumor histology type: An analysis based on Surveillance, Epidemiology, and End results (SEER) data, 1973–1991. Journal of Neurosurgery, 1998; 88:1–10.
2. Tod DW, et al. A family affected with intestinal polyposis and gliomas. Annals Neurology, 1981; 10:390–392.
3. Laterra J, Brem H. Primary brain tumors in adults. In: Asbury A, McDonald I, McKhann G, Goadsby P, McArthur J, eds. Diseases of the Nervous System: Clinical Neuroscience and Therapeutic Principles, 3rd Edition. Cambridge University Press, Cambridge, UK., (Chap 87) 2002:1431–1447.
4. Bohan E. Brain Tumors. In: Barker E, ed. Neuroscience Nursing-Spectrum of Care, 2nd edition, Mosby, Inc., St. Louis, Missouri, 2002:269–301.
5. Burger PC, Scheithauer BW, Vogel FS, Surgical pathology of the nervous system and its coverings. 4th ed., New York, NY: Churchill Livingstone, 2002.
6. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jaaskelainen J, Ram Z. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuor-Oncology 2003; 5(2):79–88.
7. Yung WKA, Patros D, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, Albright R, Olson J, Chang SM, O'Neill AM, Friedman AH, Bruner J, Yue N, Dugan M, Zaknoen S, Levin VA. Multicenter Phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. 1999; 17(9):2762–2771.
8. Stupp R, Mason WP, Van Den Bent MJ, et al. Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized Phase III trial by the EORTC Brain & RT Groups and NCIC Clinical Trials Group (Abstr.). CNS tumors, ASCO Annual Meeting 2004; 2.
9. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Schold SC, and the Polymer-Brain Tumor Group. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas The Lancet 1995; 345:1008–1012.
10. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T. Interstitial chemotherapy with carmustine-loaded polymers for high-grad gliomas: A randomized double-blind study. Neurosurgery 1997; 41(1):44–49.
11. Kleinberg L, Slick T, Enger C, Grossman S, Brem H, Wharam MD, Jr. Short course radiotherapy is an appropriate option for most malignant glioma patients. Int J Radiation Oncology Biol Phys 1997; 38(1):31–36.
12. Tatter SB, Shaw EG, Rosenblum ML, et al. An inflatable balloon catheter and liquid 125I radiation source (GliaSite Radition Therapy System) for treatment of recurrent malignant glioma: multicenter safety and feasibility trial. J Neurosurg 2003; 99:297–303.
13. Medical Research Council Brain Tumour Working Party. Randomized trial of procarbazine, lomustiine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A medical research council trial. Journal of Clinical Oncology 2001; 19(2):509–518.
14. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. The New England Journal of Medicine 2000; 343(190:1350–1354.
15. Friedman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry A, Ashley DM, Krischer J, Lovell S, Rasheed K, Marchev F, Seman AJ, Cokgor I, Rich J, Stewart E, Colvin OM, Provenzale JM, Bigner DD, Haglund MM, Friedman AH, Modrich PL. DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. J Clin Oncol 1998; 16(12):3851–3857.
16. Guruangan S, Cokgor I, Rich JN, Edwards S, Affronti ML, Quinn JA, Herndon JE, Provenzale JM, McLendon RE, Tourt-Uhlig S, Sampson JH, Stafford-Fox V, Zaknoen S, Early M, Friedman AH, Friedman HS. Phase I study of Gliadel™ wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. Neuro-Oncol 2001; 246–250.

Oligodendroglioma 7

Michael Weller

Epidemiology – 140

Symptoms and Clinical Signs – 140

Diagnostics – 140

Staging and Classification – 140

Treatment – 140
Surgery
Radiotherapy
Chemotherapy
Other
Specific Treatment Recommendations

Prognosis, Follow-up and Quality of Life – 143

Specific Problems and Measures – 143

Future Perspectives – 143

References – 143

Epidemiology

Approximately 5% of all primary brain tumors are oligodendroglial tumors. Their incidence is in the range of 0.5 per 100,000 per year. The median age at diagnosis is 40–45.

Symptoms and Clinical Signs

Oligodendrogliomas are infiltrative, mostly supratentorial tumors which frequently originate in the frontal lobes (50%), often bilaterally affecting the white matter. Corpus callosum and basal ganglia may also be involved. Seizures are the most common mode of presentation (50–70%), followed by focal neurological signs such as aphasia and personality changes. The tumors tend to spread within the central nervous system, and extraneural metastases are rare.

Diagnostics

Synopsis. The tentative diagnosis of an oligodendroglial tumor may be made by neuroimaging criteria, but the diagnosis should always be confirmed histologically. Molecular markers, notably the loss of genetic information on chromosomes 1p and 19q in the tumor cells, may assume a role in shaping individual treatment strategies in the future.

Neuroimaging plays a central role in the diagnosis and follow-up of oligodendroglial tumors (Fig. 1). MRI is superior to CT because of a better delineation of tissue structure and the availability of imaging in all planes and is therefore the imaging method of choice. CT may aid in the detection of calcification which is a common feature (70–90%). T1-weighted MRI or CT delineate areas of contrast enhancement, whereas T2-weighted images are sensitive for the detection of tumor extension into the brain parenchyma. Oligodendrogliomas and oligoastrocytomas may not be differentiated by imaging but can be distinguished from astrocytomas by the higher frequency of calcification, cystic regressive changes, and hemorrhages. Perifocal edema and contrast enhancement are more often found in anaplastic (grade III) than in grade II tumors but are not reliable parameters for the differential diagnosis. PET and SPECT are experimental imaging techniques that have no role in the standard care of these tumors. Cerebral angiography is performed prior to surgery as requested by the surgeon.

Staging and Classification

Synopsis. Oligodendroglial tumors encompass WHO grade II oligodendrogliomas and oligoastrocytomas and their anaplastic variants (WHO grade III). Distinction is made by histopathological criteria.

The definitive diagnosis is made by histopathology alone [11]. Oligodendrogliomas are well-differentiated, diffusely infiltrating lesions which consist of cells resembling oligodendrocytes. The typical features of these tumors may only be appreciated in paraffin-embedded tissue. Oligoastrocytomas contain two distinct cell populations which correspond to tumor cells characteristic of oligodendrogliomas and grade II astrocytomas (Fig. 2). Immunohistochemical markers for the diagnosis of the oligodendroglial component have not been identified. Anaplastic tumors exhibit higher cellular density, pleomorphic cells, and an increase in mitoses and microvascular proliferation. According to the WHO classification, the detection of necroses in an anaplastic oligodendroglial tumor per se does not make this tumor a glioblastoma. The loss of genetic material on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is a common finding in oligodendroglial tumors which predicts longer survival and favorable responses to radiotherapy and chemotherapy. The genes mediating this differential course of the disease in histologically indistinguishable tumors have not been identified. The lower frequency of 1p and 19q losses in temporal tumors compared with frontal, parietal, and occipital tumors may be responsible for a less benign course of temporal tumors [12].

Treatment

Synopsis. Surgery, radiotherapy, and chemotherapy have a role in the treatment of oligodendrogliomas. Currently, there are no results from clinical trials to define the comparative efficacy of these treatment modalities administered alone or in combination. The response to therapy is assessed by neuroimaging using the Macdonald criteria [8].

Almost all data on the clinical course and response to therapy of these tumors are retrospective. The histological diagnoses are controversial and were often not re-evaluated by a central neuropathology review. It is therefore difficult to derive differential standards of care for pure oligodendroglial vs mixed and for grade II vs grade III lesions from the literature. Some oligodendroglial tumors appear not to grow for years. These features make firm treatment recommendations rather difficult.

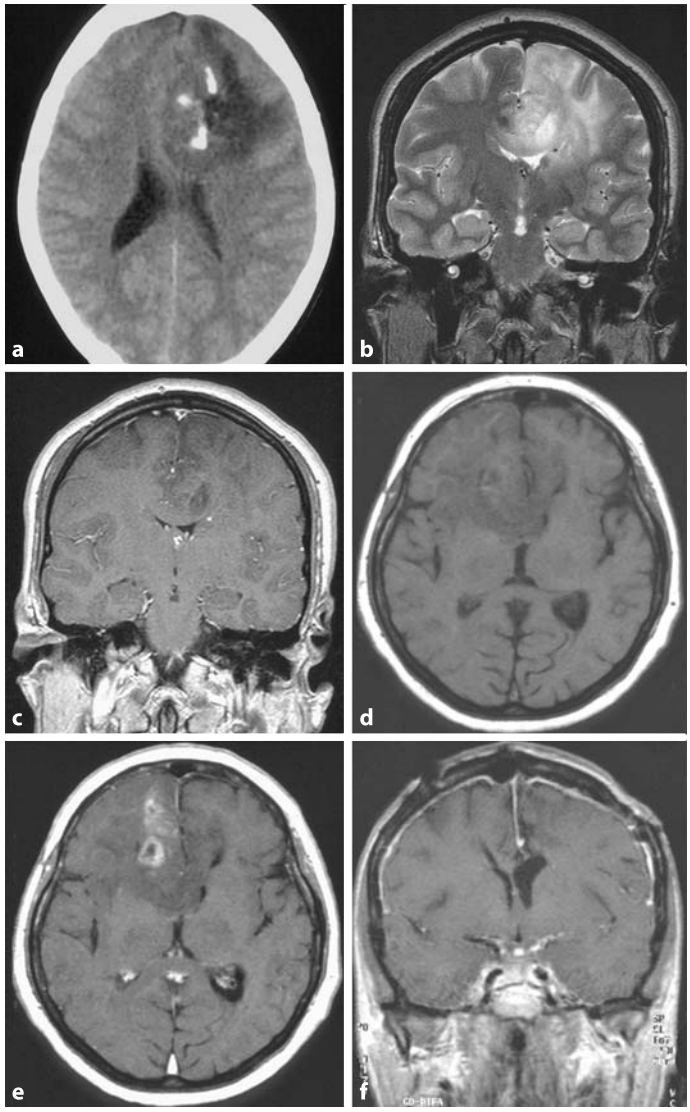


Fig. 1 a–f. Typical neuroimaging features of oligodendroglioma. **a** Axial CT of a left frontal oligodendroglioma characterized by calcification. **b** Coronary T_2-weighted MRI of left frontal oligodendroglioma with thickening of the cortex and spread into the corpus callosum. **c** The corresponding contrast-enhanced T_1-weighted sequence shows no enhancement in the tumor. **d** T_1-weighted MRI of a right frontal anaplastic oligodendroglioma with tumor extension crossing the midline. **e** Contrast enhancement delineates areas of cystic regression in this tumor. **f** Coronary T_1-weighted MRI after resection of a left frontal oligodendroglioma shows meningeal enhancement across the convexity of both hemispheres and in the basal subarachnoid space, suggestive of leptomeningeal tumor cell dissemination (U. Ernemann, Tübingen, Germany)

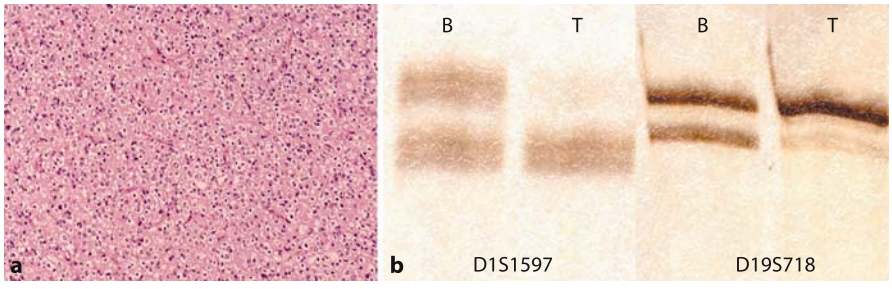


Fig. 2 a,b. Histological and molecular diagnostics of oligodendrogliomas. **a** Typical histological features of oligodendroglioma; **b** allelic losses on chromosomes 1p and 19q in an oligodendroglioma: two microsatellite markers, D1S1597 and D19S718, demonstrate two (heterozygous) parental alleles in the DNA of peripheral blood leukocytes (blood, *B*), but only one allele in the DNA of the oligodendroglioma (loss of heterozygosity; *T*, tumor) (W. Müller and A. v. Deimling, Berlin, Germany)

Surgery

The surgical procedure required to make the histological diagnosis of an oligodendroglial tumor can be a stereotactic biopsy with a purely diagnostic intent or an effort at a gross surgical resection. Stereotactic biopsies are performed at locations which preclude resection, with multiple lesions possibly representing primary cerebral lymphoma or metastatic disease or in elderly, high-risk patients. Surgical resections aim at a reduction of overall tumor volume, relieve elevated intracranial pressure and thereby restore neurological function. The high response rates of oligodendroglial tumors to radiotherapy and chemotherapy suggest that the extent of neurosurgical resection is less critical for the outcome than in astrocytic gliomas. This consideration, however, is limited by the failure to diagnose oligodendroglioma with certainty from nonembedded specimens during surgery. Surgeons will therefore either require a biopsy prior to the decision for the type of resection approach or will be guided by neuroimaging features. The result of resection should be verified by postoperative MRI or CT within 48–72 h after the procedure.

Radiotherapy

Retrospective series provide no firm evidence that radiotherapy is an effective treatment for oligodendroglial tumors. There is nevertheless little doubt that radiotherapy at doses of 54–60 Gy administered in 1.8–2 Gy fractions provides enduring local control for many patients [1]. The target volume encompasses the tumor area defined by T2-weighted MRI or by the contrast-enhancing lesion where applicable plus a safety margin of 2 cm. Despite the high incidence of leptomeningeal seeding in the course of the disease (30%), prophylactic craniospinal radiotherapy is not recommended.

Chemotherapy

Chemotherapy using the PCV regimen consisting of procarbazine (60 mg/m^2 p.o. D8–21, lomustine/CCNU 110 mg/m^2 p.o. D1, vincristine 1.4 mg/m^2 i.v. D8+29, for 6–8 weeks) produces response rates of more than 50% and median survival times of 15–24 months in patients with recurrent oligodendroglial tumors [2, 6]. The response rates for anaplastic tumors may be even higher when chemotherapy is administered prior to radiotherapy [9]. More recently, the efficacy of temozolomide (150–200 mg/m^2 D1–D5 for 4 weeks) for recurrent disease has been demonstrated [3, 4]. The most important side-effects of standard chemotherapy other than myelosuppression include allergy for procarbazine, pulmonary fibrosis for nitrosoureas, and polyneuropathy for vincristine. Experimental chemotherapeutic approaches for oligodendroglial tumors failing conventional treatments include, amongst others, carboplatin (300 mg/m^2 D1) plus etoposide (VP16, 150 mg/m^2 D2–3) for 4 weeks, or intensified PCV regimens plus autologous stem cell transplantation. Specifically, the response to PCV has been linked strongly to the loss of 1p and 19q [7]. Since the absence of such genetic changes does not predict the failure of PCV or any other treatment, it is not justified to withhold chemotherapy from patients with tumors lacking these genetic changes.

Other

A role for treatments other than surgery, radiotherapy, or chemotherapy has not been defined. Inhibition of migration, invasion, or angiogenesis, or gene therapy should preferentially be performed after the established treatment options have failed and in the context of clinical trials.

Specific Treatment Recommendations

WHO grade II oligodendrogliomas and oligoastrocytomas should be treated accordingly since the presence of the oligodendroglial component in a mixed glioma probably determines the better prognosis for mixed tumors compared with pure astrocytic gliomas. Histologically confirmed tumors, which are asymptomatic except for seizures, may be managed using a *wait-and-see* strategy, especially in younger patients (<40 years). Symptomatic and, by radiology, well-circumscribed lesions in accessible locations should be resected microsurgically. If surgery has a high risk of neurological morbidity, symptomatic or radiologically progressive lesions should be treated with radiotherapy or chemotherapy. Younger patients are candidates for primary chemotherapy using PCV [5] or temozolomide [10]. When the tumor shows a complete or partial response or remains stable, chemotherapy may be discontinued after 4 cycles of nitrosourea-based chemotherapy or 8 cycles of temozolomide, although some centers prefer to administer chemotherapy until relapse or prolonged myelosuppression. Elder patients or patients with contraindications for chemotherapy may receive radiotherapy (54 Gy, 1.8–2 Gy fractions) as the first-line therapy. These recommendations are based on the assumption that younger patients survive longer and are therefore more likely to experience the neurotoxic side-effects of radiotherapy whereas the long-

term toxicity of chemotherapy is considered to be less prominent and is at least less well defined. Treatment options at recurrence include second surgery and, depending on prior treatment, radiotherapy or chemotherapy. Radiotherapy should not be withheld when one first-line chemotherapy has failed, and a second-line chemotherapy should be considered only after radiotherapy has failed. Grade II tumors often exhibit imaging and histological features of anaplastic (grade III) lesions at recurrence.

WHO grade III anaplastic tumors should not be managed with surgery alone because of their less benign natural course. First-line treatment options include radiotherapy (54–60 Gy in 1.8–2 Gy fractions), chemotherapy, or combined modality treatment. The most extensive chemotherapy data are available for PCV, but other nitrosourea-based regimens or temozolomide are probably also effective. The options at recurrence depend on the first-line therapy as outlined for the grade II tumors.

Prognosis, Follow-up and Quality of Life

Younger age, frontal localization, macroscopic resection, high Karnofsky performance score, and lack of contrast enhancement on neuroimaging are favorable prognostic factors. After the tumor-specific treatment has been completed, patients with grade II tumors should have clinical and radiological examinations at 6-monthly intervals, and patients with grade III lesions at 4-monthly intervals, at least for the first 3–5 years. The quality of life is often unaffected for years. The morbidity associated with neurosurgery has steadily decreased. Long-term survivors may experience neurotoxic side-effects from radiotherapy and chemotherapy, but their incidence in patients treated according to current standards of care is probably low. The survival rates at 2 and 5 years are in the range of 70–80% and 50–60% with grade II and 60% and 30–40% with grade III lesions.

Specific Problems and Measures

Oligodendroglial tumors spread within the central nervous system and cause leptomeningeal seeding in up to 30% of the patients. MRI of the spinal cord and cerebrospinal fluid analysis are therefore necessary when clinical symptoms or signs suggest leptomeningeal disease. The outcome for patients with leptomeningeal disease from oligodendroglial tumors is not inevitably poor compared with other malignancies. The management should follow the recommendations summarized above and may sometimes require craniospinal radiotherapy. Gliomatosis cerebri is defined as the diffuse growth of neoplastic cells, verified by histology, in more than two cerebral lobes, verified by neuroimaging, and has been attributed WHO grade III. Histology may show a diffuse oligodendroglial tumor. Response to treatment and course of the disease are highly variable, but median survival is only 1 year. Some younger patients may be managed by observation alone, whereas symptomatic or progressive lesions should be treated with chemotherapy or large volume radiotherapy to 45–54 Gy in 1.8–2 Gy fractions as outlined above.

Future Perspectives

Establishing the best sequence of the effective modes of therapy will be the next step in defining standards of care for patients with oligodendroglial tumors. EORTC trial 26951 will define the advantages and safety of the addition of PCV to radiotherapy as the first-line treatment of anaplastic oligodendroglial tumors (www.eortc.be). The German NOA-04 trial will determine whether chemotherapy alone is a reasonable treatment strategy for these patients (www.neuroonkologie.de). Ultimately, it will be essential to establish therapeutic approaches with a curative intention for these tumors.

References

1. Allison RR, Schulsinger A, Vongtama V, Barry T, Shin KH. Radiation and chemotherapy improve outcome in oligodendroglioma. Int J Radiat Oncol Biol Phys 1997; 37:399–403.
2. Van den Bent MJ, Kros JM, Heimans JJ, Pronk LC, Van Groeningen CJ, Krouwer HGJ, Taphoorn MJ, Zonnenberg BA, Tijssen CC, Twijnstra A, Punt CJ, Boogerd W, for the Dutch Neuro-oncology Group. Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU, and vincristine chemotherapy. Neurology 1998; 51:1140–1145.
3. Van Den Bent MJ, Chinot O, Boogerd W, Bravo Marques J, Taphoorn MJ, Kros JM, Van der Rijt CC, Vecht CJ, De Beule N, Baron B. Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. Ann Oncol 2003a; 14:599–602.
4. Van den Bent MJ, Taphoorn MJ, Brandes AA, Menten J, Stupp R, Frenay M, Chinot O, Kros JM, van der Rijt CC, Vecht CJ, Allgeier A, Gorlia T. Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol 2003b; 21:2525–2528.
5. Buckner JC, Gesme D Jr, O'Fallon JR, Hammack JE, Stafford S, Brown PD, Hawkins R, Scheithauer BW, Erickson

BJ, Levitt R, Shaw EG, Jenkins R. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol 2003; 21:251–255.

6. Cairncross JG, Macdonald D, Ludwin S, Lee D, Cascino T, Buckner J, Fulton D, Dropcho E, Stewart D, Schold C, Wainman N, Eisenhauer E, for the National Cancer Institute of Canada Clinical Trials Group. Chemotherapy for anaplastic oligodendroglioma. J Clin Oncol 1994; 12:2013–2021.
7. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, Silver JS, Stark PC, Macdonald DR, Ino Y, Ramsay DA, Louis DN. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998; 90:1473–1479.
8. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990; 8:1277–1280.
9. Paleologos NA, Macdonald DR, Vick NA, Cairncross JG. Neoadjuvant procarbazine, CCNU, and vincristine for anaplastic and aggressive oligodendroglioma. Neurology 1999; 53:1141–1143.
10. Quinn JA, Reardon DA, Friedman AH, Rich JN, Sampson JH, Provenzale JM, McLendon RE, Gururangan S, Bigner DD, Herndon JE 2nd, Avgeropoulos N, Finlay J, Tourt-Uhlig S, Affronti ML, Evans B, Stafford-Fox V, Zaknoen S, Friedman HS. Phase II trial of temozolomide in patients with progressive low-grade glioma. J Clin Oncol 2003; 21:646–651.
11. Reifenberger G, Louis DN. Oligodendroglioma: toward molecular definitions in diagnostic neuro-oncology. J Neuropathol Exp Neurol 2003; 62:111–126.
12. Zlatescu MC, Tehrani Yazdi AR. Sasaki H, Megyesi JF, Betensky RA, Louis DN, Cairncross JG. Tumor location and growth pattern correlate with genetic signature in oligodendroglial neoplasms. Cancer Res 2001; 61:6713–6715.

Ependymomas and Ventricular Tumors

8

Manfred Westphal

Definition – 146

Epidemiology – 146

Molecular Genetics – 146

Etiology and Prevention – 147

Signs and Symptoms – 147

Staging and Classification – 148

Diagnostic Procedures – 149

Treatment – 151

Follow-up and Prognosis – 154

References – 156

Definition

Ependymomas arise from the ventricular surface, which is made up of ependymal cells. They occur throughout the whole central nervous system including the filum terminale. They may occur outside the ventricular structures, representing the rare ectopic ependymoma.

Ventricular tumors include the ependymomas but also all tumors which arise from the matrix of the choroid plexus, mainly plexus papillomas. Meningiomas can also occur in the choroid plexus, as can hemangioblastomas, which are either sporadic or associated with von Hippel-Lindau disease.

In addition, all glial tumors can extend into and compromise the ventricles but should be considered exophytic and can have any glial histology from pilocytic astrocytoma to glioblastoma. The only specific astrocytoma of the ventricular system is the subependymal giant-cell astrocytoma which is associated with tuberous sclerosis and arises from the subventricular zone. A neuroglial tumor arising preferentially in the ventricles is the neurocytoma.

Secondary tumors to the intraventricular choroid plexus are metastases. The most frequent types of origin are renal cell carcinoma and melanoma because they seem to have a certain tropism for this kind of highly vascularized tissue matrix [36].

Epidemiology

A comprehensive source for the epidemiology of tumors is the CBTRUS (2002): Statistical Report published by the Central Brain Tumor Registry of the USA. Adjusted to the US 2000 standard population, ICDO code C71.5 (ventricular tumors) produced an adjusted rate of 0.19 (per 100,000 person-years). In the actual survey, a total of 527 cases was reported among 23,906 cases of primary CNS tumors, translating into 2.2%.

Ependymomas. Given the relative rarity of these tumors and possibility for error in the histological diagnosis, especially for ependymoma, numbers have to viewed with caution. Also, the epidemiological numbers for ependymomas frequently do not contain subdivisions between intraparenchymal, intraventricular, intramedullary, and cauda equina. The numbers vary between 3% and 9% of all neuroepithelial tumors in different reports, most of which have another primary focus. In children, ependymomas are the third most common tumor and account for 10% of all posterior fossa tumors in this population [34].

Choroid plexus tumors. In a recent survey, the prevalence of choroid plexus tumors was given as 0.3 cases per one million people [37]. This translates into 0.4% to 0.6% of all reported intracranial tumors. The tumors are more frequent in children [1], with a mean age at diagnosis of 3.5 years and no clear gender preference either in children or adults. Choroid plexus carcinomas form only a small subgroup of these tumors, and they tend to occur even at younger ages, with a median age of 3 years at presentation.

Neurocytomas make up 0.25% to 0.5% of intracranial tumors [7]. They occur in all age groups but mainly in young adulthood, so that 75% of the cases are diagnosed between the age of 20–40 years [19]. They affect women and men equally. The most common site of occurrence is the anterior part of the lateral ventricle.

Ventricular meningiomas. In larger series of unselected meningiomas, a ventricular location was seen in only 1.3–1.5%, but there was a much higher incidence of 9.4% in the pediatric age group (reviewed in [23]). They are mostly located in the lateral ventricles with locations in the third or fourth ventricle being very rare. They originate from the choroid plexus.

Metastases are becoming more frequent with the extended life-spans of patients with cancer. Ventricular metastases are still rare and make up 6% of all ventricular tumors and less than 1% of intracranial metastases [14].

Molecular Genetics

Ependymomas appear to have a distinct genetic phenotype which is different from other glial tumors. The otherwise characteristic mutations of p53, deletions or mutations of CDKN2A and CDKN2B, PTEN or amplification of EGF-R are not found [5]. The only association is with NF-2, correlating to the epidemiological finding that in these patients there is an increased frequency of intramedullary ependymomas. There seems to be a different genetic pattern for intramedullary ependymomas and supratentorial lesions [18]. No specific gene alterations which lend themselves to the development of targeted therapeutics have been detected for intracranial ependymomas dealt with in this chapter.

Plexus papillomas have provided even fewer cytogenetic or molecular genetic findings. Some anomalies were found in the 9p region, but no further specific characterization has been done [1].

There are no extensive investigations on the molecular genetics of neurocytomas. The limited available data indicate only a gain of chromosome 7 in some cases but no specific regions or genes have been implied [1, 7].

No specific genetic alterations have been reported for ventricular meningiomas which would distinguish them genetically from the majority of the other meningiomas.

Etiology and Prevention

No specific causes are known for ependymomas or other ventricular tumors. Thus, there is no specific strategy for prevention. Except for the association with NF-2 [5], there are not even environmental or epidemiological predictors for these tumors. In known NF-2 cases, careful observation given the possibility of developing such tumors may lead to earlier detection and an optimal timing for therapy. Likewise, there is one other genetic syndrome associated with a pediatric ventricular tumor, which is the subependymal giant-cell astrocytoma associated with tuberous sclerosis [41].

Neurocytomas are considered neuroglial progenitor tumors [39, 40] and as such may be attributable to a deficit in definitive differentiation. There is no consistent coincidence with genetic syndromes or any kind of environmental exposure or ethnic preference.

Signs and Symptoms

Intracranial ependymomas occur mainly in children, especially in the posterior fossa. When confined to the fourth ventricle, they may cause obstructive hydrocephalus with sudden headache of undulating intensity, nausea, vomiting (projectile), diplopia, and papilledema (Fig. 1). When they invade the floor of the fourth ventricle, they may also cause cranial nerve disorders, mostly again diplopia but also facial weakness. A preferred site is the foramen of Luschka where the tumors extend partly into the fourth ventricle and partly into the cerebellopontine angle. This causes similar symptoms but frequently also unilateral problems with the caudal cranial nerves and, in cases of major compression of the medulla, also hemiparesis or hemidystaxia because of loss of sensation. Spinal intramedullary ependymomas have different symptoms and will be discussed elsewhere.

The less frequent supratentorial intraventricular/periventricular ependymomas occur preferably in adults and will cause some kind of hydrocephalus. In a location within the lateral ventricle, it could be a trapped compartment or a univentricular hydrocephalus. When located around the foramen of Monro, hydrocephalus can be biventricular (Fig. 2) with intermittent crises of severe headache like in the colloid cysts of the third ventricle. Ependymomas in the third ventricle can cause severe endocrinological problems when involving the hypothalamus, or memory disorders when involving the fornices. The more dorsal locations lead to compression of the Sylvian aqueduct and cause triventricular hydrocephalus.

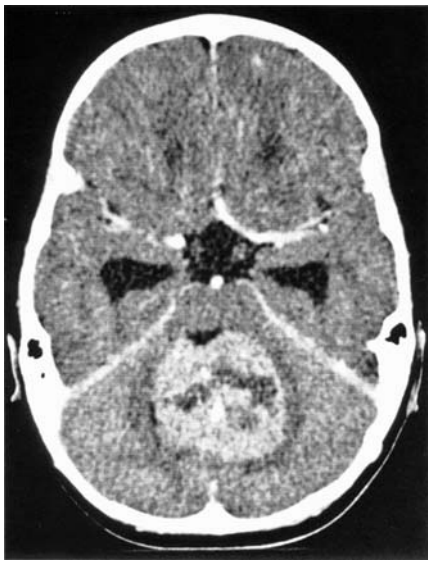


Fig. 1. Ependymoma in the fourth ventricle causing acute obstructive hydrocephalus. An immediate direct approach is desirable to avoid any complications from shunting-associated relief of supratentorial pressure

Ependymomas in adults have a tendency to also occur ectopically intraparenchymally, somewhere in the hemispheres (Fig. 3). There they will lead to the local symptoms identical to any other glioma including paresis, speech disorders, visual field impairment well as seizures. The histology is usually unexpected, and there are no specific neuroradiological clues despite the high incidence of anaplastic tumors in this group. A dysembryogenic component of faulted migration pattern possibly in association with inadequate apoptotic potential must be suspected as part of their development.

In contrast to the ependymomas, plexus papillomas usually do not infiltrate their surroundings and respect the ependymal layer. Therefore, the symptoms are those of local compression and of hydrocephalus which ranges between partial hydrocephalus from a trapped compartment to complete internal, noncommunicating, obstructive hydrocephalus due to a lesion in the caudal part of the fourth ventricle. The same symptomatology pattern is true for the ventricular meningiomas and metastases. Meningiomas by virtue of their capacity to secrete large amounts of vascular endothelial growth factor may cause edema and metastases even more often as they may originate from the subependymal layer, or

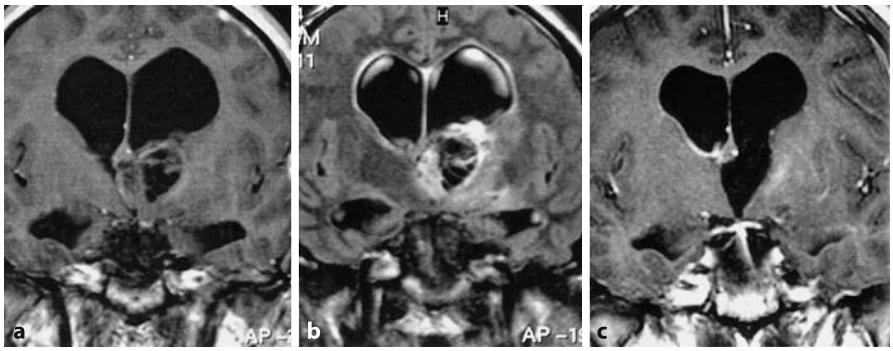


Fig. 2. Ependymoma arising from the ventricular wall around the area of the foramen of Monro. The lesion is inhomogeneously enhancing and has a cystic component and causes biventricular hydrocephalus. Via a frontal transcortical approach, this tumor can be removed, but because of the broad base there is an extreme likelihood of recurrence warranting regular follow-up intervals. Because of the immediate vicinity of the hypothalamus and the yet undefined role of radiation for ependymoma, radiation is delayed until the activity of this tumor reveals itself

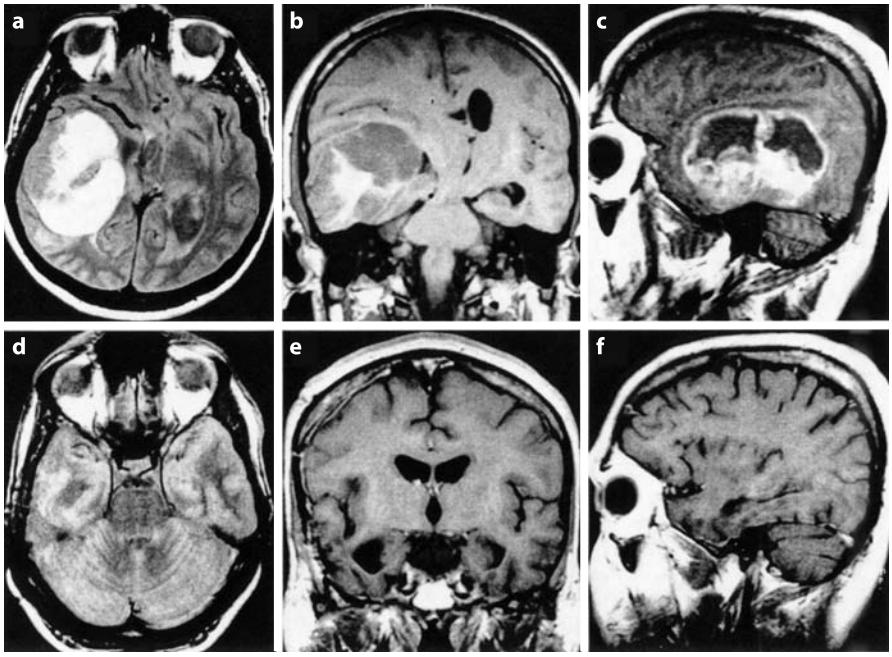


Fig. 3. Intraparenchymal ependymoma in a 46-year-old adult male patient which was not suspected when the lesion was approached. The patient was treated afterwards with external beam radiation and has been stable with a follow-up of 4 years

when originating from the plexus, they have less respect for the ependyma than meningiomas or plexus papillomas.

Staging and Classification

According to the WHO classification, subependymomas and the myxopapillary ependymomas of the filum terminale are considered to be grade WHO I tumors. There are four variants of grade II ependymoma: cellular, papillary, clear cell, and tanycytic. Anaplastic ependymoma is considered to be grade III [42].

Tumors of the choroid plexus are either classified as grade I, corresponding to choroid plexus papilloma, or grade III, corresponding to choroid plexus carcinoma [1].

Astrocytomas, oligodendrogliomas, or oligoastrocytomas which extend exophytically into the ventricular system are graded according to the WHO grading system.

Neurocytoma is considered to be grade II in the latest edition of the WHO [1, 7]. There is much dis-

cussion about anaplasia in neurocytomas [16, 21], but at present it is preferred to speak about atypical neurocytomas in the context of the ventricular location and leave the term anaplastic for the extraventricular location [35].

Diagnostic Procedures

Clinical signs. As most of these tumors occur in children, the experienced neuropediatrician will suspect a posterior fossa tumor or another intracranial lesion causing hydrocephalus due to obstruction of the CSF pathways from some of the typical symptoms described above. Drowsiness, nausea, vomiting, papilledema, and singultus will be grave warning signs. The 'stiff neck', when children try to avoid neck pain from descended tonsils by holding their head upright and almost fixed, is a pathognomonic sign which must not be missed.

Ventricular tumors cause obstruction of the CSF pathways and thus create a pressure gradient which results in a vector of forces which can be activated by selectively decompressing one compartment by puncture, i.e., lumbar. This can create downward or in rare cases upward herniation, and therefore, lumbar puncture may only be performed when this possibility has been excluded. If obstruction of the CSF pathways warrants relief, a ventriculocisternostomy is preferable to a shunting procedure. In any case, CSF must be sampled to look for markers and cytology.

Neuroradiology. Overall, imaging is the most important diagnostic modality. CT allows the detection of calcifications in tumors and the assessment of the type and severity of hydrocephalus. Much more information is obtained with MRI, which allows us to detect or at least speculate about the area of origin of the tumor. Furthermore, the three planes of representation are crucial for the planning of the surgical approach.

Ependymomas will most often be located infratentorially. They show extension into the cerebellopontine angle (Fig. 4) or are located exclusively in the fourth ventricle (Fig. 1). They can have cystic components, show signs of prior hemorrhage, and vary between minimal to intensive enhancement after contrast, sometimes within the same tumor. When located in the lateral ventricles, they can have a broad base of ependymal attachment and appear like an exophytic lesion of the brain (Fig. 2). On the other hand, they may arise from the septum pellucidum or any other area including the roof of the ventricles and then are sometimes indistinguishable from neurocytoma by imaging (Fig. 5).

Choroid plexus papillomas tend to show a heterogeneous internal structure, frequently calcifications and very little reaction of the surrounding brain. They show intense staining due to their vasculari-

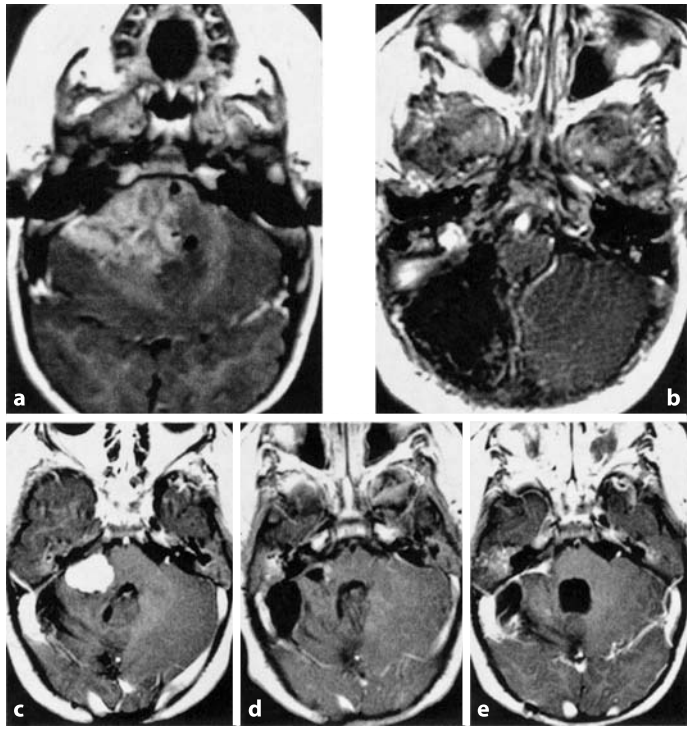


Fig. 4. Ependymoma of the foramen of Luschka of a 9-month-old child with extension around the brain stem and into the fourth ventricle. After near total resection and radiation, the condition was stable for 2.5 years, and then a recurrence developed (**c**) which was again resected with radiation of residuals which were tightly adherent to the nerve root exits of the caudal nerves and the facial nerve

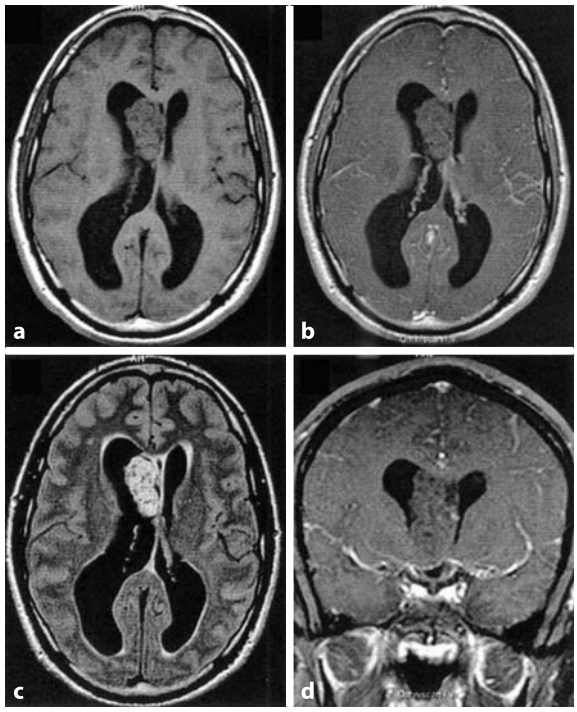


Fig. 5. Ependymoma of the region of the foramen of Monro which was suspected to be neurocytoma but has clearly not that histology and a different immunohistochemical marker profile typical of a differentiated ependymoma (WHO II)

zation from the choroid plexus. They are usually located centrally in the ventricles and occur anywhere that a choroid plexus can be found. They are more frequent in children than in adults and are usually found in the lateral ventricles. In adults, they tend to be more frequently located in the fourth ventricle (Fig. 6).

Ventricular meningiomas have few calcification on CT, are homogeneously enhancing, and show very little reaction of the surrounding brain when only moderately distending the ventricles. As they slowly grow expansively in their 'empty' compartment, they may reach a considerable size before being detected (Fig. 7). When they are large and lead to compression of the veins in the ventricles, they can cause congestive edema. The best imaging is obtained by MRI, which is also needed for the planning of the surgical approach. In the case of a suspected meningioma, angiography is still sometimes performed, but it does not provide much useful information and is an unnecessarily added procedural risk for the patient. The blood supply is usually from the vessels of the choroid plexus, and nothing more but a faint blush can be seen. Because of this very peripheral vascularization, no high capacity feeding vessels can be distinguished and as much as there is no option for embolization, there is no reason.

Neurocytomas are usually located in the lateral ventricles, have a broad attachment to the ependyma,

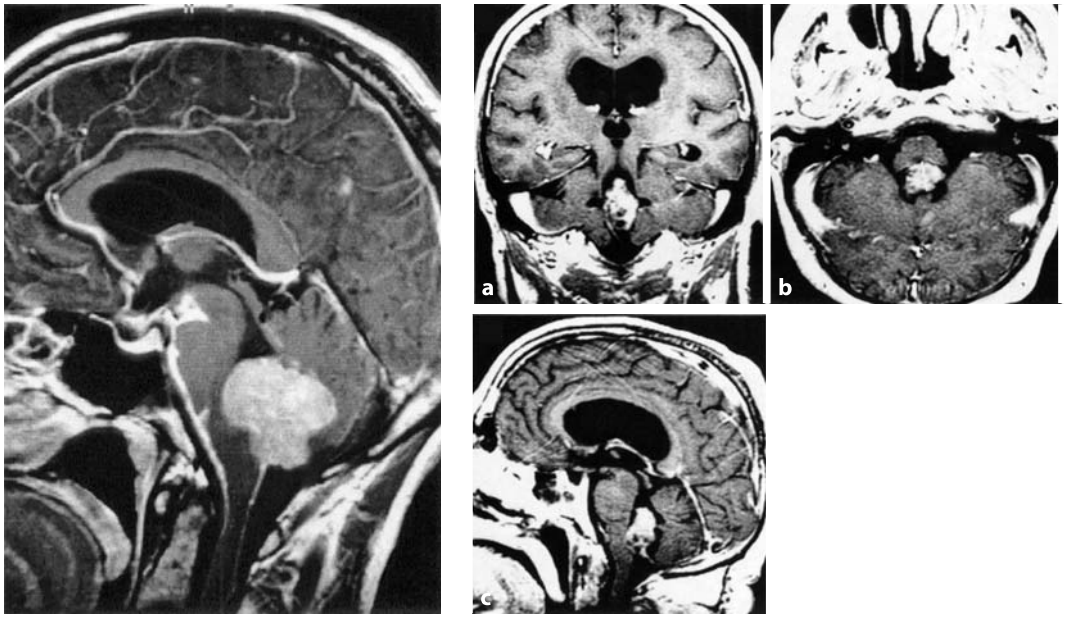


Fig. 6 a,b. Two examples of adult patients with plexus papillomas of the fourth ventricle. **a** MRI with contrast of a large tumor in the fourth ventricle which was suspected to be adult medulloblastoma in a 38-year-old male patient but turned out to be a plexus papilloma which has been removed [11]. **b** Plexus papilloma at the exit of the fourth ventricle in a 60-year-old man

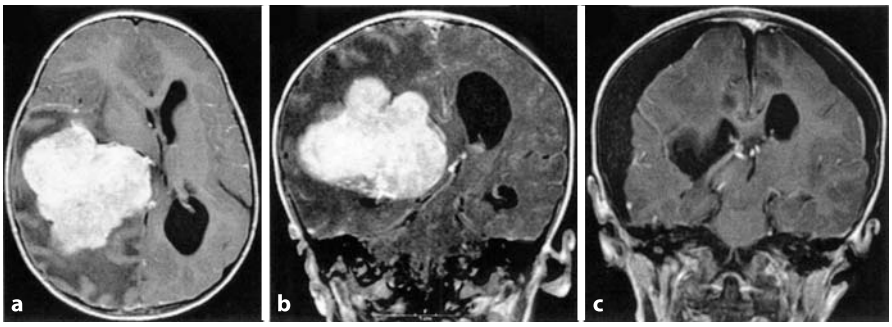


Fig. 7. Homogeneously enhancing tumor in the right trigonal area in a 4-year-old boy which turned out to be a ventricular meningioma that could be removed without sequelae. Ventricular meningiomas tend to be more frequent in boys, which is in contrast to that disease elsewhere and later in life

are homogeneous in texture even when large, and show moderate enhancement after application of contrast media (Fig. 8). They tend to occur more frequently in the area around the foramen of Monro.

The major differential diagnosis for all intraventricular tumors is metastasis. The diagnosis of a metastasis is usually made in the context of a known primary. For intracranial metastases in general, one finds 20% in the absence of a known primary, but this does not apply for the types which preferentially metastasize into the choroid plexus, namely renal cell carcinoma and melanoma. They may have any of the appearances mentioned above. Interestingly, metastases seem to have an increased angiogenic activity which is known to be associated with an increased production of VEGF, and therefore edema is much more frequent and intense than with plexus papilloma, meningioma, or ependymoma.

Hemangioblastoma of the choroid plexus is another rare entity and may be very similar to a renal cell carcinoma but usually has more prominent (venous) blood vessels which can be seen as flow voids in its surroundings. As in other locations of hemangioblastomas, there may be cysts or signs of prior hemorrhage. In many cases, a von Hippel-Lindau disease is known.

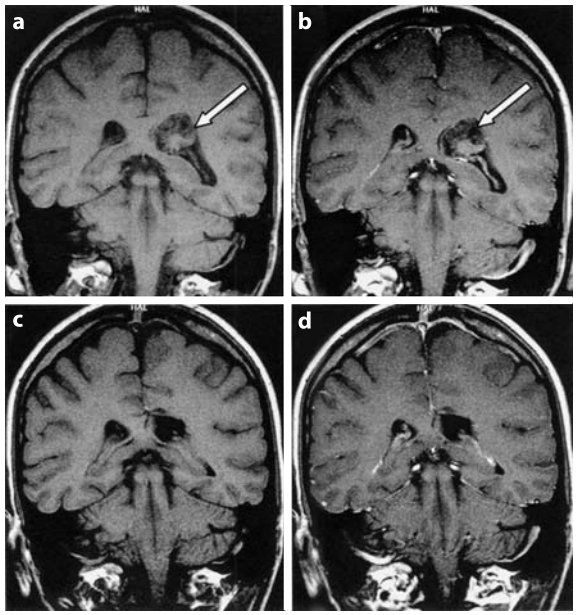


Fig. 8. Histologically confirmed neurocytoma which (arrow) has grown in size over 4 years as documented in the patient's follow-up for a microprolactinoma. The lesion has only a weak contrast enhancement, seems to be nonreactive inside the lateral ventricle, and is homogeneously granulated from its internal texture. This tumor was practically radically removed via an interhemispheric/lateral transcallosal approach in the postcentral region to get to the roof of the trigone

Treatment

Nearly all patients with ventricular tumors require a surgical intervention. Only rarely will a tumor in the anterior part of the third ventricle (infundibulum) or posterior part (pineal region) turn out to be a germinoma, be diagnosed purely by CSF cytology, and be treated by radiation only.

Hydrocephalus is frequently a presenting sign and needs special consideration in respect to the timing of surgery. During the removal of a ventricular tumor, it may be very helpful to have distended ventricles to work in, and therefore definitive surgery is usually scheduled within a short period after diagnosis or even as an emergency. It is undesirable to have a shunt placed as a first measure in a center which cannot definitively deal with the lesion and then see the patient referred weeks later when the ventricular system has become normal or even slim. Also, placing a shunt prematurely before the definitive diag-

nosis can be dangerous. There is a danger for peritoneal seeding, although in one of the larger series which analyzed this phenomenon, this was more frequent for germinomas and medulloblastoma than ependymoma or plexus papilloma [30]. In a series of patients with extraneural metastasis of ependymoma, two patients with peritoneal seeding had shunts [26]. If surgery and relief of hydrocephalus cannot be done in close timely association, a third ventriculostomy (IIIVS) is indicated because it is a small procedure, will leave no external drains which potentially could become infected, and also provides a biopsy opportunity so that a histology can be obtained [17]. The ventricular collapse after IIIVS is also less compared with ventriculoperitoneal shunting or external drainage so that the situation for surgery does not deteriorate as much.

The approaches to the ventricular system are standardized for every location and are plentiful [2]. The approaches to the lateral ventricle depend on the location of the tumor and the hemispheric dominance. The approaches are always transcortical and are symmetrical for the hemispheres except for the trigonal area, where special consideration has to be given to the dominant side, and a more basal or dorsal approach taken which leaves the angular gyrus area undisturbed. The third ventricle can be approached from the subfrontal region by the translaminar route or the transcortical, transforaminal route in the case of a distended foramen of Monro. The interhemispheric, interforniceal approach is used for all processes in the central part of the third ventricle, but here a subchoroidal approach is a valid alternative [38, 43]. The posterior part can easily be reached via a supracerebellar, infratentorial approach [12, 33] which gives easy access to all processes originating around the pineal region (Fig. 9). Should the venous system be placed inferiorly or if there is only limited extension into the pineal region, transcallosal or transtentorial approaches may be more opportune [20]. Most infratentorial processes are approached by suboccipital craniotomy and direct midline approach from the foramen of Magendie into the fourth ventricle. The further the head is anteflected, the more it is possible to work underneath the vermis without splitting it, thus avoiding the posterior fossa syndrome mainly associated with prolonged mutism [6, 28].

Ependymomas. Few therapies for intracranial tumors are discussed as controversially and inconclusively as those for ependymoma. There is general agreement that they should usually be resected as radically as possible, and a wealth of information exists, predominantly in the pediatric literature, that the extent of resection is the most important prognostic variable, correlating positively with survival (reviewed in [10]). There is, however, no agreement on the use of adjuvant therapies at the present time [34].

The role of surgery is firmly established. In the microsurgical age, mortality has dropped dramatically, and morbidity is related mainly to involvement of the brain stem and cranial nerves. The number of patients surviving 5 years after complete (surgical microscope) resection vs subtotal/partial resection shows a statistically highly significant difference (reviewed in [34]). In addition to extending survival, complete resection apparently leads to a significant reduction of spinal seeding. As spread of tumor beyond the site of origin can already be seen on preoperative imaging, it is not surprising that the neuroradiological evidence of spread is a negative prognostic sign [4]. The pattern for adults is somewhat different, because the tumors arise more often in the supratentorial compartment and thus have a different surgical morbidity pattern than when arising in the third ventricle [31]. Another poor sign seen in adults is the more frequent intraparenchymal localization because these tumors are nearly always anaplastic and correlated with poor survival [9].

The role of adjuvant chemotherapy is defined in the pediatric population and extrapolated to adults.

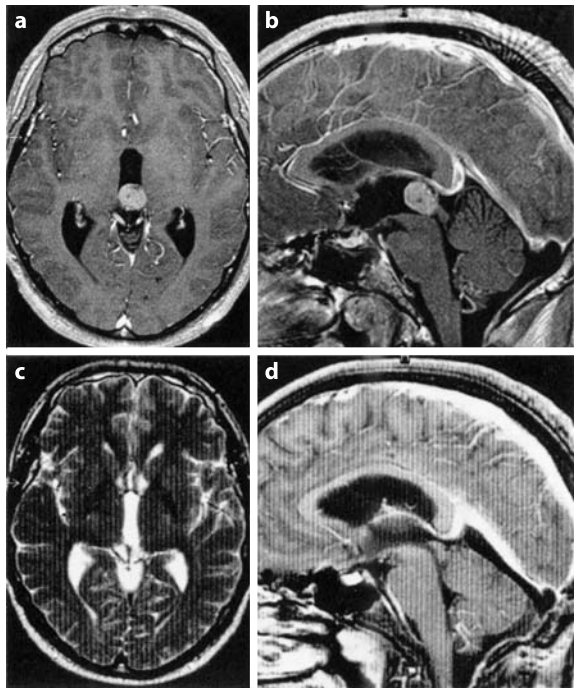


Fig. 9. Tumor in the posterior part of the third ventricle/pineal region which was removed in toto via the supracerebellar approach and turned out to be pineocytoma with small proportions of pineoblastoma which otherwise could have easily been missed by stereotactic biopsy

It is still not firmly established, and no highly efficient regimen evaluated by a large study has been reported to date. The efficacy of chemotherapy is about the same as that of radiation, sparing the children the radiation-induced sequelae. There is a promising study of alternating between a combination of carboplatin with vincristine and ifosfamide with etoposide [25]. The main goal of all chemotherapy in children is the delay of radiation which can be successfully achieved [8].

The role of radiation is controversial in many aspects. As for the indication for craniospinal irradiation vs local radiation to the posterior fossa where most cases occur, there is apparently no difference in the rate of distant failures between groups receiving local radiation only compared with craniospinal regimens. When recurrences occur, they are almost always earlier in the posterior fossa before going to the spinal compartment. The doses delivered to the tumor area range between 45 and 50 Gy, and areas of macroscopic disease are given an extra 10 Gy. In the pediatric age group, there is now sufficient evidence that intensity of radiation, involved field, and age at the time of treatment will cause significant neuropsychological sequelae [24]. On the other hand, these are experiences from the past, and with the modern radiation techniques allowing for extreme limitation of the target volumes and minimization of collateral damage, the outcomes may be much better when present day treatment series are evaluated. There is already a small study indicating that radiosurgery for focal residual or recurrent disease may extend the survival time [22].

Plexus papillomas are resected and then followed at regular intervals. As they can be easily resected, there is no use for adjuvant therapies [15, 44] and that is an accepted regimen for children as well as for adults. Even local recurrences of well-differentiated plexus papillomas in adults are reoperated [11]. Carcinomas of the plexus are much more difficult, occur mostly in children, and carry a poor prognosis. They are treated with combination of surgery, radiation, and chemotherapy. The prognosis is significantly worse than for papilloma [44].

Plexus meningiomas are resected like papillomas and then followed [23]. Radiosurgery may be considered in selected cases, but the high incidence of increased radiation toxicity and unsatisfactory tumor control in the long term restricts this modality to patients who cannot be given surgical treatment for any reason [23].

Neurocytomas, although a potentially benign, well-differentiated tumor entity, are difficult to treat. They can be completely resected in the anterior part of the lateral ventricles when not encasing the fornices. When they extend too far into the third ventricle and the fornices cannot be distinguished, a subradical approach must be taken. The same is true when the tumors arise with a broad ventricular base in the middle part of the ventricles or the trigonal area (Fig. 8). When rapid regrowth is seen during follow-up, the patients should undergo radiation which will lead to long-term control or complete cures [29]. There is also a report about chemotherapy which was successfully given to patients with recurrence despite resection and radiation [3].

Neuroendoscopy has an important role in the treatment of ventricular tumors, mostly for the relief of hydrocephalus and biopsy [17]. In particular, lesions in the posterior part of the third ventricle which are related to the complex pathology of the pineal region need a ventriculostomy rather than external ventricular drainage or shunt (Fig. 10) unless the patient has a combination of obstructive and malresorptive hydrocephalus. During ventriculostomy, it is possible to take an endoscopic biopsy so that chemotherapy or radiation may be started before a surgical option is considered.

There are tumors which do not arise from the proper ventricular tissue matrix but nevertheless have exophytic growth into the ventricles, leading to partial hydrocephalus. These are frequently best approached

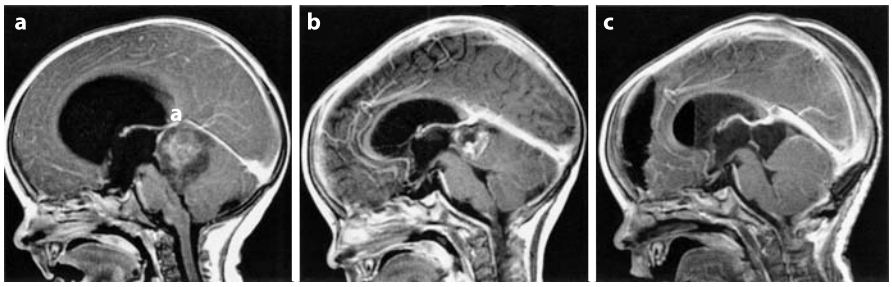


Fig. 10. Histologically confirmed atypical teratoid/rhabdoid tumor (ATRT) in an 8-month-old boy which was biopsied on the occasion of a ventriculostomy (**a**). The diagnosis led to chemotherapy, after which the tumor shrank significantly (**b**) and was then removed completely (**c**). A malresorptive component of the hydrocephalus required shunting after the ventriculostomy

by a direct transventricular route to get to the exophytic part, which in some cases may be the only part which can be resected (Figs. 11–13). Craniopharyngiomas and optic nerve gliomas which also frequently affect the third ventricle can sometimes easily be decompressed via the translaminar approach (Fig. 14) but may not be approachable when recurrent and no dissection plane is present to the hypothalamic boundaries (Fig. 15). Aggressive surgical approaches to the third ventricle and its surroundings have unwanted sequelae, in particular eating and weight disorders [27, 32]. Therefore, radiation is indicated when tumors are infiltrative or recurrent [13].

Follow-up and Prognosis

In all patients with ependymomas, the extent of resection is documented by postoperative MRI, preferably within 2 days after surgery. In the more aggressive tumors (WHO III), a spinal MRI is always performed to obtain staging information. Depending on the treatment protocol chosen, patients are observed without any further treatment and followed at regular intervals or treated with radiation and/or chemotherapy, after which they are also followed. The intervals for imaging are initially every 6 months but can be shorter when the tumors are WHO III and the treatment protocols call for shorter intervals. When the situation is stable, the periods between the follow-up visits can be extended to yearly to eventually biannual visits. There is much controversy as to what are the prognostic parameters because histology is not predictive of outcome and even the occurrence of extraneural metastases occurs to the same degree with grade II and grade III lesions [26].

Plexus papillomas and meningiomas and hemangioblastomas are followed with initially 6-month intervals, then yearly visits after 2 years, and then biannual follow-up after 5 years. Neurocytomas may require radiation already after the first operation when they are grade III. Thereafter, they are followed up at 6-month intervals. Also for the grade II lesions, close

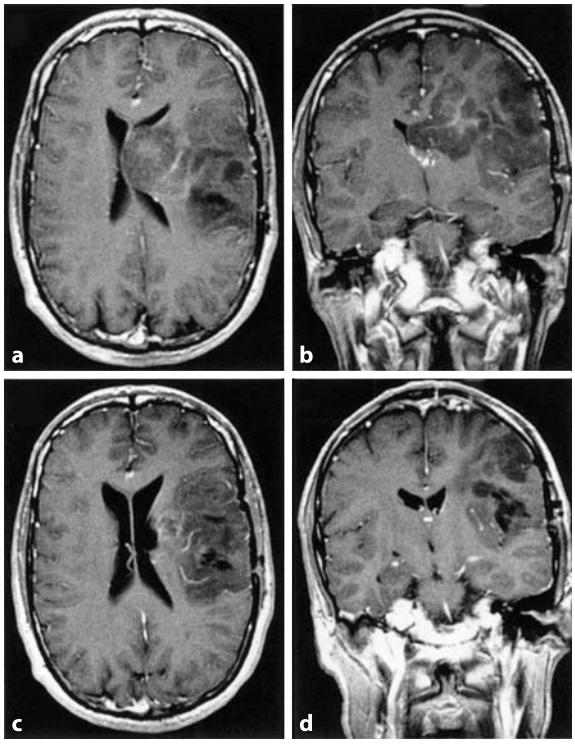


Fig. 11. A case of a hemispheric glioma in a 40-year-old male patient which extends into the lateral ventricles with a large exophytic component. In this case, this was a histologically proven oligodendroglioma of the left insular region which had remained stable over several years without treatment but then developed a nodular satellite obliterating parts of the lateral ventricle. This was removed by direct transcortical approach

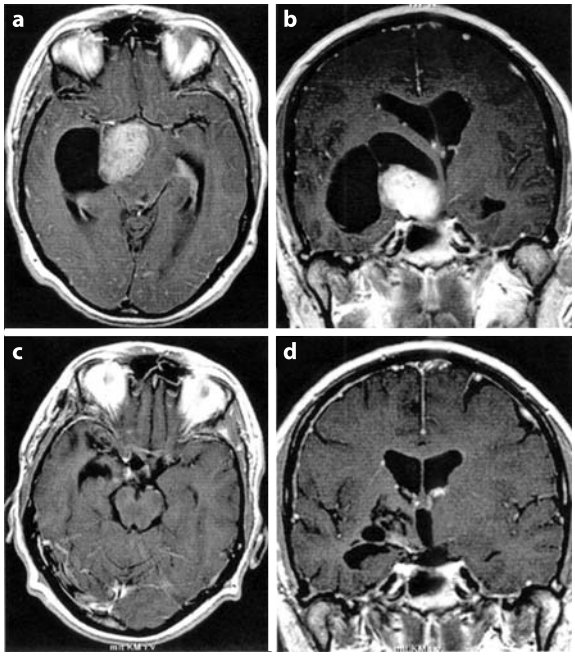


Fig. 12. Very complex pediatric (5 years, female) pilocytic astrocytoma of the optic nerve involving basal ganglia and brain stem which intermittently forms contrast-enhancing rapidly growing foci, one of which protruded into the ventricle, was well delineated, and could be removed completely by direct transcortical approach, like other foci which were removed at later stages

observation for regrowth is required for 3 years at 6-month intervals.

Metastases are treated and followed according to the histology of the primary tumor and the development of the disease outside the brain. With neurological deterioration in the absence of solid tumor and no local recurrence, the development of meningeal carcinomatosis has to be considered.

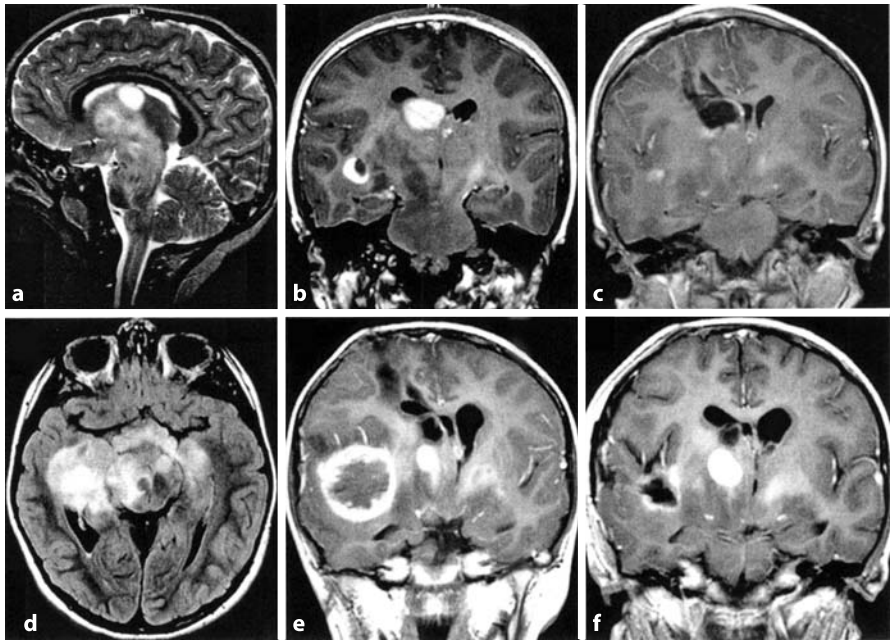


Fig. 13. Large tumor of the temporal horn which after near-complete microsurgical removal turned out to be an exophytically grown pilocytic astrocytoma of the optic tract in a 40-year-old woman

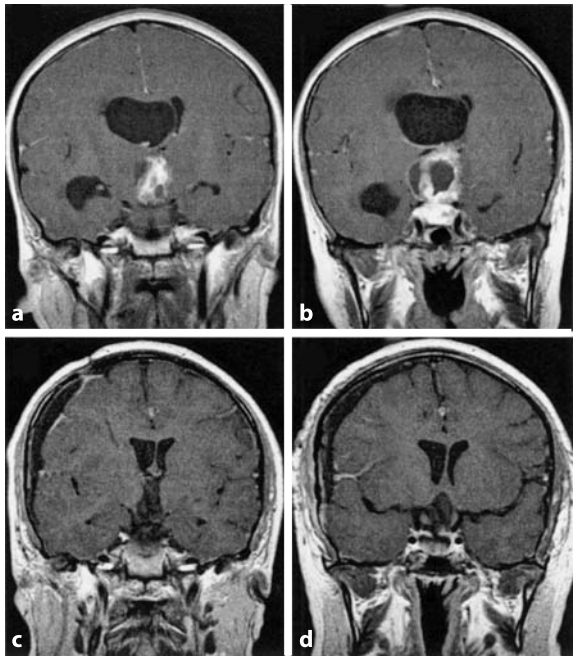


Fig. 14. Gross total microsurgical resection of a mostly cystic, recurrent craniopharyngioma of the third ventricle which is presently stable for 3 years after adjuvant radiotherapy

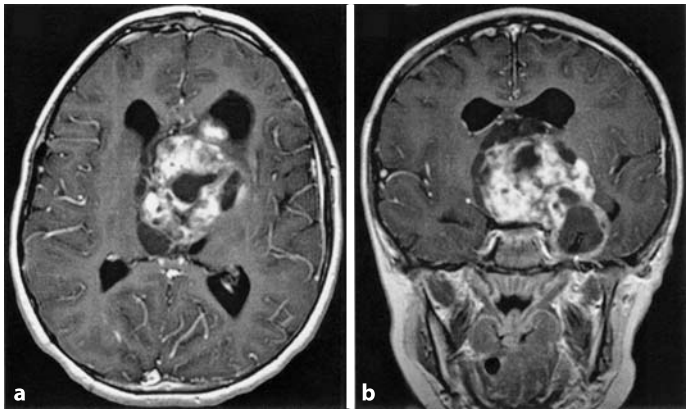


Fig. 15. Progressive development of an optic nerve glioma (pilocytic) which had been subradically approached already a few years earlier. As the cysts turned out to be part of the tumor all around, a dissection plane could not be expected so that in the absence of major neurological deficits, shunting and adjuvant therapies were preferred to a resective attempt

References

1. Aguzzi A, Brandner S, Paulus W. Choroid plexus tumors. In: Kleihues P, Cavanee W, eds. Tumours of the Nervous System: Pathology and Genetics. Lyon, IARC Press, 2000.
2. Anderson RC, Ghatan S, Feldstein NA. Surgical approaches to tumors of the lateral ventricle. Neurosurg Clin N Am 2003; 14:509–525.
3. Brandes AA, Amist inverted question marka P, Gardiman M, Volpin L, Danieli D, Guglielmi B, Carollo C, Pinna G, Turazzi S, Monfardini S. Chemotherapy in patients with recurrent and progressive central neurocytoma. Cancer 2000; 88:169–174.
4. Chen CJ, Tseng YC, Hsu HL, Jung SM. Imaging predictors of intracranial ependymomas. J Comput Assist Tomogr 2004; 28:407–413.
5. Ebert C, von Haken M, Meyer-Puttlitz B, Wiestler OD, Reifenberger G, Pietsch T, von Deimling A. Molecular genetic analysis of ependymal tumors. NF2 mutations and chromosome 22q loss occur preferentially in intramedullary spinal ependymomas. Am J Pathol 1999; 155:627–632.
6. Ersahin Y, Mutluer S, Cagli S, Duman Y. Cerebellar mutism: report of seven cases and review of the literature. Neurosurgery 1996; 38:60–65;discussion 66.
7. Figarella-Branger D, Söylemezoglu F, Kleihues P, Hassoun J. Central neurocytoma. In: Kleihues P, Cavanee W, eds. Tumours of the Nervous System: Pathology and Genetics. Lyon, IARC, 2000.
8. Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol 2001; 19:1288–1296.
9. Guyotat J, Signorelli F, Desme S, Frappaz D, Madarassy G, Montange MF, Jouvet A, Bret P. Intracranial ependymomas in adult patients: analyses of prognostic factors. J Neurooncol 2002; 60:255–268.
10. Hamilton RL, Pollack IF. The molecular biology of ependymomas. Brain Pathol 1997; 7:807–822.
11. Heese O, Lamszus K, Grzyska U, Westphal M. Diffuse arachnoidal enhancement of a well differentiated choroid plexus papilloma. Acta Neurochir (Wien) 2002; 144:723–728.
12. Herrmann HD, Winkler D, Westphal M. Treatment of tumours of the pineal region and posterior part of the third ventricle. Acta Neurochir (Wien) 1992; 116:137–146.
13. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH. Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. Med Pediatr Oncol 2003; 40:214–218.
14. Kohno M, Matsutani M, Sasaki T, Takakura K. Solitary metastasis to the choroid plexus of the lateral ventricle. Report of three cases and a review of the literature. J Neurooncol 1996; 27:47–52.
15. Krishnan S, Brown PD, Scheithauer BW, Ebersold MJ, Hammack JE, Buckner JC. Choroid plexus papillomas: a single institutional experience. J Neurooncol 2004; 68:49–55.
16. Kuchiki H, Kayama T, Sakurada K, Saino M, Kawakami K, Sato S. Two cases of atypical central neurocytomas. Brain Tumor Pathol 2002; 19:105–110.
17. Kunwar S. Endoscopic adjuncts to intraventricular surgery. Neurosurg Clin N Am 2003; 14:547–557.
18. Lamszus K, Lachenmayer L, Heinemann U, Kluwe L, Finckh U, Hoppner W, Stavrou D, Fillbrandt R, Westphal M. Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 2001; 91:803–808.
19. Lee J, Chang SM, McDermott MW, Parsa AT. Intraventricular neurocytomas. Neurosurg Clin N Am 2003; 14:483–508.
20. Lozier AP, Bruce JN. Surgical approaches to posterior third ventricular tumors. Neurosurg Clin N Am 2003; 14:527–545.
21. Mackenzie IR. Central neurocytoma: histologic atypia, proliferation potential, and clinical outcome. Cancer 1999; 85:1606–1610.
22. Mansur DB, Drzymala RE, Rich KM, Klein EE, Simpson JR. The efficacy of stereotactic radiosurgery in the management of intracranial ependymoma. J Neurooncol 2004; 66:187–190.

23. McDermott MW. Intraventricular meningiomas. Neurosurg Clin N Am 2003; 14:559–569.
24. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004; 5:399–408.
25. Needle MN, Goldwein JW, Grass J, Cnaan A, Bergman I, Molloy P, Sutton L, Zhao H, Garvin JH, Jr., Phillips PC. Adjuvant chemotherapy for the treatment of intracranial ependymoma of childhood. Cancer 1997; 80:341–347.
26. Newton HB, Henson J, Walker RW. Extraneural metastases in ependymoma. J Neurooncol 1992; 14:135–142.
27. Pinto G, Bussieres L, Recasens C, Souberbielle JC, Zerah M, Brauner R. Hormonal factors influencing weight and growth pattern in craniopharyngioma. Horm Res 2000; 53:163–169.
28. Pollack IF. Posterior fossa syndrome. Int Rev Neurobiol 1997; 41:411–432.
29. Rades D, Fehlauer F, Schild SE. Treatment of atypical neurocytomas. Cancer 2004; 100:814–817.
30. Rickert CH. Abdominal metastases of pediatric brain tumors via ventriculo-peritoneal shunts. Childs Nerv Syst 1998; 14:10–14.
31. Schwartz TH, Kim S, Glick RS, Bagiella E, Balmaceda C, Fetell MR, Stein BM, Sisti MB, Bruce JN. Supratentorial ependymomas in adult patients. Neurosurgery 1999; 44:721–731.
32. Skorzewska A, Lal S, Waserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. Neuropsychobiology 1989; 21:17–20.
33. Stein BM. The infratentorial supracerebellar approach to pineal lesions. J Neurosurg 1971; 35:197–202.
34. Teo C, Nakaji P, Symons P, Tobias V, Cohn R, Smee R. Ependymoma. Childs Nerv Syst 2003; 19:270–285.
35. Vallat-Decouvelaere AV, Gauchez P, Varlet P, Delisle MB, Popovic M, Boissonnet H, Gigaud M, Mikol J, Hassoun J. So-called malignant and extra-ventricular neurocytomas: reality or wrong diagnosis? A critical review about two over-diagnosed cases. J Neurooncol 2000; 48:161–172.
36. Vecil GG, Lang FF. Surgical resection of metastatic intraventricular tumors. Neurosurg Clin N Am 2003; 14:593–606.
37. Waldron JS, Tihan T. Epidemiology and pathology of intraventricular tumors. Neurosurg Clin N Am 2003; 14:469–482.
38. Wen HT, Rhoton AL Jr, de Oliveira E. Transchoroidal approach to the third ventricle: an anatomic study of the choroidal fissure and its clinical application. Neurosurgery 1998; 42:1205–1217; discussion 1217–1209.
39. Westphal M, Meissner H, Matschke J, Herrmann HD. Tissue culture of human neurocytomas induces the expression of glial fibrilary acidic protein. J Neurocytol 1998; 27:805–816.
40. Westphal M, Stavrou D, Nausch H, Valdueza JM, Herrmann HD. Human neurocytoma cells in culture show characteristics of astroglial differentiation. J Neurosci Res 1994; 38:698–704.
41. Wiestler OD, Lopes BS, Green AJ, H.V.V. Tuberous sclerosis complex and subependymal giant cell astrocytoma. In: Kleihues P, Cavanee W, eds. Tumours of the Nervous System: Pathology and Genetics. Lyon, IARC, 2000.
42. Wiestler OD, Schiffer D, Coons S, Prayson RA, Rosenblum MK. Ependymoma. In: Kleihues P, Cavanee W, eds. Tumours of the Nervous System : Pathology and Genetics. Lyon, IARC Press, 2000.
43. Winkler PA, Ilmberger J, Krishnan KG, Reulen HJ. Transcallosal interforniceal-transforaminal approach for removing lesions occupying the third ventricular space: clinical and neuropsychological results. Neurosurgery 2000; 46:879–888; discussion 888–890.
44. Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM. Choroid plexus tumours. Br J Cancer 2002; 87:1086–1091, .

Adult Tumors of Pediatric Origin 9

(Medulloblastomas-PNETs, Craniopharyngiomas, Ependymomas-Ependymoblastomas)

Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

Epidemiology – 160

Symptoms and Clinical Signs – 160

Diagnostics – 160
Medulloblastomas
Craniopharyngioma
Ependymoma

Staging and Classification – 162
Medulloblastoma
Craniopharyngioma
Ependymoma

Treatment – 163
Medulloblastoma
Craniopharyngioma
Ependymoma

Prognosis/Quality of Life/Follow-up/Specific Problems and Measures – 163
Medulloblastoma
Craniopharyngioma
Ependymoma

Future Perspectives – 164

References – 164

Epidemiology

According to the new WHO classification, embryonal tumors comprise medulloblastomas, primitive neuroectodermal tumors (PNET), medulloepitheliomas, ependymoblastomas, and neuroblastomas. We include here also craniopharyngiomas and ependymomas.

A detailed description of medulloblastomas, PNETs, craniopharyngiomas, and ependymomas is given in the pediatric chapter. We will focus in the following on specific features that characterize adult tumors of these entities. Neuroblastomas are rarely found in neuro-oncological patients except when they metastasize in the central nervous system (CNS).

Medulloblastomas derive from primitive neuroectodermal precursor cells, are primarily pediatric tumors, and occur in 80% below the age of 15 years (median age 5–9 years) [26]. They represent 15–25% of all childhood brain tumors, but only 1% of adult intracranial neoplasms [11]. There is a certain male preponderance. Several reports found adult tumors more often located lateral in the hemisphere, whereas pediatric medulloblastomas are more frequent in the midline [26]. Consecutively, the desmoplastic medulloblastoma variant, which is found more often in the lateral distribution, occurs in a higher percentage in adults (35–73%), while the classical variant prevails in children (70–85%) [26]. Another very rare variant, found only in adults, is the lipomatous medulloblastoma with a favorable prognosis. Only 15 cases are reported so far in the literature [7].

Rare variants of embryonal tumors are the medulloepithelioma, the ependymoblastoma, and the cerebral neuroblastoma. Medulloepitheliomas occur predominantly during the first 5 years of age in the cerebral hemispheres.

Craniopharyngiomas arise in 40% after the age of 16 years and have a second peak incidence between 50 and 60 years of age.

Ependymomas in adults are typically located in the spinal cord and represent 20–45% of all intramedullary tumors [10]. Intracranial ependymomas are exceptionally rare in adults, they have a peak incidence between the age of 8 and 15 years [23].

Symptoms and Clinical Signs

The leading symptoms in approximately 90% of patients with medulloblastomas are headaches (due to occlusive hydrocephalus), followed by nausea and vomiting in about 75%, and ataxia in 67% [18].

In contrast, craniopharyngiomas become clinically evident through symptoms deriving from disturbance of the pituitary gland, the hypothalamus, or the brain stem, including adjacent cranial nerves. Hormonal dysfunction occurs in up to 60%, with hypogonadism in adults and growth retardation in children. A diabetes insipidus is present in 15–30%. Visual disturbances with reduced visual acuity or visual field defects are very common in 50–75%, followed by headaches in 57% [25].

Ependymomas of intracranial location lead in most cases to obstructive hydrocephalus with headaches, nausea, vomiting, and papillary edema. Epileptic seizures are also not uncommon [19].

Diagnostics

Medulloblastomas

In general, medulloblastomas appear as ill-defined, hyperdense lesions in the posterior fossa on CT images, with no consistent contrast enhancement. The MR characteristics, however, can be rather variable in children and particularly in adults. Most adult medulloblastomas are located in the cerebellar hemisphere, whereas the pediatric tumors are found in the vast majority in the vermis/midline. Medulloblastomas appear as low-or isointense signal on T1-weighted and isointense signal on T2-weighted images. Cystic or necrotic areas are particularly visible on T2-weighted images (Fig. 1). Contrast enhancement is extremely variable from none to intense. A detailed analysis by Malheiros et al. [17] showed no distinction between different histological medulloblastoma types (classic versus desmoplastic) by MRI.

Craniopharyngioma

Characteristic features of craniopharyngiomas, which may extend intra- as well as suprasellar, are calcifications, erosion of the clinoid processes and the dorsum sellae on CT scans, cyst formation (hyperintense on T2-weighted MR images), and strong contrast enhancement in hypointense tumor parts on T1-weighted MR images (Fig. 2) [20].

Ependymoma

Infra- and supratentorial ependymomas are often fairly well delineated. The neuroradiological features can be rather inhomogeneous. They often present as isointense to hypointense lesions on T1-weighted images, with inhomogeneities on T2-weighted images. They exhibit intratumoral cysts and hemorrhages to a high degree and enhance to a variable extent, sometimes rather strongly after gadolinium admin-

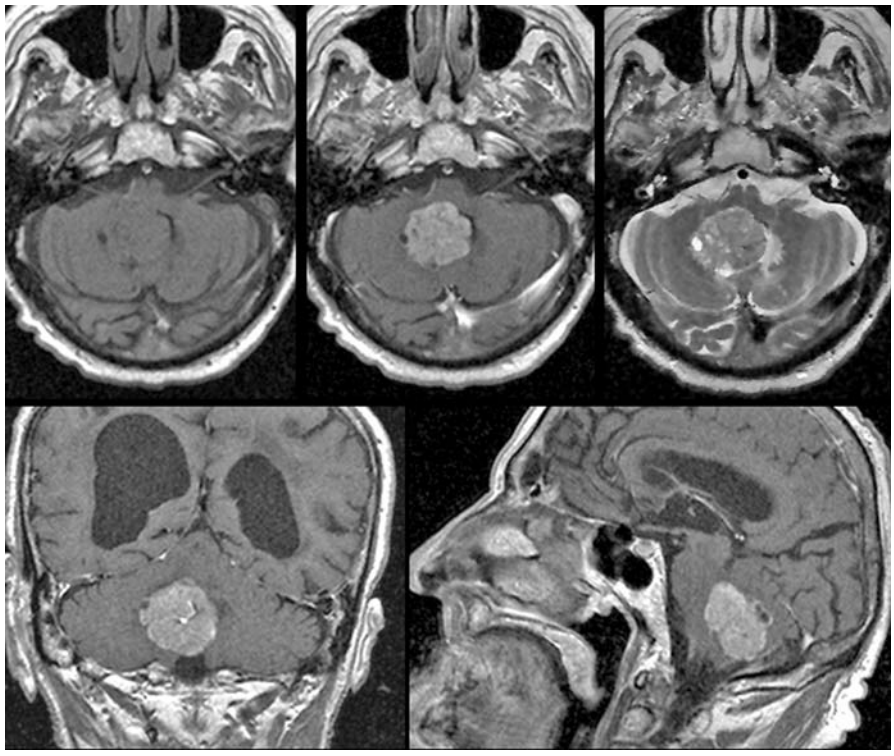


Fig. 1 a–e. Medulloblastoma of an 81-year-old male patient. Axial T1-weighted image demonstrates an isointense lesion in the fourth ventricle (**a**) with some cystic areas (**c**). Axial (**b**), coronal (**d**), and sagittal (**e**) images show inhomogeneous contrast enhancement

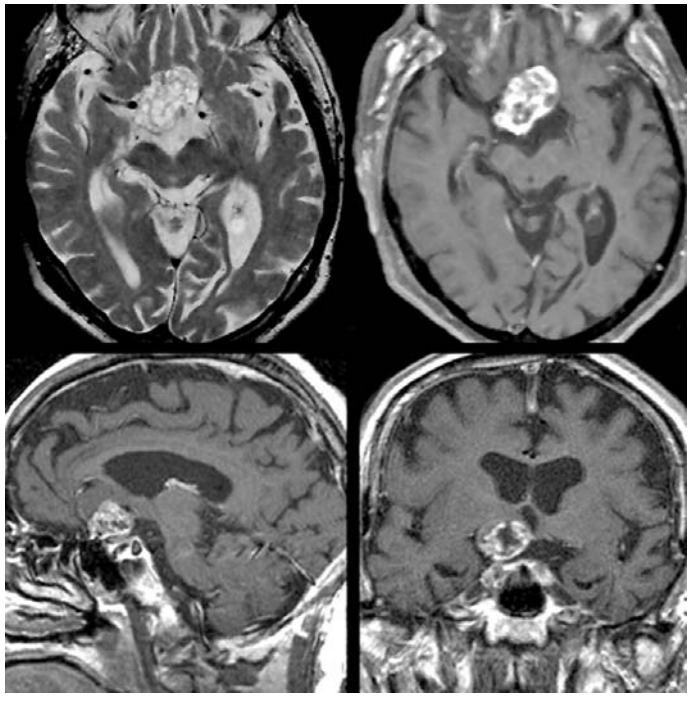


Fig. 2 a–d. Craniopharygioma of an 82-year-old male patient. Cystic tumor with suprasellar extension on T2-weighted MR image (**a**), and strong but irregular gadolinium uptake (**b, c, d**)

istration [5, 16]. The perifocal edema may be less than expected in relationship to the often large tumor volume (Fig. 3). Typically, ependymomas of the fourth ventricle can extend through the foramen of Magendie or Luschka. CSF seeding is seen in anaplastic tumors.

Staging and Classification

Medulloblastoma

Medulloblastoma is an invasive, malignant, neuroectodermal embryonal tumor, corresponding to WHO grade IV. Classic and desmoplastic medulloblastomas are the most common histological variants. The classic variant is composed of densely packed cells with highly hyperchromatic nuclei and scanty cytoplasm, whereas the desmoplastic variant is characterized by the presence of reticulin-free nodules ('pale islands') with reduced cellularity surrounded by highly proliferative cells which produce a dense intercellular reticulin fiber network [11]. The lipomatous variant is very rare and only present in adults with a uniquely favorable prognosis. Apart from the typical blue, small-cell tumor features, this variant is dominated by multiple lipid vacuoles and adipocytes. On the molecular basis, several developmentally regulated genes have been detected that are involved in the pathogenesis of medulloblastomas. The sonic hedgehog signaling pathway directs the embryonic development of external granular cells of the cerebellum and is disrupted in medulloblastomas [29]. A panel of upregulated genes and overexpressed proteins in medulloblastoma including Unc33-like protein (ULIP), SOX4, Neuronatin, BARHL1, nuclear matrix protein NRP/B, and the homebox gene OTX2, as well as a reduced expression of the HIC-1 gene, have been identified [34, 35].

Medulloepitheliomas characteristically exhibit tube-like epithelial formations comparable to the neural tube.

Craniopharyngioma

This tumor derives from epithelial cell remnants of the former Rathke cleft, which later forms the pars intermedia of the anterior pituitary lobe. An adamantinomatous and a papillary type are discerned, without any known difference in the prognosis of both variants.

Ependymoma

The WHO classification discerns three grades. The myxopapillary ependymoma of the filum and the subependymoma correspond to WHO grade I, the classical ependymoma to WHO grade II, and the anaplastic ependymoma with increased cellularity, mitoses, nuclear atypia, and neovascularisation to WHO grade III. According to cytogenetic and immunohistochemical results, different prognostic factors can be discriminated [4, 12, 13, 28]. There is a con-

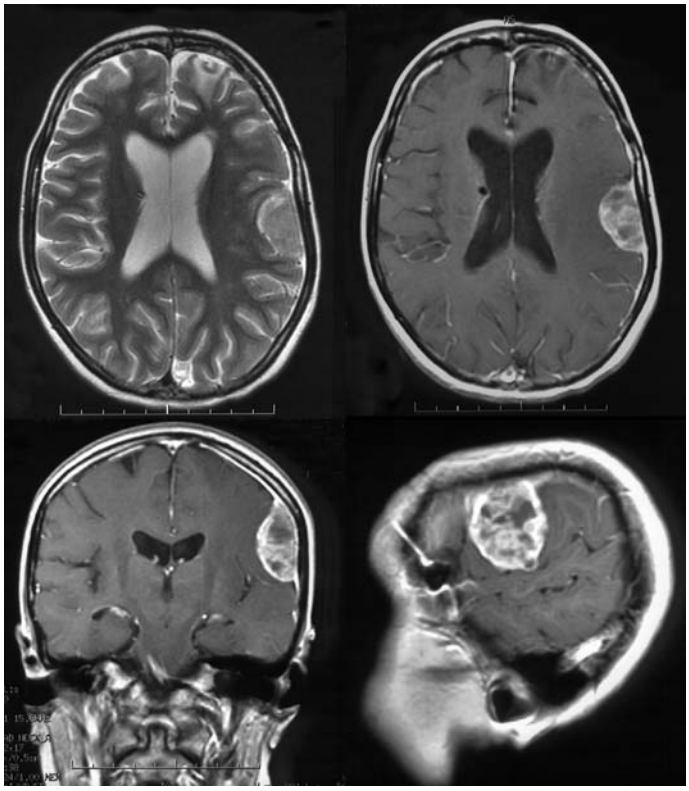


Fig. 3 a–d. Ependymoma of a 20-year-old female patient. Supratentorial central tumor of the left hemispheric convexity showing strong, irregular contrast enhancement on axial (**b**), coronal (**c**), and sagittal (**d**) T1-weighted images. Axial T2-weighted image exhibits only discrete perifocal edema (**a**)

siderable body of evidence that ependymomas display a LOH on chromosome 22q which might carry a tumor suppressor gene and, moreover, that cranial and spinal ependymomas are genetically distinct tumors [9, 14, 33].

The ependymoblastoma shows features of a malignant ependymoma as well as of a primitive neuroectodermal tumor.

Treatment

Medulloblastoma

Medulloblastomas in adults are very rare, and the sole available data are derived from small retrospective series collected over long periods, during which morbidity and mortality in neurosurgical procedures have drastically changed, radiotherapeutic techniques have improved, and treatment strategies including different chemotherapeutic protocols have been optimized. Brandes et al. [3] performed the first prospective study and included 36 patients over the age of 18 years.

Surgical resection of the lesion still remains the first-line treatment in medulloblastoma patients. According to Brandes et al., low-risk patients with no residual disease should receive craniospinal radiation of 36 Gy and a boost to the posterior fossa of about 18 Gy. High-risk patients with residual or metastatic disease should receive additional chemotherapy with cisplatin, etoposide, and cyclophosphamide [3]. Preradiotherapy chemotherapy did not affect the final outcome or result in tumor progression as postulated in children, although some authors recommend a few chemotherapeutic cycles prior to radiotherapy [18]. However, chemotherapy-related toxicity seemed to be higher and median survival time shorter than in the pediatric patient group [8]. In patients with recurrent medulloblastomas, high-dose chemotherapy with autologous stem-cell transplantation seemed to be effective [36].

Craniopharyngioma

Gross total resection, in most cases through a transcranial approach (solely intrasellar tumors can be resected by a transsphenoidal route), should be the primary goal. Although the mainstay of treatment is still the attempt to radically remove a craniopharyngioma at the initial surgical procedure, removal of the dorsoapical parts of the tumor capsule, especially in patients of older age, can lead to severe neuropsychological deficits and hypothalamic syndromes. Thus, in these patients a more conservative approach is preferable. In case of a cystic tumor or recurrent cysts, stereotactic catheter placement for cyst aspiration is another option [22, 27, 31]. Radiotherapy either as conventionally fractionated radiotherapy or radiosurgery is recommended by some authors for recurrent tumors [2, 22, 30, 32].

Ependymoma

The primary treatment of intracranial ependymomas is surgical resection. Data from pediatric series showed no survival benefit from immediate radiotherapy and rather recommended close surveillance [21]. Reni et al. came to the same conclusion for adult patients with intracranial ependymomas WHO grade II [23]. Radiotherapy should be reserved for anaplastic tumors or those that recur.

Prognosis/Quality of Life/Follow-up/Specific Problems and Measures

Medulloblastoma

In general, the prognosis of medulloblastomas has significantly improved over the last decade due to new achievements in chemotherapeutic and radiotherapeutic regimens. The overall 5-year survival ranges between 65 and 84% [1, 15, 18], while the progression-free survival at 5 years is 51–74% [1, 3, 15]. The prognosis in adults compares favorably with that in children, mostly due to the benefit of adjuvant radiotherapy [1, 15, 18]. According to the study of Sarkar et al. the survival benefit in adults does not seem to be related to the histological variant (classical versus desmoplastic medulloblastoma variant), but rather to age [26]. The one exception, the lipomatous medulloblastoma variant, which occurs in adults only, has a uniquely favorable prognosis, even with incomplete resection or multicentric appearance [7].

Craniopharyngioma

Effenterre et al. retrospectively analyzed the outcome in 122 adult and pediatric craniopharyngiomas [31]. The functional results in both groups was excellent in 85%, good in 9%, and fair in 5% (usually due to ophthalmologic deficits), provided treatment was started at an early stage. The 5- and 10-year survival rates were 92% and 85%, respectively. Disturbances of the water-electrolyte system due to affection of the pituitary stalk with subsequent diabetes insipidus are common. However, this can be treated effectively today with ADH substitution as nasal spray or

tablets. One can conclude that radical resection leads to good outcome in terms of survival, full recovery, and quality of life for both adults and children.

Ependymoma

Intracranial ependymomas are uncommon tumors in adults, and only a few studies are available in the literature. The largest series so far is from Reni et al. summarizing their experience with 70 patients over the age of 17 years. The 5- and 10-year overall survival rates were 67% and 50%, the 5- and 10-year progression-free survival rates were 43% and 24%, respectively. Younger age, WHO grade II, and infratentorial tumor location were positive prognosticators [23]. Donahue et al. reported on their experience with 10 patients treated with surgery and adjuvant local radiotherapy. Seven patients were disease-free at a median follow-up of 64 months [6]. Rezai et al. concluded that younger patients with subtotally resected, myxopapillary or high-grade tumors are at substantial risk for the development of disseminated disease [24]. The tumor site has a significant impact on overall survival, with spinal location exhibiting the best prognosis, followed by the infratentorial and supratentorial location [19].

Future Perspectives

With the refinement of molecular diagnostics, an increasing number of genetic and epigenetic alterations in medulloblastomas and ependymomas have been found [9, 14 33, 29, 35]. Spinal ependymomas are clinically and genetically distinct from their intracranial counterpart. They have a more favorable prognosis than intracranial ependymomas of the respective WHO grade. Allelic loss on chromosome 22q were detected in anaplastic intracranial ependymomas in children, and in a subset of adult intraspinal tumors [9]. Detailed analysis suggested that there may be two distinct genes on chromosome 22q involved in ependymoma pathogenesis [14]. Another putative tumor suppressor gene HIC-1 residues on chromosome 17p, which was found to be hypermethylated significantly more often in intracranial tumors and in tumors of younger patients [33]. Knowledge of different molecular genetic factors which may influence the prognosis can be of importance for the clinical evaluation and treatment decisions in the future.

Stereotactic radiosurgery is becoming an interesting treatment option for craniopharyngiomas after incomplete resection or recurrent tumors in delicate locations such as the cavernous sinus.

References

1. Abacioglu U, Uzel O, Sengoz M, Turkan S, Ober A. Medulloblastoma in adults: treatment results and prognostic factors. Int J Radiat Oncol Biol Phys 2002; 54:855–860.
2. Amendola BE, Wolf A, Coy SR, Amendola MA. Role of radiosurgery in craniopharyngiomas: a preliminary report. Med Pediatr Oncol 2003; 41:123–127.
3. Brandes AA, Ermani M, Amista P, Basso U, Vastola F, Gardiman M, Iuzzolino P, Turazzi S, Rotilio A, Volpin L, Mazza C, Sainati L, Ammannati F, Berti F. The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys 2003; 57:755–761.
4. Carter M, Nicholson J, Ross F, Crolla J, Allibone R, Balaji V, Perry R, Walker D, Gilbertson R, Ellison DW. Genetic abnormalities detected in ependymomas by comparative genomic hybridisation. Br J Cancer 2002; 86:929–939.
5. Choi JY, Chang KH, Yu IK, Kim KH, Kwon BJ, Han MH, Kim IO. Intracranial and spinal ependymomas: review of MR images in 61 patients. Korean J Radiol 2002; 3:219–228.
6. Donahue B, Steinfeld A. Intracranial ependymoma in the adult patient: successful treatment with surgery and radiotherapy. J Neurooncol 1998; 37:131–133.
7. Elshihabi S, Husain M, Linskey M. Lipomatous medulloblastoma: a rare adult tumor variant with a uniquely favorable prognosis. Surg Neurol 2003; 60:566–570.
8. Greenberg HS, Chamberlain MC, Glantz MJ, Wang S. Adult medulloblastoma: multiagent chemotherapy. Neuro-oncol 2001; 3:29–34.
9. Huang B, Starostik P, Kuhl J, Tonn J.C., Roggendorf W. Loss of heterozygosity on chromosome 22 in human ependymomas. Acta Neuropathol (Berl) 2002; 103:415–420.
10. Iwasaki Y, Hida K, Sawamura Y, Abe H. Spinal intramedullary ependymomas: surgical results and immunohistochemical analysis of tumour proliferation activity. Br J Neurosurg 2000; 14:331–336.
11. Kleihues P, Cavenee WK. Pathology and genetics of tumours of the nervous system. IARC press, Lyon, 2000
12. Korshunov A, Golanov A, Sycheva R, Timirgaz V. The histologic grade is a main prognostic factor for patients with intracranial ependymomas treated in the microneurosurgical era: an analysis of 258 patients. Cancer 2004; 100:1230–1237.
13. Korshunov A, Golanov A, Timirgaz V. Immunohistochemical markers for intracranial ependymoma recurrence. An analysis of 88 cases. J Neurol Sci 2000; 177:72–82.
14. Kraus JA, de Millas W, Sorensen N, Herbold C, Schichor C, Tonn J.C., Wiestler OD, von Deimling A, Pietsch T. Indications for a tumor suppressor gene at 22q11 involved in the pathogenesis of ependymal tumors and distinct from hSNF5/INI1. Acta Neuropathol (Berl) 2001; 102:69–74.
15. Kunschner LJ, Kuttesch J, Hess K, Yung WK. Survival and recurrence factors in adult medulloblastoma: the M.D. Anderson Cancer Center experience from 1978 to 1998. Neurooncol 2001; 3:167–173.

16. Li MH, Holtas S. MR imaging of spinal intramedullary tumors. Acta Radiol 1991; 32:505–513.
17. Malheiros SM, Carrete H Jr, Stavale JN, Santos AJ, Borges LR, Guimaraes IF, Pelaez MP, Franco CM, Gabbai AA. MRI of medulloblastoma in adults. Neuroradiology 2003; 45:463–467.
18. Malheiros SM, Franco CM, Stavale JN, Santos AJ, Borges LR, Pelaez MP, Ferraz FA, Gabbai AA. Medulloblastoma in adults: a series from Brazil. J Neurooncol 2002; 60:247–253.
19. McLaughlin MP, Marcus RB Jr, Buatti JM, McCollough WM, Mickle JP, Kedar A, Maria BL, Million RR. Ependymoma: results, prognostic factors and treatment recommendations. Int J Radiat Oncol Biol Phys 1998; 40:845–850.
20. Molla E, Marti-Bonmati L, Revert A, Arana E, Menor F, Dosda R, Poyatos C. Craniopharyngiomas: identification of different semiological patterns with MRI. Eur Radiol 2002; 12:1829–1836.
21. Palma L, Celli P, Mariottini A, Zalaffi A, Schettini G. The importance of surgery in supratentorial ependymomas. Long-term survival in a series of 23 cases. Childs Nerv Syst 2000; 16:170–175.
22. Pollock BE, Natt N, Schomberg PJ. Stereotactic management of craniopharyngiomas. Stereotact Funct Neurosurg 2002; 79:25–32.
23. Reni M, Brandes AA, Vavassori V, Cavallo G, Casagrande F, Vastola F, Magli A, Franzin A, Basso U, Villa E. A multicenter study of the prognosis and treatment of adult brain ependymal tumors. Cancer 2004; 100:1221–1229.
24. Rezai AR, Woo HH, Lee M, Cohen H, Zagzag D, Epstein FJ. Disseminated ependymomas of the central nervous system. J Neurosurg 1996; 85:618–624.
25. Rohrer T, Gassmann K, Buchfelder M, Wenzel D, Fahlbusch R, Dorr HG. Clinical symptoms in 35 children and adolescents with craniopharyngeoma at the time of diagnosis. Klin Padiatr 2002; 214:285–290.
26. Sarkar C, Pramanik P, Karak AK, Mukhopadhyay P, Sharma MC, Singh VP, Mehta VS. Are childhood and adult medulloblastomas different? A comparative study of clinicopathological features, proliferation index and apoptotic index. J Neurooncol 2002; 59:49–61.
27. Shirane R, Ching-Chan S, Kusaka Y, Jokura H, Yoshimoto T. Surgical outcomes in 31 patients with craniopharyngiomas extending outside the suprasellar cistern: an evaluation of the frontobasal interhemispheric approach. J Neurosurg 2002; 96:704–712.
28. Takeuchi H, Kubota T, Sato K, Llena JF, Hirano A. Epithelial differentiation and proliferative potential in spinal ependymomas. J Neurooncol 2002; 58:13–19.
29. Taylor MD, Mainprize TG, Rutka JT. Molecular insight into medulloblastoma and central nervous system primitive neuroectodermal tumor biology from hereditary syndromes: a review. Neurosurgery 2000; 47:888–901.
30. Ulfarsson E, Lindquist C, Roberts M, Rahn T, Lindquist M, Thoren M, Lippitz B. Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. J Neurosurg 2002; 97:613–622.
31. van Effenterre R, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. J Neurosurg 2002; 97:3–11.
32. Varlotto JM, Flickinger JC, Kondziolka D, Lunsford LD, Deutsch M. External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. Int J Radiat Oncol Biol Phys 2002; 54:492–499.
33. Waha A, Koch A, Hartmann W, Mack H, Schramm J, Sorensen N, Berthold F, Wiestler OD, Pietsch T, Waha A. Analysis of HIC-1 methylation and transcription in human ependymomas. Int J Cancer 2004; 110:542–549.
34. Waha A, Waha A, Koch A, Meyer-Puttlitz B, Weggen S, Sorensen N, Tonn J.C., Albrecht S, Goodyer CG, Berthold F, Wiestler OD, Pietsch T. Epigenetic silencing of the HIC-1 gene in human medulloblastomas. J Neuropathol Exp Neurol 2003; 62:1192–1201.
35. Yokota N, Mainprize TG, Taylor MD, Kohata T, Loreto M, Ueda S, Dura W, Grajkowska W, Kuo JS, Rutka JT. Identification of differentially expressed and developmentally regulated genes in medulloblastoma using suppression subtraction hybridization. Oncogene 2004; 23:3444–3453.
36. Zia MI, Forsyth P, Chaudhry A, Russell J, Stewart DA. Possible benefits of high-dose chemotherapy and autologous stem cell transplantation for adults with recurrent medulloblastoma. Bone Marrow Transplant 2002; 30:565–569.

Glioneuronal Tumors 10

Johannes Schramm, Rudolf Kristof

Neuronal and Mixed Neuronal-Glial Tumors – 169

Ganglioglioma – 170
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Gangliocytoma – 171
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment and Prognosis/Quality of Life

Desmoplastic Infantile Ganglioglioma/Astrocytoma – 172
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos) – 173
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Dysembryoplastic Neuroepithelial Tumors – 173
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Central Neurocytoma – 175
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Cerebellar Liponeurocytoma – 176
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

Paraganglioma of the Cauda Equina – 177
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Prognosis/Quality of Life

References – 178

Neuronal and Mixed Neuronal-Glial Tumors

Neuronal and mixed neuronal-glial tumors belong to the tumors of the neuroepithelial tissue and comprise ganglioglioma, gangliocytoma, desmoplastic infantile ganglioglioma, dysplastic cerebellar gangliocytoma, dysembryoplastic neuroepithelial tumor, central neurocytoma, cerebellar liponeurocytoma, and paraganglioma of the cauda equina. All of these tumors have in common cells of neuronal and sometimes of glial differentiation. In general, both cell lineages are well differentiated. Some of these tumors may be associated with dysplasia, hamartomas, and other malformations. Neuronal and mixed neuronal-glial tumors usually have a benign favorable prognosis.

Neuronal and mixed neuronal-glial tumors are rare. In a consecutive series of 4076 adult and pediatric patients with intracranial tumors surgically treated at our institution, including epilepsy surgery, neuronal and mixed neuronal-glial tumors were diagnosed in 254 (6.2%) patients (Table 1).

Table 1. Prevalence of neuronal and mixed neuronal-glial tumors in our collective of adult and pediatric patients surgically treated for intracranial tumors from January 1992 to June 2004, including epilepsy surgery. Rare intracranial tumors other than neuronal and mixed neuronal-glial tumors are not considered. Values kindly provided by Prof. Dr. T. Pietsch and Dr. A. Becker, Institute of Neuropathology, University of Bonn

	n	% of subtotal
Neuronal and neuronal-glial tumors (6.2% of total)		
Gangliogliomas	181	71.0
Anaplastic gangliogliomas	4	1.6
Desmoplastic infantile gangliogliomas	1	0.4
Gangliocytomas	2	0.8
Dysplastic cerebellar gangliocytomas	1	0.4
Dysembryoplastic neuroepithelial tumors	51	20.1
Central neurocytomas	4	1.6
Cerebellar liponeurocytomas	0	0.0
Paragangliomas of the filum terminale	10	3.9
Total	254	100.0
Frequent intracranial tumors (93.8% of total)		
Gliomas	1253	32.7
Meningiomas	1111	29.0
Metastases	607	15.8
Hypophyseal adenomas	482	12.6
Neurinomas	266	6.9
Ependymomas/subependymomas	59	1.5
Lymphomas	44	1.1
Subtotal	3822	100.0
Total	4076	

Ganglioglioma

Epidemiology

Ganglioglioma (GG) is the most frequent neoplasm within the group of neuronal and mixed neuronal-glial tumors. In our series of 4076 patients with intracranial tumors, GG were diagnosed in 4.4% of the cases. In the literature, their incidence is rated at 0.3–5.2% of intra-axial tumors in adults and up to 14% of intra-axial tumors in pediatric patient series [11, 16, 24]. In pediatric series, the mean age of patients at diagnosis is at the end of the first decade, while in adult patient series, it is in the third decade. There is a slight female predominance.

Symptoms and Clinical Signs

GG may occur throughout the CNS. The vast majority are located supratentorially, with a preference for the temporal lobe. Infratentorial and spinal GG are rare. In our recently evaluated series of 184 supratentorial GG, the tumor was temporal in 79% and frontal in 12% of cases [16]. GG present with epileptic seizures in 85–97% of the cases, the majority of which are long-standing (mean of 10–15 years) and pharmacoresistant [9, 16]. Focal neurological deficits are rare in supratentorial GG. Due to their location, infratentorial and spinal GG will manifest with focal neurological deficit and increased intracranial pressure. Also, their medical history is shorter (months to a few years) than in supratentorial GG [14, 20]. The rare cases of anaplastic GG will also have shorter medical histories.

Diagnostics

The majority of GG are hypo- to isointense on T1-weighted MRI (90%) and hyperintense on T2-WI (70%). Tumor cyst formation occurs in 30–50% of the cases. The classic MRI pattern of GG, consisting of a cystic mass with a solid mural nodule, is found in about 40% of cases. Contrast enhancement of the solid portion is of a variable pattern and occurs in 35–50% of tumors. Usually, there is little mass effect and no peritumoral edema. MRI does not allow differentiation between anaplastic and non-anaplastic GG (Fig. 1). CT discloses tumor calcifications in 30–50% of the cases. Pressure erosions of the overlying calvaria may be present [25].

Staging and Classification

GG are composed of neoplastic mature ganglion and neoplastic glial (usually astrocytic, rarely oligodendrocytic) cells. They correspond histologically to WHO grade I, rarely to WHO grade II. Anaplastic GG WHO grade III are exceedingly rare. In our recently evaluated series of 184 patients, GG WHO grade I constituted 93%, WHO grade II 6%, and WHO grade III 1% of the cases [16]. Anaplastic GG (WHO grade III) may evolve from previously non-anaplastic GG or may be diagnosed de novo. The malignant transformation of the tumor occurs almost invariably in the glial component of GG, and may ultimately result in the histological picture of glioblastoma. GG may be associated with glioneuronal hamartias and other cortical dysplasias [9, 16, 18].

The papillary glioneuronal tumor is considered to be a variant of GG. These tumors are regularly markedly cystic and, unlike GG, arise in the periventricular white matter. The prognosis of papillary glioneuronal tumors is similar to that of GG [18].

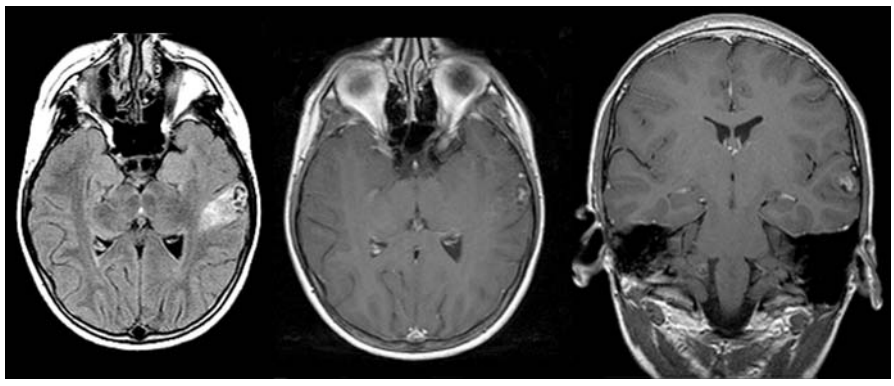


Fig. 1. Ganglioglioma of the left temporal lobe. The tumor is hyperintense and partially cystic on proton-WI (*left*). On T1-WI the mural module within the cyst is contrast-enhancing (*middle* and *right*). There is little mass effect and no peritumoral edema

Treatment

Surgery. Complete tumor resection of supratentorial GG can be achieved in 73–79% of the cases. In tumors situated in the insula and basal ganglia, complete resection may not be possible. If total tumor removal cannot be achieved, regrowth seems to be rare or very slow. In the large series of Luyken et al. [16], 21% of the tumors were subtotally resected, and mean follow-up was 8 years. A re-operation was deemed necessary in only 8% of these cases, two of which were grade III recurrent tumors. In patients with supratentorial GG presenting with pharmacoresistant epilepsy, additional presurgical epileptological evaluation is mandatory, in order to assess whether additional perilesional resection of epileptogenic tissue is required. Following complete tumor resection (and additional resection of perilesional tissue if required), epilepsy is cured in 80–85% of patients. Residual epilepsy may be associated with incomplete tumor resection and the presence of additional cortical dysplasia [9, 16]. Surgical morbidity is usually transient and occurs in about 2.4% of the patients. Perioperative mortality is low (0.5%). In brain stem GG, radical surgery is rarely if ever possible. In spinal GG, gross total tumor removal is reported in up to 80% of the cases. The rate of surgical morbidity in brain stem and spinal GG is higher than in supratentorial ones [14, 20].

Radiotherapy. Radiotherapy following complete resection of GG WHO grades I and II is not indicated. Radiotherapy following subtotal tumor removal appears not to be routinely indicated, because relapses and malignant transformations may occur despite radiation [24]. Routine postoperative radiotherapy should be assigned for anaplastic GG WHO grade III and for recurrences not amenable to re-operation. The role of γ-knife surgery is completely unclear.

Chemotherapy. The role of postoperative chemotherapy has not yet been established. It may be used in residual anaplastic ganglioma WHO grade III, and possibly for recurrences not amenable for re-operation [11].

Prognosis/Quality of Life

In our series of 184 supratentorial GG, the 7.5-year recurrence-free survival was 97%. Lower recurrence rates were associated with WHO grade I, complete tumor removal, temporal location, and long-standing history of seizures [16]. Recurrence rates reported in smaller series are highly variable (0–40%), depending on tumor grading, extent of surgery, location of the tumors, and follow-up [9, 24]. Regular follow-up MRIs at 1.5–2 year intervals may be advisable, even if seizures have stopped. During follow-up, malignant transformation (to WHO grades III and IV) was observed in 2–9% of the cases [9, 16]. In these tumors, subarachnoid seeding may occur. Survival times of GG WHO grade III are worse than those of grade I and II, but seem to be better than in astrocytoma WHO grade III. Death due to progressive disease occurs in 1–9% of the patients [11, 16]. Quality of life in supratentorial GG is good for the majority of cases, since seizures cease postoperatively in 80–85%, and morbidity and rate of recurrences are low.

The prognosis for brain stem GG is probably similar to the prognosis for supratentorial GG. Despite the fact that surgery is rarely if ever radical, survival of up to 10 years without progressive disease can occur. Primary anaplastic GG and malignant transformation of formerly WHO grades I and II GG may also occur [14].

The recurrence rates of spinal GG are thought to be higher than those of cerebral GG, and have been described to be up to 27%. Malignant transformation of spinal GG has also been noted [20].

Gangliocytoma

Epidemiology

Gangliocytoma (GC) is clinically, radiologically, and histologically closely related to GG, and they are therefore routinely considered together. GC is clearly less common than GG. In a consecutive series of 4076 patients with surgically treated intracranial tumors, we encountered 2 GC, but 181 GGs. GC is usually diagnosed in children and young adults.

Symptoms and Clinical Signs

The most common sites of occurrence of GC are the cerebral hemispheres, especially the temporal lobes. As in GG, they often present with years of long-standing epilepsy. Focal neurological impairment is less common and often associated with infratentorially and spinally located GC [4, 13, 25]. GC may also occur in the pituitary, hypothalamus, and pineal regions. In the pituitary, GC occurs more often in the anterior than in the posterior lobe and is usually associated with pituitary adenomas [8, 25]. In these cases, the clinical presentation of GC corresponds to that of pituitary adenomas.

Diagnostics

GC and GG are indistinguishable on MRI and CT. However, some GC are cortically located and present a dural tail mimicking a meningioma [25].

Staging and Classification

GC is composed of large neoplastic neural cells situated in a stroma of non-neoplastic glial cells. In some instances, a clear-cut delineation of GC and GG is difficult. However, as opposed to GG, GC always correspond to WHO grade I. A malignant transformation of GC is not known to occur [18].

Treatment and Prognosis/Quality of Life

Whenever feasible, complete tumor resection should be accomplished. If required, the principles of epilepsy surgery have to be applied. There are no specific data available regarding postoperative long-term outcome with GC, but recurrence and survival times comparable to GG WHO grade I may be assumed.

Desmoplastic Infantile Ganglioglioma/Astrocytoma

Epidemiology

Desmoplastic infantile ganglioglioma/astrocytoma (DIG) is a rare supratentorial tumor with an incidence of 1.25% in pediatric tumor series. In our series of 4076 intracranial tumors of adult and pediatric cases, 1 DIG was found. However, because the vast majority of DIG occur within the first year of life, these tumors are not uncommon in infants [28, 29]. DIG may exceptionally occur in older children and adults. There is a slight male predominance.

Symptoms and Clinical Signs

Since DIG occur in very young children and since these supratentorial tumors tend to be huge, the medical history is of short duration. Signs of raised intracranial pressure, including abnormal increase of head circumference, tense fontanelles, and sunset signs prevail. Focal neurological deficits are often encountered, and seizures may occur [28, 29].

Diagnostics

DIG are always supratentorial tumors involving the cerebral surface and overlying dura. These large tumors disclose a cystic, often septate component oriented towards the brain and a solid part attached to the cortex and dura. The cysts are hypointense on T1-WI and hyperintense on T2-WI. The solid part is inhomogeneous (mostly isointense) on T1- and T2-WI. Contrast enhancement of the solid part is intense on T1-WI and extends to the adjacent meninges. The cyst walls do not enhance. Peritumoral edema is not present [25]. CT does not provide additional information, and calcifications have not been described.

Staging and Classification

DIG are composed of neoplastic astrocytic and ganglion cells embedded in a prominent desmoplastic stroma. Poorly differentiated neuroepithelial cells that may show foci of mitosis and necrosis are also present. The presence of this latter cell population does not alter the favorable prognosis of DIG. Tumors without a neoplastic ganglion cell population are termed desmoplastic infantile astrocytoma. Their biological behavior corresponds to DIG. DIG corresponds to WHO grade I [28].

Treatment

Surgery. Surgery of these tumors is often challenging, because they are usually large, often encounter eloquent brain areas, may be adherent to venous sinus walls, and because the children are very young. Thus, complete tumor removal is not always possible, and surgical morbidity may be high [27].

Radiotherapy and Chemotherapy. Radiotherapy and chemotherapy should not be carried out primarily as adjuvant therapy, even if the tumor has been incompletely resected. Chemotherapy is indicated in recurrent and progressive residual tumors if they are not amenable for re-operation. If necessary, radiotherapy has been advised in children who failed chemotherapy and who are over 5–6 years of age [3, 27].

Prognosis/Quality of Life

Gross total tumor removal results in long-term survival documented for up to two decades. Patients with incomplete tumor resection have also been followed up for years without progression of residu-

al tumor [28]. Notably, some of the infants presented spontaneous regression of residual DIG after incomplete tumor removal [27]. However, in exceptional cases, DIG have been described to behave malignantly [3].

Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos)

Epidemiology

Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos) (DCGC) is a very rare, cerebellar mass lesion, representing the major CNS manifestation of the phakomatosis termed Cowden disease. In our series of 4076 patients with surgically treated intracranial tumors, including 254 neuronal and neuro-glial tumors, DCGC was diagnosed in 1 patient. These tumors may occur at any age but are common in the third and fourth decade of life [19].

Symptoms and Clinical Signs

As part of Cowden disease, DCGC may arise de novo or may be autosomal-dominantly transmitted [31]. At the time of diagnosis of DCGC, Cowden disease is present in 50–90% of the patients. The diagnosis of DCGC may precede the diagnosis of Cowden disease by years [30, 31]. The medical history of patients with DCGC usually lasts for years (mean 3–4 years). Signs and symptoms of raised intracranial pressure occur in 60–70%, cerebellar dysfunction in 50%, and cranial nerve deficits in 30% of the patients. Concomitant frequent CNS malformations associated with DCGC include megalencephaly, hydrocephalus, and syringomyelia [19]. While evaluating patients with DCGC, it is mandatory to also evaluate them for other manifestations of Cowden disease (trichilemmomas, cutaneous keratoses, oral papillomas, gastrointestinal polyps, thyroid tumors, breast tumors, and urogenital tumors) [19, 31].

Diagnostics

MRI shows a cerebellar hemispheric mass with a characteristic hypo-/isointense striated pattern on T1- and iso-/hyperintense striated pattern on T2-WI. The mass itself does not enhance, although some cases may show superficial linear enhancement of cerebellar veins. There is no perifocal edema. On CT, DCGC are hypodense or mixed hypo-/isodense. The characteristic striated pattern of the lesion observed on MRI is not obvious on CT. Scattered calcifications may be present [25].

Staging and Classification

DCGC consists of an outer layer of abnormally myelinated axons originating in an inner layer of dysplastic, disorganized neurons. The proliferative activity is very low. Due to these changes, the foliae of the cerebellum are dysmorphic and thickened (see MRI appearance of DCGC). DCGC corresponds to WHO grade I. However, it is not yet clear whether this lesion is of hamartomatous or true neoplastic nature [31].

Treatment

Surgery. Due to their superficial cerebellar location, these lesions are easily accessible. Poorly defined borders constitute the major technical issue during surgery. Incomplete resection of the lesion is thus not unusual [19]. Neuronavigation may be helpful in this respect. If required, additional surgery for hydrocephalus has to be performed.

Radiotherapy. Radiotherapy has been performed in a few patients with contradictory results. Also, considering the benign and very slow-growing nature of DCGC, radiotherapy should not be considered in these patients even if the lesion has been incompletely resected. Progression of DCGC may take several years to reoccur and can be treated by re-operation [19].

Chemotherapy. Chemotherapy has not been reported for these lesions to date.

Prognosis/Quality of Life

The prognosis of DCGC is good. However, due to the rarity of these lesions, the recurrence-free survival times following complete resection are not yet known. Following incomplete resection, recurrence-free survival for up to 4 years has been described [19]. It is of vital importance to also evaluate and follow-up these patients for other neoplastic manifestations of Cowden disease (increased risk of thyroid, breast, and urogenital malignancies) [19, 30, 31].

Dysembryoplastic Neuroepithelial Tumors

Epidemiology

Dysembryoplastic neuroepithelial tumor (DNT) is the second most common neuronal and neuroglial tumor. In our series of 254 neuronal and neuroglial

tumors, DNT were diagnosed in 20.1% of the cases. As DNT are linked to chronic epilepsy, their incidence in epilepsy surgery series is 0.8–5% of all resective cases and up to 14% in tumor-related resective epilepsy surgery [6, 15]. However, in nonselected patient cohorts, DNT are rare. In our mixed series of 4076 patients surgically treated for intracranial tumors, DNT were diagnosed in 1.25% of the cases. The majority of patients diagnosed with DNT are in their second or third decade of life. The tumors occur more often in male patients.

Symptoms and Clinical Signs

The vast majority of DNT are located supratentorially intracortically, preferably in the temporal lobe. DNT of the basal ganglia, cerebellum, and brain stem are rare. Supratentorial intracortical DNT are invariably linked to long-standing, usually partial epilepsy. In an own series of 19 patients evaluated in the early 1990s, the mean duration of epilepsy was 14 years (range 3–38 years). DNT do not cause neurological deficits, unless located in the basal ganglia or infratentorially [6].

Diagnostics

On MRI, DNT are hypointense on T1-WI and hyperintense on T2-WI. On both sequences, they give the impression of being multimicrocystic/nodular, while true cysts are observed in less than 10% of the cases. Contrast enhancement is not common (20% of the cases). DNT are located intracortically and may involve the adjacent white matter. Mass effect and perifocal edema are absent. The tumor may have been detected on MRI years prior to surgery, without any evident growth (Fig. 2). On CT, the tumor is usually hypodense without contrast enhancement. Calcifications occur in 20–30% of the cases. In tumors situated at the convexity, erosions of the adjacent skull are observed in 50–70% of the patients [25].

Staging and Classification

Characteristic of DNT is its unique glioneuronal element composed of bundles of axons oriented perpendicularly to the cortex and surrounded by small oligodendroglia-like cells. The normal neurons the axons originate from are floating in interstitial flu-

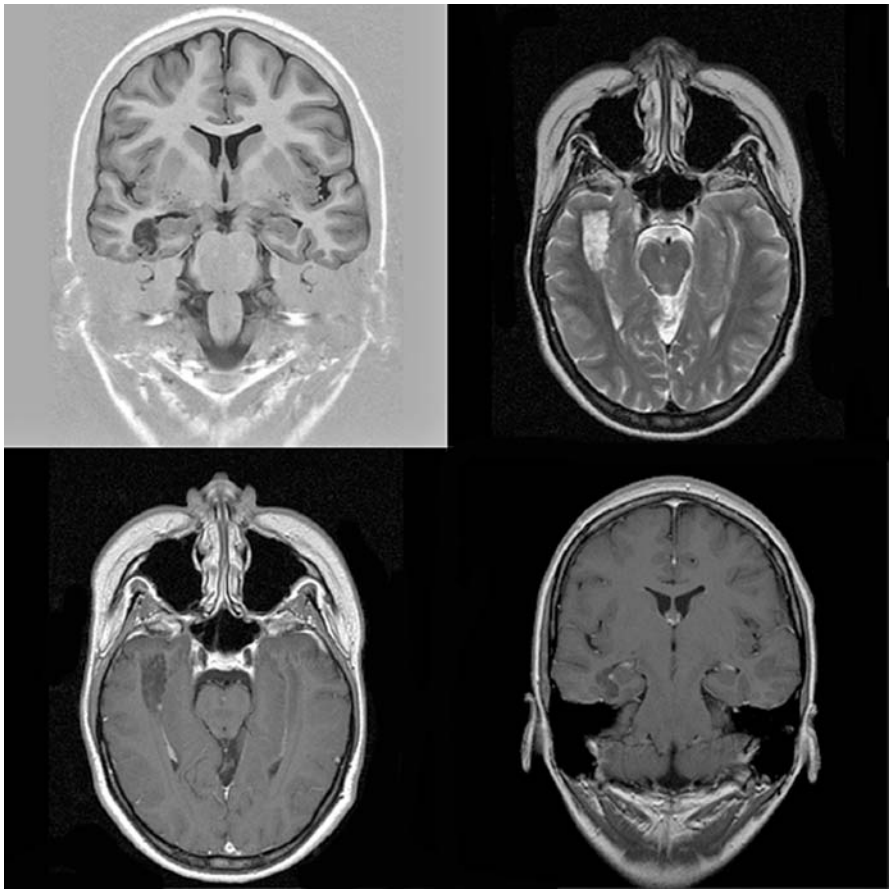


Fig. 2. Dysembryoplastic neuroepithelial tumor of the right temporal lobe. The tumor is hypointense on inversion recovery (upper left), as well as on T1-WI (lower left and right). There is no contrast enhancement (lower left and right). On T2-WI, the tumor is hyperintense (upper right). The tumor appears to be multinodular on all sequences. There is no notable mass effect or peritumoral edema

id. Foci of cortical dysplasia are associated with the tumor. If the above-mentioned simple form of DNT exhibits additional glial nodules resembling gliomas, it is termed the complex form of DNT. Both of these two forms of DNT present with similar clinical behavior. The possible existence of a third form of DNT, a so-called nonspecific form, that is histologically indistinguishable from astrocytoma, oligodendroglioma, and oligoastrocytoma is controversial. DNT corresponds to WHO grade I. Due to their histological characteristics and clinical behavior, DNT are thought to be of dysembryoplastic origin [6].

Treatment

Surgery. Intraoperatively, DNT are of soft, nodular consistency and are well delineated from the surrounding brain tissue. Since these tumors almost always manifest with chronic epilepsy, the principles of epilepsy surgery have to be considered. The rate of complete tumor resection has been reported to be 60–90%, with low perioperative morbidity and mortality [5, 15]. Recurrence/progression rates of DNT are extremely low.

Radiotherapy and Chemotherapy. There is no evidence suggesting radio- and chemotherapy as primary adjuvant therapy, not even in incompletely resected DNT. Malignant DNT transformation following radio- and chemotherapy has been reported [23].

Prognosis/Quality of Life

Following surgery, 60–85% of patients are seizure-free [15]. Completely resected DNT have a very low recurrence rate. Incompletely resected DNT have a very low progression rate. Tumor recurrences and progressions have been reported merely in isolated cases. In recurrences, repeat surgery should be performed before radio- or chemotherapy is considered [23].

Central Neurocytoma

Epidemiology

Central neurocytomas (CN) are very rare tumors. In our series of 254 neuronal and neuronal-glial tumors, CN were diagnosed in 1.6% of the cases. They are indicated to occur in 0.25–0.5% of all intracranial tumors [7]. In our series of 4076 intracranial tumors, CN were diagnosed in 0.09% of the patients. The vast majority of patients with CN are diagnosed in their second to fourth decade of life. There is no gender predominance [7].

Symptoms and Clinical Signs

CN are almost always located in the supratentorial ventricles, with approximately 2/3 of them in the anterior part of the lateral ventricles, near the foramen of Monro. The third ventricle is rarely, the fourth ventricle exceptionally involved [7]. Thus, the clinical symptomatology is usually that of raised intracranial pressure due to hydrocephalus, and is of short duration (a few months). When the third ventricle is involved, hypothalamic-hypophyseal dysfunction may occur. In the rare cases of extraventricular central neurocytoma, focal neurological disturbances may occur [7].

Diagnostics

On T1-weighted MRI, CN are inhomogeneously iso- to hypointense and on T2-WI inhomogeneously iso- to hyperintense. Smaller tumor cysts may be present. Contrast enhancement is somewhat inhomogeneous and moderate to marked. CT features of CN resemble those of T1-weighted MRI. Calcifications are present in approximately 50% of the cases [25].

Staging and Classification

CN consists of a neuronal tumor cell population of uniformly round shape, embedded in clusters in a variably developed fibrillary matrix. The proliferation rate is low. CN corresponds to WHO grade II. Some CN may disclose anaplastic features, such as increased mitotic activity (MIB-1 index >2%), microvascular proliferation, and necrosis. Shorter recurrence-free intervals are more likely to be associated with a MIB-1 labeling index >2% than with other anaplastic features. Extraventricular CN have to be delineated from other extraventricular neoplasms that may contain neurocytic cells in addition to other tumor cells [7].

Treatment

Surgery. Complete tumor resection has been reported to be achievable in approximately 35% of the cases [21]. Due to the intraventricular location and often large tumor size, operative morbidity and mortality may be quite high. The 5-year recurrence-free rate survival is 85% in completely resected tumors, and 46% in incomplete resections [21]. Recurrence

with craniospinal dissemination is very rare [7]. If present, hydrocephalus must be treated adequately.

Radiotherapy. Radiotherapy should be applied to patients with incompletely resected CN. In the entire group of CN, adjuvant radiotherapy improves the 5-year progression-free survival rate of incompletely resected tumors from 46% to 83%, and in the group of atypical CN (MIB-1 index >2%) incompletely resected from 7% to 70% [21, 22]. It is not clear yet whether adjuvant radiotherapy should be done early following incomplete tumor resection, or whether it should be delayed until the first sign of tumor progression on MRI [7, 21]. At least in small tumor remnants, γ-knife surgery can be effectively used early postoperatively while minimizing the risks of conventional radiotherapy [2]. In completely resected CN, whether atypical or not, adjuvant radiotherapy does not seem to improve the recurrence-free survival time [21, 22].

Chemotherapy. The data regarding adjuvant chemotherapy of CN are very limited. Therefore, it should be reserved for tumors which cannot be controlled by surgery and radiotherapy alone.

Prognosis/Quality of Life

Following complete tumor resection, the 5-year survival rate in the entire group of CN is 99%, and in the group of atypical CN, it is 93%. Radiotherapy is of no additional benefit in either of these groups of patients. In incompletely resected CN, the corresponding 5-year survival rates are 86% and 43% without adjuvant radiotherapy, and 90% and 78% with adjuvant radiotherapy. The improvement of the 5-year survival rate of incompletely resected atypical CN with adjuvant radiotherapy seems to be significant [21, 22]. Compared with other neuronal and neuroglial tumors, the recurrence and survival rates of CN are relatively unfavorable. Therefore, long-term clinical and MRI follow-up of these patients is mandatory.

Cerebellar Liponeurocytoma

Epidemiology

Cerebellar liponeurocytoma (CLN) is an extremely rare tumor. Probably fewer than 20 cases have been reported to date [10]. In our series of 4076 successive intracranial tumors, including 254 neuronal and neuroglial tumors, no CLN were diagnosed. The mean age of patients at diagnosis is 50 years. There seems to be a slight male predominance [1].

Symptoms and Clinical Signs

The length of the medical history ranges from several weeks to several years, with a mean of several months. Due to the cerebellar location of CLN, the most frequent symptoms result from a posterior fossa mass effect, such as headaches, vomiting, and dizziness, followed by cerebellar signs, such as ataxia, dysmetria, and nystagmus. Other focal neurological signs, such as cranial nerve deficits, are rare. Occlusive hydrocephalus may be present [1].

Diagnostics

On T1-weighted MRI, the tumors are hypo- to isointense, containing irregular areas of hyperintensity due to tumor lipidization. Contrast enhancement is minimal or moderate and usually irregular. On T2-WI images, CLN are iso- to slightly hyperintense, disclosing irregular areas of hyperintensity due to tumor lipidization. Tumor cysts and hemorrhagic areas are rare. No or only minimal perifocal edema exists. The tumor may extend from the vermis or the cerebellar hemispheres into the subarachnoid cisterns. On CT, the tumor is hypo- to isodense and may disclose markedly hypodense irregular areas due to tumor lipidization. Contrast enhancement is minimal and irregular [1].

Staging and Classification

CLN consists of round isomorph neoplastic cells of advanced neuronal differentiation, resembling CN. Focally, these tumor cells undergo lipomatous differentiation. The mitotic activity is low. Microvascular proliferation and necrosis are absent (but may be present in recurring tumors). CLN corresponds to WHO grade I or II [12].

Treatment

Surgery. Although these tumors are usually described as soft and well delineated from the cerebellum, complete resection of the often large tumors is not always possible, since they may extend into the subarachnoid space and encroach on cranial nerves. Operative morbidity and mortality correspond to other intra-axial cerebellar tumors. Following tumor resection, recurrence-free survival of up to 10 years has been reported. However, recurrences have also been reported to occur as late as 10 years postoperatively [1].

Radiotherapy. There is no evidence suggesting primary adjuvant radiotherapy. Following incomplete tumor resection, progression of residual CLN has been observed with or without additional radiotherapy [1, 10].

Chemotherapy. Adjuvant chemotherapy of CLN has been reported so far in one single case.

Prognosis/Quality of Life

In two of three cases of a series of 15 reviewed CLN, recurrences were noted 10 and 12 years following initial surgery [1]. In the remaining case, early tumor recurrence 1 year postoperatively was reported [10]. All but one of the five reviewed patients with a follow-up of >5 years survived, whether re-operation for tumor recurrence was required or not. The fifth patient died due to complications at surgery for tumor recurrence [1]. Thus, even with an apparently good prognosis of CLN, long-term follow-up is mandatory, regardless of initially complete tumor resection or not.

Paraganglioma of the Cauda Equina

Epidemiology

Paraganglioma of the cauda equina (PCE) is a rare neuroendocrine tumor. In our series of 254 neuronal and neuroglial tumors, these were diagnosed in 3.9% of the cases. They account for 3.5% of all cauda equina tumors [17]. Other CNS localizations of paraganglioma (parasellar region, pineal region, intracerebral, cerebellopontine angle, other spinal regions) are extremely rare. In our series of 4076 patients with intracranial tumors, no other paragangliomas were diagnosed. Most patients with PCE are in their fourth to seventh decade of life (mean age 48 years), with a slight male predominance [17, 26].

Symptoms and Clinical Signs

Clinically, PCE behaves like other slow-growing tumors of the cauda equina. The mean duration of the medical history is about 4 years. Major symptoms are low back pain (90%) and leg pain (70%). Sensory and motor deficits occur in 35% and sphincter dysfunction in 15% of the patients. Paraplegia as well as a vasomotor amine syndrome (as in other paragangliomas) are very rare [17].

Diagnostics

On T1-weighted MRI, PCE is iso- to slightly hypointense and usually discloses marked and homogeneous contrast enhancement. On T2-WI images, the tumor is hyperintense. Serpiginous hypointensities are due to the usually rich vascularisation. Signs of subacute hemorrhage and rarely tumor cyst formation may be present. Routine lumbar spine CT (without contrast administration) is of very limited value because the tumor can be completely missed when indirect signs of intraspinal mass are absent [17].

Staging and Classification

PCE consists of tumorous, uniformly round chef cells disposed in nests and surrounded by an inconspicuous single layer of sustentacular cells embedded in a capillary network. In approximately 50% of these tumors, transition forms between chef cells and mature ganglionic cells and ganglionic cells are present. Electron microscopy discloses neurosecretory granules in the chef cells. Several histological variants of PCE exist, without clinical significance. These tumors correspond to WHO grade I [26].

Treatment

Surgery. Approximately 85% of PCE are attached to the filum terminale. In 15% of the tumors, an infiltrative growth is present. Thus, a complete tumor resection is reported in only 90% of the patients [17]. Surgical complication rates are low. Following complete tumor excision, recurrence rates are estimated to be about 2%. However, recurrences are reported to occur as late as 22 years following surgery. Following incomplete resection, tumor regrowth occurs in about 10% of the patients. Primary arachnoidal seeding or seeding at tumor regrowth is very rare [17, 26].

Radiotherapy. Despite there being no beneficial evidence for radiotherapy, some authors consider it to be indicated in incompletely resected and in recurring tumors [17].

Chemotherapy. The role of adjuvant chemotherapy in PCE is unclear.

Prognosis/Quality of Life

The prognosis of PCE is good. The majority of tumors can be completely extirpated with low perioperative risks, recurrence rates are low, and unlike

in some other paraganglioma, tumor dissemination rates are very low. However, due to a potentially very long-term span to tumor recurrence, long-term follow-up of these patients is advised.

References

1. Alkadhi H, Keller M, Brandner S, Yonekawa Y, Kollias SS. Neuroimaging of cerebellar liponeurocytoma. Case report. J Neurosurg 2001; 95:324–331.
2. Anderson RC, Elder JB, Parsa AT, Issacson SR, Sisti MB. Radiosurgery for the treatment of recurrent central neurocytoma. Neurosurgery 2001; 48:1231–1237.
3. Bachli H, Avoledo P, Gratzl O, Tolnay M. Therapeutic strategies and management of desmoplastic infantile ganglioglioma: two case reports and literature overview. Childs Nerv Syst 2003; 29: 359–366.
4. Choi YH, Kim IO, Cheon JE, Kim WS, Yeon KM, Wang KC, Cho BK, Chi JG. Gangliocytoma of the spinal cord: a case report. Pediatr Radiol 2001; 31: 377–380.
5. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, et al. Dysembryoplastic neuroepithelial tumor: A surgically curable tumor of young patients with intractable partial seizures. Neurosurgery 1988; 23: 545–556.
6. Daumas-Duport C, Pietsch T, Lantos PL. Dysembryoplastic neuroepithelial tumor. In: Keihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC- Press Lyon, 2000:103–106.
7. Figarella-Branger D, Söylemezoglu F, Kleihues P, Hassoun J. Ventral neurocytoma. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC- Press Lyon, 2000:107–109.
8. Geddes JF, Jansen GH, Robinson SF, Gomori E, Holton JL, Monson JP, Besser GM, Revesz T. 'Gangliocytomas' of the pituitary: a heterogeneous group of lesions with differing histogenesis. Am J Surg Pathol 2000; 24: 607–613.
9. Im SH, Chung CK, Cho BK, Lee SK. Supratentorial ganglioglioma and epilepsy: postoperative seizure outcome. J Neurooncol 2002; 57: 59–66.
10. Jankinson MD, Bosma JJ, Du Plessis D, Obgaki H, Kleihues P, Warnke P, Rainov NG. Cerebellar liponeurocytoma with an unusually aggressive clinical course: case report. Neurosurgery 2003: 53: 1425–1427.
11. Johnson JHJ, Hariharan S, Berman J, Sutton LN, RokkeLB, Molloy P, Phillips PC. Clinical outcome of pediatric gangliogliomas: ninety-nine cases over 20 years. Pediatr Neurosurg 1997; 27: 203–207.
12. Kleihues P, Chimelli L, Giangaspero F. Cerebellar liponeurocytoma. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC-Press, Lyon, 2000:110–111.
13. Koerbel A, Prevedello DM, Tatsui CE, Pellegrino L, Hanel RA, Bleggi-Torres LF, Araujo JC. Posterior fossa gangliocytoma with facial nerve invasion: case report. Arq Neuropsiquiatr 2003; 61: 274–276.
14. Lagares A, Gomez PA, Lobato RD, Ricoy JR, Ramos A, de la Lama A. Ganglioglioma of the brainstem: report of three cases and review of the literature. Surg Neurol 2001; 56: 315–322.
15. Luyken C, Blümcke H, Fimmers R, Urbach H, Elger CE, Wiestler OD, Schramm J. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia 2003; 44: 822–830.
16. Luyken C, Blümcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J. Supratentorial gangliogliomas: Histopathological grading and tumor recurrence in 184 patients with a median follow-up of eight years. Cancer 2004: 101: 146–155.
17. Miliaras GC, Kyritsis AP, Polyzoidis KS. Cauda equina paraganglioma: a review. J Neurooncol 2003; 65: 177–190.
18. Nelson JS, Bruner JM, Wiestler OD, VandenBerg SR. Ganglioglioma and gangliocytoma. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC-Press, Lyon 2000:96–98.
19. Nowak DA, Trost HA. Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma): a malformation, hamartoma or neoplasm? Acta Neurol Scand 2002; 105: 137–145.
20. Park CK, Chung CK, Choe GY, Wang KC, Cho BK, Kim HJ. Intramedullary spinal cord ganglioglioma: a report of five cases. Acta Neurochir 2000; 142: 547–552.
21. Rades D, Fehlauer F. Treatment options for central neurocytoma. Neurology 2002; 59: 1268–1270.
22. Rades D, Fehlauer F, Schild SE. Treatment of atypical neurocytomas. Cancer 2004; 100: 814–817.
23. Rushing EJ, Thompson LD, Mena H. Malignant transformation of a dysembryoplastic neuroepithelial tumor after radiation and chemotherapy. Ann Diagn Pathol 2003; 7: 240–244.
24. Selch MT, Goy BW, Lee SP, El-Sadin S, Kincaid P, Park SH, Withers HR. Gangliogliomas. Experience with 34 patients and review of the literature. Am J Clin Oncol 1998; 21: 557–564.
25. Shin JH, Lee HK, Khang SK, Kim DW, Jeong AK, Ahn KJ, Choi CG, Suh DC. Neuronal tumors of the central nervous system: radiologic findings and pathologic correlation. Radiographics 2002; 22: 1177–1189.
26. Soffer D, Scheithauer BW. Paraganglioma. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system: IARC-Press Lyon, 2000:112–114.
27. Tamburrini G, Colosimo C Jr, Giangaspero F, Riccardi R, Di Rocco C. Desmoplastic infantile ganglioglioma. Childs Nerv Syst 2003; 19: 292–297.
28. Taratuto AL, VanDenberg SR, Rorke LB. Desmoplastic infantile astrocytoma. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC-Press, Lyon, 2000:99–102.

29. VanDenberg SR. Desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy. Brain Pathol 1993; 3: 275–281.
30. Vantomme N, Van Calenbergh F, Goffin J, Sciot R, Demaerel P, Plets C. Lhermitte-Duclos disease is a clinical manifestation of Cowden's syndrome. Surg Neurol 2001; 56: 201–204.
31. Wiestler OD, Padberg GW, Steck PA. Cowden disease and dysplastic gangliocytoma of the cerebellum/Lhermitte-Duclos disease. In: Kleihues P, Cavenee WK, eds. World Health Organization Classification of Tumors: Pathology and genetics of tumors of the nervous system. IARC-Press, Lyon 2000:235–237.

Inactive Adenomas

11

John A. Jane Jr, Aaron S. Dumont, Jason P. Sheehan, Edward R. Laws Jr

Epidemiology – 182

Symptoms and Clinical Signs – 182

Diagnostics – 182

Classification and Staging – 183

Treatment – 184
Surgery
Radiotherapy
Medical Therapy

Prognosis/Quality of Life – 185

Follow-up/Specific Problems and Measures – 186
Incidentalomas

Future Perspectives – 186

References – 186

Epidemiology

Pituitary adenomas are benign tumors of the adenohypophysis and are the most common sellar neoplasm. Most tumors remain undiagnosed, and autopsy series have reported a frequency of up to 27% [1]. When data have been pooled from multiple series, however, the frequency appears closer to 11% [1]. Modern CT and MRI series substantiate this latter figure [1–3]. The overwhelming majority of these undiagnosed tumors are microadenomas [1].

Overt adenomas account for about 12–15% of all primary intracranial tumors and are the third most common tumor treated by neurosurgeons after gliomas and meningiomas [4, 5]. Amongst black men, these tumors account for as high as 23% of primary brain tumors [6]. The prevalence of symptomatic pituitary tumors is approximately 20 per 100,000 with an annual incidence of 2 per 100,000 [6, 7]. Inactive adenomas account for approximately 25–35% of all pituitary tumors removed transsphenoidally [8, 9]. Their prevalence has been reported to be 70–90 per million [10]. The incidence appears to increase with age and likely affects men and women equally [9].

Symptoms and Clinical Signs

Patients generally present with signs and symptoms relating to local (sellar) and extrasellar mass effect. Local intrasellar growth may cause varying degrees of pituitary dysfunction. Dysfunction of at least one anterior pituitary hormone can be observed in three-quarters of patients [11]. The cell populations that appear most susceptible are the gonadotrophs [luteinizing hormone (LH) and follicle stimulating hormone (FSH)], followed by the thyrotrophs (TSH), somatotrophs, and corticotrophs. Hypothyroidism may be present in one-third and adrenal insufficiency in as many as one-quarter of patients [11].

Hypogonadism in men causes diminished libido and erectile dysfunction. Female hypogonadism causes amenorrhea and diminished libido. Hypothyroidism can cause an array of symptoms including headache, weight gain, constipation, cold intolerance, depression, and diminished mental acuity. Growth hormone deficiency is characterized by decreased exercise tolerance, increased central adiposity, anxiety, and mood changes. Relative adrenal insufficiency manifests with proximal weakness, fatigue, anorexia, myalgias, arthralgias, gastrointestinal symptoms, and orthostasis. Sudden pituitary insufficiency may occur in the setting of pituitary apoplexy. When acute, cortisol deficiency or Addisonian crisis may cause headache, visual disturbance, hyponatremia, mental status changes, and cardiovascular collapse.

As the tumor expands beyond the confines of the sella, neurological signs begin to manifest. Headache, a common complaint, occurs as the expanding tumor stretches the sellar dura and diaphragma sellae. Suprasellar growth and resultant chiasmatic compression commonly cause varying degrees of visual disturbance and bitemporal hemianopsia. Massive suprasellar growth may, less commonly, cause obstructive hydrocephalus. Lateral growth into the cavernous sinus can result in diplopia and facial pain or numbness. Further lateral growth into the mesial temporal lobe can provoke seizures. An expanding tumor often compresses the pituitary stalk and disrupts the tonic hypothalamic inhibition of prolactin secretion. This 'stalk effect' causes increased prolactin levels mimicking those seen with prolactinomas; however, prolactin levels secondary to stalk effect should be mild and generally do not exceed 150 ng/ml.

Diagnostics

The diagnosis and evaluation of patients begin with a careful neurological and endocrinological history and physical examination. Guided by this evaluation, the subsequent biochemical assessment should screen for preoperative endocrine insufficiency. Reasonable laboratory evaluation includes a baseline PRL, GH, insulin-like growth factor type 1 (IGF-1), ACTH, cortisol, LH, FSH, TSH, thyroxine, testosterone, and estradiol. Of particular importance is the detection of cortisol and thyroid deficiency because failure to establish this preoperatively can have dire consequences. Also prior to the initiation of therapy, patients should have neuro-ophthalmologic testing including fundoscopy, formal visual field testing (automated perimetry), and quantified visual acuity.

The diagnostic imaging modality of choice is MRI. MRI provides multiplanar views and superior anatomical detail of the relationship of the tumor to the optic chiasm and cavernous sinus. In particular, the gadolinium-enhanced sagittal and coronal planes are most helpful in surgical planning. The next generation of high-field magnets offer improved signal-to-noise ratios, allowing excellent spatial resolution and quality without increasing image acquisition times. Compared with standard MR images, the high-field 3-Tesla MR images more accurately correlate with the intraoperative finding of cavernous sinus invasion [12]. A preoperative awareness that the cavernous sinus is invaded can significantly affect the surgical strategy. Knowledge that the cavernous sinus is invaded may encourage surgeons to safely debulk tumors but terminate surgery prior to opening into the sinus. Conversely, if the cavernous sinus is intact, surgeons can more aggressively remove the lateral extensions of the tumors.

The role of CT is limited. Although the bony anatomy is well demonstrated by CT, this imaging modality is not obtained unless there is concern for the diagnosis of craniopharyngioma or other commonly calcifying lesions. In the pediatric population, CT may be useful to assess the extent of aeration of the sphenoid sinus and, therefore, provide important information for surgical planning.

The differential diagnosis of patients with sellar lesions includes craniopharyngiomas, Rathke's cysts, lymphocytic hypophysitis, meningioma, metastatic tumors, aneurysms, and granulomatous processes. Active adenomas can often be diagnosed with a high degree of accuracy using clinical examination and biochemical tests. However, inactive adenomas can be clinically and biochemically more difficult to distinguish from other lesions. The presence of diabetes insipidus, an unusual presentation for an adenoma, should alert the clinician to the possibility of a nonpituitary lesion. In addition, the presence of calcification within the lesion makes craniopharyngioma or meningioma more likely. Although other imaging characteristic and historical features can give clues to the diagnosis, confirmation may not be possible until surgical pathological examination is performed.

Classification and Staging

Using the original histological criteria, pituitary tumors were divided into three types: (1) the acidophilic adenoma (growth hormone secreting), (2) the basophilic adenoma (corticotroph adenoma), and (3) the chromophobic adenoma which was assumed to represent the endocrinologically inactive adenoma. However, it is now recognized that there are many more subtypes, and these can be distinguished using clinical, biochemical, immunohistochemical, and ultrastructural features [13].

Clinically, we define inactive pituitary adenomas (also termed nonfunctioning adenomas) as those tumors that are associated with no syndrome of hypersecretion. These tumors include the gonadotroph adenoma, the null cell adenoma, and the oncocytoma. The gonadotroph adenoma is immunoreactive for the β-subunit of FSH, α-subunit, or β-subunit of LH. Although increased serum levels of FSH, LH, or α-subunit may be encountered, hyergonadism is exceptionally rare. In fact, male patients more often present with a paradoxical hypogonadism. The null cell adenoma produces no elevated serum hormone but may be immunoreactive for α-subunit of the glycoprotein hormones, the β-subunit of LH, FSH, TSH, as well as GH, PRL, or even ACTH. The oncocytoma, a variant of the null cell adenoma, also produces no elevated serum hormone but is composed of enlarged cells with eosinophilic cytoplasm secondary to abundant mitochondrial accumulation.

Some overlap exists with the hormonally active tumors. Although rare, gonadotroph adenomas can be hormonally active and cause hypergonadism [14]. The silent corticotroph adenoma subtypes 1, 2, and 3 have immunohistochemical and ultrastructural concordance with corticotroph adenomas but are clinically inactive and associated with no clinical or biochemical evidence of corticotrophin hypersecretion [15, 16]. Similarly, there are also inactive or 'silent' somatotroph and mammotroph adenomas.

Despite these subcategorizations and exceptions, these tumors are grouped together clinically and considered under the umbrella of inactive (or nonfunctioning) adenomas. Clinically, inactive pituitary adenomas are further distinguished based on size. Tumors less than 10 mm are termed microadenomas, while those larger are macroadenomas (Fig. 1). A more detailed staging and grading system proposed by Hardy also has gained broad acceptance and classifies tumors based on tumor geometry and its effects on the sella turcica [17].

Stage 0 tumors are intrasellar. Stages A, B, and C are differentiated based on their progressive suprasellar growth. Tumors extending into but not beyond the basal cisterns are termed Stage A. When tumors extend more superiorly into the floor of the third ventricle, they are classified as Stage B. Those tumors that extend further to the foramen of Monro are termed Stage C. Stage D tumors have primarily either retrosellar extension or growth along the planum sphenoidale. Stage E tumors are those that mainly invade the cavernous sinus.

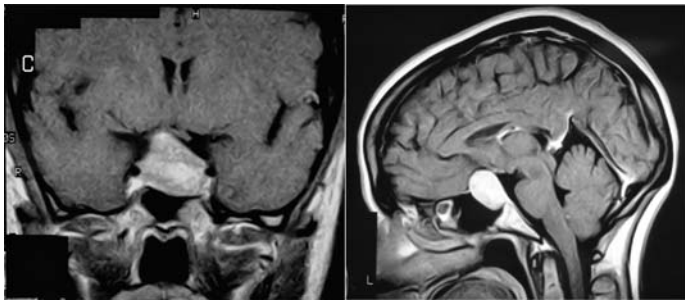


Fig. 1. Pituitary macroadenoma. *Left*, coronal T1-weighted MRI with contrast; *right*, sagittal T1-weighted MRI with contrast of same patient. Note the compression of the optic chiasm on the coronal image

When the sella is of normal appearance and size, tumors are considered grade I. Grade II tumors are those that enlarge the sella but remain enclosed within it. Tumors that cause an enlarged sella with evidence of sellar floor erosion are classified as grade III. Finally, grade IV tumors are those that cause complete sellar erosion.

Treatment

The therapeutic goals include: (1) an improved quality of life and survival, (2) elimination of mass effect and reversal of related signs and symptoms, (3) preservation or recovery of normal pituitary function, and (4) prevention of recurrence of the pituitary tumor. Although most pituitary lesions can be radiologically and biochemically differentiated from benign pituitary adenomas, at times lesions do require definitive histological confirmation and characterization. This effort requires a multidisciplinary team approach that includes endocrinologists, neurosurgeons, neuro-ophthalmologists, radiation therapists, and neuroradiologists.

Surgery

The primary treatment of NFAs is transsphenoidal surgery. The standard technique involves either an endonasal or sublabial approach to the sella with microsurgical resection of the tumor. Pediatric patients, adults with small nares, and patients with very large tumors are often approached via a sublabial incision. In the vast majority of patients, however, the endonasal corridor provides adequate exposure. More recently, endoscopic techniques have been developed that have added to the surgical armamentarium [18, 19]. The endoscope allows for a relatively atraumatic approach to the sella and provides an excellent panoramic view of the regional anatomy and its relationship to the tumor. The angled views allow inspection of suprasellar regions that are simply not possible with the microscope. In our hands, we have found it most useful as an adjunct in verifying the adequacy of microsurgical resection. Studies confirming improved outcomes using the endoscope, however, are not yet available.

Those patients undergoing surgery are administered perioperative hydrocortisone for the first 24 h following surgery. Morning cortisol levels are measured on postoperative days 2 and 3. Patients with serum cortisol levels <8 μg/dl (225 nmol/L) are given steroid replacement. Those with preoperative cortisol deficiency are tapered postoperatively to their preoperative regimen. Patients are also monitored closely for diabetes insipidus by monitoring daily weight, urine specific gravity every 4 h, fluid intake and output, and serum sodium.

Radiotherapy

Prior to the late 1960s, fractionated external beam radiotherapy was considered the first-line treatment for pituitary adenomas. Since the resurgence of the transsphenoidal approach, radiotherapy has assumed an adjunctive role in the surgical management of inactive pituitary adenomas. Reasonable indications include either significant residual after primary resection (particularly within the cavernous sinus) or after second surgery for recurrent tumor [20, 21]. Our practice has been to delay radiation therapy until there is evidence of progressive regrowth of the tumor. In many such cases, repeat transsphenoidal surgery for debulking is recommended prior to radiation therapy.

Fractionated external beam radiotherapy can provide excellent (94%) long-term (10-year) progression-free survival when used in all postoperative patients [22]. When used selectively for recurrent or residual tumors, control at 10 years remains around 90% [23]. When compared with patients who do not undergo irradiation postoperatively, radiotherapy improves the 10-year progression-free survival from 47% to 93% [24]. Although this therapy effectively reduces the risk of recurrent disease, there are several distinct disadvantages [22, 25]. These include the inconvenience of repeated treatments over time, the high incidence of progressive pituitary dysfunction, the albeit small risk of late secondary tumors, delayed cognitive deficits, and slow regression response [26]. Progressive hypopituitarism occurs in 50% by 19 years, and there is an approximately 2% incidence of secondary brain tumor formation within 20 years [22]. Postirradiation optic neuropathy has been reported in about 1–2% of patients [22, 23].

More recently, stereotactic radiosurgery (SRS) has emerged in the treatment of residual or recurrent, hormonally inactive pituitary adenomas. Several systems are available including the gamma knife, linear accelerator-based stereotactic radiosurgery (LINAC SRS), and the cyberknife. These stereotactic devices are typically limited to tumors less than 3–4 cm in diameter and require a margin of 3–5 mm from the optic apparatus. Larger tumors continue to require fractionated external beam radiotherapy. Although the incidence of hypopituitarism, optic nerve injury, and radiation-induced neoplasia appear lower for SRS than fractionated radiotherapy, the long-term risks following radiosurgery are still not precisely known. Moreover, a randomized study of these two modalities has not been performed.

Nevertheless, with short-term follow-up, SRS appears to provide a comparable rate of tumor control or reduction [27–30]. Control of tumor growth is reported in up to 100% of microadenomas and 90% of macroadenomas [29, 31–33]. Volume reduction of greater than 50% has been reported in nearly 30% of patients [28]. Among the less quantifiable benefits of these modalities over conventional fractionated radiotherapy is convenience. With conventional radiotherapy, patients must return for 20–25 treatments as opposed to the single session using radiosurgical methods.

New endocrinopathy and cranial nerve dysfunction have been reported to occur less frequently than with external beam radiotherapy [34]. Indeed, preoperative cavernous sinus cranial neuropathies have actually been reported to improve or resolve in the overwhelming majority [33]. New cranial nerve deficits are rare and appear to occur in less than 5%. New hormonal deficits are, in some series, reported to be quite rare, occurring in less than 5% [28, 34]. However, this is likely a function of the generally short follow-up in each study. In studies with longer follow-up (4.6 years), new hormonal deficits are seen most commonly in thyroid function (24%) and least commonly in cortisol levels (9%) [27]. With even longer follow-up, a higher rate of endocrinopathy may become evident.

Medical Therapy

The medical treatment of inactive adenomas is limited and does not form a part of our routine practice. Nevertheless, some physicians do start patients on dopamine agonists or somatostatin analogues during the interim between initial diagnosis and specialist referral. This practice is based on a few studies with small patient numbers that have reported tumor volume reduction in patients with gonadotroph adenomas [35]. These regimens may be used in the small number of patients who either refuse surgery or are high surgical risks.

Medical therapy, however, has a significant role in the treatment of patients with hypopituitarism. Except for adrenocortical insufficiency and hypothyroidism, replacement is generally not initiated until after surgery because a return of function can be expected in some patients. Growth hormone deficiency is associated with reduced lean body mass, osteoporosis, and an increased mortality from cardiovascular disease [36]. Although no study has clearly demonstrated a benefit to GH replacement therapy, it is our practice to initiate replacement when a deficiency is documented. Low testosterone in male patients is associated with sexual dysfunction as well as decreased muscle and bone mass. Hypogonadism in woman can cause infertility, diminished libido, osteoporosis, and premature cardiovascular disease. The specific medical therapy initiated depends on whether the woman is pre- or post-menopausal and whether she desires fertility.

Prognosis/Quality of Life

Visual field deficits improve in 70–87% and are restored in approximately 25% [8, 37, 38]. Improvement in pituitary deficiency is seen in up to 27% and normalized endocrine function in nearly 15% [8, 37]. Normal pituitary function is preserved in approximately 70%, and 90% of premenopausal women with preserved menstruation preoperatively retain normal menstruation postoperatively [39, 40]. Regular menstruation is restored in those with preoperative amenorrhea in 56% [39].

New endocrine deficits, seen more frequently with macroadenomas, have been reported in up to 40% [37, 38, 40]. Immediate postoperative polyuria occurs in about 30% of patients but is persistent in only 3–10% [41, 42]. Delayed hyponatremia, occurring most often 7–10 days after surgery, is evident in 1–2.4% [41, 42]. Deterioration in vision can be seen in 1–4% [43, 44]. Anatomic complications include nasal septal perforations in 7% and fat graft hematomas in 4% [40, 44]. Postoperative cerebrospinal fluid leaks and meningitis are reported in 0.5–3.9% [44, 45].

Recurrence does develop over time, and in our series, 16% experience recurrent disease at 10 years [43]. However, recurrence requiring repeat surgery occurs in only 6% of patients. Completeness of resection as judged on postoperative MRI can predict recurrence. Residual tumor after transsphenoidal surgery predictably increases the rate of progressive tumor enlargement from 20% to 52.5% [46, 47]. The presence of cavernous sinus invasion on preoperative imaging and the extent of suprasellar residual tumor are significant predictors for tumor enlargement postoperatively [46].

Follow-up/Specific Problems and Measures

Proper follow-up should include an assessment of the need for hormone replacement. Because some return of anterior pituitary function can occur, the mere preoperative presence of endocrinopathy should not deter this assessment. Premenopausal women should be questioned regarding the resumption of menses, and an estradiol level should be drawn from those who have not experienced its return. Testosterone levels in male patients should also be checked. IGF-1 levels may also be drawn. Thyroid

function can be screened using a free serum T4 level. We routinely screen patients while in hospital on the 2nd and 3rd postoperative days for adrenocortical insufficiency. Patients not discharged on hydrocortisone are screened during follow-up only if they report symptoms of adrenal insufficiency. Patients who are sent home on hydrocortisone are evaluated at 6 weeks to 3 months postoperatively and screened using a morning serum cortisol.

Incidentalomas

Because of the increased availability and use of MRI, increasing numbers of patients present with incidentally diagnosed pituitary adenomas. About two-thirds are microadenomas at diagnosis, and these are most often appropriately followed conservatively. Several studies have shown that the risk of significant growth of microadenomas is small. Indeed, the overwhelming majority of microadenomas remain stable, and some even regress [48–50].

Nevertheless, incidentalomas are not necessarily asymptomatic. On further evaluation, approximately 5% will have evidence of visual deficits, and around 15% will have some degree of pituitary dysfunction [51]. More than one-third of incidental macroadenomas will show significant growth on serial imaging [1, 49, 51–53]. The risk of pituitary apoplexy is small and does not appear to be a major factor in determining intervention [54].

Patients with incidentally discovered adenomas must be screened for subclinical hypersecretory syndromes as well as hypopituitarism. An incidental microadenoma should at very least be screened with a serum prolactin level. A more complete endocrine panel or follow-up imaging may not be necessary or cost effective should the patient not have any clinical signs or symptoms of hypopituitarism or hypersecretion [55]. Patients with macroadenomas should be evaluated for hypopituitarism, especially cortisol and thyroid deficiency. These patients should also be evaluated with formal visual field testing. Although our recommendation is to remove these tumors, if clinicians chose to treat these tumors expectantly, follow-up imaging and serial visual field testing should be performed.

Future Perspectives

Gene therapy may play a role in the future treatment of pituitary adenomas. Rats harboring estrogen-induced prolactinomas were treated with a tetracycline regulated adenovirus carrying the gene for tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis). Researchers found a significant reduction in both tumor growth and plasma prolactin levels [56].

Tissue-specific promoters may also play a role in directing gene therapy. Researchers have shown that stereotactically injected recombinant adenoviruses containing the human growth hormone and the human glycoprotein hormone α-subunit promoter can selectively drive the expression of the β-galactosidase gene in cells expressing those hormones [57, 58]. Tissue culture experiments have also indicated that these tissue-specific promoters can selectively drive the expression of toxic gene therapy with excellent cytotoxicity to specific pituitary cell lines. Future in vivo studies evaluating the efficacy of tissue-specific promoters that drive the expression of toxic gene therapy agents are anticipated.

References

1. Molitch ME, Russell EJ. The pituitary 'incidentaloma' [see comments]. Annals of Internal Medicine 1990; 112(12):925–931.
2. Chidiac RM, Aron DC. Incidentalomas. A disease of modern technology. Endocrinology and Metabolism Clinics of North America 1997; 26(1):233–253.
3. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Annals of Internal Medicine 1994; 120(10):817–820.
4. Monson JP. The epidemiology of endocrine tumours. Endocrine-Related Cancer 2000; 7(1):29–36.
5. Percy AK, Elveback LR, Okazaki H, Kurland LT. Neoplasms of the central nervous system. Epidemiologic considerations. Neurology 1972; 22(1):40–48.
6. Gold EB. Epidemiology of pituitary adenomas. Epidemiologic Reviews 1981; 3:163–183.
7. Radhakrishnan K, Mokri B, Parisi JE, O'Fallon WM, Sunku J, Kurland LT. The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. Annals of Neurology 1995; 37(1):67–73.
8. Laws ER, Jane JA Jr. Pituitary tumors–long-term outcomes and expectations. Clinical Neurosurgery. 2001; 48:306–319.
9. Mindermann T, Wilson CB. Age-related and gender-related occurrence of pituitary adenomas.[erratum appears in Clin Endocrinol (Oxf) 1994 Nov;41(5):700]. Clinical Endocrinology 1994; 41(3):359–364.
10. Clayton RN. Sporadic pituitary tumours: from epidemiology to use of databases. Best Practice and Research Clinical Endocrinology and Metabolism 1999; 13(3):451–460.
11. Young WF Jr, Scheithauer BW, Kovacs KT, Horvath E, Davis DH, Randall RV. Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. Mayo Clinic Proceedings 1996; 71(7):649–656.
12. Wolfsberger S, Ba-Ssalamah A, Pinker K, et al. Application of three-tesla magnetic resonance imaging for diagnosis

and surgery of sellar lesions. Journal of Neurosurgery 2004; 100(2):278–286.
13. Kovacs K, Scheithauer BW, Horvath E, Lloyd RV. The World Health Organization classification of adenohypophysial neoplasms. A proposed five-tier scheme. Cancer 1996; 78(3):502–510.
14. Snyder PJ. Gonadotroph cell adenomas of the pituitary. Endocrine Reviews 1985; 6(4):552–563.
15. Horvath E, Kovacs K, Smyth HS, et al. A novel type of pituitary adenoma: morphological features and clinical correlations. Journal of Clinical Endocrinology and Metabolism 1988; 66(6):1111–1118.
16. Lloyd RV, Fields K, Jin L, Horvath E, Kovacs K. Analysis of endocrine active and clinically silent corticotropic adenomas by in situ hybridization. American Journal of Pathology 1990; 137(2):479–488.
17. Hardy J, Vezina JL. Transsphenoidal neurosurgery of intracranial neoplasms. In: Thompson RA, Green JR, eds. Advances in Neurology. New York: Raven Press; 1976:261–274.
18. Cappabianca P, De Divitiis E. Endoscopy and Transsphenoidal Surgery. Neurosurgery 2004; 54:1043–1050.
19. Jho HD, Carrau RL. Endoscopy assisted transsphenoidal surgery for pituitary adenoma. Technical note. Acta Neurochirurgica 1996; 138(12):1416–1425.
20. Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV. Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. Journal of Neurosurgery 1986; 64(5):713–719.
21. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA. Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation – a follow-up study. Clinical Endocrinology 1999; 51(3):281–284.
22. Brada M, Rajan B, Traish D, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clinical Endocrinology 1993; 38(6):571–578.
23. Flickinger JC, Nelson PB, Martinez AJ, Deutsch M, Taylor F. Radiotherapy of nonfunctional adenomas of the pituitary gland. Results with long-term follow-up. Cancer 15 1989; 63(12):2409–2414.
24. Gittoes NJ, Bates AS, Tse W, et al. Radiotherapy for nonfunction pituitary tumours. Clinical Endocrinology 1998; 48(3):331–337.
25. McCollough WM, Marcus RB Jr, Rhoton AL Jr, Ballinger WE, Million RR. Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. International Journal of Radiation Oncology, Biology, Physics 1991; 21(3):607–614.
26. Littley MD, Shalet SM, Beardwell CG. Radiation and hypothalamic-pituitary function. Baillieres Clinical Endocrinology and Metabolism 1990; 4(1):147–175.
27. Feigl GC, Bonelli CM, Berghold A, Mokry M. Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. Journal of Neurosurgery 2002; 97(5 Suppl):415–421.
28. Petrovich Z, Yu C, Giannotta SL, Zee CS, Apuzzo ML. Gamma knife radiosurgery for pituitary adenoma: early results. Neurosurgery 2003; 53(1):51–59; discussion 59–61.
29. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. Journal of Neurosurgery 2002; 97(5 Suppl):408–414.
30. Wowra B, Stummer W. Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow up with magnetic resonance imaging-based volumetric analysis. Journal of Neurosurgery 2002; 97(5 Suppl):429–432.
31. Ganz JC, Backlund EO, Thorsen FA. The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. Stereotactic and Functional Neurosurgery 1993; 61(Suppl 1):30–37.
32. Izawa M, Hayashi M, Nakaya K, et al. Gamma knife radiosurgery for pituitary adenomas. Journal of Neurosurgery 2000; 93(Suppl 3):19–22.
33. Laws ER Jr, Vance ML. Radiosurgery for pituitary tumors and craniopharyngiomas. Neurosurgery Clinics of North America 1999; 10(2):327–336.
34. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for nonfunctioning pituitary adenoma. Neurosurgical Focus 2003; 14(5):Article 9.
35. Vance ML, Ridgway EC, Thorner MO. Follicle-stimulating hormone- and alpha-subunit-secreting pituitary tumor treated with bromocriptine. Journal of Clinical Endocrinology and Metabolism 1985; 61(3):580–584.
36. Carroll PV, Christ ER, Bengtsson BA, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. Journal of Clinical Endocrinology and Metabolism 1998; 83(2):382–395.
37. Colao A, Cerbone G, Cappabianca P, et al. Effect of surgery and radiotherapy on visual and endocrine function in nonfunctioning pituitary adenomas. Journal of Endocrinological Investigation 1998; 21(5):284–290.
38. Kurosaki M, Ludecke DK, Flitsch J, Saeger W. Surgical treatment of clinically nonsecreting pituitary adenomas in elderly patients. Neurosurgery 2000; 47(4):843–848; discussion 848–849.
39. Arita K, Uozumi T, Yano T, et al. Effect of surgery on gonadal function of premenopausal women with pituitary adenomas other than prolactinomas. Endocrine Journal 1996; 43(2):131–138.
40. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. Journal of Clinical Endocrinology and Metabolism 1999; 84(10):3696–3700.
41. Hensen J, Henig A, Fahlbusch R, Meyer M, Boehnert M, Buchfelder M. Prevalence, predictors and patterns of postoperative polyuria and hyponatraemia in the immediate course after transsphenoidal surgery for pituitary adenomas. Clinical Endocrinology 1999; 50(4):431–439.

42. Laws ER Jr, Thapar K. Pituitary surgery. Endocrinology and Metabolism Clinics of North America 1999; 28(1):119–131.
43. Laws ERJJA Jr. Pituitary tumors–long-term outcomes and expectations. Clinical Neurosurgery 2001; 48:306–319.
44. Woollons AC, Balakrishnan V, Hunn MK, Rajapaske YR. Complications of trans-sphenoidal surgery: the Wellington experience. Australian and New Zealand Journal of Surgery 2000; 70(6):405–408.
45. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 1997; 40(2):225–236; discussion 236–227.
46. Greenman Y, Ouaknine G, Veshchev I, Reider G, II, Segev Y, Stern N. Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clinical Endocrinology 2003; 58(6):763–769.
47. Losa M, Franzin A, Mangili F, et al. Proliferation index of nonfunctioning pituitary adenomas: correlations with clinical characteristics and long-term follow-up results. Neurosurgery 2000; 47(6):1313–1318; discussion 1318–1319.
48. Chacko AG, Chandy MJ. Incidental pituitary macroadenomas. British Journal of Neurosurgery 1992; 6(3):233–236.
49. Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. Archives of Internal Medicine 1995; 155(2):181–183.
50. Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W. The 'incidentaloma' of the pituitary gland. Is neurosurgery required?[see comment]. JAMA 1990; 263(20):2772–2776.
51. Feldkamp J, Santen R, Harms E, Aulich A, Modder U, Scherbaum WA. Incidentally discovered pituitary lesions: high frequency of macroadenomas and hormone-secreting adenomas – results of a prospective study. Clinical Endocrinology 1999; 51(1):109–113.
52. Molitch ME. Pituitary incidentalomas. Endocrinology and Metabolism Clinics of North America 1997; 26(4):725–740.
53. Nishizawa S, Ohta S, Yokoyama T, Uemura K. Therapeutic strategy for incidentally found pituitary tumors ("pituitary incidentalomas"). Neurosurgery 1998; 43(6):1344–1348; discussion 1348–1350.
54. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y. A survey of pituitary incidentaloma in Japan. European Journal of Endocrinology 2003; 149(2):123–127.
55. King JT Jr, Justice AC, Aron DC. Management of incidental pituitary microadenomas: a cost-effectiveness analysis. Journal of Clinical Endocrinology and Metabolism 1997; 82(11):3625–3632.
56. Williams JC, Stone D, Smith-Arica JR, Morris ID, Lowenstein PR, Castro MG. Regulated, adenovirus-mediated delivery of tyrosine hydroxylase suppresses growth of estrogen-induced pituitary prolactinomas. Molecular Therapy: the Journal of the American Society of Gene Therapy 2001; 4(6):593–602.
57. Lee EJ, Anderson LM, Thimmapaya B, Jameson JL. Targeted expression of toxic genes directed by pituitary hormone promoters: a potential strategy for adenovirus-mediated gene therapy of pituitary tumors. Journal of Clinical Endocrinology and Metabolism 1999; 84(2):786–794.
58. Lee EJ, Thimmapaya B, Jameson JL. Stereotactic injection of adenoviral vectors that target gene expression to specific pituitary cell types: implications for gene therapy. Neurosurgery 2000; 46(6):1461–1468; discussion 1468–1469.

Functioning Adenomas 12

Dieter K. Lüdecke, Takumi Abe, Jörg Flitsch,
Stephan Petersen, Wolfgang Saeger

Introduction – 191
Dieter K. Lüdecke, Takumi Abe, Jörg Flitsch,
Stephan Petersen, Wolfgang Saeger

Prolactinomas – 191
Stephan Petersen, Dieter K. Lüdecke, Wolfgang Saeger

Epidemiology
Symptoms and Clinical Signs
Diagnostics
Synopsis
Staging and Classification
Synopsis
Treatment
Synopsis
Observation
Medical Treatment
Surgery
Radiotherapy
Follow-up/Specific Problems and Measures
Pregnancy in Women with Prolactinomas

Acromegaly – 196
Stephan Petersen, Dieter K. Lüdecke, Wolfgang Saeger

Classification and Epidemiology
Symptoms and Clinical Signs
Diagnostics
Synopsis
Treatment
Synopsis
Surgery
Medical Treatment
Radiotherapy

Thyrotropin-Secreting Pituitary Adenomas, Thyrotroph Adenomas – 200
Takumi Abe, Dieter K. Lüdecke, Wolfgang Saeger

Introduction and Epidemiology
Symptoms and Clinical Signs
Endocrinological Evaluation
Classification
Radiological Examination
Pathological Studies
Medical Treatment

Surgery
Prognosis/Quality of Life
Future Perspectives

Cushing's Disease – 202
Jörg Flitsch, Dieter K. Lüdecke, Wolfgang Saeger

Epidemiology
Symptoms and Clinical Signs
Diagnostics
Classification
Treatment
Surgery
Radiotherapy
Pharmacotherapy
Prognosis/Quality of Life
Follow-up/Specific Problems and Measures
Future Perspectives

References – 206

Introduction

Dieter K. Lüdecke, Takumi Abe, Jörg Flitsch, Stephan Petersen, Wolfgang Saeger

Pituitary adenomas with clinically relevant hypersecretion comprise approximately 40% of all pituitary adenomas. The most frequent is the prolactinoma, which for 25 years has mostly been treated primarily by dopamine agonists. A parallel comparison of pretreated and only surgically treated patients showed significant differences which are of importance to the surgeon and pathologist. In acromegaly, specific medications with somatostatin analogues became available 20 years ago. In most cases with or, more and more rarely, without pretreatment, transnasal microsurgery is performed with the option of a long-lasting clinical remission. In incompletely resectable adenomas, the discussed indication for surgery lies in the reduction of the radiation field. New pharmaceutical methods challenge the surgical options. Thyrotropinomas are extremely rare and may also be successfully treated by somatostatin analogues. All these adenomas have tumor markers with a short half-life in plasma and may be checked during or shortly after surgery. In Cushing's disease, measurement of ACTH and cortisol the day after surgery mostly clarifies the effect of surgery. Nowadays, the diagnosis and follow-up of Cushing's disease can easily be done with just saliva cortisol. These active adenomas have in common that the results of different treatment options can be compared by exact criteria. Less than 1 mm functioning adenoma which is far beyond the sensitivity of the best MRI may produce the full clinical syndrome. The diagnostic and therapeutic approaches are so different that these adenomas can be described only separately.

Prolactinomas

Stephan Petersen, Dieter K. Lüdecke, Wolfgang Saeger

Epidemiology

By analysis of a stable population around Stroke-on-Trent, UK, with 1 million inhabitants and a single referral centre, R.N. Clayton estimated the incidence and prevalence of prolactinomas during a 10-year period (1988–1998) to be 6–10 cases/million/year and 60–100 cases/million, respectively. Based on clinical endocrine activity, prolactinomas were found to be the most frequent type of pituitary adenomas, accounting for 50.1% of 2252 patients in Italy and 39.0% of 2230 surgical cases in San Francisco. Whereas the lower incidence in surgical patients probably reflects the significant percentage treated by medication alone, both studies may overestimate the incidence of prolactinomas due to the inclusion of nonfunctioning adenomas with hyperprolactinemia caused by pituitary stalk disturbance. Using stricter histological criteria, two large studies from North America found true PRL cell adenomas in only 27–27.5% of surgical cases, nearly equal to nonfunctioning adenomas with 25–26%.

Symptoms and Clinical Signs

The clinical features of prolactinomas are composed of the endocrine effects due to the hyperprolactinemic state and local tumor mass effects [1]. In adult premenopausal women, central hypogonadism may lead to ovulatory dysfunction with anovulation and infertility, as well as menstrual dysfunction with oligo/amenorrhea (>90% of patients). Consecutive estrogen deficiency causes vaginal dryness, edema, and osteopenia. Acne, hirsutism, and obesity may result from an imbalance between androgen and estrogen levels. Decreased libido and mood effects are related to estrogen deficiency and hyperprolactinemia. Galactorrhea is a common symptom, being present in approximately 80% of the women. Premenopausal women usually seek medical attention because of their hormonal symptoms long before the tumor has grown large. In the adult postmenopausal woman, the only expression of hyperprolactinemia may be decreased libido and galactorrhea. The most common clinical symptoms in the adult male relate to central hypogonadism and include decreased libido and potency, infertility due to oligospermia, and osteopenia. Gynecomastia and galactorrhea are unusual. Local tumor mass effects include severe headache, visual field abnormalities, and partial or complete hypopituitarism, each being observed in about one-third of male patients. Tumors invading into the cavernous sinus may entrap the cranial nerves III, IV, and VI, with the unusual occurrence of ophthalmoplegias. These patients may rarely also develop pain or hyperesthesia in the distribution of the first division of the trigeminal nerve. Extrasellar extension may cause hydrocephalus and temporal lobe epilepsy.

Diagnostics

Synopsis

In addition to prolactinomas, various other causes of a hyperprolactinemic state must be considered. The diagnostic steps should include the exclusion of pregnancy, the exclusion of offending drugs, and the exclusion of a variety of functional causes. If hyperprolactinemia persists despite adequate man-

agement of a reversible cause, MRI should be performed. In the absence of clinical symptoms, macroprolactinemia should be considered.

PRL is secreted episodically, so that some levels during the day may be above the normal range established for a given laboratory. Furthermore, stress may induce a 2- to 3-fold rise in PRL levels that lasts less than an hour. Once hyperprolactinemia is confirmed, a number of etiologies have to be considered. In premenopausal women, pregnancy should be excluded. Postpartum PRL levels remain elevated in lactating women. Sexual breast stimulation and breast suckling may also cause a reflex release of PRL in the nonlactating condition. The most common causes of nonphysiological hyperprolactinemia are medications that alter the central bioaminergic pathways. Neuroleptics are dopamine receptor blockers, which uniformly result in elevated PRL levels, generally to less than 100 ng/ml. Tricyclic antidepressants cause modest hyperprolactinemia in about 25% of patients, whereas monoamine oxidase inhibitors may cause only minimal elevations of PRL levels. The antihypertensive drugs α-methyldopa and reserpine may cause a moderate increase in PRL levels. In patients taking verapamil, PRL levels are found elevated in up to 8.5% of patients. Recently, galactorrhea caused by a significant increase of PRL levels was observed in patients treated with protease inhibitors. Chronic abuse of cocaine or opiates has been associated with mild hyperprolactinemia. Hyperprolactinemia is also found in a number of medical conditions. Elevated PRL levels are found in most patients with end-stage renal disease. Furthermore, about one-quarter of patients with renal insufficiency not requiring dialysis have PRL levels in the 25–100 ng/ml range. Basal PRL levels may also be increased in patients with alcoholic or nonalcoholic liver cirrhosis. Primary hypothyroidism is associated with hyperprolactinemia, although PRL levels exceed 25 ng/ml in only 10% of patients. Adrenal insufficiency has rarely been reported as a cause of hyperprolactinemia. Elevated PRL levels have also been found after chest wall and cervical cord lesions, after mastectomy and thoracotomy, and after spinal cord injuries. Ectopic production of PRL is exceedingly rare.

A careful history and physical examination, screening blood chemistry, thyroid function test, and a pregnancy test will exclude virtually all causes of hyperprolactinemia mentioned so far. Stimulation and suppression tests give nonspecific results and have largely been abandoned. If a reversible cause of elevated PRL levels is found, its treatment or discontinuation should allow resolution of the hyperprolactinemia. Otherwise, a radiologic evaluation by MRI of the hypothalamic-pituitary region must be performed to detect an underlying prolactinoma. MRI will also reveal hypothalamic or pituitary stalk disease where the hyperprolactinemia is due to a disturbance of the neuroendocrine control of PRL secretion. In these patients with craniopharyngioma, empty sella, Rathke's cleft cyst, or nonfunctioning pituitary adenoma, PRL levels rarely exceed 250 ng/ml, with PRL levels below 100 ng/ml in the majority of cases. In the vast majority of macroprolactinomas, PRL levels are well above 250 ng/ml, with virtually all above 100 ng/ml. A specific caution is needed when two-site immunoradiometric assays or chemiluminometric assays are used [2]. Incubation with extremely high PRL concentrations saturates both antibodies and prevents sandwich formation ('high-dose hook effect'). Patients with macroprolactinomas and very high PRL levels may seem to have only moderately elevated levels. Therefore, confusion with nonfunctioning macroadenomas associated with pituitary stalk disease may arise. When suspected, PRL levels should be remeasured at a 1:100 dilution. In the absence of any clinical symptoms, macroprolactinemia should be considered as a potential cause of increased PRL levels [3]. The major circulating form of prolactin is little PRL with a molecular weight of 23 kDa, the remainder consisting of big PRL (MW 50 kDa) and big-big PRL (MW>150 kDa). However, in 10–26% of hyperprolactinemic populations, a high proportion of big-big prolactin is found in the serum. Several reports suggest that anti-PRL autoantibodies bound to little PRL contribute to big-big PRL and therefore macroprolactinemia. The diagnosis is made mainly by two methods, a polyethylene glycol method and gel chromatography. Repeated hormone or neuroradiological examinations and unnecessary treatments should be avoided in patients with proven macroprolactinemia (Fig. 1).

Staging and Classification

Synopsis

Prolactinomas are classified into micro- and macroprolactinomas depending on their size. These may represent two different disease entities. Malignant prolactinomas are exceedingly rare.

Microprolactinomas are less than 10 mm in size, whereas macroprolactinomas are at least 10 mm in size. Macroprolactinomas can be intrasellar or can extend into the extrasellar neighborhood and invade the dura, sphenoid bone, cavernous sinuses, suprasellar cisterns, and adjoining parts of the brain. Careful studies of the natural history of patients who refused treatment revealed a very low risk of approximately 6.5% for the progression of microprolactinomas into macroprolactinomas. These may therefore be considered two separate disease entities. In agreement, virtually all prolactinomas found at autopsy of subjects

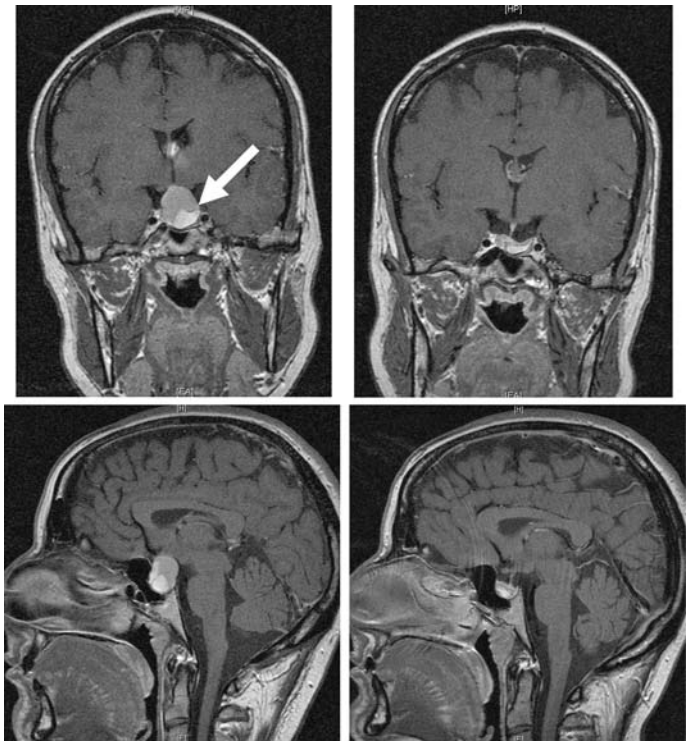


Fig. 1. Coronary (*upper panel*) and sagittal (*lower panel*) MRI sections of a patient with macroprolactinoma before (*left*) and after (*right*) therapy with a dopamine agonist. Significant tumor shrinkage is observed

not suspected of having pituitary disease while alive were microprolactinomas. True malignant prolactinomas with distant metastasis are exceedingly rare.

By histochemical analysis, frequent sparsely granulated PRL cell adenomas (95% of PRL-producing adenomas) and rare densely granulated prolactin cell adenomas (3%) but also rare acidophil stem cell adenomas (2%) can be differentiated.

Treatment

Synopsis

Observation may be an option in patients with microprolactinomas in the absence of any relevant clinical symptoms. In all other patients with prolactinomas, medical therapy is the initial treatment of choice. Due to its efficacy and tolerability, cabergoline may be the preferred dopamine agonist except for pregnant women, in whom bromocriptine has the most extensive safety record. Transsphenoidal surgery remains an option in patients with resistance to or intolerance of dopamine agonists.

Observation

Observation may be considered as an option for the treatment of microprolactinomas. Indications for active treatment are tumor progression and symptoms of hyperprolactinemia. However, it has been clearly demonstrated that the vast majority of microprolactinomas will not enlarge. In the absence of specific symptoms, these tumors may be closely followed without any specific treatment. In the premenopausal woman, estrogen deficiency should be substituted to prevent the development of osteopenia. Follow-up may be limited to serial PRL levels, as progression of the tumor without an increase in PRL levels is very unlikely. As macroprolactinomas follow a more aggressive course, these tumors should always be treated.

Medical Treatment

Medical therapy is employed as the primary therapy of prolactinomas in most centers now. It is based on the use of dopamine agonists. Worldwide, the most experience has been gained with bromocriptine. In several large studies, bromocriptine was able to normalize PRL levels in 70–80% of treated patients. A return of ovulatory menses or normoprolactinemia was observed in 80–90% of patients. The onset of bromocriptine effects is rapid and usually occurs within hours. In premenopausal women, galactorrhea ceases in a few weeks, and ovulatory cycles may return within 2–3 months. In men, restoration of normal sexual/reproductive functions may take 3–

6 months. In addition to its effects on PRL levels, bromocriptine often leads to a reduction in lactotroph size and to tumor size reduction. In macroprolactinomas, a significant tumor reduction of at least 25% was found in 68.8% of 112 patients studied in a total of 10 studies. Long-term treatment for up to 10 years was well tolerated. Dopamine agonist treatment induces severe alterations of tumor tissue. The cells become dramatically smaller. The cytoplasm shrinks more markedly than the nuclei so that the nuclear: cytoplasmic ratio is increased, and the adenoma appears as small-cell tumor. The nuclei are irregular and hyperchromatic. In patients with longer-term treatment, adenomas develop extensive perivascular and interstitial fibrosis. Single-cell necroses are rarely found. Most series suggest that bromocriptine-induced fibrosis has little effect on later surgical results for microprolactinomas. However, some studies suggest that bromocriptine pretreatment for more than 6–12 weeks may limit complete tumor removal in macroprolactinomas.

Normal PRL levels are maintained in 10–20% of patients stopping treatment. Furthermore, tumor size may remain stable after withdrawal of treatment, especially in patients with marked tumor size reduction during the initial treatment. Substantial visual field improvements were found in 80–90% of patients treated with bromocriptine, with significant changes occurring in some patients within 24–72 h after initiation of therapy. Therefore, even in the patients with macroprolactinomas and visual field abnormalities, immediate surgical decompression is not necessary. The most common side-effects of bromocriptine are nausea (50% of patients) and vomiting (10–15%). Other, mostly self-limiting side-effects include headaches, orthostatic hypotension, nasal congestion, and constipation. Rare symptoms mostly seen with high doses of bromocriptine are digital vasospasm, alcohol intolerance, and psychotic reactions. Symptoms of the latter include hallucinations, delusional ideas, and mood changes. They usually resolve within 72 h of stopping the drug. Rarely, CSF rhinorrhea is observed, owing to tumor regression. Starting with 1.25 mg once daily with a snack at bedtime minimizes the side-effects. The dose is gradually increased to 2.5 mg bid, always taken with meals. Doses higher than 7.5 mg are rarely necessary. In tumors showing an initial response to treatment, regrowth often points to noncompliance.

Second-generation dopamine agonists are currently licensed in many countries for the treatment of prolactinomas. Due to their fewer side-effects and ease of application, they may be preferable as the primary treatment in most patients. Cabergoline has a very long half-life and can be given orally (0.25–1 mg) one to three times a week. Treatment should be started with 0.25–0.5 mg weekly, with the dosage gradually being increased. To minimize side-effects, cabergoline should be taken at bedtime. In a large prospective, double-blind comparison study, cabergoline was found to be at least as effective as bromocriptine in lowering PRL levels, but with substantially fewer side-effects. Furthermore, cabergoline was found to be very effective in reducing tumor size. In a small study of 23 macroprolactinomas without long-term bromocriptine pretreatment, 91% exhibited a greater than 25% reduction in tumor size. In another study of 107 macro- and 97 microprolactinomas, a greater than 30% reduction in tumor size was noted in 71% and 53.6% of patients, respectively. In patients with normalized PRL levels and no evidence of tumor rest, a withdrawal of cabergoline treatment can be safely tried during long-term follow-up. A recent study of 105 micro- and 70 macroprolactinomas found low recurrence rates of 31% and 36%, respectively, during the follow-up of at least 18 months after withdrawal of cabergoline [4]. For inclusion in the study, PRL levels had to be normalized and tumor size reduced by at least 50% during previous treatment. Several studies have demonstrated that cabergoline may be effective in patients who were previously shown to be resistant to treatment with bromocriptine or quinagolide [5]. Quinagolide is a non-ergot, long-acting dopamine agonist. Its efficacy is comparable to bromocriptine, with fewer side-effects. It is applied once daily at bedtime in a dose of 75–300 µg. Approximately 50% of patients resistant to bromocriptine were found to respond to quinagolide.

Surgery

In most centers, surgery is used as an adjunctive therapy for patients who are intolerant of or resistant to medical therapy. In patients who refuse therapy with dopamine agonists or patients with other specific conditions, surgery may also be used as primary therapy. In most patients, transsphenoidal surgery is the surgical procedure of choice [6]. Transcranial surgery is reserved for patients with macroprolactinomas with extensive extrasellar extension. The surgical results depend on the size and the extent of the tumor, but also to a large degree on the expertise of the neurosurgical team. In virtually all cases, prolactin levels fell promptly after tumor removal. In specialized centers, PRL levels may even be measured intraoperatively to check for complete resection of the adenoma. In a large meta-analysis of 34 publications, normalization of PRL levels by 1–12 weeks following surgery was found in 74% of microprolactinomas and 32% of macroprolactinomas. Tumor recurrence, evidenced by hyperprolactinemia, occurred in 21% and 20% of these microprolactinomas and mac-

roprolactinomas, respectively. Because most recurrences were observed within the first year after surgery, they have been attributed to regrowth of tumor remnants. Incomplete tumor removal may be due to invasion of surrounding tissues, as has been found in 69% of microprolactinomas. Based on these surgical cure rates and recurrence rates, the long-term cure rates following surgery for micro- and macroprolactinomas were calculated as 58% and 26%, respectively. In patients with giant prolactinomas and those with considerable invasion of the cavernous sinus, surgery is virtually never curative.

Radiotherapy

Experience with radiotherapy for the treatment of prolactinomas is limited in comparison to the other two treatment modalities. In most studies, only a small percentage of patients reached normal PRL levels, and then only after a latent period of several years. Hypopituitarism is a major side-effect occurring in the majority of patients during long-term follow-up. Other potential side-effects include cerebrovascular accidents, neurologic dysfunction, second malignancies, brain necrosis, and optic nerve damage. In most centers, radiotherapy is reserved for the treatment of very aggressive tumors, when treatment with dopamine agonists and surgery has failed. Stereotactic radiotherapy may be more effective and have fewer side-effects, but experience is very limited at this point.

Follow-up/Specific Problems and Measures

Pregnancy in Women with Prolactinomas

In an analysis of over 6000 pregnancies, bromocriptine has not been found to increase the risk of spontaneous abortions, ectopic or multiple pregnancies, trophoblastic disease, or congenital malformations when treatment is stopped at the first sign of pregnancy. Long-term follow-up of children born by mothers taking bromocriptine in this fashion did not reveal any ill effects. Experience is naturally more limited for cabergoline, with no increased risk of preterm, ectopic, or multiple birth deliveries, or malformations being observed in 265 pregnancies. Most centers still prefer bromocriptine to restore fertility, although pregnant women may be reassured when taking cabergoline prior to conception. The rising estrogen levels during pregnancy have a marked stimulatory effect on the normal lactotrophs. Hypertrophy and hyperplasia result in an up to 1.5-fold increase in pituitary size. Such an increase in size may also occur with prolactinomas, mostly in the second and third trimesters. In a meta-analysis of 19 publications, 1.2% of 363 pregnant women with microprolactinomas and 24% of 82 pregnant women with macroprolactinomas had symptoms of tumor enlargement (headaches and/or visual disturbances). In 69 women with macroprolactinomas treated with surgery or radiotherapy prior to pregnancy, the risk of symptomatic tumor enlargement was considerably attenuated, being 4% in that compilation. Bromocriptine has been used successfully during pregnancy to reduce symptomatic tumor enlargement, with no ill effects on the infant, but experience is limited so far.

In women with microprolactinomas or small infrasellar or inferiorly extending macroprolactinomas, therapy is discontinued following conception and reinitiated only if symptoms of tumor growth develop. In women with larger macroprolactinomas, one should advocate the patient to aim at maximal tumor size reduction by medical treatment prior to pregnancy. At very least, responsiveness of tumor size to medical treatment should be established. Following conception, treatment with bromocriptine may be stopped or continued during pregnancy, depending on the aggressiveness of the tumor. If symptoms of tumor regrowth develop in the former, therapy may be reinitiated. If medical treatment fails, surgery is recommended. A more conservative approach would be to perform a surgical debulking prior to pregnancy, thereby greatly reducing the risk of symptomatic tumor enlargement during pregnancy. This may be an option especially in patients with tumors unresponsive in size to medical treatment. In patients with macroprolactinomas, once or twice monthly visual field testing is recommended during pregnancy. Postpartum PRL levels and tumor size may be reduced compared with values before pregnancy, possibly due to minor infarctions in the tumor. Breast feeding is possible in women with prolactinomas.

References

1. Molitch ME. Disorders of prolactin secretion. Endocrinol Metab Clin North Am 2001; 30:585–610.
2. Barkan AL, Chandler WF. Giant pituitary adenoma with falsely low serum prolactin: the pitfall of the 'high dose hook effect'. Neurosurgery 1998; 42:913–915.
3. Hattori N. Macroprolactinemia: a new cause of hyperprolactinemia. J Pharmacol Sci 2003; 92:171–177.
4. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. NEJM 2003; 349:2023–2033.
5. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L,

Lombardi G. Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. JCEM 2000; 85:2247–2252.
6. Lüdecke DK, Herrmann H-D, Hörman C, Desaga U, Saeger W. Microsurgery and combination with dopamine agonist treatment of prolactinomas. In: Prolactin and prolactinomas, eds. Tolis G et al., Raven Press, New York, 1983:453–467.

Acromegaly

Stephan Petersen, Dieter K. Lüdecke, Wolfgang Saeger

Classification and Epidemiology

Acromegaly is defined by the excessive secretion of growth hormone (GH) into the circulation, leading to its typical clinical features. Most commonly, it is due to a GH-secreting pituitary adenoma [1]. Pituitary carcinoma may be associated with acromegaly, but this is very uncommon. Acromegaly caused by tumors other than a GH cell pituitary tumor accounts for less than 1% of patients. Ectopic production of GHRH may arise from carcinoid tumors of the lung, pancreas, and gastrointestinal tract. Furthermore, entopic GHRH production by intracranial tumors such as hypothalamic hamartomas has been reported. Even more rarely, ectopic GH production by pancreatic tumors, breast and bronchial carcinomas, and ovarian tumors has been demonstrated in a few cases. Rare familial acromegaly syndromes include the multiple endocrine neoplasia 1 (MEN-1) syndrome, McCune-Albright syndrome, Carney syndrome, and isolated familial somatotropinomas of unknown origin.

The prevalence rates of acromegaly reported so far are remarkably similar, being 5.3–6.9/100,000 inhabitants in different countries like the UK, Ireland, Spain, and Sweden. The yearly incidence rates described in these countries were 0.3–0.4/100,000 inhabitants, equivalent to approximately 240–320 new cases in Germany every year. The peak occurrence was observed in the 5th decade. If a GH cell adenoma develops before the epiphyseal growth plates are fused during adolescence, excess growth may result. Therefore, this disease is specifically termed gigantism. Whereas some studies did not find any sex predominance of acromegaly, others reported a female preponderance with a sex ratio of 1.8–2.0:1. Comparisons of the incidence of various types of pituitary adenomas demonstrated GH cell adenomas in 21.4% of 2252 patients from Italy and 16.4% of 2230 surgical cases from the USA, based on the clinical activity of the tumors. By immunohistochemical analysis, Terada and co-workers described a similar incidence. They found pure GH cell adenomas and mixed GH and PRL cell adenomas in 13.1% and 6.2% of cases, respectively.

Symptoms and Clinical Signs

Acromegaly is characterized by progressive somatic disfigurement and a wide range of systemic manifestations. Patients generally exhibit coarsened facial features, exaggerated growth of hands and feet, and soft-tissue hypertrophy. Skin changes include skin tags and acanthosis nigricans. Many patients complain about increased 'oily' sweating. Cardiovascular features are biventricular hypertrophy, diastolic dysfunction, arrhythmias, hypertension, and endothelial dysfunction, with coronary heart disease and congestive heart failure as possible consequences. Respiratory disease is characterized by macroglossia, upper airway obstruction, and ventilatory dysfunction. Sleep apnea syndrome appears to be common in acromegaly and is probably a cause of major morbidity in these patients. Metabolic changes include insulin resistance, impaired glucose tolerance, and diabetes mellitus, as well as hypertriglyceridemia. Skeletal manifestations are a leading cause of morbidity and functional disability in patients with acromegaly. The acromegalic arthropathy affects both axial and peripheral sites and is generally noninflammatory. A symptomatic carpal tunnel syndrome is a common condition. An increased risk for malignancies in acromegaly is a matter of debate. Acromegaly clearly stimulates the development of benign colon adenomatous polyps. Such colon adenomas are thought to identify patients at increased risk of developing colonic cancer. However, there are conflicting data about the incidence of colon carcinomas in acromegaly. Whereas most studies point to an increased morbidity and mortality, some investigators found similar rates as in their control populations. Obviously, the choice of controls will largely affect the interpretation of the data. We advise patients to undergo routine full-length colonoscopy at the age of 50 years, with further examinations every 3–5 years, depending on the presence of colon polyps. There is no clear evidence for an increased risk of other malignancies. However, the rate of benign tumors in various tissues is increased. Thyroid goiter is considered one typical aspect of the visceromegaly developing in acromegaly. The chance of developing thyroid nodules increases with longer disease duration. Furthermore, acromegaly predisposes to benign prostate hypertrophy and to uterine leiomyomas.

Whereas all the symptoms described above are attributed to the GH and IGF1 excess, others may be due to the mass effects of the pituitary adenoma. These include visual field defects caused by compression of the optic nerve tract or chiasm, cranial nerve

Fig. 2. Clinical features of acromegaly. The patient exhibits typical coarsened facial features (*left panel*), especially when compared to an old photograph taken 20 years earlier (*right panel*)

palsies, headache, hydrocephalus, and various degrees of pituitary insufficiencies (Fig. 2).

Diagnostics

Synopsis

Random GH and IGF1 levels may be used as screening parameters in patients with suspected acromegaly. An adequate age- and gender-matched reference range must be used for interpretation of IGF1 levels. If acromegaly is not excluded by determination of basal levels, an oral glucose tolerance test with measurement of GH levels will help to make the diagnosis.

Current guidelines recommend a fasting or random GH and IGF1 measurement in patients with suspected acromegaly [2]. If GH is less than 0.4 ng/ml and IGF1 is in the age- and gender-matched normal range, acromegaly is excluded in patients with no other intervening disease. Otherwise, an oral glucose tolerance test is recommended with 75 g glucose and subsequent measurement of GH every 30 min over 2 h. GH levels should be suppressed below 1 ng/ml at least at one time-point for acromegaly to be excluded. With the introduction of newer, more sensitive GH assays, it is anticipated that lower cut-off values will be defined in the future. It should be considered that systemic diseases, including catabolic states, hepatic or renal failure, and malnutrition might result in lowered IGF1 levels. On the other hand, false-positive results with the failure of normal GH suppression during oGTT may occur in patients with diabetes mellitus, liver disease, renal disease, anorexia nervosa, and during adolescence. Therefore, the evaluation of typical clinical signs and both GH and IGF-1 levels is important, especially in patients with the above-mentioned diseases. Repeat determination of IGF1 may be helpful when IGF1 levels are borderline, or clinical and biochemical data are not congruent. Stimulation by TRH, GHRH, or GnRH, measurement of IGF-BP3, and studies of spontaneous GH secretion do not offer additional information for the diagnosis. In the rare case of suspected ectopic GHRH production, circulating GHRH levels may be measured. For follow-up of patients with acromegaly, the same criteria used for the diagnosis are applied to define cure.

The size and extension of an underlying pituitary adenoma are documented by MR tomography. Gadolinium-enhanced coronal and sagittal views in 2 mm slices will give optimal results. In the case of a macroadenoma with a diameter of more than 1 cm, an ophthalmologic examination must be carried out to determine visual field defects. Furthermore, other insufficiencies of the pituitary axis should be investigated in these patients. In contrast, visual field defects or pituitary axis insufficiencies are very rare in patients with microadenomas (diameter of 1 cm). Prior to invasive therapy, co-morbidities should be investigated to determine the individual risk of the patients for the procedure planned.

Treatment

Synopsis

Treatment options for acromegaly include surgery, medical therapy, and radiation. Especially in the case of microadenomas, transsphenoidal resection may allow normalization of biochemical parameters in the vast majority of patients. In all other cases, medical treatment may be used as adjunctive therapy. Dopamine agonists are not very effective, but of-

fer oral availability and low costs. Somatostatin analogues have been studied for many years. Long-release formulations effectively lower GH secretion. Furthermore, they may reduce tumor size. GH antagonists are very effective to normalize IGF1 levels. However, tumor growth due to blockade of GH feedback at the pituitary level remains a concern. Both efficacy and side-effects of irradiation are a matter of debate. In most centers, irradiation is considered an adjunctive therapy to surgical and medical interventions.

Surgery

Selective transsphenoidal surgery is the treatment option offered first to most patients with acromegaly due to a GH-secreting pituitary adenoma [3]. Only very large tumors extending above the sellar region may require a primary or secondary transcranial approach. The aim of the surgical procedure should be complete resection of the GH cell adenoma, with preservation or subsequent restoration of pituitary function. The surgical success rates vary greatly depending on the surgeon's experience. Therefore, especially difficult cases should always be operated on in specialized centers. Criteria suggested for such centers include peer-reviewed publication of surgical results and an annual surgical activity of more than 25 cases/surgeon. Other factors influencing the effectiveness of surgery are size and extension of the tumor mass and preoperative GH levels. Tumor resection generally results in rapid reduction of GH levels. Clinical symptoms improve in >90% of patients, and visual field defects in >80%. However, if the rigorous biochemical criteria described above are used to evaluate the success rates of surgery, approximately 80–90% of patients with microadenomas but fewer than 50% of patients with macroadenomas are cured. In patients with surgically accessible residual or recurrent tumor remnants visualized on MRI, reoperation by a specialized pituitary surgeon may be considered. Intraoperative measurements of GH levels can help to confirm complete resection of the tumor, but experience is limited to a few specialized centers so far. Other techniques introduced recently include neuronavigation, endoscopy, and intraoperative MRI, but definitive data on the impact of these procedures are not yet available. Possible side-effects of surgery are newly developed hypopituitarism or visual field defects, permanent diabetes insipidus, hemorrhage, and meningitis. Cerebrospinal fluid leak is treated by lumbar drainage and may require reoperation to seal the sellar defect. Although these complications may occur in up to 10% of patients, experienced pituitary surgeons report significantly lower rates. Intra- or postoperative arterial bleeding may be fatal, but fortunately occurs in very few patients. Altogether, the mortality rate is low at less than 0.5%.

Medical Treatment

Drugs currently available for the treatment of acromegaly are dopamine agonists (DA), somatostatin analogues, and GH antagonists. They differ in their efficacy on biochemical parameters and tumor proliferation, in their mode of application, and in their costs.

DA were the first drugs effectively employed in the medical treatment of acromegaly. In contrast to the physiological stimulation of GH by DA in healthy subjects, a significant suppression of GH may be observed in acromegalic patients. Normalization of IGF1 may be obtained in up to one-third of patients. Significant tumor shrinkage is observed in less than 15%. Second-generation DA like cabergoline and quinagolide demonstrate better efficacy compared with bromocriptine, probably due to better tolerability. Dosages are higher than those required for the treatment of prolactinomas. Side-effects include gastrointestinal upset, transient nausea and vomiting, headache, hypotension, nasal congestion, mood disorders, and cold-induced peripheral vasospasm. Due to their significant efficacy in single patients, their oral availability, and their lower cost, we recommend a treatment trial for 3 months in patients with surgically uncontrolled acromegaly.

SSA have been the medical therapy of choice for a considerable time. The two currently available SA, octreotide and lanreotide, act by binding predominantly to the somatostatin receptor subtype 2, which is especially relevant for suppression of GH secretion. Octreotide is currently available in a short-acting sc-administered form and a long-acting release (LAR) preparation. LAR is usually applied intramuscularly every 4 weeks, but dosing intervals of 6–8 weeks may be sufficient in single patients. Whereas the first slow-release SR preparation of lanreotide was not available in some countries, a newly developed gel preparation will be introduced to the market in the near future. Although it may offer some advantages in handling, its efficacy remains to be proven in large studies. New somatostatin receptor ligands with higher affinity to other receptor subtypes are currently under development.

In a large analysis of published reports [4], adjunctive therapy with octreotide LAR over 12–36 months allowed for sufficient GH suppression in 47–75% of patients (average 56%), with IGF1 normalization in 41–75% (average 66%). Tumor shrinkage was observed in about 30% of patients, with a mass reduction of 20–50% in most cases. A bias in some of these studies cannot be excluded, with patients being se-

lected on the basis of their octreotide responsiveness. Interestingly, a recent report demonstrated a significant biochemical improvement in SA-resistant acromegalic patients after addition of cabergoline. Therefore, a combined treatment may be considered in specific patients. Side-effects of depot SA therapy include gastrointestinal symptoms like diarrhea, nausea, and abdominal discomfort (≤49% during the early phase of treatment, <10% with persistent symptoms), abnormalities of glucose metabolism (hypoglycemia in 2%, hyperglycemia in 7–15%), injection site pain (4–31%), transient hair loss (3–6%), hypothyroidism (2%), sinus bradycardia, and vitamin B12 deficiency. Biliary tract abnormalities occur in approximately 50% of patients, with development of new gallstones in 4–22% of patients. However, most of these patients remain asymptomatic.

SA have also been suggested as the primary treatment of acromegaly, considering the low success rates of surgery in patients with macroadenomas. Our review of 6 studies including 108 patients treated primarily with SA revealed sufficient GH and IGF1 suppression in 62% and 62% of cases, respectively, and significant tumor reduction in 47%. We consider primary therapy with SA an option in patients at significant risk from surgery. However, a randomized study comparing the success rates of surgery and medical treatment has not been presented so far. SA pretreatment in patients destined for surgery may be useful in those with serious medical complications of acromegaly. There are conflicting reports about whether such a pretreatment may also improve the surgical outcome. So far, no placebo-controlled, randomized trial has been performed to address this issue.

Recently, the GH receptor antagonist pegvisomant became available. Whereas DA and SA function at the level of the pituitary, pegvisomant acts on peripheral GH receptors to block GH action [5]. Therefore, the primary goal of therapy is normalization of IGF1, which has been demonstrated in up to 97% of patients treated for more than 12 months. The fall in serum IGF1 was accompanied by a significant improvement in the signs and symptoms of acromegaly, and notable insulin resistance. However, a major concern with this very effective drug is its influence on the pituitary tumor volume. In theory, withdrawal of GH feedback at the pituitary level may enhance tumor growth. A recent follow-up on tumor size from 131 patients treated with pegvisomant for a mean of 1 year found relevant tumor growth in two patients. The significance of this observation is currently unknown. Clearly, long-term monitoring of tumor volumes in patients treated with pegvisomant is necessary. Pegvisomant is given as daily subcutaneous injections at doses between 10 and 40 mg. In Germany, it is currently licensed for patients with an inadequate response to or intolerability of other forms of medical treatment. Due to the unknown effect on tumor growth, we do not recommend its use in patients with large pituitary tumors extending near the optic chiasm or tract. Side-effects include reversible abnormalities of liver function tests and mild, self-limiting injection site reactions (11% of patients). Due to the former, regular monitoring of liver function is necessary in all patients commencing pegvisomant.

Radiotherapy

In principle, pituitary irradiation may be applied as fractionated conventional radiotherapy or by stereotactic modalities. The latter include gamma-knife, linear accelerators, and particle accelerators, which all offer highly precise, circumscribed delivery of radiation to the target. Radiosurgery is defined as stereotactic radiation in a single session. There are conflicting reports about the efficacy of conventional radiotherapy for the treatment of acromegaly, administered in fractionated doses not exceeding 1.75 Gy/session, as a slow decrease of GH and IGF1 levels is observed. In a recent study by Biermasz et al. using strict biochemical criteria, normalization of IGF1 was observed in 60%, 74%, and 84% of patients after 5, 10, and 15 years of follow-up, respectively [6]. Normalization of GH suppression during oGTT was found in 65%, 69%, and 71%, respectively. Side-effects included pituitary hormone deficiencies, as demonstrated in 29%, 54%, and 58% of patients, respectively. Other possible complications are optic neuropathy, temporal lobe radiation injury, cerebrovascular disease, secondary extrapituitary neoplasms, and neuropsychological disturbances, although causal relations for some of these are controversial. Stereotactic radiosurgery may be an attractive therapeutic alternative, by sparing tumor-surrounding tissue. In a recent report by Attanasio et al. with a median follow-up of 46 months (range 9–96 months), IGF1 levels normalized in 23% of patients treated by gamma-knife, and GH levels fell below 2.5 ng/ml in 37% [7]. Interestingly, tumor shrinkage >25% occurred in 79% of patients at 4 years. Therefore, the gamma-knife may be a valid adjunctive tool to control tumor proliferation. However, efficacy and side-effects of this new form of irradiation need to be studied in more detail. Overall, radiotherapy modalities are viewed as adjunctive therapies to surgical and medical interventions in most centers. Often, medical therapy is required to bridge the latency period before the onset of radiation effectiveness.

References

1. Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, von Werder K, Wass J, Giustina A. Guidelines for acromegaly management. J Clin Endocrinol Metab 2002; 87:4054–8.
2. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, von Werder K, Melmed S. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000; 85:526–9.
3. Lüdecke DK. Recent developments in the treatment of acromegaly. Neurosurg Rev 1985; 8: 167–73.
4. Freda PU. Somatostatin analogs in acromegaly. J Clin Endocrinol Metab 2002; 87:3013–18.
5. Clemmons DR, Chihara K, Freda PU, Ho KKY, Klibanski A, Melmed S, Shalet SM, Strasburger CJ, Trainer PJ, Thorner MO. Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. J Clin Endocrinol Metab 2003; 88:4759–67.
6. Biermasz NR, van Dulken H, Roelfsema F. Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. J Clin Endocrinol Metab 2000; 85:2476–82.
7. Attanasio R, Epaminonda P, Motti E, Giugni E, Ventrella L, Cozzi R, Farabola M, Loli P, Beck-Peccoz P, Arosio M. Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. J Clin Endocrinol Metab 2003; 88:3105–12.

Thyrotropin-Secreting Pituitary Adenomas, Thyrotroph Adenomas

Takumi Abe, Dieter K. Lüdecke, Wolfgang Saeger

Introduction and Epidemiology

Thyrotroph adenomas are unusual endocrine lesions that comprise approximately 0.5–2% of all pituitary adenomas [2, 3]. Therefore, such patients are often mistakenly treated for Graves disease and have long histories of thyroid dysfunction. Consequently, thyrotroph adenomas often present as macroadenomas with symptoms related to mass effect and hyperthyroidism.

Although thyrotroph adenomas are more easily recognizable as of late due to the wide availability of sensitive and specific thyrotropin assays [2] as well as MRI, they remain uncommon.

In this chapter we briefly describe the clinical features and results of medical as well as transnasal surgically treated patients with thyrotropin-secreting pituitary adenomas since the introduction of improved methods of visualization and microsurgical techniques [1]. For a more detailed description, we refer the reader to consult references [2, 3].

Symptoms and Clinical Signs

The preoperative duration of symptoms range from 1 to 15 years (mean 6 years). The patients present with goiter and symptoms of hyperthyroidism such as tachycardia, palpitations, diarrhea. Signs of other hormonal abnormalities may be present in relation to tumor size or concomitant hyperprolactinemia like: amenorrhea, hypogonadism, and gynecomastia. Hemianopsia or visual loss is rarely the leading symptom though most tumors are macroadenomas.

Endocrinological Evaluation

Serum thyrotropin levels (normal range 0.3–3.0 mU/l) are measured by endocrinologists using highly specific thyrotropin assays. The range of TSH in untreated patients with thyrotroph adenomas lies in a wide range between rare normal levels and 568 mU/l. Measurements of serum-free T3 (normal range 2.2–4.7 pg/ml), free T4 (normal range 0.8–1.8 ng/dl) reveal the hyperthyroidism with non-suppressed TSH. The α-subunit of glycoprotein (normal range 0.1–0.3 ng/ml) is nowadays also measured. The α-subunit/thyrotropin molar ratio may be calculated to exclude the rare differential diagnosis of resistance to TSH [6].

Other endocrinological findings are assessed on the basis of hormonal levels as described above. Among the endocrine stimulation tests, the thyrotropin-releasing hormone (TRH) stimulation test may be of some value and mostly shows no increase of the already elevated TSH levels. Since there have been reports about tumor bleeding during this test, the indication has to be carefully considered and explained to the patient. DA and SA should be tested since they may be used as medical treatment.

Classification

Radiological Examination

MRI scans are taken before and after gadolinium injections. The tumor classification does not differ from other types of adenomas as described above by E. Laws. Invasion into the cavernous sinus may be sometimes only confirmed or excluded at surgery. Gross nonresectable tumor extension may be classified by MRI and is of great importance for further treatment options [1]. Ectopic sources of TSH hypersecretion have not been reported so far to our knowledge.

Pathological Studies

Histological examination of resected tissue consists of routine staining with hematoxylin & eosin, as well as immunohistological analysis. On light-microscopic studies, adenoma cells are chromophobic. They contain PAS-positive, small, cytoplasmatic granules. Immunohistology reveals TSH and often α-TSH positivity in a higher number of cells than in the normal pituitary within an adenomatous tissue structure. A large number of thyrotroph adenomas show plurihormonal reactions to prolactin, HGH, gonadotropins, and even ACTH. Ultrastructurally, thyrotroph adenomas cells are mostly well-differentiated like the normal thyrotrophs [8].

Medical Treatment

Medical therapy is the first line of treatment in all patients with thyrotroph adenomas. A rare exception are adenomas with rapid deterioration of visual fields and vision where pituitary surgery may be acutely indicated. Regularly, all patients need medical treatment to achieve normalization of elevated thyroid hormones.

With long-acting SA [2, 4], a normalization of TSH and thyroxin as well as a considerable adenoma shrinkage has been observed in a high percentage of macroadenomas. Therefore, nowadays a long-term medical therapy has to be considered, especially if the adenoma is not resectable. Side-effects like abdominal discomfort, diarrhea if persistent, may limit its use. Gallstones should be prevented by additional medication if signs occur during ultrasound investigation.

Surgery

Side-effects of specific tumor suppressive medication, insufficient results, or the high chance to cure the patient by complete selective adenoma removal are the main present indications for the mostly feasible transnasal surgery.

Direct transnasal, minimally invasive resection of the adenomas is performed according to the described operative technique [1]. At the site of the suprasellar or lateral tumor extension, the pseudocapsule e.g. of the cavernous sinus is inspected in each case using mirrors and a micro-pressure suction-irrigation, or with endoscopic systems until the site of invasion is detected or excluded. A micro-Doppler instrument is of great value to locate the carotid arteries near or at the adenoma. The main reason for incomplete resection is an overlooked small invasion or a nonresectable adenoma extension. The operative field should be at least completely cleaned at the compressed pituitary site. Microbiopsies of questionable areas may be immediately processed by methylene blue staining of smears or cryohistology of fibrous parts to clarify the border to the anterior or posterior lobe. Thus, in case of an adenoma rest, the pituitary function may be better preserved by circumscribed localization of radiotherapy.

Intraoperative thyrotropin measurements may be performed using a chemiluminescence assay under continuous anesthesia to calculate the serum half-life of thyrotropin. If the result is less than 60 min, the completeness of adenoma removal is confirmed, and further risky explorations may be avoided. This method as well as the surgical treatment by highly experienced surgeons may improve the results which have been disappointing in the past [7] to remission rates close to 90%.

There are rarely deaths related to the surgery, none of the patients in our series. Cerebrospinal fluid leakage with revision may occur in up to 8% in these often invasive and firm tumors. A temporary diabetes insipidus was observed at a similar rate. Postoperative isolated transient or even persistent central hypothyroidism may be a result even of selective and radical extirpation of the adenoma, while partial hypopituitarism in experienced hands is rare.

Prognosis/Quality of Life

Criteria for surgical remission [6] not only include total resection of the tumor mass with reduction of serum thyrotropin, free T3, and free T4 levels to normal, but also normalization of the syndrome of inappropriate secretion of thyrotropin (SIST). If thorough, endocrinological and radiological examination after at least 4–6 months and a year of follow-up reveals full remission, the prognosis of long-lasting curative effect can be anticipated in about 90% of the patients. A recurrence with both SIST and tumor regrowth, as determined by MRI, may develop in about 10% even several years after surgery.

Future Perspectives

A subtotal thyroidectomy, or subtotal thyroidectomy with either radioiodine thyroid ablation or treatment with antithyroid medication, or radioiodine thyroid ablation have been performed in about half of the patients before the definite causal treatment of the underlying pituitary adenoma was initiated. With a greater awareness and nowadays refined diagnostic tools, the delay before diagnosis might be reduced. With combined medical-microsurgical as well in last instance radiation methods, most patients

with thyrotroph adenomas may be cured or at least effectively controlled.

References

1. Abe T, Lüdecke DK. Effects of preoperative octreotide treatment on different subtypes of 90 growth hormone-secreting pituitary adenomas and outcome in one surgical center. Eur J Endocrinol 2001; 145:137–45
2. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996; 17:610–38.
3. Buchfelder M, Fahlbusch R. Thyrotroph adenomas. In: Thapar K, Kovacs K, Scheithauer BW, Lloyd RV, eds. Diagnosis and management of pituitary tumors. Totowa, NJ: Human Press, 2001:333–42.
4. Chanson P, Weintraub BD, Harris AG. Octreotide therapy for thyroid stimulating-secreting pituitary adenomas. A follow-up of 52 patients. Ann Intern Med 1993; 119:236–40.
5. Kourides IA, Ridgway EC, Weintraub BD, Bigos ST, Gershengorn MC, Maloof F. Thyrotropin-induced hyperthyroidism: use of α and β subunit levels to identify patients with primary tumors. J Clin Endocrinol Metab 1977; 45:534–43.
6. Losa M, Giovanelli M, Persani L, Mortini P, Faglia G, Beck-Peccoz P. Criteria of cure and follow-up of central hyperthyroidism due to thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab 1996; 81:3084–90.
7. McCutcheon IE, Weintraub BD, Oldfield EH. Surgical treatment of thyreotroph adenomas. J Neurosurg 1990; 73:674–83.
8. Saeger W, Lüdecke DK. Pituitary adenomas with hyperfunction of TSH: frequency, histological classification, immunocytochemistry and ultrastructure. Virchows Arch [Pathol Anat] 1982; 394:255–67.

Cushing's Disease

Jörg Flitsch, Dieter K. Lüdecke, Wolfgang Saeger

Epidemiology

Cushing's disease is caused by ACTH-secreting (corticotroph) pituitary adenomas. It was first systematically described by Harvey Cushing (1869–1939) in 1932 [2]. In general, Cushing's disease is a rare condition. The estimated prevalence is 2–5 cases per 100,000 with an incidence of 0.25 cases per 100,000 per year. ACTH-secreting pituitary adenomas account for about 10% of all diagnosed pituitary adenomas. Cushing's disease can develop at any age, but signs usually appear between the 3rd and 5th decade. Cushing's disease is predominantly found in women, with a gender ratio of 3:1 to 5:1.

Symptoms and Clinical Signs

The symptoms and clinical signs associated with Cushing's disease are caused by the pathological cortisol production, which results in increased peripheral proteinolysis and lipolysis, as well as glycogenolysis and glyconeogenesis. Consequently, a hyperglycemic (diabetic) state develops, causing increased insulin secretion. This leads to stronger lipogenic than lipolytic effects in the trunk, but rarely in the extremities. This pathomechanism causes the most obvious clinical signs including truncal obesity, buffalo hump, and moon facies. The increased protein catabolism leads to muscle atrophy, osteoporosis, and skin atrophy. The skin atrophy coupled with the stretching of the subcutaneous tissue and increased subcutaneous venous plexus result in striae rubrae distensae. A typical complication of muscle atrophy is proximal myopathy, which renders patients incapable of standing up from a squatting position. Impaired bone mineralization and enteral calcium absorption lead to osteoporosis, kyphosis, and pathological fractures. Hypertension is commonly found in Cushing's disease cases. Fatigue, psychological changes (depression), and impaired physical performance are generally found. Patients have an increased risk of thrombosis. Decreased lymphocytes and neutrophil/eosinophil granulocytes cause immunosuppression and thus a higher frequency of (fungal) infections, acne, and impaired wound healing. In children, growth is often impaired. In men, impaired libido, erectile dysfunction, and oligospermia are characteristic due to decreased testosterone levels. In women, oligo- or amenorrhea, hirsutism, and acne are common due to increased adrenal androgen secretion.

Diagnostics

In suspected Cushing's disease, the initial diagnostic step is to prove the state of hypercortisolism. Day profiles of plasma or saliva cortisol levels, 24-h urine sampling of free cortisol or 17-hydroxycorticoids secretion, or the low-dose dexamethasone suppression test (1 or 2 mg) are widely used to prove the hypercortisolemic state. Recently, late night salivary or plasma cortisol levels (between 10 pm and midnight) have proven to be very reliable in the detection of hypercortisolism. Once the hypercortisolism is established, the etiology of the disease should be determined. The next step is ACTH testing. Normal or slightly elevated ACTH levels are highly suspicious for a pituitary pathology. The combination of the high-dose dexamethasone suppression test (8 mg) and the CRH-stimulation test (1 µg/kg) is generally accepted for the differentiation of pituitary-depend-

ent and ectopic Cushing's syndrome [5, 8]. If both tests are positive, a pituitary origin is found in more than 95% of patients.

After endocrinological testing, MRI of the pituitary is essential (T1WI coronal and sagittal sequences, gadolinium-DTPA enhanced, thin slice technique). Despite advances in imaging techniques, up to 50% of MRIs show no signs of an adenoma. Pituitary exploration using the transsphenoidal approach will reveal the hidden microadenoma in most of these cases [5].

In cases where endocrinological results are ambiguous, invasive catheter studies with venous blood sampling from the inferior petrosal sinus (IPSS) [10] and cavernous sinus (CSS) [4] have been developed to distinguish further between pituitary and ectopic Cushing's syndrome. CSS is also gaining wider acceptance as a localization aid for the mostly lateralized adenomas within the pituitary [5, 14] (Fig. 3).

Classification

Pituitary adenomas are generally classified by size and hormone secretion. In Cushing's disease, about 90% of all adenomas are microadenomas of less than 10 mm diameter, 75% of all adenomas are under 5 mm. In older classifications, the tumors were histologically described as basophil or chromophobe adenomas. Using improved techniques including Epon embedding and immunostaining with specific ACTH antibodies, a subdivision into densely or sparsely granulated corticotroph adenomas can be made [11].

ACTH-cell hyperplasias are rarely found to be the source of pituitary-dependent hypercortisolism. For some time, increased hypothalamic CRH secretion was considered a possible cause of Cushing's syndrome (hypothalamic Cushing's syndrome), but this has not been confirmed except in true CRH-secreting tumors [1].

Up to 30% of patients with ACTH adenomas develop Nelson's syndrome after bilateral adrenalectomy [7]. Nelson's syndrome is often characterized by an aggressive growth of the pituitary ACTH adenoma with skull base infiltration. Histologically, the tumors do not differ from other ACTH adenomas. Hyperpigmentation due to ACTH and MSH (melanocyte-stimulating hormone) co-secretion is common.

Pituitary carcinomas, defined by brain invasion and/or proven metastatic tumor spread, are found in only 0.1% of all pituitary tumors [13]. Systemic metastasis is extremely rare. Of nearly 800 treated Cushing's disease cases in Hamburg over the last 30 years, there were only 2 ACTH-secreting pituitary carcinomas with proven metastatic tumor spread. In these cases, the patients underwent adrenalectomy and pituitary radiation prior to carcinoma development (Fig. 4).

Treatment

A synopsis is provided in Fig. 5.

Surgery

Transsphenoidal Surgery

Currently, the selective adenomectomy of the ACTH-secreting pituitary adenoma via the transsphenoidal approach (microscopically or [less frequently] endoscopically) is the treatment of choice for Cushing's disease. Only the pathologic tissue and a small rim of the surrounding anterior lobe as a safety zone are resected. Specialized pituitary surgeons, using additional techniques like intraoperative cavernous sinus sampling, cytology, ACTH measurement from tissue samples, or intraoperative MRI, have published remission rates for microadenomas of 70–96% [5]. In macroadenomas (~10%) remission after surgery is

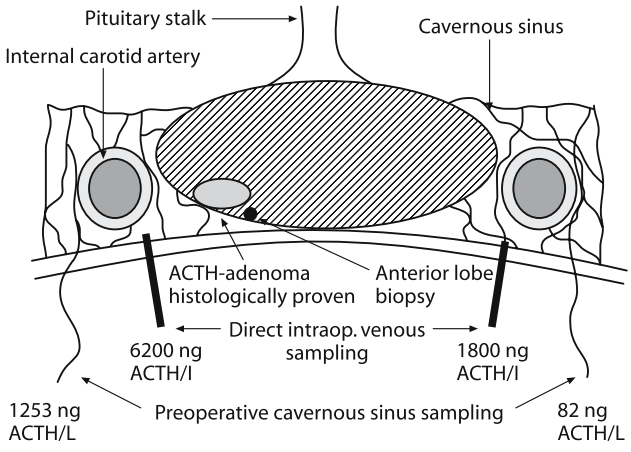


Fig. 3. Example of pre- and intraoperative hormone findings using special techniques; preoperative cavernous sinus sampling, intraoperative cavernous sinus sampling

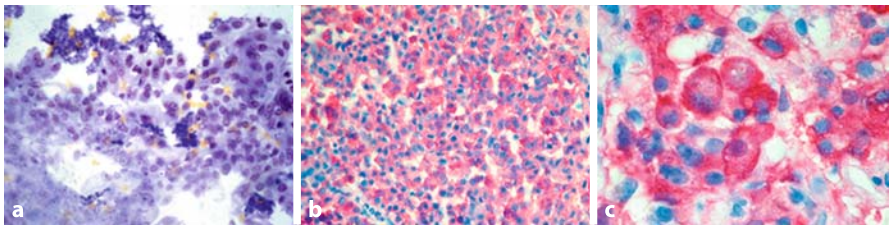


Fig. 4. Cushing's disease. Intraoperative cytology (**a**; methylene blue staining [1%], magnification ×100) and postoperative immunohistology (**b**; anti-ACTH staining, magnification ×100) of an ACTH-cell adenoma; **c** adjacent anterior lobe tissue with typical changes of hypercortisolism (Crooke cells, ACTH-positive cells with annular intracytoplasmatic hyalinization, paranuclear vacuoles, and sparse mucoid residual granulation), anti-ACTH staining, magnification ×250

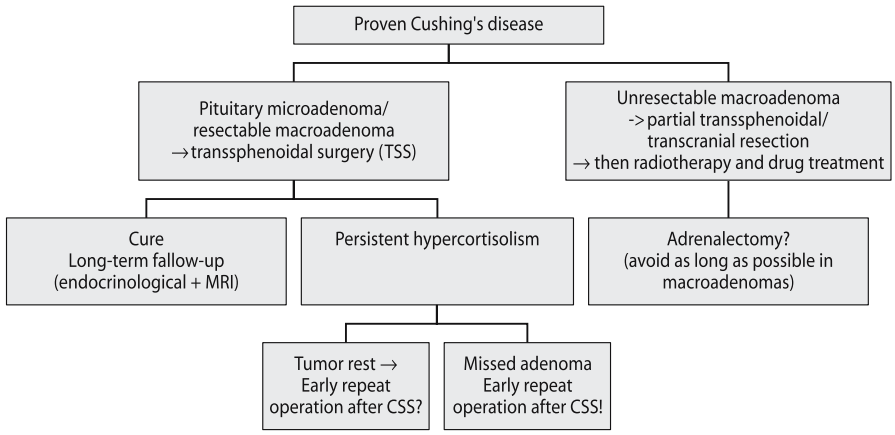


Fig. 5. Treatment algorithm for ACTH-secreting pituitary adenomas. In special cases, consider transcranial surgery and/or bilateral adrenalectomy

achieved in only about 50–60%. Para- and suprasellar invasive tumor extension may hinder complete surgical resection. Complications following transsphenoidal surgery are rare [12]. The mortality after surgery by experienced hands is approximately 1–2%. Injuries to the internal carotid artery can occur. CSF leaks are reported in 2–4% of cases, meningitis cases are rare. A transient phase of diabetes insipidus (DI) is found in 10–15%; seldom is it persistent. Oculomotor palsy (mostly transient) occurs in about 1% of patients. Hormonal insufficiencies of the anterior lobe (partial or complete) are reported in 6–19%. Recurrence rates of hypercortisolism range between 9 and 23%.

Transcranial Surgery

The transcranial approach (pterional/frontotemporal) is usually reserved for patients with an extensive para- and suprasellar tumor extension, inaccessible via the transsphenoidal approach. In specialized centers, transcranial surgery for Cushing's disease is performed on less than 5% of all patients. Complication rates are higher than with transsphenoidal surgery and may include damage to the pituitary stalk (complete hypopituitarism), optic nerves/chiasm, or frontal lobe (via retraction).

Bilateral Adrenalectomy

Historically, the surgical treatment of Cushing's disease has progressed from the total bilateral adrenalectomy to the selective, transsphenoidal adenomectomy. The removal of the adrenal glands immediately results in persistent hypocortisolism, requiring lifelong glucocorticoid and mineralocorticoid replacement. Surgically, the endoscopic technique is gradually replacing the open approach. Due to the permanent adrenal insufficiency and the risk of Nelson's syndrome, bilateral adrenalectomy is now mostly reserved for persistent Cushing's disease after transsphenoidal surgery and radiation therapy.

Radiotherapy

Conventional Radiation Therapy

Conventional radiotherapy usually consists of an overall dosage of 45–50 Gy, applied over 5–6 weeks at 180–200 cGy fractions. The present techniques include the three-field (lateral, opposed, and vertex), 360° rotational field, and moving arcs radiation. Remission rates of 50–60% have been published after radiation therapy for Cushing's disease. Lower overall dosages led to significantly lower remission rates.

Stereotactic Radiosurgery and Fractioned Stereotactic Radiation Therapy

The development of stereotactic radiation methods has made high precision radiation of one or more isocenters possible. Local radiation dosages of 20 Gy and more are achieved in one session, with a significantly lower radiation dosage to the border tissue. Possible stereotactic radiosurgery methods include gamma-knife and Linac-based systems. The use of heavy charged particle (protons or alpha) beams has become less common. Successful correction of hypercortisolism after gamma-knife radiosurgery of 63–100% within 1–5 years has been published. Long-term follow-up in gamma-knife radiosurgery reported neither radiation-related deaths nor visual loss. However, anterior lobe insufficiencies occurred in 66% of cases.

The use of multiple convergent radiation beams in fractions of 180–200 cGy per fraction with a total dose of 50 Gy can reduce the risk of optic system damage [6].

Interstitial Brachytherapy

Stereotactic or transsphenoidal implantation of radioactive labeled seeds (Y-90, J-125, Au-198) was performed in some specialized centers, either as primary treatment or as secondary treatment for invasive, nonresectable adenomas. Success rates of up to 77% have been reported, but anterior lobe deficits are common. Noninvasive stereotactic radiotherapy methods have essentially replaced interstitial brachytherapy.

Pharmacotherapy

ACTH-Release Inhibition

Serotonin antagonists, GABA inhibitors, dopamine agonists, and somatostatin analogues have been tested for the treatment of Cushing's disease due to these drugs' possible effects on CRH or ACTH synthesis or release. All these substances showed insufficient results alone, but dopamine agonists are sometimes used in combination with steroid synthesis inhibitors [9].

Inhibition of Steroid Synthesis or Effects at the Receptor

Steroid synthesis inhibitors like metyrapone, ketoconazole, aminoglutethimide, or o,p-DDD act via the direct inhibition of one or more enzymatic steps of cortisol synthesis. At higher doses (>4 g/d), o,p-DDD achieves remission rates of up to 80%. However, side-effects like adrenal cortex destruction and hepatopathy are common. At doses of 400–1600 mg, effective cortisol reduction was reported in 70% of patients treated with ketoconazole [9].

Mifepristone (RU 486) competitively binds to the glucocorticoid receptor and inhibits cortisol effects. Experience is so far very limited, and the substance is available for research purposes only.

Overall, transsphenoidal surgery is currently the primary treatment of choice for Cushing's disease. The available pharmacotherapy and radiotherapy are generally secondary treatment options. Pharmacotherapy at lower doses has limited effects and often has severe side-effects at higher doses. The major disadvantage of any kind of radiation therapy is the delay between treatment and the desired effects. Remission after radiation therapy usually takes 2–10 years. Another disadvantage lies in the commonly resulting anterior lobe insufficiencies (24–65% in 5–10 years), especially following conventional radiation therapy. For severely ill Cushing's disease patients who are unable to undergo surgery, stereotactic radiotherapy should nevertheless be considered as a primary option.

Prognosis/Quality of Life

The average time span between the first symptoms of Cushing's disease and consultation of professional help is approximately 1 year. However, the delay between first consultation and diagnosis averages over 4 years. Untreated, Cushing's disease increases the risk of premature death within 5–15 years due to diabetes mellitus, hypertension, and myocardial damage. With symptomatic treatment alone, survival times of 20 years after onset of disease have been reported. About 2 of 3 patients with Cushing's disease show significant symptoms of excitability and depression before treatment.

After diagnosis and successful correction of hypercortisolism, most patients notice an increase of physical well-being within 6–8 months [3]. The risk of premature death decreases after successful treatment unless secondary changes have already manifested.

Follow-up/Specific Problems and Measures

After successful surgery, cortisol levels usually drop to subnormal levels within 20 h, necessitating glucocorticoid replacement. This period of secondary adrenal insufficiency lasts an average of 18 months. In a minority of successfully treated patients, normocortisolism is achieved without an initial period of hypocortisolism. These patients need careful follow-up to rule out recurrence of disease. Proper tools for the initial assessment of surgical results are determination of cortisol and ACTH decrease in plasma (or lately cortisol in saliva) in the early postopera-

tive phase prior to hydrocortisone substitution. Others recommend perioperative glucocorticoid substitution, followed by later assessment of the pituitary-adrenal axis. In either case, the anterior lobe and posterior lobe function of the pituitary should also be evaluated. Patients should have a careful endocrinological re-evaluation of the corticotroph function twice a year for the first 2 years, and annual follow-ups thereafter. MRI of the pituitary is recommended about 6 months postoperatively and should be repeated at 2- to 3-year intervals [5]. After radiotherapy, a normalization of cortisol levels may occur as soon as 1–2 years. Follow-up should be performed semiannually. Life-long follow-up is important after all therapies to detect recurrences as early as possible. One of the best tools for early detection is late-night salivary cortisol sampling.

Future Perspectives

Due to the success of transsphenoidal surgery in most cases, future research should focus on solutions for 'problematic' cases with undetectable, minute adenomas or invasive tumors. Further localization techniques, e.g., improved visualization via MRI and specific contrast enhancement, could improve the preoperative diagnostics of minute adenomas. For invasive (macro-)adenomas, unresectable by surgery, advances in pharmacotherapy (e.g., specific receptor-bound drug delivery to adenoma cells) could lead to improved results.

Acknowledgements. We thank Mrs. H.P. Flitsch for her assistance with the English language.

References

1. Asa SL, Kovacs K, Tindall GT, Barrow DL, Horvath E, Vecsei P. Cushing's disease associated with an intrasellar gangliocytoma producing corticotropin-releasing factor. Ann Intern Med 1984; 101:789–793.
2. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bull Johns Hopkins Hosp 1932; 50:137–195.
3. Flitsch J, Spitzner S, Lüdecke DK. Emotional disorders in patients with different types of pituitary adenomas and factors affecting the diagnostic process. Exp Clin Endocrinol Diabetes 2000; 108:480–485.
4. Lüdecke DK. Intraoperative measurement of adrenocorticotrophic hormone in peripituitary blood in Cushing's disease. Neurosurg 1989; 24:201–204.
5. Lüdecke DK, Flitsch J, Knappe UJ, Saeger W. Cushing's disease: a surgical view. J Neuro-Oncol 2001; 54:151–166.
6. Mahmoud-Ahmed AS, Suh JH. Radiation therapy for Cushing's disease: a review. Pituitary 2002; 5:175–180.
7. Nelson DH, Meakin JF, Dealy JW, Matson DD, Emerson K, Thorn GW. ACTH-producing tumor of the pituitary gland. N Engl J Med 1958; 259:161–164.
8. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 1998; 19:647–672.
9. Nieman LK. Medical therapy of Cushing's disease. Pituitary 2002; 5:77–82.
10. Oldfield EH, Chrousos GP, Schulte HM, Schaaf M, Mc Keever PE, Krudy AG, Cutler Jr GB, Loriaux DL, Doppman JL. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. N Engl J Med 1985; 312:100–103.
11. Saeger W, Wilczak P, Lüdecke DK, Buchfelder M, Fahlbusch R. Hormone markers in pituitary adenomas: Changes within last decade resulting from improved method. Endocri Pathol 2003; 14:49–54.
12. Semple PL, Laws Jr ER. Complications in a contemporary series of patients who underwent transsphenoidal surgery. J Neurosurg 1999; 91:175–179.
13. Solcia E, Klöppel G, Sobin LH, Capella C, de Lellis RA, Heitz PhU, Horvath E, Kovacs K, Lack EE, Lloyd RJ, Rosai J, Scheithauer BW. Histological typing of endocrine tumors. 2nd edition. Springer, Berlin-Heidelberg-New York-Barcelona-Hong Kong-London-Milan-Paris-Singapore-Tokyo, 2000
14. Teramoto A, Nemoto S, Takakura K, Sasaki Y, Machida T. Selective venous sampling directly from the cavernous sinus in Cushing's syndrome. J Clin Endocrinol Metab 1993; 76:637–641.

Tumors of the Pineal Region 13

Yutaka Sawamura, Nicolas de Tribolet

Epidemiology – 208

Symptoms and Clinical Signs – 208

Diagnosis – 209

Staging and Classification – 210

Treatment – 210
Surgery
Radiotherapy and Chemotherapy

Prognosis/Quality of Life – 213

Follow-up/Specific Problems and Measures – 214

Future Perspectives – 214

References – 214

Epidemiology

The term 'pineal region tumors' includes both the neoplasms originating from the pineal body and those originating from the adjacent anatomical structures, such as the thalamus, the tegmentum of the midbrain, and the falcotentorium. The term 'pineal tumors' indicates the former. Astrocytic tumors originating from the tegmentum and meningiomas originating from the falcotentorial junction are not true pineal tumors. Primary pineal tumors are mainly composed of two categories of brain neoplasms, pineal parenchymal tumors and germ-cell tumors (Table 1).

They are very rare neoplasms in the central nervous system (CNS) and predominantly occur in the pediatric population. Pineoblastomas and teratomas are often found in very young children. The Brain Tumor Registry of Japan [20] recorded 966 pineal region tumors (806 male patients:160 female patients) in 2003; there were 585 germinomas (60.6%), 80 pineocytomas (8.3%), 56 teratomas (5.8%), 49 pineoblastomas (5.1%), 50 malignant teratomas (5.2%), and others. A clear male predominance was observed in each histological type of germ-cell tumor, where the male:female ratio was approximately 10:1. Pineal parenchymal tumors, however, show no gender difference for incidence [13, 15]. It is well known that the incidence of pineal tumors is higher in Asia than in Europe. This is attributed to a significantly higher incidence of germ-cell tumors in Far-East Asia than in the Western countries. It should be noted that germinoma is the most common type of pineal origin neoplasm both in Asian and Western countries. Pineal teratomas occasionally present as a congenital tumor in the newborn.

Table 1. WHO classification of tumors primarily originating from the pineal gland

Pineal parenchymal tumors
pineoblastoma
pineocytoma
pineal parenchymal tumor of intermediate differentiation (PPTID)
Germ-cell tumors
germinoma
teratoma
mature
immature
teratoma with malignant transformation
yolk-sac tumor
embryonal carcinoma
choriocarcinoma
mixed germ-cell tumors

Symptoms and Clinical Signs

Pineal region tumors generally present symptoms of increased intracranial pressure due to obstructive hydrocephalus and/or impairment of ocular movements such as Parinaud's syndrome (upward gaze palsy). The obstructive hydrocephalus is mostly chronic and gradually progressive, presenting with headache, inattention, mental deterioration, double vision, gait imbalance, vomiting, emaciation, and finally disturbance of consciousness.

The clinical course depends on the histological nature of the neoplasm. Patients with pineocytoma or mature teratoma may have a long history of chronic headache, whereas patients with an aggressive tumor may show acute and severe aggravation of neurological symptoms.

The disturbance in vertical eye movements is related to three main neuronal structures near to the pineal gland, i.e., the posterior commissure, the rostral interstitial nucleus of the medial longitudinal fasciculus, and the interstitial nucleus of Cajal in the midbrain. Among a variety of disease processes that affect the posterior commissure, pineal tumors are the most representative disorder to produce Parinaud's syndrome. A pineal tumor induces Parinaud's syndrome either by direct compression on the posterior commissure or by causing an obstructive hydrocephalus. Hydrocephalus alone produces this syndrome by enlarging the aqueduct, the third ventricle, and the suprapineal recess, thereby stretching or compressing the posterior commissure. A pineal tumor occasionally causes dorsal midbrain syndrome that includes disturbance of horizontal eye movements, especially convergence. A large benign cystic tumor can compress the trochlear nerve, resulting in minor double vision, and chronic increased intracranial pressure due to hydrocephalus may lead to abducens palsy.

Neurosurgeons who operate on pineal neoplasms should be aware of these anatomical structures and neuro-ophthalmological physiology. In particular, the superior colliculus and the posterior commissure can be easily injured by a radical procedure during tumor resection. Acquaintance with these fragile and important neuronal structures may alter the strategy of neurosurgical intervention to treat pineal tumors, especially germinomas and pineoblastomas that frequently invade the surrounding neuronal structures.

It is notable that pineal germinoma occasionally involves both the pineal and hypothalamic/pituitary sites and may present with diabetes insipidus as its

initial manifestation. Germ-cell tumors that exhibit elevated levels of serum human chorionic gonadotropin (HCG) may cause precocious puberty, mainly in young children aged below 10 years.

Pineal tumors also, but infrequently, present with cerebellar ataxia due to a compression of the superior cerebellar peduncle, and pyramidal tract signs. Malignant tumors disseminating through the subarachnoid pathways produce meningeal signs, back pain, radiculopathy, or other diverse neurological symptoms depending on the site of metastasis.

Diagnosis

Although they are essential tools for the diagnosis of pineal tumors, MRI and CT do not permit a differential diagnosis of pineal parenchymal tumors from germ-cell tumors. A craniotomy offers an exact histological diagnosis, and a stereotactic biopsy is feasible for large tumors. Serological examinations for alpha-fetoprotein (AFP) and HCG-beta will assist in defining their malignancy. Endoscopic technique through the third ventricle can also be applied to obtain a biopsy sample and to treat hydrocephalus by a third ventriculostomy.

As germ-cell tumors consist of embryonic-type cells, they produce a variety of embryonic proteins, which are recognized as tumor markers. In addition to being a useful diagnostic aid, AFP and HCG-beta can be used for monitoring efficacy of treatment, assessing activity of a residual disease, and detecting a recurrence. Using immunohistochemistry, placental alkaline phosphatase (PLAP) is positive in most germinomas. The germ-cell tumors which show elevations of AFP levels are yolk-sac tumor, embryonal carcinoma, immature teratoma, and mixed germ-cell tumors. An AFP level of more than 1000 ng/ml is characteristically a hallmark of the presence of the yolk-sac tumor component. Serum HCG-beta is elevated in all cases of choriocarcinoma, and also some embryonal carcinomas and mixed germ-cell tumors. Germinomas frequently produce a very low level of HCG-beta in serum and CSF.

Pineocytomas are well-circumscribed masses that remain locally confined, whereas pineoblastomas are malignant, demonstrating local invasion as well as distant spread through the CSF space. Biopsy is necessary to distinguish pineal parenchymal tumors from other pineal tumors. The imaging appearance of pineocytomas and pineoblastomas overlaps considerably [9], although pineocytomas tend to be smaller, round, and homogeneous, while pineoblastomas tend to be larger, lobulated, and heterogeneous. Pineocytomas occasionally appear entirely cystic, similar to a pineal cyst. The peripheral rim-like calcification surrounding a pineal region mass is characteristic of pineal parenchymal tumors, especially pineocytomas. More than half of pineocytomas have either central or peripheral calcifications, and pineoblastomas may also have similar calcifications, but less frequently. The MR appearance of pineal parenchymal tumors is nonspecific; they are usually iso- to hypointense on T1-WI, either isointense, hyperintense, or mixed-intense on T2-WI, and homogeneously or heterogeneously enhanced on contrast-enhanced T1-WI.

Large pineal cysts, a non-neoplastic pineal mass, cause a slight impression on the superior colliculi. The contents of the pineal cyst are homogeneous and are either isointense or slightly hyperintense to CSF on all pulse sequences. After intravenous contrast administration, the rim of the cyst is typically enhanced, either entirely or partially.

Pineal germinoma is usually an oval or lobulated solid mass, which is isointense or slightly hypointense on T1-WI and isointense or slightly hyperintense on T2-WI. Its enhancement pattern is homogeneous and usually well marginated. Multiple cystic areas exist, and a small intratumoral hemorrhage may be seen as well. Pineal germinomas have a propensity to invade the midbrain and thalamus, causing thalamic edema that appears as a hyperintense area on T2-WI. On CT, a calcified pineal gland is commonly seen as being surrounded and engulfed by the tumor tissue. A pineal calcification seen in children less than 6 years old is considered as 'premature calcification' and is often associated with a germ-cell tumor or a pineal parenchymal tumor.

Both on CT and MRI, pineal teratomas are extremely heterogeneous masses with an irregular, lobulated outline. They have a solid component, multiple cysts, and calcifications. Fatty components are frequent constituents, and a small intratumoral hemorrhage may be found. Enhancement following contrast administration is observed in the majority of cases, but is absent in some cases. CT is essential in detecting unusual calcifications and adipose tissue of teratomas. Distinction of mature teratomas, immature teratomas, or other teratomas is impossible on imaging studies alone.

A striking feature of pineal choriocarcinoma, an extremely rare neoplasm, is intratumoral hemorrhage. A massive hemorrhage within a pineal tumor found in a child or young adult is suggestive of a choriocarcinoma. Patterns of focal hyperintensity on T1-WI may differentiate choriocarcinomas or teratoma from other pineal tumors. Angiography usually shows pronounced tumor vascularity. The imaging features of yolk-sac tumor and embryonal carcinoma are nonspecific. These tumors often occur as a part of mixed germ-cell tumor including an immature teratoma component. They usually appear as a slightly high-density mass on CT and show marked

enhancement either homogeneously or heterogeneously after contrast administration. Mixed germ-cell tumors, any combination of the above-mentioned histological types, may occur, and any findings on images are not predictive of a detailed histology of these germ-cell tumors.

Staging and Classification

Because each histological type of primary pineal tumors is rare, and little is known regarding their clinical behavior, no prospective study to elucidate a proper staging has been reported in the literature. Furthermore, the similarity of the clinical presentation and radiological findings among the pineal tumors with different histological malignancies makes their management complex.

A number of pineal parenchymal tumors do not fit precisely into pineocytoma or pineoblastoma and have been termed 'pineal parenchymal tumors of intermediate differentiation (PPTID)' by WHO, 'mixed pineocytoma/pineoblastoma', or 'pineocytoma with anaplasia'.

The category of PPTID raises the most problematic issue, both in terms of histological definition and treatment selection. Jouvet et al. proposed a new prognostic classification scheme comprising four grades: grade I for pineocytoma, grade II for pineal parenchymal tumor with fewer than six mitoses and positive immunostaining for neurofilaments, grade III for pineal parenchymal tumor with six or more mitoses but without immunostaining for neurofilaments, and grade IV for pineoblastoma [13]. Older age is clearly associated with low-grade tumors that are less malignant [15]. Fauchon et al. reported that the mean patient ages were 13, 27, 40, and 47 years in patients with pineoblastoma, PPTID (grade III), PPTID (grade II), and pineocytoma, respectively [11]. In addition to the histological grading, an initial clinical staging should include examination of the CSF and MRI of the whole neuraxis because the extent of disease at diagnosis is an important prognostic factor for malignant pineal parenchymal tumors [8, 13, 15].

The histopathological entity 'germ-cell tumor' encompasses a number of histological subtypes whose prognoses and responses to adjuvant therapy are extremely diverse. For selecting a therapeutic regimen, CNS germ-cell tumors have been traditionally divided into two major groups, germinomas and nongerminomatous germ-cell tumors, as a simple extrapolation from gonadal germ-cell tumors. However, considering the prognoses and to select a treatment plan, CNS germ-cell tumors can be grossly divided into three categories: namely good, intermediate, and poor prognostic groups [17]. Solitary germinoma and mature teratoma are highly curable and classified into the good prognostic group. Embryonal carcinoma, yolk-sac tumor, choriocarcinoma, teratoma with malignant transformation, and mixed GCT including a component of cancer or sarcoma leave patients with a poor prognosis. Between these good and poor prognostic groups, there are other types of germ-cell tumors with an intermediate prognosis, such as immature teratoma, mixed germ-cell tumors composed of teratoma and germinoma, and disseminated germinoma.

Treatment

Planning of the neurosurgical management greatly depends on the biological nature of the individual neoplasm and should be determined by evaluating preoperative radiological findings, levels of serum/CSF tumor markers, and an intraoperative histological diagnosis using frozen sections, as well as the surgeon's experience. Germinoma, which is the most common tumor originating from the pineal body, can be cured by low-dose radiotherapy in combination with chemotherapy, and nowadays needs only to be biopsied (Fig. 1). On the other hand, mature teratomas, pineocytomas, and meningiomas can be cured only by a radical surgical resection. Other tumors, such as malignant teratomas, pineoblastomas, embryonal carcinomas, choriocarcinomas, and yolk-sac tumors need a sophisticated combination therapy that includes surgery, craniospinal radiation therapy, and intensive chemotherapy. For such tumors, neurosurgeons have to recognize that a surgical resection is only part of the combination therapy. For instance, an application of an appropriate neoadjuvant therapy prior to radical surgical removal will remarkably reduce the surgical risk for a complete resection of a highly malignant, large pineal neoplasm.

The goal of treatment should be tightly focused on the reduction of post-treatment sequelae including surgical morbidity, but not on a complete microsurgical resection itself. Both the occipital transtentorial approach and the infratentorial supracerebellar approach have become safe surgical procedures in the experienced neurosurgeon's hands. Recently, a majority of surgeons prefer the occipital approach to the infratentorial route, although small tumors located in a confined area of the midline quadrigeminal cistern and the posterior third ventricle are safely treated by the infratentorial approach.

Surgery

Approximately one-third of pineal region tumors are benign, including pineocytomas, mature teratomas,

falcotentorial meningiomas, neurocytomas, hemangioblastomas, cavernous hemangiomas, gangliogliomas, and symptomatic pineal cysts, and microsurgery alone can be curative. These tumors are the target of surgical eradication.

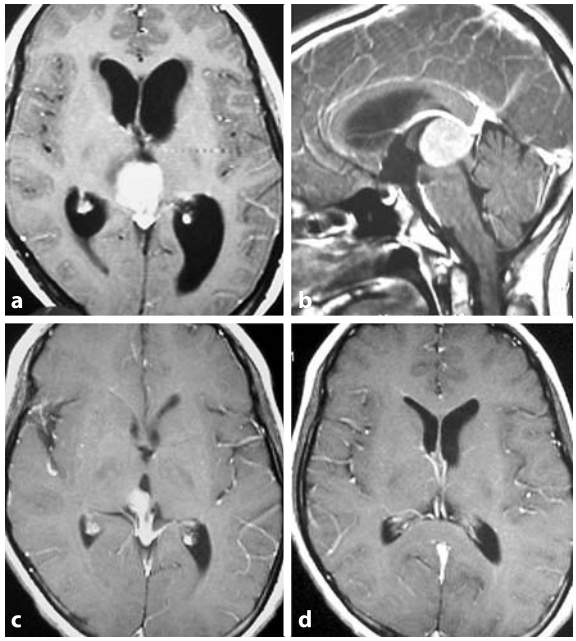


Fig. 1. a,b A large pineal tumor occurring in a 12-year-old girl presenting with Parinaud's syndrome, vomiting, and bilateral abducens palsy. Germinoma was verified by a biopsy using a CT-guided stereotactic procedure. **c** Two weeks after the initiation of the first course of a cisplatin-based chemotherapy, the tumor shrunk remarkably in size, and the hydrocephalus was resolved with symptoms. During the chemotherapy, the hydrocephalus was controlled by a ventricular drainage placed during the biopsy. Shunting surgery is not necessary in cases of germinoma. **d** After three courses of chemotherapy and before radiation therapy, the germinoma completely disappeared on MR image

Although in general a greater resection of the malignant neoplasm is associated with a better prognosis for patients, a radical surgical resection of invasive tumor carries a certain risk of operative morbidity. The primary goal of surgery for pineal germinomas should be to obtain a sufficient volume of tumor tissue for an accurate histological examination. If preoperative radiological studies indicated a strong suspicion of germinoma, biopsy samples should be obtained by a craniotomy, stereotactic, or endoscopic procedure. When an intraoperative histological diagnosis of germinoma was made during craniotomy, no risk should be taken in continuing the resection, because near the end of tumor resection, we often encounter a residual mass invading the periaqueductal, the superior colliculus, and the posterior thalamus. Stopping the procedure at this point will reduce the complication rate significantly without reducing the cure rate of this unique neoplasm.

There are two major surgical approaches to the pineal tumors, the infratentorial supracerebellar approach and the occipital transtentorial approach [18]. Krause was the first to use the infratentorial supracerebellar approach to the quadrigeminal plate, and by the 1920s he had successfully treated three cases. Using microsurgical techniques, Stein developed this approach further during the 1970s. Poppen experimented with the right suboccipital approach in one case; he lifted the occipital lobe after having introduced a catheter into the ventricle to drain the cerebrospinal fluid. Jamieson modified this approach by mobilizing the occipital pole laterally rather than using an approach below it.

On the way to the pineal body, the prominent obstacle is the Galenic venous system (Fig. 2). The vein

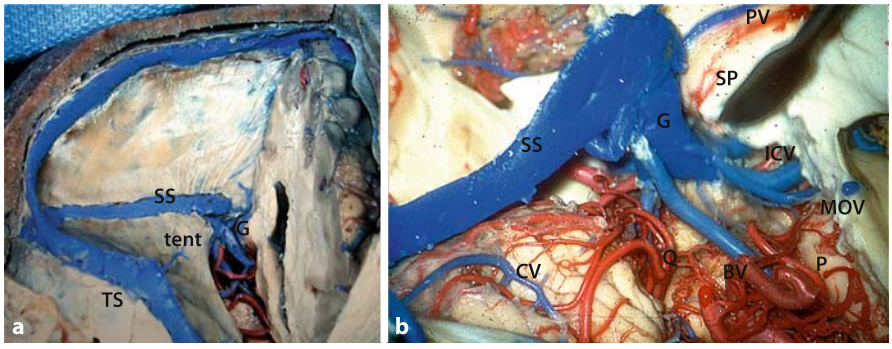


Fig. 2 a,b. Overview of the pineal region through the right occipital area. The occipital lobes, the falx, the tentorium, and the arachnoid membranes have been removed. *BV* basal vein of Rosenthal, *CV* cerebellar vermis, *G* great vein of Galen, *ICV* internal cerebral vein, *MOV* medial occipital vein, *P* pulvinar, *PV* pericallosal vein, *Q* quadrigeminal plate, *Sp* splenium, *SS* straight sinus, *TS* transverse sinus

of Galen gathers several important tributaries. The superior vermian vein and the precentral cerebellar vein run in the midline and into a dorsocaudal part of the great vein of Galen. The internal cerebral veins and the pineal veins join ventrally. With pineal tumors, the posterior portion of the internal cerebral veins is always elevated rostrally, and the veins are occasionally separated from each other. On the lateral aspect of the great vein, the medial occipital veins, the third segment of the basal veins of Rosenthal, and the posterior mesencephalic veins join. The pineal veins which are the draining veins of pineal tumors drain into either the posterior portion of the internal cerebral veins or the vein of Galen. The superior vermian vein, the precentral cerebellar vein, and the pineal veins can be sacrificed, but all the other veins must be preserved. An injury to the basal vein or the internal cerebral vein will yield major complications, and a transection of a major medial occipital vein may cause homonymous hemianopsia or visual seizures.

The choice of approach will depend on the angle of the straight sinus, the size and location of the tumor, the presence or absence of obstructive hydrocephalus, and in particular the direction of displacement of the quadrigeminal plate (Fig. 3).

The angle of the straight sinus is quite variable from one patient to another. When we apply the infratentorial approach, a very steep angle of the straight sinus makes it necessary to retract the cerebellum downwards rather extensively. Lateral exposure of the surgical space is also restricted for a large tumor, although this is not a problem in the case of a small tumor. In cases with a steep angle of the straight sinus, the occipital transtentorial approach is preferable.

A pineal tumor may lie more or less ventrally in the pineal area. Its relationship with the quadrigeminal plate, the splenium of the corpus callosum, and the venous system varies. The tumors lying strictly in the midline and in the posterior part of the third ventricle anterior to the pineal gland, and compressing the tegmentum of the midbrain caudally, are approached infratentorially because this approach will allow direct access and symmetrical exposure of the walls of the third ventricle and the internal cerebral veins on both sides. This approach, however, requires a sacrifice of the veins bridging the straight sinus, the cerebellum, and the tentorium such as the superior vermian vein and the precentral vein. It may occasionally cause venous infarction and postsurgical ataxia. Given these drawbacks, we have recently been using the occipital transtentorial approach more frequently than the infratentorial approach.

Pineal tumors often extend into the supratentorial segment of the aqueduct, and as a consequence the tumors depress the quadrigeminal plate dorsally. In such cases, the infratentorial approach is not applicable, because the colliculi definitely obstruct the tumor. A large tumor compressing or invading the pulvinar thalami is approached by the occipital transtentorial route, which gives a wider lateral exposure than the infratentorial route does.

Obstructive hydrocephalus is frequently present, but no preoperative shunting should be performed before craniotomy. Indeed, taping the lateral ventricle at the beginning of operation makes retraction of the occipital lobe extremely easy and opens a highway to the pineal area. On the other hand, if there is no hydrocephalus or if shunting was placed previously, the retraction of the occipital lobe may be somewhat difficult. Shunting should be avoided in cases of germinomas or other malignant neoplasms because of the potential for peritoneal metastasis through the shunt.

Infiltrative tumors may invade the posterior commissure and the periaqueductal neuronal tissue. In such cases, an extremely careful observation is

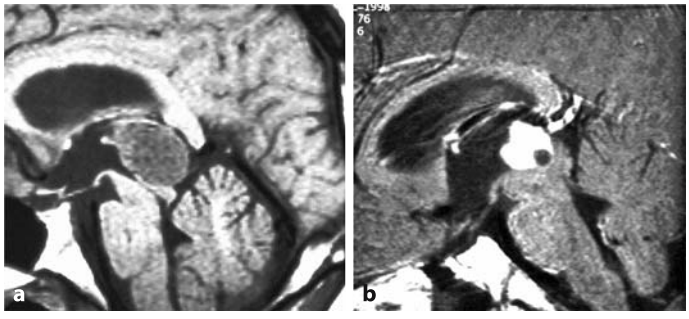


Fig. 3. **a** An embryonal carcinoma in a 19-year-old man. A pineal tumor like this, lying strictly in the midline and in the posterior part of the third ventricle and compressing the quadrigeminal plate caudally, can be approached infratentorially. **b** A pineal germinoma in a 9-year-old boy. When a tumor lies more caudally and pushes the quadrigeminal plate dorsally, the occipital approach is more appropriate. Pineal tumors often extend into the supratentorial segment of the aqueduct

necessary in order to keep these neuronal tissues intact during a tumor resection, otherwise, postsurgical gaze palsy will remain permanently. A potential complication of the infratentorial approach is ataxia and that of the occipital approach is hemianopsia. A lethal complication may occur as a result of an injury to the great vein of Galen, an uncontrollable arterial bleeding in the ambient cistern, or an air embolism while the patient is in the sitting position. Major complications are induced by impairment of venous circulation through the deep major veins, in particular the internal cerebral veins or the basal veins, whose injury will cause venous infarction in the areas including the diencephalon, the internal capsule, and/or the corticospinal tract.

Radiotherapy and Chemotherapy

Pineocytomas may be curable by a total surgical resection or a partial surgical resection with adjuvant radiation therapy. Some pineocytomas in the pediatric population, however, are aggressive, with a high propensity for leptomeningeal dissemination [10]. On the other hand, all patients with a pineoblastoma should be treated with intensive adjuvant therapy. PPTID also requires postsurgical adjuvant therapy. For malignant pineal parenchymal tumors, the median total dose administered to the pineal region was approximately 54 Gy [15, 19]. Pineoblastomas that frequently disseminate through the CSF pathway require craniospinal irradiation, as the CCG-921 trial report suggested that craniospinal irradiation has a significant impact on survival with a 3-year event-free survival of 61% in children [12]. In the literature, various chemotherapeutic agents and response to chemotherapy are also documented only in pediatric series. However, no standard regimen has been established for young children with malignant pineal parenchymal tumors [11, 12].

A complete surgical removal alone will inevitably cause an early relapse of the germinoma, and there is no significant difference in outcome related to the extent of the surgical resection. It is, therefore, clear that a radical resection of pineal germinoma offered no benefit over biopsy [16]. Germinomas are so radiosensitive that they occasionally show regression even after the radiation for diagnostic angiography. A tumor regression after a very small dose of radiation in a child or young adult is strongly suggestive for germinoma. If a mixed GCT is mistakenly interpreted as 'pure germinoma' after a biopsy, at least the germinoma component can be eradicated by an adjuvant therapy, and other components may remain. After that, a second-look surgery is feasible to resect the residual tumor that was resistant to the adjuvant therapy.

Germinomas tend to be treated with a lower dose of irradiation applied to a smaller volume than those used with conventional radiotherapy of 40–55 Gy [5]. Bayens et al. suggested that the outcomes of patients with germinoma treated with a dose of 30 Gy were comparable to those of patients with testicular germinoma treated with a similar dose [6]. The efficacy of a dose less than 30 Gy has not been determined.

Preirradiation chemotherapy has been advocated as an adjuvant therapy to further decrease the total volume of irradiation [2]. It is known that germinomas are highly chemosensitive tumors, and the agents which have been examined in previous clinical studies are bleomycin, carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, and vinblastine [1, 2, 3, 4, 7]. The most common combination in chemotherapeutic regimens includes carboplatin/cisplatin plus etoposide. An European study has suggested that preirradiation chemotherapy followed by 30–40 Gy of irradiation may be adequate for treating germinomas [7].

Aoyama et al. reported the results of an induction chemotherapy followed by 24 Gy of irradiation in 12 fractions to the involved field. With a mean follow-up duration of 58 months, 6 of 27 patients with germinoma had a relapse [3]. This high relapse rate is attributed to the small radiation field that they employed. The whole-ventricle field is at least necessary for the majority of patients with non-disseminated germinoma.

Neoadjuvant therapy, including chemotherapy and radiation therapy, has recently been advocated in the treatment of large and malignant pineal tumors [14]. After giving an effective neoadjuvant therapy and obtaining tumor-bulk reduction visible on neuroimaging, a safer and complete surgical resection can be performed. For the malignant germ-cell tumors, no standard chemotherapeutic regimen has been established.

Prognosis/Quality of Life

Pineocytomas are found in older individuals than pineoblastomas, and show better prognosis after surgery. Except for certain pediatric cases, a complete removal usually yields long-term control or cure. In contrast, pineoblastomas and PPTID have a poor prognosis as malignant neoplasms. Fauchon et al. reported a series of 76 patients with pineal parenchymal tumors in which the 5-year survival was 91%, 74%, 39%, and 10% for grades I, II, III, and IV tumors, respectively. Histology and tumor volume were significant prognostic factors, but the extent of surgery and radiotherapy had no clear influence on survival [11].

In a multicenter, large, retrospective study reported by Lutterbach et al. [15], the median survival of 101 patients at least 18 years of age who received radiation therapy for a malignant pineal parenchymal tumor was 100 months, and the 10-year survival rate was 41%. In their study, the variables that significantly influenced the survival were the extent of disease at diagnosis (localized vs disseminated), histological differentiation (PPTID vs pineoblastoma), and residual disease after initial treatment (no residual vs major residual). Late relapses were common, and the median overall survival in patients with local or spinal failure was only 15 months.

The prognosis for each subtype of germ-cell tumor is diverse. Sawamura et al. have analyzed the records of 109 patients undergoing treatment mainly with radiation therapy [17]. With a median follow-up duration of over 6 years, the probability of surviving 5 years was better than 90% for patients with a pure germinoma or mature teratoma. The 5-year overall survival rate in patients with an immature teratoma with or without a germinoma component was approximately 65%. Patients with germ-cell tumors that included a highly malignant component, such as an embryonal carcinoma or yolk-sac tumor, exhibited a poor prognosis with an approximately 40% chance of 5-year survival.

Quality of life of long-term survivors depends on the severity of the initial manifestation and densities of treatments including surgical intervention, dosage of radiation therapy, and intensity of chemotherapy. Although no data were available in the literature concerning the quality of life, at least the delayed toxicity of craniospinal irradiation has to be considered before selecting an initial treatment plan, especially in young children whose CNS are vulnerable to radiation therapy. The CCG-921 trial reported that all 12 children aged 9 years or less who received craniospinal radiation therapy for malignant pineal tumor had significant neurocognitive deficits [12].

Follow-up/Specific Problems and Measures

Malignant pineal tumors often disseminate from the pineal region by direct infiltration or spread along the CSF pathways. Treatment failure is found both in the pineal region and distant sites with evidence of relapse. An adequate neurological examination and craniospinal MRI scans are, therefore, necessary for patient follow-up. For germ-cell tumors, monitoring of the levels of HCG-beta and AFP have proven useful for the early detection of tumor recurrence or relapse. Measurement of the tumor markers often serves for more sensitive detection of the recurring disease than does MRI of the whole neuraxis.

Future Perspectives

Curability and quality of life in patients with a benign pineal tumor have been dramatically improved along with the development of modern neurosurgery. In contrast, many fundamental issues regarding the therapeutic management of malignant pineal tumors remain to be investigated such as the prognostic effect of the extent of resection, the curative radiation dosages, and the role of chemotherapy. These needs to be clarified in future prospective trials, although the low incidences of each pineal tumor may make the trial design difficult.

References

1. Allen JC, Kim JH, Packer RJ. Neoadjuvant chemotherapy for newly diagnosed germ-cell tumors of the central nervous system. J Neurosurg 1987; 67:65–70
2. Allen JC, DaRosso RC, Donahue B, Nirenberg A. A phase II trial of preirradiation carboplatin in newly diagnosed germinoma of the central nervous system. Cancer 1994; 74:940–944
3. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y. Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 2002; 20:857–865
4. Balmaceda C, Heller G, Rosenblum M, Diez B, Villablanca JG, Kellie S, Maher P, Vlamis V, Walker RW, Leibel S, Finlay JL. Chemotherapy without irradiation – A novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. J Clin Oncol 1996; 14:2908–2915
5. Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, Harms D, Gobel U. Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol 1999; 17:2585–2592
6. Bayens YC, Helle PA, Van Putten WL, Mali SP. Orchidectomy followed by radiotherapy in 176 stage I and II testicular seminoma patients: benefits of a 10-year follow-up study. Radiother Oncol 1992; 25:97–102
7. Calaminus G, Bamberg M, Baranzelli MC, Benoit Y, di Montezemolo LC, Fossati-Bellani F, Jurgens H, Kuhl HJ, Lenard HG, Curto ML. Intracranial germ cell tumors: a comprehensive update of the European data. Neuropediatrics 1994; 25:26–32
8. Chang SM, Lillis-Hearne PK, Larson DA, Wara WM, Bollen AW, Prados MD. Pineoblastoma in adults. Neurosurgery 1995; 37:383–390
9. Chiechi MV, Smirniotopoulos JG, Mena H. Pineal parenchymal tumors: CT and MR features. J Comput Assist Tomogr 1995; 19:509–171
10. D'Andrea AD, Packer RJ, Rorke LB, Bilaniuk LT, Sutton LN, Bruce DA, Schut L. Pineocytomas of childhood. A reappraisal of natural history and response to therapy. Cancer 1987; 59:1353–1357

11. Fauchon F, Jouvet A, Paquis P, Saint-Pierre G, Mottolese C, Ben Hassel M, Chauveinc L, Sichez JP, Philippon J, Schlienger M, Bouffet E. Parenchymal pineal tumors: a clinicopathological study of 76 cases. Int J Radiat Oncol Biol Phys 2000; 46(4):959–68
12. Jakacki RI, Zeltzer PM, Boyett JM, Albright AL, Allen JC, Geyer JR, Rorke LB, Stanley P, Stevens KR, Wisoff J, et al. Survival and prognostic factors following radiation and/or chemotherapy for primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Childrens Cancer Group. J Clin Oncol 1995; 13:1377–1383
13. Jouvet A, Saint-Pierre G, Fauchon F, Privat K, Bouffet E, Ruchoux MM, Chauveinc L, Fevre-Montange M. Pineal parenchymal tumors: a correlation of histological features with prognosis in 66 cases. Brain Pathol 2000; 10(1):49–60
14. Kochi M, Itoyama Y, Shiraishi S, Kitamura I, Marubayashi T, Ushio Y. Successful treatment of intracranial nongerminomatous malignant germ cell tumors by administering neoadjuvant chemotherapy and radiotherapy before excision of residual tumors. J Neurosurg 2003; 99:106–114
15. Lutterbach J, Fauchon F, Schild SE, Chang SM, Pagenstecher A, Volk B, Ostertag C, Momm F, Jouvet A. Malignant pineal parenchymal tumors in adult patients: patterns of care and prognostic factors. Neurosurgery 2002; 51:44–55
16. Sawamura Y, de Tribolet N, Ishii N, Abe H. Surgical management of primary intracranial germinomas: diagnostic surgery or radical Resection ? J Neurosurg 1997; 87:262–266
17. Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H. Germ cell tumors of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. Eur J Cancer 1998; 34:104–110
18. Sawamura Y, de Tribolet N. Neurosurgical management of pineal tumors. Adv Tech Stand Neurosurg 2001; 27:1–22
19. Schild SE, Scheithauer BW, Schomberg PJ, Hook CC, Kelly PJ, Frick L, Robinow JS, Buskirk SJ. Pineal parenchymal tumors. Clinical, pathologic, and therapeutic aspects. Cancer 1993; 72:870–880
20. The Committee of Brain Tumor Registry of Japan (BTRJ). Brain Tumor Registry of Japan (BTRJ 1969–1996), 11th edition, Neurol-Med Chir 2003; 43(suppl):29

Tumors of the Cranial Nerves 14

Berndt Wowra, Jörg-Christian Tonn

Epidemiology – 218

Symptoms and Clinical Signs – 218

Diagnostics – 219

Staging and Classification – 219

Treatment – 220
Meningioma Associated with Cranial Nerves
Optic Nerve Glioma
Schwannomas
Orbital Cavity Schwannoma
Vestibular Schwannoma
General Aspects

Prognosis/Quality of Life – 228

Follow-up/Specific Problems and Measures – 228

Future Perspectives – 228

References – 229

Epidemiology

The most frequent tumors of the cranial nerves are referred to as schwannomas (formerly neuromas). They may develop in most cranial nerves, except I and II which do not have Schwann cells except for very rare cases of ectopic pediatric olfactory schwannomas. CNS account for 8% of intracranial tumors. The incidence is rising since the distribution of MRI became widespread. The incidence of the most common CNS, the vestibular schwannoma (VS), is estimated to be 1.3 (per 100,000 inhabitants per year) nowadays compared with 0.8 in the period between 1976 and 1983 [136]. Furthermore, the incidence of CNS is higher in patients with neurofibromatosis type 2 (NF2) [14].

Another group of tumors with a frequent relation to cranial nerves is the meningiomas. However, they originate from the arachnoidal cell layer and not directly from neural structures. Therefore, it seems appropriate to focus this contribution on those meningiomas which have a similar close relation to cranial nerves like the schwannomas. These are the optic nerve sheath meningioma (ONSM) and the meningiomas extending into the optic canal. Meningiomas like the fronto-orbital tumors compressing the olfactory nerve are not dealt with. Meningiomas of the cavernous sinus or the petroclival meningiomas which may compress optic pathway structures are also excluded. ONSM and the meningiomas extending into the optic canal account for 1–2% of all meningiomas [25].

There are further very rare cranial nerve tumors. Optic pathway glioma (optic nerve glioma, ONG) emerge in NF1 children below the age of 7 years, and as a separate entity in non-NF1 patients also in older children and in adults [8, 23, 65, 144]. ONG are increasingly considered as markers of enhanced risk in patients and their families for subsequent development of central nervous system tumors [144]. The incidence of ONG is about 1:10,000.

Malignant peripheral nerve sheath tumors (MPNST) account for about 5% of malignant soft-tissue tumors. The involvement of cranial nerves is very seldom [13, 39, 57], and if it occurs, the trigeminal nerve or the vestibulo-cochlear nerve is affected predominantly [2, 10, 13, 39, 151]. The prevalence of neurofibromatosis type 1 (NF1) is around 1:4000 [14], and NF1 patients have an approximately 10% lifetime risk of developing MPNST [35]. Esthesioneuroblastoma (synonym: olfactory neuroblastoma) is a small round-cell tumor type originating from the olfactory epithelium [14]. About a thousand examples of this very rare tumor have been described so far [66].

Symptoms and Clinical Signs

Clinical symptoms of the CNS depend on three factors: the cranial nerve which is associated with the tumor; the tumor's growth velocity, which is slow in most benign lesions; and the size of the tumor. Larger tumors may compromise other cranial nerves and functional areas of the brain in the vicinity of the lesion (Fig. 1). In general, the first clinical symptoms are specific deficits of the cranial nerve involved by the tumor.

Optic gliomas and meningiomas of the optic nerve sheath may cause progressive loss of vision, bulbar protrusion, and congestion of sclera vessels. The malignant esthesioneuroblastoma is frequently associated with recurrent epistaxis.

Facial neuropathy is frequent in trigeminal schwannomas. Vertigo, tinnitus, and hearing loss are key symptoms of VS. Peripheral facial nerve palsies indicate schwannomas of the ganglion geniculi. Swallowing difficulties and the sensation of having a lump in the throat are signs of schwannomas of the jugular foramen and the caudal cranial nerves. With increasing tumor size, further symptoms may develop: trigeminal deficits in VS, ataxia and cardiac arrhythmia in schwannomas of the caudal cranial nerves. If the craniospinal fluid (CSF) passage is compromised by larger schwannomas, the symptomatology of obstructive hydrocephalus may develop.

Fig. 1. Autopsy specimen of a patient who died because of a large vestibular schwannoma (VS) displacing the brain stem

Diagnostics

Diagnostic means include clinical examination, neurophysiology, and neuroimaging. Clinical examination may include neurology, ophthalmology, and audiology. Neurophysiology helps to analyze the specific function of a cranial nerve compromised by a tumor. Imaging basically includes MRI and CT. Nowadays, sophisticated MRI techniques and contrast media are used to characterize a tumorous lesion noninvasively and to support the therapeutic decision-making.

Differential diagnostic considerations for a mass of the optic nerve within the orbit include ONG or ONSM, schwannoma and granulomatous disease, specifically neurosarcoidosis, cavernous hemangioma, dermoid, and metastases. The circumferential, homogenously enhancing appearance of the lesion with a thin residual segment of the optic nerve centrally strongly suggests a meningioma. However, ONG and ONSM are sometimes difficult to differentiate even with elaborate imaging [7, 9, 23, 48, 52, 73, 107]. In cases of canalicular optic nerve meningioma, the diagnosis may be missed for a longer time period. Clinical features can lead to a misdiagnosis of optic neuritis or ischemic optic neuropathy, and the diagnosis can sometimes be made only by high-spatial-resolution contrast-enhanced MR findings, including native and contrast-enhanced scanning and fat-suppression sequences [41, 51].

The differentiation in tumors of the sinus cavernosus and the cavum Meckeli between schwannoma of the trigeminal nerve and meningioma can be made without difficulty in most cases. Here, the clinical symptoms may be of help, because meningiomas are frequently associated with mild oculomotor deficits whereas schwannomas are associated with trigeminal neuralgia or neuropathy. Furthermore, the topographic extension is quite specific for each of the two entities. This can be evaluated reasonably well by MRI. The rare cases of cavernous sinus cavernomas may require digital angiography for diagnosis before resection.

Difficulties in the differential diagnosis between meningioma and schwannoma frequently arise in lesions of the cerebellopontine angle. Since the presenting symptoms are not specific, a refined MRI analysis revealing the matrix structure of the tumor under study will predict the histology with high probability in most instances. The differential diagnosis of lesions in the cerebellopontine angle furthermore comprises inflammatory or vascular lesions and metastases (Fig. 2) [121]. The latter may imitate bilateral VS as they are found in NF2 patients. Further lesions of the cerebellopontine angle to be taken into account in the differential diagnosis are the glomus tympanicum tumors and cholesteatoma (epidermoid cysts).

The differential diagnosis of lesions associated with the caudal cranial nerves and with the area of the foramen jugulare comprises schwannomas, meningiomas, metastases, and a few very rare lesions like the chloroma. Of clinical significance are the tumors of the glomus jugulare (formerly also referred to as paraganglioma). However, these tumors originate from specialized neural crest cells and affect the cranial nerves only by compression or displacement, and thus they are not cranial nerve tumors in the strict sense of the word. Tumors of the glomus jugulare usually present with pulsatile tinnitus, hearing loss, hoarseness and dysphagia. The chromaffin tumor type may be associated with hypertension. In such tumors, radionuclide imaging may support the diagnosis. Angiography shows highly vascularized tumors which therefore lend themselves to embolization (see later).

Staging and Classification

Most nerve tumors are benign (according to WHO grade 1). Optic nerve gliomas are the principal CNS neoplasm in NF1. Although the histology of these tumors typically reveals pilocytic astrocytoma (WHO grade I) [57, 58], they can present within the entire spectrum of astrocytic neoplasias including glioblastoma (WHO grade IV)[20]. Still, malignant optic gliomas are rare tumors. They are usually found in adults [143]. Meningiomas in close contact to cranial nerves and schwannomas are normally benign. Although schwannomas associated with NF2 may have a higher proliferative activity, this does not indicate malignant behavior [57, 58]. Apparently, loss of merlin expression constitutes a genetic alteration shared by all schwannomas [149].

In contrast, malignant peripheral nerve sheath tumors (MPNST) correspond to WHO grade III or IV. These tumors are also referred to as malignant

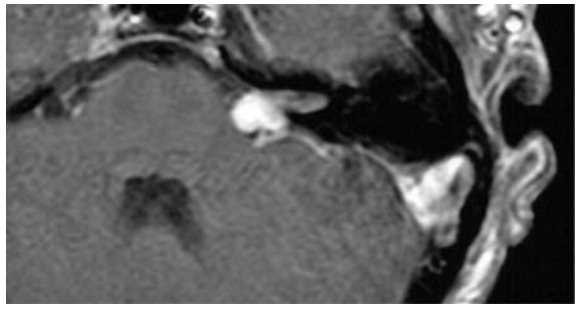


Fig. 2. A fast-growing lesion in the left cerebellopontine angle mimicking a VS. The tumor turned out to be a malignant lymphoma

schwannomas and as malignant triton tumor, if they show rhabdomyosarcomatous differentiation [13, 39, 57]. They are associated with NF1 [57], and as a basic principle they arise de novo [149]. Several variants of MPNST have been identified. A minority of MPNST show epithelioid or perineurial cell differentiation. These tumors carry a more favorable prognosis than anaplastic or glandular MPNST or malignant triton tumor [43, 57, 59].

Esthesioneuroblastomas (synonym: neuroblastomas of the olfactory nerve) are malignant neuroectodermal tumors of WHO grade IV which tend to metastasize. Their matrix consists of the olfactory receptor cells in the upper nasal cavity [57].

Clinical classification is normally done for the purpose of assigning an appropriate therapy to any individual cranial nerve tumor. For ONSM, the crucial question is whether there is an extension into the intracranial space or not. In pure intraorbital meningiomas, the tumor is amenable to complete excision if necessary. In case of intracranial extension of an ONSM, surgical therapy is not useful. On the other hand, if intracranial meningiomas (not ONSM) extend into the optic canal, the surgical approach depends on the localization of the meningioma in relation to the optic nerve and on the origin of the tumor [119].

Several classifications have been proposed for VS. They all categorize according to tumor size, which is the most decisive outcome predictor. A summary of the classification systems is given in Table 1 [64, 115, 135].

A surgical classification of trigeminal schwannomas (TNS) was published by Samii and co-workers in 1995 [117] (Table 2). This classification uses the topographic extension of trigeminal schwannomas as a guideline to determine the best surgical approach in order to achieve complete resection.

In a very similar way, Samii also classified the surgical approaches to the tumors of the foramen jugulare, including the schwannomas of the caudal cranial nerves (Table 3) [116].

Kadish and co-workers developed a staging system of esthesioneuroblastoma which suggests a treatment policy correlated to the anatomical extension of these tumors [53]. The Kadish classification is given in Table 4.

Treatment

Treatment options for benign tumors comprise watchful waiting, microsurgery, radiosurgery, and the variants of modern fractionated radiation therapy. In the era of MRI, slowly growing tumors no longer implicate a vital risk (Fig. 1). They mainly constitute a functional problem for the patient concerning a specific neural deficit. Since many of them are diagnosed in patients in their most active period of professional and social life, the benign behavior of these lesions has to be taken into account when deciding on therapy. In this respect, radiosurgery has been established as an alternative to microsurgery for VS and meningiomas. For large tumors, radiosurgery may be used as an adjunct to microsurgery if a lesion cannot be completely removed without significant risk. Stereotactic radiotherapy (and intensity-modulated conformal radiotherapy) is specifically indicated in large schwannomas and meningiomas diag-

Table 1. Classification of vestibular schwannoma (VS). Synopsis according to Tos [32], Koos [64], and Samii [115]

Size (Tos)	Grade (Koos)	Class (Samii)	Definition of tumor size
	Grade I	T1	Purely intracanalicular lesion
	Grade II	T2	VS protruding into the cerebellopontine angle without brain stem contact
<1 cm	IIA	T2	Tumor diameter <1 cm
1–1.8 cm	IIB	T2	Tumor diameter 1–1.8 cm
	Grade III	T3a	Filling cerebellopontine angle cistern
		T3b	Reaching the brain stem
	Grade IV	T4a	Brain stem compression
		T4b	Severely dislocating the brain stem and compressing the fourth ventricle

nosed in inoperable patients and in patients with optic nerve gliomas and optic nerve sheath meningiomas if the vision is spared. Classic whole-brain radiation therapy no longer plays a role in the treatment of benign tumors of the cranial nerves.

Malignant tumors as a rule deserve resection and adjunct fractionated radiation therapy and/or chemotherapy.

Table 2. Surgical classification of trigeminal schwannomas (TNS) according to Samii [117]

Type	Definition of tumor extension
Type A	Intracranial predominantly in the middle fossa
Type B	Intracranial predominantly in the posterior fossa
Type C	Intracranial dumbbell-shaped in the middle and posterior fossa
Type D	Extracranial with intracranial extension

Table 3. Surgical classification of jugular foramen schwannomas (CNS) according to Samii [116]

Type	Definition of tumor extension
Type A	Primarily at the cerebellopontine angle with minimal enlargement of the FJ
Type B	Tumors primarily in the FJ with intracranial extension
Type C	Primarily extracranial tumor with extension into the FJ
Type D	Dumbbell-shaped tumors with both intra- and extracranial components

FJ Foramen jugulare

Table 4. Staging of esthesioneuroblastoma according to Kadish [53]

Group	Definition
Group A	Tumor is limited to the nasal cavity
Group B	Tumor is localized to the nasal cavity and paranasal sinuses
Group C	Tumor extends beyond the nasal cavity and paranasal sinuses

Meningioma Associated with Cranial Nerves

Meningiomas associated with the optic nerve may be either ONSM or sinus cavernous meningiomas extending into the optic canal or suprasellar meningiomas displacing the optic chiasm. Except for ONSM, in all other meningiomas compressing or displacing segments of the optic nerve, surgery is generally the first-line treatment in order to relieve the optic nerve and to achieve at least partial tumor resection. Some of these meningiomas cannot be removed completely. In such cases, either radiosurgery or fractionated stereotactic radiation therapy are indicated as a second-line treatment.

The natural course of ONSM is slow progression leading to progressive optic neuropathy and proptosis. Until today, the treatment of ONSM remains controversial to some degree. In addition to surgery and radiation therapy, even chemotherapy with hydroxyurea has been applied [109]. Because ONSM are typically circumferential to the optic nerve and adhere tightly to the perineural microvessels, it is impossible to avoid trauma to the optic nerve during surgery and, therefore, to not compromise the patient's vision. In blind patients, excision of the tumor including the optic nerve and sheath is possible. Tumor extension posteriorly beyond the optic canal to the intracranial side excludes the chance of surgical cure. These cases are indications for radiotherapy which has experienced great progress due to the development of computerized and stereotactically guided methods of three-dimensional conformal radiation therapy. Stereotactic fractionated radiation and conformal radiotherapy have been used increasingly to treat ONSM. Favorable results have been published at least in the short term, and primary stereotactic fractionated radiation therapy has been advocated to preserve vision in patients with ONSM better than observation alone [4, 11, 60, 70, 95, 97, 111, 138]. Some authors even assume that this type of radiation therapy may become a standard treatment approach for ONSM [4, 11, 111]. However, very recently, radiation retinopathy and loss of vision after fractionated stereotactic radiotherapy for ONSM were reported [126]. This observation warrants caution not to overestimate the potential of fractionated stereotactic and three-dimensional conformal radiotherapy because of the well-known long latency of radiation damage to other sensitive structures than the optic nerve itself. Radiosurgery does not play a role in pa-

tients with ONSM and preserved vision, but in blind patients and small tumors, it can substitute for any other type of therapy very elegantly.

For meningiomas extending into the optic canal from the inside of the skull, surgical unroofing is the preferred treatment. The surgical approach in this situation depends on the localization of the meningioma in relation to the optic nerve [119].

Meningiomas in association with other cranial nerves are found among the meningiomas of the middle or posterior fossa cerebri. In general, such lesions are primary candidates for resection if they are progressive, symptomatic, or of considerable size at diagnosis. If complete resection turns out to be too risky in an individual case, adjunct radiosurgery is recommended for small tumor remnants. In residual meningiomas too large for radiosurgery and in progressive meningiomas en plaque, fractionated radiation therapy is used. Today these lesions are indications for stereotactic radiotherapy or intensity-modulated (highly conformal) radiation therapy. For small skull-base meningiomas with progressive growth proven by appropriate sequential MRI, primary radiosurgery turns out to be an effective and only minimally invasive treatment.

Optic Nerve Glioma

Progressive intraorbital optic nerve gliomas (ONG) are best treated by surgical 'en bloc' resection [23]. However, surgical intervention in ONG of childhood is a subject of debate. In this situation, intraoperative MRI guidance may be of great help in the future, especially in combination with imaging-guided biopsy to define the tumor extensions better [142, 144]. Progressive chiasmatic tumors are best treated by fractionated radiotherapy [16]. Modern variants of radiotherapy (stereotactic fractionated radiotherapy, proton therapy) allow effective treatment of ONG. In contrast to conventional radiotherapy, it provides the potential of sparing the pituitary gland in chiasmatic lesions. In some instances, vision may even improve after this type of radiotherapy [21, 37]. Exophytic chiasmatic tumors may be treated by chiasm-preserving surgery and subsequent radiotherapy [8, 16]. Radiosurgery can also be used as an effective adjuvant therapy in selected cases [74].

Rare cases of adult malignant optic nerve glioma have been published. These tumors may mimic optic neuritis in their initial presentation. On MRI, malignant glioma cannot be distinguished from optic nerve enlargement due to other causes. Although radiotherapy appears to prolong the life expectancy, all presently available treatment options (radiation, surgery, radiochemotherapy) are of limited value. Most patients go blind and die within 1 or 2 years [143].

Schwannomas

Orbital Cavity Schwannoma

Among the tumors of the orbit, patients with intraorbital schwannoma have the most favorable prognosis in terms of both visual function and long-term quality of life. Therefore, removal of orbital cavity schwannomas should not be postponed since the surgical outcome is excellent [23].

Vestibular Schwannoma

General Aspects

Vestibular schwannoma (VS; formerly acoustic neuroma) nowadays are not life-threatening tumors. Presenting symptoms are vertigo, tinnitus, and/or hearing loss which compromise the patients' quality of life. After longer periods of growth, VS may additionally cause hydrocephalus, facial nerve palsy, trigeminal neuropathy, and ataxia by brain stem compression. The degree of hearing loss depends on the width of the internal auditory canal (in relation to the tumor size) and the extension of the VS into the depth of the internal auditory canal. The incidence of both facial and trigeminal nerve deficits is correlated to the extension of the tumor at diagnosis and found in 6% and 9%, respectively [84]. Typically VS grow slowly but not continuously. The proliferative activity of VS seems to be higher in younger patients and with NF2. However, in many patients, there are longer periods of very slow growth or growth arrest [3, 19, 22, 36, 45, 54, 68, 92, 98, 99, 123, 130, 137, 145, 150]. Even spontaneous regression has been described in 6–13% of VS [19, 45, 137, 145]. Taking into account this naturally heterogeneous behavior of VS, the appropriate timing of any therapeutic intervention is an important issue. Apart from a strategy of 'watchful waiting', surgery and radiation therapy are available.

There is no specific chemotherapy for VS. However, concerning the exceptionally rare situation of patients with both metastasizing cancer and (true) VS, it has to be kept in mind that a VS is normally sufficiently treated by a collateral chemotherapy and that some anticancer agents are powerful radiosensitizers.

There are different surgical approaches, and there are several types of radiation therapy including radiosurgery. All types of therapy have been proven to be highly effective in VS, although tumor recurrences are always possible, even in up to 10% in the long term after complete resection [132]. The historical evolution of surgery and radiosurgery developed rather in parallel for the last three decades. In or-

der to help understand the controversial discussions arising in the therapeutic decision-making process, the history of surgery and radiosurgery (including radiotherapy) for VS will be briefly summarized.

Evolution of Microsurgery. Surgery for acoustic neuroma has a long history. Sir Charles Balance is known to have performed the first resection of one acoustic neuroma in 1894 and to have published the initial results in 1907. In his series, the mortality was around 80%. In 1917, Harvey Cushing, one of the early pioneers of neurosurgery, reported a reduced mortality rate of 11%. Just two decades later, Walter E. Dandy, another pioneer of neurosurgery, succeeded in reducing the lethal outcomes in his surgical series of acoustic neuroma below 5%. Today, the surgical mortality rate is around 1%. In the time of the pioneers, all patients were deaf and had complete facial nerve palsy after surgery. However, in 1949 Givre and Olivecrona proceeded to spare the facial nerve in 30% of their surgical cases. In the 1960s, House left an unscathed facial nerve in 95% of small acoustic tumors operated on by the transtemporal approach.

By introducing the microscope to improve vision intraoperatively, the era of microsurgery began around 1975. With microsurgical approaches, the rate of postoperative facial nerve deficit dropped below 3% for small tumors. Nevertheless, it has become accepted since the late 1970s that the rate of preserved facial nerve function after surgery is closely correlated to the size of the tumor. In large tumors, the percentage of moderate to severe facial nerve palsies peaks around 40%. Fortunately, MRI became available in the middle of the 1980s, and since then, increasingly numbers of small tumors were detected. This technical advance in conjunction with the evolution of intraoperative facial nerve monitoring improved the chance to preserve the facial nerve function during surgery [134]. However, the possibility of sparing the facial nerve function after surgery is dependent also on the anatomical extension of the tumor in relation to the facial nerve [124]. Furthermore, facial nerve preservation is significantly reduced in recurrent tumors. By analogy, the chance to preserve hearing increased also due to both the advent of microsurgery and the development of intraoperative neuromonitoring [83, 86, 134]. In small and medium-sized VS (classes T1 to T3; Fig. 3), a useful level of hearing can be preserved in about 60% of the patients. However, the real chance of hearing preservation depends on the presurgical hearing level, the anatomical extension (intra- vs extracanalicular), the size of the tumor, and the surgical approach. Furthermore, it continues to remain difficult to compare hearing results of different series due to the lack of a generally accepted standard of reporting hearing preservation results.

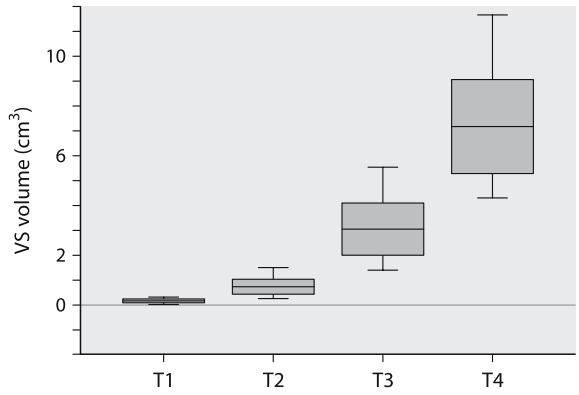


Fig. 3. Correlation between tumor volume (y-axis, cm^3) and T-classification (x-axis, T1, T2, T3, T4) in 300 patients treated for VS by gamma-knife surgery. T-classification according to Tos [135], Samii [85], and Koos [64]

Neurosurgeons and ENT surgeons have developed different avenues to access VS. In small intracanalicular tumors with ipsilateral deafness, a translabyrinthine approach can be used. In small intracanalicular tumors with ipsilateral hearing, the subtemporal approach is recommended. Larger tumors are resected via a suboccipital-retromastoid craniotomy. There are also combined surgical approaches, for example the translabyrinthine-transtentorial access. Planned partial resection can be used in large VS with tumors tightly adhering to the facial nerve or the brain stem in order to minimize functional trauma.

Evolution of Radiosurgery. Radiosurgery as a therapeutic concept has a history of more than half a century. Lars Leksell conceived the radiosurgical treatment principle in 1951, he developed the prototype of the gamma-knife, and he was the first to apply it to an acoustic neuroma in 1968. His initial treatment report was published in 1971 [72]. Subsequently, the gamma-knife therapy for VS evolved into an evidence-based treatment standard. Until today, claim is laid on this gamma-knife standard by the other radiological treatment methods.

Pilot studies on gamma-knife radiosurgery have been performed by the Swedish group headed by Georg Noren since the 1970s [44, 104, 105]. The first North American gamma-knife treatment of acoustic neuroma started in 1989 [78, 79]. The early experience was reported 1 year later [77]. Since this time period, increasingly more gamma-knife centers have started operation worldwide.

Technical progress in gamma-knife radiosurgery for VS translating into improved clinical outcome was achieved by the introduction of MRI for use in treatment planning and follow-up [76, 133]. Although a milestone in neuroimaging, CT is not

required for gamma-knife treatment planning, and therefore, when compared with microsurgery, CT became less significant for gamma-knife radiosurgery. An important step forward was the introduction of the multiple isocenter treatment in the gamma-knife method in 1990 [33]. Biological risk parameters of radiosurgery were identified as well as the tolerance doses of the cranial nerves associated with VS [27, 29, 32, 50, 75, 91, 106]. Leveling off the marginal dose to an optimum of 12–13 Gy was shown to be effective in suppressing tumor growth while better preserving neurological function [29, 30, 42, 102]. Tumor volumetry was shown to be adequate to quantify the treatment outcome following radiosurgery [152]. There is now broad awareness that radiosurgically treated schwannomas are subjected to a chronic and dynamic process which includes transient increase of size due to tissue swelling (interstitial edema). Several centers have documented unequivocally the favorable long-term outcomes of radiosurgery for acoustic neuromas [62, 103, 110, 139]. The gamma-knife indication has also been established for VS recurring after surgery [112] and for NF2 schwannomas [125]. Gamma-knife radiosurgery as an alternative to microsurgery was postulated by Lunsford in 1992 [31, 80]. In 1994, Hudgins and co-workers published a decision analysis comparing microsurgery and radiosurgery. They concluded that when patients prefer the preservation of facial nerve function even if that requires leaving a tumor remnant, then gamma-knife radiosurgery is a better treatment strategy than microsurgical resection [47].

Munich Gamma-Knife Series. According to this outline, gamma-knife radiosurgery has been performed in ambulatory patients in Munich, Germany, since 1994. The results are in agreement with other current published data. Primary gamma-knife radiosurgery was applied to 169 (71%) patients, while 70 (29%) were treated by radiosurgery for residual or recurrent tumor after surgery. At 6 years, the tumor control rate in unilateral VS was 97% with a minimum follow-up time of 2 years after gamma-knife radiosurgery (Figs. 4, 5). Four patients were operated or re-operated for failure of radiosurgery without obvious technical difficulties that could indicate a sequel of radiosurgery. Ten other tumor recurrences were finally controlled by radiosurgical retreatment. Hence, including salvage radiosurgery, the tumor control rate was 99%. The interval between the first and the salvage radiosurgery was 2.4 years. In patients with complete facial nerve function, this was preserved after gamma-knife surgery in all instances. In patients treated twice with the gamma-knife, no facial deficit occurred. In the subpopulation of patients with some degree of facial neuropathy before radiosurgery, the risk of additional facial neuropathy was 10%. These

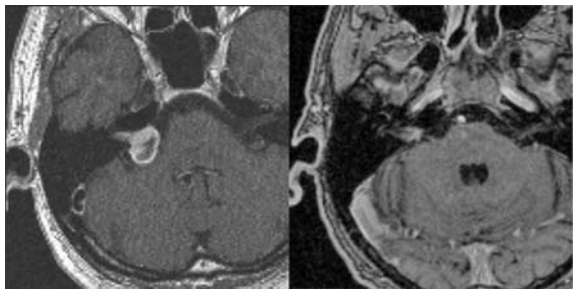


Fig. 4. VS on the right side treated by gamma-knife surgery (*left image*). Follow-up examination after 6 years reveals subtotal regression (*right image*)

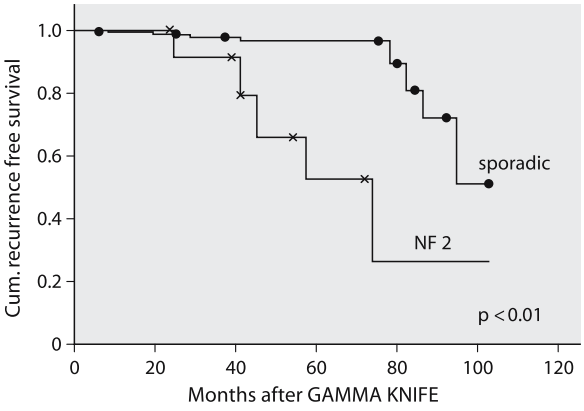


Fig. 5. Tumor control after outpatient gamma-knife radiosurgery (225 sporadic VS; 14 NF2 tumors). The recurrence rate for NF2 schwannomas is significantly ($p<0.01$) higher due to a reduced dose level intentionally given to preserve hearing better. The maximum dose to the tumor was 25.0 (range 15.3–31.1) Gy in sporadic tumors and 23.0 (range 15.7–27.0) Gy in NF2 tumors

symptoms were mild to moderate and transient. Trigeminal neuropathy was observed for larger tumors (class T3 and T4) and pertained also to two patients treated twice. Trigeminal neuropathy was transient, required no medication, and correlated to transient tumor swelling. In 17 patients treated for NF2 schwannomas, the recurrence rate was higher due to a reduced dose level accepted in order to spare hearing better (Fig. 5).

Linear Accelerator Radiosurgery. The principle of radiosurgery can also be performed by other radiation delivery devices, e.g., linear accelerators. These are either adapted for stereotactic irradiation or are dedicated systems. There are several reports on linear accelerator radiosurgery for VS [12, 82, 89, 90, 122, 127]. In general, linear accelerator radiosurgery yielded a high tumor control rate equivalent to the

gamma-knife results. However, the radiological complication rate seems to be somewhat higher, and the published database is quite heterogeneous and less founded compared with the gamma-knife method.

Stereotactic Fractionated Radiation Therapy. Fractionated stereotactic radiotherapy offers an additional therapeutic approach for VS. The rationale for the strategy is that fractionation will allow complications to be reduced while maintaining the same degree of long-term tumor control achieved by radiosurgery [28, 69, 128, 147]. In a single institution trial in particular, a higher rate of serviceable hearing preservation was claimed for fractionated stereotactic radiotherapy than with gamma-knife radiosurgery [5]. However, there are also reports of hearing loss after fractionated stereotactic radiotherapy [113, 114]. On the contrary, another single institution trial concluded that linear accelerator-based single-fraction radiosurgery seems to be as good as linear accelerator-based fractionated stereotactic radiation therapy in VS patients, except for a small difference in the trigeminal nerve preservation rate in favor of a fractionated schedule [88]. Proton beam irradiation is another type of fractionated stereotactic radiotherapy. A tumor control rate reported for proton therapy of VS was similar to the results of gamma-knife radiosurgery. However, the facial nerve toxicity was higher [40, 146].

Most studies on fractionated stereotactic radiotherapy are handicapped by a rather short follow-up time. This aspect is especially noteworthy because fractionation delays the tissue response significantly in comparison to radiosurgery. The time interval for the manifestation of radiation toxicity is less than 1 year in radiosurgery, but it may take several years in fractionated stereotactic radiotherapy. This makes valid comparisons of both treatment methods difficult. Furthermore, in fractionated stereotactic radiotherapy, a higher total dose of radiation has to be applied to compensate for a fractionation effect compromising tumor control. In contrast to radiosurgery, the structures of the inner ear are in the range of fractionated stereotactic radiotherapy. This may cause hearing loss due to radiation toxicity affecting the hair cells in the inner ear [6, 129].

Taking into consideration the argument of radiation protection, it seems rational to restrict fractionated stereotactic radiotherapy to selected patients with large tumors and risk factors for surgery.

Key Issues of Decision-Making. In order to identify in a practical manner the best type of treatment in an individual patient, the following key issues and answers to the major questions may be used:

I. There are differences in the invasiveness and risk profile of the treatment modalities.
II. Concerning the variants of radiation therapy (mainly radiosurgery or fractionated radiotherapy), there are considerable distinctions in dose burden to normal tissue.
III. Different anatomical structures may account for radiation-induced sensorineural hearing loss when either radiosurgery or fractionated (stereotactic) radiation is considered.
IV. Radiation therapy kills the tumor cells but leaves the tumor mass at the disposal of the biological capacity of the body to resolve it. With surgery, the tumor mass is removed, but at the expense of the invasiveness of trephination and tissue dissection.
V. In case of surgery, the choice of the surgical approach depends on the residual hearing level and the size of the tumor.

Further questions determining the surgical indication are the following:

a. is it a sporadic VS or is it a case of NF2?
b. is the hearing preserved in the contralateral ear or not?
c. is it a native tumor, or is it tumor recurrence:
   i. after surgery or
   ii. after radiation therapy.
d. are there conditions indicating an elevated surgical risk for the patient?

Questions with impact on the radiosurgical (or radiotherapeutic) indication are:

a. is the diagnosis of the tumor histology certain enough to allow noninvasive therapy?
b. how active is the tumor concerning clinical symptoms, and how fast growing is the tumor as documented by follow-up imaging?
c. is the size (volume) small enough for radiosurgery?
d. are there conditions associated with increased radiosensitivity (diabetes mellitus)?
e. what is the psychological condition of the patient concerning radiation therapy?
f. what is the comparative profile of other treatment options?
g. concerning the issue of radiation protection: which type of radiotherapy is effective by delivering the lowest dose?

Considering these key issues and questions, it becomes clear that there is no simple or unique solution for every VS patient. In many clinical situations, several treatment strategies are conceivable, indicating a possibility for patients to select the therapy according to their own needs or preferences. On the other hand, there are very critical situations in which not even one reasonable, favorable therapeutic solution exists.

Bearing in mind the various treatment alternatives, it is not surprising that there is no general agreement regarding therapeutic decisions. There is no prospective randomized trial comparing microsurgery (including the various surgical approaches), radiation therapy (including radiosurgery, stereotactic radiation therapy, proton beam therapy), and the 'watchful waiting' strategy. It is clear that both surgery and radiation therapy have experienced a considerable synchronous progress during the last three decades. It is further clear that tumor size remains a decisive prognostic factor in terms of functional outcome for any type of therapy. Radiation therapy is free of the risks predetermined by general anesthesia, opening the skull, and direct tissue manipulation. However, in the situation of primary radiosurgical treatment, the differential diagnosis of the lesions in the cerebellopontine angle has to be regarded. It includes inflammatory, vascular, and neoplastic lesions [121]. Because also metastatic lesions (Fig. 2) may seed in the cerebellopontine angle mimicking a VS, it is not recommended to treat VS-like lesions by radiosurgery in patients with a settled diagnosis of cancer. Although it is an important issue of concern, the risk of carcinogenesis or malignant transformation due to radiosurgery of VS is exceptionally low [120]. Malignant schwannomas (MPNST) arise de novo as a basic principle and not secondary to radiosurgery or radiotherapy [149].

Primary Treatment of Sporadic VS. Large tumors with significant brain stem compression usually require surgical resection. Large tumors in inoperable patients can be treated by stereotactic fractionated radiotherapy. However, nowadays more and more smaller sized tumors are being identified. For such VS, microsurgery and radiosurgery are equivalent therapeutic methods. Radiosurgery is associated with a lower rate of immediate and long-term development of facial and trigeminal neuropathy, postoperative complications, and hospital stay. Radiosurgery yields better measurable hearing preservation than microsurgery and equivalent serviceable hearing preservation rate and tumor growth control [55]. Concerning radiosurgery as a management option, a statement of Kondziolka published in 2003 reads as follows: 'Patients must be able to accept the concept of tumor control rather than tumor removal. Physicians should strive to educate their patients with information from the peer-reviewed literature. Confusion exists among patients because the information from Internet sources, newsletters, support groups, and physicians has not always been validated and supported by outcomes data. Although we are asked to provide our opinions, our comments should not be based on myth, conjecture, training bias, or socioeconomic concerns' [61].

Neurofibromatosis type 2. Patients with NF2 pose specific challenges, particularly in regard to preservation of hearing and other cranial nerve function. In NF2 patients with bilateral tumors, the questions arise: which side should be treated first, and which type of therapy is preferable. If useful hearing is preserved on both sides, it can be recommended to start treatment directed to the more active tumor (in clinical and radiological terms). If radiosurgery is used for this first approach, one should wait for at least 2, better 3 years thereafter to see how well the hearing is preserved on the treated side and how the therapeutic effect (tumor control, tumor shrinkage) manifests. In such situations, we tend to reduce the radiosurgical dose by about 10% in order to spare the hearing better. This is basically at the expense of a reduced tumor control rate, however, and therefore it seems important to know the individual radiosensitivity of the patient's VS before treatment of the other side is performed. If the bilateral tumors are too large for radiosurgery, either a surgical resection (preferentially approaching the larger tumor) or a stereotactic radiotherapy with a classic fractionation scheme (30 times 1.8 Gy) is indicated. Surgery should be conservative in order to minimize the risk of deafness, and in case of tumor remnants, they could be treated by second-line radiosurgery. Our own experience with VS patients with preserved useful hearing after partial tumor resection including opening of the internal auditory canal shows that the risk of radiation-induced hearing loss is quite low in this situation.

Recurrent or Residual VS: Combined Treatment. In cases of recurrences after radiosurgery, both radiosurgical retreatment and surgery are possible. In contrast to earlier experiences when higher doses were used in radiosurgery and when the dose planning was not as precise as today, there is nowadays no increased surgical difficulty due to the delivered gamma-knife dose. Furthermore, it has to be considered that recurrent VS treated with gamma-knife radiosurgery has a lower proliferation potential compared with recurrences following microsurgery. Radiation-induced apoptosis is thought to contribute to the lower tumor cell proliferation of radiosurgically treated tumors [71]. In VS recurring after surgery, radiosurgery is used preferentially because the risk of (additional) damage to the facial nerve is lower than with a second operation. In order to avoid surgical trauma to the cranial nerves or to the brain stem in VS tightly adhering to such a critical structure, a staged procedure is indicated. In the first step, the tumor mass is resected by conservative surgery, and then, in a second step, radiosurgery is used to control tumor remnants.

VS Associated with the Only Hearing Ear. A further issue of importance is the situation in patients with a VS associated with the only hearing ear. This situation is more common in NF2 patients. There is no method available to compare objectively and prospectively the outcome of hearing concerning surgery, radiosurgery, and fractionated stereotactic radiotherapy in such situations. However, there are guidelines common to these treatment options. Firstly, the chance of preserving any useful hearing is better the higher the pretreatment hearing level is. Secondly, the chance of hearing preservation depends strongly on the size of the tumor. Both issues would speak in favor of early proactive treatment. However, for all treatment options including surgery, there is some risk of delayed hearing loss, even in the absence of residual tumor. The time course of hearing loss may be different in regard of the type of therapy. In general, hearing decreases within a few days after surgery, within a few months after radiosurgery, and within a few years after stereotactic fractionated radiotherapy [113]. However, there are considerable individual variations [18, 114]. It is therefore advisable to present this situation to the individual patient and to identify the treatment of choice together with the patient.

Non-Vestibular Schwannoma. Surgery has been the first line treatment for non-vestibular schwannoma (NVS) for 5 decades. The results of surgery have considerably improved during this time period [56, 63, 87, 116–118]. Nowadays mortality is no more a matter of concern. The risks of microsurgery are characterized by a low percentage of general morbidity (CSF leakage, hemorrhage, etc.) and between 30% and 60% specific morbidity, e.g., new or increased cranial nerve deficits. The latter are mostly transient and/or mild. There are specific treatment reports dealing with selected CNS treated by surgery [49, 56, 63, 117, 118], radiosurgery [46, 81, 96, 156], or stereotactic fractionated radiotherapy [153]. Radiosurgery and radiation therapy are free of the risks of the invasive surgical approaches. However, radiosurgery is useful for small tumors only. The drawback of fractionated radiation therapy is the higher dose load (an issue of radiation protection) and the much longer time needed compared with radiosurgery. Therefore, fractionated stereotactic radiation therapy should be restricted to NVS which are both inoperable and too large for gamma-knife surgery. In many instances, a combined approach of microsurgery and radiosurgery is preferable. According to the literature, this strategy has been applied in about half of the radiosurgically treated NVS. Regarding the specific risk of radiation toxicity to the cranial nerve, radiosurgery and stereotactic fractionated radiation therapy are not inferior to the specific risks of surgery.

Although microsurgical resection in general remains the method of choice for NVS, radiosurgery with the Leksell gamma-knife or the stereotactic linear accelerator can be used as an additional or alternative method in suitable patients. The therapeutic profile of radiosurgery is characterized by a very high tumor control rate (over 95%), mostly associated with significant tumor shrinkage. As a rule, specific side-effects are mild and transient.

Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNST) derive from Schwann cells or pluripotent cells of the neural crest. Delay of diagnosis is common, especially in lesions affecting proximal parts of the peripheral nervous system. Patients with centrally located tumors have a poorer prognosis than those with peripheral tumors [67]. The management of patients with MPNST involves a multimodality approach. The goal of surgery is complete resection with negative margins. Adjuvant irradiation with doses up to 60 Gy and more, and other means of local dose escalation are associated with improved local control of disease [148]. Tumor diameter of <5 cm, gross total resection of the tumor, and younger age are favorable prognostic variables [10].

Esthesioneuroblastoma. Esthesioneuroblastoma is potentially curable by surgical resection and radiation therapy. Surgical treatment alone is effective for low-grade tumors if tumor-free margins can be obtained (Kadish stage A) [94, 131]. So far, surgical approaches for esthesioneuroblastoma have in the main been transnasal, with high recurrence rates and ultimately patient death. Nowadays with modern imaging used for diagnostic work-up, esthesioneuroblastoma should be approached with a craniofacial resection [15, 34, 94, 131]. Kadish stage B ought to be treated by surgical tumor resection in combination with radiotherapy [131]. Large tumors (Kadish stage C) should be considered for preoperative chemotherapy and postoperative radiotherapy.[24, 131]. Preoperative tumor extension with skull base penetration, intraorbital growth, and Kadish C stage compromise the disease-free survival significantly [38]. Multimodality treatment (surgery plus pre- or postoperative chemotherapy plus postoperative radiation therapy) appears to be highly efficient in preventing local and systemic relapse in patients with such advanced esthesioneuroblastoma [26, 38, 93]. Nevertheless, tumor recurrence is not uncommon. Neck metastases, when present, should be excised using a modified neck dissection. Distant metastases may present at any time during the course of the disease and may respond to local radiotherapy or systemic chemotherapy [15, 34, 94]. Five-year survival currently appears to be optimized by surgery followed by postoperative

radiotherapy and is approximately 65% [15, 34]. Because recurrence can appear after 5 or even 10 years, long-term follow-up is mandatory [94, 131]. Recently, it was concluded that the technical progress of stereotactically guided conformal radiotherapy translated into a clinical advantage due to the possibility of dose escalation [154]. This advantage is expected to be further extrapolated with inverse planned intensity-modulated radiation therapy [155]. The role of radiosurgery for esthesioneuroblastoma is not that significant [140].

Prognosis/Quality of Life

The prognosis and the quality of life have synchronously improved during the last decades for patients with benign tumors of the cranial nerves. The reason for this favorable development is the progress achieved in diagnostic imaging and simultaneously the technical advances of microsurgery and radiation therapy including the success of radiosurgery. Early diagnosis leads to superior treatment results. Lifetime tumor control is routine for benign tumors. Nowadays, preservation of neurological function is no longer a claim but reality in many aspects. Much of the success can be attributed to the fact that in many clinical settings, treatment alternatives are available, offering the choice of less invasive and less risky therapeutic strategies. Further considerable progress has become possible by combined treatment. The treatment of large VS by conservative microsurgery and adjunct radiosurgery to spare the facial nerve function may serve as a suitable example. An other example is the surgical relief of optic pathway structures to enable radiosurgery for inoperable skull base meningiomas. Radiosurgery as a nearly non-invasive single day treatment has evolved to a primary treatment option for small circumscribed benign cranial nerve tumors. Tailoring dose distributions to biologically defined clinical target volumes including dose escalation became possible by conformal stereotactic radiotherapy and intensity-modulated dose planning. This increases the control rate in malignant tumors while sparing organs at risk better.

Follow-up/Specific Problems and Measures

Considerable knowledge has accumulated to show that a life-long follow-up is mandatory in all cases of cranial nerve tumors, even in patients with complete resection. Tumor recurrences may develop in the long term due to a manifestation of biological tumor heterogeneity. MRI is the method of choice to perform sequential imaging over years. The timing of the follow-up examinations depends on the individual treatment applied and on the histology of the tumor. In completely resected schwannomas, the follow-up interval may be 1 or 2 years in the first period after surgery. It can be extended to 3–5 years later. In cases with radiation therapy or radiosurgery, the first follow-up examination should be after 6 months and then once a year. In tumors showing a regular response to radiosurgery, after 5 years the examination intervals may be expanded to 3–5 years for the remaining lifetime. In cases with tumor swelling or in cases showing questionable tumor progression or recurrence, a re-examination should be performed earlier, e.g., after 6 months. In irregular cases, the examination intervals should be scheduled individually according to the further development of the treated tumor. It has to be kept in mind that there is a dynamic response of benign cranial nerve tumors to radiation therapy and to radiosurgery. After single-dose irradiation, there may be a continuous shrinkage of the treated tumor over years. However, there are also cases with transient tumor increase before shrinking. Other tumors remain stable, indicating growth arrest, while other tumors show a tumor increase in the first period after radiosurgery and then remain stable. Because of these different reactions of benign cranial nerve tumors to radiation therapy/radiosurgery, it seems impossible to define a treatment failure or tumor recurrence before 2 years have elapsed after radiosurgery. This peculiarity demands a sophisticated follow-up regimen under the responsibility of the radiosurgical team.

For malignant tumors of the cranial nerves a tighter follow-up time schedule is necessary which is again based on MRI. In this setting, not only the local tumor control but also the issue of distant metastases are evaluated. This requires an more extensive examination protocol which is dependent on the type of the tumor under question.

Future Perspectives

Progress and future perspectives of therapy for cranial nerve tumors fall into four major categories:

1. Assessment of the individual risk and predisposition for the various tumors by genetic screening. This will enable a very early diagnosis of emerging cranial nerve tumors by high resolution MRI. Such situations will increasingly demand noninvasive or minimally invasive therapeutic methods like radiosurgery and stereotactic surgery. A prominent example of this issue is given by the tumors associated with neurofibromatosis.
2. Progress in diagnostic imaging will help to define the therapeutic requirements in the individ-

ual patient and how to approach the tumor. The surgical approach including the resection boundaries in poorly demarcated tumors will be designed specifically by computer graphics [17], and intraoperative MRI will attain increased importance and guide the surgeon [100, 101, 142]. Metabolic imaging reflecting the biological activity of the lesion in question will merge with improved spatial and topographic resolution of MRI, thus leading to improved tailoring of radiation geometry and dose escalation. Robotics will render stereotactic frames unnecessary for high precision radiotherapy and radiosurgery [1].

3. Combined approaches aiming to reduce both natural and treatment-related morbidity will be further refined. The systematics of combining minimally invasive surgery and high precision radiosurgery (or high precision 3D radiotherapy) will define new treatment standards.
4. Novel drugs targeting biological key features of the tumors and eventually specifically targeting genetic markers will be developed. For example, very recently, biologic-based therapeutic approaches have been initiated, using drugs that target the molecular genetic underpinnings of plexiform neurofibromas or cytokines believed to be important in tumor growth [108].

In summary, the principle of biological guidance will gain more and more significance for surgery, radiotherapy, and targeted drug delivery in tumors of the cranial nerves. Further technical advances in imaging and robot technology will support more and more and finally substitute the direct manual or surgical approach to the cranial nerve tumors.

References

1. Adler JR Jr, Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL. The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 1997; 69:124–128
2. Akimoto J, Ito H, Kudo M. Primary intracranial malignant schwannoma of trigeminal nerve. A case report with review of the literature. Acta Neurochir (Wien), 2000; 142:591–595.
3. Amadasun JE. The growth of acoustic neurinomas. Arch Otorhinolaryngol 1977; 217:99–102.
4. Andrews DW, Faroozan R, Yang BP, Hudes RS, Werner-Wasik M, Kim SM, Sergott RC, Savino PJ, Shields J, Shields C, Downes MB, Simeone FA, Goldman HW, Curran WJ Jr. Fractionated stereotactic radiotherapy for the treatment of optic nerve sheath meningiomas: preliminary observations of 33 optic nerves in 30 patients with historical comparison to observation with or without prior surgery. Neurosurgery 2002; 51:890–902; discussion 903–894.
5. Andrews DW, Suarez O, Goldman HW, Downes MB, Bednarz G, Corn BW, Werner-Wasik M, Rosenstock J, Curran WJ Jr. Stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of acoustic schwannomas: comparative observations of 125 patients treated at one institution. Int J Radiat Oncol Biol Phys 2001; 50:1265–1278.
6. Anteunis LJ, Wanders SL, Hendriks JJ, Langendijk JA, Manni JJ, de Jong JM. A prospective longitudinal study on radiation-induced hearing loss. Am J Surg 1994; 168:408–411.
7. Arnold AC, Hepler RS, Badr MA, Lufkin RB, Anzai Y, Konrad PN, Vinters HV. Metastasis of adenocarcinoma of the lung to optic nerve sheath meningioma. Arch Ophthalmol 1995; 113:346–351.
8. Astrup J. Natural history and clinical management of optic pathway glioma. Br J Neurosurg 2003; 17:327–335.
9. Backhouse O, Simmons I, Frank A, Cassels-Brown A. Optic nerve breast metastasis mimicking meningioma. Aust N Z J Ophthalmol 1998; 26:247–249.
10. Baehring JM, Betensky RA, Batchelor TT. Malignant peripheral nerve sheath tumor: the clinical spectrum and outcome of treatment. Neurology 2003; 61:696–698.
11. Becker G, Jeremic B, Pitz S, Buchgeister M, Wilhelm H, Schiefer U, Paulsen F, Zrenner E, Bamberg M. Stereotactic fractionated radiotherapy in patients with optic nerve sheath meningioma. Int J Radiat Oncol Biol Phys 2002; 54:1422–1429.
12. Bendel M, Kocher M, Müller R-P, Sturm V, Voges J. Stereotaktische Einzeldosiskonvergenzbestrahlung am Linearbeschleuniger bei Akustikusneurinomen. Strahlenther Onkol 1998; 174 (Sondernr 1):35.
13. Best PV. Malignant triton tumour in the cerebellopontine angle. Report of a case. Acta Neuropathol (Berl) 1987; 74:92–96.
14. Bockmuhl U, You X, Pacyna-Gengelbach M, Arps H, Draf W, Petersen I. CGH pattern of esthesioneuroblastoma and their metastases. Brain Pathol 2004; 14:158–163.
15. Bradley PJ, Jones NS, Robertson I. Diagnosis and management of esthesioneuroblastoma. Curr Opin Otolaryngol Head Neck Surg 2003; 11:112–118.
16. Brand WN, Hoover SV. Optic glioma in children. Review of 16 cases given megavoltage radiation therapy. Childs Brain 1979; 5:459–466.
17. Burekhovich S, Ghosh BC. Computer graphic to design the approach for resection of esthesioneuroblastoma. J Surg Oncol 2002; 80:222–223.
18. Chang SD, Poen J, Hancock SL, Martin DP, Adler JR Jr. Acute hearing loss following fractionated stereotactic radiosurgery for acoustic neuroma. Report of two cases. J Neurosurg 1998; 89:321–325.
19. Charabi S, Tos M, Thomsen J, Charabi B, Mantoni M. Vestibular schwannoma growth–long-term results. Acta Otolaryngol 2000; Suppl 543:7–10.
20. Cirak B. Optic nerve glioma. J Neurosurg 2003; 99:246; author reply 246.
21. Debus J, Kocagoncu KO, Hoss A, Wenz F, Wannenmacher M. Fractionated stereotactic radiotherapy (FSRT) for optic glioma. Int J Radiat Oncol Biol Phys 1999; 44:243–248.

22. Deen HG, Ebersold MJ, Harner SG, Beatty CW, Marion MS, Wharen RE, Green JD, Quast L. Conservative management of acoustic neuroma: an outcome study. Neurosurgery 1996; 39:260–264; discussion 264–266.
23. Delfini R, Missori P, Tarantino R, Ciapetta P, Cantore G. Primary benign tumors of the orbital cavity: comparative data in a series of patients with optic nerve glioma, sheath meningioma, or neurinoma. Surg Neurol 1996; 45:147–153; discussion 153–144.
24. Dias FL, Sa GM, Lima RA, Kligerman J, Leoncio MP, Freitas EQ, Soares JR, Arcuri RA. Patterns of failure and outcome in esthesioneuroblastoma. Arch Otolaryngol Head Neck Surg 2003; 129:1186–1192.
25. Dutton JJ. Optic nerve sheath meningiomas. Surv Ophthalmol 1992; 37:167–183.
26. Eich HT, Hero B, Staar S, Micke O, Seegenschmiedt H, Mattke A, Berthold F, Muller RP. Multimodality therapy including radiotherapy and chemotherapy improves event-free survival in stage C esthesioneuroblastoma. Strahlenther Onkol 2003; 179:233–240.
27. Flickinger JC, Kondziolka D, Lunsford LD. Dose and diameter relationships for facial, trigeminal, and acoustic neuropathies following acoustic neuroma radiosurgery. Radiother Oncol 1996; 41:215–219.
28. Flickinger JC, Kondziolka D, Lunsford L. Fractionation of radiation treatment in acoustics. Rationale and evidence in comparison to radiosurgery. Neurochirurgie 2004; 50:421–426.
29. Flickinger JC, Kondziolka D, Niranjan A, Lunsford LD. Results of acoustic neuroma radiosurgery: an analysis of 5 years' experience using current methods. [In Process Citation]. J Neurosurg 2001; 94:1–6.
30. Flickinger JC, Kondziolka D, Niranjan A, Voynov G, Maitz A, Lunsford LD. Acoustic neuroma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys 2003; 57:S325.
31. Flickinger JC, Kondziolka D, Pollock BE, Lunsford LD. Evolution in technique for vestibular schwannoma radiosurgery and effect on outcome. Int J Radiat Oncol Biol Phys 1996; 36:275–280.
32. Flickinger JC, Lunsford LD, Linskey ME, Duma CM, Kondziolka D. Gamma knife radiosurgery for acoustic tumors: multivariate analysis of four year results. Radiother Oncol 1993; 27:91–98.
33. Flickinger JC, Lunsford LD, Wu A, Maitz AH, Kalend AM. Treatment planning for gamma knife radiosurgery with multiple isocenters. Int J Radiat Oncol Biol Phys 1990; 18:1495–1501.
34. Foote RL, Morita A, Ebersold MJ, Olsen KD, Lewis JE, Quast LM, Ferguson JA, O'Fallon WM. Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1993; 27:835–842.
35. Frahm S, Mautner VF, Brems H, Legius E, Debiec-Rychter M, Friedrich RE, Knofel WT, Peiper M, Kluwe L. Genetic and phenotypic characterization of tumor cells derived from malignant peripheral nerve sheath tumors of neurofibromatosis type 1 patients. Neurobiol Dis 2004; 16:85–91.
36. Fucci MJ, Buchman CA, Brackmann DE, Berliner KI. Acoustic tumor growth: implications for treatment choices. Am J Otol 1999; 20:495–499.
37. Fuss M, Hug EB, Schaefer RA, Nevinny-Stickel M, Miller DW, Slater JM, Slater JD. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. Int J Radiat Oncol Biol Phys 1999; 45:1117–1126.
38. Gruber G, Laedrach K, Baumert B, Caversaccio M, Raveh J, Greiner R. Esthesioneuroblastoma: irradiation alone and surgery alone are not enough. Int J Radiat Oncol Biol Phys 2002; 54:486–491.
39. Han DH, Kim DG, Chi JG, Park SH, Jung HW, Kim YG. Malignant triton tumor of the acoustic nerve. Case report. J Neurosurg 1992; 76:874–877.
40. Harsh GR, Thornton AF, Chapman PH, Bussiere MR, Rabinov JD, Loeffler JS. Proton beam stereotactic radiosurgery of vestibular schwannomas. Int J Radiat Oncol Biol Phys 2002; 54:35–44.
41. Henchoz L, Borruat FX. Intraosseous meningioma: a rare cause of chronic optic neuropathy and exophthalmos. Klin Monatsbl Augenheilkd 2004; 221:414-417.
42. Hirato M, Inoue H, Zama A, Ohye C, Shibazaki T, Andou Y. Gamma Knife radiosurgery for acoustic schwannoma: effects of low radiation dose and functional prognosis. Stereotact Funct Neurosurg 1996; 66:134–141.
43. Hirose T, Scheithauer BW, Sano T. Perineurial malignant peripheral nerve sheath tumor (MPNST): a clinicopathologic, immunohistochemical, and ultrastructural study of seven cases. Am J Surg Pathol 1998; 22:1368–1378.
44. Hirsch A, Noren G, Anderson H. Audiologic findings after stereotactic radiosurgery in nine cases of acoustic neurinomas. Acta Otolaryngol 1979; 88:155–160.
45. Hoistad DL, Melnik G, Mamikoglu B, Battista R, O'Connor CA, Wiet RJ. Update on conservative management of acoustic neuroma. Otol Neurotol 2001; 22:682–685.
46. Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for trigeminal schwannomas. Neurosurgery 1999; 45:11–16; discussion 16.
47. Hudgins WR. Patients' attitude about outcomes and the role of gamma knife radiosurgery in the treatment of vestibular schwannomas. Neurosurgery 1994; 34:459–463; discussion 463–455.
48. Ing EB, Garrity JA, Cross SA, Ebersold MJ. Sarcoid masquerading as optic nerve sheath meningioma. Mayo Clin Proc 1997; 72:38–43.
49. Isono N, Tamura Y, Kuroiwa T, Nagasawa S, Yamashita M, Tanabe H, Ogawa N. [Combined therapy with surgery and stereotactic radiosurgery for facial schwannoma: case report]. No Shinkei Geka 2002; 30:735–739.
50. Ito K, Shin M, Matsuzaki M, Sugasawa K, Sasaki T. Risk factors for neurological complications after acoustic neurinoma radiosurgery: refinement from further experiences. Int J Radiat Oncol Biol Phys 2000; 48:75–80.
51. Jackson A, Patankar T, Laitt RD. Intracanalicular optic nerve meningioma: a serious diagnostic pitfall. AJNR Am J Neuroradiol 2003; 24:1167–1170.

52. Jennings JW, Rojiani AM, Brem SS, Murtagh FR. Necrotizing neurosarcoidosis masquerading as a left optic nerve meningioma: case report. AJNR Am J Neuroradiol 2002; 23:660–662.
53. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 1976; 37:1571–1576.
54. Kameyama S, Tanaka R, Honda Y, Hasegawa A, Yamazaki H, Kawaguchi T. The long-term growth rate of residual acoustic neurinomas. Acta Neurochir 1994; 129:127–130.
55. Karpinos M, Teh BS, Zeck O, Carpenter LS, Phan C, Mai WY, Lu HH, Chiu JK, Butler EB, Gormley WB, Woo SY. Treatment of acoustic neuroma: stereotactic radiosurgery vs. microsurgery. Int J Radiat Oncol Biol Phys 2002; 54:1410–1421.
56. Kim CS, Chang SO, Oh SH, Ahn SH, Hwang CH, Lee HJ. Management of intratemporal facial nerve schwannoma. Otol Neurotol 2003; 24:312–316.
57. Kleihues P, Cavenee WK. Pathology and Genetics of Tumours of the Nervous System. Lyon: International Agency for Research on Cancer; 1997
58. Kleihues P, Burger PC, Scheithauer BW The new WHO classification of brain tumours. Brain Pathol 1993; 3:255–268.
59. Klijanienko J, Caillaud JM, Lagace R, Vielh P. Cytohistologic correlations of 24 malignant peripheral nerve sheath tumor (MPNST) in 17 patients: the Institut Curie experience. Diagn Cytopathol 2002; 27:103–108.
60. Klink DF, Miller NR, Williams J. Preservation of residual vision 2 years after stereotactic radiosurgery for a presumed optic nerve sheath meningioma. J Neuroophthalmol 1998; 18:117–120.
61. Kondziolka D, Lunsford LD, Flickinger JC. Acoustic tumors: operation versus radiation–making sense of opposing viewpoints. Part II. Acoustic neuromas: sorting out management options. Clin Neurosurg 2003; 50:313–328.
62. Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. Long-term outcomes after radiosurgery for acoustic neuromas [see comments]. N Engl J Med 1998; 339:1426–1433.
63. Konovalov AN, Spallone A, Mukhamedjanov DJ, Tcherekajev VA, Makhmudov UB. Trigeminal neurinomas. A series of 111 surgical cases from a single institution. Acta Neurochir (Wien) 1996; 138:1027–1035.
64. Koos WT, Day JD, Matula C, Levy DI. Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas. J Neurosurg 1998; 88:506–512.
65. Kornreich L, Blaser S, Schwarz M, Shuper A, Vishne TH, Cohen IJ, Faingold R, Michovitz S, Koplewitz B, Horev G. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. AJNR Am J Neuroradiol 2001; 22:1963–1969.
66. Kumar M, Fallon RJ, Hill JS, Davis MM. Esthesioneuroblastoma in children. J Pediatr Hematol Oncol 2002; 24:482–487.
67. Kunisada T, Kawai A, Ozaki T, Sugihara S, Taguchi K, Inoue H. A clinical analysis of malignant schwannoma. Acta Med Okayama 1997; 51:87–92.
68. Laasonen EM, Troupp H. () Volume growth rate of acoustic neurinomas. Neuroradiology 1986; 28:203–207.
69. Lederman G, Lowry J, Wertheim S, Fine M, Lombardi E, Wronski M, Arbit E. Acoustic neuroma: potential benefits of fractionated stereotactic radiosurgery. Stereotact Funct Neurosurg 1997; 69:175–182.
70. Lee AG, Woo SY, Miller NR, Safran AB, Grant WH, Butler EB. Improvement in visual function in an eye with a presumed optic nerve sheath meningioma after treatment with three-dimensional conformal radiation therapy. J Neuroophthalmol 1996; 16:247–251.
71. Lee F, Linthicum F Jr, Hung G. Proliferation potential in recurrent acoustic schwannoma following gamma knife radiosurgery versus microsurgery. Laryngoscope 2002; 112:948–950.
72. Leksell L. A note on the treatment of acoustic tumours. Acta Chir Scand 1971; 137:763–765.
73. Liauw L, Vielvoye GJ, de Keizer RJ, van Duinen SG. Optic nerve glioma mimicking an optic nerve meningioma. Clin Neurol Neurosurg 1996; 98:258–261.
74. Lim YJ, Leem W. Two cases of Gamma Knife radiosurgery for low-grade optic chiasm glioma. Stereotact Funct Neurosurg 1996; 66 Suppl 1:174–183.
75. Linskey ME, Flickinger JC, Lunsford LD. Cranial nerve length predicts the risk of delayed facial and trigeminal neuropathies after acoustic tumor stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 1993; 25:227–233.
76. Linskey ME, Lunsford LD, Flickinger JC. Neuroimaging of acoustic nerve sheath tumors after stereotaxic radiosurgery. AJNR Am J Neuroradiol 1991; 12:1165–1175.
77. Linskey ME, Lunsford LD, Flickinger JC. Radiosurgery for acoustic neurinomas: early experience. Neurosurgery 1990; 26:736–744; discussion 744–735.
78. Lunsford LD, Flickinger J, Lindner G, Maitz A. Stereotactic radiosurgery of the brain using the first United States 201 cobalt-60 source gamma knife. Neurosurgery 1989; 24:151–159.
79. Lunsford LD, Kamerer DB, Flickinger JC. Stereotactic radiosurgery for acoustic neuromas. Arch Otolaryngol Head Neck Surg 1990; 116:907–909.
80. Lunsford LD, Kondziolka D, Flickinger JC. Radiosurgery as an alternative to microsurgery of acoustic tumors. Clin Neurosurg 1992; 38:619–634.
81. Mabanta SR, Buatti JM, Friedman WA, Meeks SL, Mendenhall WM, Bova FJ. Linear accelerator radiosurgery for non-acoustic schwannomas. Int J Radiat Oncol Biol Phys 1999; 43:545–548.
82. Martens F, Verbeke L, Piessens M, Van Vyve M. Stereotactic radiosurgery of vestibular schwannomas with a linear accelerator. Acta Neurochir 1994; Suppl, 62:88–92.
83. Matthies C, Samii M. Direct brainstem recording of auditory evoked potentials during vestibular schwannoma resection: nuclear BAEP recording. Technical note and preliminary results. J Neurosurg 1997; 86:1057–1062.
84. Matthies C, Samii M. Management of 1000 vestibular schwannomas (acoustic neuromas): Clinical presentation. Neurosurgery 1997; 40:1–10.

85. Matthies C, Samii M. Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation. Neurosurgery 1997; 40:1–9; discussion 9–10.
86. Matthies C, Samii M. Management of vestibular schwannomas (acoustic neuromas): the value of neurophysiology for intraoperative monitoring of auditory function in 200 cases. Neurosurgery 1997; 40:459–466; discussion 466–458.
87. McCormick PC, Bello JA, Post KD. Trigeminal schwannoma. Surgical series of 14 cases with review of the literature. J Neurosurg 1988; 69:850–860.
88. Meijer OW, Vandertop WP, Baayen JC, Slotman BJ. Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: a single-institution study. Int J Radiat Oncol Biol Phys 2003; 56:1390–1396.
89. Mendenhall WM, Friedman WA, Bova FJ. Linear accelerator-based stereotactic radiosurgery for acoustic schwannomas [see comments]. Int J Radiat Oncol Biol Phys 1994; 28:803–810.
90. Mendenhall WM, Friedman WA, Buatti JM, Bova FJ. Preliminary results of linear accelerator radiosurgery for acoustic schwannomas. J Neurosurg 1996; 85:1013–1019.
91. Miller RC, Foote RL, Coffey RJ, Sargent DJ, Gorman DA, Schomberg PJ, Kline RW. Decrease in cranial nerve complications after radiosurgery for acoustic neuromas: a prospective study of dose and volume. Int J Radiat Oncol Biol Phys 1999; 43:305–311.
92. Modugno GC, Pirodda A, Ferri GG, Fioravanti A, Calbucci F, Pezzi A, Ceroni AR, Pirodda E. Small acoustic neuromas: monitoring the growth rate by MRI. Acta Neurochir 1999; 141:1063–1067.
93. Monroe AT, Hinerman RW, Amdur RJ, Morris CG, Mendenhall WM. Radiation therapy for esthesioneuroblastoma: rationale for elective neck irradiation. Head Neck 2003; 25:529–534.
94. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993; 32:706–714; discussion 714–705.
95. Moyer PD, Golnik KC, Breneman J. Treatment of optic nerve sheath meningioma with three-dimensional conformal radiation. Am J Ophthalmol 2000; 129:694–696.
96. Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for jugular foramen schwannomas. Surg Neurol 1999; 52:172–179.
97. Narayan S, Cornblath WT, Sandler HM, Elner V, Hayman JA. Preliminary visual outcomes after three-dimensional conformal radiation therapy for optic nerve sheath meningioma. Int J Radiat Oncol Biol Phys 2003; 56:537–543.
98. Niemczyk K, Vaneecloo FM, Lecomte MH, Lejeune JP, Lemaitre L, Skarzynski H, Vincent C, Dubrulle F. Correlation between Ki-67 index and some clinical aspects of acoustic neuromas (vestibular schwannomas). Otolaryngol Head Neck Surg 2000; 123:779–783.
99. Niemczyk K, Vaneecloo FM, Lemaitre L, Lejeune JP, Skarzynski H, Dubrulle F, Vincent C. The growth of acoustic neuromas in volumetric radiologic assessment. Am J Otol 1999; 20:244–248.
100. Nimsky C, Ganslandt O, Fahlbusch R. Functional neuronavigation and intraoperative MRI. Adv Tech Stand Neurosurg 2004; 29:229–263.
101. Nimsky C, Ganslandt O, von Keller B, Fahlbusch R. Preliminary experience in glioma surgery with intraoperative high-field MRI. Acta Neurochir 2003; Suppl, 88:21–29.
102. Niranjan A, Lunsford LD, Flickinger JC, Maitz A, Kondziolka D. Dose Reduction Improves Hearing Preservation Rates after Intracanalicular Acoustic Tumor Radiosurgery. Neurosurgery 1999; 45:753–765.
103. Noren G. Long-term complications following gamma knife radiosurgery of vestibular schwannomas. Stereotact Funct Neurosurg 1998; 70 Suppl 1:65–73.
104. Noren G, Arndt J, Hindmarsh T. Stereotactic radiosurgery in cases of acoustic neurinoma: further experiences. Neurosurgery 1983; 13:12–22.
105. Noren G, Arndt J, Hindmarsh T, Hirsch A. Stereotactic radiosurgical treatment of acoustic neurinomas. In: Lunsford DL, ed. Modern stereotactic neurosurgery. Boston: Matinus Nijhoff, 1988:481–489.
106. Ogunrinde OK, Lunsford LD, Flickinger JC, Kondziolka DS Cranial nerve preservation after stereotactic radiosurgery for small acoustic tumors. Arch Neurol 1995; 52:73–79.
107. Ortiz O, Schochet SS, Kotzan JM, Kostick D. Radiologic-pathologic correlation: meningioma of the optic nerve sheath. AJNR Am J Neuroradiol 1996; 17:901–906.
108. Packer RJ, Gutmann DH, Rubenstein A, Viskochil D, Zimmerman RA, Vezina G, Small J, Korf, B. Plexiform neurofibromas in NF1: toward biologic-based therapy. Neurology 2002; 58:1461–1470.
109. Paus S, Klockgether T, Urbach H, Schlegel U. Meningioma of the optic nerve sheath: treatment with hydroxyurea. J Neurol Neurosurg Psychiatry 2003; 74:1348–1350.
110. Pellet W, Regis J, Roche PH, Delsanti C. Relative indications for radiosurgery and microsurgery for acoustic schwannoma. Adv Tech Stand Neurosurg 2003; 28:227–282; discussion 282–224.
111. Pitz S, Becker G, Schiefer U, Wilhelm H, Jeremic B, Bamberg M, Zrenner E. Stereotactic fractionated irradiation of optic nerve sheath meningioma: a new treatment alternative. Br J Ophthalmol 2002; 86:1265–1268.
112. Pollock BE, Lunsford LD, Flickinger JC, Clyde BL, Kondziolka D. Vestibular schwannoma management. Part I. Failed microsurgery and the role of delayed stereotactic radiosurgery. J Neurosurg 1998; 89:944–948.
113. Sakamoto T, Shirato H, Takeichi N, Aoyama H, Fukuda S, Miyasaka K. Annual rate of hearing loss falls after fractionated stereotactic irradiation for vestibular schwannoma. Radiother Oncol 2001; 60:45–48.
114. Sakamoto T, Shirato H, Takeichi N, Aoyama H, Kagei K, Nishioka T, Fukuda S. Medication for hearing loss after fractionated stereotactic radiotherapy (SRT) for vestibular schwannoma. Int J Radiat Oncol Biol Phys 2001; 50:1295–1298.
115. Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and

how to avoid them. Neurosurgery 1997; 40:11–21; discussion 21–13.
116. Samii M, Babu RP, Tatagiba M, Sepehrnia A. Surgical treatment of jugular foramen schwannomas. J Neurosurg 1995; 82:924–932.
117. Samii M, Migliori MM, Tatagiba M, Babu R. Surgical treatment of trigeminal schwannomas. J Neurosurg 1995; 82:711–718.
118. Schisano G, Olivecrona H. Neurinomas of the Gasserian ganglion and trigeminal root. J Neurosurg 1960; 17:306–322.
119. Shimano H, Nagasawa S, Kawabata S, Ogawa R, Ohta T. Surgical strategy for meningioma extension into the optic canal. Neurol Med Chir (Tokyo), 2000; 40:447–451; discussion 451–442.
120. Shin M, Ueki K, Kurita H, Kirino T. Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. Lancet 2002; 360:309–310.
121. Slooff JL. () Pathological anatomical findings in the cerebellopontine angle. A review. In: Pfaltz CR, ed. Advances in Oto-Rhino-Laryngology. Basel-München-Paris-London: S, Karger. Vol. 34, 1984:89–103.
122. Spiegelmann R, Lidar Z, Gofman J, Alezra D, Hadani M, Pfeffer R. Linear accelerator radiosurgery for vestibular schwannoma. J Neurosurg 2001; 94:7–13.
123. Strasnick B, Glasscock ME 3rd, Haynes D, McMenomey SO, Minor LB. The natural history of untreated acoustic neuromas. Laryngoscope 1994; 104:1115–1119.
124. Strauss C. The facial nerve in medial acoustic neuromas. J Neurosurg 2002; 97:1083–1090.
125. Subach BR, Kondziolka D, Lunsford LD, Bissonette DJ, Flickinger JC, Maitz AH. Stereotactic radiosurgery in the management of acoustic neuromas associated with neurofibromatosis Type 2 [see comments]. J Neurosurg 1999; 90:815–822.
126. Subramanian PS, Bressler NM, Miller NR. Radiation retinopathy after fractionated stereotactic radiotherapy for optic nerve sheath meningioma. Ophthalmology 2004; 111:565–567.
127. Suh JH, Barnett GH, Sohn JW, Kupelian PA, Cohen BH. Results of linear accelerator-based stereotactic radiosurgery for recurrent and newly diagnosed acoustic neuromas. Int J Cancer 2000; 90:145–151.
128. Szumacher E, Schwartz ML, Tsao M, Jaywant S, Franssen E, Wong CS, Ramaseshan R, Lightstone AW, Michaels H, Hayter C, Laperriere NJ. Fractionated stereotactic radiotherapy for the treatment of vestibular schwannomas: combined experience of the Toronto-Sunnybrook Regional Cancer Centre and the Princess Margaret Hospital. Int J Radiat Oncol Biol Phys 2002; 53:987–991.
129. Talmi YP, Finkelstein Y, Zohar Y. Postirradiation hearing loss. Audiology 1989; 28:121–126.
130. Tang BH. Vestibular schwannoma growth. J Neurosurg 2004; 100:734–735; author reply 735.
131. Theilgaard SA, Buchwald C, Ingeholm P, Kornum Larsen S, Eriksen JG, Sand Hansen H. Esthesioneuroblastoma: a Danish demographic study of 40 patients registered between 1978 and 2000. Acta Otolaryngol 2003; 123: 433–439.
132. Thomassin JM, Pellet W, Epron JP, Braccini F, Roche PH. [Recurrent acoustic neurinoma after complete surgical resection]. Ann Otolaryngol Chir Cervicofac 2001; 118:3–10.
133. To SY, Lufkin RB, Rand R, Robinson JD, Hanafee W. Volume growth rate of acoustic neuromas on MRI post-stereotactic radiosurgery. Comput Med Imaging Graph 1990; 14:53–59.
134. Tonn J.C., Schlake HP, Goldbrunner R, Milewski C, Helms J, Roosen K. Acoustic neuroma surgery as an interdisciplinary approach: a neurosurgical series of 508 patients. J Neurol Neurosurg Psychiatry 2000; 69:161–166.
135. Tos M, Thomsen J. () Proposal of classification of tumor size in acoustic neuroma surgery. In: Tos M, Thomsen J, eds. Proceedings of the First International Conference on Acoustic Neuroma Copenhagen, Denmark, August 25–29, 1991, Amsterdam/New York: Kugler Publications, 1992:133–137.
136. To M, Stangerup SE, Caye-Thomasen P, Tos T, Thomsen J. What is the real incidence of vestibular schwannoma? Arch Otolaryngol Head Neck Surg 2004; 130:216–220.
137. Tschudi DC, Linder TE, Fisch U. Conservative management of unilateral acoustic neuromas. Am J Otol 2000; 21:722–728.
138. Turbin RE, Thompson CR, Kennerdell JS, Cockerham KP, Kupersmith MJ. A long-term visual outcome comparison in patients with optic nerve sheath meningioma managed with observation, surgery, radiotherapy, or surgery and radiotherapy. Ophthalmology 2002; 109:890–899; discussion 899–900.
139. Unger F, Walch C, Papaefthymiou G, Eustacchio S, Feichtinger K, Quehenberger F, Pendl G. Long term results of radiosurgery for vestibular schwannomas. Zentralbl Neurochir 2002; 63:52–58.
140. Unger F, Walch C, Stammberger H, Papaefthymiou G, Haselsberger K, Pendl G. Olfactory neuroblastoma (esthesioneuroblastoma): report of six cases treated by a novel combination of endoscopic surgery and radiosurgery. Minim Invasive Neurosurg 2001; 44:79–84.
141. Vermeulen S, Young R, Posewitz A, Grimm P, Blasko J, Kohler E, Raisis J. Stereotactic radiosurgery toxicity in the treatment of intracanalicular acoustic neuromas: the Seattle Northwest gamma knife experience. Stereotact Funct Neurosurg 1998; 70 Suppl 1:80-87.
142. Vitaz TW, Hushek S, Shields CB, Moriarty T. Intraoperative MRI for pediatric tumor management. Acta Neurochir 2003; 85 Suppl:73–78.
143. Wabbels B, Demmler A, Seitz J, Woenckhaus M, Bloss HG, Lorenz B. Unilateral adult malignant optic nerve glioma. Graefes Arch Clin Exp Ophthalmol 2004.
144. Walker D. Recent advances in optic nerve glioma with a focus on the young patient. Curr Opin Neurol 2003; 16:657–664.
145. Walsh RM, Bath AP, Bance ML, Keller A, Tator CH, Rutka JA. The natural history of untreated vestibular schwan-

nomas. Is there a role for conservative management? Rev Laryngol Otol Rhinol 2000; 121:21–26.
146. Weber DC, Chan AW, Bussiere MR, Harsh GRt, Ancukiewicz M, Barker FG 2nd, Thornton AT, Martuza RL, Nadol JB Jr, Chapman PH, Loeffler JS. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. Neurosurgery 2003; 53:577–586; discussion 586–578.
147. Williams JA. Fractionated stereotactic radiotherapy for acoustic neuromas: preservation of function versus size. J Clin Neurosci 2003; 10:48–52.
148. Wong WW, Hirose T, Scheithauer BW, Schild SE, Gunderson LL. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. Int J Radiat Oncol Biol Phys 1998; 42:351–360.
149. Woordruff JM, Kourea HP, Louis DN. Schwannoma. In: Kleihues P, Cavenee WK, eds. Pathology and Genetics of Tumours of the Nervous System. Lyon: International Agency for Research on Cancer. 1997:126–132.
150. Yamamoto M, Hagiwara S, Ide M, Jimbo M, Arai Y, Ono Y. Conservative management of acoustic neurinomas: prospective study of long-term changes in tumor volume and auditory function. Minim Invasive Neurosurg 1998; 41:86–92.
151. Yamashiro S, Nagahiro S, Mimata C, Kuratsu J, Ushio Y. Malignant trigeminal schwannoma associated with xeroderma pigmentosum–case report. Neurol Med Chir (Tokyo) 1994; 34:817–820.
152. Yu CP, Cheung JY, Leung S, Ho R. Sequential volume mapping for confirmation of negative growth in vestibular schwannomas treated by gamma knife radiosurgery. J Neurosurg 2000; 93 Suppl 3:82–89.
153. Zabel A, Debus J, Thilmann C, Schlegel W, Wannenmacher M. Management of benign cranial nonacoustic schwannomas by fractionated stereotactic radiotherapy. Int J Cancer 2001; 96:356–362.
154. Zabel A, Thilmann C, Milker-Zabel S, Schlegel W, Zuna I, Wannenmacher M, Debus J. The role of stereotactically guided conformal radiotherapy for local tumor control of esthesioneuroblastoma. Strahlenther Onkol 2002; 178:187–191.
155. Zabel A, Thilmann C, Zuna I, Schlegel W, Wannenmacher M, Debus J. Comparison of forward planned conformal radiation therapy and inverse planned intensity modulated radiation therapy for esthesioneuroblastoma. Br J Radiol 2002; 75:356–361.
156. Zhang N, Pan L, Dai JZ, Wang BJ, Wang EM, Cai PW. Gamma knife radiosurgery for jugular foramen schwannomas. J Neurosurg 2002; 97:456–458.

Hemangioblastoma and Von Hippel-Lindau Disease

15

Juha E. Jääskeläinen, Mika Niemelä

Epidemiology – 236
Hemangioblastoma
Von Hippel-Lindau Disease
VHL Protein

Symptoms and Clinical Signs – 236
Hemangioblastoma
Hemangioblastoma of the Retina
Von Hippel-Lindau Disease

Diagnostics – 238
Synopsis
Histopathology of Hemangioblastoma
Imaging of Hemangioblastoma
Diagnosis of Hemangioblastoma of the Retina
Diagnosis of Von Hippel-Lindau Disease

Staging and Classification – 239

Treatment – 239
Synopsis
Microsurgery of Hemangioblastoma
Stereotactic Radiotherapy of Hemangioblastoma
Treatment of Hemangioblastoma of the Retina
Treatment of Hemangioblastomas in VHL
Chemotherapy of Hemangioblastoma

Prognosis/Quality of Life – 240
Hemangioblastoma
Hemangioblastoma of the Retina
Von Hippel-Lindau Disease

Follow-up/Specific Problems and Measures – 241
Hemangioblastoma
Hemangioblastoma of the Retina
Von Hippel-Lindau Disease

Future Perspectives – 241
Novel Drug Therapies of Hemangioblastoma
Novel Drug Therapies of Renal Cell Carcinoma

References – 241

Epidemiology

Hemangioblastoma

Hemangioblastoma (HB) is an infrequent, benign (WHO grade I), highly vascular, well-demarcated, slowly growing, solid or cystic neoplasm of unspecified cellular origin [1, 13, 20]. It is confined to the central nervous system (CNS), the brain, spinal cord, and retina, rarely occurring in the nerve roots or peripheral nerves. HB accounts for about 10% of tumors of the posterior fossa, the site of its predilection, but only about 2% of all intracranial tumors. HB of the retina [1, 9, 13, 14, 16, 17], originating from the inner mid-peripheral retina, is histologically identical to HB elsewhere in the CNS. Some 25% of HBs (up to 50% of retinal HBs) are associated with von Hippel-Lindau disease (VHL), but estimates may be too low because not all patients are screened for other manifestations of VHL [1, 9, 10, 13, 14, 17, 18, 20]. VHL-related HBs occur at 20–30 years of age and sporadic ones at 40–50 years.

Von Hippel-Lindau Disease

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant tumor syndrome, estimated to occur in 1 of 36,000 live births [1, 2, 6, 9, 10, 13, 14, 16, 17, 18, 20]. VHL is caused by a germline mutation or deletion in one allele of the *VHL* tumor suppressor gene (a coding sequence of three exons) on chromosome 3p25. Somatic inactivation of the other *VHL* allele results in tumor formation in the VHL target organs, typically multiple tumors at an earlier age than in sporadic cases: HBs of the CNS and retina; clear-cell renal cell carcinomas (RCC) [7]; pheochromocytomas [3]; pancreatic cystadenoma, islet cell tumor, and carcinoma; epididymal cystadenoma; endolymphatic sac tumor of the inner ear. In addition, VHL predisposes to multiple visceral cysts, including those of the kidneys, liver, and pancreas. Half of the VHL cases are familial, and half are caused by new mutations. Almost all carriers of a mutant VHL allele will develop manifestations of VHL, and so their children have a 50% risk of getting the dominantly inherited disease. The VHL phenotype is highly variable. VHL families are divided according to the absence (type 1) or presence (type 2) of pheochromocytoma [2]. Most type 1 families have deletions or premature termination mutations, whereas most type 2 families are affected by missense mutations. Type 2 families (7–20% of VHL families) are further subdivided according to the presence (type 2A) or absence (type 2B) of RCC. VHL clearly reduces the length of life, with a mean age of 40–50 years at death, which is mainly caused by RCCs and HBs of the CNS [13].

VHL Protein

HB is obviously caused by functional inactivation of the *VHL* gene and the VHL protein (pVHL), but the exact mechanisms of tumorigenesis and possible role of other genes have not been elucidated [6]. pVHL is widely expressed, also in organs not developing VHL manifestations. *VHL* –/– mice die in utero because of vascular abnormalities of the placenta, while *VHL* –/+ ones appear phenotypically normal [19]. pVHL has multiple functions, e.g., in the regulation of angiogenesis and the cell cycle, with multiple signaling pathways involved. As to the vascular nature of VHL-related tumors, pVHL significantly interacts with the hypoxia inducible factor 1 (HIF-1). The α-domain of pVHL forms a complex with elongin B, elongin C, cullin-2, and Rbx1, and this complex exhibits ubiquitin ligase (E3) activity towards the α-subunit of HIF-1 (HIF-1α). In normoxic cells, the β-domain of pVHL is able to bind HIF-1α for ubiquitin-mediated degradation. In pVHL-deficient cells, the HIF-1α and HIF-1β accumulate, resulting in elevated transcription of a variety of HIF-controlled genes, including the vascular endothelial growth factor (VEGF) gene. HB tissue expresses VEGF and its receptors as well as other angiogenic factors which apparently play a prominent role in its development [1]. HB tissue may produce erythropoietin, also detectable in the cyst fluid, possibly due to a dysregulated function of HIF-1α.

Symptoms and Clinical Signs

Hemangioblastoma

Most sporadic HBs are single lesions occurring in the cerebellum (Figs. 1 and 2) or the brain stem, occasionally in the spinal cord (Fig. 3), and rarely in the cerebrum [13, 20]. They often produce an adjoining cyst (Fig. 1) or a syrinx in the spinal cord (Fig. 3). In the posterior fossa, the fourth ventricle may become compressed, causing hydrocephalus with symptoms and signs of increased intracranial pressure. Focal symptoms include ataxia, dysmetria, tremor, unstable gait, and vertigo. Patients may also present with polycythemia and increased hematocrit in blood tests. In the spinal cord, HBs may present with spinal pain, spasticity, weakness, sensory changes, hyperactive reflexes, and impaired urination, due to the solid tumor or the syrinx. Rarely, HBs manifest by bleeding into the adjacent brain or spinal cord, or into the subarachnoid space.

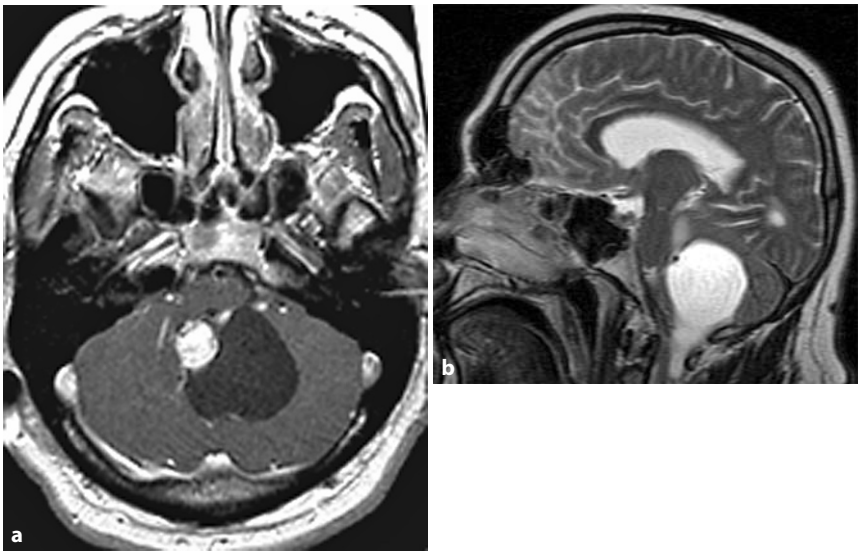


Fig. 1 a,b. Cystic hemangioblastoma of the cerebellum. MRI with an axial T1 image with contrast enhancement (**a**) and a sagittal T2 image (**b**)

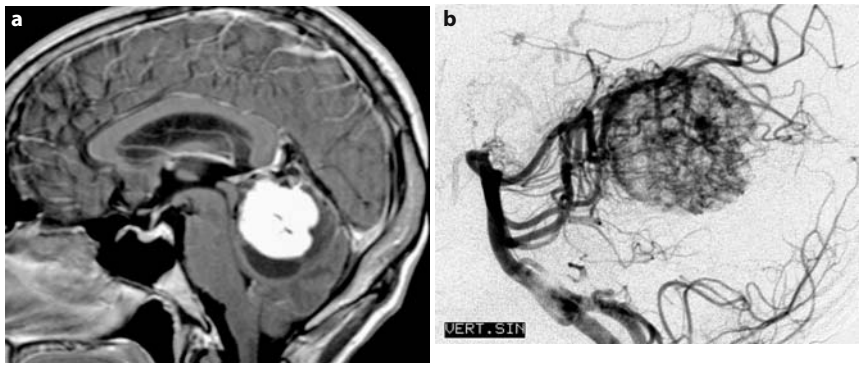


Fig. 2 a,b. Large recurrent hemangioblastoma of the posterior fossa. MRI (**a**) and angiography (**b**)

Hemangioblastoma of the Retina

HB of the retina can be asymptomatic for years [9, 13, 14, 16, 17]. Usually, visual symptoms such as flashing and floaters occur, and there is progressive visual impairment due to leakage from incompetent capillary walls of HB tissue. This leads to secondary changes in the vitreous and retina such as premature posterior vitreous detachment, retinal break, vitreous hemorrhage, lipid exudates and edema in the macula, or preretinal fibrosis. In large HBs, total retinal detachment may occur either due to accumulation of fluid between the photoreceptor layer and the retinal pigment epithelium, or by vitreous traction caused by vitreous strands and epiretinal membranes and/or retinal breaks.

Von Hippel-Lindau Disease

In VHL, HBs are typically multiple, occurring as incipient or symptomatic lesions in different sizes and combinations in the cerebellum, brain stem, spinal cord, and retina, depending on the severity, progression, and stage of the disease [1, 13, 14, 20]. HB of the retina is the first manifestation in half of the VHL patients, at the average age of 25 years, and it is usually bilateral and multifocal, or becomes so over the years. RCC develops in about 45% of VHL patients, at the average age of 35 years, often as multifocal lesions in association with cysts in both kidneys, but showing lower grade histology than the sporadic form of RCC. Pheochromocytoma, a catecholamine-producing tumor of the adrenal medulla and ectopic locations, occurs in 20–35% of VHL patients at the average age of 30 years, often as bilateral and multiple lesions but rarely malignant. Tumors of the pancreas, cystadenomas and islet cell tumors, may occur but rarely carcinomas. Epididymal cystadenomas may impair fertility when bilateral. Endolymphatic sac tumors in the petrous bone in the region of the vestibular aqueduct cause tinnitus, hearing loss, and vertigo. VHL also predisposes to multiple cysts in the kidneys, pancreas, and liver, and

they require follow-up because of possible adjoining malignancy.

Diagnostics

Synopsis

HB of the retina is an ophthalmological diagnosis, and HBs elsewhere in the CNS are imaged by MRI, sometimes supported by invasive angiography. Patients with HB should undergo exclusion of VHL by the following: family history; contrast-enhanced MRI of the brain, the spinal cord, and the organs of the abdominal cavity; retinal microscopy by an ophthalmologist. Mutation analysis has also to be considered in selected cases.

Histopathology of Hemangioblastoma

Histologically, HB tissue is composed of stromal cells, the neoplastic cells of still undefined origin, as well as endothelial cells, pericytes, and mast cells [1]. HB tissue is characterized by large vacuolated stromal cells and a rich capillary network. The 'clear cell' morphology due to lipid-containing vacuoles in stromal cells may suggest metastatic RCC, but in immunostaining HB is negative for cytokeratin, epithelial membrane antigen (EMA), and pan-epithelial antigen. The cell proliferation rate is low, with Ki67 index less than 1% [1]. HB of the retina is histologically identical to HB elsewhere in the CNS. HB tissue may maintain by unknown mechanisms intratumoral and paratumoral cysts with no actively secreting capsule. HB tissue may produce erythropoietin, detectable in the cyst fluid, an obvious cause for polycythemia and increased hematocrit in blood tests.

Imaging of Hemangioblastoma

MRI shows HB as an intensively enhanced, well-circumscribed, possibly nodular, either homogeneous or variably hypodense tumor on T1 images due to necrotic or intratumoral cystic areas, often with clearly demarcated paratumoral cyst(s) with no capsular enhancement (Figs. 1–3). It is of the utmost importance to detect even the smallest HB nodules, because they maintain cysts and may be the origin of later recurrences if left unnoticed. MRI may suggest high vascularity with tortuous feeding arteries and

Fig. 3 a–c. Large spinal hemangioblastoma. MRI with a sagittal T1 image showing the contrast-enhanced tumor (**a**) and T2 image showing the adjacent syrinx (**b**). Angiography showing a prominent feeding artery from the vertebral artery (**c**)

draining veins. In some cases, digital subtraction angiography (DSA) is indicated to demonstrate the vascularity and true nature of the lesions, or to demonstrate the smallest HB nodules. Diagnostic DSA might be followed by endovascular embolization to reduce the vascularity of the solid part, but this requires careful weighing of possible surgical gains against embolization hazards.

Diagnosis of Hemangioblastoma of the Retina

Mature HBs of the retina, resembling 'sugar-powdered' raspberries, with adjoining dilated, tortuous arterioles and venules (feeder vessels) are distinctive enough to permit visual diagnosis after pupillary dilatation with indirect ophthalmoscopy, Goldmann 3-mirror contact lens or non-contact lens fundus examination [9, 13, 16, 17]. Fluorescein angiography (FA) shows arteriovenous shunt with leakage of dye due to incompetent capillary walls. Incipient HBs are small, reddish or grayish dots without abnormal adjoining vessels, and incipient lesions may fail to fill with fluorescein. In the differential diagnosis, HBs of the optic disc may resemble papillitis, papilledema, chorioiditis, or chorioidal hemangioma. Cavernous hemangiomas of the retina appear as grape-like clusters of dilated vascular sacs without pronounced alteration in the adjacent arterioles and venules. Coats disease with dilated, tortuous, and leaking retinal venules may cause exudative detachment of the retina in children and teenagers.

Diagnosis of Von Hippel-Lindau Disease

A patient with HB of the CNS or retina is classified as having VHL if he or she has a germline mutation, family history of VHL, or other VHL-related neoplasms [1, 2, 13, 14, 20]. Diagnosis of VHL is based on the VHL gene mutation analysis and/or the demonstration of clinical manifestation during long-term follow-up. In families with definite VHL, 100% mutation detection rate can be achieved. Mutations are heterogeneous in type and position, and VHL shows intra- and interfamilial differences in phenotype. Germline mutations are spread over the three exons. Missense mutations are most common, but nonsense mutations, microdeletions/insertions, splice site mutations, and large deletions also occur. It is still not possible to reliably predict the severity and spectrum of VHL manifestations based on any single VHL gene defect.

Staging and Classification

Hemangioblastoma (HB) is a benign (WHO grade I), highly vascular, well-demarcated, slowly growing, solid or cystic neoplasm of unspecified cellular origin. It is confined to the CNS, the brain, spinal cord, and retina. In most cases, complete microsurgical removal of the HB nodule proves curative. HB of the retina is histologically identical to HB elsewhere in the CNS. In most cases, laser coagulation or cryocoagulation of the lesion is curative and prevents deterioration of vision. Some 25% of HBs (up to 50% of retinal HBs) are associated with von Hippel-Lindau disease (VHL), a rare autosomal dominant tumor syndrome. VHL predisposes to multiple tumors at an early age, most importantly HBs of the CNS and retina, bilateral RCCs, pheochromocytomas, and pancreatic tumors. VHL clearly reduces the length of life, with mean age of 40–50 years at death which is mainly caused by RCCs and HBs of the CNS.

Treatment

Synopsis

Sporadic HB in the retina and elsewhere in the CNS is a benign tumor that is in most cases curable at low morbidity with excellent preservation of function. VHL-associated HBs are often multiple and recurrent, defying established modes of therapy.

Microsurgery of Hemangioblastoma

Under the operation microscope, HB is a solid, well-circumscribed, highly vascular, red tumor, a nodule in the wall of a cyst, or a solitary tumor, embedded more or less in the cerebellum, brain stem, or spinal cord [13, 20]. Microsurgery is the treatment of choice, aiming at seemingly complete removal of the HB nodule. Subtotal removals and mere biopsies should be avoided at all costs. The solid part should be removed in one piece with circumferential coagulation of the feeders. This also suffices to eradicate adjoining cyst(s), indicating that they are maintained by the solid part by mechanisms thus far unknown and not by a secreting capsule. In large or huge HBs of the cerebellum, the brain stem, or the spinal cord, the utmost microsurgical skill and delicacy in bleeding control and atraumatic dissection between the HB surface and the adjacent gliotic neural tissue are required. Preoperative endovascular embolization of feeders to reduce vascularity may be helpful in selected cases. HB is microsurgically curable, but the

risk of late recurrences may be higher than generally expected.

Stereotactic Radiotherapy of Hemangioblastoma

Stereotactic radiotherapy, given in one session as radiosurgery (SRS) with the gamma knife or the stereotactic linear accelerator with a micromultileaf collimator, would seem an ideal therapy as HBs are well-delineated, highly vascular, usually small and rounded, and often multiple or recurrent in VHL patients, defying repeated microsurgery [5, 11, 13, 20]. In the present literature, there is huge variation in the dose given to the margin of the solid part, ranging from 10 Gy to 40 Gy, with fewer responses at lower doses but more volume-dependent radiation-induced edema and injury at higher doses. The margin dose might be 15–18 Gy in medium-sized and small lesions [5]. Similar to other solid tumors of WHO grade I such as meningiomas and schwannomas, HBs respond to SRS by slow volume reduction but hardly become extinct. The slow radiosurgical response in the solid HB tissue may not suffice to prevent the adjoining cysts from enlarging [11]. Consequently, both the cyst and the solid part require long-term MRI follow-up.

Treatment of Hemangioblastoma of the Retina

Retinal HBs should be treated with laser or cryocoagulation when small or even asymptomatic for better prognosis of vision and lower risk of complications [9, 13, 14, 16, 17]. In HBs of the papillary or macular area, however, coagulation may cause a central visual field defect, and it is not advised until exudation develops. Laser coagulation often requires multiple sessions to scar the entire HB. At 2 months, attenuation of feeders and absence of fluorescein leakage from the HB suggest a good result. In cryocoagulation of larger lesions, the cryoprobe is located over the HB transsclerally in indirect ophthalmoscopy. If the feeders have not attenuated by 2 months, cryotherapy should be repeated. At 6 months, the HB should appear as a pigmented scar, with surrounding exudate diminished or disappeared, feeders atrophic, and the macula dry. Brachytherapy with episcleral isotope plaques has also been used to treat large lesions. Late recurrences may develop due to incomplete primary destruction, but in VHL new tumors may be mistaken for recurrences. In VHL, the appearance of new, multiple, and bilateral HBs of the retina may threaten vision. Retinal detachment without vitreous traction may be treated by scleral encircling procedures. Macular preretinal fibrosis, vitreous hemorrhage, or retinal detachment threatening the macula may necessitate vitreoretinal surgery. Cataract and neovascular glaucoma following total retinal detachment are late complications with a poor prognosis. Finally, enucleation may become mandatory in the case of a blind and painful eye.

Treatment of Hemangioblastomas in VHL

In VHL, microsurgical treatment of multiple HBs often fails in the long run [13, 20]. Removed tumors tend to recur, and new ones develop, some are symptomatic, others incidental. It is often difficult to decide which tumors should be removed, and operative risks should be weighed against the natural course. The gold standard is to treat only tumors that are symptomatic or clearly growing. In VHL, more often than in sporadic cases, HBs are located in the brain stem and spinal cord, increasing the risk of operative morbidity and mortality. Stereotactic radiotherapy is an option to treat HBs in eloquent areas, but overlapping fields in multiple HBs increases the risk of radiation injury in the adjacent brain.

Chemotherapy of Hemangioblastoma

So far, there is no proven drug therapy against HB tissue. Increasing data on the signaling cascades related to the VHL gene have raised huge interest in novel growth factor or tyrosine kinase-modulating drugs in the experimental treatment of advanced RCC [15] as well as in HBs that defy established modes of therapy [4, 8, 12, 14].

Prognosis/Quality of Life

Hemangioblastoma

Sporadic hemangioblastoma is a microsurgically curable benign tumor [13, 20]. The operative morbidity and mortality for classic cerebellar cystic tumors is very low. Operative risks increase for spinal HBs and, in particular, for large solid lesions in the brain stem. Stereotactic radiotherapy appears to be a valuable method to control but not ablate HBs in selected cases [5, 13, 20].

Hemangioblastoma of the Retina

Hemangioblastoma of the retina, if truly sporadic as some 50% may be, can be ablated safely in most cases with permanent sparing of the vision in the eye.

Von Hippel-Lindau Disease

VHL is a deadly disease affecting young patients of child-bearing age. RCC has become the leading cause of death due to advances in the treatment of HB of the CNS. Multiple and recurrent HBs – as well as ill-balanced efforts to treat them – may cause devastating morbidity. In patients with bilateral RCCs, decisions have to be made between nephron-sparing surgery, renal ablation, dialysis, and renal transplantation.

Follow-up/Specific Problems and Measures

Hemangioblastoma

Patients with HB should undergo general exclusion of VHL by the following examinations: family history; contrast-enhanced MRI of the brain, the spinal cord, and the organs of the abdominal cavity; retinal microscopy by an ophthalmologist. Mutation analysis should also be considered. In the long run, recurrences after completely removed lesions may appear at an undefined risk. In the Helsinki series, with the primary operation taking place between 1953 and 1993, 9 of 74 non-VHL patients developed a local recurrence at a median of 11 years (range 3–35) [10].

Hemangioblastoma of the Retina

In HBs of the retina, it is even more crucial than in HBs elsewhere in the CNS to achieve early diagnosis and pursue definitive ablative treatment in the early phase – to preserve vision – as well as to exclude the presence of VHL.

Von Hippel-Lindau Disease

Patients with VHL should be evaluated and monitored yearly by a dedicated VHL team, composed of a coordinator specialized in VHL who consults and works together with a neurosurgeon, an ophthalmologist, a nephrologist, a urologist, or an endocrinologist, and others, depending on the patient's phenotype. Patients and families should be offered genetic counseling and mutation analysis. VHL Family Alliance, active in many countries, plays an extremely important role by providing established data on VHL as well as upgrades of novel therapies on their web pages (www.vhl.org).

Future Perspectives

Novel Drug Therapies of Hemangioblastoma

Many VHL patients with HBs and some sporadic HB patients would benefit from novel effective modes of systemic drug therapy against HBs [13, 14]. In VHL, HBs are often multiple and recurrent, in eloquent areas with increased risks associated with microsurgery and stereotactic radiotherapy. An ideal therapy would abolish the existing HBs and prevent the appearance of new ones, but tumor shrinkage or stable disease for years would also be satisfactory if the treatment were well tolerated. HBs of the CNS and the retina could be targets for 'antiangiogenic therapy' as they are highly vascular and express a number of growth factor receptors [1]. In addition, HB is receiving scientific attention because of the association with the mutated biology of *VHL* and pVHL [6]. However, the emerging view from early studies using interferon [12] or small molecules [4, 8, 14] is that some reduced vascularity or tumor stability but no tumor eradication or remarkable regression could be achieved – at least by single-agent approaches. Another line, apart from the *VHL* and pVHL biology, would be to finally elucidate the origin and qualities of the precursor cell for the HB stromal cell that confines HBs to the CNS and, in particular, to the retina [1].

Novel Drug Therapies of Renal Cell Carcinoma

The need for novel therapies is even more urgent in RCC as the leading cause of death in VHL [13, 14], as well as in advanced sporadic RCC [15] that is 50 times more frequent than VHL-associated RCC [13].

References

1. Böhling T, Plate K, Haltia MJ, et al. von Hippel-Lindau disease and capillary hemangioblastoma. In: Kleihues P, Cawenee W, eds. Pathology and Genetics of Tumors of the Nervous System. Lyon: WHO International Agency for Research on Cancer, 2000:223–226
2. Friedrich CA. Genotype-phenotype correlation in von Hippel-Lindau syndrome. Hum Mol Genet 2001; 10:763–767
3. Gimm O, Koch CA, Januszewicz A, Opocher G, Neumann HP. The genetic basis of pheochromocytoma. Front Horm Res 2004; 31:45–60
4. Girmens JF, Erginay A, Massin P, Scigalla P, Gaudric A, Richard S. Treatment of von Hippel-Lindau retinal hemangioblastoma by the vascular endothelial growth factor recep-

tor inhibitor SU5416 is more effective for associated macular edema than for hemangioblastomas. Am J Ophthalmol 2003; 136:194–196
5. Jawahar A, Kondziolka D, Garces YI, Flickinger JC, Pollock BE, Lunsford LD. Stereotactic radiosurgery for hemangioblastomas of the brain. Acta Neurochir (Wien) 2000; 142:641–644
6. Kondo K, Kaelin WG. The von Hippel-Lindau tumor suppressor gene. Exp Cell Res 2001; 264:117–125
7. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003; 170:2163–2172
8. Madhusudan S, Deplanque G, Braybrooke JP, Cattell E, Taylor M, Price P, Tsaloumas MD, Moore N, Huson SM, Adams C, Frith P, Scigalla P, Harris AL. Antiangiogenic therapy for von Hippel-Lindau disease. JAMA 2004; 291:943–4
9. Niemelä M, Lemeta S, Sainio M, et al. Hemangioblastoma of the retina: impact of von Hippel-Lindau disease. Invest Ophthalmol Vis Sci 2000; 41:1909–1915
10. Niemelä M, Lemeta S, Summanen P, et al. Long-term prognosis of haemangioblastoma of the CNS: impact of von Hippel-Lindau disease. Acta Neurochir 1999; 141:1147–1156
11. Niemelä M, Lim YJ, Söderman M, et al. Gamma knife radiosurgery in 11 hemangioblastomas. J Neurosurg 1996; 85:591–596
12. Niemela M, Maenpaa H, Salven P, Summanen P, Poussa K, Laatikainen L, Jaaskelainen J, Joensuu H. Interferon alpha-2a therapy in 18 hemangioblastomas. Clin Cancer Res 2001; 7:510–516
13. Niemelä M. Hemangioblastomas. In: Loeffler JS, Black PMcL eds. Cancer of the Nervous System, 2nd Edition. Lippincott, Williams & Wilkins, 2004:563–572
14. Richard S; French VHL Study Group. von Hippel-Lindau disease: recent advances and therapeutic perspectives. Expert Rev Anticancer Ther 2003; 3:215–33
15. Rini BI, Weinberg V, Small EJ. Practice and progress in kidney cancer: methodology for novel drug development. J Urol 2004; 171:2115–2121
16. Schmidt D, Natt E, Neumann HP. Long-term results of laser treatment for retinal angiomatosis in von Hippel-Lindau disease. Eur J Med Res 2000; 28:47–58
17. Singh AD, Nouri M, Shields CL, Shields JA, Smith AF. Retinal capillary hemangioma: a comparison of sporadic cases and cases associated with von Hippel-Lindau disease. Ophthalmology 2001; 108:1907–1911
18. Sora S, Ueki K, Saito N, Kawahara N, Shitara N, Kirino T. Incidence of von Hippel-Lindau disease in hemangioblastoma patients: the University of Tokyo Hospital experience from 1954–1998. Acta Neurochir (Wien) 2001; 143:893–896
19. Ward JM, Devor-Henneman DE. Mouse models of human familial cancer syndromes. Toxicol Pathol 2004; 32 Suppl 1:90–8
20. Vates GE, Berger MS. Hemangioblastomas of the central nervous system. In: Winn RH. ed. Youmans Neurological Surgery. W.B. Saunders Company, 2004:1053–1066

Tumors of the Skull Base 16

Kadir Erkmen, Ossama Al-Mefty, Badih Adada

Introduction – 244

Chordoma and Chondrosarcoma – 244
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Surgery
Radiotherapy
Chemotherapy
Prognosis/Quality of Life
Future Perspectives

Skull-Base Meningiomas – 249
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Meningioma Surgery
Surgery for Clinoidal and Cavernous Sinus Meningiomas
Radiotherapy
Chemotherapy

Paragangliomas – 261
Epidemiology
Symptoms and Clinical Signs
Diagnostics
Staging and Classification
Treatment
Surgery
Radiation
Chemotherapy
Embolization
Prognosis/Quality of Life

References – 268

Introduction

The skull base is affected by a wide range of tumor pathologies. They are often slow-growing, benign, extra-axial tumors that cause symptoms by involvement of cranial nerves or mass effect on the brain stem and cerebellum. They are often located in critical areas within the cranium that are especially hard to reach with routine surgical techniques. Involvement of cranial nerves and vessels makes these lesions particularly challenging to treat surgically. Due to the benign nature of most of these lesions, complete surgical removal often affords a cure, although some skull-base tumors require a combination of surgical and radiation therapies.

According to the Central Brain Tumor Registry of the United States (CBTRUS), the incidence of all primary benign and malignant brain tumors is 14.0 cases per 100,000 persons per year [1]. If we exclude metastatic lesions to the skull base and include pituitary tumors, neoplasms involving the base of the skull would constitute 25% of all primary intracranial tumors.

This chapter will focus on three specific pathologies within the skull base: chordomas, meningiomas, and paragangliomas. Other tumors that involve the skull base, including schwannomas and other nerve sheath tumors, pituitary tumors, metastases, and carcinomas, are covered in other chapters of the text.

Chordoma and Chondrosarcoma

Chordomas and chondrosarcomas are often considered together because of their similarities in presentation, location, radiographic appearance, and surgical treatment. Despite this fact, these tumors are distinct pathological entities and display different biological behavior and prognosis.

Chordomas and chondrosarcomas are rare, slow-growing tumors within the skull base. Chordomas are thought to originate from remnants of the primitive notochord, while chondrosarcomas are thought to originate from mesenchymal cells or embryonic rests of the cartilaginous matrix of the cranium [2]. Virchow originally described chordomas in 1846 as small, soft, jelly-like tissues arising from the synchondrosis spheno-occipitalis, which he thought were associated with cartilaginous tumors. The tumors were named *eccondrosis physaliphora* due to the large vesicular, plant-like cells called *physaliferous cells* which are within chordomas [3]. Muller called these tumors *chordomas* or *ecchordosis* in 1925, after identifying their origin as remnants of the notochord.

Epidemiology

Chordomas are rare tumors that are thought to originate from the remnants of the primitive notochord. The annual incidence is 0.2–0.5 per 100,000 persons per year and account for 0.1–0.7% of intracranial tumors and 6% of all primary skull-base tumors. Chordomas arise in patients of all ages, but typically become symptomatic in the third to fifth decades of life. The average age at diagnosis is 43 years. Fewer than 5% of chordomas occur in children [4]. There appears to be a male preponderance with a ratio of ~2:1 reported in some series, while others report no sex preponderance. It has been described that chordomas do not occur in people of African-American decent, but that does not seem to be true for chondrosarcomas. These are often slow-growing tumors, and the time from first symptom to diagnosis often exceeds 12 months. Recent increases in the use of CT and MRI have allowed earlier diagnosis. Chordomas are found to be metastatic in 10% of cases.

Chondrosarcomas are thought to originate from mesenchymal cells or from embryonic rests of the cartilaginous matrix of the cranium. They are also extremely rare tumors with a similar presentation to chordoma. Chondrosarcomas have a male preponderance and present at younger ages (within the second and third decades of life).

Due to the fact that chordomas originate from remnants of the notochord, they can occur anywhere along the spinal axis. They most frequently arise in the sacrococcygeal area (~50% of the time), followed by the skull base (~25–35%), and finally in the remainder of the spine (~15%). Within the skull base, chordomas usually arise from the midline clivus and are thought to originate specifically from the spheno-occipital synchondrosis, and may be entrapped by bone. They often have extensions to the sella, parasellar region, sphenoid sinus, cavernous sinus, foramen magnum, prepontine cistern, posterior fossa, occipital condyle, infratemporal fossa, first cervical vertebra, and retropharyngeal spaces. The cavernous sinus is found to be involved in up to 50% of cases. Chondrosarcomas often originate laterally along the petrous apex or sphenoid ridge as opposed to the midline origin of chordomas.

Symptoms and Clinical Signs

As with other skull-base tumors, chordomas cause symptoms and signs depending on their location and direction of extension. The most common complaints reported are headaches, diplopia, visual changes, and lower cranial nerve pareses. Tumors that are located more cephalad in the basisphenoid tend to cause dysfunction of the extraocular muscles, usually

through dysfunction of the sixth cranial nerve. Permanent or intermittent diplopia is the first symptom reported in most patients. Tumors in this location also present with endocrine dysfunction and other upper cranial nerve symptoms such as decreased visual acuity, and facial numbness. More caudally located tumors in the basiocciput cause dysfunction of the lower cranial nerves, resulting in facial weakness, hearing loss, dysphagia, hoarseness, and swallowing difficulties. Patients with tumors in this location often have compression of the brain stem and cerebellum, resulting in the presence of long-tract signs, motor and sensory deficits, as well as cerebellar dysfunction with ataxia and dysmetria. Tumors extending further into the occipital condyles may cause occipital headaches which are worsened by movement of the neck. Involvement of the anterior portion of the occipital condyles causes hypoglossal nerve dysfunction seen with unilateral tongue weakness. Retropharyngeal and nasal extension can cause symptoms including Eustachian tube blockage, nasal obstruction, epistaxis, dysphagia, dysarthria, and throat fullness. When the tumor extends laterally, unilateral symptoms are found.

Cranial neuropathies are detected on neurological examination and are found in 40–90% of patients at presentation. The most frequently noted symptom on physical examination is extraocular muscle weakness secondary to sixth nerve involvement. Often a retropharyngeal mass can be seen on examination of the nasopharynx with an office endoscope.

Diagnostics

Synopsis. The diagnosis of chordoma requires pathological evaluation of tumor tissue. The suspicion of chordoma can be raised using brain MRI and CT in combination for a radiographic diagnosis. Chordoma is suspected in a patient with a clival mass demonstrating destruction of the bony clivus without hyperostosis, along with nasopharyngeal extension. A tumor mass within the nasopharynx can be biopsied for diagnosis.

The radiographic diagnosis of chordoma requires the use of both MRI and CT in combination. CT scanning typically demonstrates a well-defined, midline, soft-tissue, expansile mass arising from the clivus, often with lytic destruction of adjacent bony structures and minimal sclerosis (Fig. 1). High-resolution, thin-cut CT scans through the skull base allow for close evaluation of the extent of bony destruction. Three-dimensional reconstructions of volumetric data can be beneficial in assessing the extent of bony destruction. Tumors are usually isodense or hypointense to brain tissue and display varying degrees of contrast enhancement. Slight to moderate contrast enhancement is seen in all cases. Calcification is seen in 47–71% of chordomas and is thought to be due to sequestered bony fragments within the tumor instead of dystrophic calcification by the tumor. Solitary or multiple zones of low attenuation are often seen within the soft-tissue mass. These zones are thought to represent myxoid and gelatinous material seen on pathology. CT is also optimal for the evaluation of tumor extension into the retropharyngeal space and sphenoid and paranasal sinuses. Assessing soft-tissue extension within the posterior fossa is limited with CT scanning due to significant levels of bony artifact.

MRI is the technology of choice in chordoma for examining the extent of soft-tissue involvement, compression of vascular structures, and intradural extension of tumor. Chordomas appear iso- to hypointense to brain on T1-weighted images and hyperintense on T2-weighted images due to the high fluid content of the vacuolated cells (Figs. 1, 2). Some tumors demonstrate multiple, scattered, small foci of very high signal on T1-weighted sequences. These areas are thought to correspond to small sites of hemorrhage and mucinous collections seen on pathologic examination. Most chordomas have heterogeneous signal intensity with lobulated regions of high signal intensity, separated by areas of low signal intensity. Gadolinium injection usually produces moderate to extensive heterogeneous contrast enhancement, although some tumors enhance homogeneously, and some tumors show no contrast enhancement. Post-contrast fat suppression sequences highlight the tumor inside the usually fatty clivus.

MR angiography and conventional catheter angiography may be used in combination with CT and MRI in cases with significant involvement of the vasculature. The vertebrobasilar and petrous internal carotid vascular systems are often displaced or encased by chordomas and are involved in up to 79% of cases. Knowledge of the vascular anatomy is often critical in treatment planning.

The differential diagnosis of tumors with this appearance includes other skull-base tumors that occur in this location. Meningiomas can often be differentiated from chordoma because they often have sclerotic bony changes and hyperostosis. Chondrosarcomas can mimic chordoma in both clinical and radiographic appearance. Chondrosarcomas are thought to be centered off-midline along the petrous apex, while chordomas are more often centered in the midline clivus. Despite this difference, pathological evaluation of tumor tissue is required to distinguish the two entities. Other tumors in the differential diagnosis are nasopharyngeal carcinomas, pituitary tumors, and metastatic tumors.

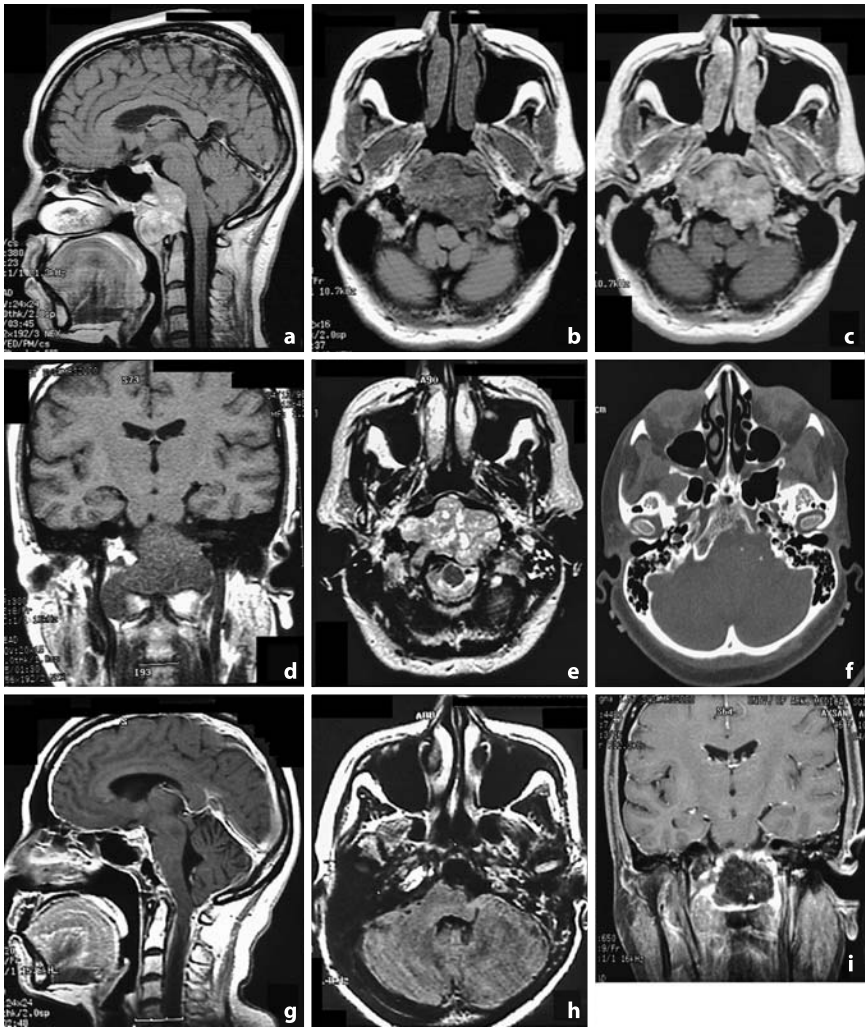


Fig. 1 a–i. Imaging of chordoma. **a** Preoperative contrast-enhanced T1 sagittal image demonstrating tumor arising from the clivus with brain stem compression. Preoperative T1 axial image without (**b**) and with (**c**) contrast. **e** High T2 signal intrinsic within chordoma. **f** Preoperative CT demonstrating erosion of the bony skull base and calcium inclusions within the tumor. **g–i** Postoperative imaging in sagittal, coronal, and axial planes demonstrating resection of tumor

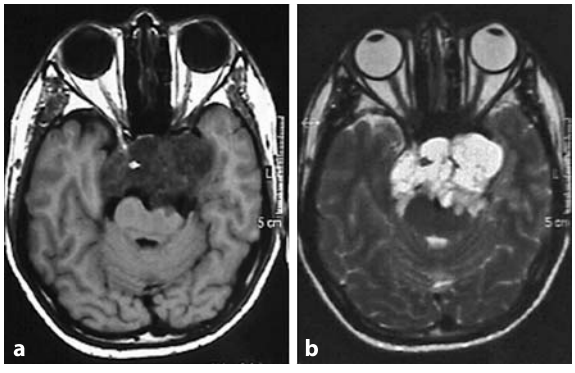


Fig. 2 a, b. Imaging of chordoma. **a** Large midline chordoma with brain stem compression. **b** Typical bright T2 signal characteristic of chordoma

Staging and Classification

Synopsis. Chordomas and chondrosarcomas are classified pathologically. Three pathological subtypes have been identified: chordoma, chondroid chordoma, and chondrosarcoma. The difference between classic chordoma and chondrosarcoma is evident with pathology and immunohistochemical staining, but chondroid chordomas lie in a continuum between chordoma and chondrosarcoma and may be difficult to differentiate. The overall pathological appearance is taken into account in combination with immunohistochemistry to make this distinction. Chondrosarcomas are further subdivided into three groups based on pathological characteristics.

The pathological characteristics of chordoma (Fig. 3a) are described to contain fibrous strands which create lobulations and pseudoencapsulation. These lobules are found to contain either sheets of physaliferous cells or pools of mucin. Physaliferous cells contain varying amounts of cytoplasmic mucin, giving these cells their characteristic vacuolated appearance. The pools of mucin contain cords of eosinophilic syncytial cells.

Chondroid chordoma is a subtype of chordoma that contains foci of cartilaginous hyaline stroma within a chordoma background in varying proportions. This subtype may have similar pathological findings to chondrosarcoma and often requires immunohistochemistry for differentiation.

Classification of chondrosarcomas takes into account the predominant cellular type on pathology to differentiate between classic, mesenchymal, and dedifferentiated chondrosarcomas. Classic chondrosarcoma (Fig. 3d) is the most common type and is identified by the large, atypical chondrocytes within a hyaline cartilaginous matrix background. Classic chondrosarcomas have further been divided into grades I-III, with higher grades displaying increased mitotic rates, cellularity, and decreased chondroid matrix. The mesenchymal class of chondrosarcomas displays regions of undifferentiated mesenchymal cells and cartilage. Dedifferentiated sarcomas are more aggressive, with characteristics similar to anaplastic sarcomas.

Immunohistochemistry has been important to differentiate the three pathological subtypes. Due to their origin from notochordal remnants, most chordomas and chondroid chordomas stain positively for the epithelial markers cytokeratin (CK) (Fig. 3b) and epithelial membrane antigen (EMA). Chondrosarcomas lack these epithelial markers and will not stain positively, thus positive staining for CK and EMA confirms the diagnosis of chordoma or chondroid chordoma. However, lack of CK and EMA staining does not exclude a diagnosis of chordoma. Many chordomas will also stain positively with carcinoembryonic antigen (CEA), whereas chondrosarcomas will not. Within the continuum of chordoid and chondroid tumors containing aspects of both types of tumors, it has been suggested that all tumors positive for CK and EMA as well as those tumors with CK and EMA negative staining which display predominantly chordoid patterns should be classified as chondroid chordomas. Tumors with predominantly chondroid patterns without CK and EMA staining should be classified as chondrosarcomas.

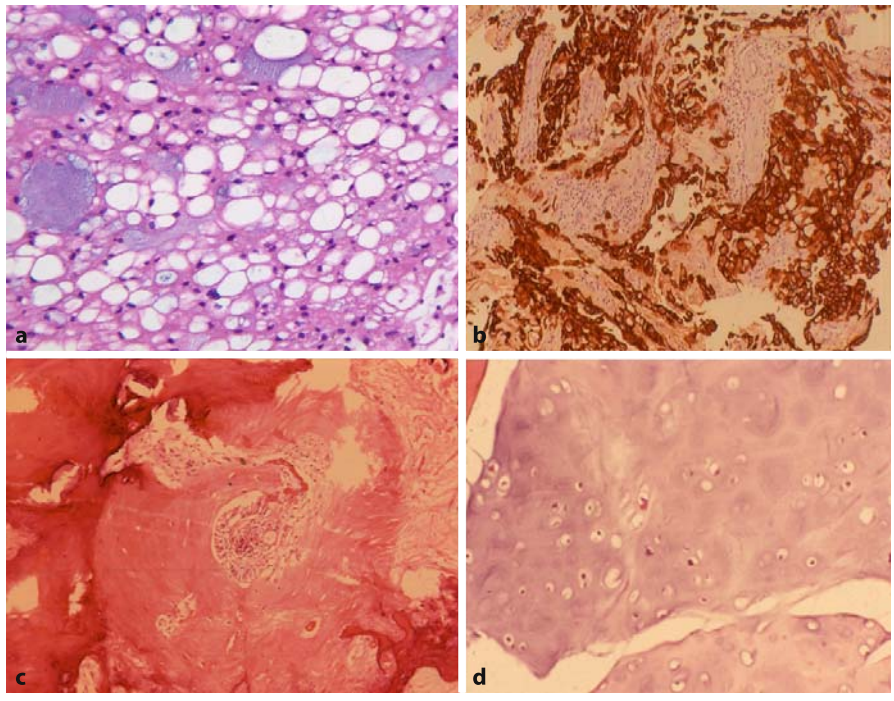


Fig. 3 a–d. Pathology of chordoma and chondrosarcoma. **a** Pathology of classic chordoma with large physaliferous cells. **b** Cytokeratin immunohistochemistry demonstrating strong positive staining of chordoma specimen. **c** Pathology slide of chordoma demonstrating bony invasion by tumor. Note the rests of tumor cells deep within the bone. **d** Histology of classic chondrosarcoma

Treatment

Synopsis. Two treatments have proven beneficial for chordomas, maximal surgical resection and high-dose radiation. The main challenge in the treatment of chordomas is local recurrence, thus a combination of radical resection and high-dose radiation therapy is required. Local recurrence is thought to be due to local bony invasion by tumor cells, with nests of tumor deeper within the skull-base bone than is seen at surgery (Fig. 3c). Due to their midline location in the bone of the skull base, surgical resection proves challenging. Even with radical surgical resection, chordomas tend to recur. The current treatment practices combine aggressive surgical resection and proton beam radiation.

Surgery

The advent of skull-base surgical techniques has allowed for the surgical exposure and radical resection of chordomas. These tumors are located in the midline skull base within the bone of the clivus, often with extensions into multiple different compartments of the cranium. Specifically, chordomas can extend into the sellar and parasellar spaces, sphenoid sinus, cavernous sinus, foramen magnum, prepontine cistern, posterior fossa, occipital condyle, infratemporal fossa, and retropharyngeal spaces. Due to this localization and extension, multiple different surgical approaches are required for the treatment of these tumors, often multiple approaches utilized within the same patient. Surgical treatment must be tailored for each case, specifically taking into account the areas of the skull base involved, overall health of the patient, and previous surgical resection.

Attempts at radical resection are crucial to the effective treatment of chordomas. Average survival with untreated chordoma is estimated at 28 months after onset of symptoms. After total or near total surgical resection, the overall survival rate at 5 years has been reported to be between 13% and 51%, and between 18% and 35% at 10 years. Recurrence rates range from 12% to 60% with a mean follow-up of 1.9–30 years [5]. Patients who have not had previous surgery have a higher chance with radical resection and better recurrence-free survival rates than patients who have undergone prior surgery [6].

Surgical approaches require the ability to access the skull base from multiple different strategies. The midline anterior skull-base approaches (transsphenoidal, extended transsphenoidal, and transmaxillary) are used for tumors in the clivus and for extensions into the nasopharynx, sella, parasellar regions, and sphenoid sinus. Lateral extension of the tumor along the petrous pyramid and cavernous sinus requires the addition of lateral approaches (middle fossa, cranio-orbito-zygomatic). Tumor extension into the posterior fossa and occipital condyles requires transpetrosal and transcondylar approaches. Patients requiring multiple different approaches often benefit from staged resection.

These multiple surgical approaches are accompanied by potential complications. Due to the location of these tumors in the midline skull base, access is limited, and thus obtaining a watertight closure of the dura is a difficult task. Cerebrospinal fluid (CSF) leakage is the main complication associated with surgical treatment of chordomas, occurring in 8–30% of patients. Since access to these regions is often through the nose and mouth, meningitis is a potential problem in patients with CSF leak, occurring in 0–10% of these patients. Surgical complications also include transient and permanent cranial neuropathies which occur in 0% to 80% of patients. Surgical mortality is reported between 0% and 8%. Patients who underwent previous surgical therapy are at higher risk of both surgical morbidity and mortality.

Care must be taken during surgical resection of chordomas due to the possibility of chordoma cells seeding and growing in distant sites [7]. Specifically, chordoma cells can seed the operative route in the nasal mucosa, bone, dura, and muscle distant from the primary tumor site, along the surgical access route. Also, tumor seeding has been reported in the abdominal fat harvest sites. Postoperative and follow-up imaging should examine the surgical route to assess for tumor seeding. The operative technique should be altered in patients with suspected chordoma. Specifically, the surgical route is coated with fibrin glue and large patties. The fat graft is harvested after changing of gowns and gloves, with a separate set of instruments, within a separate surgical field. The fat graft is placed into the resection bed after surgical patties have been removed from the surgical route. Closure takes place after changing surgical drapes and towels, and gowns and gloves.

Radiotherapy

Adjuvant radiotherapy has become a mainstay in the treatment of chordomas, although chordomas were once considered radioresistant tumors. The dose required to treat mesenchymal tissue tumors is in the range of 70–80 Gy, while the radiation tolerance of surrounding neural structures including the brain stem is 60 Gy. However, improving technology has allowed more conformal dosing of photon and proton radiation to the tumor beds. Intensity-modulated radiotherapy and three-dimensional conformal radiotherapy technologies have allowed the treatment of

these tumors with fractionated photon beam therapy with higher accuracy and conformal dosing.

Radiosurgery with gamma-knife and LINAC-based systems are being used for patients with chordoma. Currently, there are insufficient published results using this technology, particularly in the long term.

Proton beam therapy has become the radiation treatment of choice for chordomas. Protons allow radiation delivery in highly conformal dose distributions without an exit dose. This also allows proton therapy to be used for irregular tumor boundaries.

Currently, there are two proton beam facilities in the USA, in Massachusetts and in California, and one in Orsay, France. With the use of proton beam therapy at doses of 65–83 cobalt gray equivalents (CGE), the 3- and 5-year local recurrence-free survival rates were between 94% and 95% for chondrosarcoma, and 67% to 73% for chordoma. Five-year survival rates were 91–100% for chondrosarcoma and ~80% for chordoma [8, 9].

Chemotherapy

There are currently no reports of chemotherapy treatments that have proven effective in treating chordoma or chondrosarcoma. There have been a few reports with limited numbers of patients using experimental treatments for chordoma [10]. Use of chemotherapy may be considered in infants with chordoma who are too young for radiation therapy. This strategy is employed to potentially halt tumor growth until the child is old enough to tolerate radiation therapy.

Prognosis/Quality of Life

Untreated chordoma is associated with an average survival of 28 months after diagnosis. A combined surgical and radiation treatment regimen affords the patient the best chance at progression-free survival. Chondrosarcoma is associated with a significantly better prognosis than chordoma when treated with both modalities. Chondroid chordomas behave similarly to chordoma.

The extent of tumor resection and adjuvant radiation therapy are related to the prognosis. Extent of resection has been shown to affect outcome. Patients who have had a gross total resection of tumor have higher 5-year survival rates and recurrence-free rates than patients who underwent only partial resection. Chordoma patients can be divided into good-prognosis and poor-prognosis groups. The former includes patients who after surgical resection have either gross total resection or small residual tumor size and absence of tumor along critical dose-limiting neural structures such as the brain stem and optic apparatus. Patients in the latter groups achieve only temporary slowing of tumor growth, even at higher radiation doses. These patients should be considered for aggressive surgical resection to improve the ability to deliver high-dose radiation.

Adjuvant radiation therapy, especially proton beam treatments, prolong the survival and recurrence-free survival of patients.

Age is a controversial prognostic factor for adult patients, with studies showing conflicting results. Age less than 5 years is associated with a worse prognosis and with a more malignant pathology.

Cytogenetic studies on tumor tissues may show prognostic differences. There was no significant difference in karyotype between patients with chordoma and chondroid chordoma. Abnormal karyotype was seen more frequently in chordoma than chondrosarcoma. An abnormal karyotype was also associated with higher recurrence rates. Tumors with loss of the tumor suppression loci at 1q and 13q demonstrated more aggressive behavior.

Future Perspectives

Since chordoma is a rare disease, there has been limited treatment information in the form of large studies. With the emergence of proton beam therapy as the adjuvant treatment of choice, most of the patients are being concentrated at two centers allowing for such large trials. The surgical management of these tumors also requires improvement to increase the number of patients with gross total resection while limiting complications. Recent advances in surgery, including intraoperative monitoring of cranial nerves, and frameless stereotactic guidance have improved the surgical results. Further understanding and study of the biology of these tumors will also be required to improve future therapies.

Skull-Base Meningiomas

Epidemiology

Meningiomas occur frequently, constituting 20% or more of all intracranial tumors. Their incidence between community-based series and clinical series varies from 1 to 6 cases per 100,000 persons per year and on average is estimated to be around 2.6 cases per 100,000 persons per year [1]. Meningiomas are frequently located at the skull base, with 40% of meningiomas being in this location. The sphenoid ridge is the most commonly involved location at the skull base (Table 1). Other locations include the olfactory

Table 1. Intracranial location of meningiomas

Falx/parasagittal	25%
Sphenoid wing	20%
Convexity	20%
Olfactory groove	10%
Posterior fossa/petrosal	10%
Suprasellar	10%
Others[a]	5%

[a] Optic sheath, clivus, foramen magnum, intraventricular, tentorial, cerebellopontine angle

groove, planum sphenoidale, tuberculum sella, anterior clinoid, cavernous sinus, cerebellopontine angle, clivus and petroclival area, and foramen magnum.

Meningiomas occur more commonly in African-Americans than in white people. Several African studies show a significantly higher incidence of meningiomas among that population. This finding may be of importance from a genetic and molecular biologic perspective. The results of three large studies of intracranial neoplasms indicate a higher incidence of meningiomas in women. The ratio of male to female incidence ranges from 1:1.4 to 1:2.8. The incidence of intracranial meningiomas increases with age, with a peak incidence of 6/100,000 population in men between 60 and 69 years of age and 9.5/100,000 population in women in the 70–79 years age group. Meningiomas are rare in the pediatric population and account for 1–2% of brain tumors in this age group. When occurring in children, the majority of these tumors affect boys.

Several analytic epidemiologic studies have been performed to identify etiologic risk factors for intracranial meningiomas. They apply to meningiomas at the skull base and meningiomas in other locations. The studies with the strongest designs and most patients are those linking ionizing radiation to the development of meningiomas. Among the first were the studies of children treated for tinea capitis using low-dose radiation. In a cohort of 10,834 children treated with a dose of radiation estimated at 1.5 Gy, 19 patients developed meningiomas, for a relative risk of 9.5. The mean interval from radiation exposure to diagnosis was 20.7 years. Most of the tumors in this study were at the convexity where the dose of radiation was 60% greater than at the skull base [11]. Several other studies demonstrated a dose-response relationship between ionizing radiation to the head and the occurrence of meningiomas. The latency of meningioma occurrence following low-dose radiation appears to be considerably longer than that for meningiomas following higher doses of radiation.

Another source of low-dose radiation that has been linked to the development of meningiomas is exposure to dental radiographic examination. The full mouth series has been performed since the introduction of dental radiography and involves taking 10–20 individual radiographs. The skin exposure with various machines varies from 1 to 3 Gy. Several studies have examined the risk of meningioma with dental radiographs. Two studies did not find an association between meningioma and dental amalgam fillings. Two other studies found that the likelihood that the meningioma was at the skull base increased with increasing numbers of full mouth radiographs. This was the region of the cranium that was presumed to have received the greatest radiation exposure. From the previous studies and discussion, it is clear that ionizing radiation may be a cause of intracranial meningioma. Less clear are the most important sources of radiation and how many meningiomas can be attributed to ionizing radiation. Three criteria have to be fulfilled to be considered a radiation-induced tumor: (1) it has to occur in the irradiated field, (2) it has to appear following an appropriate, usually long, period of latency following irradiation, (3) it has to differ from any pre-existing neoplasm.

Radiation-induced meningiomas have been shown to behave differently than non-radiation-induced meningiomas [12]. The age at presentation with radiation-induced meningiomas appears to be related to the dose of radiation received, and on average is at a younger age. The latency period from exposure to the diagnosis of meningioma also appears to be dose related. These tumors behave more aggressively and have a 100% recurrence rate (Fig. 4). On pathological examination, these tumors are higher grade, stain for a higher proliferative index, and have multiple, complex, cytogenetic alterations including chromosomes 1p and 6q.

Other factors that have been clearly linked to the occurrence of intracranial meningiomas are genetic. It has been recognized for many years that meningiomas occur with a higher frequency in patients with neurofibromatosis type 2 as well as in certain familial aggregates. It is now accepted that meningiomas arise when there is loss of NF-2 or other tumor suppressor genes in combination with the activation of proto-oncogenes. Most meningiomas with deletions on chromosome 22 map to 22q12, which is the same locus responsible for producing the NF-2 tumor suppressor gene. The NF-2 gene locus is not involved in familial meningiomas, however; rather a different tumor suppressor gene is speculated to be responsible.

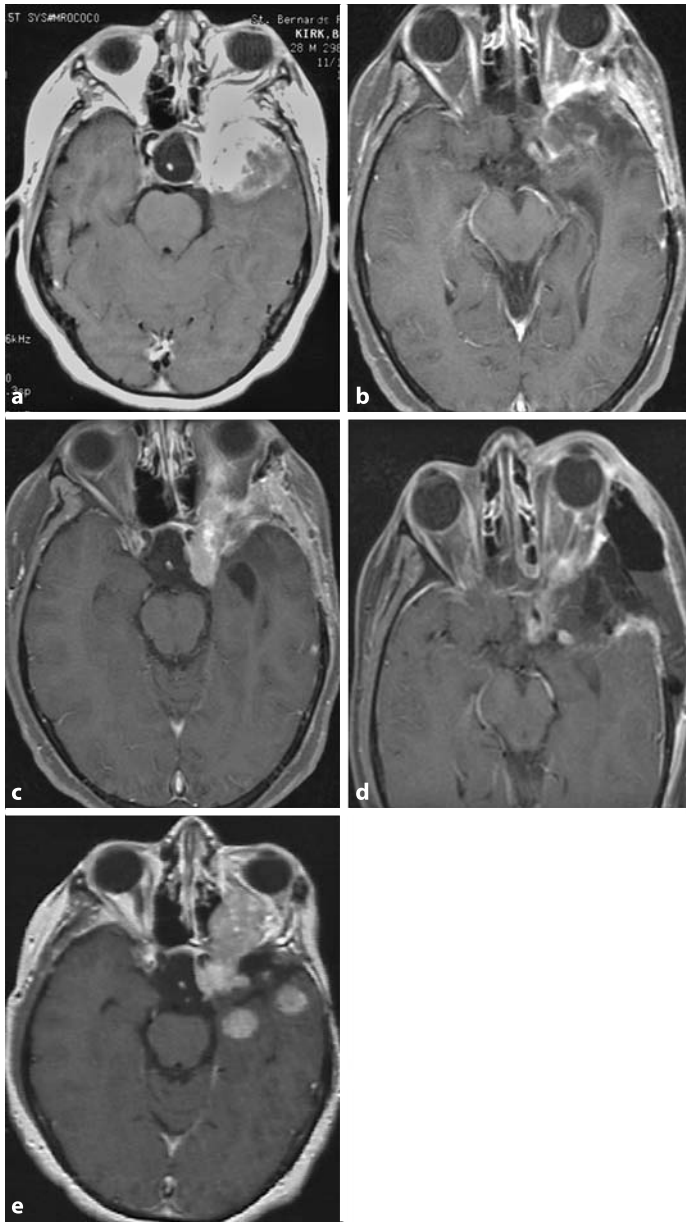


Fig. 4 a–e. Radiation-induced meningioma demonstrating multiple recurrences. **a** Meningioma imaging at diagnosis. **b** MRI demonstrating gross total resection. **c** Tumor recurrence 1 year later. **d** MRI after repeat resection. **e** Repeat recurrence after another year

Sex hormones and their receptors seem to play an important role in the development of meningiomas as suggested by epidemiologic features of this tumor: It is two to four times more common in women; it grows more rapidly during pregnancy and during the luteal phase of the menstrual cycle, and it has been linked with breast carcinoma. It is also well established that estrogen and progesterone receptors are present in meningiomas. Most estrogen receptors identified in meningiomas are type II receptors, which have a lower affinity and specificity for estrogen than the type I receptor classically found in breast cancers. It is currently believed that estrogen binds in less than 20% of meningiomas. Progesterone receptors are much more common, occurring in 50–100% of tumors tested. The biologic significance of these receptors remains uncertain, with their presence correlating with less aggressive tumors.

Although it is known that certain viruses will produce central nervous system tumors when inoculated in laboratory animals, their actual role if any in the development of meningiomas is still undefined.

Head trauma has initially been suggested by Cushing to play a role in the development of meningiomas. Several recent studies have failed to show an increase in the incidence of meningiomas in cohorts of patients with head injuries.

Symptoms and Clinical Signs

There is no single symptom or sign that can identify which patients harbor an intracranial meningioma. Indeed, some tumors are identified fortuitously in patients who have no symptoms or signs of intracranial disease. Other patients have a variety of presenting features including headaches, paresis, seizures, personality changes, confusion, and visual impairment. In population-based studies, headaches and paresis were found to be the most common symptom and sign. An increased incidence of abnormal physical findings was found in patients with malignant meningiomas. Patients with skull-based meningiomas may have additional signs and symptoms depending on where the lesion is located. Olfactory groove meningiomas present most commonly with slow onset of changes in mental status, particularly in mood, insight, judgment, and motivation. Late in their course, the patients may have headache, reduced vision, and seizures. Rarely do patients complain of loss of sense of smell, and only 3 of 29 cases reported by Cushing and Eisenhardt had this as their primary symptom. The Foster Kennedy syndrome of anosmia, unilateral optic atrophy, and contralateral papilledema is, in fact, uncommon. Most patients with tuberculum sellae meningiomas present with an insidious onset of progressive visual loss, usually a chiasma syndrome with ipsilateral optic atrophy and incongruous bitemporal hemianopsia. Panhypopituitarism can happen but is rare.

Clinoidal meningiomas most often present with monocular visual loss. Cavernous sinus meningiomas may result in proptosis, diplopia, facial hypoesthesias, or aberrant oculomotor regeneration. Meckel's cave meningiomas may present with a petrous apex syndrome consisting of facial numbness or pain and diplopia secondary to a sixth nerve palsy. Petroclival meningiomas usually present with signs and symptoms of brain stem compression as well as facial numbness, diplopia, hearing loss, and facial weakness. Foramen magnum tumors are usually associated with nuchal and suboccipital pain as well as a stepwise, appendicular sensory and motor deficit.

Diagnostics

CT scanning can detect the majority of meningiomas and can in most instances determine their extent. CT at wide window and level settings optimally identifies bone involvement, either hyperostosis or bone lysis. This capability is especially used for skull-base tumors because it aids in the specificity of diagnosis and in planning the extent of surgical resection required to rid the patient of the meningioma. On nonenhanced CT scans, the typical meningioma is isodense to slightly hyperdense to brain and of homogenous density, although calcification may be present and may range from tiny punctate areas to dense calcification of the entire lesion. Edema, which appears as low density on CT, is often evident to various degrees, the extent of which has few predictable correlates. Bone changes, which are best imaged with CT, occur in approximately 25% of meningiomas and vary from hyperostotic to destructive lesions (Fig. 5). Intravenous contrast usually shows intense, homogeneous enhancement, and morphologic features, such as sharp demarcation and a broad base against the bone or free dural margins, are easily seen. On CT, approximately 15% of benign meningiomas have an unusual appearance. Areas of hyperdensity, hypodensity, and nonuniform enhancement may be seen and may represent hemorrhage, cystic degeneration, or necrosis, respectively. Aggressive meningiomas may at times be distinguished by preoperative imaging, findings of indistinct or irregular margins, or mushroom-like projections from the main tumor mass.

High-resolution CT, MRI, and MR angiography have to a large extent supplanted angiography, which once played a preeminent role in the diagnosis of intracranial meningiomas. Indeed, the determination of venous sinus patency, historically the purview of the angiogram, can be well visualized on MRA, thus eliminating this indication for angiography. Some suggest that angiography can still be performed routinely for old meningiomas to help identify any pial vascular supply to the tumor. However, from a practical point of view, this information is unlikely to alter the management of these patients significantly. Angiography remains a vital means by which the feasibility and safety of preoperative embolization can be determined. Furthermore, pertinent collateral circulation can be identified. To date, only selected angiography can resolve the generally small communicating branches present between the internal carotid arteries and vertebral arteries and the external carotid arteries, the presence of which to a large extent determines the safety of embolization of intracranial meningiomas. Angiography helps also in the preoperative evaluation of the venous complex of the vein of Labbe, especially when the petrosal approach is indicated or when the tentorium needs to be cut. This venous anatomy can sometimes be evaluated with an MRV, but angiography remains the best study to do so.

The high-field MRI characteristics of meningiomas are relatively consistent. On T1-weighted images, 60–90% of meningiomas are isointense, whereas 10–30% are mildly hypointense compared with gray matter. T2-weighted imaging reveals that 30–45% of meningiomas are of increased signal intensi-

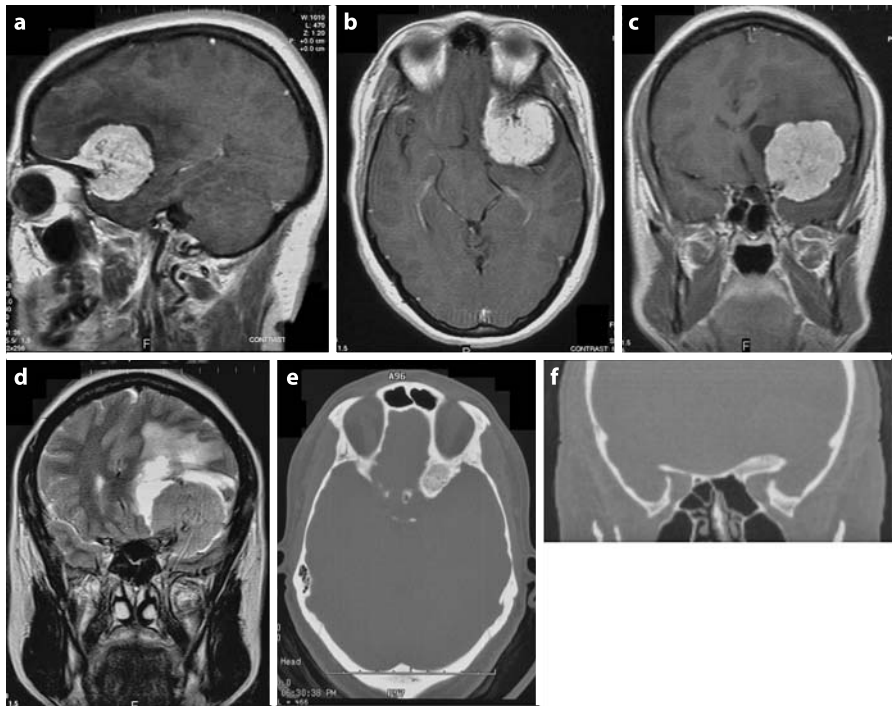


Fig. 5 a–f. Imaging of meningioma. **a–c** Sagittal T1 imaging of basal clinoidal meningioma demonstrating bright, homogeneous contrast enhancement and the dural tail. **d** T2 imaging of meningioma demonstrating significant vasogenic edema with surrounding brain. **e, f** Preoperative axial and coronal CT scans demonstrating hyperostosis of the underlying skull base at the sphenoid wing and clinoid

ty, whereas approximately 50% are isointense to gray matter. MRI better assesses vascular distortion or encasement and tumor vascularity than CT scanning. Flow voids produced by flowing blood identify the vasculature local to the tumor. The ability to decide on an extra-axial localization of a neoplasm is also heightened on MRI. Typical marginating characteristics include displacement of blood vessels, the presence of CSF clefts between the tumor and the brain, and inward displacement of the gray/white junction. The ability of T2-weighted images to subtype meningiomas is controversial, with some studies showing 75–90% accuracy and others finding no correlation. The amount of cerebral edema present in association with meningioma may also help to subtype some of these tumors. However, making such distinctions is of little clinical value in the treatment of meningiomas. High signal intensity on T2-weighted images has also been correlated with microscopic hypervascularity and soft tumor consistency. It may also help to predict the ease with which the tumor can be resected from the surrounding brain. Contrast-enhanced MRI provides the highest level of detection of meningiomas. Most meningiomas enhance intensely and homogeneously with intravenous paramagnetic contrast material (Fig. 6), and in approximately 10% of cases, small additional meningiomas are encountered that are missed on unenhanced MR images. Likewise, contrast enhancement of the dura extending away from the margins of the mass is typical of meningioma, although it can be seen with other dural-based lesions (Figs. 5, 6). This dural tail can represent tumor extension, and its resection is important to lessen the risk of recurrence. Postoperative enhanced MRI has also been found to be more sensitive and specific in the detection of residual or recurrent meningioma (Fig. 6). Thick and nodular enhancement has a high correlation with recurrent or residual neoplasm.

Meningiomas express somatostatin receptors, allowing the use of octreotide scintigraphy in their imaging (Fig. 7). All meningiomas show an intensely positive scan, while other skull-base tumors are negative. This technology may be used to differentiate between meningiomas and other skull-base tumors, or may be used in the follow-up of patients to assess for recurrence.

Staging and Classification

Most meningiomas are benign and can be graded as WHO grade I. However, certain histological subtypes are associated with a less favorable clinical outcome and correspond to WHO grades II and III [14] (Table 2). Grade II meningiomas include chordoid meningiomas, clear-cell meningiomas, and atypical meningiomas. Chordoid meningiomas contain regions that are histologically similar to chordoma with trabeculae of eosinophilic vacuolated cells in a myxoid background. They are interspersed with typical regions of meningioma. Clear-cell meningiomas

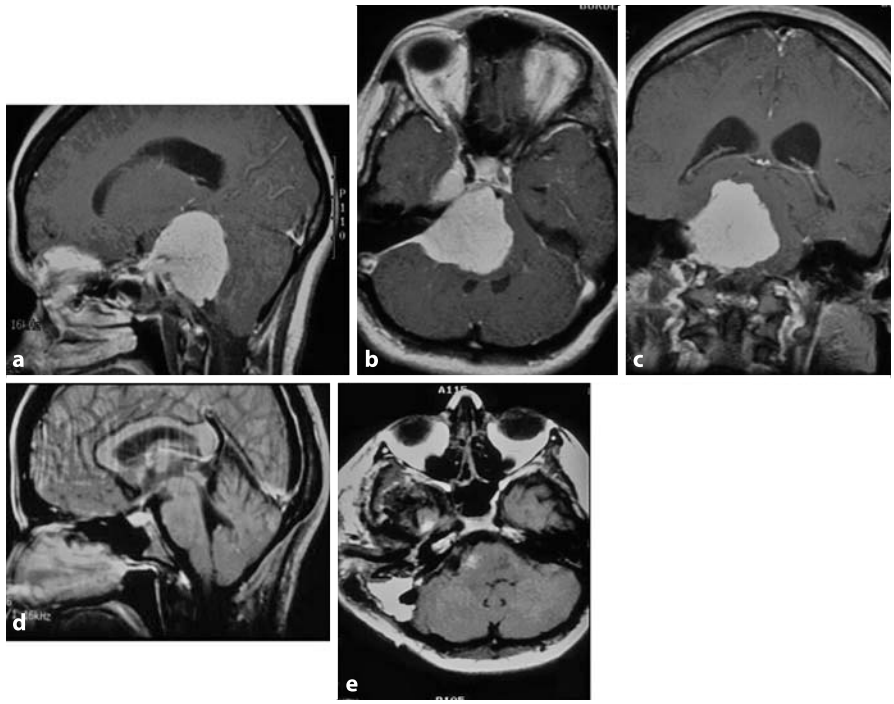


Fig. 6 a–e. Imaging of meningioma. **a–c** Preoperative T1, postcontrast images of large petroclival meningioma demonstrating bright homogeneous contrast enhancement and dural tail. **d, e** Postoperative images in the same patient after surgical resection using petrosal skull-base approach demonstrating complete resection. Note fat within area of mastoid resection used in the surgical approach

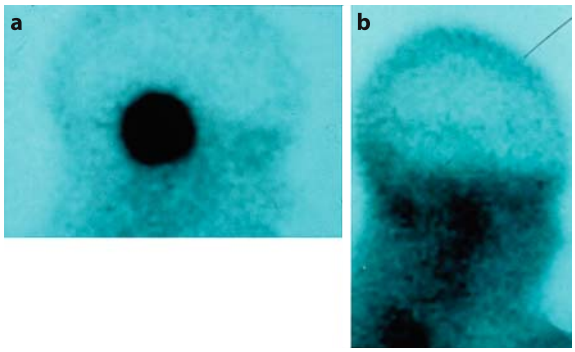


Fig. 7 a, b. Octreotide scintigraphy of meningioma. **a** Preoperative octreotide scan of a patient with a skull-base meningioma. The tumor demonstrates bright octreotide uptake. **b** Postoperative scan in the same patient demonstrating lack of octreotide uptake

are often patternless meningiomas composed of polyclonal cells with a clear glycogen-rich cytoplasm. A meningioma with increased mitotic activity or 3 or more of the following features (increased cellularity, small cells with high nuclear-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and focus of spontaneous necrosis) is considered atypical [15, 16] (Table 3). Papillary meningiomas as well as rhabdoid and anaplastic meningiomas are considered WHO grade III. A papillary meningioma is a rare meningioma, a variant defined

Table 2. Revised World Heath Organization grading of meningiomas [14]

Meningiomas with low risk of recurrence and aggressive growth:

Grade I
- Meningothelial
- Fibrous/fibroblastic
- Transitional (mixed)
- Psammomatous
- Angiomatous
- Microcystic
- Secretory
- Lymphoplasmocyte rich
- Metaplastic

Meningiomas with greater likelihood of recurrence and/or aggressive behavior:

Grade II
- Atypical
- Clear cell
- Chordoid

Grade III
- Rhabdoid
- Papillary
- Anaplastic

Meningioma of any subtype with high proliferation index and/or brain invasion

Table 3. Mayo Clinic criteria for atypical and anaplastic meningiomas [15, 16]

Criteria for atypical meningiomas:
High mitotic index: ≥4 mitoses/10 HPF (≥ 2.5/mm^2)
or presence of 3 of the following 4 features:
- Sheeting
- Prominent nucleoli
- Small-cell formation
- Hypercellularity (≥53 nuclei/HPF; ≥118/mm^2)

or
Brain invasion

Criteria for anaplastic meningiomas:
Excessive mitotic activity: ≥20 mitotic figures/10 HPF (≥12.5/mm^2)
or
Focal or diffuse loss of meningothelial differentiation resulting in carcinoma-, sarcoma-, or melanoma-like appearance

by the presence of a very vascular pseudo-papillary pattern in at least part of the tumor. They tend to occur in children. A rhabdoid meningioma is also an uncommon tumor containing patches or extensive sheets of rhabdoid cells, which are rounded tumor cells with eccentric nucleoli. Finally, a meningioma is considered anaplastic if it has histologic features of frank malignancy far in excess of the abnormalities present in atypical meningiomas [16].

Malignant progression of benign meningiomas has also been described [17]. There has been documented progression from benign to atypical and anaplastic histologic grades based on pathological evaluation of tumors at original presentation and at recurrence. Along with progression of histological grading, there has also been an increase in the proliferative indices as the tumor becomes more malignant. These tumors are associated with complex cytogenetic abnormalities, with deletions at chromosomes 22, 1p, and 14q. Interestingly, these complex chromosomal changes are present at the time the tumors are benign. This indicates that tumors with complex genetic alterations are at risk of recurrence and malignant progression [17].

Treatment

Meningioma Surgery

Harvey Cushing described surgery for meningiomas in 1938: 'Few procedures in surgery may be more immediately formidable than an attack upon a large tumor [meningioma] and that the ultimate prognosis hinges more on the surgeon's wide experience with the problem in all its many aspects than is true of almost any other operation that can be named' [18]. This description still holds true over 60 years later.

Positioning of the patient should be done in a fashion that maximizes the patient's safety, the accessibility of the tumor, the allowance for unimpeded venous drainage, the beneficial effects of gravity, and the surgeon's comfort. Most patients with either supra- or infratentorial meningiomas may be placed in the supine position. Monitoring for air embolism, which should be used with any position that involves placing the head above the heart level, is particularly important during meningioma surgery since many tumors are closely related to the venous sinuses and their large tributaries. As well as taking advantage of the effects of gravity, several methods are employed to minimize brain retraction, among which is spinal drainage. However, contraindications such as large tumors or obstructive hydrocephalus should be considered. Hyperventilation to a PCO2 of 25–30 contributes to the degree of brain relaxation. The best means of reducing brain retraction, however, is to eliminate the need to do so by using one of the basal approaches. Since these approaches utilize orbital and zygomatic osteotomies and increase removal of the bony skull base, they allow a low, flat route to basally located tumors. Scalp flaps, which should be wide-based to allow for a rich blood supply and designed to facilitate any subsequent reoperation, should be linear, gently curvilinear or bicoronal incisions rather than horseshoe flaps. In the vast majority of first operations for meningiomas, a layer of arachnoid separates the tumor from the brain parenchyma, cranial nerves, and blood vessels. When it does, the chances of neural and/or vascular injury can be greatly reduced by defining and staying within the surgical plane. One maneuver that facilitates the definition of this arachnoid border is extensive debulking of the tumor, thus allowing the tumor capsule to collapse inward. The method used to debulk the tumor, which may be suction, coagulation, sharp excision, or use of the ultrasonic aspirator or the surgical laser, depends on the tumor consistency, vascularity, and location. Once the mass of the meningioma is resected, careful attention must be given to removing the involved dura and bone. The extent of bone that must be removed can be determined by inspection of the preoperative CT scan's bone windows. All of the hyperostotic bone should be considered contaminated by neoplastic cells. In fact, areas of hyperostosis resected at the time of surgery show tumor invasion histologically in most patients [19]. The fear of entering the mastoid air cells or paranasal sinuses is not cause for failing to remove this diseased bone. A wide margin of dura should be resect-

ed, and the defect should be repaired with pericranium, temporalis fascia, or fascia lata.

Cushing and Eisenhardt established a landmark particularization of meningiomas, and since that time, the common practice has been to classify meningiomas by their site of origin [18]. This has been helpful not only in planning the surgical approach but also in understanding the relationship of the tumor to the surrounding brain parenchyma, neurovascular structures, and arachnoid cisterns. When the site of origin of the meningioma is determined, its pattern of growth in relation to the surrounding critical structures and the number of arachnoid layers separating it from them is better understood. Using those layers of arachnoid separating the tumor from the adjacent elements is the essence of safe surgical resection of meningiomas.

Meningiomas of the Anterior Cranial Base: Tuberculum Sellae Meningiomas. Small tuberculum sellae meningiomas are usually resected through the unilateral supraorbital approach. Bigger lesions in this location, as well as olfactory groove meningiomas, are resected through the bilateral supraorbital approach. For both approaches, the patient is placed supine and the trunk elevated 20 deg, the head moderately hyperextended and fixed in a Mayfield headrest to allow the frontal lobes to fall backward. The head is kept straight to facilitate orientation. The scalp incision is started 1 cm anterior to the tragus and continued behind the hairline to the level of the superior temporal line on the opposite side. In this manner, the superficial temporal artery course is posterior to the incision, while the branches of the facial nerve are anterior. The scalp behind the incision is elevated and freed from the pericranium, leaving the thick areolar tissue with the pericranium. A large pericranial flap base on the supraorbital and frontal vessels is then incised as far posteriorly as possible, dissected forward, and reflected over the scalp flap. Both layers of the temporalis fascia are incised posterior to and along the course of the upper branches of the facial nerve until muscle fibers are seen. The deep fascia, the fat pad, and the superficial fascia are then retracted anteriorly. The upper portion of the temporal muscle is detached from its insertion anteriorly and is retracted posteriorly, exposing the junction of the zygomatic, sphenoidal, and frontal bones. The bone flap used depends on the size and location of the tumor. The flap can be either unilateral supraorbital for small tuberculum sellae meningiomas or bifrontal supraorbital for bigger tuberculum sellae meningiomas and olfactory groove meningiomas. In adults, the midline hole will invariably pass through the anterior and posterior walls of the frontal sinus. The mucosa is exenterated after the bone flap is removed. The posterior wall of the sinus is removed, and the sinus is packed with a small piece of temporal muscle. After the bone flap is removed, the dura is tacked up and opened under the microscope. Once the bifrontal approach is used, the sagittal sinus is divided between two silk sutures, and the falx is cut at its lowest limit. Elevation of the frontal lobe should be minimal. The olfactory nerve is located and preserved by dissecting it for some distance from the base of the frontal lobe. Tumor feeders are intercepted early; they are coagulated and severed on the basal aspect of the tumor. Devascularization is restricted to midline to avoid injury to the optic nerve on either side. Midline orientation is maintained by observing the falx position. The tumor is debulked with suction, ultrasonic aspirator, or a bipolar coagulator and microscissors. Once the dissection approaches the neurovascular structures, only bipolar cautery and microdissection should be used. After the tumor is debulked, the optic nerves, which are displaced laterally, are identified. The tumor is slowly stripped from the flattened or engulfed nerve. Despite apparent encasement of or severe adherence to the nerve, a plane of dissection can be obtained under high magnification. To preserve any remaining vision, dissection of the optic nerve and its blood supply must be meticulous. Dissection may need to begin at the chiasm so that the surgeon can locate and dissect an obscured optic nerve on the opposite side. Arterial structures should be preserved through the same method of sharp microdissection into an arachnoidal plane. The carotid artery is dissected free from the tumor with an array of microinstruments, including bipolar forceps, microdissectors, and scissors. Carotid dissection continues to free the ophthalmic artery, the posterior communicating artery, the anterior thalamic perforators, and the choroidal artery. Further dissection of the tumor progresses to the bifurcation of the internal carotid artery and into the Sylvian fissure. Dissection is then continued to free the middle and anterior cerebral arteries. In most cases, the tumor has simply displaced each vessel and their perforators and rarely actually engulfs them. The A1 segments in particular are usually severely stretched or adherent and tend to tear. Should this occur, temporary clips should be applied distal and proximal to the bleeding point and the arterial wall sutured with fine 8.0 Prolene sutures. Although arterial twigs of the anterior cerebral arteries may supply the tumor, the surgeon must first be certain that these vessels are, indeed, tumor feeders and not hypothalamic perforators or the optic tract blood supply. Thus, each arterial branch should be dissected and followed to ascertain its eventual course. Particular precision is needed to spare the artery of Heubner and the vital branches to the striatum. As dissection continues, both A1 arteries and the anterior communicating artery are freed from the tumor. The mem-

brane of Liliequist is intact, making tumor removal from the posteriorly displaced basilar artery easy. The pituitary stalk can be recognized by its distinctive color and vascular network. A tumor extending backward under the hypothalamus usually displaces the pituitary stalk backward and to one side. Some tumors actually engulf the pituitary stalk and require meticulous and tedious dissection. The blood supply to the pituitary gland should be preserved. The tumor impinging on the hypothalamus can be removed gently if the surgeon maintains a plane of cleavage. Excessive downward retraction of the tumor, however, should be avoided. The arachnoid membrane of Liliequist provides an excellent plane of dissection for tumor removal. Often this membrane comes away with the tumor, leaving the rostral pons, midbrain, oculomotor nerves, and basilar artery and its branches in full view. When the tumor extends into the cavernous sinus or optic canal, the anterior clinoid process, the roof of the optic canal, and the roof of the superior orbital fissure are drilled away with the diamond bit of the high-speed air drill. The dura is then opened along the optic nerve. Tumor tissue around the optic nerve is removed with bipolar and microdissectors, and the surgeon must pay particular attention to preserving the hypothalamic and central retinal arteries. This bony drilling exposes the superior aspect of the cavernous sinus, and the internal carotid artery emerges through the superior wall and is surrounded and firmly anchored to the dura by a ring. Beginning at this emergence, an incision is made in the exposed dura and extended posteriorly toward the posterior clinoid process. The internal carotid artery is then followed in retrograde fashion into the cavernous sinus where it is dissected. In the cavernous sinus space, the tumor is dissected with bipolar coagulation and microdissectors. Venous hemorrhage is controlled with surgical paddies. After the tumor has been removed, its dural attachment should be resected or coagulated. Involved bone should be removed with a diamond bit of a high-speed air drill. Any opening into a paranasal sinus requires thorough repair of the dural defect. If the sphenoid sinus was entered, its mucosa is exenterated, and the sinus is packed with fat taken from the patient's thigh. A large piece of fascia lata is laid intradurally and secured with sutures along the lesser sphenoid wing. The graft is then spread to cover the frontal fossa and then sutured to the frontal dura. The preserved pericranial flap in the frontal region is turned over the frontal sinus and extended over any defect in the floor of the frontal fossa. Titanium microplates are used here to reattach the bone flap to the cranial vault. The temporal muscle is sutured to the fascia at the lateral orbital rim, and the skin is closed in two layers.

Meningiomas of the Middle Cranial Base. Meningiomas of the middle cranial base involve the sellar and parasellar area. The most frequent are meningiomas of the sphenoid wing, but as mentioned earlier, lateral and middle sphenoid wing meningiomas will not be discussed as skull-base meningiomas since extensive removal of the sphenoid wing extradurally transforms them into convexity meningiomas.

Clinoidal Meningiomas. Clinoidal meningiomas are of three types [20] (Fig. 5). Type I originates from the inferior aspect of the anterior clinoid process, which is proximal to the carotid cistern. Thus, the tumor will engulf the carotid artery adhering directly to that adventitia without an interfacing arachnoidal membrane. As the tumor grows, this direct attachment of the vessel wall advances to the carotid bifurcation and along the middle cerebral artery, pushing the arachnoid membrane ahead of it. This anatomic arrangement accounts for the inability of the surgeon to dissect the tumor from the carotid artery and the middle cerebral branches. Type II clinoidal meningiomas originate from the superior or lateral aspect of the anterior clinoid process above the segment of the carotid artery which has already been invested in the arachnoid of the carotid cistern. This is why these tumors are separated from the intracerebral vessels by an arachnoid membrane. This plane allows dissection of the tumor from the vessels even though they may be totally engulfed and narrowed. In type I and type II clinoidal meningiomas, the optic system is separated from the tumor by an arachnoid membrane, making microsurgical dissection of the tumor from these structures possible. Type III clinoidal meningiomas originate at the optic foramen medially to the anterior clinoid. They usually extend into the optic canal and cause visual symptoms early in tumor progression. The arachnoidal membrane investing the carotid artery separates this type of tumor from the vascular structures and makes dissection feasible. However, because these tumors are proximal to the chiasmatic cistern, there may be no arachnoid layer between the optic nerve and the tumor.

Cavernous Sinus Meningiomas. The second type of parasellar meningioma is meningiomas of the cavernous sinus. They are usually of two general types: those that originate in and may be confined to the cavernous sinus and those that invade the cavernous sinus but originate in an adjacent area. Meningiomas originating from the cavernous sinus and confined to it present with extraocular movement disorders and facial paresthesias. Their management is controversial, with options including surgery, radiosurgery, or observation alone.

Meckel's Cave Meningiomas. The third type of parasellar meningiomas is Meckel's cave meningiomas. They usually originate within the cave itself and are rarely confined to it. Patients with these kinds of tumors usually present with facial pain and diplopia. These meningiomas may grow and extend anteriorly into the middle fossa and the cavernous sinus and proceed into the upper clivus and petroclival area. If the extension goes in both directions, it becomes impossible to differentiate these tumors from sphenopetroclival meningiomas.

Surgery for Clinoidal and Cavernous Sinus Meningiomas

Clinoidal meningiomas and cavernous sinus meningiomas are best approached through the cranial orbitozygomatic route. The skin incision originates 1 cm in front of the tragus, going behind the hairline up to the superior temporal line on the contralateral side. The cutaneous flap is elevated while preserving the pericranium and the thick areolar tissue. As a subfacial dissection of the temporal muscle is performed to preserve the branches of the facial nerve, an osteotomy of the zygoma is performed using an oscillating saw, and the bone flap is elevated in one piece containing the orbital rim. The orbital roof and the lateral wall of the orbit are then resected in one piece for later reconstruction. The rest of the sphenoid wing is resected, and the anterior clinoid is then drilled using a diamond bit under microscopic magnification and abundant irrigation to avoid thermal injury to the optic nerve. The dura is then opened and the Sylvian fissure exposed and opened widely, identifying the branches of the middle cerebral artery and following it proximally to the carotid bifurcation that is usually either pushed laterally and superiorly by the tumor or engulfed by it in cases of clinoidal meningiomas. The tumor is then debulked using the cavitron ultrasonic aspirator, microscissors and instruments, and suction. The optic apparatus is then identified and preserved, and the optic sheath of the optic nerve is opened and tumor followed into the optic canal. The carotid rings are opened proximally and distally to permit mobilization of the carotid artery. For tumors involving the cavernous sinus, entering into this area may be either through the medial triangles or through the lateral triangles. Dissection of the tumor progresses in a stepwise fashion beginning by opening the optic nerve sheath longitudinally along the length of the optic canal. The distal dural ring is opened next with the opening extending posteriorly to the ocular motor trigone and thereby also freeing the proximal dural ring and allowing a wide entry into the anterior and superior cavernous sinus space. The carotid artery can be mobilized laterally by releasing it from its proximal and distal dural rings, which then allows entry to the medial cavernous sinus space. Lateral entry into the cavernous sinus begins by an incision beneath the projected course of the third nerve, allowing elevation of the outer dural layer of the lateral wall of the cavernous sinus that is peeled away. The internal carotid artery can be located by dissection between the third and fourth nerves and the first division of the trigeminal nerve; this is Parkinson's triangle. The course of the sixth nerve, which runs lateral to the internal carotid artery and is usually directly opposed to it, is usually parallel but deep to V1. The tumor is removed from the cavernous sinus space using suction bipolar coagulation and microdissection. A plane of cleavage along the carotid artery can usually be developed. Venous bleeding is typically not a problem when the tumor fills the sinus. It may occur as the venous plexus is decompressed during tumor removal. In that event, hemostasis can be obtained by packing the cavernous sinus space with oxidized cellulose or another similar hemostatic agent. In our series [21], total removal of the cavernous sinus meningiomas was possible in 76% of the patients. The major surgical morbidity and mortality rates were 4.8% and 2.4%, respectively. Preoperative cranial nerve deficits improved in 14%, remained unchanged in 80%, and permanently worsened in 6%. Seven patients experienced ten new cranial nerve deficits. Meckel's cave meningiomas are best approached through an extended middle fossa craniotomy with an osteotomy of the zygoma. After performing a resection of the petrous apex, most of the dissection is performed extradurally until Meckel's cave is exposed and the posterior part of the cavernous sinus is entered. The tumor in the posterior part of the cavernous sinus is resected using bipolar coagulation, suction, and microdissection. These patients will usually experience some facial numbness postoperatively, which is temporary in nature.

Meningiomas of the Posterior Cranial Base. The posterior cranial fossa can harbor a diversified group of meningiomas. Among them are clival, petroclival, sphenopetroclival, jugular foramen, and foramen magnum meningiomas.

Clival/Petroclival Meningiomas. Clival meningiomas originating from the mid-clivus are rare. Typically, they totally encase the basilar artery and its perforators, making them most formidable to expose and dissect. Petroclival meningiomas are, by definition, tumors that originate in the upper two-thirds of the clivus at the petroclival junction medial to the fifth nerve (Fig. 6). They often displace the brain stem and the basilar artery to the opposite side. Sphenopetroclival meningiomas are the most exten-

sive of these lesions. They invade the posterior cavernous sinus and grow into the middle and posterior fossa. The bony clivus and the petrous apex are involved, and the sphenoid sinus is invaded. They frequently require an extended perusal approach or a combination of the petrosal and cranio-orbital zygomatic approaches. Jugular foramen meningiomas are rare. They extend intracranially and extracranially along the lower cranial nerves. They mimic the clinical presentation of glomus jugulare tumors in every aspect. The major morbidity of these lesions stems from paralysis of the lower cranial nerves. Similar to glomus tumors, they are removed through the infratemporal approach.

As mentioned earlier, clival and petroclival meningiomas are resected through the petrosal approach or a total petrosectomy if hearing is completely lost preoperatively. These approaches expose a tumor that extends from the middle fossa to the foramen magnum. It requires only minimal retraction of the cerebellum and temporal lobe. The operative distance to the clivus is shortened by 3 cm, and the surgeon has a direct line of sight to the lesion and the anterior/lateral aspect of the brain stem. The transverse and sigmoid sinuses as well as the vein of Labbé are preserved. The vascular supply to the tumor is interrupted early during the procedure. For petroclival meningiomas, the patient is placed supine with his/her shoulder elevated and his/her head turned 45 deg away from the side of the tumor. The head is also lowered and tilted towards the opposite side to bring the base of the petrous bone to the highest point of the operative field. The bone flap is carefully elevated, exposing the transverse and sigmoid sinuses. A mastoidectomy is performed exposing the sigmoid sinus and the dura anterior to it, the jugular bulb, the lateral and posterior semicircular canals, and the facial nerve in the fallopian canal. Next, the bone overlying the sinodural angle is removed, exposing the superior petrosal sinus. If hearing is absent, a total labyrinthectomy can be performed at this point, thereby increasing the anterior lateral exposure of the tumor. Then the dura matter is opened along the anterior border of the sigmoid sinus and along the floor of the temporal fossa. The vein of Labbe is identified and protected. The superior petrosal sinus is coagulated and divided, and this division is carried medially through the tentorium, avoiding injury to the trochlear nerve and the superior petrosal vein. Complete sectioning of the tentorium allows the sigmoid sinus along with the cerebellar hemisphere to fall back, thus decreasing the need for retraction. Angling the microscope allows the fourth through twelfth cranial nerves as well as the entire vertebral basilar system and the anterolateral brain stem to be visualized. The cranial nerves of the posterior fossa have a relatively constant relationship to petroclival meningiomas. The trochlear nerve is usually superior and lateral to the tumor, whereas the trigeminal nerve is superior and anterior. The abducens nerve is found anterior and inferior and may be encased by the tumor. The seventh and eighth cranial nerves are posterior and lateral, and the ninth through eleventh cranial nerves are inferior. The basilar artery may be displaced posteriorly or to the opposite side, or it may be encased. The posterior cerebellar artery, superior cerebellar artery, AICA and PICA, are usually posterior and medial to the tumor, but they too may be encased by it. Tumor removal begins with progressive devascularization of the tumor by coagulating and dividing its vascular supply from the tentorium and from its insertion on the petrous pyramid and clivus. The arachnoid over the tumor is opened to allow entry through the capsule and central debulking. As noted above, neurovascular structures may be embedded in the meningioma, requiring that great care be taken, especially when using tools such as the ultrasonic aspirator. The tumor capsule is then dissected free from the surrounding structures, but this must be done gently to avoid hypotension and bradycardia from vagal stimulation. The need to preserve the small perforating arteries of the brain stem and cranial nerves cannot be overemphasized. As for other meningiomas, the point of dural attachment is vaporized and hyperostotic bone removed with a high-speed diamond-tipped drill working under constant irrigation between the cranial nerves. After the dura is closed in a watertight manner, the drilled petrous bone is covered with autologous fat, and the soft tissues are closed in multiple layers.

When the patient has lost hearing preoperatively, a total petrosectomy is done to take advantage of the additional exposure for meningiomas of the clivus-petroclival area and sphenopetroclival area. This technique simply adds a translabyrinthine and transcochlear resection to the petrosal approach.

In patients with a tumor that extends into the middle fossa or anterior cavernous sinus or where the temporal lobe's venous anatomy forbids elevation of the posterior temporal lobe, the petrosal approach is extended anteriorly. The skin incision begins at the zygoma in front of the tragus and extends upward behind the hairline to the superior temporal line. It is then extended posteriorly to circle the ear and continues down behind the mastoid in the neck as described in the petrosal approach. The anterior part of the skin flap is elevated as described in the cranial orbital approach. The initial dissection of soft tissue is similar to that done in the petrosal approach. The superficial temporal artery is preserved. After the bone flap is removed, the temporal bone is drilled, the dura is opened, and the tentorium is incised as in the petrosal approach. The anterior exten-

sion, however, allows the tumor to be exposed and removed from the cavernous sinus, the infratemporal area, and the parasellar area. If necessary, the Sylvian fissure is split, and dissection and tumor removal are done through the transsylvian approach.

Jugular Fossa Meningiomas. Primary meningiomas arising within the jugular fossa have also been reported [22]. Tumors in this location are rare and often have a similar presentation to glomus jugulare tumors. Meningiomas in this location are fraught with more surgical challenges, due to the intimate relationship with the lower cranial nerves. Surgical approaches must be tailored specifically for each patient based on preoperative imaging and intraoperative findings. Radical resection with low cranial nerve morbidity is possible with these lesions [22].

Foramen Magnum Meningiomas. Meningiomas of the craniovertebral junction are either located posteriorly and approached through a laminectomy and suboccipital craniotomy or placed laterally and anteriorly and removed through the transcondylar approach. For the transcondylar approach, the patient is placed in the supine position with the ipsilateral shoulder and back elevated 30–45 deg. A C-shaped incision begins above the ear and is extended caudally along the edge of the sternocleidomastoid muscle to expose the suboccipital area. The scalp flap is elevated in the subcutaneous plane to the level of the external auditory canal, and next the sternocleidomastoid is detached from the mastoid and retracted inferomedially. Injury to the accessory nerve must be avoided. The lateral mass of C1 is palpated, and the muscles are dissected in a subperiosteal plane from the lamina of the first and second vertebra. Once the inferior oblique muscle is detached, the ventral ramus of the second cervical root is followed medially to the vertebral artery between C1 and C2. The vertebral artery may be transposed medially once the transverse foramen of C1 is opened. A lateral suboccipital craniotomy is fashioned, the sigmoid sinus is skeletonized to the jugular bulb if necessary, and a C1 and C2 laminectomy is performed. The occipital condyle and the lateral mass of C1 are then drilled. Next the dura is incised posterior to the sigmoid sinus with the opening extending inferiorly to the entry of the vertebral artery. The dural incision circumscribes the dural entry of the vertebral artery, allowing its complete mobilization. The uppermost dentate ligament and, if necessary, the posterior C2 nerve root are divided. The accessory nerve is located between the dentate ligament and the posterior spinal nerve root. While the hypoglossal nerve may be either anterior or posterior to the tumor, depending on the tumor's point of origin; if anteriorly placed, it may involved both hypoglossal nerves. The tumor capsule is opened carefully, particular care being taken to avoid injury to the cranial nerves or blood vessels, and debulked. It may be detached from its clival base to decrease the vascularity. Careful separation of the tumor from the medulla and upper cervical spinal cord, the lower cranial nerves, and the vertebral artery may be accomplished by its dissection in the arachnoidal plane surrounding the tumor. The area of dural attachment is removed, as is any hyperostotic bone, and the dura is closed in a watertight manner to prevent CSF leakage. If the entire occipital condyle has been removed, an occipitocervical fusion should be performed. Postoperatively, the patient is managed in either a hard collar or a halo thoracic brace depending on the nature of the fusion construct.

Complete surgical treatment of meningiomas is attempted in all locations of origin. Due to the benign nature of most meningiomas, complete surgical resection offers the patient a cure. Complete resection includes resecting the involved meningeal attachment, dural tail, and areas of hyperostotic bone. Recurrence does happen after incomplete resection. The risk of recurrence decreases with more complete resection [23]. The extent of resection is described by the Simpson grade [23] (Table 4).

Radiotherapy

External beam radiation seems to be beneficial for aggressive meningiomas such as atypical and malignant meningiomas. To date, very little information exists to support this thesis. Several combined studies found a 58% recurrence rate following gross total resection and a 90% recurrence rate following subto-

Table 4. Simpson grade of surgical resection [23]

Grade I	Macroscopically complete tumor removal with excision of tumor, dural attachment, and abnormal bone
Grade II	Macroscopically complete tumor removal with coagulation of dural attachment
Grade III	Macroscopically complete resection of tumor without resection or coagulation of dural attachment or extradural extension
Grade IV	Subtotal removal of tumor
Grade V	Simple decompression of tumor

tal resection of malignant meningiomas, which decreased to 36% and 40%, respectively, when surgery was followed by external beam radiation. The recommended radiation dose and target volume for malignant meningiomas average at least 6,000 cGy with a 3- to 4-cm margin. The effectiveness of high radiation doses must be weighed against possible complications. Stereotactic radiosurgery to treat intracranial meningiomas began in the 1960s, and since then it has been used increasingly often. It has been reported that patients with skull-base meningiomas treated with gamma-knife radiosurgery had an 88% control rate of their tumors; however, these series had a mean length of follow-up of less than 5 years [24]. Several series report a growing interest in gamma-knife radiosurgery for the specific treatment of cavernous sinus and other skull-base meningiomas either as primary treatment or following microsurgery. Cranial nerves passing through the cavernous sinus can tolerate radiation doses up to 40 Gy, whereas the optic nerves are considerably more radiosensitive. A recent study in which 88 patients were treated by gamma-knife for skull-base meningiomas found that 12–16 Gy could be tolerated by the optic apparatus if only a short segment is placed at risk. In accordance with this finding, some groups now claim that it is possible to treat some tumors that come as close as 1 mm to the optic chiasm. Three recent studies report 100% tumor control rates, but the follow-up period ranges from 17 to 39 months. Two of these studies report no permanent morbidity. Similarly, good results have been described from gamma-knife treatment of meningiomas involving the foramen magnum and the tentorium.

Chemotherapy

Little information is available on the efficacy of traditional antineoplastic agents against either benign or malignant meningiomas. Adjuvant chemotherapy for malignant meningiomas and for recurrences of benign or atypical meningiomas has been administered to a small number of patients, but chemotherapeutic regimens have generally been unsuccessful. Tamoxifen and antiestrogen has been used to treat patients with refractory meningiomas. The success of this treatment is still under investigation; however, preliminary results have been disappointing. This has also been true for mifepristone or RU-486. Recombinant interferon alpha 2b has been used for the treatment of a small number of patients with recurrent, aggressive meningiomas, and the initial reports indicate that it is more effective in traditional chemotherapeutic regimens with lower associated toxicity. Hydroxyurea has been shown to arrest meningioma cell growth in the S-phase of the cell cycle and to induce apoptosis in cell lines from 20 different meningiomas. In one report, use of this medication has been found to have a beneficial effect in treating a small subgroup of patients with recurrent and unresectable meningiomas, but the selection criteria of patients who responded are unclear, and further successful studies using this agent have yet to be published.

Paragangliomas

Paragangliomas or glomus tumors of the head and neck are tumors that originate from the paraganglia tissue from the extra-adrenal chromaffin cell system and have a close relationship to the arterial and venous structures in the neck and skull base. These tumors are named according to their specific location of origin in the neck and skull base. Tumors that arise from the carotid bifurcation are called carotid body tumors. Glomus jugulare tumors originate from the superior vagal ganglion, while glomus tympanicum tumors arise from the auricular branch of the vagus nerve and glomus intravagalae tumors arise from the inferior vagal ganglion. Intravagal paragangliomas often occur lower than glomus jugulare tumors and are differentiated from carotid body tumors by their infiltration of the vagus nerve, and they have no involvement with the carotid body [25] (Fig. 8). This chapter will focus on glomus jugulare tumors due to their involvement in the skull base and multiple lower cranial nerves.

Glomus jugulare tumors arise from glomus bodies surrounding the jugular bulb. They tend to be very vascular tumors that are usually slowly growing and benign. They invade and destroy the temporal bone, traveling along nerves, arteries, and veins. Often they will invade through the skull base and have

Fig. 8. Sagittal MRI demonstrating intravagal paraganglioma

an intracranial intradural extension. The intracranial portions can involve the petrous bone, foramen magnum, and clivus.

Epidemiology

Paragangliomas are rare tumors, but they are the second most common tumor involving the temporal bone after vestibular schwannomas, and the most common tumor involving the middle ear. The incidence is ~1 per 1.3 million people per year. They account for <3% of intracranial tumors, and <1% of head and neck tumors, and are thus not seen often in neurosurgical practice. Glomus tumors most commonly become symptomatic in the fourth decade of life, but can arise throughout a wide age range. They occur 3–6 times more commonly in women. Approximately 10% of patients with glomus tumors have paragangliomas in multiple locations, and all patients with suspicion of a glomus tumor should undergo a detailed assessment of other sites. The multiple sites can include any glomus body site in the head, neck, chest, and retroperitoneum. The most common association is the presence of a carotid body tumor along with an ipsilateral glomus jugulare tumor, which occurs in up to 7% of cases. Bilateral glomus jugulare tumors are found in ~2% of patients. These present a more significant treatment challenge due to the risk of lower cranial nerve involvement bilaterally. An autosomal dominant familial form exists which is passed from father to daughter, in which there can be up to 55% rate of multiple tumors.

Glomus tumors are slow-growing in nature and are often large before becoming clinically evident. There is an average of 3–6 years from time of first symptom to diagnosis.

Symptoms and Clinical Signs

Specific clinical symptoms depend upon the exact location of the tumor, the structures it invades, and the size. The most common presentation is gradual onset of unilateral hearing loss, conductive in nature if the external ear canal is involved, and sensorineural if the hearing apparatus is invaded. Patients with hearing loss often also experience dizziness. Pulsatile tinnitus may be present in highly vascular tumors. Lower cranial nerve involvement produces symptoms of hoarseness, difficulty swallowing, aspiration, shoulder weakness, tongue atrophy, and fasciculation. Cranial nerve paresis is noted in up to 35% of patients. The Xth cranial nerve is invaded most commonly (61%), followed by the VII (54%), the XI (52%), the IX (48%), and least commonly the XII. Larger tumors can produce facial weakness from facial nerve involvement and Horner's syndrome from involvement of the sympathetic chain.

Larger tumors with extensive intracranial extension can cause compression of the brain stem with weakness and sensory deficits, compression of the cerebellum with ataxia and dysmetria, and compression of CSF flow pathways with hydrocephalus and papilledema.

Glomus tumors can secrete low levels of catecholamines manifested by symptoms such as hypertension, excessive perspiration, tachycardia, and headache. Surgical manipulation of these tumors can result in the release of neuropeptides and possibly wide-ranging changes in blood pressure during the operation. Only 1–3% of paragangliomas present with clinical symptoms of catecholamine secretion, due to the fact that detectable symptoms require a high level of catecholamine secretion. Serum catecholamine levels need to rise by four- to five-fold to produce clinical symptoms. Measurement of catecholamine levels in the serum and urine should be a part of the preoperative work-up in anyone suspected of having a paraganglioma. Patients with secreting glomus tumors require pre- and intraoperative alpha- and beta-adrenergic blocking medicines.

Serotonin-secreting tumors produce the carcinoid syndrome with bronchoconstriction, abdominal pain, violent headaches, diarrhea, cutaneous flushing, and electrolyte abnormalities. The presence of the carcinoid syndrome is evident by clinical symptomatology, and specific laboratory testing is not required in the absence of symptoms. Octreotide can be used in the preoperative phase for symptomatic relief.

On otologic examination, a pulsatile red mass is often seen behind the tympanic membrane within the middle ear cavity. While this finding is not 100% specific for glomus tumors, the presence of a middle ear pulsatile mass increases the suspicion of this diagnosis.

Diagnostics

Synopsis. The diagnosis of glomus jugulare tumors requires the use of both high-resolution thin-cut CT scanning as well as MRI. Conventional catheter angiography adds information about the vascular nature of the tumor and can also be used to assist in treatment with presurgical embolization. The differential diagnosis of tumors in this location includes schwannoma of lower cranial nerves, meningioma of the jugular tubercle, chordoma, chondrosarcoma, and other temporal bone lesions including cholesteatomas, cholesterol granulomas, and carcinomas.

High-resolution CT scanning is used in the radiographic diagnosis of glomus jugulare tumors. Bone

windows can be used to assess the region of the jugular fossa and the bony crest that arises between the carotid artery and the jugular fossa. CT scans also provide detail into areas of bony destruction (Fig. 9).

MRI scans are useful for assessing the soft-tissue component of glomus tumors. These tumors show heterogeneous intensity on both T1- and T2-weighted images. The highly vascular nature of paragangliomas creates serpiginous areas of vascular signal void throughout the tumor (Fig. 9). This is most evident in tumors >2 cm in diameter. This appearance of a tumor in the jugular fossa is often diagnostic of glomus jugulare tumors. Glomus tumors show strong contrast enhancement after the administration of gadolinium. MRI can be useful in assessing the intracranial intradural extension as well as extension into the neck. It is also possible to investigate the relationships of the tumor to arterial and venous vascular structures with MRI.

Conventional catheter angiography has a role both in the diagnosis and treatment of glomus tumors. Angiograms provide information about the blood supply to the tumor and the involvement of the internal carotid artery. Branches of the external carotid artery, specifically the ascending pharyngeal artery and the occipital artery, usually provide the main blood supply to glomus jugulare tumors, and a dense tumor stain is often seen with angiography in these tumors. Tumors that extend intracranially can recruit blood supply from the internal carotid and vertebral arteries (Fig. 9). Angiography is also helpful to identify the presence of multiple glomus tumors in a patient.

The differential diagnosis of tumors within the jugular foramen includes paragangliomas, meningiomas, and schwannomas. The difference between these tumors can often be seen on preoperative radiographic imaging (Fig. 10). Meningiomas often enhance intensely with contrast and have a dural tail and cause hyperostosis of underlying bone (Fig. 10A). Schwannomas are often cystic and cause sclerotic changes in bone (Fig. 10B). Finally, glomus tumors show serpiginous flow voids and cause lytic destruction of bone (Fig. 10C). Preoperative diagnostic evaluation looking for these characteristics may be extremely helpful for surgical planning.

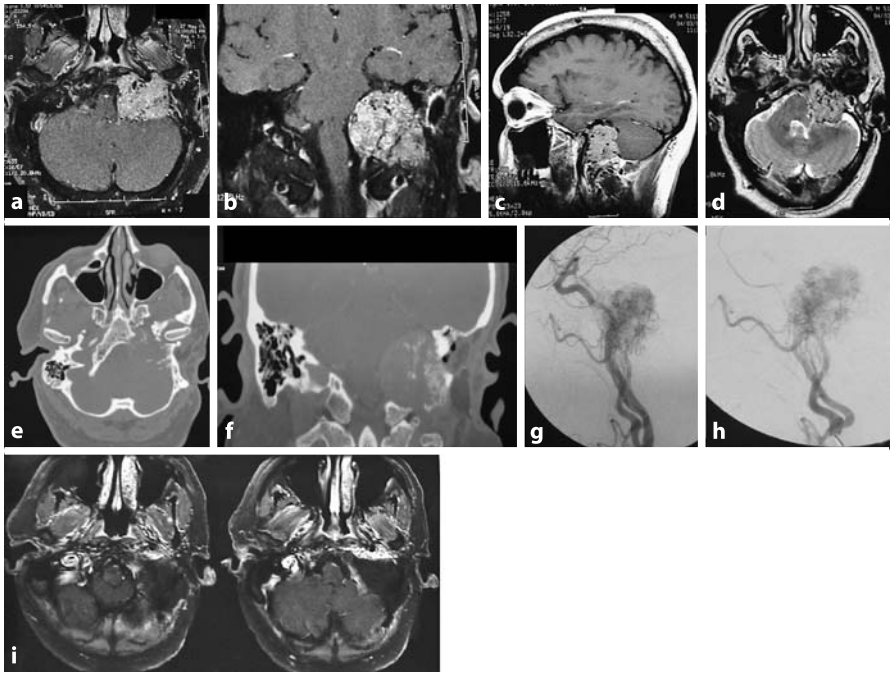


Fig. 9 a–i. Imaging of glomus jugulare tumors from one patient. **a–c** Preoperative postcontrast T1 imaging of glomus jugulare tumor in axial, coronal, and sagittal planes demonstrating heterogeneous contrast enhancement. **d** T2 MRI of glomus tumor demonstrating serpiginous dark regions corresponding to large flow voids. **e, f** CT scan in the axial plane and coronal reconstruction demonstrating bony destruction of the skull base. External carotid artery (**g**) and vertebral artery (**h**) angiogram in a patient with a glomus jugulare tumor demonstrating large tumor blush and high vascularity. **i** Postoperative MRI from the same patient showing radical resection of tumor

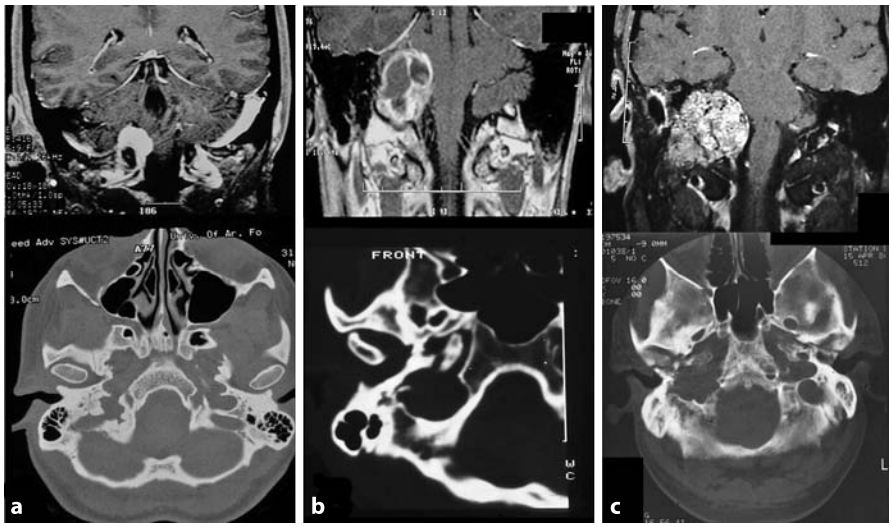


Fig. 10 a–c. Comparison imaging of different tumors within the jugular fossa. **a** MRI and CT of jugular foramen meningioma demonstrating features of homogeneous contrast enhancement, presence of a dural tail, and hyperostosis of the jugular tubercle. **b** MRI and CT of jugular foramen schwannoma demonstrating presence of large cyst, dumbbell shape, and sclerosis of bone. **c** Glomus jugulare tumor demonstrating heterogeneous contrast enhancement, serpiginous flow voids, and bony destruction on CT

Staging and Classification

Synopsis. There have been many different classification schemes for glomus tumors in the literature. The first classification system was proposed in 1962 by Alford and Guilford. This system took into account the patient's symptoms, physical findings, radiographic findings, and neurological exam. Later classification systems by Fisch [26] and then by Glasscock and Jackson [27] consider anatomical location, tumor extension, and size and are used more frequently today.

The pathological evaluation is uniform for paragangliomas. There are few pathological criteria that can distinguish between benign and malignant tumors. The designation of malignant or benign is based on the clinical course as opposed to histological features of the tumors.

Fisch proposed a classification system of glomus tumors, taking into account the extent of temporal bone erosion, carotid artery involvement, and intracranial extension [26]. Tumors with intracranial extension are classified in class D. These tumors are further divided into those with extradural (De) and those with intradural (Di) extension (Table 5).

Glasscock and Jackson proposed a classification system that divided glomus tumors into glomus tympanic and glomus jugulare locations [27]. Table 6 gives the classification for glomus jugulare tumors. Types 2–4 can have intracranial extension.

Patel et al. in 1994 considered brain stem compression and vascular encasement as more important factors than size of intradural extension alone, as these factors displayed more prognostic value.

Al-Mefty et al. consider a subset of glomus tumors as 'complex' [28]. These complex tumors fulfill one or more of the following criteria: giant size, multiple lo-

Table 5. Fisch classification of glomus tumors [26]

Class A: Glomus tympanicum. No evidence of bony erosion, tumor confined to the tympanum

Class B: Glomus hypotympanicum. Tumors arise from the hypotympanum with intact cortical bone over the jugular bulb

Class C: Glomus jugulare. Tumors erode the bone over the jugular bulb
- C1: Involves the carotid foramen only
- C2: Vertical segment of the carotid canal involved
- C3: Horizontal segment of the carotid canal involved
- C4: Foramen lacerum and cavernous sinus involved

Class D: Intracranial extension of tumor
- De1: Intracranial extradural extension up to 2 cm
- De2: Intracranial extradural extension >2 cm
- Di1: Intracranial intradural extension up to 2 cm
- Di2: Intracranial intradural extension >2 cm

Table 6. Glasscock-Jackson classification of glomus tumors [27]

Type	Physical findings
Glomus jugulare:	
I	Tumor within jugular bulb, middle ear, and mastoid
II	Tumor extending beneath internal auditory canal
III	Tumor extending to petrous apex
IV	Tumor extending into clivus, infratemporal fossa
Glomus tympanicum:	
I	Small mass limited to promontory
II	Tumor filling middle ear
III	Tumor filling middle ear, extending to mastoid
IV	Tumor filling middle ear, extending to mastoid or through tympanic membrane, filling external auditory canal, may extend anterior to internal carotid artery

Table 7. Al-Mefty criteria for complex glomus tumor [28]

Giant size
Multiple locations (bilateral, ipsilateral)
Malignant
Catecholamine-secreting (plasma catecholamine levels increased 4-fold)
Association with other lesions (adrenal tumor, intracranial aneurysm, etc.)
Previous treatment with adverse outcome that increases risk of surgery (sacrifice of carotid artery, postradiation, postoperative deficits, complications of embolization)

cations (bilateral or ipsilateral), malignant, catecholamine secreting, association with other lesions (adrenal tumor), previous treatment with adverse outcome (sacrifice of carotid artery, prior radiation, postoperative deficits, complications of embolization) (Table 7). These factors increase the risks associated with surgical resection.

Glomus tumors in all anatomical locations have a similar pathological appearance. They demonstrate clusters of epithelioid cells (chief cells) within a vascular stroma background. The background stroma contains many capillary-sized vessels. The histopathology does not correlate with clinical behavior. There are no pathological features associated with malignant behavior. The designation of malignant or benign is a factor of the patients' clinical course. Malignant behavior is associated with fast growth with aggressive bony erosion and invasion. Often these patients will have associated anemia, early distant metastases, and rapid progression to death.

Treatment

Synopsis. Surgical resection of glomus tumors has historically been associated with high morbidity and mortality rates. With newer skull base techniques and improved preoperative embolization possibilities, surgery for these tumors is possible with decreased morbidity and mortality, and it has become possible to achieve long-term disease control [28]. Surgical planning must be tailored for each patient based on the location, extension, and invasion from the tumor. Preoperative endovascular embolization has taken on a critical role in the surgical treatment of these tumors. Glomus tumors have been considered radioresistant in the past, but newer studies using radiosurgery for these lesions have proven promising. Treatment planning is essential for patients with multiple tumors, especially in patients with bilateral tumors. These patients present a particular management challenge as bilateral lower cranial nerve deficits are associated with high morbidity.

Surgery

With advances in skull base surgical techniques, intraoperative cranial nerve monitoring, intraoperative frameless stereotactic navigation systems, and expertise, surgical resection of glomus tumors has become feasible with decreased morbidity and mortality. Complete surgical resection can produce a cure from this disease. The specific surgical approach is tailored for each patient depending on the location of the tumor, extent of bony invasion, the patient's clinical condition, and pre-existing neurological deficits. Multiple steps are essential for safe surgery of glomus tumors: (1) proximal and distal control of the internal carotid artery, (2) coagulation/ligation of feeding arteries, (3) proximal control of the sigmoid sinus, (4) identification and preservation of the cranial nerves, (5) reconstruction to prevent CSF leak and infection. The intracranial and extracranial

aspects of the tumor are exposed together, allowing single-stage resection of the entire tumor (Fig. 11). Preservation of the lower cranial nerves can be accomplished with intrabulbar dissection (Fig. 12), but this technique is not effective in cases of tumor invasion through the outer venous wall or invasion of the actual cranial nerves. Preservation of the internal carotid artery is achieved by careful dissection under microscopic visualization. A cleavage plane is usually discovered between the tumor and arterial adventitia. Carotid sacrifice and bypass are seldom warranted. Surgery for glomus tumors should be similar to surgery for arteriovenous malformations due to the high vascularity and arteriovenous shunting through the tumor. Venous ligation is delayed until the end of the procedure, after feeding vessels are coagulated and ligated.

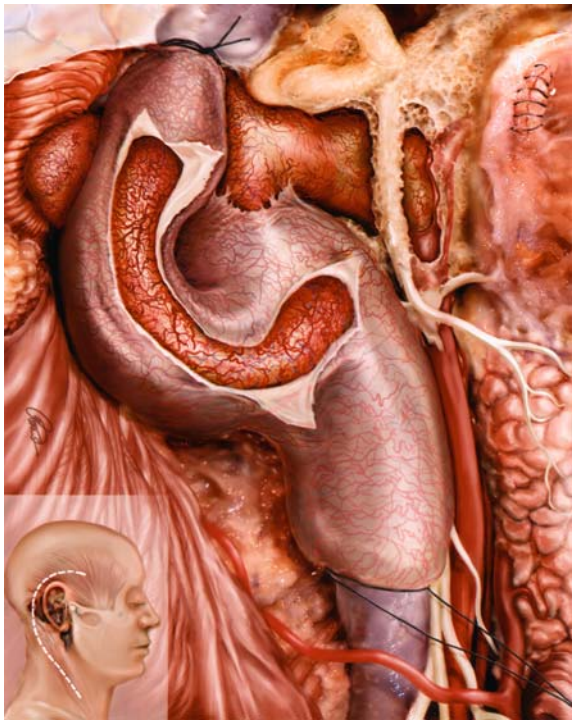


Fig. 11. Surgical exposure of glomus jugulare tumors demonstrating complete tumor exposure and isolation prior to resection through the postauricular incision (*inset*). This illustration demonstrates ligation of the sigmoid sinus and jugular vein. The facial nerve is maintained within its bony canal to decrease the risk of facial weakness. From [28]

Intraoperative neurophysiologic monitoring of cranial nerves correlates with improved outcome in skull base surgery. This fact is especially true for tumors within the jugular foramen. Monitoring of electroencephalography (EEG) and somatosensory evoked potentials (SSEP) are complemented by cranial nerve monitoring. Specifically for tumors in this anatomical location, monitoring of cranial nerve VII, brain stem auditory evoked potentials, and cranial nerves IX, X, XI, XII is an essential part of a surgeon's armamentarium.

Recent surgical results demonstrate that with the combination of skull base surgical techniques, preoperative embolization, intraoperative neurophysiologic monitoring, and surgical expertise, safe and complete resection of glomus tumors is achieved. Al-Mefty et al. examined the surgical results in 28 patients with 'complex' glomus jugulare tumors [28]. Gross total resection was achieved in 86% of patients. There was no mortality and minimal morbidity, with few new permanent cranial nerve deficits. CSF leak and infection were reported surgical complications.

While the surgical approach is similar for other tumors within the jugular foramen [29], surgical planning is crucial in patients with paragangliomas as many patients will harbor multiple tumors. Preoper-

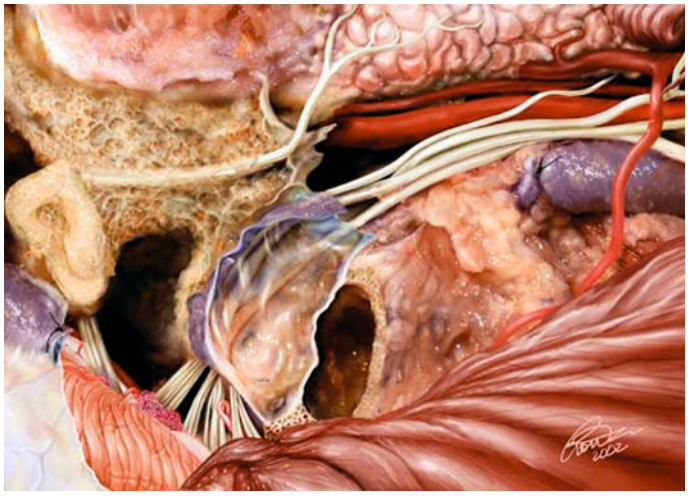


Fig. 12. Illustration demonstrating intrabulbar resection of tumor used to preserve the lower cranial nerves within the jugular foramen. The medial and anterior walls of the jugular bulb are kept intact to prevent manipulation of these nerves. From [28]

ative evaluation is particularly important in patients with bilateral glomus tumors. In this patient population (10% of all patients), surgical goals and plans must be modified to prevent bilateral lower cranial nerve deficits. Specifically, care must be taken in the dissection of the facial nerve. Leaving a thin rim of bone on the nerve and proceeding with dissection with transposition of the facial nerve decreases the risk of facial paresis postoperatively. Additionally, the surgeon avoids closing the external auditory canal to prevent loss of conductive hearing loss. Most importantly, intrabulbar dissection is crucial to prevent lower cranial nerve injury. Unfortunately, this dissection technique does not work when the tumor has infiltrated the posterior wall of the jugular bulb or has penetrated the cranial nerves.

Surgery on patients with catecholamine-secreting tumors presents further challenges. Manipulation of the tumor during surgery can cause release of the catecholamines, causing wide swings in blood pressure and hypertensive crisis. Preoperative planning with the anesthesiologist is required to perform surgery safely. The secreted catecholamines can be counteracted with α- and β-adrenergic blockade. It is crucial that α-blockade be started before β-blockade to prevent hypertensive crisis.

Radiation

Historically, glomus tumors have been considered to be radioresistant. Within the last 10 years, radiosurgery with gamma-knife or LINAC systems have been used more frequently for glomus tumors. Recent results have shown promising results with glomus tumors that are within the treatment size limit for radiosurgery [30]. Treatment of these tumors with radiosurgery is safe, with 8.5% rate of cranial neuropathy and a 2.1% rate of permanent morbidity. Tumor growth was controlled in ~98% of patients, although only 36% had a decrease in the size of the tumor. With these promising results, radiosurgical treatment of glomus tumors is likely to become more common. Longer-term follow-up is required to assess growth rates over time with radiosurgery. The advantages of surgery include complete removal of tumor and alleviation of mass effect. Surgical resection is also able to treat tumors that are larger than the size limits of radiosurgery. Thus, surgical resection remains the treatment of choice for patients who desire complete removal and immediate cure of tumor, for large and giant tumors, for tumors with brain stem compression or significant intracranial extension, and for tumors with severe vascular encasement. Radiosurgery may have indications for residual tumors after surgical resection, and for elderly patients with small tumors.

Chemotherapy

There are currently no reports of chemotherapy regimens beneficial in the treatment of benign paragangliomas. There are a few studies using chemotherapy in the treatment of patients with malignant glomus tumors, but there are no accepted treatment regimens for this disease.

Embolization

Increasing endovascular technologies have improved the ability to perform superselective catheterization of feeding arteries to embolize glomus tumors. Recent advances in catheter systems, newer embolic materials, and improved quality of imaging allows for safer embolization procedures. Preoperative embolization techniques allow devascularization of the tumor prior to surgical manipulation. Due to the highly vascular nature of these tumors, preoperative embolization decreases subsequent blood loss during surgery, and thus makes surgery safer. The common feeding arteries are the ascending pharyngeal artery, other external carotid artery branches, and in large tumors the internal carotid artery and vertebrobasilar system. Embolization is indicated for large or complex tumors.

There are risks associated with embolization. Strokes may be caused by catheter manipulation or reflux of embolic material into the internal carotid artery system. Often there is significant arterial shunting from the external carotid system to the internal carotid and vertebrobasilar systems through the large vascular channels within the tumor, allowing embolic material to enter vessels supplying the brain. Cranial nerve palsies are also possible, as the embolized arteries often supply the lower cranial nerves. Due to these significant possible complications of embolization, the treating surgeon requires careful patient selection for this procedure. Small tumors without significant intracranial extension often do not require preoperative embolization.

Prognosis/Quality of Life

The prognosis for benign glomus tumors depends mostly on the cranial neuropathies caused by the tumor itself, and in the treatment of the tumor. Gross total resection is possible in up to 88% of tumors and up to 86% of complex tumors. Gross total resection offers a cure from the disease in benign forms of paragangliomas. Malignant tumors result in rapid recurrence, metastasis, and death within a short time.

Lower cranial nerve deficits can alter the patient's quality of life after treatment for glomus tumors. Most

patients present with some form of lower cranial neuropathy caused by the tumor itself. Treatment of these tumors may increase the cranial nerve deficits, in the form of facial weakness, hearing loss, difficulty swallowing, aspiration, hoarseness, and tongue weakness. Additional procedures such as medialization of the vocal cords may be necessary, and a few patients require tracheostomy and gastrostomy. Intrabulbar dissection techniques are used to minimize such deficits. Surgical planning is required in patients with bilateral tumors, as bilateral cranial neuropathies cause significantly higher morbidity. In these patients, subtotal resection and adjuvant radiosurgery for residual tumor may be the best treatment option.

References

1. Surawicz TS, McCarthy BJ, Kupelian V. Descriptive epidemiology of primary brain and CNS tumors: results from the central brain tumor registry of the united states. Neuro-oncology 1999; 1(1): 14–25
2. Heffelfinger MJ, Dahlin DC, MacCarty CS, Beabout JW. Chordomas and cartilaginous tumors at the skull base. Cancer. 1973; 32(2):410–20
3. Krayenbuhl H, Yasargil MG. Cranial Chordomas. Prg Neurol Surg 1975; 6:380–434
4. Borba LA, Al-Mefty O, Mrak RE, Suen J. Cranial chordomas in children and adolescents. J Neurosurg 1996; 84(4):584–91
5. al-Mefty O, Borba LA. Skull base chordomas: a management challenge. J Neurosurg 1997; 86(2):182–9
6. Colli B, Al-Mefty O. Chordomas of the craniocervical junction: follow-up review and prognostic factors. J Neurosurg 2001; 95(6):933–43
7. Arnautovic KI, Al-Mefty O. Surgical seeding of chordomas. J Neurosurg 2001; 95(5):798–803
8. Hug EB, Loredo LN, Slater JD, DeVries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JM. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg 1999; 91(3):432–9
9. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlenther Onkol 1999; 175 Suppl 2:57–63
10. Casali PG, Messina A, Stacchiotti S, Tamborini E, Crippa F, Gronchi A, Orlandi R, Ripamonti C, Spreafico C, Bertieri R, Bertulli R, Colecchia M, Fumagalli E, Greco A, Grosso F, Olmi P, Pierotti MA, Pilotti S. Imatinib mesylate in chordoma. Cancer 2004; 101(9):2086–97
11. Ron E, Modan B, Joice JD, Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. New England Journal of Medicine 1988; 319:1033–1039
12. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. J Neurosurgery 2004; 100(6):1002–1
13. Maini CL, Sciuto R, Tofani A, Ferraironi A, Carapella CM, Occhipinti E, Mottolese M, Crecco M. Somatostatin receptor imaging in CNS tumours using 111In-octreotide. Nucl Med Commun 1995; 16(9):756–66
14. Kleihues P, Cavenee W, eds. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Nervous Sytem. Lyon, France, IARC Press, 2000
15. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol 1997; 21(12):1455–65
16. Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC. "Malignancy" in meningiomas: a clinicopathologic study of 116 patients, with grading implications. Cancer 1999; 85(9):2046–56
17. Al-Mefty O, Kadri PA, Pravdenkova S, Sawyer JR, Stangeby C, Husain M. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. J Neurosurg 2004; 101(2):210–8
18. Cushing h, Eisenhardt L. Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results. Springfield, Ill, Charles c Thomas, 1938
19. Pieper DR, Al-Mefty O, Hanada Y, Buechner D. Hyperostosis associated with meningioma of the cranial base: secondary changes or tumor invasion. Neurosurgery 1999; 44(4):742–6; discussion 746–7
20. Al-Mefty O. Clinoidal meningiomas. J Neurosurg 1990; 73(6):840–9
21. DeMonte F, Smith HK, al-Mefty O. Outcome of aggressive removal of cavernous sinus meningiomas. J Neurosurg 1994; 81(2):245–51
22. Arnautovic KI, Al-Mefty O. Primary meningiomas of the jugular fossa. J Neurosurg 2002; 97(1):12–20
23. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurochem 1957; 20(1):22–39
24. Pollock BE, Stafford SL, Utter A, Giannini C, Schreiner SA. Stereotactic radiosurgery provides equivalent tumor control to Simpson Grade 1 resection for patients with small- to medium-size meningiomas. Int J Radiat Oncol Biol Phys 2003; 55(4):1000–5
25. Borba LA, Al-Mefty O. Intravagal paragangliomas: report of four cases. Neurosurgery 1996; 38(3):569–75; discussion 575
26. Fisch U. Infratemporal fossa approach for glomus tumors of the temporal bone. Ann Otol Rhinol Laryngol 1982; 91(5 Pt 1):474–9
27. Jackson CG, Glasscock ME 3rd, McKennan KX, Koopmann CF Jr, Levine SC, Hays JW, Smith HP. The surgical treatment of skull-base tumors with intracranial extension. Otolaryngol Head Neck Surg 1987; 96(2):175–85
28. Al-Mefty O, Teixeira A. Complex tumors of the glomus jugulare: criteria, treatment, and outcome. J Neurosurg 2002; 97(6):1356–66
29. Kadri PA, Al-Mefty O. Surgical treatment of dumbbell-shaped jugular foramen schwannomas. Neurosurg Focus 2004; 17(2):E9
30. Gottfried ON, Liu JK, Couldwell WT. Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. Neurosurg Focus. 2004; 17(2):E4

Orbital Tumors

17

Christoph Hintschich, Geoff Rose

Introduction – 271

Epidemiology – 271

Orbital Anatomy – 271
Dimensions
Bony Walls
Orbital Foramina and Fissures
Periorbita and Surgical Spaces

Symptoms and Signs – 273

Clinical History and Orbital Examination – 274
History
Examination
Additional Examinations
Imaging

An Approach to Differential Diagnosis – 277
Acute Onset
Subacute Onset
Chronic Onset
'Acute-on-Chronic' Onset

Common Orbital Tumors – 279
Benign Orbital Tumors
Orbital Cystic Tumors
Orbital Vascular Tumors
Benign Lacrimal Gland Lesions
Benign Optic Nerve Tumors
Benign Tumors of Peripheral Nerve, Bone or Mesenchyme
Malignant Orbital Tumors
Malignant Orbital Tumors of Childhood
Orbital Lymphoma in Adults
Lacrimal Gland Carcinomas
Secondary Orbital Malignancy from the Eyelids, Paranasal Sinuses or Globe
Orbital Metastases in Adults
Rare Adulthood Malignancies of Mesenchymal or Neural Origin

Principles of Surgical Management – 286
Principles of Anterior Orbitotomy
Principles of Lateral Orbitotomy
Principles of Orbital Exenteration

Suggested Reading – 289

Introduction

Orbital tumors can either be developmental, such as dermoid cysts, or acquired lesions (inflammatory masses, vascular anomalies, and benign or malignant neoplasms). Only the diagnosis and management of discrete structural lesions of the orbit will be presented in this chapter, and we shall not address vascular or inflammatory disease.

Epidemiology

As orbital tumors are rare, the exact incidence of orbital tumors is difficult to obtain, but based on the tumor register of the former German Democratic Republic and the American Cancer Society, the estimated incidence is less than 1 per 100,000 population. Better estimates are available for sex- and age-related incidences for orbital conditions: A relatively high incidence in the first decade of life is followed by the lowest risk during the second decade. The frequency of orbital tumors gradually increases from 25 to 75 years of age, after which a fairly sharp decrease occurs, amounting to more than 50% of all tumors occurring between the 5th and 7th decade. There is no significant male or female preponderance.

Excluding cystic and vascular lesions, orbital neoplasms comprise about 20% of orbital conditions – the most common being Graves' ophthalmopathy – and the diversity of tumors reflects the wide spectrum of orbital tissues. The five most common primary tumors in adults are cavernous haemangioma, lymphoma, orbital inflammatory masses, meningiomas and optic nerve glioma. The most common secondary tumors are very different entities: Sinus mucocoele, squamous cell carcinoma, cranial meningioma, vascular malformations and malignant melanoma. Children show a different spectrum of orbital tumors: dermoid cysts, capillary haemangioma, lymphangiomas, rhabdomyosarcoma, neuroblastoma and optic nerve tumors are some of the more common masses.

Orbital Anatomy

Dimensions

The bony orbit is a confined space in the skull, which contains and protects the eyeball and its accessory organs with the orbital soft tissues. It is pyramidal with four walls narrowing posteriorly towards the apex, at which site many nerves and vessels pass to the cranial cavity. The bony orbital volume averages about 27 ml, with the globe taking up about 7–8 ml volume, the extraocular muscles about 5 ml and the fat about 10–13 ml. The optic canal is usually 40–45 mm behind the medial orbital rim and a simple '24–12–6' rule helps to memorise orbital distances: 24 mm from the medial orbital margin to the anterior ethmoidal neurovascular bundle, 12 mm further to the posterior ethmoidal bundle, and 6 mm from the latter to the optic canal. The anterior and posterior ethmoidal bundles also serve to define the upper limit of the medial orbital wall at the skull base.

Bony Walls

Each orbital wall has a particular relation to neighbouring structures: The orbital *roof*, formed by the frontal and sphenoid bones, lies beneath the frontal sinus and the anterior cranial fossa. The *medial wall* – formed from the ethmoid, lacrimal, sphenoid and maxillary bones – has the ethmoid and part of the sphenoid sinuses lying medially. The *orbital floor*, formed by the maxillary, zygomatic and palatine bones, lies above the maxillary antrum. Finally, the *lateral wall* – comprising part of the zygoma, sphenoid and frontal bones – has the temporalis fossa (with the temporalis muscle) lying laterally and posterolaterally neighbours the middle cranial fossa. Anteriorly, the orbit is defined by the globe and the eyelid complex, with its medial and lateral canthal tendons and orbital septum; the septum, a thin and elastic membrane, acting as an important barrier between the intra- and extraorbital spaces. The bony orbital entrance is the strongest part of the orbit, the weakest part being the orbital floor and medial wall.

Orbital Foramina and Fissures

A number of fissures and foramina in the bony walls accommodate neurovascular structures, which are essential for normal ocular function and also provide valuable landmarks during orbital surgery (Fig. 1). The supraorbital neurovascular bundle may pass through a canal or notch in the superior orbital rim, the nerves being the frontal and lacrimal branches of the ophthalmic division of the trigeminal nerve. The infraorbital neurovascular bundle – passing from the inferior orbital fissure, along the infraorbital canal and reaching the cheek through the *infraorbital foramen* – contains fibres from the maxillary division of the trigeminal nerve and subserves sensation for the cheek, upper lid and upper anterior teeth.

The *infraorbital fissure*, which is 20 mm long, separates the orbital floor from the lateral wall and contains fat, the infraorbital nerve, and veins leaving the orbit for the pterygopalatine fossa. Further posteri-

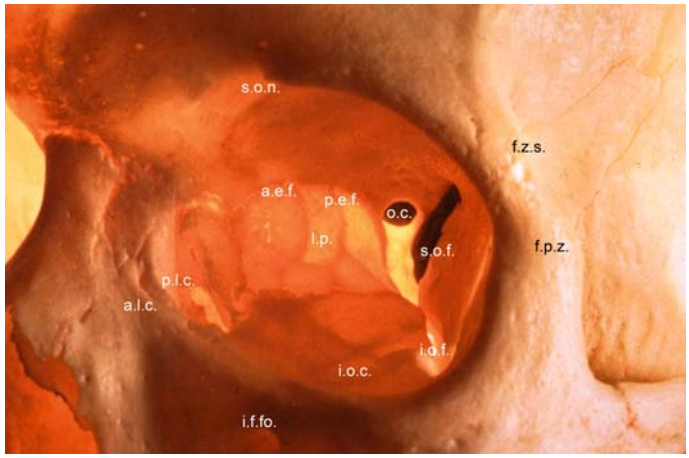


Fig. 1. Osteology and foramina of the left orbit: The orbit is bounded anteriorly by the anterior (*a.l.c.*) and posterior lacrimal crests (*p.l.c.*) and the frontal process of the zygoma (*f.p.z.*), limited superiorly by the frontozygomatico suture (*f.z.s.*). The supraorbital ridge is indented on its inner one-third by the supraorbital notch (*s.o.n.*). The medial wall comprises the thin lamina papyracea (*l.p.*) of the ethmoid air cells, the upper limit of which is marked by the anterior (*a.e.f.*) and posterior ethmoidal foramina (*p.e.f.*); the floor is traversed by the infraorbital canal (*i.o.c.*) passing from the inferior orbital fissure (*i.o.f.*) anteromedially to exit on the cheek as the infraorbital foramen (*i.f.fo.*). The superior orbital fissure (*s.o.f.*) and optic canal (*o.c.*) are also clearly seen

orly and superiorly, at the junction of the lateral wall and the roof, lies the shorter *superior orbital fissure*, through which several important structures pass: the superior and inferior divisions of the oculomotor nerve, the trochlear nerve, the abducens nerve, the first division of the trigeminal nerve, and the venous connections between the orbit and the cavernous sinus. The superior orbital fissure is divided into a lateral and a medial part by the fibrous annulus of Zinn, the origin of the recti: The lateral part transmits the lacrimal, frontal and trochlear nerves, the superior ophthalmic vein and the anastomosis of the recurrent lacrimal and middle meningeal arteries, whilst the medial part of the fissure transmits the superior and inferior divisions of the oculomotor nerve, the nasociliary nerve, the abducens nerve and the sympathetic nerves. Finally, in the orbital apex, medial to the superior orbital fissure, lies the optic foramen through which the optic nerve in its meninges and the ophthalmic artery pass. The optic nerve, about 4 mm diameter, takes an 'S'-shaped course for its 30 mm orbital part, has a 9-mm-long intracanalicular section and about 10 mm of intracranial length before joining the chiasm. The intraorbital nerve is surrounded by dura, arachnoid and pia mater from the optic canal to the globe. The intracanalicular part is immobile as its dural sheath is fused to the periosteum of the optic canal – the latter making the intracanalicular nerve particularly vulnerable to blunt trauma and oedema.

The zygomatic neurovascular bundle passes inferolaterally through the orbital wall just behind the orbital rim, and division during surgery only rarely causes a clinically significant deficit. In its very anterior part, between the anterior and posterior lacrimal crest, the medial wall forms the nasolacrimal fossa with the opening of the nasolacrimal duct, and this area should generally be avoided during orbital exploration, to avoid damage to the lacrimal drainage apparatus.

Periorbita and Surgical Spaces

The periorbita covers all bones of the orbit and is only loosely attached to the underlying bone (except at the orbital rim and at suture lines), giving readily available extraperiosteal spaces that can be used to surgical advantage, or in which an abscess can develop.

Multiple connective tissue septa have been described between all orbital structures, these maintaining the spatial separation of structures – such as the extraocular muscles – and also defining the so-called surgical spaces, which are relevant for the description of orbital pathology and for planning surgery. The orbit can be divided into four surgical spaces: the subperiosteal (extraperiosteal), the extraconal, the intraconal, and the sub-Tenon's space.

The Subperiosteal (Extraperiosteal) Space. The subperiosteal space, existing only when created surgically or when filled by a pathological process, lies between the periorbita and the bony orbital walls and is crossed by a number of structures. The subperiosteal space can be reached through several approach-

es, such as transcutaneous or transconjunctival incisions, and the periosteum should be incised outside the orbit and then elevated over the rim.

Extraconal Space. Lying behind the orbital rim in the superotemporal quadrant, the lacrimal gland is the dominant extraconal structure, and it is readily approached through an upper lid skin-crease incision; lateral orbitotomy is readily performed through a lateral extension of this incision where intact excision of the gland is required, as with suspected pleomorphic adenomas. Other structures in the extraconal space are the oblique muscles, trochlea, orbital fat, sensory nerves, trochlear (motor) nerve and some vessels.

Intraconal Space. The intraconal space lies within the recti and interconnecting septa and contains the optic nerve, intraconal orbital fat, motor nerves and some blood vessels. The ophthalmic artery enters through the optic foramen and divides to form the central retinal artery (most importantly), which arises near the apex, passes forward beneath the optic nerve and enters its dura in a variable position, usually in the inferomedial aspect about 1 cm behind the globe.

Optic nerve tumors lying within the intraconal space may be accessed by several routes such as a superomedial upper lid incision, through a medial conjunctival incision (with disinsertion of the medial rectus muscle in some cases), or laterally via a lateral canthotomy with or without bone removal. During a lateral orbitotomy approach with bone resection, the intraconal space is usually entered by passing below the lateral rectus muscle.

Sub-Tenon's Space. This potential space, located between the globe and the anterior surface of Tenon's capsule, can be enlarged by inflammatory fluid – as in posterior scleritis – or infiltrated by extraocular growth of intraocular tumors (for example, choroidal melanoma).

Symptoms and Signs

Orbital symptoms include lid swelling, globe displacement, a 'pressure' feeling, ocular discomfort due to corneal exposure and drying, or epiphora. Abnormal ocular motility can cause double vision (diplopia), and a patient may notice visual failure due to direct nerve compression or raised intraorbital pressure; visual failure being manifest as loss of acuity, loss of colour perception, impaired stereoscopic functions, poor distance judgement, field loss, or premature presbyopic symptoms. Pain – generally due to inflammation – may be a rare, but important, symptom of orbital malignancy.

Tumor growth inside the orbital confines causes an expansion of orbital soft tissues and, in some cases, a rise in orbital pressure. Proptosis – an axial protrusion of the globe – is a significant sign often caused by a retrobulbar mass, such as intraconal cavernous haemangiomas (Fig. 5a) or optic nerve tumors. The globe may, in addition, be displaced vertically or horizontally, inferomedial displacement, for example, being due to a lacrimal gland mass (Fig. 10a) or intraorbital dermoid cyst. Inferolateral displacement is typically due to frontoethmoidal mucocoeles (Fig. 3f), vascular lesion, neural tumors or dermoid cysts. Common masses in the inferonasal quadrant are lymphoma, vascular lesions or mes-

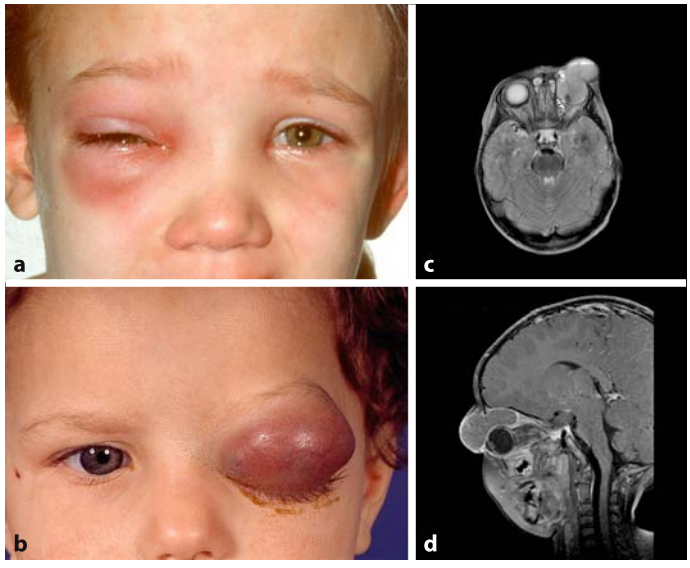


Fig. 2 a–d. Childhood orbital lesions of acute onset. **a** Acute orbital cellulitis in an unwell child, due to spread of bacterial infection from the right ethmoid sinus. **b** Overnight onset of massive left orbital haemorrhage from a lymphangiomas/varix; MRI demonstrates a lobulated mass (**c**) throughout the upper part of the orbit, with evidence of a fluid level with the characteristics of layering blood (**d**). Clinical photographs from Moorfields Eye Hospital, London (Figs. 2a, 10d, e) and Augenklinik der Universität München (Figs. 2b–d, 3, 4, 5, 6, 7, 8, 9, 10a–c)

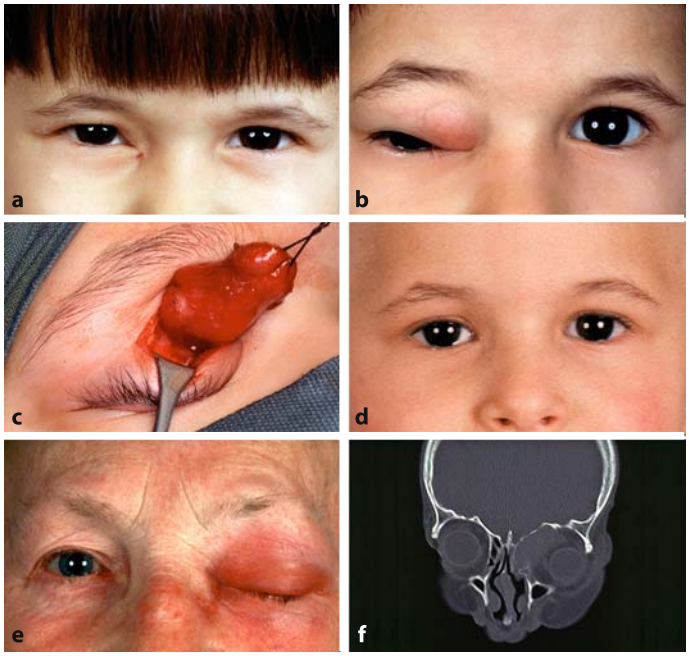


Fig. 3 a–f. Orbital lesion of subacute onset. **a** Slight painless swelling of a child's right upper lid, which developed into a significant superonasal quadrant mass within a month of onset (**b**). The mass, an embryonal rhabdomyosarcoma, was excised intact (**c**), and after adjuvant chemotherapy, the child was still disease-free 5 years later (**d**). e Within days, increasing left upper lid redness and swelling due to a chronic frontoethmoidal mucocoele erupting into the left orbit; the mass, originating within the sinuses, is shown on coronal CT (**f**)

enchymal tumors, and the inferotemporal quadrant is the location of lymphoma, arteriosclerotic haemorrhage and rare tumors.

Other signs of orbital disease include disturbance of ocular motility, eyelid asymmetry (Fig. 3a, 9a), conjunctival inflammation and swelling (chemosis) (Fig. 2a, 7a), optic nerve head swelling (Fig. 9c), choroidal folds (Fig. 5b) and periocular sensory loss.

Clinical History and Orbital Examination

History

A thorough history will characterise the disease and its progression and, in most cases, provide the likely diagnosis. As well as the current state of general health, enquiry should be made about previous sinus disease or surgery, endocrine (especially thyroid) dysfunction, immunological disease, malignancies, infections, injuries and any abnormal skin pigmentations; café-au-lait spots being almost pathognomonic for neurofibromatosis (Fig. 6b,c). Systemic medication, in particular anticoagulants, should also be recorded and any prior orbital surgery noted.

The temporal sequence of symptoms will often indicate the nature of the disease: The onset of proptosis, taken with age, is a valuable criterion for the differential diagnosis, and we distinguish onsets that are 'acute', 'subacute', 'chronic' or 'acute-on-chronic' (see below). If disease progression is slow, a patient might not notice the changes, and in most cases, it is invaluable to compare their actual appearance with old portrait photographs. The order in which symptoms occur can also suggest the position of an orbital mass: Anterior masses often cause globe displacement and diplopia before affecting visual acuity, whereas apical tumors generally cause visual loss with only minimal diplopia.

Accurate symptoms from an observant patient are valuable in making a preliminary diagnosis: With optic neuropathy, the patient might notice a different colour balance in each eye, mention a reduction in colour 'brightness' or have difficulty with depth perception and coordination. Obscurations of vision on extremes of gaze or on suddenly standing occur with compromised optic nerve circulation, as seen with optic nerve meningiomas, large retrobulbar masses or severe thyroid eye disease. The nature of the pain gives a clue to the cause of the orbital disease: Dull retro-ocular 'pressure' or ache is generally due to a deep intraorbital mass, whereas sharp pain is due to corneal exposure problems. Orbital myositis causes a background periorbital ache with severe lancinating pain on looking out of the field of action of the affected muscle. Severe persistent pain, most common with inflammation, may be a rare symptom of orbital malignancy, with periocular sensory loss being present in some patients.

Examination

Examination should start with a general examination of the patient, ideally under daylight, looking for facial asymmetry, for displacement of the globe, or

for orbital or periorbital masses. Skin changes, such as discoloration, may indicate an underlying vascular anomaly or neurofibroma (Fig. 6b,c), whereas skin infiltration and induration may occur with systemic lymphoma or sarcoid.

Asymmetry or changes of the eyelids – such as swelling, erythema, ptosis, loss of the eyelid sulcus or skin crease (Figs. 2a, 3c, 5a, 9a) – should be sought. A record should be made of an eyelid's relationship to the corneal limbus: If the upper lid does not cover the upper limbus by 2 mm (or if there is upper scleral show), upper eyelid retraction is present, and this is the most commonest and most sensitive clinical sign of thyroid eye disease (Graves' disease), lid retraction and hang-up on downgaze being rarely due to orbital malignancy. Lower lid scleral show is less specific, since this is mainly due to involutional lower lid laxity or significant proptosis. Upper lid movements (levator excursion), position on downgaze (lid hang-up) and failure of eyelid closure (lagophthalmos) are important clinical details. Levator function is measured as difference (mm) in lid position between maximal up- and downgaze, with the frontalis action blocked by pressing the thumb against the forehead. Facial weakness and lagophthalmos should be recorded, with particular attention being paid to the presence of frontalis sparing – this indicating an upper motor neuron (central) facial nerve palsy. Hearing should always be checked with facial nerve lesions, this being easily tested clinically by rustling two fingertips together near the patient's ear. The eyelids should be everted and fornices examined for masses, such as fat prolapse, lacrimal gland enlargement or prolapse, or a subconjunctival 'salmon patch' (typical for lymphoma) (Fig. 7b).

Palpation. The orbital margin should by examined for palpable discontinuity, notches or foreign body, and the shape, size, surface texture and attachment of any mass should be assessed. A lesion can be well- or ill-defined, with a round or irregular shape, soft or hard, and non-tender or painful. Some masses will be palpable only on posterior ballottement of the globe or – if attached near the globe – on certain positions of gaze. Variation in the size of a mass with Valsalva manoeuvre or a 'filling-and-emptying' sign with pressure may indicate a low-pressure vascular malformation or a meningocoele.

Palpation of the preauricular, submandibular and clavicular lymph-node regions is important in the clinical evaluation of orbital masses, especially malignancy.

Examination of Globe Position. The globe may be displaced in any dimension and thereby indicate the location of a mass: In most cases the eyeball is displaced away from a tumor (Fig. 3f, 5c, 10a,b), although fibrosis due to scirrhous carcinomas (for example, breast metastases) or inflammation may cause enophthalmos. Proptosis, axial anterior displacement of the globe, is readily assessed when unilateral by an 'up-the-nose' view, but is formally measured by exophthalmometry. The exophthalmometer is placed firmly on the lateral orbital rims and, with the examined eye in the primary position, the corneal position is noted on the instrument scale; parallax errors should be avoided, and the distance between both orbital rims is noted for reproducibility. There is variation in exophthalmometer readings between different examiners or instruments, but any readings greater than 22 mm are probably abnormal. Of greater importance, however, is an interocular difference of more than 2 mm, or a changing value. Non-axial globe displacement may be assessed clinically be placing a ruler horizontally across the nasal bridge and estimating the position of the pupillary centre in the horizontal and vertical axes.

Proptosis is mainly due to retrobulbar masses, but it is important to differentiate between real proptosis and 'pseudo-proptosis', where a condition mimics a proptotic eye: Upper eyelid retraction with widening of the palpebral aperture and upper scleral show can easily be mistaken for proptosis. The elongated myopic globe leads to abnormally high exophthalmometer readings and is a cause of pseudo-proptosis. Unilateral enophthalmos due, for example, to breast metastases can give the appearance of a relative protrusion of the other globe. An abnormal orbital rim or the shallow orbits of cranial anomalies may mimic proptosis.

Extraocular Muscle and Periorbital Sensory Functions. Extraocular muscle function is assessed by asking the patient to follow a finger tip, for example, and any restriction is recorded. Double vision may be present in primary position or in extreme gaze, most commonly due to mechanical restriction and more rarely to neurological deficit. Any limitation, if present, needs quantification by a detailed orthoptic examination.

The sensory function of the ophthalmic and maxillary branches of the trigeminal nerve should be assessed, as it can be impaired by orbital masses and tends to indicate the site, rather than the nature, of orbital disease.

Assessment of Visual Functions. Visual assessment is of paramount importance: Although a normal acuity does not exclude orbital disease, the best acuity for distance and near must be recorded. Colour testing, particularly a difference between two eyes (tested with the 'hue panel D-15' test), often gives an early indication of optic neuropathy.

The test for a relative afferent pupillary defect (RAPD) is the least subjective method and a very sensitive test for optic neuropathy. It is performed using a bright torch light, with the patient gazing into distance in a semi-dark room: The light is directed into one pupil from just off the visual axis and swung, alternately, from one to the other pupil, remaining for 2–3 s at each pupil. As both pupils should remain small, a positive RAPD is indicated by an anomalous dilatation of the pupil on the side with loss of afferent stimulus, this generally being due to optic nerve or extensive retinal disease (distinguished by fundal examination).

Additional Examinations

Visual Field Assessment. Confrontational visual field testing will reveal major defects, such as hemianopia, but field examination with Goldmann or automated perimetry provides a more accurate permanent record. Goldmann perimetry is particularly useful when the visual acuity is reduced, whereas automated perimetry can better distinguish the depth of a field defect (Fig. 8d). Visual field testing should be repeated to check for reproducibility.

Tumors of the orbit, optic canal or chiasm frequently impair visual function and cause visual field defects, which may be typical for certain locations: Field defects due to apical orbital disease are predominately centrocaecal scotomas; scotomas due to intraorbital optic nerve lesions are typically central, centrocaecal or enlargement of the blind spot; a generalised constriction of the peripheral field may be a non-specific sign of optic neuropathy. Compression of the intracranial optic nerve causes a 'junctional scotoma', in which an ipsilateral central scotoma is associated with a contralateral superotemporal scotoma, the latter being due to involvement of contralateral inferonasal optic nerve fibres at the knee of von Willebrand.

Disease progression or improvement of optic nerve function may be monitored with ongoing visual fields, for example, with review or treatment of orbital meningiomas.

Visual Evoked Potentials. Normal pattern visual evoked potentials (VEP) help to distinguish the cause of a decreased visual capacity. A prolonged delay, reduced voltage and a change of the configuration indicate optic neuropathy, and VEP is a sensitive and objective method for detecting, quantifying and monitoring optic neuropathy.

Imaging

Orbital Ultrasonography. Orbital ultrasonography provides useful information about the location, size, shape, tissue characteristics and vascular features of orbital tumors; as it is a non-invasive technique, it is very helpful for long-term follow-up assessments. Ultrasound examination is especially useful for intraocular pathology involving the orbit, such as extrascleral extension of choroidal melanoma, for confirming the cystic nature of a mass, in the sizing of orbital lesions and (with Doppler flow studies) the vascular flow within orbital tumors. Because of the bony confinement and the ultrasound frequency used, echography is poor for masses within the posterior half of the orbit.

Computed Tomography. The natural difference in X-ray attenuation between the orbital structures and fat provides the excellent soft-tissue resolution of CT; it also provides superb bone detail and is very sensitive for tissue calcification or radio-opaque foreign bodies. With its high resolution, thin-slice (1.5–

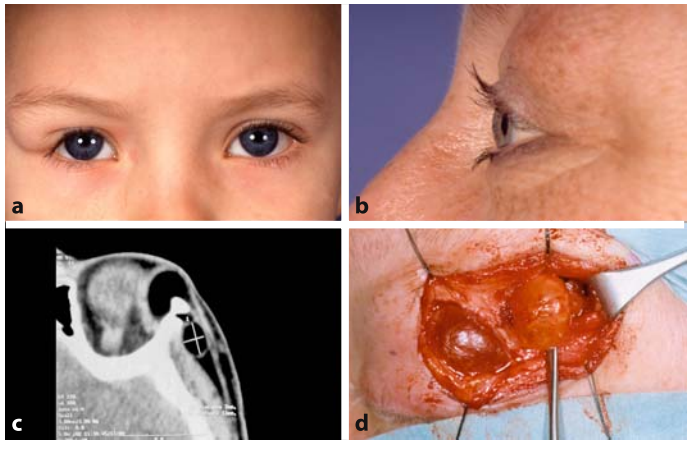


Fig. 4 a–d. Dermoid cysts of the orbit, with history of slow progression. **a** A typical mobile cyst at the superotemporal rim of the child's right orbit. **b** A more complex, dumbbell dermoid straddling the orbital rim with both an orbital and a temporalis fossa component, shown well on imaging (**c**) and at surgery (**d**)

2 mm) CT with contrast is still the single most instructive imaging technique and should be the first choice for imaging adult orbital disease; in most cases CT will indicate the site and probable nature of the lesion, and no other imaging will be required (Fig. 4c, 7c,d, 8e, 10b).

Magnetic Resonance Imaging. MRI, free of ionising radiation and able to provide soft-tissue differentiation, can provide images in several planes, but it is expensive and time-consuming. MRI is, however, rarely specific for a diagnosis and is not routinely required for orbital patients. Specific indications include the evaluation of optic nerve lesions (especially in the region of the optic canal and chiasm), for suspected radiolucent orbital foreign bodies, where coexistent central nervous system disease is suspected (such as demyelination), and to define the extent of sphenoid wing meningioma (Fig. 9c).

An Approach to Differential Diagnosis

An accurate history and examination are the basis for any diagnosis, with imaging providing further definition of the extent of the mass, or extra evidence in favour or against the provisional diagnosis.

Proptosis, the most common clinical sign of an orbital tumor, can be used as an approach to diagnosis when considered in relation to the patient's age. The rate of onset can be considered as 'acute' (minutes to hours), 'subacute' (days to weeks), 'chronic' (over months) or 'acute-on-chronic'; the latter being a chronic condition with recent dramatic acceleration.

Acute Onset

(1) Orbital haemorrhage, often of overnight onset, resolves only slowly, and bruising may appear a few days later (Fig. 2). Children generally have an underlying vascular anomaly, whereas adults are often arteriopathic and taking anti-platelet drugs. Children may suffer vagally induced vomiting. The management consists of CT (if there is diagnostic doubt) and visual monitoring, with drainage indicated if there is significant progression or persistent proptosis.

(2) Acute infective orbital cellulitis shows a progression over hours, generally after a prodromal illness with headache, nasal discharge and fever. The orbit is painful and tense, active and passive ocular motility shows marked impairment, and eventually there may be visual loss. Orbital infection is an ophthalmological emergency and needs *immediate* treatment with intravenous antibiotics (prior to imaging), close monitoring of vision, and then orbital CT to confirm the diagnosis. Drainage is indicated for acute compressive optic neuropathy or persistent orbital abscess.

(3) Arteriovenous shunts, generally in patients with arterial disease, develop within minutes to hours and are characterized by a painless protrusion, acute 'red eye' with chemosis, and a global reduction of orbital functions. CT and ultrasound echography should be performed, visual acuity and intraocular pressure monitored, and where ocular complications occur, interventional radiology should be considered.

Subacute Onset

(1) Childhood malignancies are characterized by subacute onset, often in an otherwise well child, and

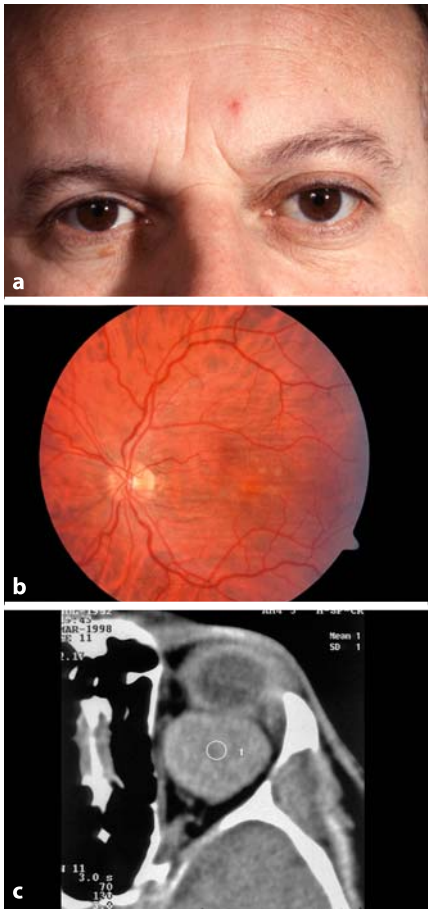


Fig. 5 a–c. Adult onset proptosis of slow progression: (**a**) Slowly progressive left proptosis with reduced visual acuity and hypermetropic refractive shift due to choroidal folds (**b**), these changes being caused by the slow growth of a well-defined, round, intraconal mass (**c**), most commonly a cavernous haemangioma

the tumor may present with a tense, inflamed and painful orbit (Fig. 3). Open incisional biopsy is always indicated, and the appropriate therapy depends on the histological diagnosis. Rhabdomyosarcomas typically are well defined and do *not* occur in extraocular muscles.

(2) Childhood capillary haemangiomas develop over months, the lesions being soft and causing only

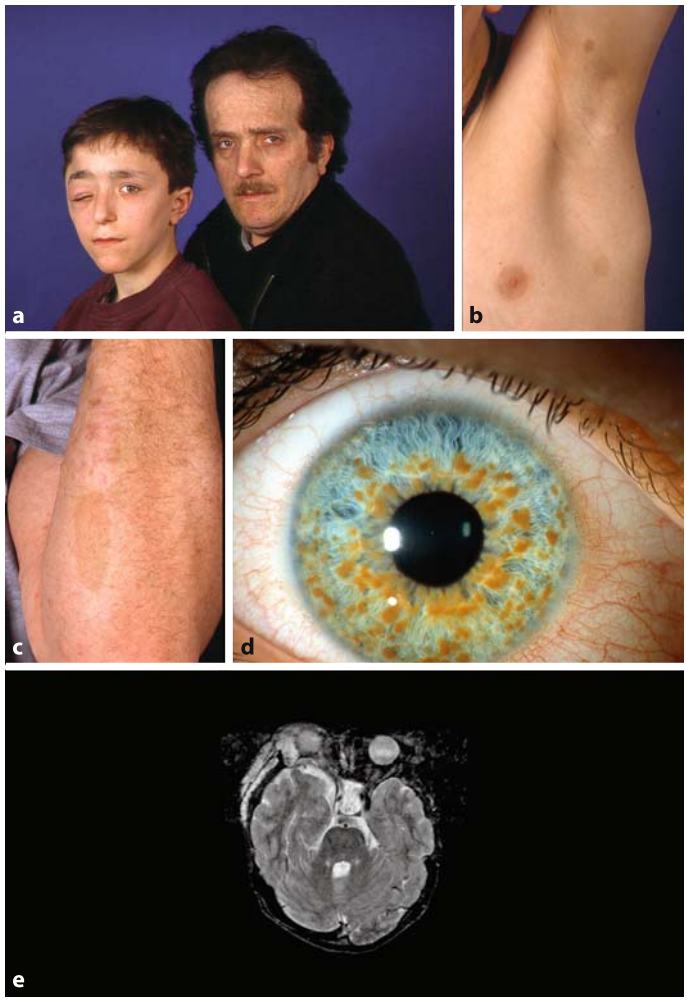


Fig. 6 a–e. Systemic involvement in chronically progressive orbital disease, neurofibromatosis. **a** Father and son with type I neurofibromatosis, the son having a large plexiform neurofibroma of the right orbit and the father having widespread cutaneous neurofibromas. Other stigmata of neurofibromatosis include axillary freckles (**b**), café-au-lait spots (**c**) and Lisch nodules of the iris stroma (**d**). MRI (**e**) demonstrates marked dysplasia and widespread involvement of the right orbit, together with parenchymal anomalies of the cerebral tissues

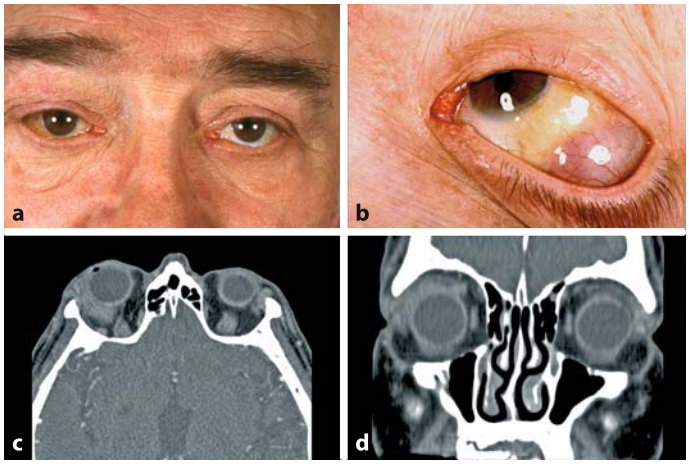


Fig. 7 a–d. Slowly progressive proptosis in adulthood, due to orbital lymphoma. **a** Subtle, right, painless proptosis due to a pink subconjunctival mass of lymphomatous tissue (**b**; viewed from above). CT shows the mass arising from the right lacrimal gland and cloaking the globe both posteriorly (**c**) and superiorly (**d**)

mild impairment of orbital functions. Often there is an expansion of the haemangioma when the child cries or catches a cold.

(3) Adult inflammation may show variable progression over weeks, with pain, tenderness, lid swelling and redness, and may be associated with a marked loss of orbital functions. Biopsy is necessary and may reveal granulomatous, xanthogranulomatous or lymphocytic inflammations. Biopsy is not required where the history and course of the disease are appropriate, as with thyroid eye disease, idiopathic orbital myositis or orbital apex inflammation. The last is characterized by an acute, rapid onset of painful, complete ophthalmoplegia, a numb forehead, mild proptosis, and often significant optic neuropathy.

(4) Orbital infections in adults may progress over weeks if due to low-grade or unusual organisms – such as fungi, parasites like hydatid disease, or tuberculosis – and these infections are often painless with only mild inflammatory signs.

(5) Adult metastatic disease may show a subacute, relentless progression over weeks, and about 75% of patients will have a known systemic malignancy. The clinical picture is typically one of painful proptosis, sometimes with inflammatory signs, and a marked reduction of orbital functions. CT scan and systemic tests are obligatory, open biopsy indicated in most cases, and treatment will often involve orbital radiotherapy and systemic chemotherapy or hormonal therapy.

Chronic Onset

(1) Childhood benign tumors, like retrobulbar dermoid or optic nerve tumors, present as slowly progressive proptosis with mild changes in orbital function. Some may be found by chance whilst imaging for other conditions, such as neurofibromatosis. Imaging may be advisable in some cases, and monitoring of visual development is compulsory.

(2) Sinus mucocoeles or tumors may progress slowly and present late, and there may be a history of sinus surgery or facial trauma. Inferior displacement of the globe is common, with some limitation of globe movements.

(3) Osseous disease like fibrous dysplasia, osteoma or sphenoid wing meningioma, develops slowly at any age, being manifest as facial asymmetry or optic neuropathy (Fig. 9).

(4) Adult benign tumors show a chronic progression over years, with globe displacement that may be axial or non-axial (Figs. 5 and 6). Generally, these tumors are painless, and often there is only a mild change in orbital functions. Observation may be appropriate if orbital function is normal and CT shows a well-defined mass, but otherwise the mass should be excised.

(5) Some adult malignant tumors, such as low-grade lymphomas or some sarcomas, may show a painless, slow progression without significant loss of orbital function (Fig. 7). All ill-defined, infiltrative orbital masses should be biopsied.

(6) Adult low-grade inflammation is usually a chronic disease with swelling, proptosis and globe displacement. It may be painless, non-erythematous and possibly organ-specific, as with dacryoadenitis. Treatment usually consists of incisional or excision biopsy followed by immunosuppression and, in some cases, low-dose orbital radiotherapy.

(7) Most adult vascular lesions, arising from an 'evolution' of venous anomalies or enlargement of arterial anomalies, are of chronic nature and may cause chronic pain and a moderate loss of function. CT scan and Doppler ultrasonography are of diagnostic help, and sometimes an MRI angiogram may be indicated. Venous anomalies should be observed, where possible, and arteriovenous malformations usually need treatment by interventional radiology.

`Acute-on-Chronic' Onset

(1) A sudden acceleration of a previously very slowly progressive proptosis suggests the malignant transformation of a formerly benign tumor, such as carcinoma in pleomorphic adenoma (Fig. 10), sarcoma in fibrous dysplasia or lymphoma in Sjögren's syndrome.

(2) Occasionally, a low-grade malignancy will transform into a higher-grade lesion as, for example, with lymphomas or in the de-differentiation of sarcomas.

(3) In both adults and children, venous anomalies may undergo spontaneous thrombosis, causing acute pain, signs of inflammation, and a dramatic increase in proptosis with a marked loss of function. Either a surgical intervention or, in some cases, anticoagulants and medical therapy may be required if orbital functions are severely impaired.

Common Orbital Tumors

The prevalence of various orbital tumors varies with age, structural anomalies and benign tumors being more common in childhood, and acquired benign or malignant neoplasms being typical of adulthood.

Benign Orbital Tumors

The likely diagnosis for many benign orbital tumors can be based on a typical history and examination, with confirmation by CT if necessary. Childhood benign lesions are relatively common, the most frequent being dermoid or epidermoid cysts (up to about one-third of referrals) and capillary haemangiomas in up to about 15% of cases. In contrast, dermoid cysts very rarely remain occult until adulthood, and benign tumors in adults tend to be acquired lesions, such as cavernous haemangiomas, benign peripheral nerve sheath tumors, optic nerve tumors and various, distinctly rare, lacrimal gland and mesenchymal tumors.

Orbital Cystic Tumors

Orbital cysts generally arise from developmental sequestration of epithelium within the orbit, by traumatic implantation, or from orbital encroachment by epithelial-lined sinus lesions.

Congenital dermoid and epidermoid cysts, often noted shortly after birth, are most commonly located near the orbital rim at the zygomatico-frontal suture and may present with firm, smooth preseptal masses that may be mobile over the bone or fixed deeply (Fig. 4a); in some cases the dermoid passes through a hole or notch in the orbital rim (Fig. 4b–d), and very rarely, a dermoid cyst is open to the skin surface and presents as an intermittently discharging sinus. These cysts slowly enlarge from the continued accumulation of epithelial debris, and leakage of the lipid contents may cause intermittent marked inflammation. Retrobulbar dermoid cysts, which may occasionally have a conjunctival epithelial lining, tend to present late in life with progressive proptosis or orbital inflammation.

Mobile, anteriorly situated and characteristic lesions do not require radiological investigation and should be excised through an upper lid skin-crease incision or through an incision hidden on the brow hairs; likewise, fixed dermoid cysts do not necessitate imaging if the surgeon is adequately experienced to follow the lesion to its limits. The tissues should be divided right down to the surface of the cyst (there being a tendency to dissect tissues remote from the lesion) and this plane followed by blunt dissection; in some cases it is necessary to remove the underlying periosteum or follow the lesion into or through the orbital wall. Deep orbital dermoids, as with any tumor presenting with proptosis, require thin-slice CT with bone windows to show associated osseous clefts or canals. CT will often show a smooth, 'scalloped' erosion of the neighbouring bone as a result of pressure from the mass, although this is a non-specific sign suggesting a long-standing benign orbital lesion. Intraoperative rupture of a dermoid cyst may lead to a marked postoperative inflammation, and any spilt contents should be removed. Incomplete excision of the epithelial lining will lead to recurrent inflammation with formation of a discharging cutaneous fistula through the operative incision.

Dermolipomas are allied to dermoid cysts in that they comprise cutaneous epithelium and fat sequestered on the ocular surface, typically overlying the lateral and superolateral sclera. The abnormal epithelium, often hair-bearing, causes a chronic ocular irritation and discharge and may be removed by micro-dissection, with care being taken to avoid damage to the neighbouring lacrimal gland ductules.

Paranasal sinus mucocoeles most commonly arise in the ethmoid and frontal sinuses, and their enlargement with mucus retention leads to a slow encroachment on the neighbouring orbit and globe displacement; orbital cellulitis may occur with secondary infection of the retained sinus secretions (Fig. 3e,f). CT scan shows a cystic cavity expanding the paranasal sinus cavity, with patchy thinning or loss of bone, and MR images can show a wide variation in signal intensities within the lesions. Once any infection has been controlled with systemic antibiotics, the mucocoele and other sinus disease should receive definitive treatment from an otorhinolaryngologist, this treatment typically being drainage of retained secretions, re-establishment of new drainage pathways for the affected sinuses, and possibly removal of the mucocoele lining.

Orbital Vascular Tumors

Many vascular anomalies, such as varices, lymphangiomas and arteriovenous anomalies, are rather diffuse within the orbit and do not form discrete, tumor-like masses. Childhood capillary haemangiomas and cavernous haemangiomas in adults do, however, present as well-defined tumors with appropriate orbital signs.

Capillary haemangiomas occur in up to 2% of infants and typically appear soon after birth, enlarge, and then undergo a spontaneous involution, with most having resolved by 7 years of age. Unlike rapidly growing malignancies of infancy (such as rhabdomyosarcoma), capillary haemangiomas show multiple vessels with very high flow rates – generally above 50 cm/s – and arterial waveform. Unless the rare necessity for surgical resection is being considered, CT scan is only rarely necessary for the diagnosis but generally shows a rather irregular lesion with marked contrast enhancement. Affected children should be monitored and treated for their visual development, and if the visual impairment is due

to tumor bulk, these haemangiomas may be treated with either systemic or intralesional steroids; only very rarely do they require resection, a procedure with some risk of morbidity.

The most common adult benign orbital tumor, cavernous haemangiomas, usually arise in retrobulbar tissues and present as painless, very slowly progressive proptosis in the 4th or 5th decades; vision may be reduced due to induced presbyopia, choroidal folds, or optic nerve compression (Fig. 5). CT scanning reveals a well-defined, round intraconal tumor, with only very slow and patchy contrast enhancement, that commonly displaces the optic nerve medially. Some haemangiomas are wedged in the orbital apex and tend to present early due to optic neuropathy. Asymptomatic tumors – discovered on imaging for other reasons – should be monitored for orbital signs, and the lesion removed through an anterior or lateral orbitotomy if there is optic neuropathy, significant proptosis or diplopia.

Benign Lacrimal Gland Lesions

Lacrimal gland masses can arise from chronic dacryoadenitis or from benign neoplasms, but the tendency for these conditions to present in a similar fashion to malignancy complicates the management of these patients. Mismanagement of benign conditions can lead to serious consequences as with, for example, malignant recurrence after biopsy of a benign pleomorphic adenoma.

Pleomorphic adenomas are a rare, benign, epithelial neoplasm of the lacrimal gland, typically arising in the orbital lobe and presenting in the 4th or 5th decade as a slow onset of painless proptosis and inferomedial displacement of the globe. To prevent inadvertent biopsy, it is imperative to diagnose the tumor based on clinical history and CT scanning: The ovoid orbital lobe tumors typically lie entirely within the orbit, show a smooth expansion of the lacrimal gland fossa, calcify rarely, and displace and flatten the globe (Fig. 10a–c). In contrast, the rare palpebral lobe tumors show a normal gland with an enlarged, rounded, anterior surface extending outside the orbital rim. The key to treatment of pleomorphic adenomas is preoperative recognition, with avoidance of biopsy. Because of the risk of late malignant transformation, tumors of the orbital lobe should be excised intact through a lateral orbitotomy, and breach of the 'pseudocapsule' of compressed tissues avoided; to this end, the tumor is handled at all times with a malleable retractor and not with any sharp-edged instruments.

Incisional biopsy should be considered wherever a persistent lacrimal gland mass is accompanied by a history and signs suggestive of chronic inflammation – as lacrimal gland carcinoma will be present in some cases. Acute inflammation presents as a painful, swollen, tender upper eyelid, often with an 'S'-shaped ptosis, whereas chronic dacryoadenitis more typically presents as a bilateral painless mass. CT or MR images show diffuse lacrimal gland enlargement with 'spillover' into the neighbouring preseptal and orbital tissues – a radiological appearance that cannot be differentiated from infiltrative malignancies, such as lymphoma.

Benign Optic Nerve Tumors

Primary optic nerve meningiomas or gliomas (juvenile pilocytic astrocytoma) are usually benign and present in children or young adults.

Glioma is the most common optic nerve tumor but comprises only 3% of orbital tumors. One-third of gliomas are related to type I neurofibromatosis, these having a better visual prognosis than those in patients without NF1. Gliomas generally cause painless proptosis and visual loss ranging from mild to severe. In the early stages, fundus examination may show a swollen optic disc, which later may become pale with the appearance of a retinochoroidal shunt vessel on the margin of the disc. Imaging shows a fusiform enlargement of the optic nerve, often with a characteristic intraorbital kink, and MRI is especially useful for detailing the intracanalicular and intracranial portions of the nerve. Gliomas show a variable clinical course: Most orbital gliomas remain stable for a long time, but some – although benign – may show infiltrative growth and systemic spread. Asymptomatic tumors should be followed clinically and radiologically. Neurosurgical resection is dictated if an optic nerve glioma is showing progression with a threat to the chiasm, whereas a transcanthal resection of the orbital tumor –sparing the eye – may be considered for gross proptosis. Microscopic control of the resection margins may be helpful as the extent of tumor is ill-defined radiologically. The prognosis is generally good for solely orbital glioma and the mortality, other than with intracerebral disease, less than 5%.

Orbital meningiomas are benign neoplasms arising from the meninges, and there are two distinct forms – optic nerve sheath meningioma (Fig. 8) and sphenoid wing meningiomas (Fig. 9) – that are both frequent in middle-aged women. Optic nerve meningiomas cause minimal proptosis but profoundly affect vision due to impairment of optic nerve perfusion. The affected eye presents with a swollen or atrophic optic disc, occasionally with retinochoroidal shunt vessels. When the tumor is confined to the optic canal, it can mimic optic neuritis, and the diagnosis may be more difficult. CT scan typical-

ly shows a diffuse expansion of the optic nerve and, in some cases, the 'train-track' parallel calcification of the optic nerve sheath. MRI may demonstrate a normal or small optic nerve passing through an enlarged sheath. Early meningioma should be suspected in any young patient with unusual visual symptoms, like obscurations, and needs careful radiological examination.

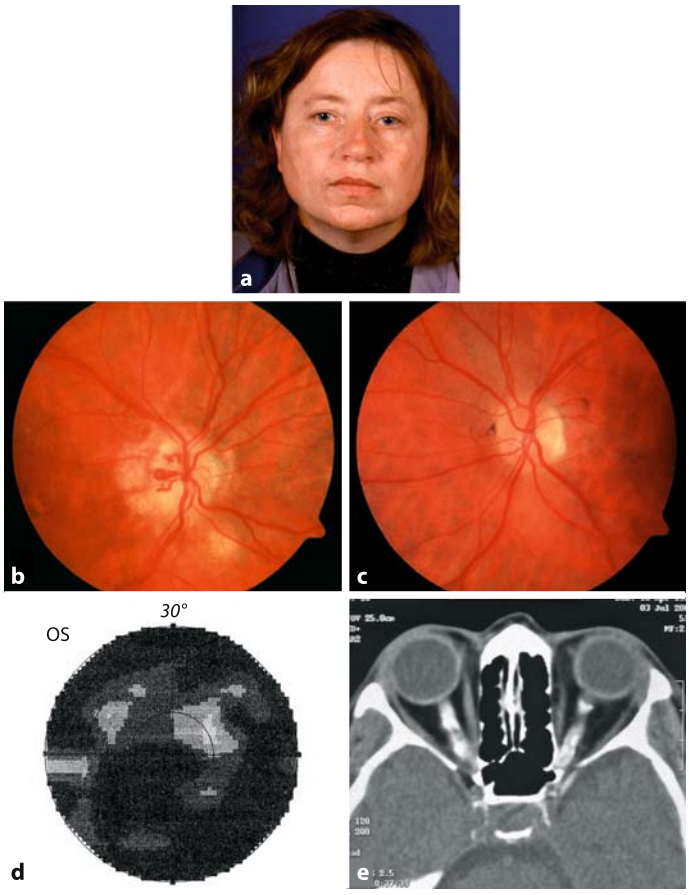


Fig. 8 a–e. Gradual onset of progressive, painless visual failure in adulthood without significant proptosis (**a**) due to bilateral optic nerve sheath meningioma. The right optic disc (**b**) is atrophic, with marked optociliary shunt vessels, and the left disc (**c**) shows temporal atrophy; visual field testing was possible only on the left eye (**d**) and shows gross impairment. Bilateral calcified optic nerves, pathognomonic of optic nerve sheath meningioma, are clearly shown on CT (**e**); a slight flattening of the posterior pole of both globes (especially the left) is also evident, due to a 'splinting' effect of the optic nerve tumors

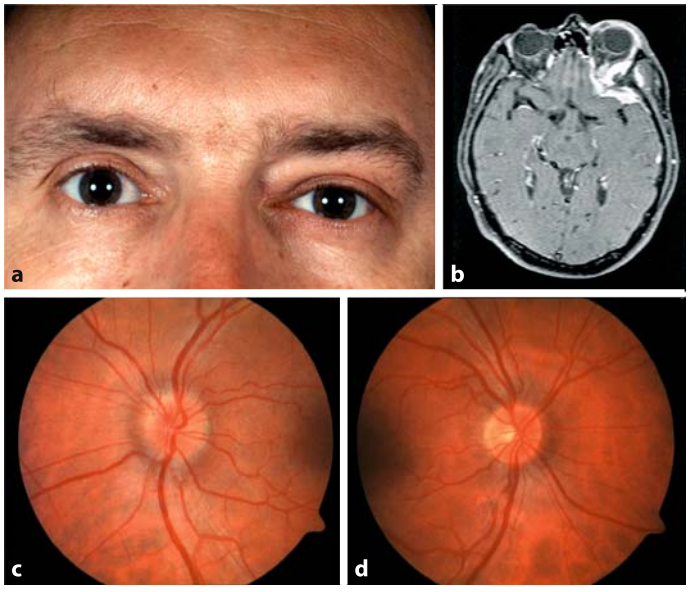


Fig. 9 a–c. Slowly progressive displacement of the left eye due to sphenoidal wing meningioma. **a** The left globe shows hypoglobus and exophthalmos, with some `fullness´ of the upper lid sulcus. **b** MRI shows a high-signal lesion 'en-plaque' to the greater wing of the sphenoid and involving the left orbit, middle cranial fossa and temporalis fossa. Compression of the left optic nerve, manifest as mild disc swelling (**c**), is associated with some impairment of function

The therapy of optic nerve sheath meningioma is conservative, since surgical excision invariably leads to blindness, and the results after radiotherapy are somewhat controversial. Optic nerve meningiomas in younger people should be considered for neurosurgical resection, as the disease appears to have a more active course in this group and carries a risk of chiasmal involvement.

Benign Tumors of Peripheral Nerve, Bone or Mesenchyme

Solitary benign nerve sheath tumors, like neurilemmoma (schwannoma) and neurofibroma, arise from peripheral nerves and comprising about 4% of orbital neoplasms. They present either in the intraconal space (with an imaging appearance like cavernous haemangiomas) or as a sausage-like mass along the orbital roof, causing slowly progressive proptosis and hypoglobus. Orbital neurilemmoma, derived from Schwann cells, usually occurs in middle-aged adults and causes painless proptosis with symptoms similar to those of cavernous haemangioma; they are readily cured by surgery. Neurofibromas are composed of a combination of Schwann, perineural, and fibroblastoid cells, and often axons are present in localized, diffuse or plexiform types of lesion. Localized neurofibromas are generally not related to NF1, whereas the plexiform type has a very strong association (Fig. 6). Although both NF1 and NF2 have ophthalmic manifestations, type 1 has the greatest ophthalmic significance as it is ten times more common than type 2 (the former with an incidence of 1:3000) and has a number of ophthalmic manifestations including Lisch nodules, neurofibromas, dysplasia of the sphenoid wing and optic nerve glioma.

Plexiform neurofibromas, the most common and complex of orbital peripheral nerve tumors, grow along the nerves and form a characteristic 'bag of worms'. They are very vascular and diffusely interconnected with normal tissues, the overlying skin being thickened, and typically affecting the upper eyelid and lacrimal gland. Although orbital plexiform neurofibromas are benign, they cause significant problems with continuous growth, to sometimes grotesque dimensions, visual impairment or blindness and, rarely, even death due to impairment of vital intracranial structures. Surgical resection presents considerable difficulty and consists of – often repeated – tumor debulking which is never curative.

There are many rare tumors that affect the orbital bone, but the most common in adulthood is sphenoid wing meningioma and, in children, osteomas. Sphenoid wing meningioma – unrelated to optic nerve meningioma – tends to present in middle age with chronic variable lid swelling, chemosis and mild proptosis. CT scan shows hyperostosis of the greater wing of the sphenoid with en plaque soft tissue on the lateral wall of the orbit, the temporalis fossa or the middle cranial fossa (Fig. 9b). Although metastases may very rarely present with a similar radiological appearance, the clinical behaviour is different – with sphenoid wing meningioma progressing very slowly and usually not requiring any active treatment; a rapidly progressing tumor should probably undergo biopsy to exclude metastatic disease with a view to radiotherapy or neurosurgical resection if shown to be meningioma.

Benign mesenchymal tumors of the orbit, such as solitary fibrous tumors or haemangiopericytomas, are very rare and typically present as painless proptosis with diplopia. The masses, generally well defined but encloaking normal orbital structures, are often located in the superonasal quadrant of the orbit and may be en plaque with the orbital periosteum. These tumors should, where possible, be excised intact, as they carry a significant risk of pervasive tumor recurrence with piecemeal primary excision.

Malignant Orbital Tumors

Primary or secondary orbital malignancy can affect all ages and should be considered wherever there is rapidly or relentlessly progressive disease, an inflammatory picture, or where a condition – presumed to be benign – fails to show appropriate clinical behaviour.

Malignant Orbital Tumors of Childhood

Rhabdomyosarcoma is the most common primary orbital malignancy of childhood and arises from pluripotent mesenchyme that normally differentiates into striated muscle cells. Showing a peak incidence at about 7 years of age, rhabdomyosarcoma often presents with signs of acute orbital inflammation, and a suspicion of underlying malignancy should be entertained with any unilateral orbital disease in childhood. The tumor mass may be located anywhere in the orbital soft tissues, most commonly in the superomedial quadrant, and typically does *not* arise in the extraocular muscles (Fig. 3a–c). Imaging will usually demonstrate a fairly well-defined, round mass with moderate contrast enhancement, arising within the orbital fat and flattening the globe; expansion of the thin bone of the childhood orbit is quite common. Doppler ultrasonography assists in differentiating rhabdomyosarcoma from capillary haemangioma, the latter showing marked vasculari-

ty. Urgent incisional biopsy will provide the diagnosis – although macroscopic excision may be possible for well-defined tumors – and a systemic evaluation (including whole-body CT and a bone marrow biopsy) is required to look for metastatic disease prior to systemic and local tumor therapy. Long-term side-effects of orbital radiotherapy include cataract, dry eye with secondary corneal scarring, loss of skin appendages (lashes and brow hair), atrophy of orbital fat and, if performed in infancy, retardation of orbital bone growth. There is also a risk of late radiation-induced periorbital malignancies, such as fibrosarcoma and osteosarcoma, and there may be an increased propensity to certain other primary tumors in adulthood.

Both neuroblastoma and acute myeloid leukaemias may present as metastases within the orbital soft tissues or bone, the clinical presentation being very similar to rhabdomyosarcoma, with rapidly progressive proptosis and orbital inflammatory signs. The Langerhans cell histiocytoses are a group of malignant diseases affecting this cell lineage, although the variant found most commonly in children (eosinophilic granuloma) verges on a benign proliferation and is readily treated – after biopsy – with intralesional or systemic steroids.

All of these childhood tumors require urgent biopsy, systemic investigation and chemotherapy with, in some cases, radiotherapy. Although the prognosis for vision with most of the haematological malignancies is generally good, there is a significant mortality, depending on prechemotherapy disease staging.

Orbital Lymphoma in Adults

Orbital lymphocytic lesions display a spectrum from benign morphology, showing well-organised follicular pattern (so-called reactive lymphoid hyperplasia) through the rare 'atypical lymphoid hyperplasia' with poorly organised or disrupted follicles, to frankly malignant lymphoma. Improved tissue diagnosis has shown that many lesions previously labelled 'atypical lymphoid hyperplasia' are, in fact, lymphomas displaying various degrees of follicular destruction. Primary lymphomas of the orbit are effectively all of the non-Hodgkin's B-cell type, and the extremely rare orbital T-cell lymphomas occur only in patients with systemic disease. Depending on the grade of lymphoma, up to about one-half of patients presenting with orbital disease will be found to have systemic involvement within 6 months of presentation.

Orbital lymphomas typically present in the over-50s with a slowly progressive, painless, pink subconjunctival mass or – if deeper in the orbit – with eyelid swelling, globe displacement or diplopia (Fig. 7). CT scan commonly shows a moderately well-defined soft-tissue mass, which may be bilateral, encloaking the globe and other orbital structures; tumor calcification and bone destruction are distinctly rare. Biopsy is mandatory, as the CT and MRI characteristics of lymphomas are indistinguishable from orbital inflammation. As the contemporary diagnosis of lymphoma depends on structural analysis, open biopsy is recommended because, in contrast to fine-needle aspiration, it provides a structured sample with minimal disruption. All patients with lymphoid lesions should undergo investigation for systemic disease, including whole-body CT scan and bone marrow biopsy if the lymphoma is of higher grades.

Although some conjunctival lymphomas progress only very slowly and may be kept under observation, most such low-grade orbital lymphomas respond very well to about 2400 cGy fractionated radiotherapy or to oral chemotherapy. Patients with high-grade lymphomas have, however, a much higher chance of systemic disease and usually require multiple cycles of more aggressive chemotherapy, and adjunctive orbital radiotherapy (often to 3500 cGy) may be used to accelerate resolution of the orbital disease. When the disease is confined to the orbit, the visual prognosis is excellent and complications unusual. The overall mortality varies according to the histological grade and staging, and at least 10 years' review is required after primary therapy.

Lacrimal Gland Carcinomas

With a peak incidence in the fourth decade, adenoid cystic carcinoma is the most common epithelial malignancy of the lacrimal gland, and other carcinomas (primary adenocarcinoma, mucoepidermoid carcinoma, squamous carcinoma or malignant mixed tumors; Fig. 10d,e) are much rarer; malignant mixed tumors arise within a long-standing pleomorphic adenoma or in recurrent tumor after incomplete resection of a benign pleomorphic adenoma. The diagnosis of lacrimal carcinoma is suggested by persistent periocular ache, ocular displacement and upper lid swelling progressing over a few months, and a non-tender lacrimal gland mass. CT scan shows an enlarged gland moulding to the globe, flecks of calcification in about one-third of tumors, extension along the lateral orbital wall with medial displacement of lateral rectus, and – in more advanced cases – erosion of cortical bone in the lacrimal gland fossa.

Biopsy of suspected lacrimal gland malignancy should be through an upper lid skin-crease incision, and adenoid cystic carcinoma is composed of cords of malignant epithelial cells, often with cystic spaces giving a 'Swiss cheese' pattern. Adenoid cystic carci-

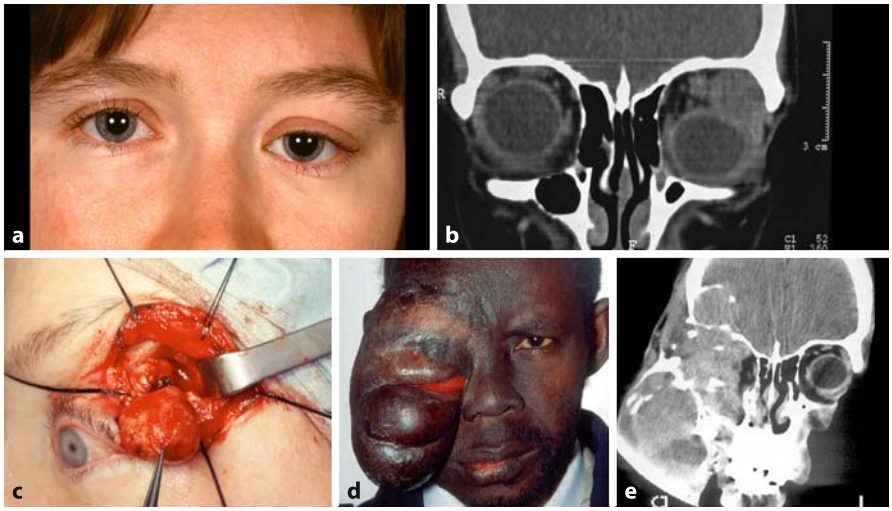


Fig. 10. **a** Pleomorphic adenoma of the left lacrimal gland, presenting as slowly progressive painless proptosis with diplopia on extreme left-gaze; the left globe is also displaced inferiorly by the well-defined mass in the lacrimal gland (**b**), which is also causing some flattening of the globe. Pleomorphic adenomas should be excised intact (**c**), as they carry a risk of later malignant transformation (so-called malignant mixed tumor), when the patient will present with an accelerated history (**d**), and imaging may then show bone invasion and destruction (**e**)

noma has a tendency to perineural spread (into the cavernous sinus and pterygopalatine fossa) and also tends to infiltrate beyond the macroscopic boundaries evident at surgery or radiologically. As recurrent lacrimal carcinoma may not present for more than a decade after primary therapy, the optimum treatment remains controversial, and treatment cannot realistically be considered a 'cure' until at least 20 years have elapsed without disease. The least disfiguring therapy is probably removal of the tumor bulk (often almost complete) through an anterior orbitotomy and subsequent fractionated beam radiotherapy (about 5500 cGy) to both the orbit and the cavernous sinus. Deliberate surgical breach of an intact lateral orbital wall should be avoided, as this may encourage tumor seeding into the cranial diploe and a relentless, fatal recurrence of local disease. Implantation brachytherapy has been used to deliver a high radiation dosage to the tumor bed whilst relatively sparing the globe, but it does not treat the cavernous sinus or pterygopalatine fossa, areas in which tumor recurrence occurs after perineural invasion. Intracarotid chemotherapy may have a role as an adjunct to radiotherapy in advanced disease.

There is no evidence to suggest that either exenteration or 'super-exenteration' (with removal of the neighbouring orbital bones) leads to reduced tumor recurrence or improved survival, and such procedures are associated with a gross disfigurement in relatively young people. However, the long-term prognosis is probably one of the worst of all orbital tumors with a 10-year survival rate of approximately 30%.

Secondary Orbital Malignancy from the Eyelids, Paranasal Sinuses or Globe

Orbital exenteration, with craniofacial resection in some cases, is generally required where there is extensive orbital involvement by secondary spread of tumors from the globe or from sites around the orbit.

Extensive Meibomian gland carcinoma and neglected basal cell or squamous carcinomas tend to invade the orbit and conjunctival fornices, causing diplopia, and tumor fixation to underlying bone suggests advanced disease. Painful perineural invasion, usually from forehead tumors with infiltration along the frontal nerve, is most common with squamous cell carcinoma and may not be associated with a significant orbital mass. Likewise, sebaceous (Meibomian gland) carcinoma may show intraepithelial pagetoid invasion across the conjunctiva or skin remote from an apparently localised eyelid mass.

Squamous carcinoma from the paranasal sinuses or pharynx is the most common secondary epithelial neoplasm of the orbit, either with direct bone destruction or microscopic perineural spread through, for example, the ethmoid foramina or the inferior orbital fissure. Management involves diagnostic biopsy,

wide surgical clearance, and later radiotherapy and chemotherapy.

Other rare tumors of the paranasal sinuses that may involve the orbit include adenoid cystic carcinoma, adenocarcinoma, esthesioneuroblastoma and melanoma.

Uveal malignant melanoma is the most common primary intraocular tumor of adulthood, and orbital extension probably occurs through the emissary veins, although aggressive tumors may reach the orbit by direct scleral invasion or through the optic nerve head. As there is often coexistent systemic disease, orbital extension of uveal melanoma carries a poor prognosis, although future advances in tumor-directed chemotherapy may improve this outlook. Extraocular extension of retinoblastoma – the most common childhood ocular malignancy – occurs in about 8% of cases and carries a poor prognosis, despite systemic chemotherapy and local radiotherapy.

Orbital Metastases in Adults

Although adulthood metastases occur more commonly in the uveal tract, orbital metastases (which occur by haematological spread in the absence of orbital lymphatics) form 2–3% of all orbital tumors and may arise from an occult primary tumor. The most common primary sites are breast, prostate, lung, kidney and the gastrointestinal tract, and such lesions typically present with painful proptosis and diplopia, in some cases resembling orbital inflammation. Malignancy should be considered whenever an orbital disease progresses despite treatment. An exception with regard to the most typical clinical sign of an orbital tumor, proptosis, is the spontaneous enophthalmos in the case of a metastatic scirrhous breast cancer. The mechanism is contraction of fibroblasts in the diffuse scirrhous breast cancer metastases, leading to a retraction of the globe.

A multidisciplinary approach involving the ophthalmologist, family physician, pathologist and oncologist is essential for an adequate management of these patients. Treatment from an ophthalmologic standpoint includes preservation of vision and relief of pain. Radiotherapy, chemotherapy and hormonal therapy can often achieve these goals. After possibly debulking the tumor, the mainstay of therapy is local treatment with about 5500 cGy fractionated radiotherapy. Radical surgery is contraindicated except in rare cases, when exenteration may be considered if the orbit is the sole metastasis (e.g. carcinoid, renal carcinoma). Most treatments are palliative, with avoidance of discomfort and preservation of vision (if possible), but dry eye and troublesome diplopia are major problems, particularly after radiation.

Rare Adulthood Malignancies of Mesenchymal or Neural Origin

Sarcomas of the orbit are extremely rare. The highly malignant osteosarcoma is often secondary to childhood orbital radiotherapy in genetically predisposed individuals (with prior retinoblastoma), and even with radical clearance, the tumor is almost uniformly fatal within 2 years. Children may present with metastatic Ewing's sarcoma or Wilms' tumor within the orbit and will require systemic therapy after diagnosis.

Fibrosarcomas arise as a primary orbital tumor or as a secondary tumor from adjacent sinuses or the site of prior radiotherapy. Exenteration is often necessary for wide clearance, or palliation with radiotherapy and chemotherapy. The prognosis for vision and life is variable, but it is best for primary juvenile fibrosarcomas.

Several rare orbital tumors present with a spectrum of disease from benign to malignant. With a poor prognosis, malignant fibrous histiocytomas generally present with a well-defined mass in the superonasal quadrant, and even after wide excision, recurrence of these radio-resistant and chemo-resistant tumors is common. Haemangiopericytoma, likewise, has a spectrum of malignancy and should be treated by wide and, if possible, intact resection.

Leiomyosarcoma, a tumor of smooth muscle, and liposarcomas of various degrees of differentiation present considerable diagnostic difficulties and have been reported to involve the orbit very rarely.

Of Schwann cell origin, the extremely rare malignant neurilemmoma may arise spontaneously or in association with neurofibromatosis. It presents as a slowly progressive lid mass or proptosis. CT scan shows an ill-defined mass, and management involves wide surgical clearance with adjunctive radiotherapy or chemotherapy. The prognosis is poor, as these tumors tend to invade the middle cranial fossa and develop pulmonary metastases.

Principles of Surgical Management

Orbital tumors generally require excision, either intact if well-defined or as an incisional biopsy or piecemeal excision if ill-defined or pervasive. Pleomorphic adenomas of the lacrimal gland must be excised intact and are the only absolute contraindication to incisional biopsy or piecemeal excision; disruption of the pseudocapsule predisposes to a late and infiltrative recurrence of these neoplasms, these recurrences often being malignant.

It is possible for the experienced orbital surgeon to approach all areas of the orbit through cosmetically 'hidden' incisions, and there is almost no indica-

tion for using transcranial approaches for solely orbital disease: Cranio-orbitotomy should be reserved for cases where there is a need to remove both an intracranial and an orbital mass, such as intracanalicular optic nerve gliomas, masses straddling the superior orbital fissure and large craniofacial osseous lesions (such as meningiomas). Likewise, the various craniofacial approaches – such as lateral rhinostomy, trans-frontal mid-face resection, or trans-oral mid-face 'degloving' – should be reserved for cases of sinus disease involving the orbit or skull base.

Principles of Anterior Orbitotomy

A skin incision of about 3 cm is placed in a suitably hidden position, generally the upper eyelid skin-crease or the lower eyelid 'tear trough', and the underlying orbicularis oculi muscle cauterised and divided at the midpoint of the skin incision. The points of a pair of scissors are inserted through the defect, opened widely along the line of the muscle to separate the fibres by blunt dissection, and any remaining bridging tissue diathermied and divided to reveal the underlying orbital septum. The septum is likewise divided along the line of incision to expose the orbital fat, and the direction of the orbital mass ascertained by analysis of the imaging and by palpation.

A closed pair of blunt-tipped scissors is gently directed through the orbital fat towards the site to be biopsied, the scissors opened widely to reveal the depths of the tissues, and – before withdrawing the scissors – a 12–16 mm malleable retractor is inserted alongside the opened scissors to maintain the plane and depth of exploration. This manoeuvre is repeated until the abnormal tissue is reached (the surgical assistant maintaining the access with a pair of malleable retractors), and meticulous haemostasis is essential as it can otherwise be almost impossible to recognise subtly abnormal orbital tissues, such as oedematous or infiltrated fat.

When the abnormal tissue is located, a relatively large biopsy should be taken using a number 11 blade or non-crushing biopsy forceps. The tissue should preferably be gripped once only, to avoid crush artefact, with a single larger piece being more diagnostic than fragments. Complete haemostasis should be established with bipolar cautery, a vacuum drain placed if there is a concern about tissue fluid collection at the orbital apex, and the orbicularis muscle and skin closed with a running 6/0 nylon suture.

Principles of Lateral Orbitotomy

An upper lid skin-crease incision is extended laterally to about 1 cm below the lateral canthus, the tissues opened to the superolateral orbital rim, and the periosteum incised 6 mm outside the rim from the lateral one-third of the supraorbital ridge to the level of the zygomatic arch. The periosteum is raised across the rim into the orbit and separated from the inner aspect of the lateral wall, with cautery and division of any bridging vessels. Two axial-plane saw cuts are made at the upper and lower ends of the osteotomy, drill holes placed either side of each cut and – using a burr – the inner aspect of the lateral wall fragment weakened about 1 cm behind the rim; the fragment is then out-fractured and trimmed, swung laterally on temporalis, and the periosteum opened to provide access for the intraorbital procedure.

After achieving intraorbital haemostasis, a vacuum drain is placed within the intraconal space and passed out through the skin overlying the temporalis fossa. The bone is swung medially into the correct position, fixed in place with a 4/0 absorbable suture passed through the drill holes, the deep subcutaneous tissues over the outer canthus, and further laterally repaired with a 4/0 or 5/0 absorbable suture, and the skin closed with a running 6/0 nylon suture. The patient should be nursed half-recumbent after surgery and excessive drainage reported. If the patient develops severe and increasing pain, the vision in the affected eye and the state of the orbit should be checked – a very tense orbit with markedly decreased vision, a relative afferent pupillary defect and loss of eye movements suggesting significant accumulation of orbital haemorrhage that might lead to irreversible visual loss. Should this emergency occur, the drain should be moved slightly to see if fluid drainage can be re-established, and if this does not succeed, the operative site should be reopened at the 'bedside' and any accumulation of blood allowed to drain. The vacuum drain is removed when active fluid drainage has ceased (usually 12–18 h after surgery), and postoperative systemic anti-inflammatory medications at high dosage are useful, particularly where there has been manipulation in the region of the superior orbital fissure or optic nerve. The patient should refrain from vigorous exercise for 10 days after surgery, normal ocular ductions encouraged, and the skin suture removed at 1 week.

Complications after lateral orbitotomy are mainly related to the nature of the intraorbital procedure, rather than the approach. It is common to develop diplopia due to mechanical weakness of ocular ductions (particularly abduction), and this typically improves over several weeks, but motor neuropraxias, fairly common with surgery near the orbital apex and superior orbital fissure, may take many months to recover. Postoperative mydriasis – probably due to denervation at the ciliary ganglion – is relatively common and may be permanent, and total loss of

vision is a distinct risk with any surgery involving the posterior half of the orbit.

Principles of Orbital Exenteration

Exenteration, necessary for the treatment of various pervasive malignant or benign orbital diseases, involves the complete removal of the eyeball, retrobulbar soft tissues and most, or all, of the eyelids. Skin-sparing exenteration provides a very rapid rehabilitation and is particularly useful for benign disease, post-septal intraorbital malignancy and for the palliation of fungating terminal orbital malignancy.

The skin incision should be placed well clear of the malignancy, either near the orbital rim if dealing with extensive eyelid malignancy invading the orbit, or alongside the lash-line for a skin-sparing exenteration, when the skin and orbicularis oculi muscle is undermined to the orbital rim. The periosteum is incised just outside the rim, raised intact over the rim and posteriorly into the orbit, with areas of adherence being found at the arcus marginalis, the trochlear fossa, the interosseous suture lines and the lacrimal crest. The anterior and posterior ethmoidal vessels should be cauterised and divided, along with the nasolacrimal duct and any vessels crossing between the orbit and the lateral orbital wall or floor. Care should be taken to avoid damage to the lamina papyracea, as ethmoidal entry leads to a chronic sino-orbital fistula. Once the orbital contents have been mobilised within the periosteum, the posterior tissues are divided about 7–10 mm from the apex, this being best achieved from the lateral side, using a monopolar diathermy in a blended cutting and coagulation mode. The ophthalmic artery should also be cauterised with bipolar diathermy, and any persistent bleeding from the bones should be plugged with bone wax. With skin-sparing exenteration, the orbicularis of the upper and lower lid flaps are sutured using buried 5/0 absorbable sutures, and the skin closed with continuous 6/0 nylon to create an air-tight closure to encourage retraction of the surface. Where complete exenteration of the eyelids and orbit has been performed, the socket can be left to granulate or lined with split-thickness skin grafts. Exenteration can be complicated by postoperative infection, necrosis of flaps and grafts or delayed socket granulation. Disruption of the lamina papyracea leads to communication between the ethmoid sinuses and the exenteration cavity (a sino-orbital fistula), and failure of closure of the nasolacrimal duct may cause a lacrimal 'blow-hole'.

Table 1 Signs of orbital tumors

Exophthalmos
Dislocation of the eyeball
Motility disorder
Visual acuity/visual field reduction

Table 2 Symptoms of orbital tumors

Double vision (diplopia)
Visual acuity/visual field reduction
Pressure feeling
Foreign body sensation
Pain
Hypaesthesia

Table 3 The five most common primary and secondary orbital tumors (acc. Henderson)

Primary orbital tumors	Secondary orbital tumors
Haemangioma	Mucocele
Malignant lymphoma	Squamous cell carcinoma
Orbital pseudotumor	Meningioma
Meningioma	Vascular Malformation
Optic nerve glioma	Malignant Melanoma

Table 4 Most common orbital tumors in childhood (acc. Henderson)

Dermoid cyst
Haemangioma
Rhabdomyosarcoma
Neuroblastoma
Glioma

Suggested Reading

Harris GJ, Logani SC. Eyelid crease incision for lateral orbitotomy. Ophthal Plast Reconstr Surg 1999; 15:9–16

Henderson JW. Orbital Tumors. New York, Raven Press Ltd, 3rd Edn. 1994

Lacey B, Chang W, Rootman J. Nonthyroid causes of extraocular muscle disease. Surv Ophthalmol 1999; 44:187–213

Lacey B, Rootman J, Marotta TR. Distensible venous malformations of the orbit: clinical and hemodynamic features and a new technique for management. Ophthalmology 1999; 106:1197–209

McNab AA, Wright JE. Lateral orbitotomy – a review. Aust NZ J Ophthalmol 1990; 18:281–6

Moreiras JVP, Prada MC, Coloma J, Beverra EP. Orbit: Examination, diagnosis, microsurgery and pathology. Panama, Highlights of Ophthalmology International, 1st Edn. 2004

Rootman J. Diseases of the orbit. A multidisciplinary approach. Philadelphia, J.B. Lippincott Company, 2nd Edn. 1999

Rootman J, Kao SC, Graeb DA. Multidisciplinary approaches to complicated vascular lesions of the orbit. Ophthalmology 1992; 99:1440–6

Rootman J, Stewart B, Goldberg RA. Orbital surgery. A conceptual approach. Philadelphia, Lippincott-Raven Publishers. 1st Edn. 1995

Rose GE. Clinical examination in orbital disease. In: Bosniak S, ed. Principals and Practice of Ophthalmic Plastic and Reconstructive Surgery. Philadelphia, W.B. Saunders, 1st Edn. 1996:860–73

Rose GE, Wright JE. Pleomorphic adenomas of the lacrimal gland. Brit J Ophthalmol 1992; 76:395–400

Rose GE, Wright JE. Trigeminal sensory loss and orbital disease. Brit J Ophthalmol 1994; 78:427–9

Wright JE, McNab AA, McDonald WI. Primary optic nerve sheath meningioma. Brit J Ophthalmol 1989; 73:960–6

Wright JE, McNab AA, McDonald WI. Optic nerve glioma and the management of optic nerve tumors of the young. Brit J Ophthalmol 1989; 73:967–74

Wright JE, Rose GE, Garner A. Primary malignant neoplasms of the lacrimal gland. Brit J Ophthalmol 1992; 76:401–7

Primary CNS Lymphoma 18

Uwe Schlegel, Fred H. Hochberg

Epidemiology – 292

Symptoms and Clinical Signs – 292

Diagnostics – 292

Staging and Classification – 294

Molecular Pathogenesis – 294

Treatment – 295

Treatment of HIV-Positive Patients and Post-Transplant Lymphoproliferation – 298

Prognosis/Quality of Life – 299

Follow-up/Specific Problems and Measures – 299

Therapy of Recurrent Tumor – 299

Future Perspectives – 299

References – 300

Epidemiology

Primary CNS lymphomas (PCNSL) affect all age groups with a peak incidence in the fifth to seventh decade in non-AIDS patients. Between 1970 and 1990, the incidence of PCNSL has increased significantly in immunocompromised as well as in immunocompetent individuals [60], and PCNSL accounts for approximately 4% of all primary intracranial tumors in the USA today [12]. It has become the most frequent brain tumor in AIDS patients, although the introduction of highly active anti-retroviral therapy (HAART) in 1995 has dramatically reduced the occurrence of all non-Hodgkin's lymphomas (NHL) [43], such that the incidence rates of primary and secondary brain lymphomas have dropped from 2.8 per 1,000 patient-years in 1990 to 0.4 in 1998 [58]. Despite this reduction, there has been no concomitant decrease in the rates for immunocompetent individuals.

Symptoms and Clinical Signs

Although PCNSL presents most commonly as diffuse and multifocal supratentorial brain masses, the clinician should be aware of four other initial appearances: These include lymphomatous infiltration of the leptomeninges or ependymal surfaces to produce lymphomatous meningitis; radicular or plexus invasion by lymphoma (neurolymphoma) in the absence of brain or spinal fluid involvement; infarcts produced by aggregates of intraluminal clonal B-cells within the brain (angiocentric or intravascular lymphoma); and lymphoma invading the vitreous, retina, and optic nerves (primary intraocular lymphoma). With all forms of PCNSL, an occult systemic lymphoma is seldom found. Fewer than 5% of PCNSL patients present with brain and systemic lymphoma [60], and a similar percentage develop systemic disease after brain involvement.

By a combination of both diffuse infiltration of the brain as well as mass effect, the tumor produces cognitive dysfunction, psychomotor slowing, personality changes, and disorientation. Many of these symptoms reflect brain edema, but the psychotic depression seen in tumor patients reflects a proclivity to invade the walls of the third ventricle and the medial nuclei of the thalamus. Raised intracranial pressure and focal symptoms affect about half of the patients; brain stem and cerebellar signs as well as cranial nerve dysfunction are present in 10–40%. Seizures complicate the course in 2–33% of patients, with a higher frequency in the AIDS population [60]. The risk of seizures is increased in the setting of infiltration of the mesial temporal lobes, hypothalamic infiltrates with resulting inappropriate secretion of antidiuretic hormone and hyponatremia, the administration of antidepressant drugs (which lower seizure thresholds), and HIV infection. Some 10–15% of PCNSL patients experience eye involvement at presentation or during their treatment [20], while 'neurolymphomatosis' (see below) and intravascular lymphoma are reportable diseases. Involvement of the ependyma or spinal fluid has been reported in 5–65% [35] of patients, with the lower figure being most likely.

Diagnostics

Synopsis. MRI is the most sensitive radiologic procedure to detect brain lymphoma. The features of tumor are often not diagnostic, and thus stereotactic biopsy is the procedure of choice prior to therapy. Histologic confirmation rests upon the demonstration of atypical B-cells or on PCR-based detection of monoclonal B-cells obtained from the brain tumor, spinal fluid, or vitreous aspirate of an affected eye.

CT reveals single or multiple, isodense or hypodense, irregularly shaped lesions with intense contrast enhancement in more than 90% of cases, indicating either unifocal or multifocal disease with perifocal edema which frequently is less prominent than edema in malignant glioma or metastases [17, 60]. The diagnostic procedure of choice is MRI. The densely cellular tumor appears as single (65–80%) or multiple lesions on unenhanced T1-weighted images, hyperintense tumor and edema on T2 or FLAIR or diffusion-weighted (DWI) images, and densely enhancing masses after the administration of gadolinium.

At least 50% of the lesions are in contact with the meninges, and meningeal enhancement appears in 10–20% [11, 17, 60]. Meningeal enhancement does not necessarily presage tumor detection in the CSF, however [17]. The patterns of PCNSL growth include periventricular growth and well-circumscribed cortical masses [17] indistinguishable from infiltrating gliomas, acute demyelinating diseases, and infections. Associated with PCNSL there may appear nonenhancing lesions, suggestive of either leukoencephalopathy or multiple sclerosis [60]. As demyelinating illnesses have accompanied PCNSL, the clinician should not assume that all FLAIR abnormalities on MRI reflect a consequence of the tumor. The masses of PCNSL in the immunocompetent patient seldom contain calcification, cyst formation, and hemorrhage [17], whereas 50% of lesions in AIDS patients appear as ring-enhancing masses. These changes have been attributed to central tumor necrosis [46]. The immunosuppressed PCNSL patient may also harbor cerebral toxoplasmosis or fungal infec-

tions. Unlike tumors, the latter infections may not enhance with thallium-SPECT or FDG-PET [60] but are denser than malignancies on diffusion-weighted MRI images (DWI). In AIDS or post-transplant patients with PCNSL, EBV viral loads may be increased in the spinal fluid, and PCR studies may identify EBV-associated genes (EBNA1 or EBERs) in brain tissue or CSF cells. As a general rule, the treating physician who is uncertain as to the contribution of toxoplasmosis and PCNSL should provide 2–3 weeks of therapy (with pyrimethamine and sulfadiazine) for toxoplasmosis prior to the performance of a stereotactic biopsy.

Stereotactic biopsy is the diagnostic procedure of choice for PCNSL [60] and can be targeted to CT- or MRI-defined masses. In our institutions, surgeons are reluctant to perform craniectomy for tumor resection; indeed, partial resection is associated with worse survival [6]. The 'routine' provision of glucocorticoids should be withheld in favor of osmotic therapy with mannitol. Often, steroid-treated lesions will disappear within hours, and 'non-diagnostic' biopsies will result [60]. As many types of brain infiltrates improve with steroid therapy, the steroid response is not diagnostic of PCNSL. Similar responses have been seen in lesions of acute disseminated encephalomyelitis, multiple sclerosis, the granulomas of sarcoidosis and granulomatous angiitis. The evaluation of spinal fluid specimens is complicated. CSF cytomorphology is positive in fewer than 5% of samples, and immunohistochemical studies of CSF cells using antibodies to lymphocytes (LCA) or

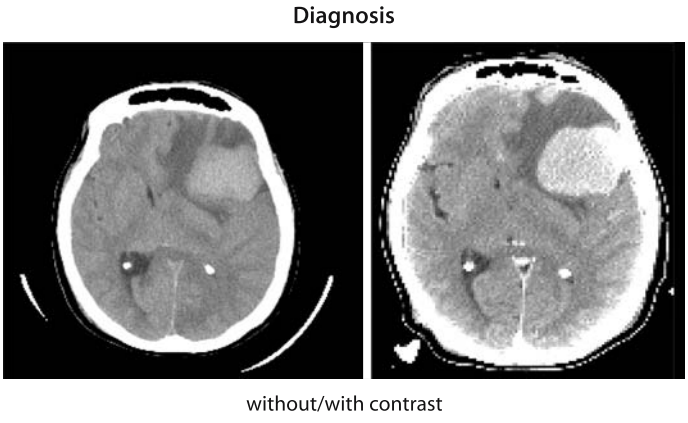


Fig. 1. CT scan of brain revealing hyperdense left frontal mass in the absence of contrast enhancement (Left image) which increases in density when contrast is injected (Right image)

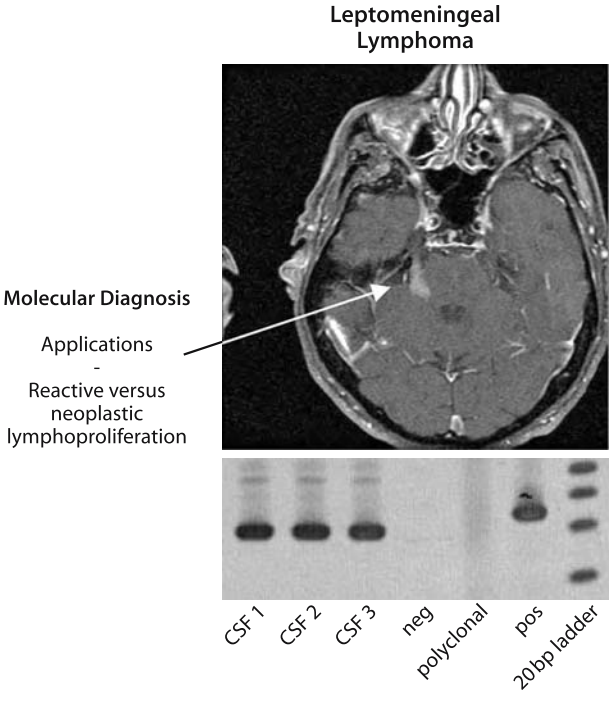


Fig. 2. MRI image with contrast reveals enhancement within pontine cistern and nerve exit zone in a patient with presumed meningeal lymphoma. To confirm this diagnosis DNA obtained from cells in a sample of lumbar spinal fluid was examined by PCR using primers directed against rearrangement of the immunoglobulin gene. All three aliquots of CSF (CSF 1, 2, 3.) relevated the same rearrangement suggesting a clonal proliferate of cells.

B-cells (CD20) are not specific for the diagnosis of a clonal proliferate in the CSF. Not uncommonly, the cytopathologist's report identifies 'atypical' cells in the setting of brain masses.

PCR identification of rearrangements of the heavy chain of immunoglobulin can be performed in specialized laboratories. Gleisner reported [29] eight examples of such rearrangements [of the complementary determining region III (CDR III) of the IgH gene] in CSF obtained from 52 patients with PCNSL. These studies are limited as the CSF from an additional 16 individuals provided insufficient DNA, and discordant cytologic and PCR results were obtained from an additional 10 of the 52 patients. The experience of Dr. J. Baehring using larger sample volumes and standardized techniques of fluid handling in two medical centers revealed a sensitivity of 62% when CSF or vitreal fluid (from PCNSL and lymphoma spreading to the neuraxis) is examined with this technique. Likely, PCR methodology will become further optimized for the evaluation of 'pauci-cellular' materials obtained from the brain, CSF, and vitreous of the eye. Examples of PCR-based diagnosis are increasingly reported, but the diagnosis still rests upon (stereotactic) brain biopsy.

As underlying systemic lymphoma is rarely identified, there is little support for the provision of ancillary examinations including CT scans of the chest and abdomen and bone marrow biopsy. The rare concordance of testicular and brain lymphoma does not support the routine use of ultrasound examination of the testes.

Staging and Classification

Synopsis. Primary CNS lymphomas are confined to the central nervous system (brain and spinal cord), may involve the meninges [5], and may extend to the eyes. More than 98% are malignant non-Hodgkin's lymphomas (NHL) of the B-cell type, the majority corresponding to diffuse large-cell lymphomas (DLCL).

According to the WHO classification [32], the majority of PCNSL are classified as diffuse large-cell lymphomas (DLCL) of the B-cell type. This classification, recognizing that tumor cells keep important features of the differentiation stage of their precursor cells, categorizes tumors according to their normal lymphoid counterpart. PCNSL corresponds to non-Hodgkin's B-cell lymphomas as evidenced by expression of the B-cell markers CD19, CD20, and CD79a.

They express monoclonal surface or cytoplasmatic immunoglobulin, most commonly IgM. In the non-immunosuppressed, the majority of the tumors are composed of large centroblasts of the B-cell lineage. Immunoblastic, Burkitt-like or large, atypical tumors in general afflict the immunosuppressed. The mitotic activity is generally high, and necrosis may occur. T-cell lymphomas are rare in the CNS [28] and likely have accounted for fewer than 40 cases in total.

The tumors are masses with poorly defined margins, reflecting their tendency to infiltrate white matter tracts including the corpus callosum and internal capsule. The infiltrating B-cells follow the walls of the ventricular system from which they likely invade the CSF spaces. Exclusively meningeal PCNSL is rare [5]. Microscopically, there is a fairly characteristic angiocentric growth pattern of cuffs of tumor cells within and around the cerebral blood vessels. These cuffs may split the fibers of the blood vessel walls. The perivascular cells invade the adjacent neuropil but as a diffuse process [60].

Molecular Pathogenesis

Several observations suggest that the vast majority of PCNSL are of germinal center (GC) origin: The

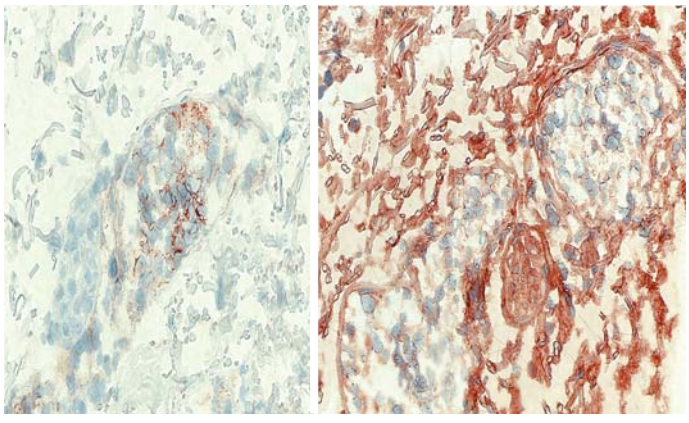


Fig. 3 CD20 and IgG staining of malignant lymphocytes within a brain arteriole as a consequence of intravascular lymphoma

majority of PCNSL exhibit bcl-6 gene overexpression and mutations in its 5'-noncoding region. These are markers of B-cell transition through the germinal center of secondary lymphatic organs [10, 22]. PCNSL further display ongoing somatic mutations. A particularly elegant description exists of clonally rearranged immunoglobulin genes with a preferential usage of the V4–34 segment of the immunoglobulin (Ig) heavy chain gene [44]. An intriguing hypothesis creates an analogy to MALT lymphomas which are related to prior *H. pylori* infection. It is possible that bacterial or viral antigens in the microenvironment of the CNS stimulate the polyclonal and then clonal expansion of B-cells. These B-cells then produce antibodies encoded by the V4–34 segment. In this regard, anecdotal examples exist relating PCNSL to EBV infection (in HIV-infected or transplant patients), patients afflicted with Lyme disease or other demyelinating events. Several molecular events central to the evolution of PCNSL have been identified, but consensus is lacking concerning their prognostic significance. These events include mutations in loci affecting proto-oncogenes (such as PIM1, c-MYC, RhoH/TTF, and PAX5) [45] and tumor suppressor genes (two-thirds of specimens of PCNSL exhibit deletions on 6q22–23, and three-quarters have reduced expression of the associated RPTRK gene) [47]. In PCNSL, chromosome 6q22–23 deletions correlate with shorter survival [47], as do lack of blc-6 overexpression [10], but there are few prognostic implications of the loss of genomic material on chromosome 6q, nor the gains on 12q, 18q, and 22q [66]. Polymorphisms in the methionine synthase (MS) gene may alter the response to therapy of PCNSL, possibly by increasing the levels of 5,10-methylene tetrahydrofolate for nucleic acid synthesis (and thus 'preserving' DNA integrity) or by reduced methylation (inactivation) of tumor suppressor genes [40]. These polymorphisms may also affect the response of individual tumors to therapy with anti-fols.

Treatment

Synopsis. The most efficient treatment of PCNSL is systemic high-dose methotrexate (MTX)-based chemotherapy alone or in combination with whole brain radiotherapy. As older patients are prone to radiation-induced cognitive and white matter changes, most investigational therapies depend on drug administration without radiation.

As PCNSL is one of the few curable malignant brain tumors, many seemingly equally efficacious therapies have been reported. Symptomatic therapy alone which results in a median survival of 2–3 months may be improved to 5 months by the provision of steroids. Rare patients experience prolonged remissions from steroid therapy, but cure is unlikely. A dramatic shrinkage of tumor volume after as little as 1 week of steroid treatment is present in 15–25% of cases [60].

Surgery. The role of surgery is limited to the provision of diagnosis by the biopsy of tumor sites in the brain, vitreous, or nerve root as well as relief of hydrocephalus.

Radiotherapy. The provision of radiotherapy has been replaced by pre-irradiation chemotherapy in most academic centers. The historical use of whole brain or craniospinal irradiation reflected publications of limited populations. Although complete disappearance of masses follows within weeks of whole brain treatment with doses of 40–50 Gy; these benefits are seldom long-lasting [49]. A prospective phase II study was performed by the Radiation Therapy Oncology Group (RTOG 83–15) in HIV-negative patients with PCNSL [48]. Forty-one patients received 40 Gy whole brain radiotherapy (WBRT) plus a focal tumor boost of 20 Gy, each dose delivered in 1.8-Gy fractions. Median survival for the whole group was 12.2 months after diagnosis and 11.6 months after initiation of radiotherapy, respectively. Patients over 60 years of age did significantly worse, with a median survival of 7.6 months after diagnosis. It is of note that 4 out of 41 patients (10%) died during administration of the therapy, and 4 others were suspected of experiencing neurotoxicities related to the treatment. These figures are likely underestimates, as subsequent reports have emphasized careful evaluation by psychometric testing and by MRI examination of leukoencephalopathy. In the RTOG trial, 28 patients developed recurrent lymphoma, of which 22 were within the 'boost' fields [48]. A careful analysis of our experience as well as that of the published literature and of the RTOG study results [49] should lead the reader to accept certain conclusions. (1) The primary provision of brain irradiation alone is insufficient to provide either durable remission or cure of PCNSL. (2) The long-term effects of whole brain irradiation include cognitive changes, alterations of white matter, as well as vascular changes (see Fig. 4) from the combination of radiation and chemotherapy. Radiation should be reserved for patients failing primary chemotherapy or those with isolated symptomatic solitary lesions of the brain or eye. Future trials will likely explore lower dose fractions of radiotherapy or radiosurgical treatments. (3) Future molecular studies will explore the basis of recurrence of PCNSL. Two hypotheses exist: PCNSL is a 'radioresistant' form of DLCL, or circulating clonal B-cells selectively reseed the nervous system.

Chemotherapy with Radiotherapy. Single-drug chemotherapy, multi-drug chemotherapy, and combination radiotherapy and chemotherapy have produced durable high rates of complete response in multicenter and unicenter trials (e.g., DeAngelis et al. 1992 [18], Schultz et al. 1996 [61], O'Brien et al. 2000 [50], Abrey et al. 2000 [2], Bessell et al. 2002 [8], Ferreri 2002 [21], DeAngelis et al. 2002 [19], Poortmans et al. 2003 [55]). Chemoradiotherapy was provided as cyclophosphamide, doxorubicin, vincristine, and dexamethasone (CHOD) followed by whole brain radiotherapy (41.4 Gy) and a tumor boost (18 Gy) in RTOG trial 88–06. Fifty-four immunocompetent patients with PCNSL achieved a median survival of 16.1 months, and 42% of patients survived 2 years [61], results not superior to those achieved with XRT alone (RTOG 83–15 cited above). The authors concluded that combination chemotherapy provided no additional benefit. Several authors [9, 57] have retrospectively analyzed studies comprising more than 200 recipients of systemic methotrexate to confirm the benefit of this single systemic drug. Benefit appears related to drug doses above 1.5 g/m^2. Systemic 'high-dose' MTX has been included in most combination chemo- and radiotherapy protocols evaluated in phase I/II trials. Virtually all trials have produced complete response rates between 50% and 75% with median durations of response in excess of 3.5 years. The trials differ in their provision of radiation therapy, their assessment of drug or radiation toxicities, the duration of treatment and underlying concerns regarding the risk of spinal fluid dissemination of tumor. DeAngelis [18] provided chemoradiotherapy (systemic MTX at 1 g/m2 for two cycles prior to WBRT [40 Gy + 15.4 Gy tumor boost] accompanied by dexamethasone and followed by high-dose systemic Ara-C). Assumptions that a majority of patients would develop CSF seeding led to the provision of five doses of intraventricular MTX and continued systemic MTX. The median survival of 44 months exceeded that of nonrandomized recipients of irradiation who were provided chemotherapy at recurrence. However, the chemoradiotherapy was associated with unacceptable treatment-induced neurotoxicity [1], which appeared as a cognitive impairment, leukoencephalopathy, and deep brain atrophy. These changes were identified in 70% of patients 2 years after therapy, especially in individuals over 60 years. Two years later, all older patients were afflicted. Modifying the treatment regimen [2] produced a median survival of 60 months. Fifty-two patients were treated, including 32 over 59 years of age. Twenty of the older patients, having achieved a complete response, refused to be irradiated. As a result, they fared less well with respect to time to recurrence than did 12 who accepted irradiation after CR. Of the 12 radiation recipients, 10 experienced dementia. Taking into account dementia-associated deaths, radiation provision did not extend survival [2]. These single-center reports have been reduplicated by the EORTC (EORTC phase II trial 20962) and the RTOG (93–10). The former accrued 52 patients and the latter 98 patients to systemic high-dose MTX and systemic and intrathecal drug combinations prior to whole brain irradiation at 45 Gy and 40 Gy, respectively. These studies achieved median survivals of 46 months [55] and 37 months [19].

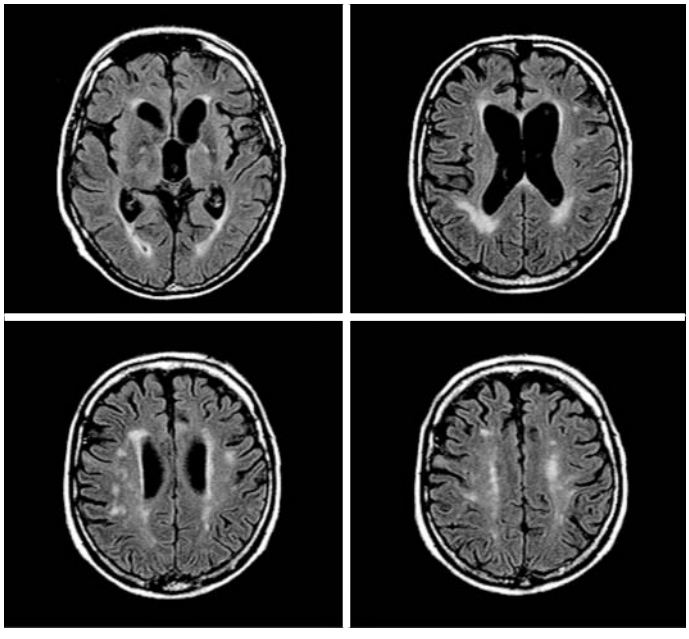


Fig. 4 MRI (FLAIR) showing white matter changes of vascular pattern, enlargement of the ventricular system and several small infarcts in a 43-year-old man 12 years after whole brain radiotherapy with 54 Gy for brain lymphoma. Cognitive disturbances and profound psychomotor slowing were present

Australian reports achieved similar survival times (33 months) using simpler regimens which excluded intraventricular drugs, steroids, and Ara-C. Two-weekly cycles of systemic MTX (1 g/m^2) preceded WBRT to a total of 50 Gy [50]. Multidrug or systemic/intraventricular drug regimens may be poorly tolerated: Bessel [8] reported five deaths in older patients who had received intensified MTX (MTX, vincristine, Ara-C, BCNU, and optional cyclophosphamide, doxorubicin, and dexamethasone). Taken in combination, these trials support the achievements of complete response rates approaching two-thirds of patients for durations of 2.5–4 years. It is uncertain whether these combined chemoradiotherapy approaches offer benefits better than those reported with chemotherapy alone or high-dose systemic MTX. Equally uncertain is the role of 'maintenance chemotherapy' provided after the establishment of a complete response.

Chemotherapy Alone. There is little support for the provision of 'consolidation' radiotherapy to PCNSL patients who respond to chemotherapy. The combination of chemotherapy and radiation therapy has not been shown to be superior to chemotherapy alone in retrospective [21, 56] nor in prospective analyses [2]. The weight of evidence points to similar rates of response and duration of response for both forms of treatment; but chemotherapy patients appear spared the long-term neurotoxicity associated with irradiation (see below). Single-center and multicenter trials have evaluated chemotherapy as a sole treatment for PCNSL. MTX, the most efficient drug in PCNSL, achieves therapeutic levels in plasma, CSF, and eye following parenteral administration. Guha-Thakurta treated 31 patients with parenteral MTX (8 g/m2 over 4 h) through 2–12 cycles until achievement of complete (CR; 65% of patients) or partial MRI response (PR; 35%). Thereafter, 'maintenance' chemotherapy (MTX 3.5 g/m^2) was provided indefinitely at 3-monthly intervals. Median response duration was 16.7 months, and median survival has not been reached at 4 years. The 12 longest responders have shown no neuropsychologic decline beyond that expected for age. These response rates could not be confirmed in a prospective multicenter German trial which provided the same single dose of MTX for fewer cycles and without 'maintenance' therapy. After enrollment of 37 patients and achievement of a CR rate of 29%, the study was closed prematurely [33]. The same protocol, lacking 'maintenance' therapy, in a single-arm multicenter trial (NABTT 96–07) achieved a CR rate of 52% and a PR rate of 22% in 23 out of 25 evaluable patients. The median survival was 22.8+ months with modest toxicity [7]. No data are available concerning the relapse rate for the initial complete responders. Similar rates of complete response (60%) have followed the intra-arterial administration of MTX after blood-brain barrier disruption with parenteral cyclophosphamide. The median survival exceeded 40 months for this complicated therapy [41]. Whether MTX treatment mandates barrier disruption remains to be proved, but the former provides extended survival without cognitive decline as measured by serial neuropsychological tests [41]. Whether multiple-drug protocols offer benefits above those of MTX alone remains uncertain. In a multidrug phase I/II trial [53] [MTX, cytarabine (Ara-C), vinca-alkaloids and alkylating agents in combination with intraventricular MTX, prednisolone, and Ara-C], 65 patients were accrued and achieved 61% CR rate and 10% PR; however, 9% treatment-related deaths were recorded. The median event-free survival was 21 months, and the median overall survival 50 months. A 48% CR rate and median survival of 14 months was achieved by the 50 patients over 59 years of age (EORTC 26952) who received multiple drugs (MTX 1 g/m2, lomustine, procarbazine, and methylprednisolone) [34].

Intrathecal Chemotherapy. There is uncertain support for prophylactic chemotherapy of the CSF in PCNSL. The true rate of CSF invasion remains uncertain. Cytostatic agents, predominantly MTX, thiotepa, and Ara-C have been given by lumbar intrathecal or ventricular (via a subgaleal reservoir) routes as part of systemic chemotherapy regimens [2, 18, 19, 53, 54]. In most of these studies, the true rate of subsequent CSF invasion by PCNSL seldom exceeded 10%. MTX (12 mg i.t. twice a week) was most commonly given [2, 18, 19]; but concentration-times-time applications provide lower daily doses to achieve sustained CSF levels [53, 54]. In general, these levels likely exceed 10 μM concentration. The subarachnoid instillation of MTX, Ara-C, steroids, or anti-CD20 antibodies (see below) provides treatment of free-floating malignant cells but does not address tumor nodules larger than 3 mm nor provides drug access to folds of tumor cells unbathed by CSF [60]. The theoretical benefits of a CSF drug are outweighed by the high risk of iatrogenic ventriculitis [53, 54], the problems of repeated access to the CSF, a 4% rate of infection, and the leukoencephalopathic effects of loculated drug within the neuraxis. In a small case-controlled retrospective study, no differences in survival, disease control, or neurotoxicity could be found between recipients and nonrecipients of intrathecal therapy [38], and Ferreri's analysis of prognostic factors for 370 PCNSL found no influence upon the outcome of intrathecal therapy [22]. Therefore, prophylactic intrathecal or intraventricular chemotherapy should be considered either investigational or of uncertain value. The use of intrathecal MTX, Ara-C, and DepoCyte should be relegated to patients with prov-

en CSF lymphoma who have failed control with systemic agents.

High-Dose Chemotherapy with Stem-Cell Transplantation. High-dose chemotherapy achieves therapeutic drug levels in the brain, CSF, and throughout the neuraxis. Phase I and II studies have been patterned upon the successful implementation of the marrow-depleting, high-dose chemotherapy regimens utilized to treat systemic lymphoma. Autologous stem cells, which are neither expanded nor sensitized in vitro, are provided to rescue the patients from drug-induced leukopenia or thrombocytopenia. Treatment has been provided to recurrent [63] or newly diagnosed PCNSL [3, 14, 37]. 'Induction therapy'to achieve a remission is provided with MTX and/or Ara-C and followed by thiotepa-based regimens [14, 37, 63] or by Ara-C, melphalan, carmustine, and etoposide [3]. For several reasons, this approach should be considered experimental: Response rates and event-free survival in newly diagnosed PCNSL are not better than with conventional therapy despite a younger median age of the study populations [3, 37]; deaths from drug toxicity or tumor progression occur in patients over 60 years old [63]; many of the drugs utilized have uncertain value in treating brain lymphoma. Thus, high-dose chemotherapy with autologous stem-cell transplantation appears an option for recurrent tumor in younger individuals. Indeed, Soussain has identified that 8 of 12 patient recipients achieved a CR after high-dose chemotherapy [63].

Other therapies. Corticosteroids have been used as single agents to inhibit the 'homing of malignant lymphocytes' to cerebral endothelial cells. Three older patients who had achieved a CR after radiotherapy experienced no relapse for more than 2 years while receiving monthly high-dose i.v. methylprednisolone [51]. It is uncertain whether this is a highly selected population or proof of 'downregulation of cell adhesion molecules in the CNS' or an apoptotic effect of steroids [51].

The monoclonal antibody CD20 identifies the vast majority of PCNSL. The humanized monoclonal anti-CD20 antibody (rituximab) has been incorporated into most treatments for systemic lymphoma and results in improved survival. The monoclonal is large and unlikely to pass the blood-brain barrier. When measured after parenteral dosing, the concentrations of rituximab in the CSF (and probably in the brain parenchyma) are <2% of corresponding serum samples [53, 54]. Despite this, anecdotal reports exist of the clearance of meningeal lymphoma after the intraventricular administration of rituximab [53, 54] and after systemic administration (Rubenstein). Radiolabelled antibody studies with rituximab or analogous Zevulon have not been provided, nor have higher doses of either drug been explored.

Special Problems – The Eye. In a retrospective analysis, ocular manifestations were identified in 22 of 170 patients with PCNSL examined by slit lamp [22]. This occurrence correlated with meningeal lymphoma, possibly with earlier relapse (ocular and brain) but not with overall survival [22]. The therapy for ocular lymphoma, either prior to or after PCNSL, has not been established: External beam irradiation of the orbits with 30 Gy is frequently followed by disappearance of the tumor but is complicated by the uniform occurrence of cataracts and uncertain control of coincident optic nerve and brain involvement by the tumor. High-dose systemic MTX and Ara-C [22] or high-dose MTX alone [15, 65] or intraocular MTX all achieve cytotoxic drug levels in the vitreous and may lead to the clearance of ocular tumor as well. Therefore, it seems justified to apply systemic MTX- and Ara-C-based chemotherapy prior to irradiation. The direct instillation of MTX (400 µg/0.1 ml up to ×12) into the vitreous has reportedly achieved a CR of 100%;complicated by cataract (73%), corneal epitheliopathy (58%), maculopathy (42%), and optic atrophy, vitreous hemorrhage [62]. The clinician should be aware that fully 60% of patients have their eye involvement as a herald of brain involvement – a figure which may support the provision of chemotherapy designed to treat both the vitreo/retinal tumor and potential neuraxis sites.

Treatment of HIV-Positive Patients and Post-Transplant Lymphoproliferation

Prior to the era of highly active antiretroviral therapy (HAART), HIV-infected patients with PCNSL usually carried a dismal prognosis [26]. A third of them died while receiving radiation for their brain lymphoma [60]. This ominous outlook has improved: First, the incidence of PCNSL has decreased dramatically with HAART (see above). AIDS patients treated concomitantly with HAART and chemotherapy for NHL are more likely to respond to chemotherapy when HAART induces a reduction of the HIV viral load [4]. In a multicenter retrospective analysis, patients with PCNSL and AIDS showed the best outcome when treated with cranial radiation and HAART (median survival 1093 days). The survival was 132 days after cranial radiation alone and 33 days without specific therapy [36]. Selected AIDS-PCNSL patients may be candidates for aggressive chemotherapy or chemoradiotherapy if: (A) their performance status is KPI >50, (B) their CD4+ cell counts are above 200/µl, (C) co-morbidities of AIDS are limited and non-neurologic [13]. For the severely ill, comfort care may be

a therapeutic option. Non-AIDS PTLD patients tend to have EBV-induced PCNSL and demonstrate elevated loads of EBV in CSF. Usually demonstrable is reactivation of latent EBV or newly acquired seroconversion. The PCNSL which emerges cannot easily be distinguished from the EBV or other infectious complications of transplant, although PCNSL may be accompanied by lymphoma invasion of the transplanted organ. Therapy is based on reduction or discontinuation of immunosuppression (most often cyclosporin, OKT3, and CelCept) in favor of low-dose steroid use with chemotherapy. Often the clinician must walk a thin line between successful control of the tumor and the avoidance of graft rejection. There are real benefits in PCNSL control of the reinfusion into peripheral blood of previously harvested T-cells. These benefits underscore the subtle T/B-cell balance that underlies PTLD. The use of antiviral agents is anecdotal.

Prognosis/Quality of Life

The therapy of PCNSL is a unique story of success during the last two decades. The progress has been made primarily due to the provision of high-dose MTX-based 'aggressive' chemotherapy regimens with or without radiotherapy: Median overall survival in unselected patients between 18 and 75 years of age ranges between 37 and 60 months in large single center and multicenter trials [2, 19, 53, 54], and it is to be assumed that a significant fraction of patients under 60 years of age will be cured of their tumor.

The issue of quality of life reflects reduction in tumor burden, avoidance of corticosteroid morbidity, and reduction of treatment-induced neurotoxicity. As a general rule, poor performance is associated with older age, multiplicity of lesions, and reduced (KPS<60) pretreatment performance status. Four years from diagnosis and treatment, all patients above the age of 60 years who received combined methotrexate (parenteral and intrathecal), Ara-C, and radiation [19] were afflicted with cognitive disturbances [1]. This dementia was identified in a subsequent study [2] but has not been seen in recipients of only MTX by vein or artery. The combination of radiation and then MTX therapy causes a rapidly progressive dementing disease often with myoclonus, reflecting a leukoencephalopathy, cortical atrophy, and ventricular enlargement. Death ensues within months or years [39]. Indeed, systematic psychometric testing of recipients of radiation therapy and chemotherapy revealed cognitive impairment in 84% [31], with concomitant self-assessed reduction of quality of life in half of the patients [16, 31]. No such deficits have been found in detailed psychometric testing of long-term survivors who were provided only chemotherapy [25, 41]. Assessed quality of life is similarly preserved in these patients [30].

Follow-up/Specific Problems and Measures

We advocate the evaluation of completely responding patients every 3 of 4 months. As with other malignant brain tumors, this frequency may be reduced, but over half of 'cured' patients will ultimately experience a late relapse. Follow-up investigations include neurological examination, MRI of the brain, CSF examination including molecular-neuropathological examination of cytospins, and ophthalmological investigation including slit lamp examination.

Therapy of Recurrent Tumor

The optimal therapy of recurrent tumor has not been established, but drug resistance is seldom documented, and most patients benefit from re-induction with chemotherapeutic agents [56, 57]. In our experience, the highest response rates are seen with provision of the previously effective chemotherapy regimen. Patients with recurrent lymphoma after chemotherapy are at least 50% likely to achieve a complete re-induction with MTX (Plotkin et al. 2004), suggesting that brain lymphoma may not recur as a function of drug resistance alone.

The benefits of other agents are unstudied, but responses are seen with temozolomide (20%), topotecan (20%), procarbazine, CCNU, and vincristine (PCV) (uncertain percentage). Some older individuals may tolerate repeated high-dose MTX infusions (e.g., 3 g/m2), and patients may continue to benefit from the provision of methylprednisolone infusions for several months.

Future Perspectives

It is to be assumed that chemotherapy protocols rather than a combination of chemotherapy and radiotherapy will be the treatment of choice for the vast majority of PCNSL patients in the near future. A number of powerful prognostic factors have been identified which will allow predictions with regard to treatment response and clinical course. Among these are molecular markers like chromosome 6q22–23 loss [47] and bcl-6 overexpression [10]; clinical factors like age, performance score, and localization of the tumor; laboratory findings including CSF protein and lactate dehydrogenase serum levels [23]; and therapeutic parameters like 'area under the curve of MTX' [24]. These factors should provide new stratifi-

cations for patients entering clinical trials as well as offer more aggressive approaches for poor prognostic groups of patients. These dose-intensive therapies may include high-dose chemotherapy with stem-cell transplant and stereotactic radiotherapy (in younger patients).

References

1. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998; 16:859–63
2. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol 2000; 18:3144–50
3. Abrey LE, Moskowitz CH, Mason WP, Crump M, Stewart D, Forsyth P, Paleologos N, Correa DD, Anderson ND, Caron D, Zelenetz A, Nimer SD, DeAngelis LM. Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. J Clin Oncol 2003; 21:4151–6
4. Antinori A, Cingolani A, Alba L, Ammassari A, Serraino D, Ciancio BC, Palmieri F, De Luca A, Larocca LM, Ruco L, Ippolito G, Cauda R. Better response to chemotherapy and prolonged survival in AIDS-related lymphomas responding to highly active antiretroviral therapy. AIDS 2001; 15:1483–91
5. Balmaceda C, Gaynor JJ, Sun M, Gluck JT, DeAngelis LM. Leptomeningeal tumor in primary central nervous system lymphoma: recognition, significance, and implications. Ann Neurol 1995; 38:202–9
6. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, Guy G, Lapierre F. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000; 92:261–6
7. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, Hochberg F, Priet R. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96–07. J Clin Oncol 2003; 21:1044–9
8. Bessell EM, Lopez-Guillermo A, Villa S, Verger E, Nomdedeu B, Petit J, Byrne P, Montserrat E, Graus F. Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: an analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. J Clin Oncol 2002; 20:231–6
9. Blay JY, Conroy T, Chevreau C, Thyss A, Quesnel N, Eghbali H, Bouabdallah R, Coiffier B, Wagner JP, Le Mevel A, Dramais-Marcel D, Baumelou E, Chauvin F, Biron P. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 1998; 16:864–71
10. Braaten KM, Betensky RA, de Leval L, Okada Y, Hochberg FH, Louis DN, Harris NL, Batchelor TT. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. Clin Cancer Res 2003; 9:1063–9
11. Buhring U, Herrlinger U, Krings T, Thiex R, Weller M, Kuker W. MRI features of primary central nervous system lymphomas at presentation. Neurology 2001; 57:393–6
12. CBTRUS. Statistical report: Primary brain tumors in the United States, 1992–1997, Chicago II; Central Brain Tumor Registry of the United States, 2000
13. Chamberlain MC, Kormanik PA. AIDS-related central nervous system lymphomas. J Neurooncol 1999; 43:269–76
14. Cheng T, Forsyth P, Chaudhry A, Morris D, Gluck S, Russell JA, Stewart DA. High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma. Bone Marrow Transplant 2003; 31:679–85
15. Ciordia R, Henson J, Batchelor T. Intra-ocular concentrations of methotrexate after high dose intravenous methotrexate therapy in patients with primary central nervous system lymphoma. Society of Neuro-Oncology, 1999; Scottsdale, Arizona
16. Correa DD, DeAngelis LM, Shi W, Thaler H, Glass A, Abrey LE. Cognitive functions in survivors of primary central nervous system lymphoma. Neurology 2004; 62:548–55
17. Coulon A, Lafitte F, Hoang-Xuan K, Martin-Duverneuil N, Mokhtari K, Blustajn J, Chiras J. Radiographic findings in 37 cases of primary CNS lymphoma in immunocompetent patients. Eur Radiol 2002; 12:329–40
18. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. J Clin Oncol 1992; 10:635–43
19. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ, Radiation Therapy Oncology Group Study 93–10. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93–10. J Clin Oncol 2002; 20:4643–8
20. Ferreri AJ, Blay JY, Reni M, Pasini F, Gubkin A, Tirelli U, Calderoni A, Zucca E, Cortelazzo S, Chassagne C, Tinguel M, Borisch B, Berger F, Ponzoni M, Cavalli F; International Extranodal Lymphoma Study Group (IELSG). Relevance of intraocular involvement in the management of primary central nervous system lymphomas. Ann Oncol 2002a; 13:531–8
21. Ferreri AJ, Reni M, Pasini F, Calderoni A, Tirelli U, Pivnik A, Aondio GM, Ferrarese F, Gomez H, Ponzoni M, Borisch B, Berger F, Chassagne C, Iuzzolino P, Carbone A, Weis J, Pedrinis E, Motta T, Jouvet A, Barbui T, Cavalli F, Blay JY. A multicenter study of treatment of primary CNS lymphoma. Neurology 2002b; 58:1513–20
22. Ferreri AJ, Abrey LE, Blay JY, Borisch B, Hochman J, Neuwelt EA, Yahalom J, Zucca E, Cavalli F, Armitage J, Batchelor T. Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, June 12 to 15, 2002. J Clin Oncol 2003a; 21:2407–14
23. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, Calderoni A, Rossi A, Vavassori V, Conconi A, Devizzi L, Berger F, Ponzoni M, Borisch B, Tinguely M, Cerati M, Milani M, Orvieto E, Sanchez J, Chevreau C, Dell'Oro S, Zucca E, Cavalli F. Prognostic scoring system for primary

CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol 2003b; 21:266–72

24. Ferreri AJ, Guerra E, Regazzi M, Pasini F, Ambrosetti A, Pivnik A, Gubkin A, Calderoni A, Spina M, Brandes A, Ferrarese F, Rognone A, Govi S, Dell'Oro S, Locatelli M, Villa E, Reni M. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. Br J Cancer 2004; 90:353–8
25. Fliessbach K, Urbach H, Helmstaedter C, Pels H, Glasmacher A, Kraus JA, Klockgether T, Schmidt-Wolf I, Schlegel U. Cognitive performance and magnetic resonance imaging findings after high-dose systemic and intraventricular chemotherapy for primary central nervous system lymphoma. Arch Neurol 2003; 60:563–8
26. Forsyth PA, DeAngelis LM. Biology and management of AIDS-associated primary CNS lymphomas. Hematol Oncol Clin North Am 1996; 10:1125–34
27. Gaidano G, Pasqualucci L, Capello D, Berra E, Deambrogi C, Rossi D, et al. Aberrant somatic hypermutation in multiple subtypes of AIDS-associated non-Hodgkin lymphoma. Blood 2003; 102:1833–1841
28. Gijtenbeek JM, Rosenblum MK, DeAngelis LM. Primary central nervous system T-cell lymphoma. Neurology 2001; 57:716–8
29. Gleissner B, Siehl J, Korfel A, Reinhardt R, Thiel E. CSF evaluation in primary CNS lymphoma patients by PCR of the CDR III IgH genes. Neurology 2002; 58:390–6
30. Guha-Thakurta N, Damek D, Pollack C, Hochberg FH. Intravenous methotrexate as initial treatment for primary central nervous system lymphoma: response to therapy and quality of life of patients. J Neurooncol 1999; 43:259–68
31. Harder H, Holtel H, Bromberg JEC, Poortmans P, Haaxmareiche H, Kluin-Nelemans, Menten J, van den bent MJ. Cognitive status and quality of life after treatment for primary CNS lymphoma. Neurology 2004; 62:544–47
32. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting–Airlie House, Virginia, November, 1997. Hematol J 2000; 1:53–66
33. Herrlinger U, Schabet M, Brugger W, Kortmann RD, Kuker W, Deckert M, Engel C, Schmeck-Lindenau HJ, Mergenthaler HG, Krauseneck P, Benohr C, Meisner C, Wiestler OD, Dichgans J, Kanz L, Bamberg M, Weller M. German Cancer Society Neuro-Oncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. Ann Neurol 2002; 51:247–52
34. Hoang-Xuan K, Taillandier L, Chinot O, Soubeyran P, Bogdhan U, Hildebrand J, Frenay M, De Beule N, Delattre JY, Baron B; European Organization for Research and Treatment of Cancer Brain Tumor Group. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. J Clin Oncol 2003; 21:2726–31
35. Hochberg FH, Miller DC. Primary central nervous system lymphoma. J Neurosurg 1988; 68: 835–853
36. Hoffmann C, Tabrizian S, Wolf E, Eggers C, Stoehr A, Plettenberg A, Buhk T, Stellbrink HJ, Horst HA, Jager H, Rosenkranz T. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. AIDS 2001; 15:2119–27
37. Illerhaus G, Marks R, Derigs G, Frichhofen N, Guttenberger R, Kubin T, Ostertag BC, Finke J. Primary CNS Lymphoma: Results of a Multicenter Phase II Study Including High-Dose-Chemotherapy with Autologous PBSCT and Hyperfractionated Radiotherapy as First-Line-Therapy. Blood 2003; 102:abstract#1450
38. Khan RB, Shi W, Thaler HT, DeAngelis LM, Abrey LE. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? J Neurooncol 2002; 58(2):175–8
39. Lai R, Abrey LE, Rosenblum MK, DeAngelis LM. Treatment-induced leukoencephalopathy in primary CNS lymphoma: a clinical and autopsy study. Neurology 2004; 62:451–6
40. Linnebank M, Schmidt S, Kolsch H, Linnebank A, Heun R, Schmidt-Wolf IG, Glasmacher A, Fliessbach K, Klockgether T, Schlegel U, Pels H. The methionine synthase polymorphism D919G alters susceptibility to primary central nervous system lymphoma. Br J Cancer 2004; 90:1969–71
41. McAllister LD, Doolittle ND, Guastadisegni PE, Kraemer DF, Lacy CA, Crossen JR, Neuwelt EA. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery 2000; 46:51–60
42. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma. The Massachusetts General Hospital experience 1958–1989. Cancer 1994; 74:1383–1397
43. Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, Chiesi A, Phillips AN, Kirk O, Lundgren JD. AIDS across Europe, 1994–98: the EuroSIDA study. Lancet 2000; 356:291–6
44. Montesinos-Rongen M, Kuppers R, Schluter D, Spieker T, Van Roost D, Schaller C, Reifenberger G, Wiestler OD, Deckert-Schluter M. Primary central nervous system lymphomas are derived from germinal-center B cells and show a preferential usage of the V4–34 gene segment. Am J Pathol 1999; 155:2077–86
45. Montesinos-Rongen M, Van Roost D, Schaller C, Wiestler OD, Deckert M. Primary diffuse large B-cell lymphomas of the central nervous system are targeted by aberrant somatic hypermutation. Blood 2004; 103:1869–75
46. Morgello S. Pathogenesis and classification of primary central nervous system lymphoma: an update. Brain Pathol 1995; 5:383–93
47. Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, Ishida E, Konishi N. Novel tumor suppressor loci on 6q22–23 in primary central nervous system lymphomas. Cancer Res 2003; 63:737–41

48. Nelson DF, Martz KL, Bonner H, Nelson JS, Newall J, Kerman HD, Thomson JW, Murray KJ. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992; 23:9–17
49. Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neurooncol 1999; 43:241–7
50. O'Brien P, Roos D, Pratt G, Liew K, Barton M, Poulsen M, Olver I, Trotter G. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. J Clin Oncol 2000; 18:519–26
51. O'Neill BP, Habermann TM, Witzig TE, Rodriguez M. Prevention of recurrence and prolonged survival in primary central nervous system lymphoma (PCNSL) patients treated with adjuvant high-dose methylprednisolone. Med Oncol 1999; 16:211–5
52. Pasqualucci L, Neumeister P, Goossens T, Nanjangud G, Chaganti RS, Kuppers R, et al. Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. Nature 2001; 412:341–346
53. Pels H, Schmidt-Wolf IG, Glasmacher A, Schulz H, Engert A, Diehl V, Zellner A, Schackert G, Reichmann H, Kroschinsky F, Vogt-Schaden M, Egerer G, Bode U, Schaller C, Deckert M, Fimmers R, Helmstaedter C, Atasoy A, Klockgether T, Schlegel U. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003; 21:4489–95
54. Pels H, Schulz H, Schlegel U, Engert A. Treatment of CNS lymphoma with the anti-CD20 antibody rituximab: experience with two cases and review of the literature. Onkologie 2003; 26:351–4
55. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, Van't Veer M, Hansen M, Soubeyran P, Taphoorn M, Thomas J, Van den Bent M, Fickers M, Van Imhoff G, Rozewicz C, Teodorovic I, van Glabbeke M, European Organization for Research and Treatment of Cancer Lymphoma Group. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial20962. J Clin Oncol 2003; 21:4483–8
56. Reni M, Ferreri AJ. Therapeutic management of refractory or relapsed primary central nervous system lymphomas. Ann Hematol 2001; 80 Suppl 3:B113–7
57. Reni M, Ferreri AJ, Guha-Thakurta N, Blay JY, Dell'Oro S, Biron P, Hochberg FH. Clinical relevance of consolidation radiotherapy and other main therapeutic issues in primary central nervous system lymphomas treated with upfront high-dose methotrexate. Int J Radiat Oncol Biol Phys 2001; 51:419–25
58. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, Becker JT, Cohen B, McArthur JC, Multicenter AIDS Cohort Study. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998. Neurology 2001; 56:257–60
59. Schlegel U, Pels H, Oehring R, Blumcke I. Neurologic sequelae of treatment of primary CNS lymphomas. J Neurooncol 1999; 43:277–86
60. Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma: clinical presentation, pathological classification, molecular pathogenesis and treatment. J Neurol Sci 2000; 181:1–12
61. Schultz C, Scott C, Sherman W, Donahue B, Fields J, Murray K, Fisher B, Abrams R, Meis-Kindblom J. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88–06. J Clin Oncol 1996; 14:556–64
62. Smith JR, Rosenbaum JT, Wilson DJ, Doolittle ND, Siegal T, Neuwelt EA, Pe'er J. Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology 2002; 109:1709–16
63. Soussain C, Suzan F, Hoang-Xuan K, Cassoux N, Levy V, Azar N, Belanger C, Achour E, Ribrag V, Gerber S, Delattre JY, Leblond V. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol 2001; 19:742–9
64. Thompsett AR, Ellison DW, Stevenson FK, Zhu D. V(H) gene sequences from primary central nervous system lymphomas indicate derivation from highly mutated germinal center B cells with ongoing mutational activity. Blood 1999; 94:1738–1746
65. Valenzuela RF and Hochberg FH. Methotrexate In: Spencer, Schaumberg, eds. Experimental and Clinical Neurotoxicology Second Edition. Oxford Press, 2000
66. Weber T, Weber RG, Kaulich K, Actor B, Meyer-Puttlitz B, Lampel S, Buschges R, Weigel R, Deckert-Schluter M, Schmiedek P, Reifenberger G, Lichter P. Characteristic chromosomal imbalances in primary central nervous system lymphomas of the diffuse large B-cell type. Brain Pathol 2000; 10:73–84

Brain Metastasis 19

Zeena Dorai, Raymond Sawaya, W. K. Alfred Yung

Introduction – 304

Frequency – 304

Incidence – 304

Method of Propagation and Distribution – 306

Clinical Presentation – 306

Radiographic Assessment – 307

Histological Assessment – 308

Prognostic Factors – 309

Specific Treatment Modalities – 309
Corticosteroids
Whole-Brain Radiation Therapy
WBRT with Surgery
Radiosensitization
Stereotactic Radiosurgery
Complications
Surgery
Treatment Goals
Clinical Decision-Making
Surgical Techniques
Technological Adjuncts to Surgery
Chemotherapy

Conclusion – 317

References – 317

Introduction

Brain metastases are the most common intracranial tumors, and their incidence is rising. By definition, these tumors originate from tissues outside the central nervous system and spread secondarily to the brain. This chapter looks at the epidemiology of these tumors, with a focus on new developments in surgical, medical, and radiation treatment.

Frequency

The exact incidence and prevalence of brain metastases are unknown. Brain metastases occur in 20–40% of all cancer patients [8, 23, 130, 172] and outnumber primary brain neoplasms by at least 10 to 1 [131, 172, 174]. Although the exact incidence is unknown, it has been estimated that 98,000 to 170,000 patients are newly diagnosed with metastatic brain tumors in the USA each year [120] (Table 1). The incidence may be increasing for several reasons, including prolonged survival of patients due to improved adjuvant therapy and improved radiological capabilities in detecting smaller tumors, as well as the use of routine staging tests that assess the central nervous system [55, 73, 92, 120]. Additionally, the increase also parallels the increase in the incidence of lung cancer and melanoma and an aging patient population.

Epidemiological studies are limited, however, and tend to underestimate the true incidence and prevalence of the disease in the population for several reasons. Brain metastases in many patients remain undiagnosed and are only discovered at autopsy (Table 2). Death certificates may fail to report co-existing brain lesions, especially if a patient has asymptomatic disease. Moreover, some studies report only parenchymal lesions, whereas others include those in the dura, leptomeninges, and other sites [132].

Incidence

The incidence of cancers that metastasize to the brain varies significantly from one type of cancer to the next. Table 2 shows that the majority of brain metastases originate from lung, breast, renal, and colon cancers and melanoma.

The histological type of primary tumor is strongly associated with the frequency and pattern of intracranial dissemination [71, 72, 84, 120]. The propensity of primary tumors to spread to the brain parenchyma differs. In general, it is known to be high in melanoma (20–45% of patients), small-cell lung cancer, choriocarcinoma, and other germ-cell tumors; intermediate in breast cancer, non-small-cell lung cancers (being more frequent in adenocarcinomas than in squamous cell tumors), and renal cancer; low

Table 1. Estimated number of patients developing brain metastases each year in the USA (reproduced from [184], with permission from Elsevier)

Primary site	Number of deaths[a]	Frequency of brain metastases (%)	Number of patients with brain metastases
Lung	160,100	32[b]	51,232
Breast	43,900	21[b]	9,219
Skin	7,300	48[b]	3,504
Colon	47,700	6[b]	2,862
Kidney	11,600	11[b]	1,276
Liver and pancreas	41,900	5	2,095
Prostate	39,200	6	2,352
Leukemia	21,600	8	1,728
Sarcoma	5,700	15	855
Female genital	27,100	2	542
Lymphoma	26,300	5	1,315
Thyroid	1,200	17	204
Others	131,200	19	24,928
Total	564,800	19	107,312

[a] Data from [84]

[b] Values estimated from Table 2, remaining frequencies estimated from data in [162].

in cancers of the prostate, gastrointestinal tract, ovary, and thyroid, and in sarcomas [154].

The most common cancer metastasizing to the brain is lung cancer, accounting for 30–60% of all brain metastases [12, 13, 26, 85, 87, 95, 100, 158, 162, 183]. The histological nature of the tumor is important in determining the frequency of metastases because small-cell lung cancer and adenocarcinomas are almost twice as likely to metastasize to the brain as squamous cell cancer [36, 145, 162].

The second most common cancer metastasizing to the brain is breast cancer, with 10–30% of all brain metastases among women originating from this tissue [12, 13, 85, 100, 164, 171, 183].

Melanoma ranks third in its tendency to metastasize to the brain. Some 5–21% of patients with brain

Table 2. Autopsy data on frequency of brain metastases in patients dying of cancer (reproduced from [184], with permission from Elsevier)

Investigators (reference)	Year	Histology of primary cancer	Number of autopsies	Percentage with brain metastases
Galluzzi & Payne [49]	1956	Lung	647	26
Newman & Hansen [111]	1974	Lung	247	23
Takakura et al. [162]	1982	Lung	747	36
Sorensen et al. [155]	1988	Adeno	87	44
Burgess et al. [21]	1979	SCLC	177	40
Hirsch et al. [66]	1982	SCLC	87	50
Cox & Komaki [36]	1986	Squamous Adeno SCLC Large	123 129 82 54	13 54 45 52
All lung cancer			2380	33
Takakura et al. [162]	1982	Breast	526	21
Tsukada et al. [164]	1983	Breast	1044	18
Lee [89][a]	1983	Breast	3846	22
All breast cancer			5416	21
Takakura et al. [162]	1982	Melanoma	49	49
Amer et al. [5]	1978	Melanoma	53	68
de la Monte et al. [38]	1983	Melanoma	56	64
Lee [88][a]	1980	Melanoma	553	46
All melanoma			711	48
Takakura et al. [162]	1982	GI	773	6
Saitoh et al. [139]	1982	Renal	1828	10
Takakura et al. [162]	1982	Renal	199	17
All renal cancer			2027	11

[a] Literature review.
Adeno, lung adenocarcinoma; SCLC, small-cell lung carcinoma; Squamous, squamous cell lung carcinoma; Large, large-cell lung carcinoma; GI, gastrointestinal.

metastases will have melanoma as a primary tumor [6, 29, 125].

In 10–15% of brain metastases, a primary cancer is not discovered [154]. In the majority of these instances, the patients suffer from lung cancer [76, 166].

Method of Propagation and Distribution

For a tumor cell to form a clinically significant brain metastasis, it must go through a number of steps, referred to as the metastatic cascade [146]. These steps include: (1) The cell divides and grows within the primary tumor. (2) It invades local tissue. (3) The cell enters the bloodstream or lymphatic channels. (4) It must survive transit until it ultimately arrests in the microvasculature of the secondary site. (5.). The cell must invade the target tissue. (6) The cancer cell proliferates at the metastatic site [75].

Most tumors spread to the brain by hematogenous dissemination. Tumor cells travel through the arterial circulation and usually seed themselves at the gray and white matter junction [35, 41, 68]. It is postulated that this occurs because the arteries themselves narrow and thereby act as a trap for the tumor cells. There is a greater tendency for brain metastases to occur at the watershed areas of the arterial circulation. Consequently, when one looks at the overall cerebral distribution of brain metastases, their numbers vary directly with the amount of arterial blood supplied to each area. This phenomenon explains the relative distribution of lesions, as 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem [41, 130]. A higher incidence of cerebral metastases occurs in the watershed areas of arterial territories, with the border zone of the middle and posterior cerebral arteries being more involved than the anterior border zone, between the anterior and middle cerebral arteries [41]. Two-thirds to three-fourths of patients with brain metastases harbor multiple lesions. Further evidence suggests that the actual percentage of multiple metastases is 80–90% [142, 160] (Table 3).

A second postulated mechanism of dissemination involves cancers spreading by direct extension into the adjacent meninges or base of the skull [116]. This is more common in cancers which have a propensity to spread to the bone, such as breast and prostate cancer.

Finally, there is a relatively high incidence of posterior fossa metastasis from retroperitoneal tumors such as those arising in the gastrointestinal tract, bladder, kidney, and uterus. These tumors theoretically spread via Batson's plexus [41, 67, 128, 163].

Clinical Presentation

In a minority of cases, brain metastases may be detected at the same time that the primary is diagnosed, which is known as synchronous presentation. Metachronous presentation accounts for over 80% of the cases where the brain metastases develop after the primary is diagnosed. The etiology of symptoms lies with elevated intracranial pressure, focal destruction of brain matter secondary to the mass itself, or the surrounding edema [120].

The tumor mass and surrounding edema can directly increase intracranial pressure, but it can also

Table 3. Studies on tumor multiplicity (reproduced from [184], with permission from Elsevier)

Authors (reference)[a]	Tumor histology	Percentage with multiple lesions	Number of patients evaluated
Ask-Upmark 1956 [9]	Mixed	65	696
Chason et al. 1963 [29]	Mixed	86	137
Graf et al. 1988 [56]	Mixed	58	230
Delattre et al. 1988 [41][b]	Lung	54	140
Galluzzi & Payne 1956 [49]	Lung	64	166
Tsukada et al. 1983 [164]	Breast	58	193
Patel et al. 1978 [123]	Melanoma	75	106
Madajewicz et al. 1984 [96]	Melanoma	73	64
Cascino et al. 1983 [25][b]	Colon	50	40
Decker et al. 1984 [40]	Renal	21	34

[a] Autopsy study unless otherwise indicated.
[b] Nonautopsy studies.

occur as a result of hydrocephalus that results from compression of the ventricular system or leptomeningeal disease. Papilledema is present in 25% of patients at presentation [86].

More than two-thirds of the patients with brain metastases have some neurological symptoms during the course of their illness [23, 66, 129] (Table 4). Headache is a common presenting symptom and is more common with multiple metastases or with posterior fossa lesions. It occurs in up to 50% of patients with brain metastases [42, 51]. Head pain is often dull and bifrontal in location. The character of these headaches, therefore, is not specific enough to distinguish brain metastases from other causes of headaches. Focal weakness is the second most common presenting symptom. Focal or generalized seizures occur in approximately 10% of patients at presentation and are more common in patients with multiple metastases. These tumors are typically located in the cerebral hemispheres and are often situated near or involve the cerebral cortex. Other clinical manifestations of the disease are highly dependent on the location of the brain lesions, resulting in symptoms such as visual field deficits, aphasia, and ataxia. The clinical picture may resemble a toxic or metabolic encephalopathy when tumors are present bilaterally and produce bilateral hemispheric dysfunction [86].

Patients tend to have a subacute progressive syndrome, but more indolent tumors can follow a chronic progressive course. Only occasionally do we see patients who present with sudden severe neurological signs or symptoms. These cases usually result from hemorrhage into the lesions, nonconvulsive status, and stroke syndromes caused by tumor emboli, endocarditis, or inherent coagulopathies [78, 129].

Radiographic Assessment

There are no pathognomonic features on CT or MR images that distinguish brain metastases from other disease processes. If one were to generalize, however, metastatic lesions often occur at peripheral locations, have a spherical shape, show ring enhancement (after gadolinium contrast administration), are surrounded by significant edema, and are usually multiple in location. Figure 1 shows an MR image from a patient with a solitary metastasis from renal carcinoma. Although the lesion is small, it is surrounded by an extensive zone of edema.

Due to the sensitivity of MRI, tumors are discovered sooner than in the past, which also may explain the apparently increasing incidence of these tumors. MRI with contrast administration has been shown to be the best diagnostic test for brain metastases [37, 61, 160]. Although highly sensitive, the false-positive rate for using MRI for the diagnosis of single brain metastases is approximately 11% [122], with half the

Table 4. Study of symptoms in patients with brain metastasis (reproduced from [184], with permission from Elsevier)

	Authors & year/number of patients (reference)					
Symptom	Paillas & Pellet 1975/178 [119] %	Hildebrand 1973/50 [65] %	Posner 1974/162 [128] %	Gamache et al. 1982/94 [50] %	Takakura et al. 1982/204 [162] %	Nisce et al. 1971/560 [112] %
Headache	44	26	53	43	57	33
Focal weakness	18	30	40	34	39	75
Mental and behavioral disturbances	22	30	31	34	22	41
Seizure	19	6	15	21	19	18
Ataxia	NS	NS	20	NS	5	NS
Aphasia	1	4	10	NS	10	14
Visual field defect	1	6	NS	13	21	15
Sensory change	10	2	NS	NS	NS	28

NS, not stated.

lesions being primary brain tumors and the other half infections. T2-weighted images on MR images are helpful in demonstrating the extent of surrounding vasogenic edema, even though this finding by itself is not pathognomonic of brain metastases [181].

Consequently, one must consider the differential diagnosis for brain metastasis to include primary brain tumors, infarctions, cerebral abscesses, hemorrhages, and demyelinating diseases. Thus, in many cases, a brain biopsy is necessary for diagnosis.

Histological Assessment

Grossly, metastatic lesions are typically discrete, spherical masses that displace rather than invade the surrounding brain parenchyma. The tumors can vary in size from a few millimeters to several centimeters in greatest diameter and often have areas of cystic or necrotic degeneration within them. Figure 2 shows a cystic brain metastasis from breast cancer in a 34-year-old woman who underwent surgical resection of the lesion. Areas of hemorrhage are also not uncommon, especially in metastatic lesions of melanoma, choriocarcinoma, and renal cell carcinoma [91, 98, 122, 140]. The most common hemorrhagic lesions, however, are metastases from bronchogenic cancer because it is a much more common neoplasm [140]. Figure 3 shows an example of an hemorrhagic metastasis from melanoma in a 58-year-old man.

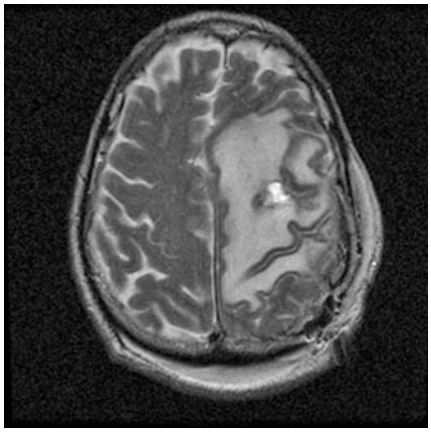


Fig. 1. A T2-weighted MR image of a solitary renal carcinoma metastasis to the brain surrounded by extensive edema

The definitive diagnosis of a brain metastasis is established by histological assessment and characteristic staining techniques. Gross microscopic examination of a metastatic tumor reveals solid, well-demarcated clusters of tumor cells [41, 67, 128, 163]. Although in most cases the histological diagnosis is straightforward, these tumors can mimic gliomas on gross inspection. Therefore, staining techniques, in some cases, are extremely valuable in differentiating metastatic lesions from gliomas. Mucin and keratin staining are often positive markers for metastatic lesions, whereas glial fibrillary protein (GFAP) staining is positive for gliomas [77, 161].

Primary tumor histology must weigh into the decision, especially in terms of tumor sensitivity to radiation and chemotherapy. For example, some tumors are highly radio- and chemosensitive, including metastases from small-cell lung cancer, lymphoma, and germ-cell tumors. On the other hand, cancers like melanoma, renal cell carcinoma, and sarcoma are relatively radioresistant, and stronger consideration should be given to surgical resection of these lesions. Tumors that are intermediately sensitive include some of the most common brain metastases, including those from non-small-cell lung cancer and breast cancer, and the treatment decision should be based on a multidisciplinary approach.

The brain parenchyma surrounding metastatic lesions is usually altered. Reactive astrocytosis is typical in the surrounding white matter, and vascular proliferation can also be present. This is believed to

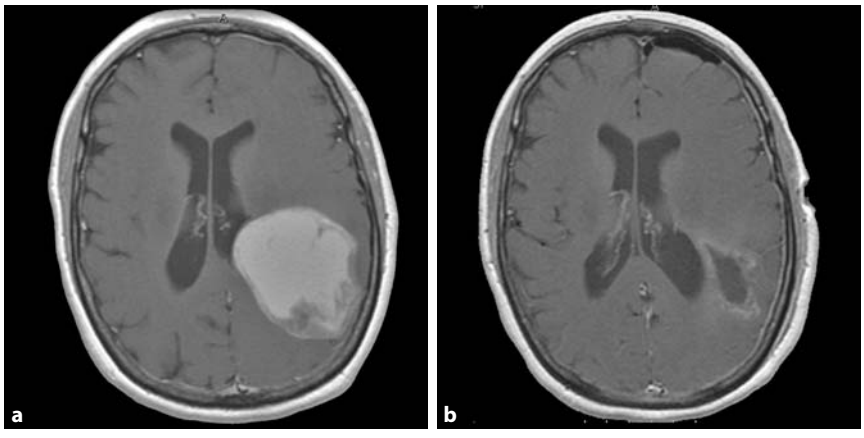


Fig. 2. **a** A T1-weighted gadolinium contrast-enhanced MR image of a solitary cystic parietal metastatic breast tumor in a 34-year-old woman. **b** Postoperative T1-weighted gadolinium contrast-enhanced MR image of the same lesion showing gross total resection of the tumor

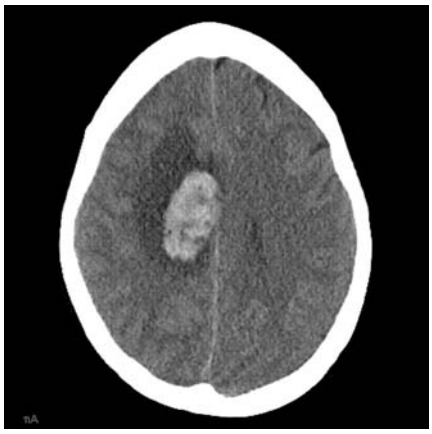


Fig. 3. CT of a posterior frontal hemorrhagic melanoma metastasis in a 58-year-old man

be the main reason for the extent of vasogenic edema surrounding brain metastases. Frequently, areas of necrosis are also surrounded by macrophagic infiltration.

Prognostic Factors

With advances in the medical and surgical treatment of metastatic brain tumors, it is sometimes difficult to predict the life expectancy of patients with the disease. Several studies have attempted to identify those who are likely to have a favorable prognosis. The following factors have been determined to be prognostically favorable in patients with brain metastases: a high Karnofsky Performance Scale (KPS) score, a solitary brain metastasis, an absence of systemic metastases, a controlled primary tumor, and a younger age (<60–65 years) [42, 69, 83, 115]. The RTOG (Radiation Therapy Oncology Group) has an extensive database from which Gaspar et al. [51] performed a recursive-partitioning analysis (RPA) on 1200 patients with brain metastases. Based on univariate analysis, the KPS score was the most important prognostic factor and became the first node of a prognostic tree. Among patients with a KPS of 70 or greater, the status of the primary tumor was the second most important prognostic factor. Age was the third factor and systemic metastases, the fourth.

Specific Treatment Modalities

Corticosteroids

The first published study on the use of corticosteroids for palliative treatment in patients with brain metastases was by Kofman in 1957 [79]. Since then, there have been numerous reports citing the benefit of steroids in the short-term treatment of patients with these tumors [144, 169]. Significantly though, as their benefit is mainly demonstrated in the reduction of symptoms, treatment should be reserved for patients with symptomatic brain lesions. Up to 75% of patients with symptomatic brain metastases show marked clinical improvement within 24–48 h after dexamethasone administration [23].

We prefer using dexamethasone because of its minimal mineralocorticoid effect and relatively lower rates of psychosis. The schedule and tapering regimen for steroids vary among institutions and have been the subject of recent studies. One such study compared dexamethasone at a dose of 4 mg per day in contrast to the previous standard dose of 4 mg four times a day. The dose of 4 mg per day provided the same palliative benefits as higher doses, allowing for fewer complications [78].

Due to the long-term side-effects of steroids, it is important to use corticosteroids as an adjuvant treatment alone and for their short-term benefits. Maintenance of long-term high-dose steroids can result in hypertension, hyperglycemia, gastrointestinal bleeding, drug psychosis, and peripheral myopathies and must therefore be avoided [78]. Once the patient's symptoms are stable and the patient is undergoing treatment, we advise steroid administration to be tapered off. This can usually be safely accomplished in a few weeks, although 25% of patients require long-term treatment to maintain neurological function [154].

Whole-Brain Radiation Therapy

The treatment of brain metastases with whole-brain radiation therapy (WBRT) and corticosteroids has been the standard of treatment for patients with brain metastases for decades. Its use was first reported by Chao in 1954 [28]. Numerous reports since then have studied its role in the palliation of patients harboring multiple metastatic lesions.

In many centers, WBRT is still used as the primary treatment for patients with multiple metastatic lesions. It is still widely regarded as the treatment of choice for patients with single brain metastases not amenable to surgical resection or radiosurgery (Table 5).

With WBRT, a balance must be reached in terms of providing treatment relatively quickly but with the least morbidity. The RTOG has studied one of the largest patient populations undergoing this treatment for brain metastases and has shown that different fractionation schedules, ranging from 10 Gy in one fraction to 40 Gy in 20 fractions, yield comparable results [18, 52, 154]. They further demonstrated

that caution should be used when applying very high single fractions as they are more likely to produce severe neurological deficits, and their clinical response rate is reduced.

In an attempt to treat patients efficiently, more centers are moving toward shorter courses of radiation treatment (7–15 days of WBRT, with relatively high doses per fraction [150–400 cGy per day]) and total doses in the range of 3000–5000 cGy. In this manner, patients receive sufficient radiation in a shorter duration of time, expediting their return home. Unfortunately, there is no consensus on the optimum radiation dose and schedule.

Table 5 shows that the expected survival time of patients treated with WBRT alone is 3–6 months. Obviously, the extent of survival depends on several factors including age, KPS score, radiosensitivity of the tumor, and extent of systemic disease.

Ultimately, despite aggressive treatment with WBRT, large retrospective studies have shown that the majority of patients still die of progressive systemic cancer and do not succumb to neurological disease [14, 23, 130].

WBRT with Surgery

Consideration of the complications of WBRT has led many to abandon its use after surgical resection of metastatic lesions. This remains controversial, however, and many studies have focused on this.

Two papers, in particular, have performed randomized, prospective trials on patients with single brain metastases comparing WBRT alone with surgical resection followed by radiation therapy and have shown that surgical resection combined with postoperative WBRT is superior to treatment with WBRT alone. In a 1990 report, Patchell et al. [122] concluded that surgical resection combined with postoperative WBRT was more effective than treatment with radiotherapy alone (Table 6).

In a prospective, randomized, follow-up study by the same group [121], 95 patients with completely resected single brain metastases were assigned randomly to adjuvant WBRT treatment or observation. All patients underwent postoperative imaging to demonstrate complete surgical resection and the presence of no other metastases. WBRT reduced the

Table 5. Results of radiation therapy in patients with brain metastases (updated from [184], with permission from Elsevier)

Investigators (reference)	No. of patients	Tumor histology	Median survival time	1-year survival (%)
Nisce et al. 1971 [112]	560[a]	Mixed	6 months	16
Hendrickson 1975 [62]	993	Mixed	18 weeks	NS
Hendrickson 1977 [63]	1001	Mixed	15 weeks	15
Borgelt et al. 1980 [18]	1812	Mixed	15–18 weeks	NS
Komarnicky et al. 1991 [80]	779	Mixed	3.9 months	15
Broadbent et al. 2004 [19]	459[a]	Mixed	4.1 months	15
Andrews et al. 2004 [7]	167	Mixed	6.5 months	NS
Fleckenstein et al. 2004 [46]	268	Mixed	3.8 months	19
Yuile & Tran 2002 [182]	378[a]	Mixed	3 months	12
Lutterbach et al. 2002 [94]	916	Mixed	3.5 months	NS
Montana et al. 1972 [106]	62	Lung	3 months	10
Guerrieri, et al. 2004 [58]	21	NSCLC	4.4 months	20
DiStefano et al. 1979 [43]	87	Breast	4 months	NS
Mahmoud-Ahmed et al. 2002 [97]	116	Breast	4.2 months	17
Choi et al. 1985 [31]	194[a]	Melanoma	3 months	9–22
Retsas & Gershuny 1988 [136]	100	Melanoma	2.5 months	8
Buchsbaum et al. 2002 [20]	74	Melanoma	6.1 months	NS
Sampson et al. 1998 [141]	180	Melanoma	3.9 months	NS
Wronski et al. 1997 [180]	119	Renal	4.4 months	16.8
Cannady et al. 2004 [24]	46	Renal	3 months	NS
Cascino et al. 1983 [25]	32	Colon	9 weeks	NS

[a] Series includes surgically treated patients; SCLC, small-cell lung carcinoma; NS, not stated.

incidence of recurrent tumors, and the study concluded that patients with single metastases to the brain who receive treatment with surgical resection and postoperative radiotherapy are less likely to die of neurological causes relative to patients treated with surgical resection alone. The article concluded that radiation is helpful as an adjuvant therapy by destroying any tumor left in the operative bed and eliminating micrometastases elsewhere in the brain. Importantly, the results did not translate into an improvement in overall survival due to risk of death from progressive systemic disease. This, along with the known adverse effects of WBRT, including cognitive impairment, make its use controversial in the setting of patients with metastatic lesions that have been completely surgically resected.

Radiosensitization

The concurrent use of radiation sensitizers, including halogenated pyrimidines and hypoxic cell sensitizers, in addition to conventional chemotherapeutic agents has been the subject of many clinical trials [146]. The use of bromodeoxyuridine (BrdU), a halogenated pyrimidine, was studied in a randomized clinical trial by RTOG 89–05 [124]. Skin and hematological toxicity was greater in patients who received BrdU, and these patients did not demonstrate increased survival time.

A recent phase III trial [102, 104] studied the use of motexafin gadolinium (MGd), an oxidative drug that sensitizes tumor cells to radiation. In this randomized trial, although MGd increased the time to progression of neurological disease and improved the neurocognitive function in selected patients, it had no effect on overall survival time.

Randomized trials by the RTOG are currently underway to define the role of these and other adjuvant agents with WBRT.

Table 6. Results of surgical treatment of patients with brain metastases (updated from [184], with permission from Elsevier)

Investigators (reference)	Tumor histology	Number of patients	Postoperative mortality (%)	Survival	
				Median Months	1-year %
Lang & Slater 1964 [85]	Mixed	208	22	4	20
Simionescu 1960 [151]	Mixed	172	38	<6	3
Vieth & Odom 1965 [171]	Mixed	155	15	<6	14
Haar & Patterson 1972 [59]	Mixed	167	11	<6	22
White et al. 1981 [173]	Mixed	122	6	7	30
Sundaresan & Galicich 1985 [158]	Mixed	125	6	12	50
Bindal et al. 1996 [16]	Mixed	62	0	16.4	58
O'Neill et al. 2003 [117]	Mixed	74	NS	NS	62
Patchell et al. 1990 [122]	Mixed	23	NS	40 weeks	NS
Mintz et al. 1996 [105]	Mixed	41	NS	5.6	12.2
Burt et al. 1992 [22]	Lung	185	3	14	55
Wronski et al. 1995 [177]	Lung	231	3	11	46
Koutras et al. 2003 [82]	NSCLC	32	NS	17	53
Wronski et al. 1997 [178]	Breast	70	NS	16.2	53
Pieper et al. 1997 [126]	Breast	63	5	16	62
Wronski and Arbit 2000 [176]	Melanoma	91	NS	6.7	36.3
Oredsson et al. 1990 [118]	Melanoma	40	18	8	NS
Stevens et al. 1992 [157]	Melanoma	45	NS	9	NS
Badalament et al. 1990 [11]	Renal	22	9	21	NS
Wronski et al. 1996 [179]	Renal	50	10	12.6	51
Wronski & Arbit 1999 [175]	Colon	73	4	8.3	31.5

NS, not stated; NSCLC, non-small-cell lung cancer.

Stereotactic Radiosurgery

In recent years, increasing numbers of patients with brain metastases have been treated with stereotactic radiosurgery (SRS), a procedure allowing the delivery of a single dose of radiation using multiple cobalt sources (gamma-knife) or a linear accelerator (LINAC) through a stereotactic device to targets of 3–3.5 cm maximum diameter. The dose is inversely related to tumor size and volume. The rapid fall-off of SRS away from the target is advantageous in that it minimizes the risk of damage to surrounding tissue. Its main advantage over surgery is that an open operation is avoided, and consequently, the procedure is performed in an outpatient setting.

A stereotactic head frame is used in all systems of SRS and is fixed to the skull of the patient. It functions to set up a stereotactic coordinate system in 3-dimensional space to allow accurate targeting and renders the patient immobile to ensure accuracy during treatment. With the frame on, patients undergo a thin-cut contrast-enhanced MRI scan of the brain. These images are used to define the lesions and plan treatment.

Recent studies (Table 7) demonstrate the advantage of SRS in the treatment of patients with newly diagnosed brain metastases, including a rapid decrease of symptoms, a local tumor response ('control') rate of 80–90%, with a reported median survival time of 7–15 months [3, 10, 45, 47, 99, 103, 150]. Another advantage of SRS is that it has been shown to be effective in highly radioresistant tumors like melanoma and renal cell carcinoma, which respond very poorly to fractionated radiotherapy.

Numerous studies also show that when compared with WBRT alone, surgery plus SRS provides patients with improved tumor control, a longer survival time, and a better quality of life [51, 93, 108]. A retrospective

Table 7. Results of stereotactic radiosurgery in patients with brain metastases (updated from [184], with permission from Elsevier)

Investigators (reference)	Radiation source	No. of lesions treated/tumor histology	Local control %	Median follow-up months	Median survival time months
Andrews et al. 2004 [7]	GK/LINAC	167/mixed	82	5.7	NS
Shehata et al. 2004 [149]	GK	468/mixed	97	7	8.2
Gerosa et al. 2002 [54]	GK	1307/mixed	93	14[b]	13.5
Vesagas et al. 2003 [170]	GK	174/mixed	85	8.4	8.4
Jawahar et al. 2004 [70]	GK	44/lung	72	18	7
Sheehan et al. 2002 [147]	GK	627/NSCLC	96	NS	10 adenocarcinoma 7 not adenocarcinoma
Combs et al. 2004 [34]	LINAC	103/breast	9 months	NS	15
Muacevic et al. 2004 [110]	GK	197/breast	94	8.3	10
Selek et al. 2004 [143]	LINAC	153/melanoma	49	6	25.2%[a]
Noel et al. 2002 [113]	LINAC	61/melanoma	84	12.6[b]	8
Herfarth et al. 2003 [64]	LINAC	122/melanoma	81 at 1 year	9.4[b]	10.6
Muacevic et al. 2004 [109]	GK	376/RCC	94	NS	11.1
Noel et al. 2004 [114]	LINAC	65/RCC	93	14	11
Sheehan et al.2003 [148]	GK	146/RCC	96	NS	15

[a] Percent surviving at 1 year.
[b] Mean follow-up time.
LINAC, modified linear accelerator; GK, gamma-knife; NS, not stated; RCC, renal cell carcinoma; NSCLC, non-small-cell lung carcinoma.

study from the Mayo Clinic [117] comparing surgical resection and SRS in the treatment of solitary metastases concluded that for patients with small and moderately sized tumors, there was no significant difference in patient survival time, although the local recurrence rate was higher in the surgical treatment group.

Recently, the RTOG performed a multicenter, randomized, prospective trial of 333 patients with 1–3 brain metastases. All of the patients received WBRT. With the addition of an SRS boost, there was a statistically significant increase in survival time, from 4.9 months to 6.5 months, as well as a significant improvement in local control [156].

Controversy surrounds the use of WBRT as an adjuvant to SRS. The main advantage in using SRS alone in the treatment of brain metastases is to avoid the neurocognitive side-effects of WBRT. In the past, single-institution retrospective reviews of patients with newly diagnosed brain metastases have confirmed an increased risk of failure of intracranial tumor control among patients managed initially with SRS alone versus those receiving SRS plus WBRT [30, 152, 153]. Yet, in a study in 2003 [60] that looked at 121 patients with brain metastases managed with SRS alone, local tumor control rates were 87%. The study concluded that brain metastases were controlled well with radiosurgery alone as initial therapy and advocated that WBRT should not be part of the initial treatment protocol for selected patients with one or two tumors and good control of their primary cancer. Other studies support this conclusion [30, 74, 127, 152]. A retrospective, multi-institutional study in which 268 patients were treated with SRS alone and 301 patients received WBRT in addition to SRS showed no significant difference in the survival rate [153].

Therefore, although most retrospective studies suggest that WBRT will improve local and distant tumor control in the brain, they do not demonstrate a survival advantage.

Another area of controversy regards the use of SRS versus surgical resection in the treatment of single metastases. This will be discussed in more detail below.

Complications

The use of WBRT is not free of morbidity. Depending on the interval until onset after treatment, complications are categorized as acute or late. Acute side-effects occur immediately and include dry desquamation, hair loss, headaches, nausea, lethargy, otitis media, and cerebral edema leading to elevated intracranial pressure. Increased fatigue, although usually transient, can also appear 1–4 months after treatment, a phenomenon often referred to as the 'somnolence syndrome'. More persistent complications include dermatitis and alopecia, and otitis media has been reported to persist for months after irradiation. Serious late effects include radiation necrosis, cerebral atrophy, leukoencephalopathy, and neurological deterioration with dementia [39, 90, 158, 159].

Because relatively few patients treated with WBRT survive for more than 1 year, the long-term side-effects of treatment are not usually an important consideration for them. The long-term side-effects of WBRT cannot be entirely ignored though, because in the past up to 11% of patients with WBRT developed dementia [39]. Although some believe that the frequency of long-term neuropsychological side-effects in these patients seems to have been overestimated because they are not reported to be as high when modern fractionation schemes are employed [120], they remain an important consideration.

In contrast to WBRT, acute and chronic complications after SRS are relatively modest [53, 101]. Intracerebral edema can occur within 2 weeks of treatment. Resulting symptoms can usually be treated with corticosteroids and are reversible in most cases. Chronic complications consist mainly of radiation necrosis, which very infrequently requires reoperation.

Surgery

Treatment Goals

The two surgical options we can offer patients with brain metastases are complete surgical resection of a tumor and surgical biopsy. These options are the only means of obtaining a histological diagnosis, an important consideration as in 5–15% of cases, pathological examination confirmed that the diagnosis was something other than a tumor. Just as important is the need to distinguish between surgery for palliation and surgery for curative proposes. There is little argument against that fact that surgery is the only modality to permanently relieve elevated intracranial pressure caused by local mass effect of the tumor and surrounding cerebral edema. Prior to this, patients were treated almost exclusively with corticosteroids and WBRT and suffered poor outcomes. Obviously, the most important goal of surgery is local cure, and with improvements in surgical techniques and technology, better outcomes support a more aggressive approach in these patients. The results in series of patients treated surgically for brain metastases are shown in Table 6.

Clinical Decision-Making

Patient selection from an oncological and medical standpoint is of the utmost importance. Numerous

studies have shown that the extent of systemic disease is the single most important factor that determines patient outcome. Progression of systemic illness accounts for up to 70% of mortality among patients undergoing surgery for metastatic brain tumors. Although opinions vary among clinicians, in general, patients are surgical candidates from an oncologic standpoint if they are expected to survive for at least 3 months. When considering surgery, other factors must be addressed including the size, location, and multiplicity of the tumors. As with any treatment modality, surgical benefits should be weighed against other treatment options including corticosteroid administration, WBRT, and SRS.

The neurological status of a patient is another important predictor of patient outcome because patients with poor neurological function have worse prognoses. Yet one must consider that patients can be symptomatic from hydrocephalus, hemorrhagic tumors, or significant surrounding vasogenic edema, all of which can be effectively treated surgically. Poor neurological function should therefore not necessarily preclude aggressive surgical intervention.

Finally, the location, extent, and size of metastatic brain tumors are important considerations in their surgical treatment.

More than other variables, tumor location is the prime determinant with respect to tumor resectability. This can be assessed in terms of two aspects: the depth of the tumor and its location relative to eloquent areas of the brain. In general, superficial tumors are more easily resectable, but now new options have allowed us to be more aggressive in the surgical resection of tumors, such as advancements in microsurgical and skull-base techniques. Further refinements described below, including intraoperative mapping techniques, allow us to operate safely within or adjacent to eloquent areas of the brain. These modalities, along with image guidance technology, allow almost all tumors to be resected. Nevertheless, the morbidity of tumor resection must be weighed against the natural history of the primary cancer.

Tumor size is the most important consideration when it comes to deciding between treating a metastatic brain lesion with surgery or SRS. Tumors greater than 3 cm in maximum diameter are more readily resected surgically as this large size precludes radiosurgery. Also, these larger lesions are more likely to produce mass effect and be clinically symptomatic. In general, therefore, the best lesions for radiosurgery are small ones (<1.5 cm in maximum diameter) that are deeply located.

Surgery for Single Brain Metastases. Patients with solitary brain metastases who have limited systemic disease are the best surgical candidates by far. Figure 4 shows MR images from a 64-year-old man with a solitary occipital brain metastasis before and after undergoing surgical resection of the lesion. Class I evidence in the literature has shown that surgical resection of a single metastatic lesion is superior to treatment with WBRT alone [122, 168]. These studies demonstrated that patients with single brain metastases, a KPS score of at least 70, and limited systemic disease who were treated with surgery lived significantly longer, had fewer recurrences, and had a better quality of life than patients treated with WBRT alone. In one randomized trial [105], no differences were observed between patient subgroups receiving surgery plus WBRT and WBRT alone. However, this trial included a greater proportion of patients with poorly controlled systemic disease, suggesting that appropriate patient selection for surgical treatment is necessary to ensure improved outcome.

One of the most controversial issues in the management of single brain metastases concerns whether to treat lesions with surgical excision or SRS. Both modalities have been shown to be effective in the treatment of small lesions. In a study from the University of Texas M.D. Anderson Cancer Center, patients matched for age, gender, primary cancer, extent of systemic disease, pretreatment KPS, and number of brain metastases who were treated with either surgery or radiosurgery were compared. The median survival times were 7.5 months for patients treated with radiosurgery and 16.4 months for patients treated with surgical resection followed by WBRT. A total of 50% of patients in the radiosurgery group died of neurological causes compared with 19% in the surgery group. The authors concluded that surgery plus WBRT was superior to radiosurgery alone in increasing survival [16].

Auchter et al. [10] compared 122 patients with single brain metastases treated with radiosurgery to a historical control group of patients treated with surgery and WBRT. The median survival time for both groups was similar: 56 weeks for radiosurgery and 43 weeks for conventional surgery. Local recurrence and neurological causes of death were also similar. In this study, the authors concluded that because radiosurgery was as effective as resection followed by WBRT, it was the treatment of choice for patients harboring small single metastatic lesions.

Several authors have discussed the need to evaluate the equivalence of SRS and surgical resection in a prospective fashion. To date, however, no prospective randomized trial has been performed to resolve the issue.

Surgery for Multiple Brain Metastases. In the past, most surgeons were hesitant to operate on patients with multiple brain metastases [59, 135]. In a retrospective study, Bindal [17] analyzed 56 patients undergoing surgical resection for multiple brain me-

tastases and divided them into two groups: group A consisted of patients with multiple tumors who underwent resection of some but not all the lesions, and group B included patients in whom all the lesions were resected. These two groups were compared with a control group (group C, who had single brain metastases that were completely resected). The study found that patients in group B had a significantly longer survival time than those in group A. Furthermore, the survival time of patients in group B was comparable to that in group C, patients with single metastases that were surgically resected. The study concluded that removing multiple metastases is as effective as removing a single metastasis, provided that all the lesions are removed. A second important finding of the study was that the morbidity associated with resecting multiple brain metastases was not significantly different from that of resecting a single brain metastasis, with a complication rate of 8%.

In deciding which patients with multiple brain metastases are reasonable surgical candidates, the risks of surgery must be weighed against the potential benefits of increased survival and improved quality of life. The most critical variable in determining poor outcome is the presence of systemic disease, and surgery should be considered for patients with controlled or limited systemic disease.

Surgical Techniques

New technology including image-guided surgery and cortical brain mapping has greatly improved the morbidity and mortality of patients with brain metastases. In addition, with a good surgical technique and a sound understanding of the intracranial anatomy, most lesions can be safely and completely resected with minimal complications.

Although there are exceptions, we approach tumors through the shortest route from the surface of the brain to the lesion itself. Certain anatomical landmarks, such as the ventricular cavity and fissures, can be used to guide the dissection. With respect to the tumors themselves, they can be located in a gyrus and are less likely to occur in a sulcus. Others appear in white matter or occur independently of a single sulcus or gyrus.

When lesions underlie the cortex, an incision is made in the cortex directly above the tumor. If the tumor is particularly large, this linear incision can be extended over noneloquent brain, and a cortical plug

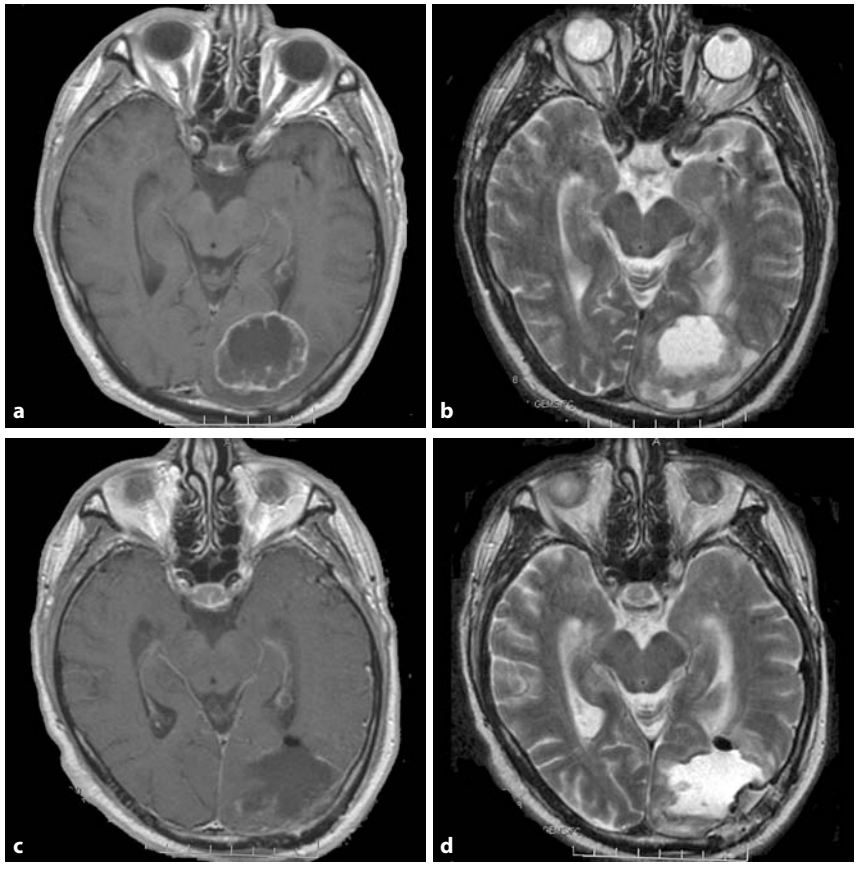


Fig. 4. **a** T1-weighted gadolinium contrast-enhanced MR image of a solitary occipital metastasis from non-small-cell lung carcinoma in a 64-year-old man. **b** T2–weighted MR image of the same tumor. **c** Postoperative T1-weighted gadolinium contrast-enhanced MR image of the same patient. **d** Postoperative T2-weighted gadolinium contrast-enhanced MR image of the same patient

of brain tissue can be removed to improve exposure. Depending on its location relative to eloquent cortex, lesions deep in the white matter are approached via a transcortical or transsulcal route.

Posterior fossa tumors are resected by performing a suboccipital craniotomy. As with supratentorial masses, the tumors are resected through an approach offering the shortest trajectory from the cortical surface. In the case of superior cerebellar lesions, exposure of the transverse sinus usually facilitates resection. For inferior lesions, the craniotomy is carried down to the foramen magnum. The vermis can be split to resect midline tumors.

In general, tumors are removed in whole though circumferential microdissection. When possible, care is taken not to enter the tumor mass itself, and the lesion is removed in a single piece. This technique is facilitated when a gliotic plane or capsule surrounds the lesion. When the tumor is especially large, it needs to be debulked and removed piecemeal. The amount of vascular supply to a tumor varies. In all cases though, these vessels need to be carefully identified, coagulated, and cut during dissection of the mass from the surrounding brain. Sulcal arteries and vessels not going into the tumor but very close to it must be identified and protected.

Technological Adjuncts to Surgery

The role of these adjuncts is twofold, tumor localization and the identification of functional or eloquent brain. This is helpful, especially in planning surgical approaches to the lesion. These techniques are especially valuable when the lesion is small and deeply located.

The intraoperative ultrasound device is most helpful in localizing tumors just beneath the cortical surface, as most metastatic brain tumors are echogenic and can be readily distinguished from the surrounding nonechogenic brain. It can be used only after the craniotomy is completed, just prior to dural opening. It is also helpful in identifying the tumor's relationship to surrounding structures such as the ventricles, falx, tentorium, or sylvian and interhemispheric fissures. One of the benefits of ultrasound is the fact that it provides visualization in 'real time', and as a consequence, the resection cavity can be examined as soon as the mass is removed for any evidence of residual tumor.

Recent advances in computer-assisted stereotaxy have greatly advanced our capabilities in the field of surgery. With this technology, preoperative images based on CT or MR images are used to construct three-dimensional constructions of the tumor relative to its surrounding structures. Intraoperatively, this allows the surgeon to choose the most direct surgical approach. Having such preoperative images allows skin incisions to be more limited and a smaller craniotomy to be fashioned. The main disadvantage of this system is that although the images are more specific, unlike ultrasonographic images, they are not in 'real time' and are best used in conjunction with intraoperative ultrasound.

Intraoperative mapping is essential when the lesion is felt to be located within or adjacent to eloquent areas of the brain, including motor, sensory, and speech areas of the cerebral cortex. This can be accomplished in two ways. The first involves cortical mapping with grid electrodes that are placed directly on the exposed surface of the brain, ideally over the motor and sensory cortex. As potentials are recorded, 'phase reversal' observed after stimulation of the median nerve can accurately identify the central sulcus and help guide surgical resection. With the second method, the brain is directly stimulated with a bipolar electrode. When the precentral gyrus is stimulated, movement on the contralateral side of the body is observed. Again, this information can help guide placement of surface corticotomies to allow resection of tumors near, or even within, the motor cortex.

Finally, an awake craniotomy can be used to identify areas of the brain controlling language areas in addition to motor cortex. As most metastatic brain tumors are fairly well-circumscribed and easily resectable, this technique is rarely employed.

Chemotherapy

As the major systemic treatment for cancer, the advantage of chemotherapy is that it treats the whole brain in addition to other sites of cancer. Unfortunately, its efficacy in the treatment of brain metastases has been limited. The poor response rate of brain metastases to chemotherapy has been attributed to several factors including the 'relatively drug-resistant nature of these tumors', the fact that brain metastases often occur in patients in whom previous chemotherapy has failed, and the blood-brain barrier [15, 27, 48, 133, 165]. This last item is often cited as the main explanation for poor response rates. Traditionally, it has been felt that the role of chemotherapy in patients with brain metastases from cancers other than those that are highly chemosensitive, including small-cell lung cancer and germ-cell tumors, is experimental.

Nevertheless, a recent paper from van den Bent [167] challenges this view and cites several studies showing that the response rates for brain metastases resemble the expected systemic response rates for the primary tumor [57, 81, 134]. For example, the author cites studies showing that in patients with non-

small-cell cancer of the lung, 30–45% of patients with untreated brain metastases responded to standard chemotherapy, and 50–60% of patients with brain metastases from breast cancer responded to a variety of multiagent regimens [33, 138]. To explain this, the authors claim that a blood-brain barrier is not present in tumors because brain metastases induce new blood vessels by an upregulation of angiogenic factors. As these newly formed blood vessels are 'leaky', the blood-brain barrier is thereby disrupted.

Studies looking at the use of WBRT instead of, or in conjunction with, chemotherapy have been limited [107, 133, 137].

Several recent studies have focused on the use of temozolomide on brain metastases. This widely used oral chemotherapeutic agent is most frequently used in the treatment of high-grade gliomas and has demonstrated good penetration beyond the blood-brain barrier. So far, the effects of this drug have been somewhat limited [2, 4, 44], and preliminary reports show that with temozolomide alone, response rates are not as high as with standard chemotherapy regimens. However, the drug has been shown to be more effective in combination with WBRT and in some cases, with radiosurgery [1, 32]. This could prove to be a promising treatment alternative.

Conclusion

As the most common intracranial tumors, brain metastases are a considerable cause of morbidity and mortality in patients with cancer. Despite advances in therapy, patients often die within 12–24 months, and it is now recognized that quality of life is perhaps as important as survival as an endpoint to patients. For many patients with limited systemic disease, surgery and radiosurgery provide the best opportunity for extending survival and improving the quality of life.

Acknowledgements. We thank David M. Wildrick, Ph.D, for editorial assistance with this manuscript.

References

1. Abrey LE, Christodoulou C. Temozolomide for treating brain metastases. Semin Oncol 2001; 28:34—42
2. Abrey LE, Olson JD, Raizer JJ, Mack M, Rodavitch A, Boutros DY, Malkin MG. A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. J Neurooncol 2001; 53:259–265
3. Adler JR, Cox RS, Kaplan I, Martin DP. Stereotactic radiosurgical treatment of brain metastases. J Neurosurg 1992; 76:444–449
4. Adonizio CS, Babb JS, Maiale C, Huang C, Donahue J, Millenson MM, Hosford M, Somer R, Treat J, Sherman E, Langer CJ. Temozolomide in non-small-cell lung cancer: preliminary results of a phase II trial in previously treated patients. Clin Lung Cancer 2002; 3:254–258
5. Amer MH, Al-Sarraf M, Baker LH, Vaitkevicius VK. Malignant melanoma and central nervous system metastases: incidence, diagnosis, treatment and survival. Cancer 1978; 42:660–668
6. Amer MH, Al-Sarraf M, Vaitkevicius VK. Clinical presentation, natural history and prognostic factors in advanced malignant melanoma. Surg Gynecol Obstet 1979; 149:687–692
7. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004; 363:1665–1672
8. Arnold SM, Patchell RA. Diagnosis and management of brain metastases. Hematol Oncol Clin North Am 2001; 15:1085–1107, vii
9. Ask-Upmark E. Metastatic tumors of the brain and their localization. Acta Med Scand 1956; 154:1–9
10. Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, Kinsella TJ, Levin AB, Noyes WR, Schultz CJ, Loeffler JS, Mehta MP. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys 1996; 35:27–35
11. Badalament RA, Gluck RW, Wong GY, Gnecco C, Kreutzer E, Herr HW, Fair WR, Galicich JH. Surgical treatment of brain metastases from renal cell carcinoma. Urology 1990; 36:112–117
12. Baker AB. Metastatic tumors of the nervous system. Arch Pathol Lab Med 1942; 34:495–537
13. Baker GS, Kernohan JW, Kiefer EJ. Metastatic tumors of the brain. Surg Clin North Am 1951; 31:1143–1145
14. Berk L. An overview of radiotherapy trials for the treatment of brain metastases. Oncology 1995; 9:1205–1212; discussion 1212–1206, 1219
15. Bernardo G, Cuzzoni Q, Strada MR, Bernardo A, Brunetti G, Jedrychowska I, Pozzi U, Palumbo R. First-line chemotherapy with vinorelbine, gemcitabine, and carboplatin in the treatment of brain metastases from non-small-cell lung cancer: a phase II study. Cancer Invest 2002; 20:293–302
16. Bindal AK, Bindal RK, Hess KR, Shiu A, Hassenbusch SJ, Shi WM, Sawaya R. Surgery versus radiosurgery in the treatment of brain metastasis. J Neurosurg 1996; 84:748–754
17. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. J Neurosurg 1993; 79:210–216
18. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, Perez CA, Hendrickson FR. The palliation of brain

metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1980; 6:1–9

19. Broadbent AM, Hruby G, Tin MM, Jackson M, Firth I. Survival following whole brain radiation treatment for cerebral metastases: an audit of 474 patients. Radiother Oncol 2004; 71:259–265
20. Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 2002; 94:2265–2272
21. Burgess RE, Burgess VF, Dibella NJ. Brain metastases in small cell carcinoma of the lung. JAMA 1979; 242:2084–2086
22. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. J Thorac Cardiovasc Surg 1992; 103:399–410
23. Cairncross JG, Posner JB. The management of brain metastases. In: Walker MD, ed. Oncology of the Nervous System. Boston, Martinus Nijhof, 1983:341–377
24. Cannady SB, Cavanaugh KA, Lee SY, Bukowski RM, Olencki TE, Stevens GH, Barnett GH, Suh JH. Results of whole brain radiotherapy and recursive partitioning analysis in patients with brain metastases from renal cell carcinoma: a retrospective study. Int J Radiat Oncol Biol Phys 2004; 58:253–258
25. Cascino TL, Leavengood JM, Kemeny N, Posner JB. Brain metastases from colon cancer. J Neurooncol 1983; 1:203–209
26. Chang DB, Yang PC, Luh KT, Kuo SH, Hong RL, Lee LN. Late survival of non-small cell lung cancer patients with brain metastases. Influence of treatment. Chest 1992; 101:1293–1297
27. Chang J, Atkinson H, R AH, Lorentzos A, Gore ME. A phase II study of the sequential administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma. Eur J Cancer 1994; 30 A:2093–2095
28. Chao J, Phillips R, Nickson J. Roentgen-ray therapy of cerebral metastases. Cancer 1954; 7:682–689
29. Chason J, Walker F, Landers J. Metastatic carcinoma in the central nervous system and dorsal root ganglia. Cancer 1963; 16:781–787
30. Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH. Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. Int J Radiat Oncol Biol Phys 2000; 47:993–999
31. Choi KN, Withers HR, Rotman M. Intracranial metastases from melanoma. Clinical features and treatment by accelerated fractionation. Cancer 1985; 56:1–9
32. Christodoulou C, Bafaloukos D, Kosmidis P, Samantas E, Bamias A, Papakostas P, Karabelis A, Bacoyiannis C, Skarlos DV, Hellenic Cooperative Oncology G. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. [see comments]. Ann Oncol 2001; 12:249–254
33. Cocconi G, Lottici R, Bisagni G, Bacchi M, Tonato M, Passalacqua R, Boni C, Belsanti V, Bassi P. Combination therapy with platinum and etoposide of brain metastases from breast carcinoma. Cancer Invest 1990; 8:327–334
34. Combs SE, Schulz-Ertner D, Thilmann C, Edler L, Debus J. Treatment of cerebral metastases from breast cancer with stereotactic radiosurgery. Strahlenther Onkol 2004; 180:590–596
35. Cotran RS, Kumar V, Robbins SL. Robbins pathologic basis of disease. Philadelphia, W. B. Saunders Co., 1994
36. Cox JD, Komaki R. Prophylactic cranial irradiation for squamous cell carcinoma, large cell carcinoma, and adenocarcinoma of the lung: indications and techniques. In: Mountain CF, Carr DT, eds. Lung cancer: current status and prospects for the future. The University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute Annual Clinical Conference on Cancer. vol 28. Chicago, IL, Year Book Medical Publishers, 1986:233–237
37. Davis PC, Hudgins PA, Peterman SB, Hoffman JC Jr. Diagnosis of cerebral metastases: double-dose delayed CT vs contrast-enhanced MR imaging. AJNR Am J Neuroradiol 1991; 12:293–300
38. de la Monte SM, Moore GW, Hutchins GM. Patterned distribution of metastases from malignant melanoma in humans. Cancer Res 1983; 43:3427–3433
39. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. Neurology 1989; 39:789–796
40. Decker DA, Decker VL, Herskovic A, Cummings GD. Brain metastases in patients with renal cell carcinoma: prognosis and treatment. J Clin Oncol 1984; 2:169–173
41. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol 1988; 45:741–744
42. Diener-West M, Dobbins TW, Phillips TL, Nelson DF. Identification of an optimal subgroup for treatment evaluation of patients with brain metastases using RTOG study 7916. Int J Radiat Oncol Biol Phys 1989; 16:669–673
43. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. Cancer 1979; 44:1913–1918
44. Dziadziuszko R, Ardizzoni A, Postmus PE, Smit EF, Price A, Debruyne C, Legrand C, Giaccone G. Temozolomide in patients with advanced non-small cell lung cancer with and without brain metastases. a phase II study of the EORTC Lung Cancer Group (08965). Eur J Cancer 2003; 39:1271–1276
45. Engenhart R, Kimmig BN, Hover KH, Wowra B, Romahn J, Lorenz WJ, van Kaick G, Wannenmacher M. Long-term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. Cancer 1993; 71:1353–1361

46. Fleckenstein K, Hof H, Lohr F, Wenz F, Wannenmacher M. Prognostic factors for brain metastases after whole brain radiotherapy. Data from a single institution. Strahlenther Onkol 2004; 180:268–273
47. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, Hudgins WR, Weiner R, Harsh GR, Sneed PK, Larson DA. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Biol Phys 1994; 28:797–802
48. Franciosi V, Cocconi G, Michiara M, Di Costanzo F, Fosser V, Tonato M, Carlini P, Boni C, Di Sarra S. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. [see comments]. Cancer 1999; 85:1599–1605
49. Galluzzi S, Payne P. Brain metastases from primary bronchial carcinoma: a statistical study of 741 necropsies. Cancer 1956; 10:408–414
50. Gamache FWJ, Posner JB, Patterson RHJ. Metastatic brain tumors. In: Youmans J, ed. Neurological Surgery. vol 5. Philadelphia, W. B. Saunders, 1982:2872–2898
51. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997; 37:745–751
52. Gelber RD, Larson M, Borgelt BB, Kramer S. Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis. Cancer 1981; 48:1749–1753
53. Gelblum DY, Lee H, Bilsky M, Pinola C, Longford S, Wallner K. Radiographic findings and morbidity in patients treated with stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 1998; 42:391–395
54. Gerosa M, Nicolato A, Foroni R, Zanotti B, Tomazzoli L, Miscusi M, Alessandrini F, Bricolo A. Gamma knife radiosurgery for brain metastases: a primary therapeutic option. J Neurosurg 2002; 97:515–524
55. Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist 2003; 8:541–552
56. Graf AH, Buchberger W, Langmayr H, Schmid KW. Site preference of metastatic tumours of the brain. Virchows Arch 1988; 412:493–498
57. Groen HJ, Smit EF, Haaxma-Reiche H, Postmus PE. Carboplatin as second line treatment for recurrent or progressive brain metastases from small cell lung cancer. Eur J Cancer 1993; 29 A:1696–1699
58. Guerrieri M, Wong K, Ryan G, Millward M, Quong G, Ball DL. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. Lung Cancer 2004; 46:107–111
59. Haar F, Patterson RHJ. Surgery for metastatic intracranial neoplasm. Cancer 1972; 30:1241–1245
60. Hasegawa T, Kondziolka D, Flickinger JC, Germanwala A, Lunsford LD. Brain metastases treated with radiosurgery alone: an alternative to whole brain radiotherapy? Neurosurgery 2003; 52:1318–1326; discussion 1326
61. Healy ME, Hesselink JR, Press GA, Middleton MS. Increased detection of intracranial metastases with intravenous Gd-DTPA. Radiology 1987; 165:619–624
62. Hendrickson FR. Radiation therapy of metastatic tumors. Semin Oncol 1975; 2:43–46
63. Hendrickson FR. The optimum schedule for palliative radiotherapy for metastatic brain cancer. Int J Radiat Oncol Biol Phys 1977; 2:165–168
64. Herfarth KK, Izwekowa O, Thilmann C, Pirzkall A, Delorme S, Hofmann U, Schadendorf D, Zierhut D, Wannenmacher M, Debus J. Linac-based radiosurgery of cerebral melanoma metastases. Analysis of 122 metastases treated in 64 patients. Strahlenther Onkol 2003; 179:366–371
65. Hildebrand J. Early diagnosis of brain metastases in an unselected population of cancerous patients. Eur J Cancer 1973; 9:621–626
66. Hirsch FR, Paulson OB, Hansen HH, Vraa-Jensen J. Intracranial metastases in small cell carcinoma of the lung: correlation of clinical and autopsy findings. Cancer 1982; 50:2433–2437
67. Hojo S, Hirano A. Pathology of metastases affecting the central nervous system. In: Takakura K, Sano K, Hojo S, Hirano A, eds. Metastatic tumors of the nervous system. Tokyo, Igaku-Shoin, 1982:5–111
68. Hwang TL, Close TP, Grego JM, Brannon WL, Gonzales F. Predilection of brain metastasis in gray and white matter junction and vascular border zones. Cancer 1996; 77:1551–1555
69. Jacot W, Quantin X, Boher JM, Andre F, Moreau L, Gainet M, Depierre A, Quoix E, Chevalier TL, Pujol JL, Association d'Enseignement et de Recherche des Internes en O. Brain metastases at the time of presentation of non-small cell lung cancer: a multi-centric AERIO analysis of prognostic factors. Br J Cancer 2001; 84:903–909
70. Jawahar A, Matthew RE, Minagar A, Shukla D, Zhang JH, Willis BK, Ampil F, Nanda A. Gamma knife surgery in the management of brain metastases from lung carcinoma: a retrospective analysis of survival, local tumor control, and freedom from new brain metastasis. J Neurosurg 2004; 100:842–847
71. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. CA Cancer J Clin 2003; 53:5–26
72. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ. Cancer statistics, 2004. CA Cancer J Clin 2004; 54:8–29
73. Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am 1996; 7:337–344
74. Joseph J, Adler JR, Cox RS, Hancock SL. Linear accelerator-based stereotaxic radiosurgery for brain metastases: the influence of number of lesions on survival. J Clin Oncol 1996; 14:1085–1092

75. Kauffman EC, Robinson VL, Stadler WM, Sokoloff MH, Rinker-Schaeffer CW. Metastasis suppression: the evolving role of metastasis suppressor genes for regulating cancer cell growth at the secondary site. J Urol 2003; 169:1122–1133
76. Khansur T, Routh A, Hickman B. Brain metastases from unknown primary site. J Miss State Med Assoc 1997; 38:238–242
77. Kleinman GM, Zagzag D, Miller DC. Diagnostic use of immunohistochemistry in neuropathology. Neurosurg Clin N Am 1994; 5:97–126
78. Klos KJ, O'Neill BP. Brain metastases. Neurologist 2004; 10:31–46
79. Kofman S, Garvin J, Nagamani D, et al. Treatment of cerebral metastases from breast carcinoma with prednisolone. JAMA 1957; 163:1473–1476
80. Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). Int J Radiat Oncol Biol Phys 1991; 20:53–58
81. Korfel A, Oehm C, von Pawel J, Keppler U, Deppermann M, Kaubitsch S, Thiel E. Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation. A multicentre phase II study. Eur J Cancer 2002; 38:1724–1729
82. Koutras AK, Marangos M, Kourelis T, Partheni M, Dougenis D, Iconomou G, Vagenakis AG, Kalofonos HP. Surgical management of cerebral metastases from non-small cell lung cancer. Tumori 2003; 89:292–297
83. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 1999; 43:795–803
84. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999; 49:9–31
85. Lang EF, Slater J. Metastatic brain tumors: results of surgical and nonsurgical treatment. Surg Clin North Am 1964; 44:865–872
86. Lassman AB, DeAngelis LM. Brain metastases. Neurol Clin 2003; 21:1–23, vii
87. Le Chevalier T, Smith FP, Caille P, Constans JP, Rouesse JG. Sites of primary malignancies in patients presenting with cerebral metastases. A review of 120 cases. Cancer 1985; 56:880–882
88. Lee YT. Malignant melanoma: pattern of metastasis. CA Cancer J Clin 1980; 30:137–142
89. Lee YT. Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol 1983; 23:175–180
90. Lee YY, Nauert C, Glass JP. Treatment-related white matter changes in cancer patients. Cancer 1986; 57:1473–1482
91. Leeds NE, Sawaya R, Van Tassel P, Hayman LA. Intracranial hemorrhage in the oncologic patient. Neuroimaging Clin N Am 1992; 2:119–136
92. Levin VA, Leibel SA, Gutin PH. Neoplasms of the central nervous system. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. Philadelphia, Lippincott Williams & Wilkins, 2001:2100–2160
93. Loeffler JS, Kooy HM, Wen PY, Fine HA, Cheng CW, Mannarino EG, Tsai JS, Alexander E. The treatment of recurrent brain metastases with stereotactic radiosurgery. J Clin Oncol 1990; 8:576–582
94. Lutterbach J, Bartelt S, Ostertag C. Long-term survival in patients with brain metastases. J Cancer Res Clin Oncol 2002; 128:417–425
95. MacGee EE. Surgical treatment of cerebral metastases from lung cancer. The effect on quality and duration of survival. J Neurosurg 1971; 35:416–420
96. Madajewicz S, Karakousis C, West CR, Caracandas J, Avellanosa AM. Malignant melanoma brain metastases. Review of Roswell Park Memorial Institute experience. Cancer 1984; 53:2550–2552
97. Mahmoud-Ahmed AS, Suh JH, Lee SY, Crownover RL, Barnett GH. Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. Int J Radiat Oncol Biol Phys 2002; 54:810–817
98. Mandybur TI. Intracranial hemorrhage caused by metastatic tumors. Neurology 1977; 27:650–655
99. Maor MH, Dubey P, Tucker SL, Shiu AS, Mathur BN, Sawaya R, Lang FF, Hassenbusch SJ. Stereotactic radiosurgery for brain metastases: results and prognostic factors. Int J Cancer 2000; 90:157–162
100. Markesbery WR, Brooks WH, Gupta GD, Young AB. Treatment for patients with cerebral metastases. Arch Neurol 1978; 35:754–756
101. McKenzie MR, Souhami L, Caron JL, Olivier A, Villemure JG, Podgorsak EB. Early and late complications following dynamic stereotactic radiosurgery and fractionated stereotactic radiotherapy. Can J Neurol Sci 1993; 20:279–285
102. Mehta MP, Rodrigus P, Terhaard CH, Rao A, Suh J, Roa W, Souhami L, Bezjak A, Leibenhaut M, Komaki R, Schultz C, Timmerman R, Curran W, Smith J, Phan SC, Miller RA, Renschler MF. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. J Clin Oncol 2003; 21:2529–2536
103. Mehta MP, Rozental JM, Levin AB, Mackie TR, Kubsad SS, Gehring MA, Kinsella TJ. Defining the role of radiosurgery in the management of brain metastases. Int J Radiat Oncol Biol Phys 1992; 24:619–625
104. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, Kunkler I, Caudrelier JM, Eisenberg PD, Meerwaldt J, Siemers R, Carrie C, Gaspar LE, Curran W, Phan SC, Miller RA, Renschler MF. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. J Clin Oncol 2004; 22:157–165
105. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, Duncan G, Skingley P, Foster G, Levine M. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 1996; 78:1470–1476

106. Montana GS, Meacham WF, Caldwell WL. Brain irradiation for metastatic disease of lung origin. Cancer 1972; 29:1477–1480
107. Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T, Tilgen W, Nguyen BB, Guillot B, Ulrich J, Bourdin S, Mousseau M, Cupissol D, Bonneterre J, de Gislain C, Bensadoun JR, Clavel M. [Randomised phase III trial of fotemustine versus fotemustine plus whole brain irradiation in cerebral metastases of melanoma]. Cancer Radiother 2003; 7:1–8
108. Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, Reulen HJ. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 1999; 91:35–43
109. Muacevic A, Kreth FW, Mack A, Tonn J.C., Wowra B. Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. Minim Invasive Neurosurg 2004; 47:203–208
110. Muacevic A, Kreth FW, Tonn J.C., Wowra B. Stereotactic radiosurgery for multiple brain metastases from breast carcinoma. Cancer 2004; 100:1705–1711
111. Newman SJ, Hansen HH. Proceedings: Frequency, diagnosis, and treatment of brain metastases in 247 consecutive patients with bronchogenic carcinoma. Cancer 1974; 33:492–496
112. Nisce LZ, Hilaris BS, Chu FC. A review of experience with irradiation of brain metastasis. AJR Am J Roentgenol 1971; 111:329–333
113. Noel G, Simon JM, Valery CA, Cornu P, Boisserie G, Ledu D, Hasboun D, Tep B, Delattre JY, Marsault C, Baillet F, Mazeron JJ. Linac radiosurgery for brain metastasis of melanoma. Stereotact Funct Neurosurg 2002; 79:245–255
114. Noel G, Valery CA, Boisserie G, Cornu P, Hasboun D, Marc Simon J, Tep B, Ledu D, Delattre JY, Marsault C, Baillet F, Mazeron JJ. LINAC radiosurgery for brain metastasis of renal cell carcinoma. Urol Oncol 2004; 22:25–31
115. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR, Brand R, Hermans J. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys 1994; 29:711–717
116. O' Neill BP, Buckner JC, Coffey RJ, Dinapoli RP, Shaw EG. Brain metastatic lesions. Mayo Clin Proc 1994; 69:1062–1068
117. O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. Int J Radiat Oncol Biol Phys 2003; 55:1169–1176
118. Oredsson S, Ingvar C, Stromblad LG, Jonsson PE. Palliative surgery for brain metastases of malignant melanoma. Eur J Surg Oncol 1990; 16:451–456
119. Paillas JE, Pellet W. Brain metastases. In: Vinken PJ, Bruyn GW, eds. Handbook of clinical neurology. vol 18. Amsterdam, North-Holland Publishing, 1975:201–232
120. Patchell RA. The management of brain metastases. Cancer Treat Rev 2003; 29:533–540
121. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998; 280:1485–1489
122. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322:494–500
123. Patel JK, Didolkar MS, Pickern JW. Metastatic pattern of malignant melanoma: a study of 216 autopsy cases. Am J Surg 1978; 135:807–810
124. Phillips TL, Scott CB, Leibel SA, Rotman M, Weigensberg IJ. Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89–05. Int J Radiat Oncol Biol Phys 1995; 33:339–348
125. Pickren JW, Lopez G, Tsukada Y, et al. Brain metastases: an autopsy study. Cancer Treat Sympos 1983; 2:295–313
126. Pieper DR, Hess KR, Sawaya RE. Role of surgery in the treatment of brain metastases in patients with breast cancer. Ann Surg Oncol 1997; 4:481–490
127. Pirzkall A, Debus J, Lohr F, Fuss M, Rhein B, Engenhart-Cabillic R, Wannenmacher M. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol 1998; 16:3563–3569
128. Posner JB. Diagnosis and treatment of metastases to the brain. Clin Bull 1974; 4:47–57
129. Posner JB. Clinical manifestations of brain metastases. In: Weiss L, Gilbert HA, Posner JB, eds. Brain Metastasis. Boston, G. K. Hall, 1980:189–207
130. Posner JB. Management of brain metastases. Rev Neurol (Paris) 1992; 148:477–487
131. Posner JB. Neurologic complications of cancer. Philadelphia, F. A. Davis, 1995, vol 45
132. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. Adv Neurol 1978; 19:579–592
133. Postmus PE, Haaxma-Reiche H, Smit EF, Groen HJ, Karnicka H, Lewinski T, van Meerbeeck J, Clerico M, Gregor A, Curran D, Sahmoud T, Kirkpatrick A, Giaccone G. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy–a phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 2000; 18:3400–3408
134. Postmus PE, Smit EF, Haaxma-Reiche H, van Zandwijk N, Ardizzoni A, Quoix E, Kirkpatrick A, Sahmoud T, Giaccone G. Teniposide for brain metastases of small-cell lung cancer: a phase II study. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 1995; 13:660–665
135. Ransohoff J. Surgical management of metastatic tumors. Semin Oncol 1975; 2:21–27
136. Retsas S, Gershuny AR. Central nervous system involvement in malignant melanoma. Cancer 1988; 61:1926–1934

137. Robinet G, Thomas P, Breton JL, Lena H, Gouva S, Dabouis G, Bennouna J, Souquet PJ, Balmes P, Thiberville L, Fournel P, Quoix E, Riou R, Rebattu P, Perol M, Paillotin D, Mornex F. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95–1. Ann Oncol 2001; 12:59–67
138. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. Cancer 1986; 58:832–839
139. Saitoh H, Shimbo T, Tasaka T, Iida T, Hara K. Brain metastasis of renal adenocarcinoma. Tokai J Exp Clin Med 1982; 7:337–343
140. Salcman M. Intracranial hemorrhage caused by brain tumor. In: Kaufman HH, ed. Intracerebral hematomas. New York, Raven Press, 1992:95–106
141. Sampson JH, Carter JH, Jr, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 1998; 88:11–20
142. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. J Neurooncol 1999; 44:275–281
143. Selek U, Chang EL, Hassenbusch SJ 3rd, Shiu AS, Lang FF, Allen P, Weinberg J, Sawaya R, Maor MH. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. Int J Radiat Oncol Biol Phys 2004; 59:1097–1106
144. Selker R. Corticosteroids: their effect on primary and metastatic brain tumors. In: Walker MD, ed. Oncology of the nervous system. Boston, Nijhoff, 1983:167–191
145. Sen M, Demiral AS, Cetingoz R, Alanyali H, Akman F, Senturk D, Kinay M. Prognostic factors in lung cancer with brain metastasis. Radiother Oncol 1998; 46:33–38
146. Shaffrey ME, Mut M, Asher AL, Burri SH, Chahlavi A, Chang SM, Farace E, Fiveash JB, Lang FF, Lopes MB, Markert JM, Schiff D, Siomin V, Tatter SB, Vogelbaum MA. Brain metastases. Curr Probl Surg 2004; 41:665–741
147. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. J Neurosurg 2002; 97:1276–1281
148. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. J Neurosurg 2003; 98:342–349
149. Shehata MK, Young B, Reid B, Patchell RA, St Clair W, Sims J, Sanders M, Meigooni A, Mohiuddin M, Regine WF. Stereotactic radiosurgery of 468 brain metastases < or =2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys 2004; 59:87–93
150. Shiau CY, Sneed PK, Shu HK, Lamborn KR, McDermott MW, Chang S, Nowak P, Petti PL, Smith V, Verhey LJ, Ho M, Park E, Wara WM, Gutin PH, Larson DA. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. Int J Radiat Oncol Biol Phys 1997; 37:375–383
151. Simionescu MD. Metastatic tumors of the brain: a follow-up study of 195 patients with neurosurgical considerations. J Neurosurg 1960; 17:361–373
152. Sneed PK, Lamborn KR, Forstner JM, McDermott MW, Chang S, Park E, Gutin PH, Phillips TL, Wara WM, Larson DA. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys 1999; 43:549–558
153. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, Regine WF, Weltman E, King VJ, Breneman JC, Sperduto PW, Mehta MP. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 2002; 53:519–526
154. Soffietti R, Ruda R, Mutani R. Management of brain metastases. J Neurol 2002; 249:1357–1369
155. Sorensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. J Clin Oncol 1988; 6:1474–1480
156. Sperduto PW. A review of stereotactic radiosurgery in the management of brain metastases. Technol Cancer Res Treat 2003; 2:105–110
157. Stevens G, Firth I, Coates A. Cerebral metastases from malignant melanoma. Radiother Oncol 1992; 23:185–191
158. Sundaresan N, Galicich JH. Surgical treatment of brain metastases. Clinical and computerized tomography evaluation of the results of treatment. Cancer 1985; 55:1382–1388
159. Sundaresan N, Galicich JH, Deck MD, Tomita T. Radiation necrosis after treatment of solitary intracranial metastases. Neurosurgery 1981; 8:329–333
160. Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. AJNR Am J Neuroradiol 1990; 11:785–791
161. Takahashi JA, Mori H, Fukumoto M, Igarashi K, Jaye M, Oda Y, Kikuchi H, Hatanaka M. Gene expression of fibroblast growth factors in human gliomas and meningiomas: demonstration of cellular source of basic fibroblast growth factor mRNA and peptide in tumor tissues. Proc Natl Acad Sci USA 1990; 87:5710–5714
162. Takakura K, Sano K, Hojo S, Hirano A. Metastatic tumors of the central nervous system. New York, Igaku-Shoin, 1982
163. Trillet V, Catajar JF, Croisile B, Turjman F, Aimard G, Bourrat C, Bret P, Carrie C, Chassard JL, Chauvin F et al. Cerebral metastases as first symptom of bronchogenic carcinoma. A prospective study of 37 cases. Cancer 1991; 67:2935–2940
164. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer 1983; 52:2349–2354

165. Twelves CJ, Souhami RL, Harper PG, Ash CM, Spiro SG, Earl HM, Tobias JS, Quinn H, Geddes DM. The response of cerebral metastases in small cell lung cancer to systemic chemotherapy. Br J Cancer 1990; 61:147–150
166. van den Bent MJ. The diagnosis and management of brain metastases. Curr Opin Neurol 2001; 14:717–723
167. van den Bent MJ. The role of chemotherapy in brain metastases. Eur J Cancer 2003; 39:2114–2120
168. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 1993; 33:583–590
169. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994; 44:675–680
170. Vesagas TS, Aguilar JA, Mercado ER, Mariano MM. Gamma knife radiosurgery and brain metastases: local control, survival, and quality of life. J Neurosurg 2002; 97:507–510
171. Vieth RG, Odom GL. Intracranial metastases and their neurosurgical treatment. J Neurosurg 1965; 23:375–383
172. Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. Neurology 1985; 35:219–226
173. White KT, Fleming TR, Laws ER Jr. Single metastasis to the brain. Surgical treatment in 122 consecutive patients. Mayo Clin Proc 1981; 56:424–428
174. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. CA Cancer J Clin 1995; 45:8–30
175. Wronski M, Arbit E. Resection of brain metastases from colorectal carcinoma in 73 patients. Cancer 1999; 85:1677–1685
176. Wronski M, Arbit E. Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients. J Neurosurg 2000; 93:9–18
177. Wronski M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. J Neurosurg 1995; 83:605–616
178. Wronski M, Arbit E, McCormick B, Wronski M. Surgical treatment of 70 patients with brain metastases from breast carcinoma [published erratum appears in Cancer 1998 Feb 15;82(4):following 800]. Cancer 1997; 80:1746–1754
179. Wronski M, Arbit E, Russo P, Galicich JH. Surgical resection of brain metastases from renal cell carcinoma in 50 patients. Urology 1996; 47:187–193
180. Wronski M, Maor MH, Davis BJ, Sawaya R, Levin VA. External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M. D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 1997; 37:753–759
181. Yuh WT, Tali ET, Nguyen HD, Simonson TM, Mayr NA, Fisher DJ. The effect of contrast dose, imaging time, and lesion size in the MR detection of intracerebral metastasis [published erratum appears in AJNR Am J Neuroradiol 1995 Jun-Jul;16(6):1384]. AJNR Am J Neuroradiol 1995; 16:373–380
182. Yuile PG, Tran MH. Survival with brain metastases following radiation therapy. Australas Radiol 2002; 46:390–395
183. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastases in solid-tumor patients: natural history and results of treatment. Cancer 1981; 48:384–394
184. Sawaya R, Bindal RK, Lang FF, Abi-Said D. Metastatic brain tumors. In: Kaye AH, Laws ER, eds. Brain tumors: an encyclopedic approach. Edinburgh, Churchill Livingstone, 2001:999–1026

Pediatric Neuro-Oncology II

Organised by James T. Rutka

20 **Neurocutaneous Syndromes – 327**
Paul Kongkham, James T. Rutka

21 **Supratentorial Hemispheric Low-Grade Gliomas in Children – 345**
Paul Chumas, Atul Tyagi

22 **Optic Gliomas – 353**
Ian F. Pollack, Regina I. Jakacki

23 **Thalamic Gliomas – 363**
Christian Sainte-Rose, Darach W. Crimmins, Jacques Grill

24 **Midbrain Gliomas – 377**
Leland Albright

25 **Supratentorial High-Grade Gliomas – 385**
Rene O. Sanchez-Mejia, Anu Banerjee, Nalin Gupta

26 **Ganglioglioma – 393**
Concezio Di Rocco, Gianpiero Tamburrini

27 **Cerebellar Astrocytomas – 401**
John C. Wellons III

28 **Diffuse Intrinsic Pontine Gliomas – 407**
Milind Ronghe, Eric Bouffet

29 **Dorsally Exophytic Brainstem Gliomas – 415**
Ian D. Kamaly-Asl, James M. Drake

30 **Cervicomedullary Gliomas – 421**
Alexa L. Reeves, Richard G. Ellenbogen

31 **Desmoplastic Infantile Gangliogliomas – 431**
Jeffrey P. Blount

32 **Pleomorphic Xanthoastrocytoma – 437**
Jean-Pierre Farmer, P. Daniel McNeely

33 **Hypothalamic Hamartoma – 443**
Jeffrey V. Rosenfeld, A. Simon Harvey

34 Ependymomas – 453
Nicholas Wetjen, Corey Raffel

35 Medulloblastoma – 461
Michael D. Taylor

36 Supratentorial Primitive Neuroectodermal Tumors – 471
Shahid Gul, Paul Steinbok

37 Dysembryoplastic Neuroectodermal Tumors – 479
Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

38 Meningiomas – 485
Abhaya V. Kulkarni, Patrick McDonald

39 Pineal Region Tumors in Children – 491
Anna J. Janss, Timothy Mapstone

40 Pituitary Tumors in Children – 499
Aaron S. Dumont, Jay Jagannathan, John A. Jane Jr

41 Craniopharyngiomas – 505
Rémy van Effenterre, Anne-Laure Boch

42 Intracranial Germ Cell Tumors – 517
Kyu-Chang Wang, Seung-Ki Kim, Sung-Hye Park, In-One Kim, Byung-Kyu Cho

43 Choroid Plexus Tumors – 529
Paul Kongkham, James T. Rutka

44 Malignant Rhabdoid Tumors of the CNS – 539
Michael R. Carter

45 Langerhans Cell Histiocytosis – 547
Clare Gallagher, Walter J. Hader

46 Tumors of the Skull Base in Children – 555
Eve C. Tsai, Gregy Hawryluk, James T. Rutka

47 Calvarial Tumors in Children – 567
Ganesh Rao, John R.W. Kestle

48 Epidural Spinal Tumors in Children – 575
Colin Kazina, Patrick McDonald

49 Spinal Column Tumors – 583
William E. Whitehead, Anna Illner

50 Pediatric Spinal Intradural Extramedullary Tumors – 599
Peter Dirks

51 Intramedullary Spinal Tumors in Children – 603
John S. Myseros

52 Peripheral Nerve Tumors in Children – 611
W. Bradley Jacobs, Rajiv Midha

Neurocutaneous Syndromes 20

Paul Kongkham, James T. Rutka

Introduction – 329

Neurofibromatosis Type I – 329
Epidemiology

Symptoms and Clinical Signs – 329

Diagnosis – 331

Treatment – 331
Surgery
Radiation Therapy
Chemotherapy

Prognosis and Quality of Life – 332

Future Perspectives – 332

Neurofibromatosis Type II – 332
Epidemiology

Symptoms and Clinical Signs – 332

Diagnosis – 333

Staging and Classification – 333

Treatment – 333
Surgery
Radiation Therapy

Prognosis and Quality of Life – 334

Tuberous Sclerosis Complex – 334

Symptoms and Clinical Signs – 334

Diagnosis – 336

Treatment – 336
Surgery
Other

Prognosis and Quality of Life – 337

Future Perspectives – 337

Von Hippel-Lindau Disease – 337
Epidemiology

Symptoms and Clinical Signs – 337

Diagnosis – 338

Treatment – 338
Surgery
Radiation Therapy

Prognosis and Quality of Life – 339

Sturge-Weber Syndrome – 339
Epidemiology

Symptoms and Clinical Signs – 339

Diagnosis – 340

Treatment – 341
Surgery
Other

Prognosis and Quality of Life – 341

References – 341

Introduction

The neurocutaneous syndromes are comprised of a heterogeneous group of disorders which have in common variable involvement of the neurologic, dermatologic, and ophthalmologic systems. This group of disorders was previously known as the *phakomatoses*, due to their many dermatologic manifestations. Among these disorders are the neurofibromatoses (NFs), tuberous sclerosis complex (TSC), von Hippel-Lindau (VHL) disease, and Sturge-Weber (SWS) syndrome. Less common disorders occasionally included are Osler-Weber-Rendu syndrome, Wyburn-Mason disease, nevoid basal cell carcinoma (Gorlin) syndrome, Cowden's disease, and ataxia-telangiectasia. A feature common to the majority of these syndromes is the propensity to develop tumors, both benign and malignant. These tumors, however, are not necessarily unique to those with neurocutaneous syndromes. By studying these disorders, significant insight has been gained into the etiology and behavior of various tumor types. This chapter will focus on the neurosurgical and neuro-oncological aspects of the most common neurocutaneous disorders.

Neurofibromatosis Type I

Epidemiology

The neurofibromatoses (NFs) encompass several disorders which have as common features both cutaneous pigmented lesions and tumors of neuroectodermal origin. Among this group, NF I and NF II are most common. NF I (also known as peripheral NF, or von Recklinghausen's disease) accounts for up to 96% of all NF cases [43]. It constitutes one of the most common inherited neurologic disorders, affecting both sexes and all racial groups equally, with an annual incidence ranging from 1/2500 to 1/4000 live births [36]. Its pattern of inheritance is autosomal dominant, with high penetrance and variable expression. Despite this, only half the cases present with a discernible family history – the other half result from new gene mutations. The NF I tumor suppressor gene has been identified, and is located on chromosome 17q11.2. It encodes a large, ubiquitous cytoplasmic protein – neurofibromin – which functions in part to decrease cell proliferation by promoting the inactivation of the p21-ras proto-oncogene [109].

Symptoms and Clinical Signs

Symptoms and signs of NF I are referable to the dermatologic, ophthalmologic, musculoskeletal, peripheral, and central nervous systems. One characteristic cutaneous lesion seen is the café-au-lait macule – an area of abnormal skin pigmentation varying in size from a few millimeters up to several centimeters in diameter, with regular borders and even coloration. These lesions are often evident at birth, and usually before the child's first birthday. Up to 95% of adults with NF I will display at least one café-au-lait macule, with 78% having six or more. A second cutaneous sign is skin-fold freckling, seen in regions such as the submammary fold, axilla, or inguinal regions. These may be absent initially, and develop later as the child approaches puberty.

Iris hamartomas (Lisch nodules) are the most common ophthalmologic abnormality in NF I patients. These nodules consist of masses of melanocytes, and appear as raised, pigmented lesions best seen by slit-lamp examination. Like skin-fold freckling, iris hamartomas are often absent in early childhood, showing increased prevalence with age.

Musculoskeletal abnormalities associated with NF I include scalloping of the vertebral bodies, kyphoscoliosis, and idiopathic vertebral dysplasia. Other bony abnormalities include thinning of long bone cortex, pseudoarthrosis, and dysplasia of the sphenoid wing. Rarely, malignances such as rhabdomyosarcoma may develop.

NF I patients may harbor abnormalities in both the peripheral (PNS) and central nervous system (CNS). Within the PNS, a cardinal feature of NF I is the presence of multiple cutaneous and subcutaneous neurofibromas, often found in the thoracoabdominal region or around the nipple-areolar complex. NF I patients may develop up to thousands of these benign lesions, making it the most common tumor associated with this disorder. Despite their frequency, these lesions pose primarily a cosmetic problem for NF I patients, with malignant transformation occurring rarely.

Neurofibromas also develop in the paraspinal region, arising from the dorsal roots in the cervical or lumbar regions. If they extend through the intervertebral foramen, they may take on a characteristic "dumbbell" shape, with further growth into the spinal canal. If large enough, these lesions may produce symptoms of myeloradiculopathy.

Plexiform neurofibromas are another lesion seen within the PNS in NF I patients. These lesions are almost exclusively congenital in nature, diffusely involving larger peripheral nerves or the sympathetic chain (Fig. 1). Although not pathognomonic, the presence of a plexiform neurofibroma is highly suggestive of underlying NF I [53]. Approximately 30% of NF I patients have plexiform neurofibromas, with multiple lesions being present in 9%–21% of cases [24, 35, 104]. Although some remain asymptomatic, these lesions have the potential to cause disfigure-

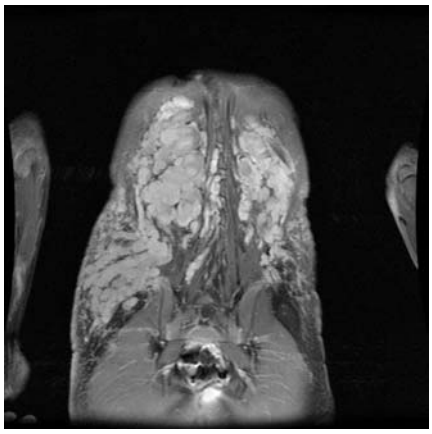


Fig. 1 Coronal, gadolinium-enhanced MRI through the chest and upper abdomen, at the level of the spinal column, demonstrating a massive plexiform neurofibroma in a 3-year-old female with NF-I

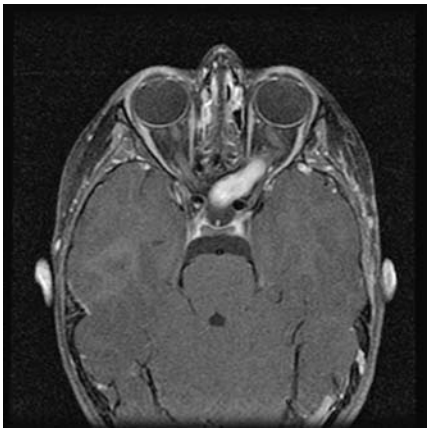


Fig. 2 Optic chiasmatic glioma as seen on gadolinium-enhanced T1-weighted axial MRI in a 4-year-old female with NF-I

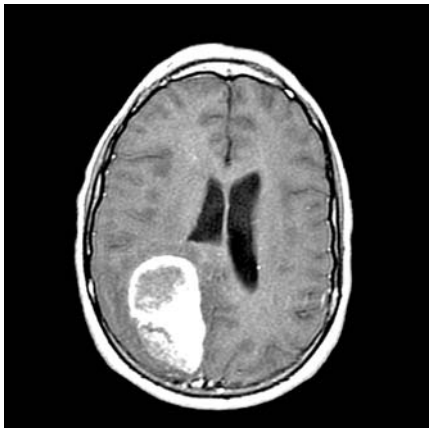


Fig. 3 Axial T1-weighted MRI of 13-year-old male with NF-1 and recent history of headache, nausea and vomiting. A large right inhomogeneously enhancing mass lesion is seen which proved to be a malignant glioma

ment (such as hemihypertrophy) or neurologic dysfunction of the involved area.

Plexiform neurofibromas possess the potential for malignant transformation, forming a neurofibrosarcoma, or malignant peripheral nerve sheath tumor (MPNST). These highly malignant Schwann cell tumors affect up to 6% of NF I patients. The development of such tumors may be heralded by the onset of new neurologic deficits, pain, or rapid growth of a plexiform neurofibroma. One must have a high index of suspicion for MPNSTs under these circumstances, given their aggressive behavior and potential to metastasize.

Within the CNS, the most common tumor seen in NF I patients is the optic pathway glioma (OPG) (Fig. 2). OPGs account for 2%–5% of all childhood brain tumors, and up to 15% of NF I patients are affected by this lesion. The period of greatest risk for developing an OPG is during early childhood, especially prior to 6 years of age. Females appear to be at higher risk than males. Generally, OPGs are slowly-growing, WHO class I pilocytic astrocytomas, with OPGs arising in the context of NF I exhibiting a more benign clinical course than spontaneous tumors [14]. OPGs may arise anywhere along the optic pathway, with prechiasmal lesions being most frequent. Rarely, these tumors develop further posteriorly, within the optic radiations themselves [58]. In the NF I patient, OPGs may remain asymptomatic in up to half the patients [56]. When symptoms arise, patients may suffer from diplopia, proptosis, altered visual fields, or impaired acuity. Hypothalamic or endocrine dysfunction (such as precocious puberty) may also occur. Even among symptomatic patients, OPGs in NF I patients may remain quite stable. As a result, presymptomatic radiologic screening is not required.

In addition to OPGs, NF I patients are susceptible to developing supratentorial, infratentorial, and brainstem gliomas of various histological grades [90]. Hemispheric gliomas (Fig. 3) and posterior fossa gliomas occur in 0.5% and 1.0% of NF I patients, respectively. As expected, the symptoms and signs of these lesions depend on their particular location, but may include those of increased intracranial pressure, hydrocephalus, focal motor or sensory deficits, cerebellar dysfunction, or seizures.

Nonneoplastic manifestations of NF I within the CNS include cognitive impairment, attention deficit hyperactivity disorder, hydrocephalus, epilepsy, and idiopathic macrocephaly. In addition, one may find the radiologic phenomenon of focal areas of increased T2-weighted signal on imaging studies – imaging correlates of possible spongiform myelinopathy, and markers of poor cognitive and fine motor performance [18].

Diagnosis

The diagnosis of NF I has remained essentially a clinical one (Table 1). Genetic tests have been developed, such as the protein truncation test, to assess for mutations in the NF I gene [32]. The utility of this test is in its ability to confirm the diagnosis of NF I, and to screen members of the same family for the identical mutation. The high spontaneous mutation rate associated with this gene, however, has made the development of broadly applicable genetic testing methods difficult. In addition, these tests are not yet able to predict the phenotype the NF I patient will exhibit, which can vary significantly in its severity.

Due to the multisystem nature of this disorder, the clinical diagnostic work-up relies on the multidisciplinary efforts of the neurologist, neurosurgeon, dermatologist, ophthalmologist, and orthopedic specialists. In particular, a complete ophthalmologic exam by either a pediatric or neuro-ophthalmologist is recommended on a yearly basis up to 10 years of age, and every 2–3 years afterwards or as symptoms arise [45]. Children with symptoms, or abnormal clinical exams, should go on to receive diagnostic imaging.

Various imaging modalities assist in the diagnostic work-up and follow-up of patients with NF I. Plain film X-rays are of utility in the diagnosis of appendicular bony abnormalities. CT scans with coronal and sagittal reformats, as well as three-foot standing plain films are informative in the NF I patient with kyphoscoliosis. The neuro-imaging modality of choice in the management of NF I patients is MRI. MRI scan of the craniospinal axis, with and without contrast, is able to detect the presence of optic pathway, brainstem, hemispheric, and posterior fossa gliomas. In addition, paraspinal lesions may be identified with this modality. Contrast-enhanced MRI may be of some utility in the diagnosis of MPNSTs as well, with these lesions appearing heterogeneous due to the presence of necrosis and intratumoral hemorrhage [64]. Additional modalities, such as positron emission tomography, may also assist in the diagnosis of malignant transformation from plexiform neurofibroma to MPNST [19].

Table 1 Diagnostic criteria for neurofibromatosis 1

The patient must have two or more of the following:
Six or more café-au-lait macules (0.5 cm or larger if prepubertal or 1.5 cm or larger if postpubertal)
Two or more neurofibromas of any kind, or one plexiform neurofibroma
Axillary/inguinal freckling
Optic pathway glioma
Two or more iris hamartomas
Distinct osseous abnormality (sphenoid wing dysplasia, pseudoarthrosis, thinning of long bone cortex
1st degree relative with NF I

(Modified from [69])

Treatment

Surgery

Surgery remains the primary treatment modality for the majority of benign and malignant tumors associated with NF I. If desired by the patient, cutaneous and subcutaneous neurofibromas may be resected for cosmetic reasons. Plexiform neurofibromas can prove to be much more difficult to treat surgically, due to their vascularity, size, and tendency to occur within a neural plexus. Often a complete resection is not feasible with this lesion. In addition, the risk of incurring a postoperative sensory or motor deficit is not insignificant. Therefore, surgical treatment of this lesion should be approached cautiously, and may not be indicated for the minimally symptomatic patient. When the malignant transformation of this tumor to a MPNST is suspected, however, prompt investigation and treatment is necessary. An initial biopsy to secure the diagnosis of MPNST is followed by either an attempt at gross total resection with clean surrounding margins, or occasionally by limb amputation. The patient then undergoes adjuvant radiation, and occasionally chemotherapy [78]. Despite this aggressive treatment, the overall 5-year survival remains only approximately 40%.

The treatment of OPGs is reviewed in detail elsewhere in this book. Briefly, treatment recommendations depend in part on the patient's symptoms, evidence of clinical progression, and the location of the tumor itself. Intraorbital or prechiasmatic lesions causing significant proptosis, visual loss, or exhibiting rapid growth may warrant treatment. The role of surgical excision, however, is limited to those cases in which visual impairment is already significant and a complete resection is feasible, or those in which significant mass effect exists necessitating debulking.

The other intracranial gliomas (brainstem, posterior fossa, hemispheric) are often followed with se-

rial radiologic follow-up. In cases of posterior fossa or hemispheric lesions which become symptomatic, or show accelerated growth, surgical excision may be warranted if the lesion is accessible.

Radiation Therapy

Radiation therapy serves a role as an adjunct to the surgical resection of MPNSTs. It may also serve as a primary treatment modality for symptomatic, progressive OPGs. Up to 80% local control rates for OPGs following radiation therapy have been described, with either tumor shrinkage or stabilization seen on follow-up imaging studies. Radiation therapy can incur significant morbidity, however, such as cognitive dysfunction, postradiation ischemic events or endocrinologic disturbances [27].

Chemotherapy

In order to avoid iatrogenic complications secondary to radiation therapy, investigators have studied the role and efficacy of chemotherapy in treating gliomas associated with NF I. Both single and multiagent regimens have been tried, with variable success [10, 23, 26, 51, 60, 62, 75, 82, 89]. Up to 89% 5-year overall, and 61% 5-year radiation therapy-free survivals have been reported [51].

Prognosis and Quality of Life

The overall prognosis and quality of life for NF I patients is limited by their propensity for tumorigenesis, which continues into adulthood [29]. Between 3%–15% of NF I patients are reported to suffer from some form of malignancy during the course of their disease [5]. This contributes to the finding that the overall life expectancy for NF I patients is approximately 15 years shorter than that of the general population [5]. Predictors of a shortened life expectancy in NF I patients include the presence of a CNS tumor located outside of the optic pathway, or the diagnosis of a symptomatic tumor in adulthood [27].

Future Perspectives

Advances in neuroimaging have allowed us to diagnose NF I-associated lesions earlier, and follow them more accurately, than was possible in the past. Future advances in the management of these patients may lie in the field of small molecule, targeted chemotherapy. The receptor tyrosine kinase inhibitor STI571 (Glivec), or other inhibitors of downstream targets in the RAS pathway, may prove to be of benefit in the treatment of NF I patients [20].

Neurofibromatosis Type II

Epidemiology

NF II is a less common form of neurofibromatosis, with an annual incidence of approximately 1/40, 000. As with NF I, NF II is an autosomal dominant disorder, with no particular predilection for race or sex. The responsible gene is located on chromosome 22q11, and encodes the protein merlin (also known as schwannomin). Loss of heterozygosity for the NF II gene has been demonstrated in multiple NF II-associated tumors. In addition, the particular gene mutation may influence the severity of the expressed phenotype, as well as the spectrum of tumors a particular patient is at risk of developing [7]. NF II patients typically become symptomatic during the second or third decade of life. Only 10% of patients are symptomatic before 10 years of age [28]. The majority, however, develop symptoms by the age of 40, often due to the presence of intracranial lesions such as vestibular schwannomas.

Symptoms and Clinical Signs

As with NF I, patients with NF II are prone to develop abnormalities of the ophthalmologic system, and multiple neoplasms involving the nervous system. In contrast, however, cutaneous findings are not a prominent feature of NF II.

Ophthalmologic manifestations of NF II include the development of juvenile posterior subcapsular lenticular opacities – occurring in up to 50% of patients. Patients may present with symptoms of visual impairment as a result. Other findings include retinal or iris hamartomas, and epiretinal membranes.

The hallmark lesions associated with NF II are bilateral vestibular schwannomas (acoustic neuromas, Fig. 4). Compared with sporadic cases, NF II patients with vestibular schwannomas often become symptomatic at an earlier age. Presenting symptoms are similar, and include sensorineural hearing loss, tinnitus, imbalance, headache, or facial nerve dysfunction. The behavior of these lesions is quite variable, with growth rates between 1–10 mm per year reported.

NF II patients are also at risk of developing additional tumors of the neuraxis. These include meningiomas, schwannomas (other than vestibular schwannomas), ependymomas, and rarely astrocytomas. Of these tumors, meningiomas are most common. They may be isolated or multiple in number. Their behavior and symptomatic presentation is similar to meningiomas occurring in the general population.

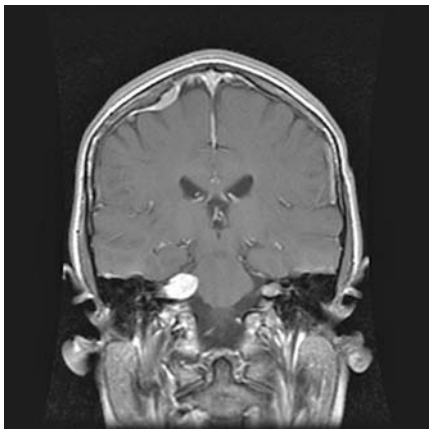


Fig. 4 Coronal, gadolinium-enhanced MRI, depicting bilateral vestibular schwannomas and a right convexity meningioma in a 14-year-old male with NF-II

Schwannomas may arise elsewhere in NF II patients, aside from the superior division of the vestibular nerves. They may involve other cranial nerves such as the trigeminal nerve, and other nerves such as the sensory roots in the cervicothoracic region, or even peripherally along cutaneous nerves. Their associated symptomatology relates to the locations in which they arise. Ependymomas are the most common intra-axial tumors in NF II patients. Again, the behavior of these lesions (both intracranial and intramedullary within the spinal cord) parallels similar lesions found spontaneously in the general population.

Diagnosis

The diagnosis of NF II remains a clinical one (Table 2). As with NF I, the diagnostic work-up of suspected NF II should involve the concerted efforts of a neurologist, neurosurgeon, neuro-otologist, ophthalmologist, and geneticist with interest and expertise in this disorder. Annual examinations for patients between the ages of 15 and 45 years have been recommended [28]. In addition to a thorough clinical exam, further work-up should include imaging of the craniospinal axis, audiometry, and possibly brainstem auditory evoked response (BAER) testing. Contrast-enhanced MRI of the brain, including images centered on the internal auditory meatus, will disclose the presence of vestibular nerve tumors as well as other intracranial pathologies. MRI of the spine may reveal the presence of intramedullary ependymomas, spinal meningiomas, or schwannomas of sensory roots. In patients with positive findings of a vestibular schwannoma, audiometry helps assess and document the severity of high-tone sensorineural hearing loss typical for the NF II patient.

Table 2 Diagnostic criteria for neurofibromatosis II

Definite NF II: Bilateral vestibular schwannomas, or Positive family history, plus unilateral vestibular schwannoma prior to age 30, or Positive family history, plus two of the following: meningioma, schwannoma, glioma, juvenile, subcapsular lenticular opacity
Probable NF II: Unilateral vestibular schwannoma before age 30, plus one of: meningioma, schwannoma, glioma, juvenile subcapsular, lenticular opacity Or Two or more meningiomas, plus one of: schwannoma, glioma, juvenile subcapsular lenticular, opacity
[Modified from the criteria for NF II, from the National Neurofibromatosis Foundation Clinical Care Advisory Board (www.nf.org)]

Staging and Classification

Two classification systems often used when treating the NF II patient with vestibular schwannomas are the House-Brackmann and Gardner-Robertson scales, for facial nerve and cochlear nerve function respectively. These systems provide a means of quantitating the degree of pre- or posttreatment nerve dysfunction.

Treatment

In patients with NF II and vestibular schwannomas, the clinical course is difficult to predict, owing to the variable growth rates described for these lesions. As such, the initial treatment strategy often consists of close observation, repeat clinical assessment and serial neuroimaging. If progressive symptomatic deterioration, rapid growth rate, or evidence of neural compression due to tumor mass are noted, intervention may be required. The optimal treatment strategy for NF II patients with bilateral vestibular schwannomas has received much attention over the years, with controversy continuing regarding which modality is most appropriate – surgery versus radiation therapy – and under what circumstances.

Surgery

Microsurgical resection has long been considered the gold standard treatment for vestibular schwannomas. Several authors view microsurgery as a superior treatment modality for achieving tumor control, compared to radiation therapy strategies [65]. In addition, it has been suggested that earlier surgery on smaller lesions will provide for the best chance for a complete resection, while preserving both hearing and facial nerve function [93]. Samii et al. reviewed their extensive surgical experience for 120 vestibular schwannomas in 82 NF II patients, treated during the period from 1978 to 1993 [93]. Among this group of patients, bilateral resections were accomplished in 38, while unilateral resections were done in 44 patients. Complete excision was possible in 105 of the tumors. Attempts at hearing preservation were successful in approximately 36% of patients, and was generally better for those with smaller lesions. Anatomic facial nerve preservation was achieved in 85% of cases. Multiple surgical approaches for these lesions have been employed, including the retrosigmoid/suboccipital, translabyrinthine, and subtemporal/middle fossa approaches. The decision regarding the most suitable surgical approach depends in part on the size of the lesion, its location (intracanalicular vs. cerebellopontine angle), and whether one aims to preserve hearing.

Patients with NF II may require surgical treatment for other lesions, such as meningioma, schwannoma, or ependymoma. Treatment decisions regarding these lesions generally parallels their spontaneously-occurring counterparts in the non-NF II population.

Radiation Therapy

Modalities for the treatment of vestibular schwannomas in the NF II patient which have gained favor more recently include fractionated stereotactic radiotherapy and stereotactic radiosurgery. Tumor control rates up to 98%–100% have been demonstrated with these modalities, along with rates of hearing preservation equal to those reported in surgical series [2, 98]. Rowe et al. reviewed their experience using stereotactic radiosurgery for the treatment of vestibular schwannomas in NF II patients [92]. They observed that only 20% of treated patients went on to require surgical treatment of the same lesion during an 8-year follow-up period. In addition, they reported complications of facial and trigeminal neuropathy in only 5% and 2% of patients, respectively. As such, radiosurgery is felt by many to represent a viable alternative to traditional microsurgical resection, providing tumor control, or at least a delay in need for subsequent resection, with acceptable treatment-related morbidity [54].

Prognosis and Quality of Life

The overall prognosis and quality of life for NF II patients is as variable as the phenotypic severity of this disorder. As mentioned, quality of life may be impaired significantly due to the development of hearing impairment. In addition, ophthalmologic abnormalities such as juvenile posterior subcapsular cataracts may add to their disability by impairing vision. Treatment-related morbidities such as facial nerve paresis can be extremely distressing and disfiguring for these patients as well, not to mention the increased ophthalmologic risks of corneal abrasion or exposure keratitis.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder, characterized by the presence of multiple, hamartomatous abnormalities affecting several organ systems, including the brain, kidneys, heart, retina, and skin. In addition, neoplasms can occur, in particular within the CNS and kidneys. TSC has an annual incidence of approximately 1/6000, making it the second most common of the neurocutaneous syndromes. It shows no preference for sex or race. Like NF I, up to half of cases are thought to be due to new mutations. Two responsible genes have been identified, and mutations of either gene may result in TSC. TSC1 is located on chromosome 9q34, and encodes the protein product hamartin. The TSC2 gene is found on chromosome 16p13.3, and encodes the protein tuberin. Of the sporadically-arising cases of TSC, nearly three quarters are thought to be due to new mutations in the TSC2 gene [40]. The protein products of these two genes – hamartin and tuberin – have been shown to function together in a complex, negatively regulating the insulin receptor/phosphoinositide 3-kinase/mTOR pathway, thereby helping to control cell growth and division [50, 61, 94].

Symptoms and Clinical Signs

Classically, the symptoms and signs of TSC were defined by Vogt's triad: seizures, mental retardation, and the presence of a facial angiofibroma (adenoma sebaceum). This triad, however, is only completely present in one third of TSC patients. As with other neurocutaneous syndromes, the symptoms and signs of TSC are referable to the dermatologic, ophthalmologic, and nervous systems. In addition, these

patients may suffer from cardiac, pulmonary, and renal abnormalities.

With respect to cutaneous findings, TSC has several well-characterized signs. Ash leaf spots (hypomelanotic macules) are one of the earliest cutaneous findings. These lesions often present at birth, appearing as dull-white polygonal regions of hypopigmentation. They are not, however, pathognomonic for TSC and can be seen among the general population. A second cutaneous sign of TSC is the shagreen patch. This lesion consists of an orange peel-textured hamartoma of the skin, found most commonly in the lumbosacral region. Up to 20% of TSC patients may exhibit a shagreen patch, often during early childhood. In nearly three quarters of TSC patients, facial angiofibromas may develop during childhood. This acneiform-like lesion usually is found in a malar distribution.

The ophthalmologic manifestations of TSC include retinal phakomas (astrocytomas), which occur in 50%–75% of patients [74]. In addition, achromic retinal patches may be seen. Neither of these lesions produce visual impairment.

Cardiac rhabdomyomas can be found in up to 50% of TSC patients. Most patients suffer little clinical impact from these lesions. Some, however, develop heart failure secondary to outflow obstruction or impaired cardiac contractility. Less frequently, these lesions may incite arrhythmias or thromboembolic events. Typically, rhabdomyomas decrease in size, and may disappear altogether, with symptomatic patients requiring medical management alone.

Pulmonary complications in TSC are uncommon, affecting approximately 2%–5% of females with TSC. A potentially fatal pulmonary manifestation of TSC is lymphangioleiomyomatosis, which typically develops during the fourth decade of life, causing symptoms of dyspnea, hemoptysis, or spontaneous pneumothorax.

Multiple different renal lesions can develop in TSC patients. These often become symptomatic during the second decade of life. The most common among these lesions is the benign angiomyolipoma – seen in approximately 70%–80% of TSC patients [11]. Renal cysts occur in approximately 20% of patients. Less common findings include angiomyoliposarcoma, oncocytoma, and renal cell carcinoma.

Within the CNS, TSC patients are prone to develop numerous lesions and cytoarchitectural abnormalities. Among these are the characteristic cortical tubers, subependymal nodules, subependymal giant cell astrocytoma (SEGA) (Fig. 5), cortical dysplasia, and radial migration abnormalities. Involvement of the spinal cord is uncommon in TSC.

Cortical tubers are the most common CNS manifestation of the disease. These hamartomas are usually situated at the grey-white matter junction within the frontal lobes, although they may occur in other lobes as well. They often achieve 1–2 cm in size, and consist of firm, pale gliotic plaques pathologically. The normal laminar cortical architecture is disrupted around these tubers. Over time, these lesions may accumulate progressive calcification, or undergo cystic degeneration.

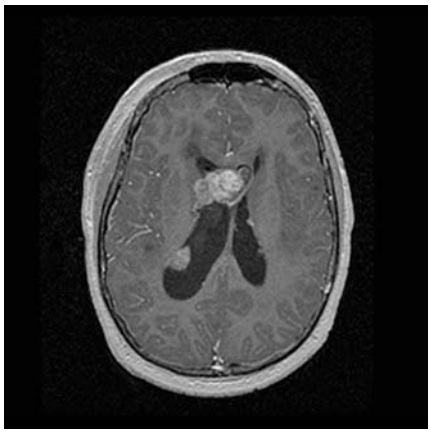


Fig. 5 Axial, T1- weighted MRI following contrast administration, showing a subependymal giant cell tumor in a 10-year-old male with tuberous sclerosis. Lesions in this location can become large enough to obstruct the foramen of Monro, requiring treatment in the form of CSF diversion or tumor removal

The presence of these cortical tubers has been linked to the development of both the seizure disorder and cognitive dysfunction seen in the TSC patients [72, 106]. Despite appearing neurologically normal at birth, up to 85% of TSC patients eventually suffer from a seizure disorder [97, 106]. In fact, the onset of seizures may be the first symptom of this disorder in a child. The majority become symptomatic within the first 2–3 years of life. The initial pattern is usually one of flexion myoclonus, with EEG evidence of hypsarrhythmia. This pattern may evolve into psychomotor or generalized tonic-clonic epilepsy as the disease progresses. Cognitive dysfunction is also common in TSC – seen in up to 50% of patients.

In addition to cortical tubers, subependymal nodules around the lateral ventricles can develop. These characteristic lesions usually range in size from 1–10 mm, and are distributed along the head of the caudate nucleus as well as the striothalamic zone of the lateral ventricle. Over time, they may increase in number, and show evidence of calcification.

A third structural lesion thought to be unique to TSC patients is the SEGA. Up to 6% of TSC patients develop this tumor. Typically, they arise within the ventricle in the region of the foramen of Monro, and are thought to arise from the transformation

and overgrowth of a subependymal nodule. On occasion, one finds a SEGA within the parenchyma itself – thought to be secondary to degeneration of a cortical tuber [12]. Symptoms of increased intracranial pressure, or a change in the patient's previous seizure pattern may signal the development of this lesion.

Diagnosis

The diagnosis of TSC is largely a clinical one (Table 3). A thorough work-up is needed in order to identify the major and minor clinical features characteristic of this disorder. The initial investigation of a patient suspected to have TSC should involve a multidisciplinary work-up, including detailed ophthalmologic and fundoscopic exams, dermatologic screen, and a clinical neurologic and neurodevelopmental assessment. In addition, the patient should undergo neuro-imaging studies, as well as echocardiography and renal ultrasound or CT scan.

Table 3 Diagnostic criteria for tuberous sclerosis complex

Definite TSC:	Two major features or one major plus two minor features
Probable TSC:	One major plus one minor feature
Possible TSC:	One major feature or two minor features
Major features:	Facial angiofibroma or forehead plaque Atraumatic ungual/periungual fibroma Ash leaf spot Shagreen patch Multiple retinal nodular hamartomas Cortical tuber Subependymal nodule SEGA Cardiac rhabdomyoma Pulmonary lymphangioleiomyomatosis Renal angiomyolipoma
Minor features:	Multiple dental enamel pits Hamartomatous rectal polyp Bone cyst Cerebral white matter migration lines Gingival fibromas Nonrenal hamartomas Retinal achromic patch Confetti-like skin lesions Multiple renal cysts

(Modified from [87])

On CT scan of the brain, cortical tubers and subependymal nodules appear as focal regions of increased attenuation, with little or no enhancement with IV contrast. The subependymal nodules have been described as resembling "candle-drippings" along the border of the lateral ventricles. MRI scan shows these lesions as being heterogeneous in appearance, with minimal peripheral contrast enhancement. Significant enhancement of a subependymal nodule, or one exhibiting rapid growth between serial imaging studies, suggests the development of a SEGA.

In patients with seizures, further work-up including EEG studies, video-EEG monitoring, magnetoencephalography, or invasive monitoring with electrocorticography may facilitate identification of the epileptic focus. In the future, additional noninvasive modalities such as diffusion-weighted MRI scans may aid in identifying which tuber, among many, is at the root of a patient's seizures [38].

Treatment

Surgery

The neurosurgical management of TSC patients generally revolves around three particular issues: the control of intractable seizures, the resection of SEGAs, and the treatment of hydrocephalus.

When medical management fails to adequately control their seizures, TSC patients may be considered for surgical treatment. Epilepsy surgery for these children can be challenging. The presence of multiple cortical tubers can make identification of the epileptogenic focus difficult. Occasionally, more than one focus may be present. Better outcomes are expected when a single cortical tuber can be identified as the epicenter of a patient's seizure activity, showing a strong correlation between imaging and EEG studies [42]. The presence of multiple tubers, however, is not an absolute contraindication to surgery. In some cases, use of invasive intracranial monitoring may allow the surgeon to pinpoint the primary seizure focus and assist with rational surgical planning [108].

Even in those patients in whom no clear seizure focus exists, surgery may provide some palliation in terms of reducing the severity or frequency of seizures. For example, corpus callosotomy may be an option, in particular if the child suffers from frequent drop attacks.

Surgery also serves a role in the treatment of TSC patients who develop SEGA. In general, the standard

of care for this lesion remains complete surgical excision, via a transcallosal or transcortical approach. Early diagnosis, followed by complete excision may minimize the morbidity and mortality associated with this complication of TSC [91, 106]. Certain patients may not tolerate surgical excision of these lesions, however. In this group of patients, a CSF diversionary procedure may be warranted if the lesion is causing obstructive hydrocephalus.

Other

The medical management of epilepsy associated with TSC depends on the pattern of seizures observed. Children with infantile spasms may respond to adrenocorticotrophic hormone (ACTH) therapy [85]. The antiepileptic medication Vigabatrin has also shown promise as an effective drug for treating infantile spasms in the context of TSC [13]. Patients with generalized seizures may benefit from treatment with benzodiazepines, with or without the addition of sodium valproate. Children with complex partial and focal motor seizures can be treated with various antiepileptic medications, including carbamazepine, phenytoin, lamotrigine, or primidone [21, 46]. Patients with greater numbers of cortical tubers may be at increased risk of having seizures that remain refractory to any medical management.

Prognosis and Quality of Life

The long-term prognosis and quality of life for TSC patients are variable. Patients with mild phenotypes can lead nearly normal lives without obvious impairment. Others may experience significant morbidity and a reduced life expectancy. The most worrisome complications relate to the CNS and renal systems. Young patients may suffer from serious morbidity or death due to the development of SEGA. Older patients are at risk of developing end-stage renal failure. Death occasionally can result from status epilepticus, or pneumonia.

Future Perspectives

Increasing understanding regarding the molecular basis of TSC may lead to the development of new, targeted therapies in the near future. As mentioned previously, the TSC1 and TSC2 gene products work together to inhibit signaling via the insulin receptor/phosphoinositide 3-kinase/mTOR pathway. Inhibitors of mammalian target of rapamycin (mTOR) have been developed. These drugs, along with others such as the farnesyltransferase inhibitors, may serve a future role in the treatment of patients with TSC [77].

Von Hippel-Lindau Disease

Epidemiology

Von Hippel-Lindau disease (VHL) is an autosomal dominant, inherited disorder characterized by cystic or neoplastic changes in many organ systems, in addition to the development of benign hemangioblastomas of the CNS. It has also been referred to as retinocerebellar angiomatosis, due to the vascular changes evident in both the ophthalmologic and nervous systems. The annual incidence of VHL is approximately 1/40,000 births – similar to NF II.

The VHL tumor suppressor gene has been identified on chromosome 3p25. Its gene product normally plays a role in targeting the alpha subunit of hypoxia-inducible factor (HIF) for ubiquitination, and subsequent proteasomal degradation, thereby helping to limit angiogenic activity [41].

Symptoms and Clinical Signs

A common ophthalmologic manifestation of VHL is the retinal hemangioblastoma. These lesions occur in over half of all VHL patients, and become symptomatic in approximately 20% of them. They typically arise bilaterally, and in multiple locations. Fluorescein retinal angiography aids in the early detection of these lesions. Early detection and treatment may minimize the risks of hemorrhage and retinal detachment. Additional systemic findings associated with VHL include pancreatic cysts and islet cell tumors, renal cysts and renal cell carcinoma, as well as pheochromocytoma.

The most common CNS manifestation of VHL is the characteristic cerebellar hemangioblastoma (Fig. 6). Within the CNS, three quarters of these lesions are cerebellar in location, with the majority of the remaining hemangioblastomas located within the spinal cord. Hemangioblastomas of the cerebral hemispheres account for only a small minority of lesions. Patients with cerebellar lesions may present with complaints due to increase intracranial pressure, such as headache, nausea, vomiting, or visual disturbances. Less often, they may present suddenly with symptoms secondary to acute hemorrhage, including gross cerebellar dysfunction or decreased level of consciousness. Compared to hemangioblastomas arising in the general population, those occurring in VHL patients tend to become symptomatic at an earlier age [12]. In addition, VHL patients are prone to developing multiple lesions within the CNS.

Fig. 6 Axial T1-weighted MRI following gadolinium depicting a posterior fossa tumor which enhances homogeneously. Note the mild degree of brainstem edema here

Spinal hemangioblastomas also occur in VHL patients. These lesions are predominantly intramedullary in location, and typically abut the pial surface of the cord at some point. The cystic component seen in cerebellar hemangioblastomas is often absent in the spinal cord; however, an associated syrinx may be evident. Patients with spinal hemangioblastomas may be asymptomatic, or may develop pain or long tract findings.

Diagnosis

The diagnosis of VHL is a clinical one, requiring the presence of one major manifestation of the disease in a patient with a positive family history, or at least two major features (at least one being a hemangioblastoma) in a patient lacking this family history [84]. Despite the fact that the majority of patients diagnosed with a cerebellar hemangioblastoma do not suffer from VHL, one should maintain a high index of suspicion for this disease. Few patients ultimately diagnosed with VHL actually have a known positive family history for this disorder. Patients with multiple lesions, or those presenting at a young age, are in a high risk group for having VHL as the underlying etiology for their hemangioblastomas.

The most common diagnostic adjunct for the diagnosis of the CNS manifestations of VHL are CT and MRI scans. On CT scan of the brain, hemangioblastomas typically appear as a cystic mass with an associated hyperdense mural nodule, which enhances brightly with IV contrast. This nodule often abuts a pial surface. Most lesions are found within the cerebellar hemispheres. MRI of the brain reveals a hypo- to isointense nodule on T1-weighted images, and hyperintense on T2-weighted images, which enhances strongly with contrast administration. Angiography remains slightly more sensitive for the detection of smaller lesions, but is not commonly used as an initial investigation in this patient population.

Upon confirmation of the diagnosis of VHL, adequate follow-up and monitoring is required. Between the ages of 0–2 years, annual physical examination including an ophthalmologic assessment is warranted. Urine catecholamines should be measured every 1–2 years after this point. At approximately age 11, serial imaging of the craniospinal axis, along with abdominal ultrasound are recommended on a biannual basis [25].

Treatment

Surgery

The treatment of cerebellar hemangioblastomas in VHL parallels the treatment used in the spontaneously-arising variety. Complete surgical excision is the goal of treatment, taking care to remove the mural nodule in order to prevent recurrence. The wall of the accompanying cyst does not need to be resected in its entirety. For asymptomatic spinal lesions, observation with serial imaging is one strategy often used. Once symptomatic, an attempt at surgical resection should be considered [67, 68]. Some authors, however, suggest selective surgical resection for asymptomatic spinal hemangioblastomas [81]. After complete resection, the appearance of additional lesions are more likely to represent new primary lesions rather than a recurrence.

Radiation Therapy

Although not common, radiosurgery has been used as a modality in the treatment of hemangioblastomas associated with VHL. Chang et al. reviewed their experience treating 29 lesions in 13 patients with underlying VHL, using linear accelerator-based radiosurgery [11]. Their mean follow-up was just under 4 years. Only one lesion (3%) showed evidence of progression during this period. Five lesions disappeared on subsequent imaging studies, 16 regressed, and seven remained unchanged. Despite somewhat limited follow-up, they suggested that radiosurgery may be an alternative to microsurgical resection of hemangioblastomas. This modality may prove useful in treating those lesions that are difficult to access, or those in which the risks of surgical resection in an asymptomatic patient may be prohibitive (e.g., high spinal cord lesions).

Prognosis and Quality of Life

The main contributors to a poor prognosis or reduced quality of life in VHL patients are the presence of CNS hemangioblastomas, or the development of renal cell carcinoma. Niemela et al. examined a series of 110 consecutive patients diagnosed with CNS hemangioblastoma during the period from 1953 to 1993, 14 of whom had underlying VHL [70]. Among the VHL patients, the mean age at diagnosis of their CNS hemangioblastoma was 33 years, and the mean age at which renal cell carcinoma developed was 43 years of age.

Sturge-Weber Syndrome

Epidemiology

Sturge-Weber syndrome (SWS) is a rare neurocutaneous syndrome involving the vasculature of the skin, eyes, meninges, and brain. It has also been referred to as encephalotrigeminal angiomatosis. Tumorigenesis is not a feature of this disorder. Little is known about the underlying genetic etiology of SWS, and no clear pattern of inheritance has been identified. The vascular anomalies seen in SWS are thought to stem from abnormal embryogenesis during weeks 5–8 of gestation. There appears to be no predilection for any particular race or sex in SWS. The incidence is thought to be approximately 1/50,000 [31]. A rare variant of this disorder is known as Klippel-Trenaunay-Weber syndrome, or spinal cutaneous angiomatosis. This subgroup of patients exhibit dermatomally distributed cutaneous hemangiomas, with spinal hemangiomas involving the same dermatomal region of the cord.

Symptoms and Clinical Signs

The cardinal clinical features of SWS include a congenital, unilateral facial nevus, seizures, mental retardation, hemiparesis, and altered vision. The characteristic facial nevus (port-wine stain or salmon patch) is typically located along the first or second division of the trigeminal nerve. This nevus may persist transiently, or permanently. On occasion, a bilateral nevus is present. In the forme fruste of SWS, this cutaneous lesion may be entirely absent. In addition, the presence of such a nevus is not pathognomonic for SWS, as most children born with this lesion do not have underlying SWS.

The ophthalmologic manifestations of SWS include glaucoma, retinal detachment, retinal vascular tortuosity, strabismus, and buphthalmos. In addition, choroidal, conjunctival, or episcleral hemangiomas may be seen. Of these disorders, glaucoma is the most common, affecting between 30%–50% of SWS patients. Glaucoma usually develops in the eye ipsilateral to the facial nevus, and often during the first 2 years of life.

Within the CNS, and ipsilateral to the facial nevus, patients with SWS may develop leptomeningeal venous angiomatosis (Fig. 7). In up to 15%, this abnormality occurs bilaterally. Pathologically, this lesion consists of thin-walled venous malformations within the pia mater, causing the meninges to take on a thick, darkened purple appearance. The underlying brain often shows evidence of cortical atrophy, calcification, as well as associated enlargement of the choroid plexus.

This leptomeningeal angiomatosis may produce symptoms including hemiparesis, visual disturbance (hemianopsia), seizures, and cognitive impairment. These findings are often present to some degree prior to 2 years of age. Seizures affect up to 80% of SWS patients. Seizure onset occurs typically during the first year of life, prior to the development of hemiparesis [88]. The seizure semiology is often that of either partial motor or generalized tonic-clonic epilepsy, and may follow a remitting and relapsing course. In addition, hypoxia and microcirculatory stasis are thought to play a role in seizure etiology. In addition to seizures, some children may show a step-wise pattern of neurologic decline, thought to be secondary to ischemic events resulting from venous occlusion [101]. SWS patients may be classified according to the presence or absence of key cutaneous, neurologic, and ocular findings (Table 4).

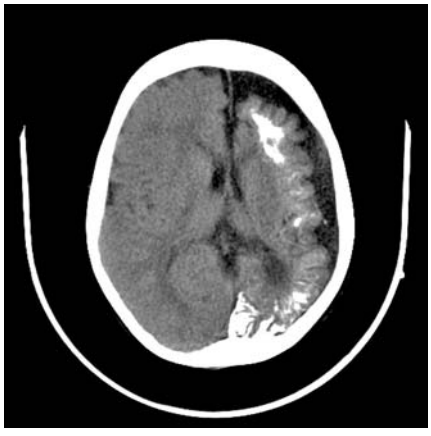


Fig. 7 Unenhanced axial CT showing profound calcification of the left hemispheric cortex in a 5-year-old male with Sturge Weber Syndrome who presented with intractable epilepsy. Such patients may be candidates for hemispherectomy to control their seizures

Table 4 Roach Scale for classification of Sturge-Weber Syndrome patients

Type I	both facial and leptomeningeal angiomas present, may have glaucoma
Type II	facial angioma alone, may have glaucoma
Type III	leptomeningeal angioma alone, usually no glaucoma

Diagnosis

The diagnosis of SWS is often possible based on the characteristic facial nevus, combined with findings at neuroimaging. On CT scan, the brain typically shows evidence of calcification of meningeal arteries, cortical/subcortical veins, and atrophy of the associated cortex (Fig. 7). MRI of the brain with IV contrast may disclose areas of meningeal angiomatosis. Since calcification may not be evident in the earliest stages of disease, MRI may be more appropriate in the initial work-up of these patients. Perfusion abnormalities may be identified using modalities such as single-photon emission computed tomography or positron emission tomography. Abnormalities seen with these modalities may precede evidence of atrophy or calcification seen later on CT or MRI scans [52].

EEG is routine in the work-up of SWS patients suffering from epilepsy. Video-EEG monitoring is useful in the preoperative planning stage. In addition, invasive cortical monitoring, or magnetoencephalography may assist in defining the seizure focus in these patients.

Treatment

Surgery

The primary role for neurosurgery in SWS patients is for control of medically-refractory epilepsy. Due to the rarity of this disorder, it is difficult to define the most appropriate treatment strategy for these patients. Early surgery has been proposed by some, in order to prevent subsequent development of hemiparesis [34]. Hoffman et al. reported on the relationship between seizure control and subsequent developmental outcome, comparing children with SWS treated surgically versus those managed medically [34]. They found a higher chance of maintaining normal or nearly normal function (as measured by intelligence quotient scores) using surgical therapy as opposed to continued medical management. Others suggest reserving surgery solely for patients with medically intractable seizures and progressive neurologic decline [86]. Many surgical strategies have been employed in the treatment of these patients, including focal cortical resection, peri-insular hemispherectomy, hemispherectomy, lobectomy, corpus callosotomy, and vagal nerve stimulation. Surgery may provide complete relief from seizure in up to 65%–81% of patients, with additional patients experiencing some degree of reduction in seizure frequency or severity [47, 88].

Other

Medical management of seizures in SWS is usually the first line treatment. Seizure control is possible in up to 40% of SWS patients using antiepileptic medications [3]. Multiple agents have been used [88, 101].

Prognosis and Quality of Life

The prognosis and quality of life of patients with SWS relate in part to whether the disease affecting the CNS is focal or holo-hemispheric [101]. Up to 50%–60% with holo-hemispheric SWS will have some degree of developmental delay. Profound delay is expected in cases of bilateral CNS SWS. Patients with focal SWS are expected to have a decent prognosis and quality of life provided that their seizures are well controlled either surgically or medically.

References

1. Al-Saleem T, Wessner LL, Scheithauer BW, et al. Malignant tumors of the kidney, brain, and soft tissues in children and young adults with tuberous sclerosis. Cancer 1998;83:2208–2216
2. Andrews DW, Suarez O, Goldman HW, et al. Stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of acoustic schwannomas: comparative observations of 125 patients treated at one institution. Int J Radiat Oncol Biol Phys 2001;50:1265–1278
3. Arzimanoglou A, Aicardi J. The epilepsy of Sturge-Weber syndrome: clinical features and treatment in 23 patients. Acta Neurol Scand 1992;140:s18–s22
4. Arzimanoglou A, Andermann F, Aicardi J, et al. Sturge-Weber syndrome. Indications and results of surgery in 20 patients. Neurology 2000;55:1472–1479
5. Bader JL. Neurofibromatosis and cancer: an overview. Dysmorphol Clin Genet 1987;1:43–48

6. Baser ME, R Evans DG, Gutmann DG. Neurofibromatosis 2. Curr Opin Neurol 2003;16(1):27–33
7. Baser ME, Kuramoto L, Joe H, et al. Genotype-phenotype correlations for nervous system tumors in neurofibromatosis 2: a population-based study. Am J Hum Genet 2004;75(2):231–239
8. Bebin EM, Gomez MR. Prognosis in Sturge-Weber disease: comparison of unihemispheric and bihemispheric involvement. J Child Neurol 1988;3:1811–1814
9. Bebin EM, Kelly PI, Gomez MR. Surgical treatment for epilepsy in cerebral tuberous sclerosis. Epilepsia 1993;34:651–657
10. Chamberlain MC, Arafe MR. Recurrent chiasmatic-hypothalamic glioma treated with oral etoposide. J Clin Oncol 1995;13:2072–2076
11. Chang SD, Meisel JA, Hancock SL, et al. Treatment of hemangioblastomas in von Hippel-Lindau disease with linear accelerator-based radiosurgery. Neurosurgery 1998;43(1):28–34
12. Conway JE, Chou D, Clatterbuck RE, et al. Hemangioblastomas of the central nervous system in von Hippel-Lindau syndrome and sporadic disease. Neurosurgery 2001;48(1):55–62
13. Curatolo P, Verdecchia M, Bombardieri R. Vigabatrin for tuberous sclerosis complex. Brain Dev 2001;23(7):649–653
14. Czyzyk E, Jozwiak S, Roszkowski M, et al. Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol 2003;18(7):471–478
15. Danoff BF, Kramer S, Thompson N. The radiotherapeutic management of optic gliomas of children. Int J Radiat Oncol Biol Phys 1980;6:45–50
16. Ducatman B, Scheithauer B, Piepgras D, et al. Malignant peripheral nerve sheath tumors: a clinicopathologic study of 120 cases. Cancer 1986;57:2006–2021
17. Farmer JP, Khan S, Khan A, et al. Neurofibromatosis type 1 and the pediatric neurosurgeon: a 20-year institutional review. Pediatr Neurosurg 2002;37(3):122–136
18. Feldmann R, Denecke J, Grenzebach M, et al. Neurofibromatosis type 1: motor and cognitive function and T2-weighted MRI hyperintensities. Neurology 2003;61(12):1725–1728
19. Ferner RE, Lucas JD, O'Doherty MJ, et al. Evaluation of 18-fluorodeoxyglucose positron emission tomography in the detection of malignant peripheral nerve sheath tumors in neurofibromatosis 1. J Neurol Neurosurg Psychiatry 2000;68:353–357
20. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis 1. Cancer Res 2002;62:1573–1577
21. Franz DN, Tudor C, Leonard J, et al. Lamotrigine therapy of epilepsy in tuberous sclerosis. Epilepsia 2001;42(7):935–940
22. Frerebeau P, Benezech J, Segnarbieux F, et al. Intraventricular tumors in tuberous sclerosis. Childs Nerv Syst 1985;1:45–48
23. Friedman HS, Krischer JP, Burger P, et al. Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study. J Clin Oncol 1992;10:249–256
24. Friedman JM, Birch PH. Type 1 neurofibromatosis. A descriptive analysis of the disorder in 1728 patients. Am J Med Genet 1997;70:138–143
25. Friedrich CA. Genotype-phenotype correlation in von Hippel-Lindau syndrome. Hum Mol Genet 2001;10(7):763–767
26. Gajjar A, Heideman RL, Kovnar EH, et al. Response of pediatric low-grade gliomas to chemotherapy. Pediatr Neurosurg 1992;19:113–121
27. Guillamo JS, Creange A, Kalifa C, et al. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. Brain 2003;126(Pt 1):152–160
28. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997;278:51–57
29. Gutmann DH, James CD, Poyhonen M, et al. Molecular analysis of astrocytomas presenting after age 10 in individuals with NF1. Neurology 2003;61(10):1397–1400
30. Habiby R, Silverman B, Listernick R, Charrow J. Precocious puberty in children with neurofibromatosis type 1. J Pediatr 1995;126:364–367
31. Haslam R. Neurocutaneous syndromes. In: Nelson WE, Behrman RE, Kliegman RM, Arvin AM, editors. Nelson textbook of pediatrics, 15th ed. Philadelphia: W.B. Saunders, 1996. p. 1707–1709
32. Heim RA, Silverman LM, Farber RA, et al. Screening for tuncated NF1 proteins. Nat Genet 1994;8:218–219
33. Hoffman HJ, Hendrick EB, Dennis M, et al. Hemispherectomy for Sturge-Weber syndrome. Childs Brain 1979;5:233–248
34. Hoffman HJ. Benefits of early surgery in Sturge-Weber syndrome. In: Tuxhorn I, Holthausen H, Beonigk H, editors. Pediatric epilepsy syndromes and their surgical treatment. London: John Libbey' 1997
35. Huson SM, Harper PS, Compston DAS. Von Recklinghausen Neurofibromatosis. A clinical and population study in South East Wales. Brain 1988;111:1355–1381
36. Huson SM, Clark P, Compston DAS, et al. A genetic study of von Recklinghausen neurofibromatosis in South East Wales. 1: prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 1991;26:704–711
37. Hyman MH, Wittemore VH. National Institutes of Health Consensus Conference: tuberous sclerosis complex. Arch Neurol 2000;57:662–665
38. Jansen FE, Braun KP, van Nieuwenhuizen O, et al. Diffusion-weighted magnetic resonance imaging and identification of the epileptogenic tuber in patients with tuberous sclerosis. Arch Neurol 2003;60(11):1580–1584
39. Jenkin D, Angyalfi S, Becker L, et al. Optic glioma in children: surveillance, resection or irradiation. Int J Radiat Oncol Biol Phys 1993;25:215–225

40. Jones AC, Danielles CE, Snell RG, et al. Molecular genetic and phenotypic analysis reveals differences between TSC1 and TSC2 associated familial and sporadic tuberous sclerosis. Hum Mol Genet 1997;6:2155–2161
41. Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer 2003;2:673–682
42. Karenfort M, Kruse B, Freitag H, et al. Epilepsy surgery outcome in children with focal epilepsy due to tuberous sclerosis complex. Neuropediatrics 2002;33(5):255–261
43. Karnes PS. Neurofibromatosis: a common neurocutaneous disorder. Mayo Clin Proc 1998;73:1071–1076
44. Kihiczak NI, Schwartz RA, Jozwiak S, et al. Sturge-Weber Syndrome. Cutis 2000;65:133–136
45. King A, Listernick R, Charrow J, et al. Optic pathway gliomas in neurofibromatosis type 1: the effect of presenting symptoms on outcome. Am J Med Genet 2003;122 A(2): 95–99
46. Kotagal P, Rothner AD. Epilepsy in the setting of neurocutaneous syndromes. Epilepsia 1993;34 (Suppl 3):s71–78
47. Kossoff EH, Buck C, Freeman JM. Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide. Neurology 2002;59(11):1735–1738
48. Kretchmar CS, Linggood RM. Chemotherapeutic treatment of extensive optic pathway tumors in infants. J Neurooncol 1991;10:263–270
49. Kwiatkowski DJ, Short MP. Tuberous Sclerosis. Arch Dermatol 1994;130:348–354
50. Kwiatkowski DJ. Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biol Therap 2003;2(5):471–476
51. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy – results of the first French prospective study for the French Society of Pediatric Oncology. J Clin Oncol 2003;21(24):4572–4578
52. Lee JS, Asano E, Muzik O, et al. Sturge-Weber syndrome: Correlation between clinical course and FDG PET findings. Neurology 2001;57:189–195
53. Lin V, Daniel S, Forte V. Is a plexiform neurofibroma pathognomonic of neurofibromatosis type I? Laryngoscope 2004;114(8):1410–1414
54. Linskey ME, Lunsford LD, Flickinger JC. Tumor control after stereotactic radiosurgery in neurofibromatosis patients with bilateral acoustic tumors. Neurosurgery 1992;31(5):829–838
55. Listernick R, Charrow J, Greenwald M. Emergence of optic pathway glioma in children with neurofibromatosis type 1 after normal neuroimaging results. J Pediatr 1992;121:584–587
56. Listernick R, Charrow J, Greenwald M, Mets M. Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. Pediatr 1994;125:63–66
57. Listernick R, Louis DN, Packer RJ, Gutmann DH. Optic pathway gliomas in children with neurofibromatosis 1: consensus statement from the NF1 Optic Pathway Glioma Task Force. Ann Neurol 1997;41:143–149
58. Liu GT, Brodsky MC, Phillips PC, et al. Optic radiation involvement in optic pathway gliomas in neurofibromatosis. Am J Ophthalmol 2004;137(3):407–414
59. MacCollin M, Kwiatkowski D. Molecular genetic aspects of the phakomatoses: Tuberous sclerosis complex and neurofibromatosis 1. Curr Opin Neurol 2001;14:163–169
60. Mahoney DH Jr, Cohen ME, Friedman HS, et al. Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study. Neuro-oncol 2000;2(4):213–220
61. Manning BD, Cantley LC. United at last: the tuberous sclerosis complex gene products connect the phosphoinositide 3-kinase/Akt pathway to mammalian target of rapamycin (mTOR) signaling. Biochem Soc Trans 2003;31(3): 573–578
62. Massimino M, Spreafico F, Cefalo G, et al. High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. J Clin Oncol 2002;20(20):4209–4216
63. Masuda A, Fisher LM, Oppenheimer ML, et al. Hearing changes after diagnosis in neurofibromatosis type 2. Otol Neurotol 2004;25(2):150–154
64. Mautner VF, Friedrich RE, von Deimling A, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis type 1: MRI supports the diagnosis of malignant plexiform neurofibroma. Neuroradiology 2003;45(9):618–625
65. Moffat DA, Quaranta N, Baguley DM, et al. Management strategies in neurofibromatosis type 2. Eur Arch Otorhinolaryngol 2003;260(1):12–18
66. Mulvihill JJ, Parry DM, Sherman JL, et al. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). Ann Int Med 1990;113:39–52
67. Neumann HPH, Eggert HR, Weigel K, et al. Hemangioblastomas of the central nervous system. A 10-year study with special reference to von Hippel-Lindau syndrome. J Neurosurg 1989;70:24–30
68. Neumann HPH, Eggert HR, Scheremet R, et al. Central nervous system lesions in von Hippel-Lindau syndrome. J Neurol Neurosurg Psychiatry 1992;55:898–901
69. Neurofibromatosis. Conference Statement. National Institutes of Health Consensus Development Conference. Arch Neurol 1988;45:575–578, Neurofibromatosis. NIH Consensus Statement Online 1987;6:1–19, http://consensus.nih.gov/cons/064/064_statement.htm
70. Niemela M, Lemeta S, Summanen P, et al. Long-term prognosis of haemangioblastoma of the CNS: impact of von Hippel-Lindau disease. Acta Neurochir (Wien) 1999;141(11):1147–1156
71. North K. Neurofibromatosis type 1. Am J Med Genet 2000;97:119–127
72. O'Callaghan FJ, Harris J, Joinson C, et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. Arch Dis Child 2004;89(6):530–533
73. Ojemann RG. Management of acoustic neuromas (vestibular schwannomas). Clin Neurosurg 1993;40:489–535

74. Osborne JP. Diagnosis of tuberous sclerosis. Arch Dis Child 1988;63:1423–1425
75. Packer RJ, Sutton LM, Bilaniuk LT, et al. Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. Ann Neurol 1988;23:79–85
76. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for progressive low-grade gliomas of childhood. J Clin Oncol 1992;11:850–857
77. Pan D, Dong J, Zhang, Gao X. Tuberous sclerosis complex: from Drosophila to human disease. Trends Cell Biol 2004;14(2):78–85
78. Perrin RG, Guha A. Malignant peripheral nerve sheath tumors. Neurosurg Clin N Am 2004;15(2):203–216
79. Peterson G. Genetic testing. Hematol Oncol Clin N Am 2000;14:939–952
80. Pierce SM, Barnes PD, Loeffler JS, et al. Definitive radiation therapy in the management of symptomatic patients with optic glioma: survival and long-term effects. Cancer 1990;65:45–57
81. Pietila TA, Stendel R, Schilling A, et al. Surgical treatment of spinal hemangioblastomas. Acta Neurochir (Wien) 2000;142(8):879–886
82. Pons MA, Finlay JL, Walker RW, et al. Chemotherapy with vincristine and etoposide in children with low-grade astrocytoma. J Neurooncol 1992;14:151–158
83. Riccardi VM. Neurofibromatosis: phenotype, natural history, and pathogenesis, 2nd ed. Baltimore: Johns Hopkins University Press; 1992
84. Richard S, Graff J, Lindau J, Resche F. Von Hippel-Lindau disease. Lancet 2004;363:1231–1234
85. Riikonen R, Simell O. Tuberous sclerosis and infantile spasms. Dev Med Child Neurol 1990;32:203–209
86. Roach ES, Riela AR, Chugani HT, et al. Sturge-Weber syndrome. Recommendations for surgery. J Child Neurol 1994;9:190–192
87. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624–628
88. Rochkind S, Hoffman HJ, Hendrick EB. Sturge-Weber syndrome: natural history and prognosis. J Epilepsy 1990;3 (Suppl):293–304
89. Rosenstock JG, Packer RJ, Bilaniuk LT, et al. Chiasmatic optic glioma treated with chemotherapy. A preliminary report. J Neurosurg 1985;63:862–866
90. Rosser T, Packer RJ. Intracranial neoplasms in children with neurofibromatosis 1. J Child Neurol 2002;17(8): 630–637
91. Roszkowski M, Drabik K, Barszcz S, Jozwiak S. Surgical treatment of intraventricular tumors associated with tuberous sclerosis. Childs Nerv Sys 1995;11:335–339
92. Rowe JG, Radatz MW, Walton L, et al. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. J Neurol Neurosurg Psychiatry 2003;74(9):1288–1293
93. Samii M, Matthies C, Tatagiba M. Management of vestibular schwannomas (acoustic neuromas): auditory and facial nerve function after resection of 120 vestibular schwannomas in patients with neurofibromatosis 2. Neurosurgery 1997;40(4):69–705
94. Sampson JR. TSC1 and TSC2: genes that are mutated in the human genetic disorder tuberous sclerosis. Biochem Soc Trans 2003;31(3):592–596
95. Scheithauer BW. The neuropathology of tuberous sclerosis. J Dermatol 1992;19:897–903
96. Schwartz MS, Otto SR, Brackmann DE, et al. Use of a multichannel auditory brainstem implant for neurofibromatosis type 2. Stereotactic and functional neurosurgery 2003;81(1–4):110–114
97. Sparagana SP, Roach ES. Tuberous sclerosis complex. Curr Opin Neurol 2000;13:115–119
98. Subach BR, Kondziolka D, Lunsford LD, et al. Stereotactic radiosurgery in the management of acoustic neuromas associated with neurofibromatosis type 2. J Neurosurg 1999;90:815–822
99. Sujansky E, Conradi S. Outcome of Sturge-Weber syndrome in 52 adults. Am J Med Genet 1995;57(1):35–45
100. Tator CH. Acoustic neuromas: management of 20 cases. Can J Neuro Sci 1985;12:353–357
101. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber Syndrome: a review. Pediatr Neurol 2004;30:303–310
102. Torres OA, Roach ES, Delgado MR, et al. Early diagnosis of subependymal giant cell astrocytoma in patients with tuberous sclerosis. J Child Neurol 1998;13:173–177
103. Vivarelli R, Grosso S, Calabrese F, et al. Epilepsy in neurofibromatosis 1. J Child Neurol 2003;18(5):338–342
104. Waggoner DJ, Towbin J, Gottesman G, et al. A clinic-based study of plexiform neurofibromas in neurofibromatosis 1. Am J Med Genet 2000;92:132–135
105. Webb DW, Fryer AE, Osborne JP. On the incidence of fits and mental retardation in tuberous sclerosis. J Med Genet 1991;28:395–397
106. Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. Dev Med Child Neurol 1996;38:146–155
107. Weiner DM, Ewalt DH, Roach ES, Hensle TW. The tuberous sclerosis complex: a comprehensive review. J Am Coll Surg 1998;187:548–561
108. Weiner HL. Tuberous sclerosis and multiple tubers: localizing the epileptic zone. Epilepsia 45(Suppl)2004;4:41–42
109. Xu GF, O'Connell P, Viskochil D, et al. The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell 1990;62:599–608
110. Yoshida K, Kobayashi T, Tanaka T, Mori Y. Radiosurgery for bilateral neurinomas associated with neurofibromatosis type 2. Surg Neurol 2000;53:383–390

Supratentorial Hemispheric Low-Grade Gliomas in Children

21

Paul Chumas, Atul Tyagi

Epidemiology – 346

Predisposing Conditions – 346

Symptoms and Clinical Signs – 346

Diagnostics – 347

Histopathologic Features – 347
Fibrillary Astrocytoma
Dysembryoblastic Neuroepithelial Tumors
Gangliogliomas
Pleomorphic Xanthoastrocytoma
Subependymal Giant Cell Astrocytoma
Desmoplastic Infantile Gangliogliomas

Imaging Features – 349

Treatment
Natural History – 350

Treatment Strategies – 350
Observation
Surgery
Chemotherapy
Radiotherapy

Follow-up/Specific Problems and Measures – 352

Recommended Reading – 352

References – 352

Epidemiology

Gliomas make up more than half of all pediatric brain tumors and over two thirds of these are "low grade." "Low-grade gliomas" (LGGs), as defined by the WHO, encompass grade I and grade II tumors. The most common grade I tumors include: pilocytic astrocytomas (PAs), dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, and pleomorphic xanthoastrocytomas (PXAs). The most common grade II tumors are astrocytoma (fibrillary), oligodendrogliomas, and mixed oligoastrocytomas.

LGGs constitute the largest group of cerebral hemispheric tumors in children (approximately 60%) and occur at an incidence of 5 per million children per year. Most series in the literature are small, retrospective, single institution studies, covering long periods during which investigation and treatment opportunities have changed. From these studies it would appear that roughly half of these LGGs are pilocytic or fibrillary astrocytomas with the rest being made up from the diverse group of lesions outlined above. In comparison, high-grade gliomas comprise approximately 20% of all hemispheric tumors.

The incidence of pediatric astrocytomas appears to be increasing – although in part this is due to the improved availability of MRI. The mean age at diagnosis and operation of this group of children is 6–11 years. Despite their diverse pathology, these tumors tend to present and behave in a similar pattern and have an indolent course. Other chapters in this book deal specifically with optic/chiasmatic and thalamic tumors and we have therefore concentrated on supratentorial hemispheric LGGs.

Predisposing Conditions

An underlying cause (genetic, environmental, or both) has not been identified for these tumors but some children will be affected by a genetic syndrome which predisposes them to develop CNS tumors – some of which will be hemispheric:

Neurofibromatosis Type I: Neurofibromatosis type I is caused by mutations within the Neurofibromin gene. This gene functions as a tumor suppressor gene located on the long arm of the chromosome 17(17q11.2). Five to fifteen percent of NF I patients have LGGs. These usually arise in the visual pathways and hypothalamus but other regions of the brain can be affected. If only visual pathway gliomas are considered, the ratio of NF I patients rises to 60%. The majority of LGGs in these patients have an indolent clinical course. Spontaneous partial regression of hypothalamic and optic pathway gliomas has been described.

Tuberous Sclerosis: Tuberous sclerosis is associated with subependymal giant cell astrocytomas in the brain and widespread hamartomas in almost every organ. Patients commonly have adenoma sebaceum, mental retardation and epilepsy. Tuberous sclerosis is an autosomal dominant disorder with mutations identified on chromosomes 16p 13 and 9q34, the former coding for tuberin – a member of the ras-GTPase-activating protein signaling pathway. Subependymal giant cell astrocytomas are classically located near the foramen of Monro and can cause obstructive hydrocephalus. Cortical tubers may be responsible for epilepsy.

Li-Fraumeni Syndrome: Li-Fraumeni syndrome LGG may be seen in these patients where a germ line mutation occurs in the p53 locus on chromosome 17p13. This triggers the susceptibility to develop multiple tumors throughout life.

Cytogenetic studies have generally been unrewarding for most LGGs, with the majority of tumors having a normal karyotype or an apparently random pattern of chromosomal abnormalities. Mutation of the p53 gene and deletions on the short arm of chromosome 17 are uncommon in pediatric LGG. This is in contrast to adult studies where these changes are seen fairly frequently and is further evidence that the cause and behavior of these tumors differs between children and adults. Likewise, adult oligodendrogliomas are frequently associated with chromosomal alterations in 1p and 19q while these changes are rarely seen in children. However, PAs in children often have deletion of the long arm of chromosome 17. This is the site of the neurofibromin gene and raises the question of the role of this gene locus in the development of sporadic PAs.

Symptoms and Clinical Signs

The clinical presentation varies depending upon the location of the tumor and usually falls into one of the following categories:

1. Seizures
2. Neurological deficit
3. Raised intracranial pressure due to mass effect or hydrocephalus

LGGs involving the cerebral hemispheres tend to present with seizures and/or neurological deficit depending upon the area affected. In the Pittsburgh series (71 children), 58% had epilepsy, 45% focal neurology, 41% headaches, and 27% papilledema. This group noted that presentation with raised ICP had become less common in the MRI era. However, delayed diagnosis is not uncommon in these patients due to the slow rate of growth of these lesions. This

is particularly the case for patients presenting with complex partial seizures and medial temporal lesions.

Acute or subacute presentations may occur due to obstructive hydrocephalus or occasionally after intratumoral hemorrhage. In particular, patients with tuberous sclerosis may present with hydrocephalus due to their associated subependymal giant cell astrocytoma. Likewise, desmoplastic infantile gangliogliomas often present with macrocephaly and symptoms of raised ICP in infants ("sun-setting," bulging fontanelle, etc.).

Diagnostics

The two main areas of diagnostic importance are the histological and imaging features of this disparate group of tumors. These will therefore be outlined in turn.

Histopathologic Features

Pilocytic astrocytomas (PAs) have two commonly described histologic patterns: juvenile and adult types, with the former predominating in children. The juvenile variety demonstrates areas of compact bipolar tumor cells with elongated nuclei and fine cytoplasmic processes that stain for glial fibrillary acidic protein (GFAP). These compact areas are interspersed with loosely packed areas of micro cysts characterized by stellate astrocytes containing eosinophilic proteinaceous material and Rosenthal fibers. Macrocysts are also frequently seen. Multinucleation, giant cell formation and nuclear hyperchromasia, vascular proliferation, and endothelial hyperplasia may be seen in these tumors but are not indicative of malignancy and PAs show a low proliferation index using Ki-67.

A histological variant has recently been reported in patients with chiasmatic/hypothalamic tumors and has been termed *pilomyxoid astrocytoma* (Fig. 1). Microscopically these tumors are monomorphous and contain piloid cells in a myxoid background. This variant tends to occur in a younger age group and overall survival and progression-free survival has been found to be significantly worse than with normal PAs (PFS at 1 year 69.2% as compared to 38.7%) [1]. The significance of this histological variant in other sites is yet to be ascertained.

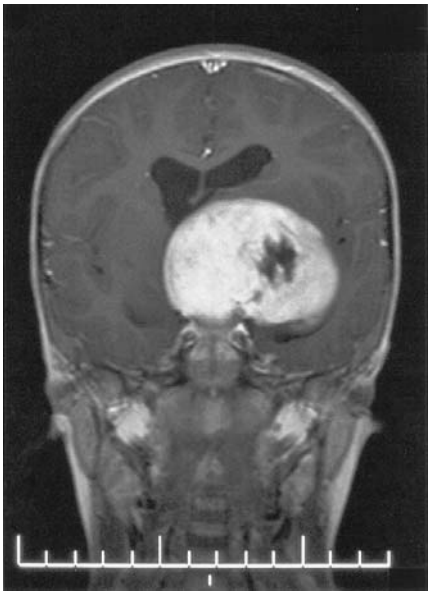


Fig. 1 Coronal T1-weighted MRI scan following gadolinium with a pilomyxoid astrocytoma in the hypothalamic/chiasmatic region

Fibrillary Astrocytoma

Compared to the other LGGs, the margins of these tumors are not as well defined. The astrocytic cells tend to be well differentiated and the density of cells is not too different from that of normal white matter. Nuclear atypia, and mitoses are rare but microcystic changes can be seen in these tumors.

Oligodendrogliomas Calcification is commonly seen in these tumors and the tumor cells show a characteristic "fried egg" appearance due to the presence of a hyperchromatic nucleus surrounded by a perinuclear halo. Some tumors show a varying degree of an astrocytic component and these tumors are called **oligoastrocytomas**. Pure oligodendrogliomas are uncommon in the pediatric age group. A third of supratentorial gliomas, however, can have an oligodendroglial component and are categorized as **mixed gliomas/oligoastrocytomas**. These tumors are most commonly located in the frontal lobes and a history of seizures for many years is a common presentation. There is some clinical evidence that those tumors presenting with epilepsy are more indolent than those that present with mass effect.

Dysembryoblastic Neuroepithelial Tumors

This tumor type was initially described by Daumas-Duport in young patients with epilepsy who were cured by surgical excision. Dysembryoblastic neuroepithelial tumors (DNETs) are commonly located superficially in the temporal lobes. The tumors microscopically consist of a glioneuronal element,

a nodular component made up of neurons, astrocytes and oligodendrocytes, and associated cortical dysplasia. The presence of foci of cortical dysplasia strongly suggests that DNETs result from disorganized embryogenesis.

Although the overall incidence is only 1% in patients under 20 years of age, this incidence increases to 5%–15% among patients with intractable seizures and temporal lobe tumors.

Gangliogliomas

These tumors make up 4%–8% of primary brain tumors in children, with 90% of gangliogliomas being supratentorial and the rest infratentorial. Seizures are a common presentation and the temporal lobe is the commonest location – though other lobes can be affected. The microscopic pattern seen is that of neoplastic neuronal cells scattered between neoplastic astrocytes. The astrocytic component, however, predominates. Calcification and cystic areas are frequently seen in these tumors. Recurrences can occur as a result of tumor in the lining of the cyst walls (Fig. 2).

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytomas usually present in the second decade of life with seizures and commonly arise in the temporal or parietal lobes (Fig. 3). The tumors tend to be well circumscribed and superficially located. The cells demonstrate intracellular accumulation of lipids and are associated with marked nuclear atypia but in the setting of a low mitotic index. However, approximately 20% of these lesions undergo malignant transformation and the presence of necrosis and increased mitotic activity are indicators of a poor prognosis.

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytomas arise from the walls of the lateral ventricle and are associated with tuberous sclerosis. The tumor consists of large astrocytic cells with abundant eosinophilic cytoplasm. These tumors may show immunoreactivity for both glial and neuronal markers. While the classical presentation for these tumors is with hydrocephalus, MR imaging has shown that most tumors are asymptomatic

Desmoplastic Infantile Gangliogliomas

These tumors tend to be large and superficially situated and adherent to the dura. Microscopically these tumors consist of fibroblast-like spindle shaped cells and show glial and ganglionic differentiation along with an intense desmoplastic reaction. The cells tend to be GFAP positive.

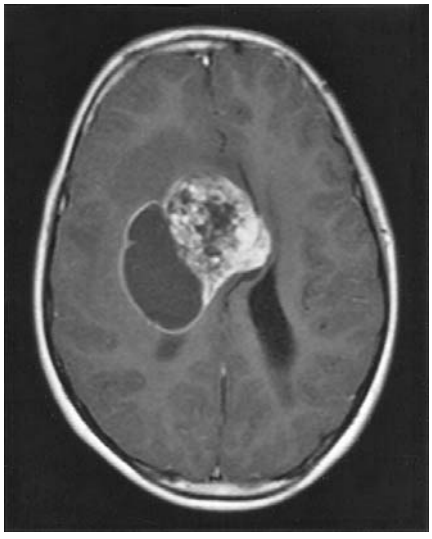


Fig. 2 A right hemispheric ganglioma is seen on the postgadolinium T1-weighted MRI scan. A solid component is seen which enhances well. The surrounding cyst walls enhance postcontrast, indicating the likelihood of tumor tissue in the walls

Fig. 3 Axial, noncontrasted CT scan showing a pleomorphic xanthoastrocytoma involving the medial temporal lobe on the left. The tumor has increased attenuation as compared to the surrounding brain

Imaging Features

MRI is the imaging modality of choice as CT may be normal in some patients with a low-grade astrocytoma. However, most LGGs are visible on CT as a low density lesion and calcification within the tumor is easily identified on CT. While imaging, in particular MRI, is sensitive in picking up abnormalities, it is not specific and the histological diagnosis can be difficult to predict. Certainly in one small adult series of 20 patients, stereotactic biopsy showed the provisional diagnosis of LGGS based on the imaging was wrong in half the patients (nine tumors were in fact grade III and one patient was found to have encephalitis). While the risk of the tumor being high grade in children is statistically smaller than in adults, the diverse tumor types seen in children means that it is difficult to be accurate regarding the pathology on imaging alone.

Pilocytic astrocytomas tend to be well defined, circumscribed lesions. PAs can be isointense, hypointense, or hyperintense on noncontrast CT examinations. Following contrast, however, these tumors enhance strongly. Surrounding cerebral edema is uncommon. A PA can present as an homogenously enhancing mass, a ring enhancing cyst or a cystic cavity with an enhancing mural nodule (Fig. 4). The enhancement may occasionally be patchy. PET scans show increased glucose metabolism in PA compared to the surrounding brain. Enhancement of the cyst wall is associated with tumor and indicates the need for the cyst wall to be excised. Involvement of the cyst wall by tumor is thought to be more common in supratentorial than infratentorial PAs. Although unusual, PAs may spread in the neuraxis and widespread meningeal dissemination can occur.

Fibrillary astrocytomas are typically hypointense or isointense to the surrounding brain on T1-weighted MRI images and hyperintense on T2-weighted images, the latter often showing much wider changes than apparent on the T1 images. Oligodendrogliomas often have areas of calcification visible on CT scans. Pleomorphic xanthoastrocytomas are seen as well-enhancing, superficially situated lesions usually associated with a cystic component and often with a mural nodule . Dysembryoplastic neuroepithelial tumors appear well demarcated areas of low attenuation on CT scans and hypointense on T1-weighted images with very little enhancement and increased signal intensity on T2-weighted images. Desmoplastic infantile gangliogliomas appear as large lesions with a solid and cystic component (Fig. 5). The solid component enhances strongly as may the cyst wall (indicating tumor). These tumors and PXAs often have extensive meningeal involvement.

Positron Emission Tomography (PET), Magnetic resonance spectroscopy (MRS), and Single Photon Emission Computer Tomography (SPECT) may have a future role in identifying progression to a more malignant grade. LGGS apart from PA are hypometabolic on PET scans but a change in the grade of the tumor results in the appearance of a hypermetabolic area. In a small study of patients with LGG who underwent MRS, an increase in choline levels over time was felt to be compatible with malignant change.

Fig. 4 T1-weighted MRI scan demonstrating a right thalamic Pilocytic astrocytoma with a central nodule surrounded by cysts

Fig. 5 CT scan with a partly cystic and solid tumor with an area of superficial calcification in the left frontal lobe. Histopathology confirmed the tumor to be a desmoplastic infantile ganglioglioma

Treatment
Natural History

The natural history of LGGS in children is yet to be defined. However, these tumors seem to be biologically distinct to those found in adults. In particular, while malignant transformation is seen in 13%–32% of adult patients with grade II gliomas, it is only rarely seen in children.

Treatment Strategies

This depends upon the age of the child, the mode of presentation and the imaging (reflecting the likely diagnosis). Table 1 is a diagrammatic overview of the various treatment strategies.

Observation

There are a number of scenarios where observation (clinical and MRI) may be appropriate. For example, in a child with an ill-defined LGG in an eloquent area picked up "incidentally" or in the setting of NFI. Likewise, patients with a history of epilepsy well controlled on anticonvulsants (Fig. 6), the proviso being that the imaging remains stable. Recent studies in adult patients have shown that significant changes in tumor volume may be missed unless specifically measured and that tumor growth may be associated with malignant transformation.

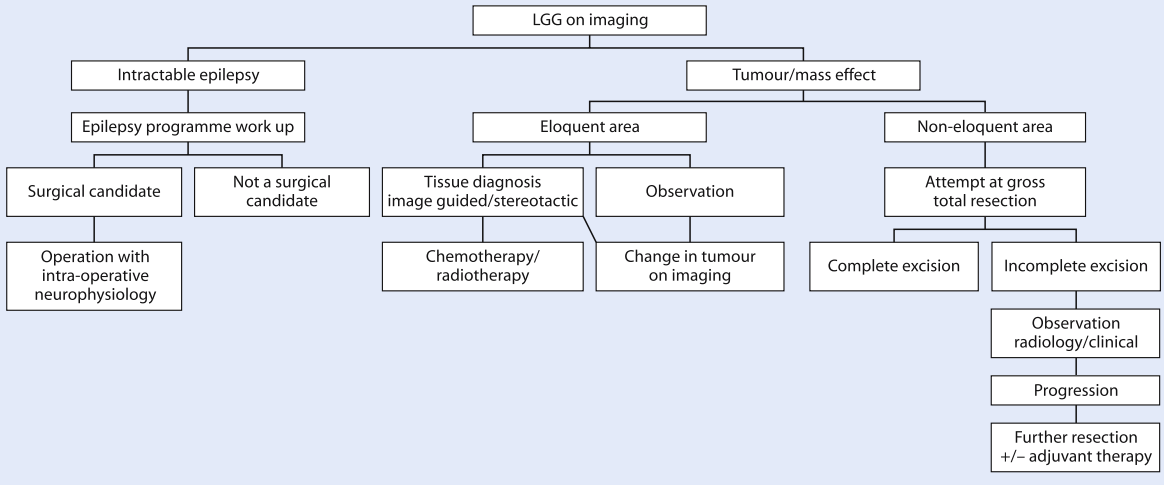
Residual tumor after surgery may also be monitored and there may be little or no change for many years. Radiological observation of LGGs shows the dynamic nature of these tumors with subtle changes in cyst size and enhancement being seen – particularly in pilocytic tumors. There are also some reports of "spontaneous involution" of LGGs over time.

Surgery

Although the evidence available is not conclusive, it would appear that the extent of tumor resection in patients with hemispheric LGGs is the most reliable prognostic factor for outcome (overall and progression-free survival) [2, 3]. Thus, if feasible, an attempt should be made at a gross total tumor removal. This will obviously depend on the location of the tumor and the type of tumor. In general, grade I tumors are more clearly defined and are therefore a more attractive surgical target than grade II tumors, which tend to be more diffuse. It is also important that the aims of surgery are clear. For "tumor surgery" the aims include obtaining a tissue diagnosis and removing as much tumor as is safe. For patients with intractable epilepsy, the decision is whether to remove the lesion alone or the lesion plus any epileptogenic "normal" tissue. Clearly patients being considered for "epilepsy surgery" need to be assessed in an epilepsy program as the aims of surgery relate to epilepsy control rather than necessarily tumor control.

The degree of tumor resection may be improved by the use of preoperative functional MRI (fMRI), or intraoperative techniques including image-guided surgery, cortical mapping, SSEPs, awake craniotomy, ultrasound, and more recently MRI. While many of these techniques are useful either preoperatively or intraoperatively for both "epilepsy surgery patients" and "tumor surgery patients," some tests, e.g., WADA,

Table 1 Treatment paradigm for hemispheric LGGs



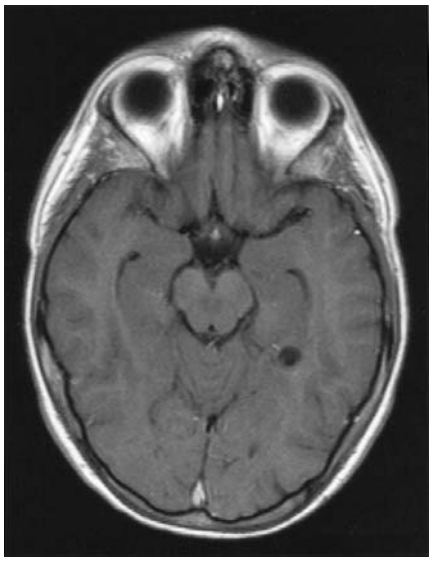


Fig. 6 Cystic lesion seen in the left posterior temporal region with faint enhancement postcontrast on T1-weighted MRI scan in a child with well-controlled epilepsy

are used almost exclusively in epilepsy surgery workups. Some of these surgical adjuncts can only be used in older children (e.g., awake craniotomy, fMRI), but Berger's group have shown that it is possible to obtain reliable information regarding speech and sensorimotor function by invasive preoperative monitoring using subdural grids.

Five-year survival rates in patients who have had a gross total resection have been reported to be up to 100% while 10-year survival rates are of the order of 80%–90% and 20-year survival rates about 75%. With regard to epilepsy control, temporal lobe surgery tends to be associated with better results than extratemporal surgery. Despite the fact that in children extratemporal surgery is more common than in adults, the results are still very encouraging with over 75% of patients being seizure free or being significantly improved. In fact, Berger and colleagues have reported a seizure-free rate of 93% after aggressive surgery utilizing intra-operative electrocorticography.

It should be stressed that while intraoperative MRI sounds appealing for these tumors, the cost-effectiveness of this technique remains to be proven. Furthermore, despite these technical advances, the MRI appearances of fibrillary tumors may be deceptive with it not being apparent until the time of surgery that the tumor is completely infiltrative and the brain may look more or less normal even under the operating microscope.

While the treatment of choice for hemispheric LGGs is surgery (at presentation and at recurrence), it is important to remember that even with residual disease these patients have a good long-term outlook and it is therefore necessary to balance aggressive surgery with possible long-term morbidity.

In patients with diffuse tumors or with tumors in eloquent areas where resection or debulking is not possible, tissue may be obtained by open surgery or stereotactically (frame or frameless).

With cystic tumors, it is necessary to decide if the cyst needs to be excised. While this decision is taken after inspection of the cyst wall at the time of surgery, it is usually possible to tell whether the cyst wall is reactive or tumoral from the uptake of contrast on the preoperative imaging. Meningeal involvement with PXA and desmoplastic infantile ganglioglioma also requires surgical consideration. In general, LGGs are not very vascular but the desmoplastic infantile ganglioglioma is a recognized exception (partly due to the age of the patients) and the surgeon and anesthetist need to be suitably prepared to prevent an ontable catastrophe.

Chemotherapy

As the blood-brain barrier is thought to be more normal in LGGs than in malignant tumors, tissue penetration of cytotoxic compounds was initially questioned. However, over recent years, the role of chemotherapy in the treatment of LGGs has become widely accepted. Most of this work has been related to the treatment of chiasmatic/hypothalamic tumors. While there is no evidence yet of chemotherapy being curative, there is good evidence of reasonable progression-free survival. Age at treatment would appear to be important with Packer et al. reporting a significant difference in 3-year progression-free survival between children under 5 years of age (74±7%) and older children (39±21%). Chemotherapy is particularly useful in this younger group as it delays the use of radiotherapy with its deleterious effects on the maturing brain. NF 1 status has been shown to be an important predictor of tumor behavior in children with LGG who receive chemotherapy. The NF 1 status predicted a prolonged progression-free survival.

The combination of vincristine and actinomycin D was the first regimen studied (1977) and found to be effective. Most studies today are based on vincristine and platinum compounds (with carboplatin having less severe nephro- and ototoxicity). While there has been no study looking specifically at supratentorial hemispheric tumors, there would appear to be reasonable evidence to offer chemotherapy if surgery is not an option (particularly in younger patients). However, the risks associated with chemotherapy need to be remembered (marrow suppression, renal toxicity, peripheral neuropathy, oto-toxicity, etc.). Late-effect studies looking at the problems caused by treatment (surgery, chemotherapy, and ra-

diotherapy) are underway and may alter the presently accepted treatment protocols.

Radiotherapy

The role of radiotherapy in adult LGGs remains ill defined. There is evidence of increased survival following radiotherapy in selected subgroups of adult patients – those with subtotally resected astrocytomas, oligodendrogliomas, and oligoastrocytomas. Even here, this positive effect of adjuvant radiotherapy appears to wane when one examines the 10-year survival figures. In children, the most experience with radiotherapy in LGGs comes from its use in patients with optic pathway gliomas. In this group, high survival (93% at 5 years and 79% at 10 years) and progression-free survival rates (82% at 5 years and 77% at 10 years) have been obtained after radiotherapy. In this particular study radiotherapy was given after the tumor was biopsied or a subtotal resection was undertaken. The vision improved in 50% and stabilized in the rest of the patients after radiotherapy.

There have been no randomized trials specifically looking at the role of radiotherapy in hemispheric LGGs in children – although there are trials underway which may shed some light on this subset of patients in due course. One single institution study concluded that radiotherapy had no role in totally resected hemispheric tumors as none of the patients who did not receive radiotherapy recurred [2]. Patients with residual disease who received radiotherapy were found to have a significant increase in progression-free survival but over-all survival was unaffected. This latter finding was attributed to the fact that tumor progression in those patients, who had not received radiotherapy, remained localized and was still amenable to further surgery.

The late effects of radiotherapy also need to be considered. These depend on the site of the brain irradiated, the volume of brain included and the dose fractionation schedule employed. Late effects include intellectual dysfunction, behavioral problems, endocrine dysfunction, second malignancies, and oto- and ocular toxicity. Cranial radiotherapy appears to increase the risk of the development of an arteritis similar to that seen in moya moya disease. The development of this complication is higher after radiotherapy in NFI patients than in sporadic cases. The second malignancies include meningiomas, gliomas, and sarcomas. Pollack et al. found that all the patients who developed malignant progression of their LGG had previously undergone radiotherapy. Similar findings have been reported in patients with optic pathway or thalamic tumors.

In an attempt to reduce these late effects, studies are underway looking at the use of conformal radiotherapy to limit dose to critical structures (e.g., hypothalamus, middle ear, etc.) and to try and relate the dose to measured late-effects. At the same time studies on the accuracy of radiotherapy (dose and volume) are also underway with comparison of the various techniques available for administration. Although there are a few reports looking at the effectiveness of radiosurgery in LGGs, this technique remains unproven.

Follow-up/Specific Problems and Measures

Table 1 is a flow chart depicting the various scenarios for patients with supratentorial LGGs. As indicated above, these patients have an excellent long-term prognosis after complete surgical excision and usually do well even in the presence of residual disease. The role of surveillance is unproven but in most studies serial imaging is included in the management protocol. In the setting of a tumor which is often indolent, the treatment aim should be to limit morbidity (as a result of either tumor growth or its treatment by surgery, chemotherapy, or radiotherapy). In patients with intractable epilepsy, improvements in epilepsy control has been shown to directly impact on their schooling and on their long-term employment prospects.

Recommended Reading

1. Kaye AH, Laws ER. Brain tumors – an encyclopedic approach. 2nd edn. Toronto: Churchill Livingstone; 2001
2. Keating RF, Goodrich JT, Packer RJ. Tumors of the pediatric central nervous system. New York: Thieme; 2001
3. Kleihues P, Cavenee WK. Pathology and genetics of tumors of the nervous system. Lyon: International Agency for Research on Cancer (IARC); 2000.

References

1. Tihan T, Fischer PG, Kepner JL, Godfraind C, McComb RD, Goldthwaite PT, Burger PC. Pediatric astrocytoma with monomorphous pilomyxoid features and a less favourable outcome. J Neuropath Exp Neurol 1999;58:1061–1068
2. Pollack IF, Claassen D, Al-Shboul Q, et al. Low grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. J Neurosurg 1995;82:536–554
3. Pollack IF. Brain tumors in children. N Eng J Med 1994;331:1500–1507

Optic Gliomas

22

Ian F. Pollack, Regina I. Jakacki

Introduction – 354

Epidemiology – 354

Symptoms and Signs – 354

Diagnostics – 354

Staging and Classification – 355

Treatment – 356
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 358

Follow-up/Specific Problems and Measures – 359

Future Perspectives – 359

References – 360

Introduction

The term "optic glioma" encompasses a diverse group of tumors that can arise anywhere along the visual pathway from the globe to the optic radiations. A particularly challenging subgroup of these tumors involves the hypothalamus in conjunction with the optic chiasm. Because complete resection of such lesions is not feasible without excessive morbidity, a variety of adjuvant management options have been explored. The success of low-intensity chemotherapy regimens in the treatment of chiasmatic-hypothalamic gliomas has led to dramatic changes in management algorithms for these tumors during the last decade. A second factor that has come to influence management in recent years is the recognition that optic pathway tumors in children with neurofibromatosis type 1 (NF1) often have a substantially more indolent course than in those without this disorder, necessitating a correspondingly more conservative approach to intervention.

Epidemiology

Optic pathway tumors account for approximately 4%–6% of all brain tumors in children [1]. Most lesions manifest during the first decade of life. Approximately half of such tumors arise in children with NF1, which is one of the most common genetic disorders, affecting one in 3,000–4,000 people [2]. The mode of inheritance is autosomal dominant, and approximately 50% of cases arise sporadically as new mutations. This syndrome results from mutations in a gene on chromosome 17q11.2 that encodes a large protein called neurofibromin. A portion of this protein is a GTPase-activator [3] that plays a role in signal transduction by favoring the conversion of the active GTP-bound form of ras and related G-proteins to the inactive GDP-bound form. The NF1 gene functions as a classical tumor suppressor gene in that loss of both alleles is needed for tumorigenesis. Because patients with NF1 are born with only one normal copy of the gene, a single mutation or deletion that inactivates the second allele would theoretically be sufficient to favor tumor formation, although additional molecular events may also contribute. At least 15% of children with NF1 have evidence of optic pathway tumors on MRI [4–7]. Apart from the association with NF1, no other genetic or epidemiological factor has been associated with the development of these tumors.

Although virtually all optic pathway gliomas in children are histologically low-grade (i.e., World Health Organization Grades I and II), they exhibit a wide spectrum of growth characteristics [8]. Some tumors, particularly in children with NF1, are detected incidentally and show little or no enlargement over time, suggesting that these lesions can have decelerating growth kinetics. In rare cases, spontaneous tumor regression has been observed [9]. Other lesions show gradual enlargement over time without treatment, leading to progressive visual compromise. Finally, some lesions exhibit rapid enlargement, leading to neurological deficits and symptoms of increased intracranial pressure. Tumors arising in infants have been noted to exhibit a more aggressive course than those in older children [10], although in both groups, the prognosis is better than that in adults, in whom many of these lesions are histologically malignant [8]. In addition, tumors that involve the hypothalamus carry a worse prognosis than those restricted to one or both optic nerves [8].

Symptoms and Signs

The presenting symptoms and signs are influenced by the age of the child and the location of the tumor. Tumors involving a single optic nerve typically present with proptosis and unilateral visual loss. Tumors arising from the optic chiasm also commonly present with visual deterioration, which is a typical complaint in older children. This symptom can be difficult to identify in infants and young children; instead, such patients may exhibit poor visual fixation, or nystagmus, and demonstrate optic atrophy on fundoscopic examination. Children with large tumors involving the chiasm and hypothalamus may present with symptoms of increased intracranial pressure from local mass effect and obstructive hydrocephalus, resulting from occlusion of the foramen of Monro, either unilaterally or bilaterally. In older children, these lesions can also manifest with endocrine disturbances, such as growth delay or precocious puberty, appetite alterations, and personality changes. In contrast, infants will commonly exhibit nonspecific signs, such as macrocephaly and failure to thrive. In some cases, the degree of emaciation in affected infants is profound, and the virtual absence of subcutaneous fat in conjunction with a hypothalamic glioma has been referred to as the "diencephalic syndrome." Large tumors may also lead to focal neurological deficits from compression of the descending sensorimotor pathways and cranial nerves 3–6.

Diagnostics

Computerized tomography (CT) or, preferably, magnetic resonance imaging (MRI) are usually the only diagnostic studies needed to establish the pres-

ence of an optic glioma. MRI has the advantage of also delineating the vessels of the circle of Willis, which avoids the need for an angiogram if surgery is contemplated. A number of characteristic lesion types may be seen, either alone or in combination. The mildest abnormalities, which are typically seen in patients with NF1, consist only of thickening of one or both optic nerves [4, 5]; although most such lesions are low-grade gliomas, others may simply represent hyperplasia of the optic nerve sheath. Other patients exhibit a globular thickening of the optic nerves and chiasm (Fig. 1A) that may occur in conjunction with T2 signal abnormalities streaking backwards along the optic pathways and upwards into the hypothalamus. The latter appearance is also usually seen in children with NF1. Biopsy of such lesions (although usually no longer required in this clinic scenario) has generally confirmed the presence of a low-grade glioma [6, 11–14]. Finally, a third group of patients present with a large mass lesion involving the optic chiasm and hypothalamus that may extend upward into the third ventricle, laterally into the temporal fossa, anteriorly beneath the frontal lobe, and posteriorly into the perimesencephalic region [10] (Fig. 1B).

Because these lesions are low-grade astrocytomas, they are typically hypodense on CT and hypointense on T1-weighted MRI in comparison to the surrounding brain. Following administration of contrast medium, some tumors show uniform enhancement, although others exhibit mixed signal characteristics or harbor sizeable cystic components. In rare cases, large hypothalamic gliomas exhibit dissemination throughout the neuraxis [15, 16], and if this is suspected, MRI of the spinal axis should be performed in conjunction with a CSF cytological examination, if not contraindicated.

If the child is clinically stable, a comprehensive neuro-ophthalmologic and endocrine evaluation is warranted. The ophthalmologic evaluation should include fundoscopy and measures of visual fixation in infants; in older children, a formal assessment of visual acuity and visual fields by perimetry testing is also recommended. Preoperative endocrinologic evaluation should include assessments of cortisol and thyroid hormone production, with institution of appropriate cortisol and thyroid hormone replacement, if warranted, including provision of stress doses of corticosteroids during the perioperative period. Prolactin levels are often elevated secondary to compression of the pituitary stalk. Diabetes insipidus is extremely uncommon, and if present should raise the possibility that the mass is either a germ cell tumor or some other histology. Evaluation of the growth hormone and gonadotrophic hormone hypothalamopituitary axes is more important after the completion of therapy. Finally, patients with hypothalamic tumors often exhibit varying degrees of cognitive impairment that may interfere with their school performance and socialization. Accordingly, detailed neuropsychology testing is often helpful.

Staging and Classification

The vast majority of optic pathway tumors are low-grade gliomas [17]. Most are juvenile pilocytic astrocytomas, and the majority of the remainder are low-grade nonpilocytic astrocytomas, such as fibrillary astrocytoma and the recently described pilomyxoid

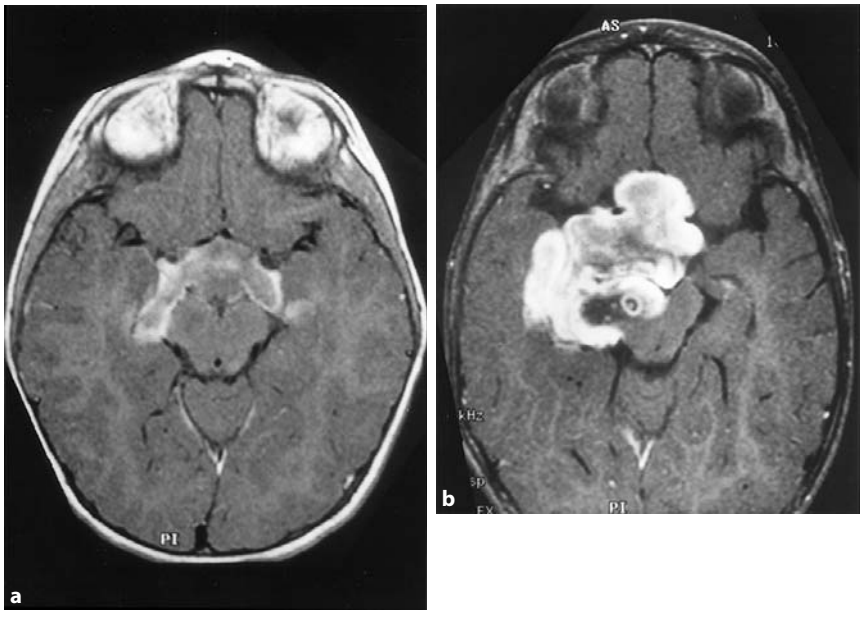


Fig. 1 This series of MR images illustrates the diverse manifestations of optic-hypothalamic gliomas. **a** Globular enlargement of the optic chiasm is depicted in a child with NF1. In this patient, T2 signal abnormality was seen along the optic tracts bilaterally. **b** A massive chiasmatic-hypothalamic glioma shows bright enhancement with intravenous contrast

astrocytoma variant [18], which seems to carry a less favorable prognosis than other low-grade gliomas. In older teenagers and adults, anaplastic optic gliomas have been described, although such tumors are exceedingly rare in younger children, unless the patient previously received radiotherapy.

In general, staging of the neuraxis is not required in patients with optic gliomas. However, as noted earlier, a small percentage of these tumors do exhibit leptomeningeal dissemination, and some investigators have recommended at least a spinal MRI for patients with large chiasmatic-hypothalamic lesions.

Treatment

The optimal management for optic gliomas remains controversial. Before the era of high-resolution CT and MRI, optic pathway tumors were generally detected only after the onset of visual impairment, hypothalamic dysfunction, or symptoms of increased intracranial pressure, which clearly mandate therapeutic intervention [6, 7, 12]. However, with the advent of sophisticated imaging technology, many lesions are now detected in asymptomatic or minimally symptomatic individuals in whom the natural history and the indications for intervention are less clear. This is a particularly common problem in children with NF1, who often undergo screening MRI studies. In such patients, the diagnosis can be established without the need for biopsy [5, 11]. Information derived from the treatment of symptomatic patients, however, is not directly applicable to the management of asymptomatic patients.

Several recent studies have reported the results of expectant management in patients with NF1 who had optic pathway tumors that either were asymptomatic or minimally symptomatic with mild visual loss or precocious puberty [6, 11, 13, 14, 19–21]. Hoffman et al. noted that, in a series of 15 such patients who either had no therapy or only a diagnostic biopsy, 13 had stable disease at long-term follow-up [11]. Similarly, Listernak et al. noted that only 3 of 33 asymptomatic or minimally symptomatic patients with optic pathway tumors exhibited progressive tumor growth or deteriorating vision after diagnosis with a median follow-up of 2.4 years [19]. Other groups have also noted that optic gliomas in children with NF1 have a distinctly more indolent course than in those without this disorder [22–25]. Our own experience is largely in agreement with the results of these studies: the detection of an initially asymptomatic or minimally symptomatic optic pathway lesion on a screening MRI does not signal the need for immediate intervention, because only 10%–20% of such lesions exhibit enlargement in tumor size or clinical deterioration that merits therapy within several years of diagnosis. In view of the unpredictable growth in any given case, ongoing imaging surveillance is prudent until the natural history can be established conclusively.

However, the aforementioned guidelines do not apply to those children with NF1 who present with severe visual impairment. In our experience, patients who exhibit significant visual compromise have a high risk of further visual deterioration and require immediate therapy. These recommendations also do not apply to young children who have sizeable, enhancing optic pathway lesions on their initial imaging studies, because in general, these patients eventually manifest clinical signs of deterioration. Because young children may not be old enough to read an eye chart, it may be very difficult to ascertain whether the tumor has actually caused visual loss until it is quite severe.

Moreover, in patients without an underlying diagnosis of NF1, histological confirmation is required to establish a diagnosis of a low-grade glioma, and to rule out other histologies. In selected cases, this may also achieve prompt relief of intracranial mass effect and improvement of neurological symptoms [10].

Surgery

Because optic pathway gliomas cannot be completely resected without unacceptable morbidity and many lesions are either indolent or respond well to adjuvant therapy, the operative indications have become increasingly controversial in recent years. Historically, surgical resection was often favored for tumors restricted to a single optic nerve, if there was evidence of severe visual compromise and proptosis, to prevent "spread" to the chiasm and contralateral side [6, 8, 21]. However, because many of these lesions arise in patients with NF1, who are generally noted on MRI to have tumor involvement in other areas of their optic pathways, the rationale for prophylactic resection of the tumor and nerve no longer applies in most cases, and such patients are generally treated with adjuvant therapy. In their comprehensive literature review, Alvord and Lofton commented that patients with NF1 appeared to have a high incidence of intracranial tumor "recurrence" after removal of an affected optic nerve [8], which is not surprising in view of the current MRI data. However, in the occasional patient with an optic nerve glioma that is clearly unilateral, in whom proptosis and severe visual loss are apparent, surgical resection of the involved nerve from the globe to the chiasm may be indicated.

Optic gliomas in patients without a diagnosis of NF1 generally involve the optic chiasm and hypothalamus and, in such cases, the two goals of surgical

intervention are to establish a histological diagnosis and, if feasible, to relieve local mass effect. Diagnosis can often be achieved relatively noninvasively by means of endoscopy or stereotactic biopsy, but in situations where this is not feasible, an open approach may be performed. Because most such tumors will respond to adjuvant therapy (Fig. 2), many centers now prefer to obtain a biopsy, reserving attempts at resection for lesions that fail to respond and exhibit increasing mass effect. In some instances, a well-timed tumor debulking will stabilize the patient sufficiently that additional chemotherapy or irradiation can be administered, leading to long-term disease control.

However, for selected tumors, extensive resection may be preferred at the time of diagnosis, particularly if the patient has significant neurological compromise or bilateral ventricular obstruction from tumor growing exophytically from the optic chiasm and hypothalamus [8, 10, 26]. In such cases, the operative approach is determined by the growth pattern of the tumor. For lesions mushrooming anteriorly or above the chiasm into the front of the third ventricle, a subfrontal and interhemispheric approach may be combined with opening the lamina terminalis. For lesions extending more posterosuperiorly, a transcallosal approach allows access to the dome of the tumor and re-establishment of intraventricular CSF flow pathways. Finally, for more laterally projecting tumors, a pterional and/or subtemporal approach can provide access to the bulk of the tumor. Although complete resection is not feasible because these lesions infiltrate the optic chiasm and hypothalamus, substantial cytoreduction can sometimes be achieved [10, 11] Because these tumors often engulf arteries of the circle of Willis, care must be taken during the resection to avoid injury to these vessels. Although several groups have advocated a general management approach of surgery for children with large tumors growing exophytically from the optic chiasm [10, 11], it remains uncertain whether the long-term results in terms of disease stability and functional outcome represent an improvement over those obtained with nonsurgical or more conservative surgical approaches [27].

Radiotherapy

Radiation therapy has long been a mainstay in the treatment of optic pathway tumors [8, 14, 28–30]. This approach provides excellent results in terms of disease stabilization and, occasionally, regression, often leading to significant improvement in visual function. For example, Pierce et al. [14] reported 6-year progression-free and overall survivals of 88% and 100% in 24 children with symptomatic chiasmal gliomas who received >4500 cGy of radiotherapy. Vision improved in seven patients and remained stable in 14 [14]. However, radiation may result in severe cognitive and endocrine deficits [31–34] and places the patient at risk for radiation-induced malignancies [35] and vasculopathy, such as moya moya syndrome [36, 37]. Patients with neurofibromatosis 1 seem to be at particular risk of developing these complications.

As a way to reduce these risks, there has been increasing interest in using stereotactic techniques to more precisely target radiation to the tumor, while sparing, as much as possible, the surrounding brain. Stereotactic radiosurgery [38, 39], which administers a high dose of radiation in a single fraction, has demonstrated efficacy against progressive low-grade gliomas, but because this approach is generally not applicable for lesions greater than 3 cm in diameter, and dose reduction is required for irradiating

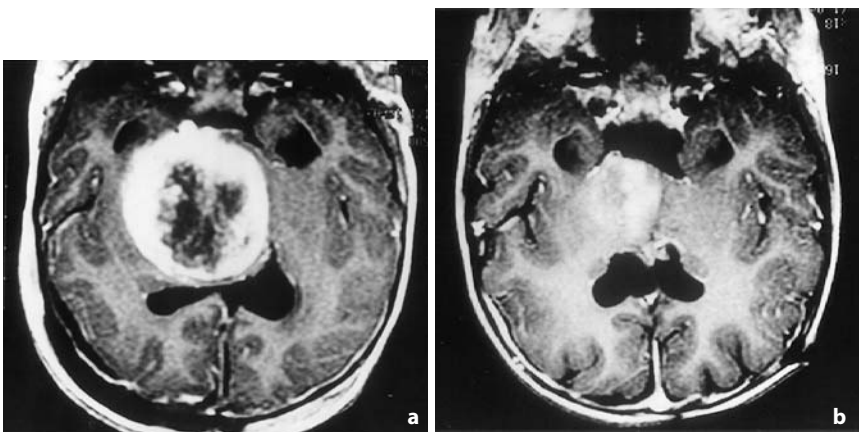


Fig. 2 **a** Large hypothalamic glioma that was treated with biopsy and limited debulking, followed by carboplatin and vincristine. **b** Follow-up MRI scan upon completion of induction chemotherapy. The patient's tumor continued to regress during treatment, but ultimately progressed off therapy 5 years later, and again responded to treatment with the above agents

the optic apparatus, this technique has limited utility for chiasmatic-hypothalamic gliomas. However, new methods of delivering fractionated radiotherapy to a conformally oriented treatment volume using three-dimensional image-based treatment planning and narrow peritumoral margins (i.e., stereotactic radiotherapy) do appear to have broad applicability for these tumors as a way to minimize treatment-induced morbidity without sacrificing long-term disease control [40, 41]. This approach has been applied in a recent pilot study involving 47 children with progressive low-grade gliomas, in whom the target included the preoperative tumor volume with a 2-mm margin, with doses ranging from 5,000 to 5,800 cGy in standard fractions. After a median follow-up of 3.4 years, there was only one local recurrence and no marginal failures [40]. However, extended follow-up will be needed to determine whether these approaches are truly beneficial in terms of prolonging long-term progression-free survival, maintaining functional status, and avoiding the potential for late malignant transformation. This strategy is currently being evaluated in detail in a cohort of 100 children in the Children's Oncology Group ACNS0221 study.

Chemotherapy

In view of the known sequelae of irradiation, chemotherapy has come to assume an increasing role in the management of these tumors, particularly for patients younger than 5 years [22, 42–45], in whom the risks of long-term radiotherapy-induced cognitive and endocrine impairment are particularly high and the potential benefits of avoiding, or at least deferring, radiotherapy are substantial. A variety of regimens have been employed, with response rates of 20%–80% and response or stabilization rates of 75%–100% [22, 42–45]. In the study of Packer et al., which used six 8-week cycles of actinomycin D and vincristine in 24 patients, the median time to disease progression was 3 years in the nine patients with tumor growth; 15 other children remained progression-free with a median follow-up of 3.1 years [42]. Based on these encouraging initial results, a variety of other regimens were subsequently examined [22, 43–45]. One regimen that has been extensively evaluated involves the combination of carboplatin and vincristine (Fig. 2). In a multi-institutional study in 78 children with unresectable, progressive disease (median age, 3.1 years), 44 patients had objective responses to treatment and 29 had stable disease, allowing a significant delay in radiotherapy in more than 85% of children. Progression-free survival at 3 years was 68 ±7% [43]. A second regimen that has been widely employed combines thioguanine, procarbazine, CCNU and vincristine [44]. In initial studies, this combination was utilized in 19 infants and young children, 12 at the time of diagnosis and seven after tumor progression. Fifteen patients either responded to therapy or stabilized. The median time to tumor progression was 30.3 months with a 5-year survival rate of 82.7% [44]. The efficacy and tolerability of these two regimens is currently being compared in the ongoing A9952 study of the Children's Oncology Group. A follow-up study (ACNS0223) will build upon the carboplatin and vincristine regimen by adding temozolomide, another potentially active agent for these tumors.

The efficacy of the carboplatin/vincristine regimen in children with NF1-associated low-grade gliomas is also being assessed in detail in the Children's Oncology Group 9952 study. Although children with NF1 do not appear to differ significantly from those without NF1 in terms of their response to chemotherapy [22, 43], concerns about their potentially increased risk of secondary leukemias from alkylating agents have provided a rationale for avoiding such agents in front-line regimens.

Prognosis/Quality of Life

Although the vast majority of optic and hypothalamic gliomas have a benign histological appearance, the inherent unresectability of these lesions leads to a substantially worse prognosis than for other low grade gliomas. Gliomas restricted to the optic nerves rarely prove fatal [8], but can lead to progressive visual compromise. In contrast, chiasmatic-hypothalamic gliomas can eventually lead to extensive morbidity and, in many cases, mortality. In the large postoperative natural history study of the CCG and POG (9891/8930), 4-year progression-free survival was approximately 50% for patients with chiasmatic-hypothalamic gliomas, with a 4-year overall survival of 90% [17]. These percentages were comparable to those of other low-grade gliomas that were not amenable to total resection. Symptomatic chiasmatic-hypothalamic tumors in NF1 patients seem to carry a more favorable prognosis for long-term disease control than comparable tumors in patients without NF1 [7, 11, 13, 20, 22–25, 46]. For example, Hoffman et al. noted that whereas only one of 23 patients with NF1 and optic-hypothalamic glioma died of disease progression, seven of 39 patients without NF1 died ($p = 0.045$) [11]. Deliganos et al. [46] also noted that time to progression among children with newly diagnosed symptomatic optic pathway gliomas arising in association with NF1 was substantially longer than for patients with sporadic tumors (8.4 years versus 2.4 years, respectively). With an average follow-up of 10.2 years, only five of 16 patients with NF1 exhibited disease progression [46]. In addition, a subset of tu-

mors exhibit spontaneous regression in the absence of surgical or adjuvant therapy [9]. Finally, among a series of children treated with chemotherapy for high-risk or progressive tumors, Gururangan et al. [22] observed that children with NF1 had a 3-year survival of 95% versus 80% in those without this disorder, a statistically significant difference.

A disappointing feature of these tumors is that given the fact that there is almost always residual disease after surgery, chemotherapy, and radiation, there is a substantial incidence of late tumor progression, particularly in the non-NF1 subgroup, a factor that is not well captured on studies having less than 10 years of follow-up. Although actuarial survival rates of 70%–90% have been reported at 10 years [28–30], survival for more than 13 years after diagnosis was achieved in only 50% of patients in one large series [26]. In the literature review by Alvord and Lofton, the cumulative frequency of progression and death were noted to progressively increase with follow-up times up to 20 years, by which time approximately 40% of children had died [8].

Although detailed quality-of-life studies in these patients have been lacking in the literature, it is clear that long-term survivors have a high incidence of visual, cognitive, behavioral, and endocrinological morbidity, as a result of both the tumor itself and its treatment with surgery and irradiation. In one report of 33 patients treated with relatively conservative surgery and a combination of irradiation and chemotherapy, five patients had died, five were functionally blind and 14 had useful vision in only one eye, all but 12 required endocrine replacement, and only half had completed or were in school [27]. Patients who have received radiotherapy are also at risk for second malignancies within the treatment volume and radiation-induced vasculopathy. It remains to be determined whether these outcomes are improved with a policy of more limited surgery and initial treatment with chemotherapy or with the use of more conformally directed irradiation. The ongoing A9952 study and the soon-to-open ACNS0221 study will help to address these issues.

Follow-up/Specific Problems and Measures

There are no objective standards for follow-up in children with optic pathway tumors. In general, for children with NF1 who have newly diagnosed, asymptomatic tumors, where intervention is deferred until there is either clinical or radiographic progression, we perform follow-up MRI and ophthalmological evaluations 3–6 months after diagnosis. If these are stable, we then perform follow-up evaluations at 6 months to yearly intervals thereafter, depending on the age of the child and the size and enhancement characteristics of the tumor. Once the child is past the middle school years, the likelihood of tumor progression is quite small and surveillance imaging can often be discontinued. For non-NF1 patients, who generally present with symptomatic tumors and are enrolled on a course of therapy, follow-up evaluations are performed at approximately 3-month intervals for the first year (with the specific timing designed to coincide with treatment milestones, such as the completion of chemotherapy induction, completion of two courses of therapy, or completion of irradiation), at 4- to 6-month intervals for the next few years if the patient is stable, and subsequently on an annual basis.

If clinically indicated, follow-up endocrinological evaluations are also warranted to detect delayed dysfunction of the hypothalamopituitary axis, which is a particular concern in patients who have received radiotherapy, and those with progressive disease. In view of the high risk of cognitive and behavioral abnormalities in children with these tumors, neuropsychological evaluation is helpful if not essential to identify educational resources as well as accommodations for visual impairment that may be required to optimize long-term functional outcome.

Future Perspectives

A major advance during the last decade has been the widespread incorporation of chemotherapy into the initial management of symptomatic, progressive or high-risk chiasmatic hypothalamic gliomas. An ongoing study is comparing the activity and tolerability of two active treatment regimens, carboplatin and vincristine versus 6-thioguanine, procarbazine, CCNU, and vincristine. Subsequent studies will examine the activity of alternative regimens, such as temozolomide plus carboplatin and vincristine. A pilot study is also in progress evaluating the activity of weekly vinblastine for these tumors, with encouraging preliminary results. Similarly, another large pilot study will test the safety of conformally administered irradiation for tumors in children older than 10 years, and those younger than 10 years who have disease progression after initial chemotherapy. As an essential element in evaluating the success of these approaches for improving not only the duration but also the quality of survival, these new studies will incorporate analyses of endocrine and functional status, using validated quality of life indicators.

Further in the future, it is anticipated that additional agents will become available for tumor control. For example, the management of malignant gliomas has advanced in recent years with the development of novel agents that target growth signaling pathways

that are aberrantly activated. Identification of the pathways that are specifically dysregulated in low-grade gliomas will determine which of these agents may be applicable for therapy. Moreover, ongoing studies of gene expression profiling and comparative genomic hybridization, which are being undertaken in large patient cohorts, should help to identify additional relevant therapeutic targets.

Acknowledgements. This work was supported in part by NIH grant NSP0140923 and NS37704.

References

1. Pollack IF. Brain tumors in children. N Engl J Med 1994;331:1500–1507
2. Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. Brain 1988;111:1355–1381
3. Xu G, O'Connell P, Viskochil D, et al. The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell 1990;62:599–608
4. DiMario FJ, Ramsby G, Greenstein R, et al. Neurofibromatosis type 1: Magnetic resonance imaging findings. J Child Neurol 1993;8:32–39
5. Listernak R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr 1989;114:788–792
6. Lewis RA, Gerson LP, Axelson KA, et al. Von Recklinghausen neurofibromatosis: II. Incidence of optic gliomata. Ophthalmology 1984;91:929–935
7. Stern J, DiGiacinto GV, Housepian EM. Neurofibromatosis and optic glioma: Clinical and morphological correlations. Neurosurgery 1979;4:524–528
8. Alvord EC Jr, Lofton S. Gliomas of the optic nerve or chiasm. Outcome by patient's age, tumor site, and treatment. J Neurosurg 1988;68:85–98
9. Perilongo G, Moras P, Carollo C, et al. Spontaneous partial regression of low-grade glioma in children with neurofibromatosis-1: a real possibility. J Child Neurol 1999;14:352–356
10. Wisoff JH, Abbott R, Epstein F. Surgical management of exophytic chiasmatic-hypothalamic tumors of childhood. J Neurosurg 1990;73:661–667
11. Hoffman HJ, Humphreys RP, Drake JM, et al. Optic pathway/hypothalamic gliomas: A dilemma in management. Pediatr Neurosurg 1993;19:186–195
12. Dutton JJ. Gliomas of the anterior visual pathway. Surv Ophthalmol 1994;38:427–452
13. Jenkin D, Angyalfi S, Becker L, et al. Optic nerve glioma in children–surveillance, resection, or irradiation. Int J Rad Oncol Biol Phys 1993;25:215–225
14. Pierce SM, Barnes PD, Loeffler JS, et al. Definitive radiation therapy in the management of symptomatic patients with optic glioma. Survival and long-term effects. Cancer 1990;65:45–52
15. Mamelak AN, Prados MD, Obana WG, et al. Treatment options and prognosis for multicentric juvenile pilocytic astrocytoma. J Neurosurg 1994;81:24–30
16. Hukin J, Siffert J, Velasquez L, Zagzag D, Allen J. Leptomeningeal dissemination in children with progressive low-grade neuroepithelial tumors. Neuro-Oncol 2002;4:253–260
17. Sanford A, Kun L, Sposto R, Holmes E, Wisoff JH, Heier L, McGuire-Cullen P. Low-grade gliomas of childhood: Impact of surgical resection. A report from the Children's Oncology Group. J Neurosurg 2002;96:427–428
18. Tihan T, Fisher PG, Kepner JL, Godfraind C, McComb RD, Goldthwaite PT, Burger PC. Pediatric astrocytomas with monomorphous pilomyxoid features and a less favorable outcome. J Neuropath Exp Neurol 1999;58:1061–1068
19. Listernick R, Charrow J, Greenwald M, Mets M. Natural history of optic pathway tumors in children with neurofibromatosis type-1. A longitudinal study. J Pediatr 1994;125:63–66
20. Packer RJ. Panel on management and treatment of optic gliomas. Optic gliomas in neurofibromatosis. Proceedings of Conference Series, Vol.2, New York; 1989. p. 137–147
21. Housepian EM, Chi TL. Neurofibromatosis and optic pathways gliomas. J Neuro-Oncol 1993;15:51–55
22. Gururangan S, Cavazos CM, Ashley D, et al. Phase II study of carboplatin in children with progressive low-grade gliomas. J Clin Oncol 2002;2951–2958
23. Singhal S, Birch JM, Kerr B, Lashford L, Evans DG. Neurofibromatosis type 1 and sporadic optic gliomas. Arch Dis Child 2002;87:65–70
24. Kornreich L, Blaser S, Schwarz M, et al. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. AJNR 2001;22:1963–1969
25. Chan MY, Foong AP, Heisey DM, Harkness W, Hayward R, Michalski A. Potential prognostic factors of relapse-free survival in childhood optic pathway glioma: a multivariate analysis. Pediatr Neurosurg 1998;29:23–28
26. Tenny RT, Laws ER Jr, Young BR, et al. The neurosurgical management of optic glioma. Results in 104 patients. J Neurosurg 1982;57:452–458
27. Sutton LN, Molloy PT, Seryak H, et al. Long-term outcome of hypothalamic/chiasmatic astrocytomas in children treated with conservative surgery. J Neurosurg 1995;83:583–589
28. Rodriguez LA, Edwards MSB, Levin VA. Management of hypothalamic gliomas in children: an analysis of 33 cases. Neurosurgery 1990;26:242–247
29. Kovalic JJ, Grigsby PW, Shephard MJ, et al. Radiation therapy for gliomas of the optic nerve and chiasm. Int J Radiat Oncol Biol Phys 1990;18:927–932
30. Flickinger JC, Torres C, Deutsch M. Management of low-grade gliomas of the optic nerve and chiasm. Cancer 1988;61:635–642
31. Donahue B. Short- and long-term complications of radiation therapy for pediatric brain tumors. Pediatr Neurosurg 1992;18:207–217

32. Lustig RH, Post SR, Srivannaboon K, et al. Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocr Metab 2003;88:611–616
33. Ellenberg L, McComb JG, Siegel S, Stowe S. Factors affecting intellectual outcome in pediatric brain tumor patients. Neurosurgery 1987;21:638–644
34. Livesey EA, Hindmarsh PC, Brook CGD, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 1990;61:622–625
35. Dirks PB, Jay V, Becker LE, et al. Development of anaplastic changes in low-grade astrocytomas of childhood. Neurosurgery 1994;34:68–78
36. Kestle JR, Hoffman HJ, Mock AR. Moya moya phenomenon after radiation for optic glioma. J Neurosurg 1993;79:32–35
37. Grill J, Couanet D, Capelli C, et al. Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. Ann Neurol 1999;45:393–396
38. Grabb PA, Lunsford LD, Albright AL, et al. Stereotactic radiosurgery for glial neoplasms of childhood. Neurosurgery 1996;38:696–702
39. Boethius J, Ulfarsson E, Rahn T, Lippittz B. Gamma knife radiosurgery for pilocytic astrocytomas. J Neurosurg 2002;97 (Suppl) 5:677–80
40. Dutton SC, Goumnerova L, Billett AL, et al. Fractionated stereotactic radiotherapy for localized pediatric brain tumors: results of a prospective study. Int J Radiat Oncol Biol Phys 1999;45 (Suppl) 1:234
41. Nishihori T, Shirato H, Aoyama H, et al. Three-dimensional conformal radiotherapy for astrocytic tumors involving the eloquent area in children and young adults. J Neuro-Oncol 2002;60:177–183
42. Packer RJ, Sutton LN, Bilaniuk LT, et al. Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: An update. Ann Neurol 1988;23:79–85
43. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 1997;86:747–754
44. Petronio J, Edwards MSB, Prados M, et al. Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy. J Neurosurg 1991;74:701–708
45. Mahoney DH Jr, Cohen ME, Friedman HS, et al. Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study. Neuro-Oncol 2000;2:213–220
46. Deliganis AV, Geyer JR, Berger MS. Prognostic significance of type 1 neurofibromatosis (von Recklinghausen disease) in childhood optic glioma. Neurosurgery 1996;38:1114–1119

Thalamic Gliomas 23

Christian Sainte-Rose, Darach W. Crimmins, Jacques Grill

Thalamic Tumors in Children – 364
Anatomy of the Thalamus

Epidemiology – 365

Symptoms and Clinical Signs – 365
Synopsis
Body

Diagnosis – 366
Synopsis
Body

Staging and Classification – 368
Synopsis
Body

Treatment – 370
Synopsis
Body
Surgery
Biopsy
Open Surgery
Treatment of Hydrocephalus
Immediate Postoperative Course
Radiotherapy
Chemotherapy

Prognosis – 374

Follow-up/Specific Problems and Measures – 374

Future Perspectives – 374

References – 374

Thalamic Tumors in Children

Thalamic tumors constitute less than 5% of all intracranial tumors with half of these presenting in childhood. They are often grouped with other tumors of the area, e.g., diencephalic, mesencephalic, which tend to behave differently, rendering accurate analysis of case series difficult. Traditionally, surgery as sole therapy has resulted in poor outcomes in these patients. However, the advent of improved imaging modalities enabling accurate anatomical localization and delineation, and the progress in anesthetic and microsurgical techniques, has meant that over the last few decades a more aggressive surgical approach is able to be undertaken. We have analyzed our personal experience (69 cases over the past 15 years) and those cases available in the literature in order to define management strategies for patients afflicted with these challenging tumors.

Anatomy of the Thalamus

The thalamus, which accounts for 2% of brain mass, is divided into three large cell groups (Table 1) by the Y-shaped internal medullary lamina of white matter:

The external medullary lamina separates the thalamus from the reticular nuclei and internal capsule inferolaterally. In addition to the above nuclei, the medial and lateral geniculi are involved in the auditory and visual pathways respectively.

The thalamus processes and distributes almost all sensory and motor information going to and from the cortex. It regulates levels of awareness and emotional and cognitive responses to sensory information. It has an important role in the integration of

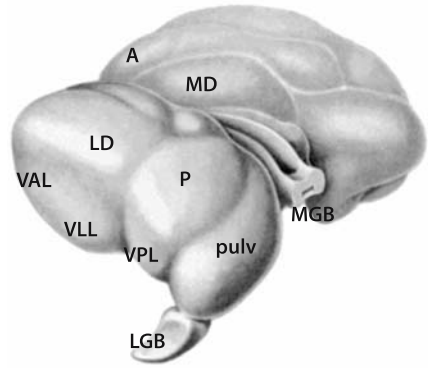


Fig. 1 Both thalami as seen from the left. A, anterior nuclear group; MD, mediodorsal nuclear group; P, posterior nucleus (lateral group); LD, dorsal nucleus (lateral group); VAL, ventral anterior nucleus (lateral group); VLL, ventral lateral nucleus (lateral group); VPL, ventral posterior nucleus (lateral group); LGB, lateral geniculate body; MGB, medial geniculate body; pulv, pulvinar

Table 1 Structure and function of the thalamus

Main nuclear group	Subgroups		Afferents	Efferents	Function
Medial dorsal			Olfactory, limbic	Prefrontal cortex	Cognition, judgment, mood
Anterior			Mammillary body	Cingulate gyrus	Memory
Lateral	Dorsal		Parietal lobe	Cingulate gyrus	Memory
	Posterior	(and pulvinar)	Superior colliculus	Visual and parietal association cortex	Extrageniculate visual pathway
	Ventral	Ventral anterior	Globus pallidus	Prefrontal cortex	Extrapyramidal motor function
		Ventral lateral	Globus pallidus,	Supplementary motor area,	Extrapyramidal motor function
			Dentate nucleus (cerebellum)		Primary motor cortex
		Ventral posterior	Sensory lemnisci	Somatic sensory cortex	Sensation

the visual pathways. The left thalamus is involved in some aspects of language.

Epidemiology

The true incidence of thalamic tumors is unknown due to the difficulty in differentiating between those that originate primarily in the thalamus and those that secondarily involve the thalamus from adjacent tissues, e.g., basal ganglia, hypothalamus, paraventricular and mesencephalic regions. Secondary invasion of the thalamus can occur in up to one third of cases.

From a surgical viewpoint primary thalamic tumors may be classified into three groups:

- 1. Pure thalamic tumors, i.e., those that arise from the thalamus and which may spread out ward from it.
- 2. Thalamo-peduncular tumors, i.e., those that arise at the junction of these two structures.
- 3. Primary bilateral thalamic tumors.

Pure thalamic tumors comprised 1%–5% of all brain tumors in children in most clinical series.

In the Necker series 6 out of 69 thalamic tumors were thalamo-peduncular in origin. Primary bilateral tumors were uncommon, with occasional case reports [5, 18] occurring in the literature (these tumors should be clearly differentiated from those unilateral tumors with contralateral extension). In the Necker series, the incidence was higher with 14% of thalamic tumors being primarily bilateral.

Children with thalamic tumors were relatively older than other children with brain tumors. In our series, the mean age at presentation was 9.5 years (SD = 4.4) and not significantly different in children with bilateral thalamic tumors. This is in keeping with the other pediatric series [2, 18].

Symptoms and Clinical Signs

Synopsis

The clinical features of thalamic tumors relate to their site (nuclear group, effect on CSF pathways), size (mass effect on adjacent structures and ventricles), and rate of growth (rapidity of symptom evolution). Symptoms of behavioral or mental changes are much less common in younger patients than in adults.

Body

Median symptom duration is around 2–3 months [2]. Some patients may have mild symptoms for more than 1 year prior to diagnosis. A short duration of symptoms is often indicative of a malignant tumor reminiscent of other deep-seated tumors, e.g., pontine gliomas. The most common symptoms and signs are attributable to raised ICP and motor deficits. Table 2 describes the symptoms present at diagnosis in our series.

Behavioral problems, though probably under recognized in children, are rarely observed. Other symptoms include thalamic pain, involuntary movements, seizures, or generalized weakness. Environmental tilt illusion has been reported once in a patient with a pilocytic astrocytoma of the pulvinar. At neurological examination, spasticity is often reported and is a good localizing sign when unilateral.

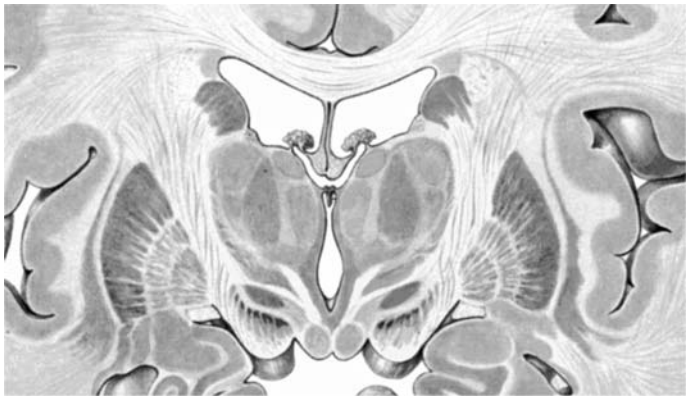


Fig. 2 From a surgical point of view, the thalamus can be seen as a tetrahedron with three free surfaces and a fourth inferolateral surface which abuts the internal capsule and subthalamic nuclei inferiorly and the caudate nucleus superiorly. The groove between the thalamus and the caudate nucleus is occupied by the thalamostriate vein, deep to which lies the internal capsule. Ventrally the thalamus is related to critical midbrain structures. For further information, the reader is directed to the review of Herrero et al. [8]

Bilateral thalamic astrocytomas can present with decrements in motor function and tremor [5, 18], subtle sensory deficits or mental changes. Dementia, reported in adults, is rare in children. These tumors are often more difficult to diagnose than unilateral thalamic tumors due to the nonspecific nature of the presenting symptoms and signs. The duration of symptoms, however, is similar.

Diagnosis

Synopsis

The pathological diagnosis may be assumed on radiological appearances. A biopsy may be useful to direct therapy when a clear decision can not be made based solely on imaging criteria. Functional imaging may help to direct the biopsy towards "hot-spots" present in the tumor.

Table 2 Symptoms at diagnosis in unilateral tumors

	N	Frequency
Motor deficits or problems	35	64%
Raised intracranial pressure	33	61%
Visual deficits	23	43%
Gait disturbances	8	26%
Sensory deficits	4	7%
Other symptoms	13	24%

Body

With MR imaging techniques the anatomical boundaries and the extension of thalamic tumors can be accurately depicted. Newer radiological modalities such as MR spectroscopy (Fig. 3) and PET are being used in the noninvasive evaluation of these tumors [3] or to direct diagnostic procedures such as stereotactic biopsies [13]. Unfortunately, current imaging modalities are insufficient to accurately predict histological diagnoses. In our recent series, no one radiological feature could unequivocally predict malignancy. Outcome, however, was able to be predicted with a poor outcome associated with edema (35.5% vs. 16.2%, $p = 0.11$) and tumor volume larger than 30 ml (76.5% vs. 43.2%, $p = 0.023$). On the contrary, the presence of a cyst was usually indicative of a benign tumor (e.g., pilocytic astrocytoma) and was associated with a better outcome (43.2% vs. 23.5%, $p = 0.137$).

Historically, extension beyond adjacent structures especially into the contralateral thalamus has indicated a more aggressive lesion [18]. Caution therefore should be used when interpreting spread into the cerebral peduncles as thalamo-peduncular tumors, in contrast, are usually benign with a good outcome provided complete surgical resection is achievable.

- Pilocytic astrocytoma (Fig. 4a, b)
  In the thalamus, pilocytic astrocytomas are usually unilateral, solid, well circumscribed and contrast enhancing. Some are cystic (Fig. 3a). They tend to displace surrounding structures rather than invade them. However in some cases the appearances may be confusing (Fig. 3b)
- Infiltrative fibrillary astrocytoma (Fig. 4c, d)
  They can be benign or malignant. In the more benign form they are typically hypointense on T1-

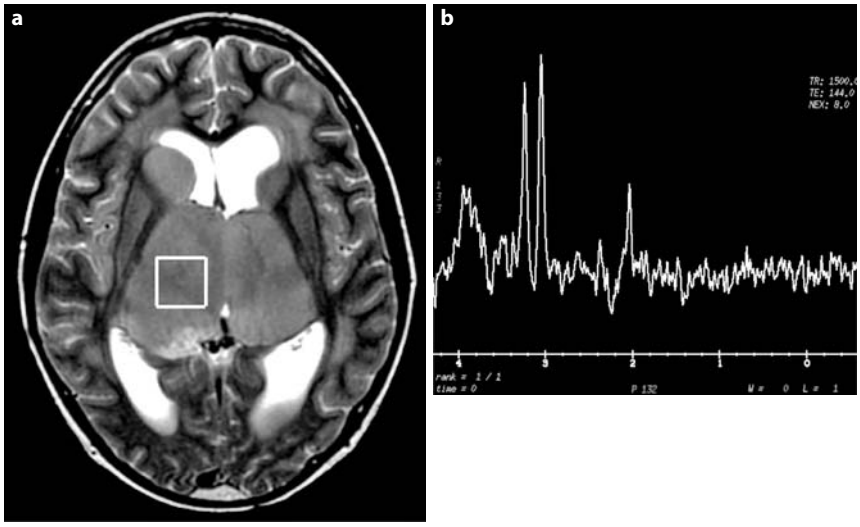


Fig. 3

weighted images (Fig. 4c) and hyperintense on T2-weighted or Flair sequences. Extension into adjacent structures is common and contrast enhancement is present in Grade IV (rim enhancing pattern) and occasionally Grade III lesions (Fig. 4d).

- Oligodendroglioma (Fig. 4e, f, courtesy of C. Di Rocco)
  CT demonstrates a well-defined mass with calcification and minimal surrounding edema (Fig. 4e). The MR image is less typical (Fig. 4f) with either relatively uniform contrast enhancement or no enhancement at all.
- Thalamo-peduncular tumor typically has the appearance of a solid pilocytic astrocytoma. These cases must be differentiated from a thalamic tumor with mesencephalic extension (Fig. 5a, b)
- Bilateral thalamic tumors have typical radiological appearances [5]. The thalami are symmetrically enlarged without any obvious interconnecting tumor tissue (Fig. 6a, b). There is symmetrical T2 hyperintensity in both thalami with minimal mass effect. There may also be symmetric extension into the adjacent basal ganglia and midbrain [18]. The radiological findings are atypical for tumor and as such bilateral thalamic tumors may be mistaken for other diseases for example encephalitis, mitochondrial encephalopathy, or acute necrotizing encephalopathy of childhood. The absence of mass effect or tissue density change renders them difficult to visualize on CT.
- Atypical "lesions" of the thalamus may have an indolent nature with no signs of progression over an

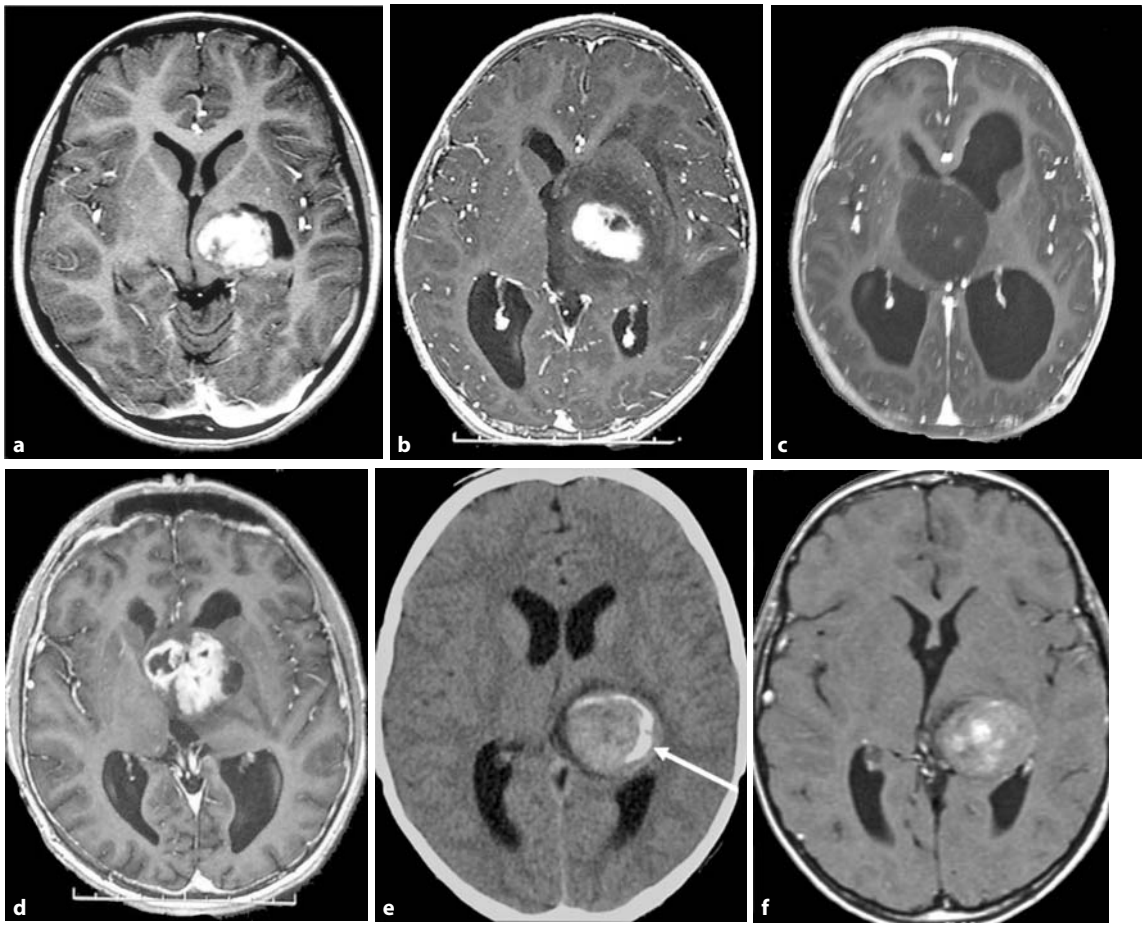


Fig. 4

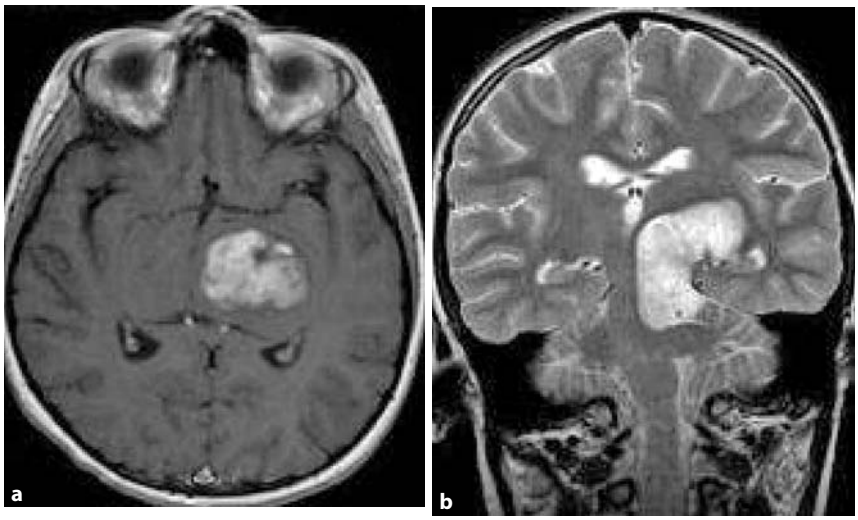


Fig. 5

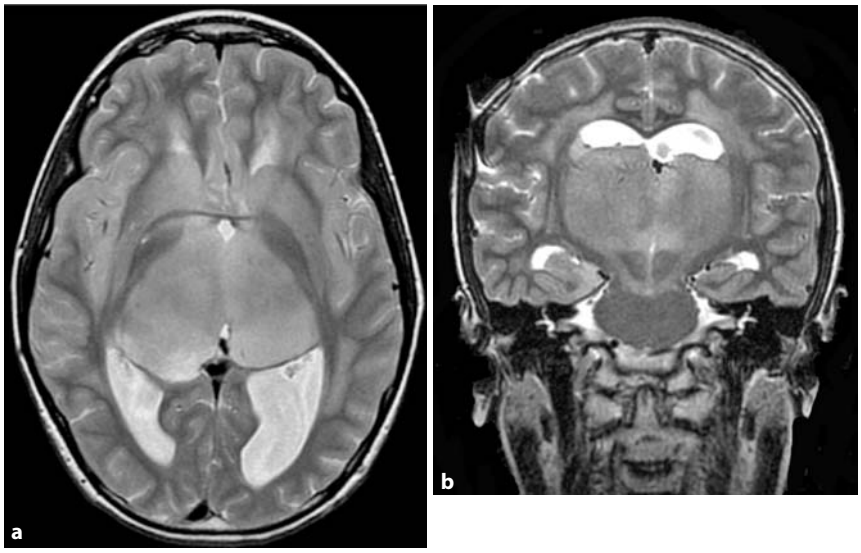


Fig. 6

extended period of follow-up. The lesion shown in Fig. 7, causing hydrocephalus treated by a third ventriculostomy was diagnosed through a stereotactic biopsy as being a "low-grade glioma." The lesion has remained stable over 12 years without treatment. These lesions need to be recognized to avoid unnecessary institution of aggressive treatment.

Staging and Classification

Synopsis

Most thalamic tumors are glial in nature, predominantly astrocytomas; with an equal distribution between high- and low-grade tumors. The prognostic implication of the grading of the tumor has been emphasized in several reports. Simple neuroimaging criteria/patterns may help to predict pathological diagnosis and to determine resectability.

Body

The diagnoses reported in most of the published series are shown in Table 3.

Table 4 shows the pathological diagnosis observed in the Necker series together with the largest pediatric series [18].

- As reported in earlier series and here, pure thalamic tumors are usually gliomas. The proportion of high-grade vs. low-grade tumors may vary slightly between series but usually low-grade as-

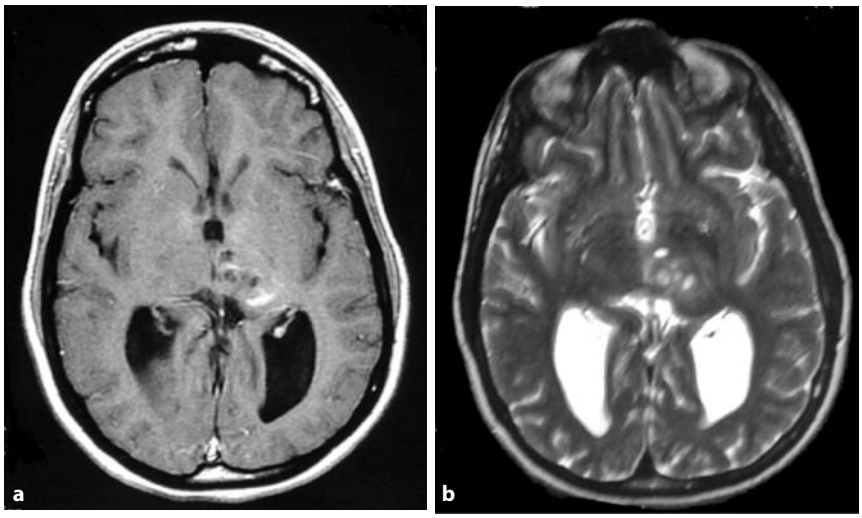


Fig. 7

Table 3 Pathological diagnosis observed in the Necker series and other reported series

Reference	Number of patients	Age group	Low-grade astrocytoma	High-grade astrocytoma	Other tumors
[4]	26 TTs (gliomas)	Children only	9	17	2 ependymomas
[7]	6 TTs (gliomas)	Children only	5		1 oligodendroglioma
[12]	20 TT & BGT	Children only	13	3	1 oligodendroglioma 1 xantho-astrocytoma 1 ganglioglioma
[16]	18 TTs	Children only	10	3	2 ependymomas 2 PNET 1 ganglioglioma
[20]	5 TTs	Children only	2	2	1 encephalitis
[1]	19 TTs (gliomas)	Children only	7	12	
[14]	57 TT (infiltrative astrocytomas only)	All ages	14	27	16 no Dx
[10]	72 TTs (astrocytomas)	All ages	31	40	
[23]	55 TTs	All ages	12	37	2 teratomas 2 mets
[26]	14 TTs (astrocytomas)	All ages	4	10	

trocytomas constitute slightly more than half of the pathologies encountered. Juvenile pilocytic astrocytomas represent one quarter to one fifth of all thalamic tumors.

- Bilateral thalamic gliomas are a variant of the fibrillary astrocytoma. The remarkably symmetrical nature of this tumor suggests that the origin is more likely to be bilaterally synchronous from the onset [3]. Most are Grade II tumors (7 out of 9 in our series) but some are Grade III or IV at presentation.
- Unusual pathologies may be observed in this location. For example the commoner sites for ectopic germinoma include the thalamus and basal ganglia. Three thalamic germinomas have been reported by Kim et al. [11] and were associated with

Table 4 Gliomas subtypes observed in the Necker and St. Jude series

Histology	Necker	St. Jude	
LGG		24 (52%)	24 (67%)
	JPA	9 (20%)	9 (25%)
	FA	7 (15%)	12 (33%)
	LGO	6 (13%)	1 (3%)
	Ganglioglioma	1 (2%)	2 (5.5%)
HGG		20 (43%)	12 (33%)
	AA/GBM	17 (37%)	11 (31%)
	AO	3 (7%)	/
PNET		2 (4%)	1 (3%)
Neurocytoma		1 (2%)	/

LGG, low-grade glioma; HGG, high-grade glioma; JPA, juvenile pilocytic astrocytoma; FA, fibrillary astrocytoma; LGO, low-grade oligodendroglioma; AA, anaplastic astrocytoma, GBM, glioblastoma multiforme; AO, anaplastic oligodendroglioma; PNET, primitive neurectodermal tumor

hemiatrophy of the brain. They advocate the inclusion of germinoma in the differential diagnosis of a hemorrhagic thalamic mass associated with cerebral atrophy in children. Other tumor types (such as ganglioglioma, pleomorphic xantho-astrocytoma, atypical teratoid rhabdoid tumors, PNET) have been described in the thalamus.

Treatment

Synopsis

From the neurosurgeon's stand point, the goal is to achieve maximal surgical resection without bilateral damage to the thalamic structures. Complementary treatment with radiotherapy is usually reserved for high-grade neoplasm. Chemotherapy may play a role in the nonresectable low-grade lesion or to facilitate surgery.

Body

Controversy exists over the optimal treatment for children with thalamic tumors. In the past, some authors advocated a more conservative approach such as radiotherapy alone or limited resection [2, 4] due to the difficulties of radical surgery [16]. Improvements in anesthetic and surgical techniques however, have allowed a more accurate and safer approach to these tumors. Total removal of low-grade tumors may be curative and radical resection may extend survival of even anaplastic tumors [4, 16]. Radical microsurgical resection of these deep-seated infiltrative lesions is beneficial in that it provides more material for histology, offers better control of intraoperative hemorrhage, and may improve the efficacy of complementary therapies.

- The treatment for thalamic or thalamo-peduncular pilocytic astrocytomas is surgical removal, with complete removal achievable in most cases. The management of benign infiltrating astrocytomas is more complex. While some studies suggest that the disease can be controlled for long periods with surgery alone, [3, 25] surgical resection remains debatable.
- In bilateral thalamic gliomas, significant surgical debulking can rarely be achieved if at all. They are often treated with multiregimen therapy including radiation and chemotherapy. The outlook is poor [3]. In one series all patients with bilateral thalamic astrocytomas were dead within 2.5 years [18]. However, their outcome may not be uniformly poor. In our experience, five out of nine were long-term survivors without progression, all with a low-grade glioma. The potential risk of degeneration of the tumor following irradiation has led us to postpone radiation therapy in stable lesions.

Surgery

Thalamic astrocytomas have a tendency for exophytic growth into the surrounding ventricles. Hydrocephalus is therefore frequent and the enlarged

ventricles may provide an ideal surgical corridor when excision is planned.

Biopsy

Stereotactic biopsy has practical constraints in children as the entire procedure is generally performed under general anesthesia and the application of a fixed frame is not possible in the very young child due to thinness of the skull. On the other hand, an improvement in the prognosis of nonresectable tumors, due to advances in adjuvant therapies, has heightened the need for histological diagnosis. Stereotactic aspiration may also necessary to reduce the intracranial pressure caused by large cystic thalamic tumors. St. George et al. [20] describe 15 stereotactic procedures in 14 children with brain tumors, five of which were in the thalamus. The youngest patient was 4 years old. Only one patient suffered complications from the procedure (seizures and confusion after biopsy of a bilateral thalamic tumor). There were no clinically significant hemorrhages. The diagnostic yield was 83%, but may be able to be improved if intraoperative pathologic evaluation was used.

Biopsy under endoscopic control is feasible in those patients with obstructive hydrocephalus. If the site of obstruction is located at the level of the aqueduct, a third ventriculostomy may be performed during the same procedure.

Open Surgery

Improvements in surgical technique have reduced perioperative mortality from 40% to 1% in children with thalamic tumors. Most neurosurgeons agree today that radical removal is the ultimate goal, particularly in lower grade lesions [16, 24]. In the case of infiltrating tumors it remains questionable as to whether attempted maximal resection improves the overall survival, particularly in Grade III and IV gliomas, compared to treatment with radiotherapy and/or chemotherapy [2, 14, 26].

Surgical resection is challenging because of the complex vascular supply, deep-seated location, and the proximity of eloquent structures such as the basal ganglia and internal capsule. This has been addressed to some extent by the use of stereotactic techniques to maximize excision with preservation of surrounding structures [7, 10, 15, 26] although brain shift following craniotomy remains a constraining factor. Electrophysiological monitoring has been used, including somatosensory evoked potentials and eye muscle EMG for smaller tumors of the medial pulvinar approached by the infratentorial supracerebellar route [26]. We frequently use direct peroperative stimulation of the pyramidal track when the internal capsule is at risk. Resection of malignant gliomas could also be aided by the use of 5-aminolevulinic acid fluorescence [26].

The surgical approaches used will depend upon the origin and the extension of the tumor and its relationship to adjacent neural elements. Several routes are possible:

- Transcortical, transventricular approaches are particularly suitable in those patients with dilatation of a lateral ventricle. Orientation with respect to ventrolateral structures (internal capsule and subthalamic nuclei) can be maintained using the thalamostriate vein as a lateral boundary. A frontal transventricular approach is used for tumors superiorly situated and the parieto-occipital transventricular approach for posteriorly located lesions. In some cases of lesions located medially in the thalamus a more lateral, pure transcortical approach is possible along the pyramidal tract, but this route requires the use of peroperative stimulation in order not to damage the motors fibers (Fig. 8a, b).
- Anterior or posterior interhemispheric approaches are favored for superiorly placed tumors. Whilst

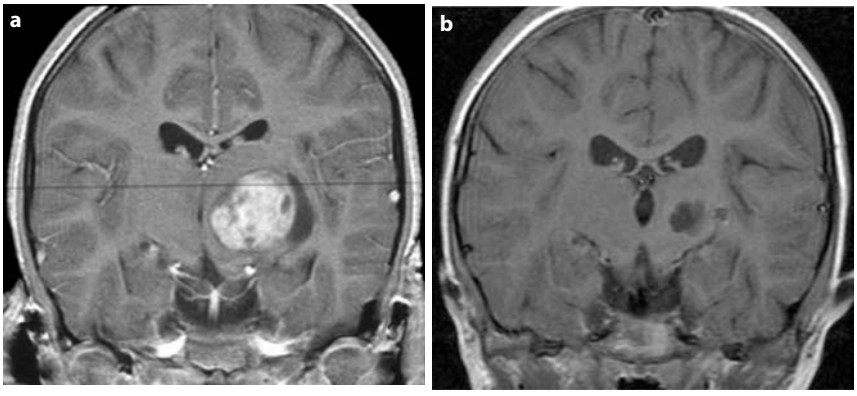


Fig. 8

the risk of seizures is lower, there is a risk of injury to cortical draining veins and to the pericallosal arteries. It is a particularly useful approach when the majority of the tumor protrudes into the lateral ventricle (Fig. 9a–c). The posterior interhemispheric approach is particularly useful in posterior thalamic/pulvinar lesions.

- The infratentorial supracerebellar and occipital transventricular approaches can also be used for these lesions, particularly those in the pulvinar. However, lateral resection of larger posterior thalamic tumors is limited due to the narrow corridor afforded between the basal veins of Rosenthal.
- Ventroposterior tumors can be removed via a transtemporal approach between the superior and middle temporal gyri. A transtemporal route reduces the risk of vascular injury, but the disadvantage of a transcortical approach is to increase the risk of postoperative seizures.

These tumors can also be approached using a pterional transsylvian-transinsular approach. A small incision is then made in the midportion of the postcentral sulcus of the insula. This approach is useful for those tumors that have a close relationship to the insula (Fig. 10a, b) and is considered to be less invasive than the transtemporal or transoccipital approaches [16].

Reading the literature, it would seem that the surgical approach utilized was guided more by surgeon preference than by tumor location:

Ozek et al. [16] report on 18 children aged 2–16 years in whom gross macroscopic resection was achieved in 16. In 14 an interhemispheric approach was used. There was no operative mortality though one patient was made permanently worse. All patients with benign tumors (12) were alive. Only one of the six patients with malignant tumors (all of whom had radiotherapy; five had chemotherapy) was alive 2 years after treatment.

Steiger [26] reported on 14 patients, four of whom were children, with thalamic gliomas where radical resection was attempted. In all cases 70%–100% resection was achieved using neuronavigation and 5-aminolevulinic acid fluorescence. They favored the supracerebellar and the posterior transventricular approaches to remove ten malignant and four low-

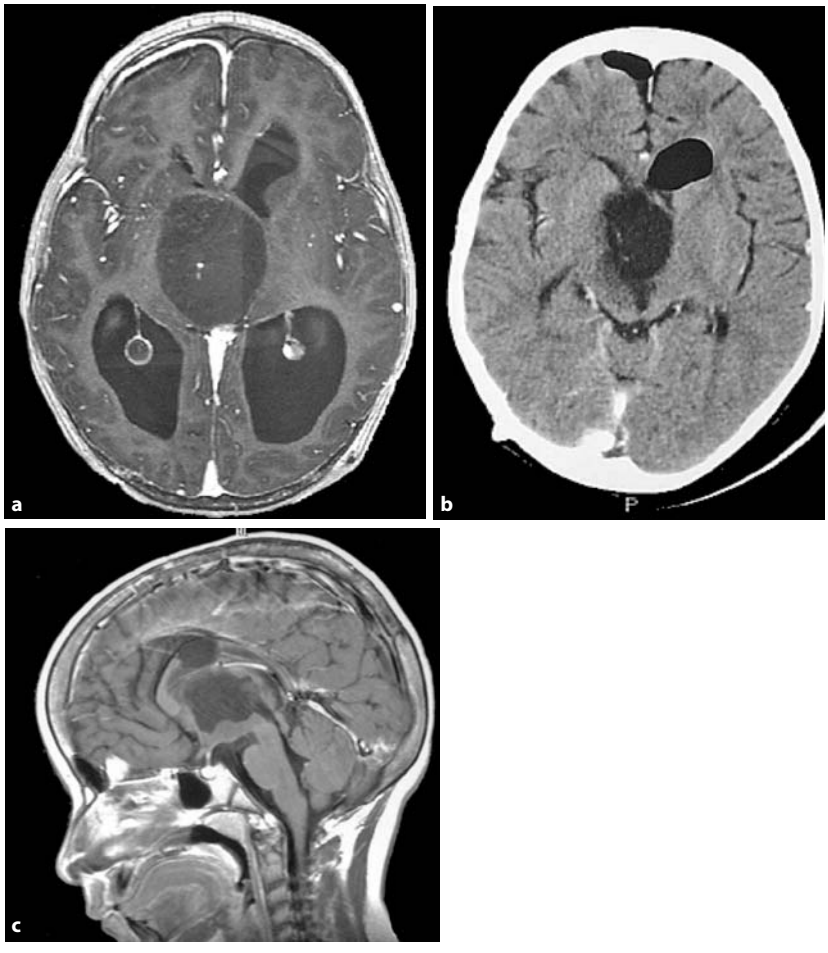


Fig. 9

grade gliomas (three pilocytic). They had no mortality but two patients developed a new visual field defect and one had worsening of an existing hemiparesis. The number was too small to comment on overall survival rates. Six of their patients required ventriculoperitoneal shunts. No postoperative imaging was reported.

Yasargil [23] describes radical resection in 49 patients with thalamic gliomas, 20 of whom were in children. He favored the posterior interhemispheric approach and had no mortality or visual field deficits. 51% had a good outcome and 58% were independent postoperatively. Again, no postoperative imaging was reported.

Treatment of Hydrocephalus

The treatment of hydrocephalus, frequently associated with these tumors, ideally should occur following the tumor surgery/biopsy as ventricular dilatation at the time of surgery may help with the exposure of the lesion and the removal/debulking of the tumor may be sufficient to re-establish a normal CSF circulation. A third ventriculostomy may be performed at the time of tumor removal or at the time of a biopsy through endoscopic guidance.

Immediate Postoperative Course

Resection of thalamic tumors usually causes temporary thalamic dysfunction with altered conscious level, and sensory and/or motor dysfunction. Occasionally visual field deficits can occur with tumors situated in the posterior thalamus. A left thalamic tumor resection may lead to anomic aphasia or alexia [19, 21]

Radiotherapy

The routine use of adjuvant radiotherapy after gross total resection of low-grade astrocytomas has been abandoned. Whilst radiotherapy in children may produce objective shrinkage of low-grade gliomas and prolong progression-free survival after incomplete resection, it has been associated with unacceptable long-term side effects such as impaired endocrine function, behavioral problems, altered intellectual development, vascular injury, and the risk of secondary brain tumors [9]. Therefore, routine use of radiotherapy following gross total resection of low-grade tumors is contraindicated and is confined to those with disease progression.

Hoffman [9] failed to show improved outcome in children with midline low-grade astrocytomas who received radiotherapy, but qualified this finding by noting that it was given to the children who had incomplete resection, larger and more infiltrative tumors.

Three dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiation therapy has been used in astrocytic tumors in eloquent areas to maximize tumor dose while avoiding large doses to the surrounding normal brain. Progression-free survival rate after radiotherapy is around 80% in low-grade tumors but is far less encouraging in high-grade tumors. Failures usually occur within the radiation field. There is no proof that any of these new techniques can improve tumor control but the limitation of the dose received by the surrounding normal brain is expected to significantly decrease radiation induced morbidity.

Chemotherapy

Though radical surgery seems to be effective in the treatment and possible cure of pilocytic astrocytomas in the thalamus, its benefit remains controversial in diffuse or progressive low-grade gliomas. Combinations of various chemotherapeutic agents have been used to treat children with progressive low-grade tumors and to delay the use of radiotherapy [17].

In the past 15 years there has been an upsurge of interest in the use of chemotherapeutic drugs in children with low-grade gliomas of the central nervous system, particularly in those under 5 years of age. To date there has been no published data exclusively looking at children with thalamic gliomas and thus inference must be drawn from more generic series.

A variety of agents have been used in the treatment of low-grade gliomas (platinum compounds, vincristine, vinblastine, alkylating agents) with most experience being with combination therapies. Earlier trials have been superseded by the use of vincristine and carboplatin. This combination is currently the standard for children with low-grade gliomas both in Europe and in North America [17]. Alternative chemotherapies are as effective but theoretically more toxic.

The aims of chemotherapy in younger children are to avoid or delay radiotherapy, or to facilitate a complete and safe surgical resection. In older children and young adults the indications are not as obvious.

For children with high-grade gliomas, there is no definitive evidence that the addition of chemotherapeutic agents to radiotherapy improves survival. However, children are often treated according to the treatment regimens validated in adults where adjuvant chemotherapy with nitrosoureas or temozolomide has been shown to be marginally effective.

Prognosis

Historically the outcome of children with thalamic tumors has been poor. The importance of high-grade histology as an adverse prognostic feature has been emphasized by several studies [2, 6, 18]. Overall survival for benign tumors is usually around 40% at 5 years in most of the series while few series report long-term survival in patients with high-grade tumors. Other risk factors for poor outcome may include: bilateral involvement, symptom duration prior to diagnosis, tumor volume, and extent of surgery (Table 5).

In high-grade lesions it is probable that complete surgery where feasible could improve survival. In our series a higher survival rate was observed after subtotal resection (five alive out of eight) compared with partial resection or biopsy (six alive out of 17). This finding has not been observed in other series [18]. Our data did not support a major role for chemotherapy in these lesions.

Follow-up/Specific Problems and Measures

Temporary thalamic dysfunction following surgery is common and includes problems with arousal as well as sensory, visual, and motor deficits. Left thalamic tumor surgery can lead to language difficulties [21].The late effects on children with thalamic tumors relate to duration of initial symptoms, tumor location, surgery, and adjuvant therapies. In the Necker series, at last follow-up, 51% of the patients were normal or independent, 15% dependant and 34% dead from disease progression. However, little information is available in the literature on the specific morbidity of thalamic tumors in children and further studies are needed [19].

Future Perspectives

The role of surgery needs to be re-evaluated in these deeply seated tumors. Aggressive surgery may be attempted in patients with a unilateral tumor but is associated with a potential increase in the risk of neurological sequelae. Improved neurosurgical tools (peroperative guidance, peroperative stimulation) and the development of centers of expertise will stimulate the development of new strategies of treatment. Potentially these will include more radical surgical resection as a staged procedure with the incorporation of chemotherapy to provide perioperative tumor reduction. This approach is likely to improve survival rates as has been shown for gliomas in other locations. Multidisciplinary care of these patients from diagnosis will become the rule rather than the exception particularly in patients with low-grade tumors.

References

1. Albright AL. Feasibility and advisability of resections of thalamic tumors in pediatric patients. J Neurosurg Spine 2004;100(5):468–72
2. Bernstein M, Hoffman HJ, Halliday WC, Hendrick EB, Humphreys RP. Thalamic tumors in children: long term follow-up and treatment guidelines. J Neurosurg 1984;61:649–656
3. Burger PC, Cohen KJ, Rosenblum MK, Tihan T. Pathology of diencephalic astrocytomas. Pediatr Neurosurg 2000;32:214–219
4. Cuccia V, Monges J. Thalamic tumours in children. Childs Nerv Syst 1997;13:514–521
5. Di Rocco C, Iannelli A. Bilateral thalamic tumors in children. Childs Nerv Syst 2002;18:440–444
6. Dropcho EJ, Wisoff JH, Walker RW, Allen JC. Supratentorial malignant gliomas in childhood: a review of fifty cases. Ann Neurol 1987;22(3):355–64

Table 5 Univariate analysis of prognostic factors in the Necker series

Histology p = 0.0053	Low-grade High-grade	5yOS = 87.5% 5yOS = 45.5%	Median OS>60 months Median OS = 21 months
Symptom duration p = 0.0009	>2 months <2 months	5yOS = 95.7% 5yOS = 48.4%	Median OS>60 months Median OS = 22 months
Tumor volume p = 0.025	<30 ml >30 ml	5yOS = 84.0% 5yOS = 40.0%	Median OS >60 months Median OS = 23 months
Extent of surgery p = 0.04	Subtotal All others	5yOS = 85.0% 5yOS = 47.1%	

7. Drake JM, Joy M, Goldenberg A, Kreindler D. Computer- and robot-assisted resection of thalamic astrocytomas in children. Neurosurgery 1991;29:27–33
8. Herrero MT, Barcia C, Navarro JM. Functional anatomy of thalamus and basal ganglia. Childs Nerv Syst 2002;18:386–404
9. Hoffman HJ, Soloniuk DS, Humphreys RP, Drake JM, Becker LE, De Lima BO. Management and outcome of low-grade gliomas of the midline in children. Neurosurgery 1993;33:964–971
10. Kelly PJ. Stereotactic biopsy and resection of thalamic astrocytomas. Neurosurgery 1989;25:185–195
11. Kim CH, Paek SH, Park IA, Chi JG, Kim DG. Cerebral germinoma with hemiatrophy of the brain: a report of three cases. Acta Neurochir 2002;144:145–50
12. Martinez-Lage JF, Perez-Espejo MA, Esteban JA, et al. Thalamic tumors: clinical presentation. Childs Nerv Syst 2002;18:405–411
13. Messing-Junger AM, Floeth FW, Pauleit D, Reifenberger G, Willing R, Gartner J, Coenen HH, Langen KJ. Multimodal target point assessment for stereotactic biopsy in children with diffuse bithalamic astrocytomas. Childs Nerv Syst 2002;18:445–9
14. Krouwer HGJ, Prados MD. Infiltrative astrocytomas of the thalamus. J Neurosurg 1995;82:548–557
15. Lyons MK, Kelly PJ. Computer-assisted stereotactic biopsy and volumetric resection of thalamic pilocytic astrocytomas. A report of 23 cases. Stereotact Funct Neurosurg 1992;59:100–104
16. Ozek M, Ture U. Surgical approaches to thalamic tumours. Childs Nerv Syst 2002;18:450–456
17. Packer RJ, Ater J, Allen J, Phillips P, Geyer R, Nicholson S, Jakacki R, Kurczynski E, Needle M, Finlay J, Reaman G Boyett JM. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 1997;86:747–754
18. Reardon DA, Gajjar A, Sanford RA, Heideman RL, Walter AW, Thompson SJ, Merchant TE, Li H, Jenkins JJ, Langston J, Boyett JM, Kun LE. Bithalamic involvement predicts poor outcome among children with thalamic glial tumours. Pediatr Neurosurg 1998;29:29–35
19. Siffert J, Allen JC. Late effects of therapy on thalamic and hypothalamic tumours of childhood: vascular, neurobehavioural and neoplastic. Pediatric Neurosurg 2000;33:105–111
20. St. George EJ, Walsh AR, Sgouros S. Stereotactic biopsy of brain tumours in the paediatric population. Childs Nerv Syst 2004;20:163–167
21. Tamhankar MA, Coslett HB, Fisher MJ, Sutton LN, Liu GT. Alexia without agraphia following biopsy of a left thalamic tumor. Pediatr Neurol 2004;30:140–142
23. Yasargil MG. Microneurosurgery, Vol. 4B. Stuttgart: Thieme; 1996. p. 252–342
24. Baroncini M, Delestret I, Vinchon M, Dhellemes P. Tumeurs thalamiques de l'enfant: indications et résultats de la chirurgie d'exérèse. Neurochirurgie 2004;50:570–572
25. Gajjar A, Sanford RA, Heideman R, Jenkins JJ, Walter A, Li Y, Langston JW, Muhlbauer M, Boyett JM, Kun LE. Low-grade astrocytoma: a decade of experience at St. Jude Children's Research Hospital. J Clin Oncol 1997 Aug;15(8):2792–2799
26. Steiger HJ, Gotz C, Schmid-Elsaesser R, Stummer W. Thalamic astrocytomas: surgical anatomy and results of a pilot series using maximum microsurgical removal. Acta Neurochir (Wien) 2000;142:1327–1336

Midbrain Gliomas 24

Leland Albright

Epidemiology – 378

Clinical Symptoms and Signs – 378

Diagnostics – 378

Staging and Classification – 378

Treatment – 378
Treatment of Hydrocephalus Caused by Midbrain Tumors
Treatment of Midbrain Tumors
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 380

Follow-up/Specific Problems and Measures – 382

References – 382

Epidemiology

Brainstem tumors include perhaps the most malignant pediatric brain tumor – the diffuse brainstem glioma – and the most benign, the tectal glioma. Brainstem tumors make up approximately 5% of pediatric brain tumors; those confined to the midbrain comprise 1%–2% of pediatric brain tumors. Midbrain tumors occur with equal frequency in the sexes. Tectal tumors are far more common than tegmental tumors: in Robertson's series of 17 children with midbrain tumors, only two were located in the tegmentum [8]. Midbrain gliomas were described by Kernohan and Sayers as "in all probability the smallest tumors in the human body that lead to the death of the patient," although death is due to untreated hydrocephalus rather than to the tumor per se.

Clinical Symptoms and Signs

Tectal gliomas are the most common cause of "late-onset aqueductal stenosis" in the USA, and a diagnosis of late-onset aqueductal stenosis mandates the procurement of an MR scan. However, tectal gliomas may be present rarely at birth and cause "congenital aqueductal stenosis."

Because of the proximity of tectal tumors to the cerebral aqueduct, their most common presenting symptoms are those of hydrocephalus: headache, nausea/vomiting, and ataxia. Parinaud's syndrome is not unusual but other cranial nerve palsies and long-tract signs are very uncommon. Less common symptoms include decline in school performance, subtle personality changes, tremor, complex partial seizures, and urinary incontinence. Parkinsonism has been reported in two children with midbrain tumors. The duration of symptoms before diagnosis ranges widely, from 1–36 months, with a mean of 16 months [1].

Tumors that involve the tegmentum may cause diplopia or hemiparesis.

In patients with von-Hippel-Lindau disease, hemangioblastomas occur in the brainstem in 5%–15% of cases, and may occur in the midbrain, where they may present with the insidious onset of hydrocephalus or the rapid onset of midbrain neurological signs secondary to a hemorrhage. Midbrain cavernomas may behave similarly.

Diagnostics

CT scans of midbrain gliomas are often normal because most midbrain tumors are isodense with brain and most do not enhance after contrast administration.

T-1 magnetic resonance (MR) images of tectal tumors reveal either iso-or hypointense lesions. T-2 images and Flair images show the classic periaqueductal hyper-intensity (Figs. 1–3). Flair scans may demonstrate the tumor even more distinctly than T2 images. These MR characteristics are present in children with tectal gliomas whether they present in infancy or as late-onset aqueductal stenosis. MR scans of infants with congenital, nonneoplastic, aqueductal stenosis never demonstrate a bulbous midbrain or hyperintensity on T-2 images.

Most tectal gliomas are less than 2 cm in diameter, and most (probably 85%) do not enhance after gadolinium. There is debate as to whether tumors that enhance are be more likely to progress clinically or radiographically.

Staging and Classification

There is no staging or classification system for midbrain tumors, other than the designation of tectal or tegmental. A tectal tumor has been reported that was disseminated through CSF at the time of presentation.

Treatment

Treatment of Hydrocephalus Caused by Midbrain Tumors

Hydrocephalus caused by tectal tumors can be treated effectively by either CSF shunts or endoscopic third ventriculostomies (ETVs). In the opinion of most pediatric neurosurgeons, ETVs are preferable. Although they have a higher rate of complications than shunts, ETVs treat the hydrocephalus definitively in 80%–90% of cases. In a series of 12 children with tectal gliomas treated with 15 ETVs, all children were shunt-free at their most recent follow-up, with a median follow-up of 31 months [5].

ETVs fail in a small percentage of cases. When that occurs, neurosurgeons usually repeat the endoscopy. If the ventriculostomy has closed, it is often refenestrated. If it is open, the hydrocephalus is managed most often by a CSF shunt, although aqueductal plasty and stenting have been reported.

If shunts are inserted, they require revisions. In the series of Daglioglu, 6/9 shunts needed to be revised in a follow-up averaging 7.1 years. When shunts are used, consideration should be given to the possibility that overdrainage may occur, resulting in the formation of subdural hygromas, a particular risk in older children with considerable macrocephaly and large

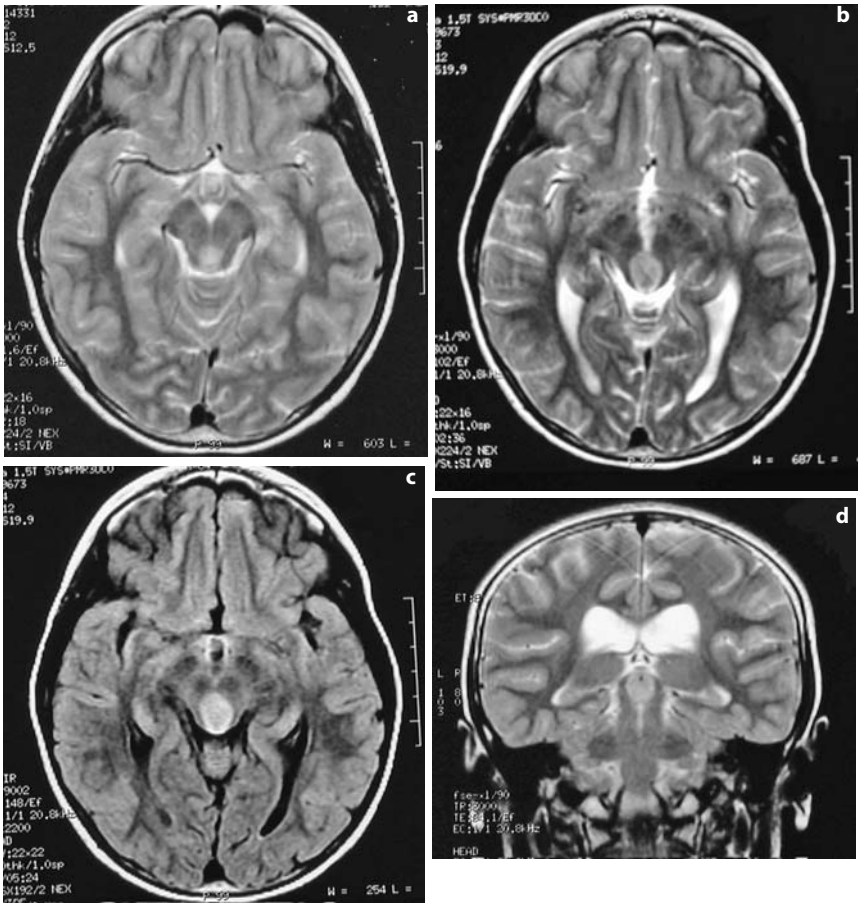


Fig. 1 Magnetic resonance images of a midbrain glioma. **a, b** Axial T2 images, **c** axial Flair image, **d** coronal T2 image

ventricles. Because of that risk, it is preferable to insert shunts with siphon-reducing or antisiphon devices when possible. In our 1994 series of 16 patients with tectal gliomas and hydrocephalus, three developed postshunt subdural hygromas. Treatment of the hygromas and subsequent reinstitution of a functioning shunt was complicated in all three by the development of low-pressure hydrocephalus, a difficult clinical problem that required CSF drainage at pressures below zero (via external ventricular catheters), for days at a time before the children would tolerate normal pressures. The days of negative drainage are necessary to remove water that has entered the interstitial spaces of the brain and altered brain compliance.

Treatment of Midbrain Tumors

Biopsies are indicated for enhancing tumors that are associated with focal neurological deficits (other than abnormal eye movements). Most such tumors will extend from the tectum into the tegmentum or adjacent thalamus. Nonenhancing tectal tumors do not need to be biopsied.

Midbrain tumors have been biopsied stereotactically and open. Focal, enhancing tumors can be treated effectively with either stereotactic biopsies and subsequent radiotherapy, or open biopsy and tumor resection. In the author's opinion, the morbidity of stereotactic biopsies is lower, but no studies have compared morbidity of the two options. Open biopsy/resection may be appropriate if a complete tumor removal seems to be reasonably feasible, but if subtotal removal and the need for postoperative irradiation is likely, the subtotal removal confers no advantage over stereotactic biopsy.

Vandertop et al. reported operating on 12 children with focal midbrain tumors treated in Toronto between 1976 and 1991 [9]. Most tumors had a focal enhancing component; 42% extended upward into the thalamus and 58% downward into the pons. Most were approached via a subtemporal route. During such operations, some neurosurgeons monitor SSEPs, BSERs, oculomotor compound action potentials in hopes of reducing the risk of postoperative neurological deficits, but there are no data to confirm that reduction.

In a series of 111 midbrain tumors from combined published series, 85% were low-grade astrocytomas

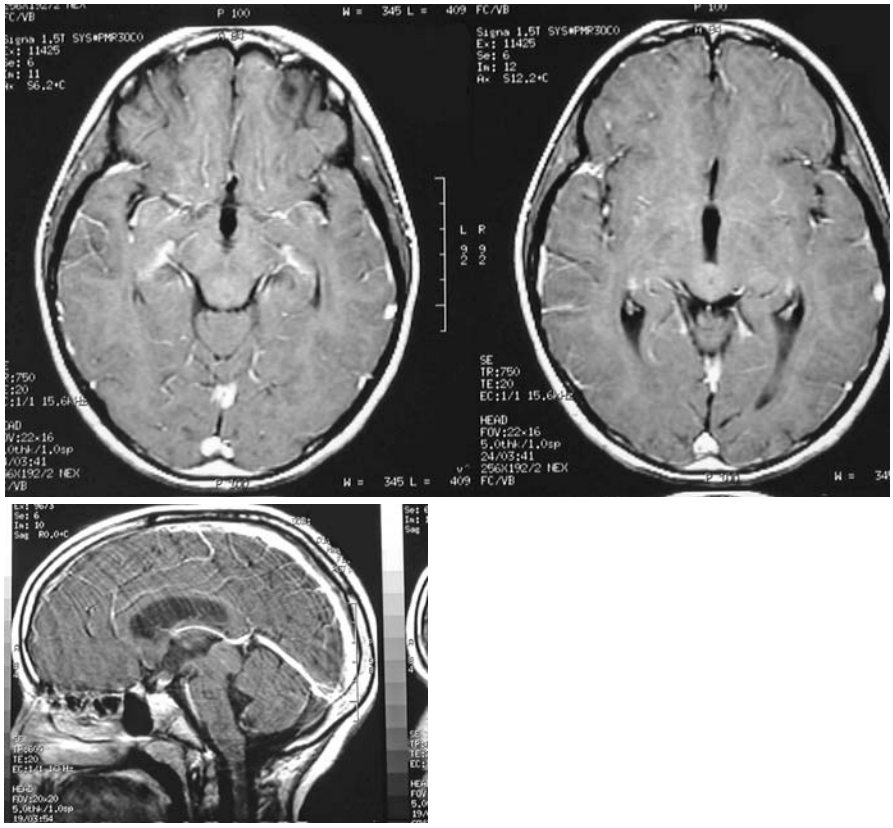


Fig. 2 MR images of a nonenhancing midbrain glioma, axial T1 (*top*), sagittal T1 (*bottom*)

or oligodendrogliomas and 15% were high-grade tumors [1]. Five percent of biopsies were inconclusive.

Midbrain hemangioblastomas should probably be removed if (1) they are symptomatic, (2) have reached a size such that surgical risks would be appreciably increased if they enlarged further, or (3) there is an enlarging cyst. Because of the propensity of hemangioblastomas to enlarge by small bleeds, and because radiosurgery has not been shown to significantly decrease the likelihood of their enlarging, open resections are indicated before serious neurological deficits develop.

Radiotherapy

Irradiation is used when low-grade midbrain gliomas progress clinically and when high-grade gliomas are diagnosed. Irradiation has been given with conventional fractionated external beams, conformal irradiation, and stereotactic radiosurgery (SR). The latter two are usually preferred at present. Conformal irradiation is given when tumor margins are relatively indistinct, particularly when the tumor is poorly enhancing. SR is used more often when there is a well-demarcated, enhancing tumor [4]. Progression of a low-grade midbrain glioma after irradiation is rare. When SR is used, median doses are usually 9–12 Gy to the tumor margin with a median isodose of 50%. A few adults with midbrain tumors have been treated with gamma knife radiosurgery but there are no significant series of pediatric midbrain tumors treated with radiosurgery.

After either external beam irradiation or radiosurgery, cystic degeneration develops in some midbrain tumors (Fig. 4). Such cysts develop insidiously and may not be associated with neurological worsening. If cysts produce neurological deficits, they can be aspirated stereotactically.

Chemotherapy

There are almost no reports of chemotherapy to treat pediatric midbrain tumors. In a single case, Robertson et al. reported a low-grade astrocytoma that progressed after irradiation and was treated with aziridinylbenzoquinone (AZQ), with a 75% decrease in tumor volume [8].

Prognosis/Quality of Life

Nonenhancing tectal tumors usually remain the same size over several years and some have been observed to get smaller [1]. In children with neurofibromatosis

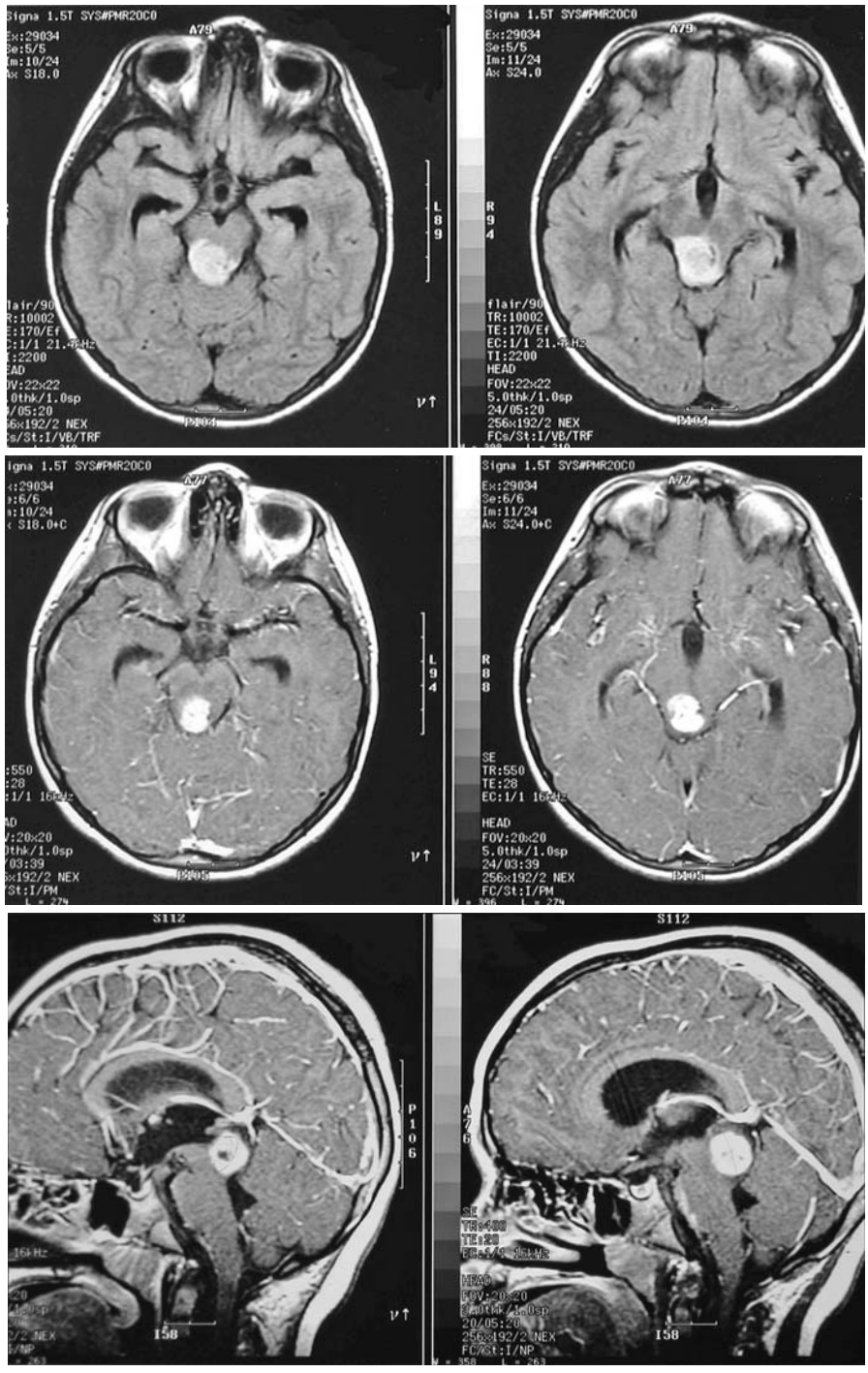


Fig. 3 MR images of midbrain glioma. Axial Flair (*top*), T1 enhanced (*middle*), sagittal T1 (*bottom*)

type 1 and a tectal mass, the mass may spontaneously regress, as do other CNS lesions in children with NF1. At the Children's Hospital of Pittsburgh, the first patient diagnosed with a tectal glioma by MR scan was in 1986; her tumor has not changed in the 18 years since then. In our series of 16 children with tectal gliomas followed for a median of 9.75 years, four tumors progressed clinically, with onset of a Parinaud's syndrome [3]. Progression occurred at a median of 7.8 years after treatment of the hydrocephalus.

Tumors may enlarge radiographically without a concomitant clinical worsening. In such cases, continued observation is appropriate. Bowers et al. followed five children with larger tumors on MR scan but normal neurological exams for 1.8–6.9 years after the first radiological enlargement [6]. None de-

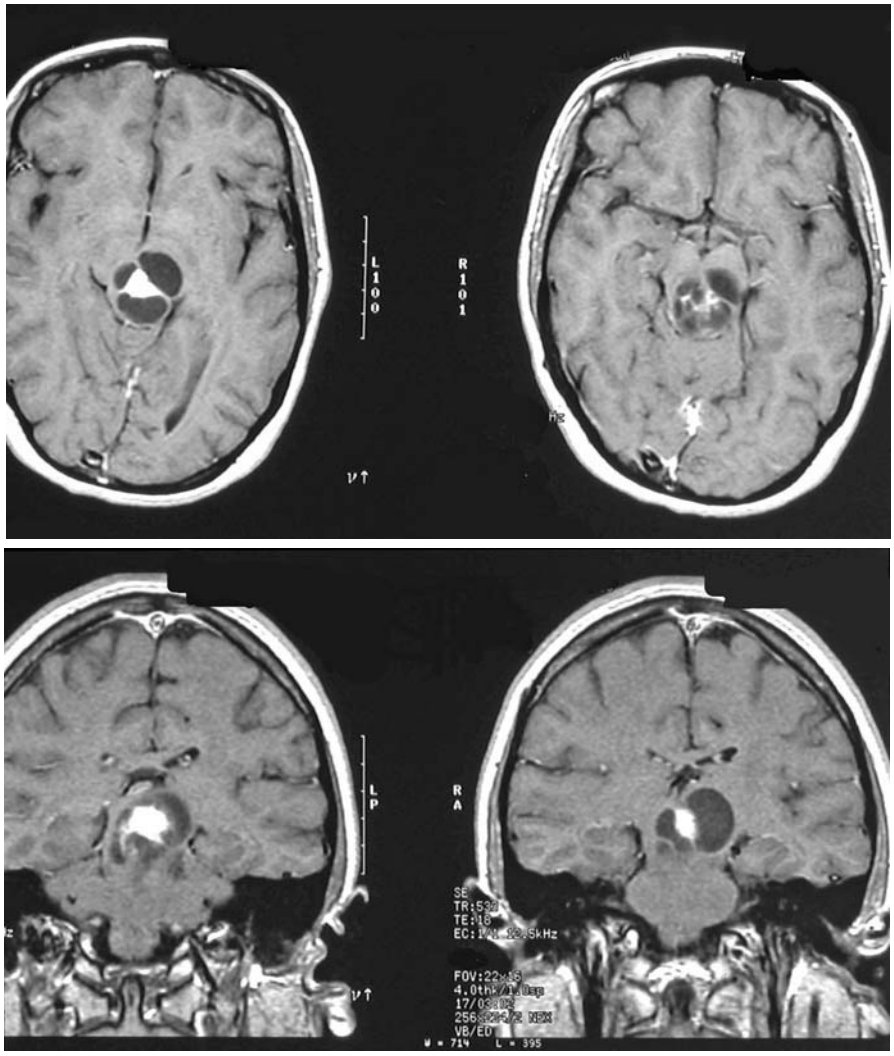


Fig. 4 Juvenile pilocytic midbrain astrocytoma with cystic changes after stereotactic radiosurgery. The patient was neurologically normal except for diplopia. Axial T1 enhanced (*top*), and coronal (*bottom*) images

veloped a neurological deficit. In the series of 11 patients reported by Grant et al. [7], three patients had enlargement of the tumors during follow-up and none had associated symptoms. In that series, and the series of Daglioglu, patients with tectal gliomas <2 cm without gadolinium enhancement did not progress clinically or radiographically [1].

Follow-up/Specific Problems and Measures

After treatment of the hydrocephalus associated with tectal tumors, follow-up MR scans to evaluate the tumor can be obtained yearly for 2–3 years, then every 2 years for 6 years, then every 3 years unless the child changes symptomatically at any time. Some authors prefer to repeat annual neurological examinations in addition to the MR scans. In general, children with tectal gliomas have a normal quality of life [2].

References

1. Daglioglu E, Cataltepe O, Akalan N. Tectal gliomas in children: the implications for natural history and management strategy. Ped Neurosurg 2003;38:223–231.
2. Poussaint TY, Kowal JR, Barnes PD, Zurakowski D, Anthony DC, Goumnerova L, Tarbell NJ. Tectal tumors of childhood: clinical and imaging followup. Am J Neuroradiol 1998;19:977–983.
3. Pollack IF, Pang D, Albright AL. The long-term outcome in children with late-onset aqueductal stenosis resulting from benign intrinsic tectal tumors. J Neurosurg 1994;80:681–688.
4. Kuhlstrom L, Lindquist C, Lindquist M, Karlson B. Stereotactic radiosurgery for tectal low-grade gliomas. Acta Neurochir (Suppl) (Wien) 1994;62:55–57.
5. Wellons J, Tubbs RS, Banks JT, Grabb B, Blount JP, Oakes WJ, Grabb PA. Long-term control of hydrocephalus via en-

doscopic third ventriculostomy in children with tectal plate gliomas. Neurosurg 2002;51:63–68.
6. Bowers DC, Georgiades C, Aronson LJ, Carson BS, Weingart JD, Wharam MD, Burger PC, Cohen KJ. Ped Neurosurg 2000;32:24–29.
7. Grant GA, Avellino AM, Loeser JD, Ellenbogen RG, Berger MS, Roberts TS. Management of intrinsic gliomas of the tectal plate in children. A ten-year review. Ped Neurosurg 1999;31:170–176.
8. Robertson PL, Muraszko KM, Brunberg JA, Axtell RA, Dauser RC, Turrisi AT. Pediatric midbrain tumors: a begign subgroup of brainstem gliomas. Ped Neurosurg 1995;22:65-73.
9. Vandertop WP, Hoffman HJ, Drake JM, Humphreys RP, Rutka JT, Amstrong DC, Becker LE. Focal midbrain tumors in children. Neurosurg 1992;31:186–194

Supratentorial High-Grade Gliomas

25

Rene O. Sanchez-Mejia, Anu Banerjee, Nalin Gupta

Epidemiology – 386

Symptoms and Clinical Signs – 386

Diagnostic Studies – 386
Computed Tomography
Magnetic Resonance Imaging
Genetic Features

Staging and Classification – 388

Treatment – 388
Surgical
Chemotherapy
Radiation Therapy

Prognosis and Outcome – 390

New Treatment Strategies – 390

References – 390

Epidemiology

Central nervous system (CNS) tumors account for 20%–25% of all childhood neoplasms, and their incidence is second only to hematologic malignancies [34]. In addition, they are the third leading cause of death in children less than 16 years of age. The majority of supratentorial primary brain tumors in children are gliomas. Fortunately, low-grade gliomas account for 60%–80% of supratentorial hemispheric tumors in children; these tumors occur at an incidence of approximately 5 in 1 million children per year [26, 36, 40]. High-grade gliomas (HGG), equivalent to malignant gliomas, account for the remaining 20%–40% [26]. Overall, HGGs account for approximately 6.5% of all newly diagnosed childhood intracranial tumors [36]. There does not appear to be any influence of gender or race on incidence [6]. Tumors metastatic to the CNS are rare in children.

Most childhood gliomas are sporadic, although underlying genetic conditions such as neurofibromatosis type 1 (NF-1), Li Fraumeni syndrome, tuberous sclerosis complex (TSC), or Turcot syndrome are known to predispose patients to the development of CNS gliomas. The phenotype of these syndromes is presumed to be dependent upon mutations within identified genes, although the origin of the observed phenotypic variability is not well understood in some disorders (e.g., NF-1). Some HGGs in adults can evolve from lower-grade lesions, but this model of tumor progression has not been fully established in children. The observation that pilocytic astrocytoma [World Health Organization (WHO) Grade I] can undergo malignant change [11] suggests that transformation to a higher grade occurs in children, but this event is not observed at the same frequency as it is in the adult population.

Environmental factors have also been implicated, but the only clear risk factor is a prior history of brain irradiation. This is most often seen in the setting of previous therapeutic radiation treatment for leukemia. The search for other environmental factors is an active area of research and may reveal other predisposing oncogenic stimuli.

Symptoms and Clinical Signs

Patients with supratentorial lesions usually present with seizures, focal neurologic deficits, or headache. Because high-grade tumors grow more rapidly, they tend to be associated with a more abrupt clinical presentation compared to low-grade tumors. For this reason, patients with low-grade tumors are more likely to present with a focal neurologic deficit or decreased level of consciousness rather than seizures, although seizures still account for the presenting clinical sign in approximately one third of patients [36]. Approximately 5%–10% of patients present with a rapid neurologic decline, either due to brain herniation or tumor-associated hemorrhage [36]. The most common finding on physical examination is papilledema secondary to increased intracranial pressure. As with other lesions in the CNS, the physical examination can be helpful in anatomically locating the lesion, but is nonspecific in determining the differential diagnosis without more advanced diagnostic tools.

Diagnostic Studies

The differential diagnosis for intrinsic supratentorial neoplasms includes low-grade or high-grade astrocytoma, oligodendroglioma, supratentorial primitive neuroectodermal tumor (PNET), ependymoma, neuronal tumors (ganglioglioma or gangliocytoma), pleomorphic xanthoastrocytoma and, rarely, metastatic tumors such as lymphoma, neuroblastoma, or sarcoma. Detailed imaging studies are required to define the anatomical relationships between the tumor and surrounding brain, and to narrow the presumed pathologic diagnosis. Increasingly, imaging studies are also necessary for surgical planning.

Computed Tomography

Computed tomography (CT) is usually the first study obtained after a patient presents with symptoms. Noncontrast images will often show the indirect effects of a mass lesion but this appearance is common to tumors, abscesses, and acute stroke. Irregular or ring enhancement on cranial CT images following contrast administration reflects the breakdown of the blood-brain barrier and/or tumor neovascularity and is more common with high-grade neoplasms. This finding is not specific since pilocytic astrocytomas routinely enhance strongly on postcontrast images. The presence of central necrosis, extension across the midline through the corpus callosum are also suggestive of a high-grade neoplasm. In general, CT images support the diagnosis of an intrinsic glioma but are rarely adequate in themselves.

CT perfusion studies are helpful in assessing tumor vascularity, and by implication, its pathologic grade. Although magnetic resonance (MR) perfusion studies are more widely used, CT perfusion studies are equally helpful in assessing perfusion without the additional anatomical detail [10].

Magnetic Resonance Imaging

For suspected intrinsic brain tumors, a high quality magnetic resonance imaging (MRI) study, both with and without gadolinium contrast, is essential. HGGs are usually isointense or hypointense on T1-weighted images [8]. Contrast enhancement varies from little or none (Fig. 1), to a more typical appearance of irregular peripheral enhancement (Fig. 2). T2-weighted and FLAIR images usually show increased signal intensity in the surrounding white matter tracts which represents infiltrative tumor and vasogenic edema (Figs. 1, 2). Areas of necrosis or enhancement support the diagnosis of a HGG, although enhancement and cyst formation occurring in low-grade tumors can mimic areas of necrosis. Pleomorphic xanthoastrocytomas typically have an enhancing solid component at the cortical surface with a deeper cyst, although more heterogeneous enhancement is occasionally observed.

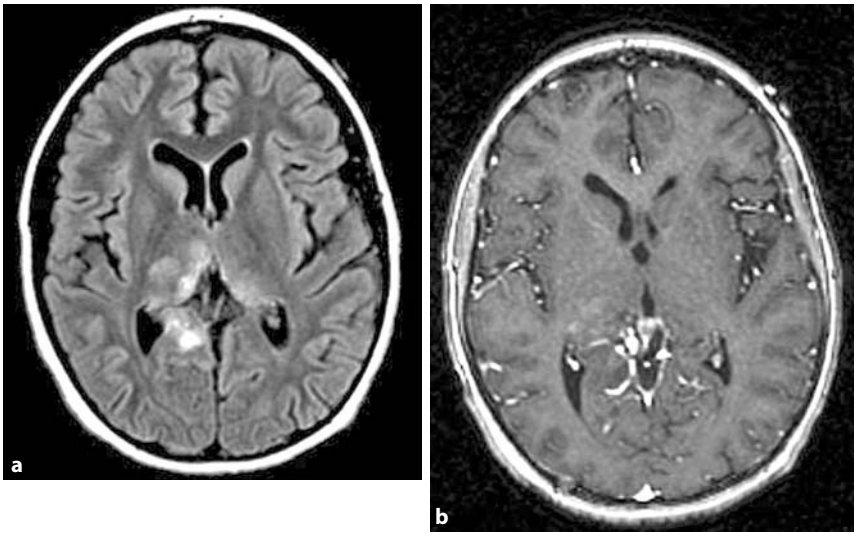


Fig. 1 Nine-year-old boy who presented with new-onset seizures. The pathologic diagnosis was anaplastic astrocytoma. (**a**) Preoperative FLAIR MR image demonstrating an infiltrative HGG in the right anterior occipital lobe, and right thalamus with extension into the midbrain and right parahippocampal gyrus. (**b**) A T1-weighted MR image following gadolinium reveals heterogeneous enhancement

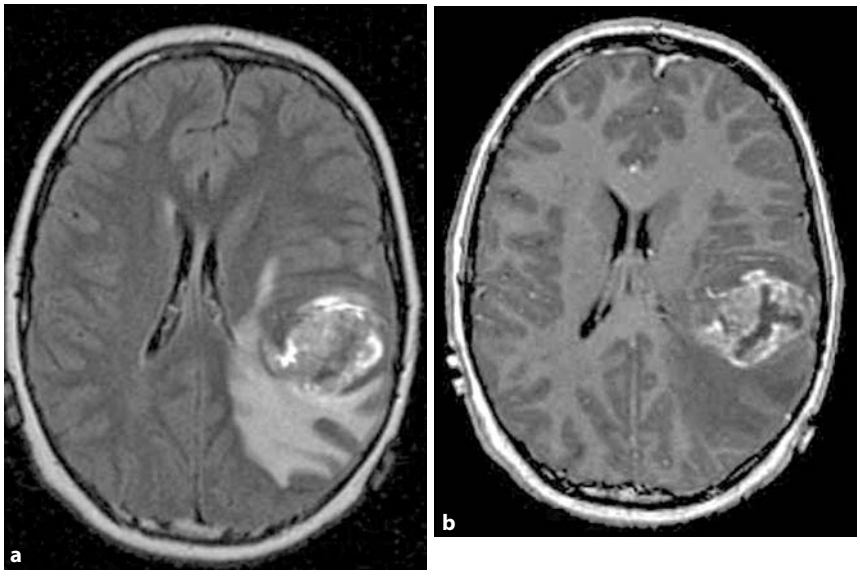


Fig. 2 Fourteen-year-old boy who presented with a progressive history of headaches, dysphasia, and nausea and vomiting. The pathologic diagnosis was glioblastoma multiforme. (**a**) Preoperative FLAIR sequence MRI demonstrating a large infiltrative mass in the anterior left parietal lobe with surrounding vasogenic edema with considerable local mass effect. (**b**) A T1-weighted MR image following gadolinium reveals heterogeneous enhancement with a central nonenhancing area consistent with central necrosis

Newer MR techniques have been developed in order to reduce the ambiguity that can occur due to overlapping features observed with conventional sequences. MR perfusion studies are used to assess tumor blood supply by measuring cerebral blood volume and contrast transit time. Increase cerebral blood volume, indicating hypervascularity, may be elevated in areas that do not demonstrate contrast enhancement [8]. This observation accounts for some of the lack of specificity of contrast enhancement with respect to the pathologic grade of a tumor. MR spectroscopy provides additional metabolic information reflecting different aspects of tumor biology. An increased choline to N-acetylaspartate ratio has been shown to predict malignancy. Presumably, this occurs in HGGs from increased cell division and turnover with reduced numbers of neurons. Increasingly, these modalities are providing more accurate preoperative diagnoses and are guiding intraoperative biopsies to assure adequate sampling of the most suspicious intratumoral areas [20].

Genetic Features

The genetic mutations underlying the development of malignant gliomas in children are presumed to be different than those in adults [39]. Recent studies have shown that chromosomal aberrations in pediatric HGGs differ from those observed in adults. For example, pediatric high-grade astrocytomas are more frequently observed to have gains in chromosome 1p, 2q, and 21q, and losses of 6q, 11q, and 16q [31]. In the same study, a correlation was reported between a gain on chromosome 1q and shorter survival, although the overall sample size was small (23 patients). Nevertheless, these lines of evidence reinforce the importance of these types of studies in terms of improving prognosis and tailoring treatment protocols for specific tumor subtypes.

Underlying genetic features predisposing patients to the formation of high-grade gliomas, such as mutations in the *neurofibromin* and *p53* genes, can also be tested. Microsatellite instability has been found to be higher in pediatric primary brain tumors compared to adult primary brain tumors and correlates with *p53* mutations [1, 28]. Microsatellite instability and *p53* mutations are also associated with decreased overall survival [1, 28]. Up to 85% of HGGs overexpress the epidermal growth factor receptor (EGFR) but the significance of this finding is unclear since outcome does not appear to correlate with degree of EGFR immunoreactivity [5, 6]. Raffel et al. report that PTEN mutations have a stronger correlation with decreased survival in pediatric HGGs [30]. Ultimately, improved genetic classification will lead to the identification of subsets of tumors separated by their responsiveness to specific therapeutic agents.

Staging and Classification

Although the broad category of gliomas includes tumors of astrocytic, oligodendroglial, and ependymal origin, this discussion will focus on malignant astrocytomas. HGGs are either WHO Grade III or IV, with Grade III astrocytomas known as anaplastic astrocytomas (AA) and Grade IV astrocytomas known as GBM. It is uncertain whether astrocytomas originate from mature glial cells or neuroectodermal stem cells [33]. AAs are characterized by their focal or diffuse hypercellularity with associated nuclear atypia, nuclear pleomorphism, and the presence of mitotic figures. GBMs exhibit many of the same features as AAs, but also have endothelial proliferation and/or necrosis on histologic examination [36]. Grade III oligodendrogliomas and some pleomorphic xanthoastrocytomas have many of the histologic characteristics mentioned above and overlap to a large degree with malignant astrocytomas. Although some gangliogliomas and juvenile pilocytic astrocytomas exhibit some of the histologic features of HGGs, they are not usually grouped together due to their more favorable clinical outcomes [3]. These two tumor types are discussed in detail in other chapters.

Treatment

Surgical

The primary goals of surgery are to obtain a definitive tissue diagnosis and to achieve gross total resection (GTR) while maintaining neurologic function. Wisoff et al. have shown that the extent of resection affects survival, with a 5-year survival for AA of 44% following GTR vs. 22% after subtotal resection (STR); and a 5-year survival following GTR of 26% vs. 4% after STR for GBM [41]. GTR of HGGs can be difficult due to the infiltrative nature of these tumors and/or their proximity to eloquent tissue. Newer techniques such as cortical and subcortical mapping have increased the ability of surgeons to define the boundaries of eloquent cortex and thereby increased the likelihood of GTR. Advances in imaging such as functional MRI (fMRI), positron emission tomography (PET), magneto-encephalography, and diffusion tensor imaging (DTI) are also leading to marked improvements in the resolution and reliability of functional maps [15]. To a large extent, electrophysiological mapping of motor, sensory, and language function combined with accurate intraoper-

ative neuronavigation have supplanted purely anatomically-based resections.

Chemotherapy

The benefit of chemotherapy for pediatric HGGs is unresolved (Table 1). Although a large, multi-institutional phase III study of adjuvant chemotherapy for pediatric HGGs suggested a benefit to chemotherapy, follow-up studies have been less convincing. Postoperative chemotherapy (CCNU, vincristine, prednisone) in addition to radiation results in improved survival in children (5-year survival of 46%) as compared to postoperative radiation alone (5-year survival of 18%) [35, 13]. Wolff et al. demonstrated that preradiation chemotherapy (cisplatin, etoposide, ifosfamide) also improves survival [42]. Using the same protocol, Lopez-Aguilar and colleagues found that both pre- and postradiation chemotherapy improved median survival significantly [22, 23]. Nevertheless, other studies have not shown a survival advantage in using chemotherapy for HGGs [16, 29, 21]. In a phase II trial, treatment of patients with recurrent or progressive, high-grade glioma and diffuse brainstem glioma with the oral alkylator temozolomide (Temodar) resulted in minimal radiographic responses, although a small number of patients did achieve transient disease stabilization with tolerable toxicity [19]. In adults, however, temozolomide improves quality of life and survival compared to other agents [4, 43, 44], suggesting that temozolomide warrants further investigation in childhood malignant glioma. Currently, the Children's Oncology Group is conducting an ongoing phase II trial of temozolomide for newly diagnosed supratentorial malignant glioma and brainstem glioma.

Children with a newly diagnosed HGG under 3 years of age are considered for preradiation chemotherapy in a number of clinical trials using conventional chemotherapy regimens, or high-dose chemotherapy with peripheral blood stem cell rescue, in an effort to avert or reduce toxicity of radiation therapy in young children. The safety and efficacy of this strategy remains to be determined although its feasibility has been established in prior trials [9, 12, 27].

Radiation Therapy

Radiation therapy has been shown to be beneficial in phase II prospective studies with pediatric low-grade gliomas, but no prospective study has shown this specifically for pediatric HGGs [24]. Nevertheless the utility of radiation treatment for high-grade gliomas has been well established in other studies [7, 14, 17, 38, 41, 42]. Standard radiation therapy consists of 55 Gy delivered by opposed external beams. Attempts to limit the damage to normal brain parenchyma has led to the adoption of conformal techniques [24]. It should be noted that conformal radiation therapy still relies on a fractionated radiobio-

Table 1 Completed chemotherapy trials evaluating treatment of supratentorial high-grade gliomas (HGGs)

Diagnosis	Chemotherapy	Number of patients	Outcome	Authors
HGGs (40 GBM, 18 AA)	CCNU, vincristine, prednisone	58	46% vs. 18% 5-year EFS	[35]
HGG	8-in-1	172	33% vs. 26% 5-year EFS (NS)	[12]
Recurrent HGG	Temozolomide	34	12% radiographic response	[19]
HGG	Cisplatin, etoposide, and ifosfamide	29	2/25 disease progression significantly vs. control	[42]
HGG	Preradiation ifosfamide, carboplatin, etoposide	13	67% overall and 56% event-free survival, 80% tumor reduction	[23]

CCNU, chloroethyl-cyclohexyl nitrosourea; 8-in-1, vincristine, carmustine, procarbazine, cytarabine, hydroxyurea, cisplatin, dacarbazine, methylprednisolone; EFS, event free survival; NS, not significant ($p>0.05$).

logical effect. Stereotactic radiosurgery, conversely, utilizes a single treatment with doses in the range of 14 Gy to 20 Gy. Radiosurgery can be delivered by multiple fixed cobalt sources (Gamma Knife, Elekta AB, Stockholm), or by a mobile linear accelerator (LINAC). In either case, the total dose delivered depends upon the treatment volume. Radiosurgery treatment minimizes the dose beyond the target volume, and can be used to boost external-beam therapy, usually in the setting of focal and limited recurrent disease [2, 17]. Close proximity to sensitive structures such as the optic nerves or brain stem can reduce the effectiveness of radiosurgery. Radiosurgery is not indicated with widespread infiltrative disease or leptomeningeal dissemination.

Prognosis and Outcome

Despite the many therapeutic advances noted in the past several years, the overall prognosis for AA and GBM in both children and adults remains poor. The overall 2-year survival for patients with malignant gliomas (Grades III and IV) is in the range of 10% to 30% [6]. Children with GBM have a 5-year survival rate of 5%–15% [25, 35, 41]. Anaplastic astrocytoma has a 20%–40% 5-year survival rate [25, 35]. Leptomeningeal dissemination can occur in 5%–20% of malignant gliomas and is associated with a worse prognosis [37]. The importance of central review of pathology in clinical trials measuring survival of pediatric malignant glioma cannot be overemphasized, as significant discordance between institutional diagnosis and central review has been observed in prior trials [45].

New Treatment Strategies

Surgical resection and radiation are limited in their efficacy, and advances in technology, while promising, are not likely to markedly increase long-term outcome in the foreseeable future. New treatment strategies that target the underlying tumor biology are, however, beginning to emerge. For instance, the observation that malignant gliomas overexpress the interleukin-13 (IL-13) receptor has led to the development of a pseudomonas exotoxin conjugated to IL-13, delivered directly into the brain parenchyma by a convection-enhanced delivery system [18, 32]. The object is to greatly increase the effectiveness of the treatment by directly targeting tumor cells while simultaneously minimizing systemic toxicity. This strategy is being tested in a phase III clinical trial in adults with safety testing beginning soon in children.

Additionally, the PBTC and the COG are investigating many new signal transduction inhibitors in phase I and II trials for both newly diagnosed and progressive malignant glioma in children, based on both adult and pediatric preclinical and clinical data. Particular signal transduction pathways of interest include PDGFR (inhibited by STI-571), Ras (inhibited by the farnesyl transferase inhibitors SCH66336 and R115777), and EGFR (inhibited by ZD1839 and OSI 774). Finally, the role of antiangiogenic agents is also under investigation; specifically utilizing cilengitide, an integrin antagonist. Novel, biologically targeted agents and innovative delivery techniques such as this represent the hope, as yet unrealized, for an effective treatment for HGGs.

References

1. Alonso M, Hamelin R, et al. Microsatellite instability occurs in distinct subtypes of pediatric but not adult central nervous system tumors. Cancer Res 2001;61(5):2124–8
2. Baumann GS, Wara WM, et al. Gamma knife radiosurgery in children. Pediatr Neurosurg 1996;24(4):193–201
3. Behin A, Hoang-Xuan K, et al. Primary brain tumours in adults. Lancet 2003;361(9354):323–31
4. Brada M, Hoang-Xuan K, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 2001;12(2):259–66
5. Bredel M, Pollack IF, et al. Epidermal growth factor receptor expression and gene amplification in high-grade non-brainstem gliomas of childhood. Clin Cancer Res 1999;5(7):1786–92
6. Broniscer A, Gajjar A. Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. Oncologist 2004;9(2):197–206
7. Burton EC, Prados MD. Malignant gliomas. Curr Treat Options Oncol 2000;1(5):459–68
8. Chang YW, Yoon HK, et al. MR imaging of glioblastoma in children: usefulness of diffusion/perfusion-weighted MRI and MR spectroscopy. Pediatr Radiol 2003;33(12):836–42
9. Duffner PK, Horowitz ME, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 1993;328(24):1725–31
10. Eastwood JD, Provenzale JM. Cerebral blood flow, blood volume, and vascular permeability of cerebral glioma assessed with dynamic CT perfusion imaging. Neuroradiology 2003;45(6):373–6
11. Fernandez C, Figarella-Branger D, et al. Pilocytic astrocytomas in children: prognostic factors—a retrospective study of 80 cases. Neurosurgery 2003;53(3):544–53; discussion 554–5
12. Finlay JL. The role of high-dose chemotherapy and stem cell rescue in the treatment of malignant brain tumors. Bone Marrow Transplant 1996;18 (Suppl) 3:S1–S5
13. Finlay JL, Boyett JM, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-

in-1-day regimen. Childrens Cancer Group. J Clin Oncol 1995;13(1):112–23
14. Gilbert MR, Friedman HS, et al. A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant glioma before radiation therapy. Neuro-Oncol 2002;4(4):261–7
15. Gupta N, Berger MS. Brain mapping for hemispheric tumors in children. Pediatr Neurosurg 2003;38(6):302–6
16. Heideman RL, Kovnar EH, et al. Preirradiation chemotherapy with carboplatin and etoposide in newly diagnosed embryonal pediatric CNS tumors. J Clin Oncol 1995;13(9):2247–54
17. Hodgson DC, Goumnerova LC, et al. Radiosurgery in the management of pediatric brain tumors. Int J Radiat Oncol Biol Phys 2001;50(4):929–35
18. Kunwar S. Convection enhanced delivery of IL13-PE38QQR for treatment of recurrent malignant glioma: presentation of interim findings from ongoing phase 1 studies. Acta Neurochir Suppl 2003;88:105–11
19. Lashford LS, Thiesse P, et al. Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J Clin Oncol 2002;20(24):4684–91
20. Law M, Yang S, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuroradiol 2003;24(10):1989–98
21. Levin VA, Hess KR, et al. Phase III randomized study of postradiotherapy chemotherapy with combination alpha-difluoromethylornithine-PCV versus PCV for anaplastic gliomas. Clin Cancer Res 2003;9(3):981–90
22. Lopez-Aguilar E, Sepulveda-Vildosola AC, et al. Preirradiation ifosfamide, carboplatin, and etoposide for the treatment of anaplastic astrocytomas and glioblastoma multiforme: a phase II study. Arch Med Res 2000;31(2):186–90
23. Lopez-Aguilar E, Sepulveda-Vildosola AC, et al. Preirradiation ifosfamide, carboplatin and etoposide (ICE) for the treatment of high-grade astrocytomas in children. Childs Nerv Syst 2003;19(12):818–23
24. Merchant TE, Zhu Y, et al. Preliminary results from a Phase II trail of conformal radiation therapy for pediatric patients with localised low-grade astrocytoma and ependymoma. Int J Radiat Oncol Biol Phys 2002;52(2):325–32
25. Phuphanich S, Edwards MS, et al. Supratentorial malignant gliomas of childhood. Results of treatment with radiation therapy and chemotherapy. J Neurosurg 1984;60(3):495–9
26. Pollack IF. Brain tumors in children. N Engl J Med 1994;331(22):1500–7
27. Pollack IF, Boyett JM, et al. Chemotherapy for high-grade gliomas of childhood. Childs Nerv Syst 1999;15(10):529–44
28. Pollack IF, Finkelstein SD, et al. Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 2002;346(6):420–7
29. Puchner MJ, Herrmann HD, et al. Surgery, tamoxifen, carboplatin, and radiotherapy in the treatment of newly diagnosed glioblastoma patients. J Neurooncol 2000;49(2):147–55
30. Raffel C, Frederick L, et al. Analysis of oncogene and tumor suppressor gene alterations in pediatric malignant astrocytomas reveals reduced survival for patients with PTEN mutations. Clin Cancer Res 1999;5(12):4085–90
31. Rickert CH, Strater R, et al. Pediatric high-grade astrocytomas show chromosomal imbalances distinct from adult cases. Am J Pathol 2001;158(4):1525–32
32. Sampson JH, Akabani G, et al. Progress report of a Phase I study of the intracerebral microinfusion of a recombinant chimeric protein composed of transforming growth factor (TGF)-alpha and a mutated form of the Pseudomonas exotoxin termed PE-38 (TP-38) for the treatment of malignant brain tumors. J Neurooncol 2003;65(1):27–35
33. Sanai N, Tramontin AD, et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 2004;427(6976):740–4
34. Saran F. Recent advances in paediatric neuro-oncology. Curr Opin Neurol 2002;15(6):671–7
35. Sposto R, Ertel IJ, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. J Neurooncol 1989;7(2):165–77
36. Tamber MSRJT. Pediatric supratentorial high-grade gliomas. Neurosurgical Focus 2003;12(2):1–8
37. Vertosick FT Jr, Selker RG Brain stem and spinal metastases of supratentorial glioblastoma multiforme: a clinical series. Neurosurgery 1990;27(4):516–21; discussion 521–2
38. Wara WM, Wallner KE, et al. Retreatment of pediatric brain tumors with radiation and misonidazole. Results of a CCSG/RTOG phase I/II study. Cancer 1986;58(8):1636–40
39. Ware ML, Berger MS, et al. Molecular biology of glioma tumorigenesis. Histol Histopathol 2003;18(1):207–16
40. Wessels PH, Weber WE, et al. Supratentorial Grade II astrocytoma: biological features and clinical course. Lancet Neurol 2003;2(7):395–403
41. Wisoff JH, Boyett JM, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg 1998;89(1):52–9
42. Wolff JE, Gnekow AK, et al. Preradiation chemotherapy for pediatric patients with high-grade glioma. Cancer 2002;94(1):264–71
43. Yung WK, Albright RE, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000;83(5):588–93
44. Yung WK, Prados MD, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol 1999;17(9):2762–71
45. Pollack IF, Boyett JM, Yates AJ, Burger PC, Children's Cancer Group. The influence of central review on outcome associations in childhood malignant gliomas: results from the CCG-945 experience. Neurooncology 2003;5(3):197–207

Ganglioglioma 26

Concezio Di Rocco, Gianpiero Tamburrini

Epidemiology – 394

Symptoms and Clinical Signs – 394

Diagnostics – 394
Synopsis
General Considerations
CT
MRI
Angiography
PET

Staging and Classification – 397
Synopsis
General Considerations
Low-Grade Ganglioglioma (WHO Grade I–II)
Anaplastic Ganglioglioma (WHO III) and Ganglioblastoma (WHO IV)

Treatment – 398
Synopsis
Surgical Treatment
Radiotherapy and Chemotherapy
Recurrence Rate and Outcome

References – 400

Epidemiology

The term ganglioglioma was first coined by Perkins in 1926 to refer to an intracranial tumor composed by both neoplastic astrocytes and atypical ganglion cells. Gangliogliomas were then described by Cushing in his monograph published in 1927 and by Courville, in 1930, who provided the first review published on 20 cases [1]. According to subsequent reports these tumors accounted for an incidence of 0.3%–0.97% of all central nervous system (CNS) tumors [1, 2]. Recent studies, however, suggest that gangliogliomas are not as uncommon as previously thought. With the more extensive use of magnetic resonance imaging (MRI) and improved sensitivity and accuracy of histological diagnosis, the incidence of gangliogliomas is actually believed to range between 1.3% and 10% of all primary central nervous system neoplasms [2, 3]. They are more frequently found in children and young adults with a mean age ranging from 8.5 to 31 years, 60%–80% of the patients being less than 30 years old [3]. There is a slight male preponderance in most series, though many authors report an almost equal distribution between the two sexes [4].

Gangliogliomas may occur at virtually any location of the Central Nervous System (CNS). However most of these tumors (up to 80%) occur within the temporal lobe, involving its mesial structures (amygdala, hippocampus) in about 70%–80% of the cases. The frontal lobe (10%) and the occipital lobe (2%) are the two more common locations after cerebral locations [1]. Posterior fossa gangliogliomas represent 4%–15% of the cases, the brain stem being primarily involved in the majority of the patients [1]. About 70 cases of spinal cord gangliogliomas have been reported up to now; their incidence is believed to be around 1.1% of all spinal neoplasms. The cervical and the thoracic tracts are involved in over 70% of the cases; involvement of the conus medullaris and of the entire spinal cord has been occasionally reported [4]. Leptomeningeal spread of ganglioglioma is rare and only few cases have been described in the literature; the majority of them presented exophytic tumor growth in the suprasellar or posterior fossa cisterns [1].

Symptoms and Clinical Signs

Most of the patients with supratentorial gangliogliomas present with long histories of seizures which represent the first clinical manifestation in 62%–100% of the cases; prevalent temporal location, direct neoplastic involvement of cortical ganglion cells, and slow tumor growth all contribute to the high rate of epileptic fits in the clinical history of these patients [1, 5]. The predominant seizure pattern is that of complex partial seizures, which are reported in about 80% of the cases [1]. Neuropsychological tests have shown a mild cognitive impairment in almost all the patients with temporal lesions and long-standing seizures. Verbal and visuospatial performances are the most frequently affected functions for dominant and nondominant tumors, respectively [5].

Focal neurological deficits are found in 10%–36% of the patients, mainly related to parietal, deep gray matter and basal ganglia extension of the tumor [1, 6].

Symptoms of increased intracranial pressure are unusual. Only two out of 49 patients (4%) with hemispheric gangliogliomas reported by Zentner et al. presented with increased intracranial pressure signs [1]. Three of the 19 patients (15.8%) with hemispheric locations described by Lang et al. complained of headache; all the patients had subcortical large-sized tumors, without any other sign of increased intracranial pressure [6].

Cerebellar gangliogliomas are more often hemispheric and present with slowly progressing cerebellar signs (ataxia, dysmetria). Hemifacial and contralateral focal motor seizures have been reported occasionally; even for such a location, the presence of heterotopic, neoplastic ganglion cells is regarded as the most probable origin of epileptic fits in these patients [1]. Brain stem lesions are revealed by cranial nerves dysfunction in about 80%–90% of the cases; focal motor deficits are associated in over 30% of the patients [6]. Due to the infiltrative nature of the tumor, its slow growth, and the prevalent hemispheric cerebellar location, hydrocephalus is rarely reported in children with posterior fossa gangliogliomas [1, 6].

Clinical manifestations in patients with spinal cord gangliogliomas are related to the site of occurrence; overall, motor deficits and associated pain represent the clinical onset in over 80% of the cases. Pain is the only clinical manifestation in about 10% of the patients. Ten percent of the patients present exclusively motor deficits, whereas sensory changes (hypoesthesia, paresthesia) are reported at diagnosis by only 3%–5% of the subjects [4].

Diagnostics

Synopsis

The solid component of low-grade (WHO I–II) gangliogliomas appear more frequently as hypodense areas on plain computed tomography (CT) scans. These tumors are isointense to normal cerebral parenchyma on T1-weighted images and hyperintense on pro-

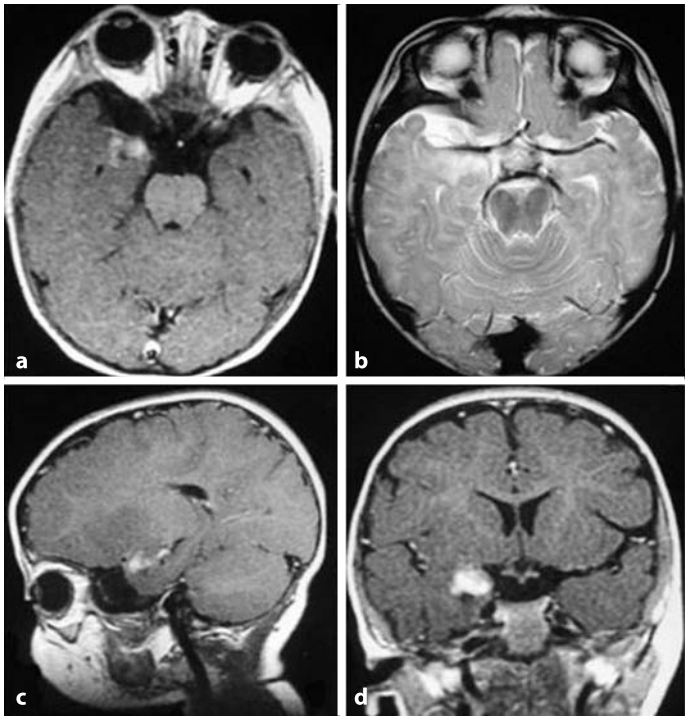


Fig. 1 **a, b** T1 after contrast injection and T2 axial MR images of a right temporal ganglioglioma; the tumor is composed by a prevalent contrast-enhancing solid nodule which involves the mesial portion of the temporal lobe and an intratumoral cystic component. An associated homolateral temporal pole arachnoid cyst is demonstrated. **c, d** Sagittal and coronal contrast-T1 slices documenting the spatial relationships of the tumor

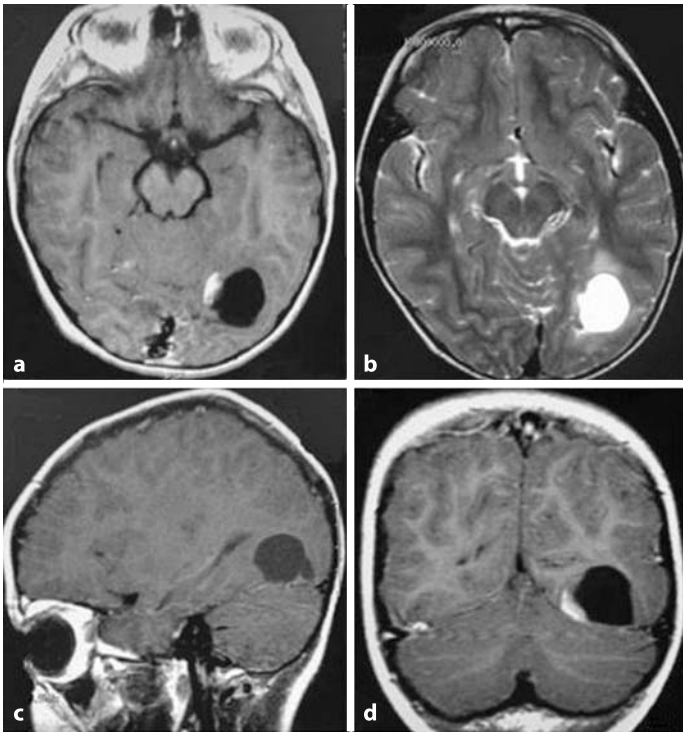


Fig. 2 **a, b** T1 after contrast injection and T2 axial MR images of an occipital ganglioglioma. Differently from the case of Fig. 1, the tumor is composed by a prevalently cystic portion and a contrast-enhancing mural nodule. **c, d** Sagittal and coronal contrast-T1 images documenting the basioccipital location of the tumor

ton density and T2-weighted Magnetic Resonance (MR) images. Calcifications and cystic components are common. Iodinated and gadolinium contrast enhancement is reported in 16%–80% and in 12%–44% of the patients, respectively. The enhancement is usually moderate and homogeneous [1, 3, 6] (Figs. 1, 2). Anaplastic variants (WHO III) are spontaneously hyperdense on CT and hyperintense on T1-weighted MRI scans; solid components are prevalent though central necrosis with irregular and intense peripher-

al enhancement has also been described [6]. On angiography gangliogliomas appear as avascular or hypovascular masses in the great majority of the cases [3]. Compared PET/MRI studies have revealed a heterogeneous metabolic behavior in low-grade tumors; increased metabolic activity has been documented in high-grade gangliogliomas [3, 7].

General Considerations

The neuroradiological appearance of gangliogliomas is variable; generally they appear as well-circumscribed lesions situated within the peripheral cortex. According to a recent study of Provenzale et al. distinctive features can be found in early childhood (<10 years old) as compared with older children and adults (>10 years old). In these authors' experience tumor size and volume were significantly greater in younger children with respect to their older counterpart, with larger cystic components and peritumoral edema. No statistically significant differences were found in the involvement of eloquent areas or in the histological patterns between the two groups. Consequently, the later diagnosis in younger patients is attributed to the higher ability of the brain and the calvaria to remodel and accommodate for the tumor mass growth in this age group [7].

CT

On CT scan intracranial low-grade (WHO I–II) gangliogliomas appear as hypodense in 59%–83% of the affected subjects, with calcifications in 20%–50% and cystic components in 35%–55% of the cases. Contrast enhancement is reported in 16%–80% of the patients [1, 3]. The cystic component may be represented by a single large cyst with a mural nodule or a multicystic mass [3]. Cerebellar lesions appear more frequently solid and iso-hypodense lesions on CT, with moderate mass effect and lacking contrast enhancement. Hydrocephalus has been only occasionally described [1]. Spinal cord tumors have no characteristic appearance; a diffuse enlargement of the spinal cord is often the only CT finding [4]. The anaplastic variants of ganglioglioma (WHO III) are revealed as spontaneously hyperdense solid tumors with diffuse contrast-enhancement in most cases; central necrosis with irregular and intense peripheral enhancement has also been described [6].

MRI

Magnetic resonance examination has proved to be more sensitive in identifying gangliogliomas than CT scan. Cystic components are hypointense on T1-weighted images and hyperintense on T2-weighted images; their signal is commonly higher than CSF on T2-weighted images; this corresponds to the intraoperative finding that cystic tumor parts may consist of a gelatinous mass (Figs. 1, 2). Irregular margins and associated soft tissue components help to distinguish tumor cysts from simple CSF cysts. Solid components present a typically pronounced signal increase on proton-density-weighted images and less pronounced hyperintensity on T2-weighted images. Though histologically benign, solid low-grade gangliogliomas are usually isointense on T1-weighted images [1, 3]; Zentner et al. also reported T2 tumor isohypointensity in 32% of their patients [1]. Gadolinium enhancement has been reported in 12%–44% of the cases and is usually moderate and homogeneous; perifocal edema is usually absent [3]. Differently from supratentorial tumors, cerebellar lesions may appear as circumscribed or laminated T1 hypointense/T2 hyperintense lesions with moderate or without contrast enhancement; the mass effect on the adjacent structures is moderate or absent [1]. Spinal gangliogliomas show high, low or irregular signal intensity on T1-weighted MRI scans; on T2-weighted images they present as hyperintense lesions. Contrast-medium enhancement is frequently observed [4]. Whatever the location, anaplastic gangliogliomas appear as isointense or spontaneously hyperintense on T1-weighted scans; marked perifocal edema and diffuse or "ring" Gadolinium enhancement are common findings [6].

Angiography

The vascular characteristics of gangliogliomas are rarely reported. Castillo mentioned that angiography is not indicated in the primary evaluation of gangliogliomas. Demierre et al., described avascular masses in 67% of cases, whereas the remainder revealed only "irregular" vessels on the arterial and venous phases. In 1987, Kalyan-Raman and Olivero published the largest series of gangliogliomas studied angiographically. In that series four of ten cases were avascular and the remainder were hypovascular masses with a small area of abnormal vascularity. Marked tumor vascularization either by the internal carotid artery or by the external carotid artery systems has been only occasionally reported [3].

PET

Kincaid et al. in 1998 described positron emission tomography (PET) imaging in 11 cases of gangliogliomas. These authors illustrated tumor hypometabo-

lism in low-grade tumors as visualized on fluoro-2-deoxy-D-glucose PET studies and increased activity in two high-grade gangliogliomas seen on 201Tl-enhanced single-photon emission computed tomographic scans. They concluded that nuclear medicine studies have an excellent correlation in preoperatively predicting the histological grade of a ganglioglioma [3]. In a subsequent study Provenzale et al. contemporarily recorded and overlapped PET and MRI images in six low-grade gangliogliomas; 16 of the 20 tumor areas within the gray matter were found to be hypermetabolic if compared with normal white matter. All the four regions within white matter were found to be hypermetabolic if compared with white matter. Arguing with previous experiences they concluded that registration of PET and MRI images allows a better appreciation of the metabolic activity of low-grade gangliogliomas indicating an heterogeneous behavior of these tumors in functional studies [7].

Staging and Classification

Synopsis

Gangliogliomas are actually staged according to WHO classification. WHO Grades I and II represent 80%–90% of the cases. Histologically they are constituted by a mixture of glial and neuron cells; glial cells may consist of mature astrocytes, gemistocytes, or oligodendroglial cells. Neurons are identified by the presence of Nissl substance and/or the presence of neuronal processes marked by Bielchowski Holmes or Bodian stains; they are clearly heterotopic or atypical, showing disorientation, bizarre shapes, and nuclei with hyperchromatism and frequent binucleation. Ki-67 is less than 10% in all low-grade gangliogliomas with 74% of the cases showing a Ki-67 <1% [1, 2, 3].

Anaplastic gangliogliomas (WHO Grade III) and ganglioblastomas (WHO Grade IV) represent 4%–6 % of all gangliogliomas. The glial component represents the malignant portion of the tumor in the majority of the cases, though neuroblastomatous gangliogliomas have been also described. In glial malignancies small, undifferentiated, and weakly GFAP-positive cells are intermingled with mature astrocytic and ganglion cells. Immunohistochemical staining for synaptophysin, neurofilaments, and neuron-specific enolase, with negative GFAP differentiate neuroblastomatous forms from glial malignancies [3, 8].

General Considerations

In the Courville definition gangliogliomas were considered to originate early in the formative period from the retarded development of undifferentiated cells that, after unknown stimulation, became neoplastic and matured into adult forms. From the presence of adult ganglion cells and astrocytes he inferred that differentiation had been completed and concluded that gangliogliomas should be essentially benign tumors [1]. The recognition of anaplastic forms with aggressive histological and clinical behavior has recently led to reconsideration of this statement. Actually, gangliogliomas are staged according to WHO classification; benign tumors represent 80%–90% of the cases and are classified as WHO Grade I (75%–85%) and WHO Grade II (5%–10%) [2, 3]. Anaplastic forms are classified as WHO Grade III and represent 4%–6% of the cases. Ganglioblastomas (WHO IV) are rare; histological criteria for their distinction from anaplastic gangliogliomas are not unequivocally established and their recognition is actually based mostly on the rate of vascular proliferation and the presence of necrosis [8, 9].

Low-Grade Ganglioglioma (WHO Grades I–II)

Macroscopically low-grade gangliogliomas are usually well-circumscribed masses with a granular appearance on cut section. Cysts and calcifications are frequent; the solid part may be composed by a mural nodule on the wall of a large cyst [1].

The microscopic criteria for the diagnosis of low-grade ganglioglioma, initially given by Courville in 1931, have been revised by Russel and Rubinstein. According to these authors, general features for the histological definition of low-grade ganglioglioma are:

1. The presence of a mixture of glial cells and neurons;
2. Glial cells consisting of mature astrocytes, gemistocytes, or oligodendroglial cells;
3. Ganglion cells identified in the presence of Nissl substance, demonstrated by cresyl violet stain or in the presence of neuronal processes demonstrated by modified Bielschowski Holmes or Bodian stains.

For neurons to be recorded as neoplastic they must be either clearly heterotopic or atypical (showing disorientation, bizarre shapes or sizes, and nuclei with hyperchromatism and frequent binucleation); they are immunoreactive to neurofilament protein, synaptophysin and neuron specific enolase. H&E staining reveals eosinophilic cytoplasm containing distinct nucleoli [1, 2, 9].

Glial cells are intermingled with neurons; their most distinctive aspects are: (1) positivity for glial fibrillary acidic protein (GFAP) and S-100 proteins, (2) lack of perineuronal satellitosis, (3) lobular pattern due to stromal reaction and lymphocytic infiltrate, and (4) benign appearance with no evidence of necrosis, endothelial proliferation, or multinucleated giant cells [1, 2, 3].

A frequently associated finding is the presence of glial hamartias, which are microscopic malformed lesions composed of glial elements and ganglion cells [1, 3].

Ki-67 is less than 10% in all low-grade gangliogliomas with 74% of the cases showing a Ki-67 proliferating index of <1% [1].

The rate of cellularity and the rate of cellular and nuclear pleomorphism of the astrocytic component are considered as main parameters for the distinction between WHO Grade I and WHO Grade II tumors [2, 3].

Anaplastic Ganglioglioma (WHO III) and Ganglioblastoma (WHO IV)

Most cases of anaplastic gangliogliomas (WHO III) and Ganglioblastomas (WHO IV) are described as malignant recurrences of previously histologically documented benign forms. The glial component represents the malignant portion of the tumor in the majority of the cases, though neuroblastomatous gangliogliomas have been also described. General features of anaplastic forms of gangliogliomas include pronounced hypercellularity and vascular proliferation. The presence of areas of necrosis and a higher rate of mitotic figures are used to differentiate WHO IV from WHO III forms [8, 9].

In cases of glial malignancy, small cells with round to oval nuclei and scanty cytoplasm are intermingled with areas of differentiated astrocytic and ganglion cells. Reticulin fibers and spindle-shaped cells surround small neoplastic cells; areas of hemorrhage and necrosis and local meningeal dissemination are common. Immunoblotting for anti-GFAP antibody is generally weak. Electron microscopy evaluation reveals absence of neurosecretory granules, basal lamina, or attachment devices with small tumor cells embedded in considerably abundant matrices. Molecular genetic analysis has shown TP53 gene mutations not associated to EGFR gene structural alterations [8, 9].

Neuroblastomatous gangliogliomas can be differentiated from glial malignancies because of positive cytoplasmic immunohistochemical staining for synaptophysin, neurofilaments, and neuron-specific enolase, with negative GFAP staining for astrocytic fibers [9].

Treatment

Synopsis

Tumor removal is considered the optimum treatment of gangliogliomas; however extensive tumor resection cannot be always obtained, especially in children with brain stem and spinal cord locations due to the related functional risks [4].

In children with supratentorial locations and medically intractable epilepsy, controversy exists whether simple lesionectomy or identification and resection of epileptogenic areas should be considered. Data from the literature suggest that tumor removal is indicated as the primary treatment in children with a brief epileptogenic clinical history, reserving intraoperative mapping and more extensive resections to patients with a long seizures history and multifocal EEG findings [5, 6].

Radiotherapy has generally been considered of little benefit. Some authors have suggested postoperative irradiation after partial tumor removal [4–6]; however no statistically significant improvement has been documented in the long term survival and event-free relapse rates. Nevertheless tumor progression and secondary intracranial tumors after radiotherapy for a primary benign ganglioglioma have been reported. The role of chemotherapy, given adjuvantly or after recurrence is not clear and cannot be determined definitely [4–6].

Surgical Treatment

Extensive surgical resection is considered the optimum treatment of gangliogliomas independently from their site. An exception is represented by patients with brain stem and spinal cord locations where preservation of normal structures is mandatory [4].

With regard to the associated epilepsy, authors' opinions differ whether lesionectomy is sufficient or intraoperative identification and resection of surrounding epileptogenic zones should be considered in all cases. In a series of 15 children with intractable epilepsy associated with gangliogliomas, Khajavi et al. described a 90% reduction of seizure frequency in all the patients who underwent a gross total tumor resection. Three of the four children in whom subtotal resection was performed had persistent epileptic fits [2]. Kalyan-Raman et al. achieved an 87% seizure-free outcome in patients with intractable epilepsy associated with gangliogliomas, using maximal tumor resection without intraoperative electrocorticography [10]. Fourteen of the twenty patients in the series of Silver et al. presented with seizures;

gross total tumor removal was achieved in eight cases that were all seizure free or had good seizure relief after surgery (mean follow-up 7.1 years); of the three patients with persistent seizures all had a subtotal resection [10]. Casazza et al. reported that 15 out of 16 patients with gangliogliomas and intractable epilepsy were seizure-free or improved postoperatively, 14 (93%) of whom had a gross total tumor removal [10].

On the other hand, some authors emphasize the importance of resecting epileptogenic foci in addition to tumor resection to improve seizure outcome. Otsubo et al. concluded that removal of the epileptogenic brain in addition to maximal tumor resection is necessary to optimize seizure control; 11 of the 15 patients in their series were seizure free following this kind of approach. No mention was made of the completeness of the surgical resection [5]. Pilcher et al. reviewed 12 patients with gangliogliomas associated with intractable epilepsy and achieved a seizure-free outcome in 11 patients with resection of the tumor and the epileptogenic focus [5]. However the seizure-free patients also had a complete tumor resection. Therefore, it cannot be excluded that only tumor removal could have achieved the same results [10]. Using electrocortical mapping techniques in pediatric patients Berger et al. reported that, of 14 children with seizures refractory to medical therapy treated by tumor removal combined with seizure focus resection, 13 were seizure free at a mean follow-up of 56 months and 11 were off of antiepileptic drugs [5].

The different indications and results described are probably influenced by different patient selection; from overall results it can be concluded that accurate identification of epileptogenic areas should be reserved for children with a long history of pharmacoresistant seizures and multifocal EEG findings, considering tumor resection as primary management in patients with a brief seizures history even if the EEG findings are extended to the brain structures adjacent to the tumor site [10].

Radiotherapy and Chemotherapy

Radiation therapy and chemotherapy have generally been considered of little usefulness in children with gangliogliomas. This belief is primarily based on retrospective studies of gangliogliomas in the cerebral hemispheres. For example, Silver et al. described 16 patients with cerebral hemisphere gangliogliomas, of whom eight underwent gross total resection (two combined with radiotherapy) and eight underwent subtotal resection followed by irradiation and/or chemotherapy. While all the patients in the former group were alive at follow-up evaluation, only four in the latter group were alive at follow-up study. They concluded that more complete resections led to better survival and that radiation therapy was of little benefit [6]. On the other hand, Johannson et al. treated ten patients with subtotal resection or biopsy followed by radiation therapy and found 80% to be alive after a mean follow-up period of 6 years [6]. Koruwer et al. recommended radiation therapy after partial removal of anaplastic gangliogliomas or gangliogliomas with a high proliferation index (LI>1%); indeed these patients presented a three-fold greater risk of recurrence in their series, if compared with benign or moderately anaplastic forms [4].

Less is known about the role of adjuvant treatments in children with brainstem and spinal cord gangliogliomas. Garrido et al. treated three cervicothoracic gangliogliomas. One patient underwent gross total resection and was alive with a mild deficit at the 2-year follow-up evaluation, one patient had subtotal resection and radiation therapy and was asymptomatic at the 5-year follow-up evaluation, and one patient underwent biopsy and irradiation and was quadriplegic at the 3-year follow-up evaluation. The authors suggested that surgical resection was more effective than biopsy and irradiation [4]. In the series of Lang et al. the majority of the patients with spinal cord or brainstem gangliogliomas were referred to their Unit after primary radiation therapy. Though the final analysis was complicated by this factor, the event-free survival rate was statistically no different based on prior radiotherapy in a linear regression analysis [6].

When evaluating the role of radiotherapy it is necessary to also consider the possible effect of this type of therapy on tumor progression and on nontumoral neural tissue. Indeed, dedifferentiation of the astrocytic component has been reported as the progression of a low-grade ganglioglioma into an anaplastic tumor. Furthermore, Otsubo et al. described the case of a child with a temporal ganglioglioma who developed a meningioma in the radiation field 15 years after complete tumor removal and postoperative radiation therapy [4, 6].

Recurrence Rate and Outcome

The recurrence rate is mainly related to three factors: (1) tumor location, (2) histological degree, and (3) extension of tumor removal. Brainstem involvement is associated with the highest rate of recurrence and the highest incidence of postoperative worsening in clinical condition. Gangliogliomas located within the cerebral hemispheres have the best outcome. In a series of 58 patients with gangliogliomas of the CNS, Lang et al. reported a 33% recurrence rate after radical excision of the tumor. In the series, subjects

with spinal cord gangliogliomas had a three- to fivefold relative risk of recurrence or death as compared to patients with supratentorial gangliogliomas, and patients with brainstem gangliogliomas had a fivefold higher relative risk. It is worthwhile to note that the presumed gross total removal of the tumor obtained in 29 out of 30 patients with spinal cord gangliogliomas in this series did not prevent tumor recurrence in 14 subjects (47%), thus suggesting that the location of the tumor influenced per se the recurrence rate.

Low-grade gangliogliomas had a 57% 5-year event-free survival rate, compared with a 15% rate of high-grade tumors; this difference was not statistically significant ($p<0.18$). Operative morbidity varied with tumor site; only one of the 19 patients with cerebral hemisphere gangliogliomas (5%) had a stable postoperative worsening of admitting neurological conditions; this was compared with a 10% of long-term worsening in children with spinal cord tumors and a 33% in patients with brainstem locations. The 10-year actuarial survival rate was 94% for gangliogliomas of the cerebral hemispheres, 87% for spinal cord tumors and 78% for those of the brainstem; the trend to a worse survival of spinal cord and brainstem tumors was, however, not statistically significant ($p=0.7$) [6].

References

1. Zentner J, Wolf KH, Ostertun B, Hufnagel A, Campos MG, Solymosi L, Schramm J. Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psych 1994;57:1497–1502
2. Kajavi K, Comair YC, Prayson RA, Wyllie E, Palmer J, Estes ML, Hahn JF. Childhood ganglioglioma and medically intractable epilepsy. A clinicopathological study of 15 patients and a review of the literature. Pediatr Neurosurg 1995;22:181–188
3. Siddique K, Zagardo M, Gujrati M, Olivero W. Ganglioglioma presenting as a meningioma: case report and review of the literature. Neurosurgery 2002;50 (5):1133–1136
4. Hamburger C, Buttner A, Weis S. Ganglioglioma of the spinal cord: report of two rare cases and review of the literature. Neurosurgery 1997;41 (6):1410–1416
5. Pilcher WH, Silbergeld DL, Berger MS, Ojemann GA. Intraoperative electrocorticography during tumor resection: impact on seizure outcome in patients with gangliogliomas. J Neurosurg 1993;78:891–902
6. Lang FF, Epstein FJ, Ransohoff J, Allen JC, Wisoff J, Abbott IR, Miller DC. Central nervous system gangliogliomas. Part 2: Clinical outcome. J Neurosurg 1993;79:867–873
7. Provenzale JM, Arata MA, Turkington TG, McLendon RE, Coleman RE. Gangliogliomas: characterization by registered Positron Emission Tomography-MR images. AJR 1999;172:1103–1107
8. Hayashi Y, Iwato M, Hasegawa M, Tachibana M, von Deimling A, Yamashita J. Malignant transformation of a gangliocytoma/ganglioglioma into a glioblastoma multiforme: a molecular genetic analysis. J Neurosurg 2001;95:138–142
9. Kurian NI, Nair S, Radhakrishnan VV. Anaplastic ganglioglioma: case report and review of the literature. Br J Neurosurg 1998;12 (3):277–280
10. Packer RJ, Sutton LN, Patel KM, Duhaime AC, Schiff S, Weinstein SR, Gaillard WD, Conry JA, Schut L. Seizure control following tumor surgery for childhood low-grade gliomas. J Neurosurg 1994;80:998–1003

Cerebellar Astrocytomas 27

John C. Wellons III

Epidemiology – 402

Symptoms and Clinical Signs – 402

Diagnostics – 402
Synopsis
Computerized Tomography (CT)
Magnetic Resonance Imaging (MRI)

Staging and Classification – 403
Synopsis
Pathology

Treatment – 403
Synopsis
Surgery
Radiation
Chemotherapy

Prognosis/Quality of Life – 405

Follow-up/Specific Problems and Measures – 406

Future Perspectives – 406

References – 406

Epidemiology

The term cerebellar astrocytoma typically refers to the WHO Grade I lesion within the cerebellum known also as a cerebellar pilocytic astrocytoma or cerebellar juvenile pilocytic astrocytoma (JPA). However, cerebellar astrocytomas may be fibrillary instead of pilocytic or may show more malignant histologic characteristics. Although pilocytic astrocytomas may occur throughout the brain or spinal cord, they mainly occur in the posterior fossa, particularly in the cerebellum, and those occurring in the cerebellum tend to be cystic with a mural nodule. Currently, brain tumors are the most common solid organ cancer of the pediatric population. Approximately 10%–15% of all pediatric brain tumors and over 25% of posterior fossa tumors in children will be identified as a cerebellar JPA [9, 10]. Aggressive, safe surgical resection is the mainstay of therapy, both at initial diagnosis and in the event of recurrence. Adjuvant chemotherapy or radiation is rarely used for patients with progressive unresectable tumors, but does play a role in therapy for malignant tumors.

Symptoms and Clinical Signs

Most commonly, pediatric cerebellar astrocytomas present with symptomatic hydrocephalus. The typical history is that of a gradually worsening headache with vomiting over weeks to months. A more rapid presentation suggests a faster-growing and therefore more malignant lesion, but this observation is certainly no rule. The mean age at presentation for children with cerebellar low-grade gliomas is 6–8 years old and no significant gender predilection exists [9]. Other symptoms can be broadly categorized into those secondary to hydrocephalus, cerebellar dysfunction, or surrounding brain dysfunction. In addition to headache and vomiting, hydrocephalus may manifest itself as lethargy, papilledema, a unilateral or bilateral sixth nerve palsy, or an enlarging head circumference in young children whose sutures are open. Those symptoms related to cerebellar dysfunction include dysmetria, ataxia, titubation, and nystagmus and those due to compression of surrounding neural structures include cranial nerve palsies, hemiparesis, gait disturbances, and pyramidal signs. Neck pain, head tilt, vertigo, and even seizures have been reported as presenting symptoms [3, 9, 10].

Diagnostics

Synopsis

Oftentimes, the first imaging study obtained on children with persistent headaches and/or vomiting through their pediatrician's clinic or the emergency department is a CT scan. If abnormalities are seen, the child should then undergo an MRI of the brain with and without gadolinium administration. Findings suggestive of a cerebellar astrocytoma do not warrant spine imaging initially. Histological confirmation obviates the need for MRI imaging of the spine in the absence of symptoms referable to the spinal cord, cauda equina, or nerve roots. If, however, preoperative history or imaging is suggestive of ependymoma or medulloblastoma then the child should undergo MRI imaging of the spine with and without gadolinium administration either preoperatively or no less than 2 weeks postoperatively to allow the blood to clear from the operative procedure. An MRI of the brain with and without gadolinium is performed within the first 48–72 h postoperatively in order to gauge resection status.

The "classic" juvenile pilocytic astrocytomas occur in the cerebellar hemisphere but also can be seen in the cerebellar median or paramedian structures. They are intrinsic to the brain and may cause mass effect on surrounding structures, including the fourth ventricle, the cerebellar peduncles, the brainstem, or the cranial nerves of the cerebellopontine angle. The demarcation from surrounding brain parenchyma is usually distinct. These lesions can also present as noncystic solid vermian or hemispheric lesions with mass effect, but again intrinsic and characteristically with an identifiable border from the surrounding brain.

Computerized Tomography (CT)

On a noncontrasted CT scan, a cerebellar JPA will typically appear as a cyst within the cerebellar hemisphere containing a nodule of varying size. Hydrocephalus due to obstruction of the fourth ventricle or aqueduct may be present. The nodule will enhance with contrast, but the cyst wall is variable. Calcification is present in only 10% [7]. Cerebellar JPAs may also be solid, mostly homogenously enhancing lesions as well and may also occur in the vermis or other midline cerebellar structures.

Magnetic Resonance Imaging (MRI)

The pre- and postoperative radiographic study of choice for assessment of tumor volume is an MRI

with and without gadolinium administration. As in CT, the most common imaging characteristics of cerebellar JPAs are of a cystic lesion with an enhancing "mural nodule" on T1-weighted, gadolinium-enhanced imaging with variable enhancement of the cyst wall (Fig. 1). Without administration of gadolinium, the nodule and/or cyst contents are hypo- or isointense on T1-weighted imaging, and on T2-weighted imaging tend to be hyperintense [7]. Again, hydrocephalus may be detected. The solid noncystic cerebellar JPAs tend to follow the same enhancement characteristics.

Staging and Classification

Synopsis

The classic cerebellar JPA is considered WHO Grade I and treated by surgical excision only. Fibrillary astrocytomas are WHO Grade II tumors and are treated by surgical excision as well, but historically have been noted to have a poorer outcome [9]. Malignant cerebellar tumors are considered Grade III or IV, require adjuvant therapy, and have a much worse outcome. Thankfully, these tumors are uncommon, making up approximately 5% of all cerebellar astrocytomas [5].

Pathology

Cerebellar JPAs may have a "biphasic pattern" in which loose cystic glial tissue is present in addition to areas of compact tissue often containing Rosenthal fibers. In actuality, the combination of these two patterns is rare and the presence of both is not mandatory for the diagnosis. Oftentimes, the hair-like processes of the bipolar cells can be seen on smear preparation. The loose glial tissue may contain microcysts or granular bodies and the compact tissue may consist of bipolar cells in addition to the Rosenthal fibers. Of note, Rosenthal fibers are intracytoplasmic eosinophilic hyaline masses and are not pathognomonic for JPA as they can be seen in gliosis as well as in Alexander's disease (a primary disease of the white matter). Rare mitosis and vascular hyperproliferation may occur, but do not signal malignancy [2].

Fibrillary astrocytomas consist of fibrillary astrocytes on a loosely structured tumor matrix with microcysts, low to moderate cell density, rare mitoses, and possible nuclear atypia [9]. Margins may be less distinct [10]. As expected, malignant cerebellar astrocytomas have a higher percentage of nuclear atypia, mitotic figures, proliferation of endothelium, and necrosis [1, 10].

Pilocytic astrocytomas are heavily GFAP (glial fibrillary acid protein) positive. The predictive value of MIB-1 staining is controversial. While MIB-1 staining may be helpful in establishing the proliferation rate in a particular tumor, it does not appear to correlate with outcome of JPAs [2]. Evidence exists that it may help predict biological activity in higher grade tumors [5].

Fig. 1 A T1 gadolinium-enhanced axial MRI depicting a large enhancing mural nodule with a cyst causing mass effect on the surrounding brain. Note the absence of enhancement of the cyst wall as well as the obvious hydrocephalus

Treatment

Synopsis

Enough variables exist in children who present with these tumors to make operative timing surgeon dependent, even within a single institution. Lethargic children with signs of brainstem compression or acute herniation unresponsive to ventriculostomy placement are usually taken to the OR urgently. Those children who present with less urgent symptoms and who respond to steroid therapy or who present without symptoms are admitted and treated electively within a period of days. Again, this paradigm varies according to presentation, institution, and surgeon.

Surgery

The placement of a preoperative external ventricular drain (EVD) is also surgeon dependent. Lesions that do not cause hydrocephalus may not need a ventriculostomy. At this institution, they are inserted through a separate sterile preparation in the operating room just prior to the formal tumor resection.

This is through a nondominant hemisphere frontal burr hole approach, 2–3 cm off the midline and 1 cm anterior to the coronal suture. The catheter is tunneled subcutaneously, connected to an adjustable closed drainage system, clamped shut, and placed on the anesthesiologist's side of the sterile drape. The instructions on opening the ventriculostomy to drain are carefully discussed with the anesthesia team. The stopcock port for the EVD is clearly labeled so as to prevent mistaken injection. Alternatively, the ventriculostomy may be placed through an occipital burr hole in the same surgical preparation as the posterior fossa craniotomy. The anterior and lateral distance from the inion of this burr hole is age specific, but in a fully grown child is 6 cm superior to the inion and 3–4 cm lateral. With the patient prone and the neck flexed, an accurate trajectory into the occipital horn is challenging.

After induction and intubation, steroids, mannitol, and antibiotics are given. Anesthesia preparation includes two large bore intravenous lines, an arterial catheter, a bladder catheter, an esophageal temperature probe, and a well-taped endotracheal tube to avoid loosening from surgical preparation or dependent positioning. After EVD placement if necessary and following application of the Mayfield clamp on the superior temporal line of both sides, the child is turned prone on chest and iliac crest rolls. Due to the risk of venous air embolus and to surgeon arm fatigue, the sitting position is not used at our institution. The neck is flexed in a "military brace" position, ensuring two-finger breaths distance between chin and chest. After final positioning is achieved, the anesthesiology team listens to the chest to ensure equal breath sounds. A discrepancy here may signal a main stem bronchus intubation caused by neck flexion and is much better dealt with here than during the procedure.

A small strip of hair beginning just above the inion is clipped. Betadine solution is applied in layers and allowed to dry. Sterile towels and an iodine-impregnated clear drape are then applied to the surgical site. The incision spans from the inion to the spinous process of C2. Electrocautery is used to dissect in the midline fascial plane between the paraspinous muscles. The muscle attachments to C2 are left intact to minimize discomfort postoperatively unless the entrance into the fourth ventricle has descended to this level. A muscle cuff is left at the superior nuchal line for reattachment of the suboccipital muscles during closure. The muscle is carefully dissected off of the suboccipital bone while meticulously coagulating or waxing any venous channels through the bone. The dissection is taken just wider than the width of the foramen magnum for midline approaches and adjusted to one side for paramedian approaches. Careful subperiosteal dissection along the posterior arch of C1 is performed, avoiding the nearby vertebral artery and encircling venous plexus. In infants and young children, this posterior arch may be incompetent in the midline or cartilaginous. The loose tissue spanning the distance between the suboccipital bone and the ring of C1 is also carefully dissected until the posterior atlanto-occipital ligament is exposed. Utilizing two initial paramedian burr holes, the bone is taken off as one piece using a high-speed drill for reattachment later in the procedure. The posterior arch of C1 is removed with rongeurs. The dura is opened in a Y-shaped fashion, the operating microscope is brought into the field, and a self-retraction system is placed. If the tumor is within the fourth ventricle and accessible via the foramen of Magendie then an attempt is made to avoid significantly disrupting the vermis. However, tumor resection should not be compromised by inadequate exposure. Otherwise, the cortical incision is made in the hemisphere and the lesion is entered. Intraoperative ultrasound may be used to identify the lesion or its cystic component and help guide the approach.

For tumors that occur in the most lateral portion of the hemisphere, a retromastoid approach may be chosen. The child is induced as above and then placed into the lateral decubitus position with the operative side up. A vertical incision is made posterior to the mastoid beginning at the asterion and extending to the level of the mastoid tip. The bone removal is performed using the high-speed drill after the muscle and soft tissue has been retracted. The decision to replace bone is surgeon dependent. Care should be taken to anticipate the posterior auricular artery in the inferior aspect of the exposure, but this vessel may be coagulated and cut if necessary. The proximity of the exposure of the transverse and sigmoid sinuses is dependent on the location of the tumor and is determined by diligent preoperative planning. For tumors centered in the superior aspect of the cerebellum, consideration should be given to an infratentorial, supracerebellar approach.

The shortest route through viable cortex should be taken to approach the lesion. It should be mentioned here that occasionally despite adequately controlled end tidal CO_2 and normal ICP as measured by direct ventricular monitoring, the cerebellum may appear to be under pressure and even herniate through the initial dural opening. If a cystic component to the tumor exists, then a ventricular needle with a stylet may be used with or without ultrasound guidance to puncture the cyst and reduce the pressure within the posterior fossa. This maneuver then affords a safe and controlled approach to the tumor.

Oftentimes, the tumor itself will have a clear demarcation from surrounding white and gray matter. Either the suction/bipolar technique or the ultrasonic surgical aspirator is used for tumor resection. Con-

ventional wisdom does not mandate removal of the cyst wall if it is not enhancing and has a smooth appearance. In fact, it is rare that enhancing cyst walls will be removed unless they appear on gross inspection to have obvious tumor burden. In tumors that are near the fourth ventricle, a cotton surgical patty is placed along the floor to assist with intraoperative localization and protection of critical brainstem structures. This simple maneuver affords the surgeon a constant reminder of the location of the floor of the fourth ventricle and hence the brainstem but does not replace constant reorientation, particularly after surgical table adjustment. Careful inspection of the postoperative tumor bed, including the "lip" of cerebellum underneath the retractor blades, is necessary to avoid small portions of tumor left behind.

Pericranium from the occipital region above the muscle cuff is harvested and sewn into the dural opening and the bone flap is replaced with heavy silk sutures. The muscle and fascia are closed along the midline and reattached to the previously left cuff along the superior nuchal line. The soft tissue and skin are closed and a sterile dressing is placed. After emergence from general anesthesia, the patient recovers in the intensive care unit with frequent neurologic evaluations. The EVD is initially allowed to drain at 10 cm H_2O and is gradually raised and removed over the next 2–5 days depending on the individual child's CSF absorptive capability. Steroids are tapered off as well.

Radiation

No role exists for standard radiation therapy as a primary treatment for cerebellar JPAs, as a standard adjunct to gross total resection, or as a means of treating residual resectable disease. The efficacy of radiation therapy in the setting of residual unresectable tumor has been assessed and while trends towards increasing a progression-free survival exist, no prolongation in overall survival is seen [9]. Malignant transformation of posterior fossa astrocytomas in children has been associated with previous radiotherapy to the area [10]. The literature regarding malignant cerebellar astrocytomas is sparse but the consensus has been that these patients receive postoperative radiation therapy in a manner similar to supratentorial high-grade gliomas [9]. Evidence of CSF dissemination of malignant disease would warrant irradiation to the craniospinal axis [10].

Conformal field radiation is typically reserved for older patients with progressive residual tumor that cannot be safely resected. This is often due to infiltration of the brainstem. Promising results from the University of Pittsburgh experience would support stereotactic radiosurgery, given as a single fraction, as a reasonable and effective choice for surgically unresectable lesions [4]. The damaging long-term effects of whole-brain radiation on the developing brain are well known and should play no role in this disease process. However, long-term effects of conformal radiation and radiosurgery are yet to be discerned.

Chemotherapy

Again, no evidence exists of a role for chemotherapy as a primary treatment for cerebellar JPAs. However, there is evidence of the efficacy of chemotherapy in patients with progressive nonresectable low-grade gliomas in patient series including tumors of the optic apparatus, diencephalon, brainstem, and other regions of the brain that tend to be less surgically accessible [9]. Single agent treatment, including high-dose cyclophosphamide, carboplatin, and etoposide, have provided periods of stable disease and combination chemotherapy has provided some degree of radiologic response [9]. A protocol combining carboplatin and vincristine is used at many institutions for patients with unresectable or progressive noncerebellar pilocytic astrocytomas. The protocol is well tolerated and survival rates are encouraging but rarely indicated for patients with cerebellar JPA unless they have progressive unresectable lesions. Malignant cerebellar glial tumors are treated with chemotherapy regiments similar to those for supratentorial high-grade gliomas of childhood [9].

Prognosis/Quality of Life

A safe gross total resection is the goal of surgery and over 95% of these children remain alive at 25 years. The majority of recurrences will occur in the first 3 years [9]. Residual tumor has a reported 30%–100% chance of enlarging on follow-up imaging [10]. Experience dictates that small amounts of residual tumor will oftentimes remain stable or involute over time. However, subtotal resections do reduce the progression-free survival [3, 6]. Desai et al. found that the extent of tumor resection, a vermian location of the tumor, and the histological grade are negatively correlated with survival [3]. Histopathology appears to be the strongest predictor of outcome [5, 6]. Bristot et al. reports four cases of malignant cerebellar astrocytomas treated with varying degrees of surgical excision, radiation therapy, and chemotherapy. One died in the immediate postoperative phase, two who underwent subtotal excision followed by radiation were dead at 5 and 10 months. The one who underwent total excision, chemotherapy, and craniospinal radiation with a boost to the tumor bed was alive

at 13 months but did have signs of pathological progression [1]. In a large series of cerebellar glial tumors, The Mayo Clinic reports that the average duration of survival of children with Grade III and Grade IV tumors was 2.3 and 0.8 years respectively despite adjuvant radiation or chemotherapy [6].

The quality of life in these patients has traditionally thought to be good, particularly when compared to children who have undergone resection and adjuvant treatment of a medulloblastoma, ependymoma, or supratentorial tumor [8]. A recent study of adults who had undergone cerebellar JPA resection as children assessed topics ranging from energy level to sex life to sense of well-being. The most striking differences were in socializing and adolescence [8]. This small report brings into question our previous notions regarding these patients' quality of life and further study from our neuropsychology colleagues may be beneficial.

Follow-up/Specific Problems and Measures

In addition to the immediate postoperative enhanced MRI, we obtain studies at 3 months then at 6-month intervals twice, then yearly for 4 years, and then every 2 years. This is institution dependent and may be modified based on residual tumor or presence of a CSF shunt.

Prior studies have reported a 10%–50% rate of CSF shunting despite adequate tumor resection [9, 10]. Recently, endoscopic third ventriculostomy (ETV) has been used to treat postresection obstructive hydrocephalus with good results. The nature of the hydrocephalus should dictate the procedure performed. For hydrocephalus due to persistent obstruction at the level of the cerebral aqueduct or fourth ventricular outlet despite adequate and safe tumor resection, ETV would be our procedure of choice. For hydrocephalus believed to be due to poor absorption at the level of the arachnoid granulations, the placement of a VPS would be performed. If residual tumor is present and hydrocephalus is persistent and due to CSF pathway obstruction, consideration should be given to a safe secondary resection in lieu of ETV or shunt placement.

Future Perspectives

Cerebellar astrocytomas are one of the most common brain tumors of childhood. The treatment of choice for initial tumors, for recurrent lesions, and for resectable enlarging residual disease is gross surgical removal. Currently, no role exists for traditional radiation therapy in localized disease; however, evaluation of conformal field radiotherapy and radiosurgery for the unresectable residual or recurrent lesion is ongoing. In addition, chemotherapy protocols for low-grade gliomas may be extrapolated to these lesions in difficult circumstances. Outcomes are poor for patients with malignant cerebellar gliomas and these patients deserve novel applications of current treatment modalities. A considerable basic science laboratory effort is underway to find more effective means to treat adult and pediatric malignant gliomas.

References

1. Bristot R, Raco A, Vangelista T, Delfini R. Malignant cerebellar astrocytomas in childhood. Experience with four cases. Childs Nerv Syst 1998;14:532–536
2. Burger PC, Scheithauer BW, Vogel FS. Surgical pathology of the nervous system and its coverings. Philadelphia: Churchill Livingstone; 2002
3. Desai KI, Nadkarni TD, Muzumdar DP, Goel A. Prognostic factors for cerebellar astrocytomas in children: a study of 102 cases. Pediatr Neurosurg 2001;35:311–317
4. Grabb PA, Lunsford LD, Albright AL, Kondziolka D, Flickinger JC. Stereotactic radiosurgery for glial neoplasms of childhood. Neurosurgery 1996;38:696–701; discussion 701–692
5. Medlock MD. Infratentorial Astrocytoma. In: Keating RF, Goodrich JT, Packer RJ, editors. Tumors of the pediatric central nervous system. New York: Thieme; 2001. p. 199–205
6. Morreale VM, Ebersold MJ, Quast LM, Parisi JE. Cerebellar astrocytoma: experience with 54 cases surgically treated at the Mayo Clinic, Rochester, Minnesota, from 1978 to 1990. J Neurosurg 1997;87:257–261
7. Osborn AG. Diagnostic Neuroradiology. St. Louis: Mosby; 1994
8. Pompili A, Caperle M, Pace A, Ramazzotti V, Raus L, Jandolo B, Occhipinti E. Quality-of-life assessment in patients who had been surgically treated for cerebellar pilocytic astrocytoma in childhood. J Neurosurg 2002;96:229–234
9. Reddy AT, Mapstone TB. Cerebellar Astrocytomas. In: McLone DG, editor. Pediatric neurosurgery. Philadelphia: W.B. Saunders; 2001. p. 835–843
10. Steinbok P, Mutat A. Cerebellar Astrocytomas. In: Albright L, Pollack I, Adelson D, editors. Principles and practice of pediatric neurosurgery. New York: Thieme Medical Publishers; 1999. p. 641–662

Diffuse Intrinsic Pontine Gliomas 28

Milind Ronghe, Eric Bouffet

Epidemiology – 408

Symptoms and Clinical Signs – 408

Diagnosis – 408
Imaging of DIPG

Surgery – 408

Staging/Classification – 409

Treatment – 409
Neurosurgery
Radiotherapy
Chemotherapy

Prognosis – 411

Specific Problems and Measures – 411
Steroids
Hydrocephalus
Bulbar Impairment
Analgesia
Neurological Disability
Family Support

Future Perspectives – 412

References – 412

Brain stem tumors account for 10%–15% of all primary childhood CNS tumors. Most of the brain tumors arising in the brain stem are gliomas. With recent advances in neuro-imaging, particularly the advent of MRI and careful correlation of clinical presentation, location, and growth pattern it has become evident that brain stem tumors are a heterogeneous group of neoplasms, divisible into distinct subgroups such as diffuse intrinsic pontine tumors, and focal, dorsal exophytic, cervicomedullary tumors. Diffuse intrinsic pontine gliomas (DIPG) constitute 80% of the pediatric brain stem tumors. These tumors are typically high-grade gliomas and have uniformly poor prognosis.

Epidemiology

The age-adjusted incidence rate of diffuse pontine gliomas is 2.0 per million children per year in the USA [1] and 3.8 per million per year in the UK (data obtained from national registry). This is likely to be underestimated, as biopsies are not routinely performed to confirm the diagnosis of DIPG, which may affect the reporting. Sex incidence is equal and the most common presenting age is 5–10 years. Classically these tumors arise from ventral pons and can extend into medulla and midbrain.

The remaining 15%–20% of brain stem tumors are low-grade gliomas and follow a much more indolent course than diffuse pontine glioma [2]. Surgery is the initial treatment of choice for dorsal exophytic and cervicomedullary tumors but when surgery is not feasible or at the time of progression, treatment options include chemotherapy and/or radiation therapy. These tumors are discussed elsewhere in the book.

Symptoms and Clinical Signs

Classical clinical presentation is stereotyped including rapid appearance of the triad: ataxia, long tract signs, and multiple cranial nerve deficits. At least two of the three clinical features are required for clinical diagnosis of DIPG. As these tumors arise in the pons, involvement of VIth (diplopia) and VIIth (LMN facial palsy) cranial nerves are common at diagnosis. Altered behavior characterized by apathy, withdrawal, and emotional lability (inappropriate laughter – particularly at night – or sadness) are reported in 10%–15% cases but this is certainly under reported. Personality changes occur more frequently in young children and can contribute to delay in the diagnosis. Short duration of symptoms prior to diagnosis predict poorer outcome. Although hydrocephalus may occur in 20%–60% of patients at diagnosis, papilledema is uncommon.

Diagnosis

Imaging of DIPG

Magnetic resonance imaging (MRI) is now the "golden standard" investigation for diagnosis of brain stem gliomas. The classification of brain stem gliomas based on CT or MRI system has proven to be of value in determining prognosis and efficacy of surgical intervention. Serial studies show uniformly poor prognosis for diffuse intrinsic pontine gliomas and better outcome for enhancing exophytic, cystic, focal, cervicomedullary, or tectal tumors as these tumors are amenable to surgical intervention. [3–4].

DIPG cause diffuse enlargement of pons (>50% or >2/3 according to the authors) and appear hypointense on T1- and hyperintense on T2-weighted imaging with very little enhancement with gadolinium. This typical appearance on MRI associated with rapid clinical deterioration is now considered to be diagnostic of DIPG. Tumors often exhibit a ventral exophytic component with basilar artery engulfment. These findings along with other radiological characteristics such as tumor extension, tumor-border definition, cyst/necrosis, T1-signal intensity, gadolinium enhancement, and associated hydrocephalus do not seem to have any prognostic significance. Recent analysis of all of the above radiological characteristics in both diagnostic and postradiation MRI scan showed no significant correlation with overall survival in children with DIPG [5]. Furthermore, slight change in the radiological features may be associated with marked clinical progression and vice versa (Figs. 1, 2). Lack of predictive power of currently available radiology raises questions regarding the value of routine postradiotherapy follow-up MRI as interpretation in terms of its correlation to clinical progression can be difficult. There might be a role for new radiology techniques including "functional imaging" such as MRS and PET to explore prognostic significance.

Surgery

Surgical debulking carries substantial risk of morbidity/mortality and has no effect on outcome. The role of diagnostic biopsy has changed with the advent of MRI and the ability to distinguish, by imaging alone atypical (good risk) brain stem gliomas (such as focal, dorsal exophytic, cervicomedullary, tectal) from the more typical (poor risk) diffuse intrinsic pontine tumors. Albright's report on behalf of Children's Cancer Group (CCG) in 1993 recommended MRI to replace biopsies in the diagnosis

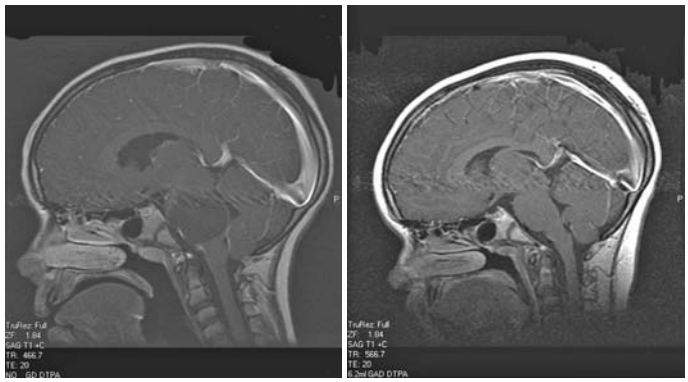
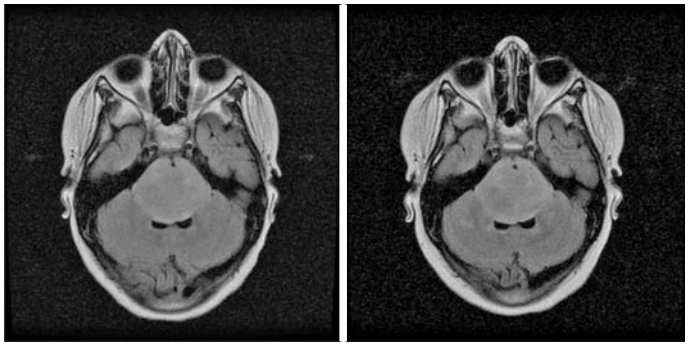


Fig. 1 Despite excellent response to radiotherapy patient died 11 months postdiagnosis



First scan:
Karnofsky index was 90%

Second scan:
4 months later, Karnofsky 40%

Fig. 2 This patient had marked clinical progression over a 4-month period in spite of minimal change in MRI. First scan: scan 4 months later: Karnofsky index was 90%; Karnofsky index was 40%

of DIPG [6]. This proposal is nowadays universally accepted.

Where biopsies have been performed, the majority of these tumors are found to be high-grade gliomas. Although some diffuse pontine gliomas are reported as low grade, often Grade II rather than I. This may be due to the superficial nature of most biopsies, which are not representative of the tumor; the natural history is more akin to those with high-grade histology [7]. Stereotactic biopsies, which are associated with less morbidity, may not be representative of the tumor as astrocytomas can be heterogeneous. Furthermore most tumors are high-grade (Grade III to IV) astrocytomas proven by autopsy studies.

Although biopsy is not considered necessary for diagnosis in presence of typical clinical and neuroradiological features, this view might change if biological or imaging markers are identified that can predict more precisely the sensitivity of the tumor to treatment or affect its management [8].

Staging/Classification

There is no generally applied staging system for childhood brain stem gliomas. Metastases outside the brain stem to other sites in the brain or spine are unusual at presentation. Thus, staging tests to look for tumor spread, such as spine MRI or lumbar puncture, are not routinely performed at diagnosis. However, leptomeningeal dissemination has been described during disease progression in up to 50% of patients [9].

Treatment

Brain stem gliomas are relatively uncommon and require complex management; children with such tumors deserve evaluation in a comprehensive cancer center where the coordinated services of dedicated pediatric neurosurgeons, pediatric neurologists, pediatric oncologists, radiation oncologists, neuropathologists, and neuroradiologists are available.

DIPG remain one of the most frustrating tumors in pediatric oncology. The prognosis is dismal with more than 90% of children dying within 2 years of diagnosis. At this point, new therapies have yielded little benefit over conventional treatment with radiotherapy alone. Focal radiation therapy is the standard treatment, leading to improvement in a majority of cases. However, the duration of response is lim-

ited and outcome of children with these tumors remains uniformly poor with median survival of 9–12 months. Kaplan et al. in a review of 119 cases registered in Children Cancer Group (CCG) studies, reported a 37% survival rate at 1 year, 20% at 2 years, and 13% at 3 years [10]. Death is almost invariably due to failure of local control.

Neurosurgery

As previously stated, this tumor is diffuse and infiltrative throughout brain stem growing between normal nerve cells, and surgery of any sort, beyond that occasionally needed to relieve hydrocephalus, is not indicated. Although present in a significant proportion of patients at diagnosis, hydrocephalus is often mild and manageable with steroids and the need for a shunt is infrequent.

Radiotherapy

Conventional focal radiotherapy at dose of 54 Gy in 30 fractions of 1.8 Gy each over 6 weeks remains the standard treatment for patients with these tumors, probably offering best palliation. Despite the fact that radiotherapy leads to neurological improvement in a majority of patients, 90% of patients with DIPG will succumb to disease within 2 years from diagnosis. Because of the transient effectiveness in conventional doses, investigators attempted to boost responses and survival times by hyperfractionating and escalating doses of radiation. Pilot and collaborative group studies in 1980–1990s (Table 1) used hyperfractionated external beam radiotherapy at doses ranging from 64.8 Gy to 78 Gy. Response rates, which included patients with stable disease (0%–24% change in tumor size), have been reported to be in the range of 62% to 77%. However, these hyperfractionated external beam radiotherapy trials have not significantly altered time-to-disease progression or provided durable responses [11]. An important multicenter randomized Phase III study involving 130 children compared conventional radiotherapy with hyperfractionated radiotherapy (total dose of 70.2, 1.17 Gy twice daily fractionation) with infusion of cisplatin as radiosensitizer [12]. Time to progression and overall survival was not improved with hyperfractionation and some authors reported increasing problems with radiation necrosis and steroid dependence [13]; hence single daily dose of 1.8 Gy to a total of 54 Gy remains the standard treatment.

Radiotherapy should start as quickly as possible following the diagnosis, ideally within 24–72 h following diagnosis. Brain stem tumors are treated with parallel opposed fields, using a linear accelerator, with the child lying face down in a mask to ensure accuracy and reproducibility in each treatment fraction. Children less than 3 years of age usually require daily anesthetics but older children seldom require sedation as long as the initial planning process is coordinated smoothly. Clear explanations through play therapy, training videos, and departmental visits before treatment ensure good cooperation in most cases.

Table 1 Hyperfractionation—results of prospective studies

Study	Reference	No. of patients	Dose/fraction of radiotherapy	Total dose	TTP	MST	Survival 1 year	Survival 2 years	Survival 3 years
POG (8495)	[22]	38	1.1 Gy	66 Gy	6.5 m	11 m	48%	6%	3%
	[22]	57	1.17 Gy	70.2 Gy	6 m	10 m	40%	23%	21%
	[22]	57	1.26 Gy	75.6 Gy	7 m	10 m	39%	6%	6%
CHOP/NYU	[23]	16	1.2 Gy	64.8 Gy	7 m	11 m	48%	–	–
	[24]	35	1 Gy	72 Gy	8 m	–	–	28%	–
CCG (9982)	[16]	53	1 Gy	72 Gy	5.5 m	9 m	38%	14%	8%
	[16]	66	1 Gy	78 Gy	8 m	9.5 m	35%	22%	11%
UCSF	[25]	20	1 Gy	72 Gy	36 w	51 w	–	–	–
	[26]	36	1 Gy	78 Gy	8.4 m	10.8 m	–	–	–

TTP, Time to Progression; MST, Median Survival Time; m, months; w, weeks

Chemotherapy

The role of chemotherapy in DIPG remains disappointing in what so far has proven to be a chemo-resistant tumor. The only randomized phase III study by Children's Cancer Group (CCG-943) which compared radiotherapy alone to the addition of vincristine, CCNU and prednisone failed to show any survival benefit of adjuvant chemotherapy [14]. In a Pediatric Oncology Group (POG) phase II study, 37 children received preirradiation chemotherapy with cisplatin and cyclophosphamide. Despite several children showing a response (including stable disease), the median survival was only 9 months and overall survival at 2 years was only 14% [15]. A similar Phase II study by CCG (CCG-9941) with preirradiation chemotherapy with cisplatin / carboplatin, etoposide, and cyclophosphamide failed to show improved response rate, event-free survival (EFS), and overall survival [16].

A literature review of phase 2 trials of drug combinations including cisplatin/cytarabine/etoposide, cisplatin/cyclophosphamide, mustine/vincristine/procarbazine/prednisolone, and thiotepa/etoposide or busulphan/thiotepa given in high dose with autologous bone marrow rescue, failed to identify any of these combinations as being capable of producing measurable sustained responses. [17].

Thus so far, various single or combination chemotherapeutic regimens used in a variety of different ways (upfront, adjuvant, or concurrent with radiation) have failed to show any significant activity in DIPG. Response rates are in the range of 0% to 20%. Indeed there has been concern that chemotherapy can be detrimental in some cases to both survival and quality of life of these children [13]. Agents given concurrently with the intent of radiosensitization are of interest but so far have shown no added benefit. Tamoxifen, immunotherapy with β-interferon and other drugs to modify biologic response have shown disappointing results.

Prognosis

Following radiation, most children experience improvement of their symptoms. Complete neurological recovery is not exceptional. The median length of clinical remission after completion of radiation is 4–6 months. The clinical or radiological response to radiation does not predict the duration of the remission [5, 12]. Poor prognostic features include (1) age less than 2 years, (2) multiple cranial nerve palsies, and (3) short duration of symptoms prior to the time of diagnosis. The overall outlook of patients with DIPG is uniformly poor, with the majority of children dying within a year of diagnosis. Long-term survival has been reported in some cases. However, caution must be taken regarding anecdotal reports on long-term survival. A review of the POG 8495 study, in which 130 patients were enrolled, revealed that only four of the nine long-term survivors had typical diffuse intrinsic pontine lesions and, conversely, that at least three of the nine patients had lesions that would now be considered relatively favorable [18].

Specific Problems and Measures

Palliative care is the essential and main component of treatment of DIPG and measures that are useful in addition to radiotherapy are corticosteroids, management of hydrocephalus, bulbar impairment, analgesia, physical rehabilitation, and social support to family. Management at the time of progression following radiotherapy should take into account the short life span of the patient.

Steroids

Dexamethasone or other oral steroids is routinely given following diagnosis to improve symptoms and the during radiation phase of treatment to prevent neurological deterioration associated with edema. The presenting symptoms of raised intracranial pressure and, to a lesser degree, neurological symptoms, are in most cases effectively improved or even relieved by dexamethasone. Although this is reassuring to the child, their family, and their doctors, prolonged treatment with steroids leads inevitably to progressive sides effects including weight gain, hirsutism, distressing alterations in mood, sleep disorders, and other adverse events. Steroids should be tapered during and/or after radiotherapy in all patients and only restarted to control symptoms of raised intracranial pressure, or if there is evidence of delayed radiation-induced neurotoxicity [19]. The minimum dose that is effective should be used for as short a time period as possible. Doses greater than 10 mg/m^2/day are associated with significant toxicity and should not be used. Short intermittent courses of dexamethasone (lasting 3–5 days) seem to be better than a prolonged course. New agents such as Corticotropin releasing Factor (CRF) analogue drugs and Cyclo-oxygenase inhibitors (COX-2) inhibitors may have a role particularly in children with DIPG who are steroid dependent. Furthermore, there is preclinical data suggesting that COX-2 inhibitor drugs may be useful as adjuvants and/or therapeutic agents to treat gliomas overexpressing COX-2 [20].

Hydrocephalus

Symptomatic hydrocephalus requiring surgical drainage is unusual at presentation in the diffuse pontine glioma. If hydrocephalus occurs following disease progression, surgical interventions require careful consideration. The overall objectives of palliative care should be central to discussion as shunt insertion following disease progression may not improve symptoms or quality of life significantly.

Bulbar Impairment

Patients with speech, swallowing, and breathing difficulties will require support by means of alternative methods of communication, nasogastric tube feeding, or gastrostomy, and rarely tracheostomy is indicated. Families often need help with appropriate specialist nursing care

Analgesia

Apart from headache as a result of raised intracranial pressure, pain is relatively infrequent in patients with diffuse pontine glioma. "Brainstem headaches" are often located in the occipital area. Standard approaches to palliative pain control with child and family support and the analgesic ladder are successful in controlling pain for most children.

Neurological Disability

Patients should be assessed early and throughout treatment. Plans should be made for rehabilitation to run in parallel with antitumor treatments. Special arrangements should be made for the rehabilitation program to be deliverable at home, in school, and in hospital.

Family Support

Patients and families coming to terms with diffuse pontine glioma pose a real challenge. It is crucial that the neurosurgeon explains the rationale behind the surgical decision and helps the family to understand that surgery is not "impossible" but "unhelpful" and could permanently compromise the quality of life in this palliative context. All the multidisciplinary health professionals should follow a "child and family centered" approach in caring for these children. Parents acquire information from multiple sources, including, but not limited to, physicians, support groups, pharmaceutical companies, and the internet. Physicians should be aware of this and have an open, informative relationship with family, empowering them to become active members of the team with regard to the decision-making process involving their child's care.

Future Perspectives

Lacking effective treatment in spite of two decades of active clinical research, it is difficult to imagine that any of the currently available conventional chemotherapeutic agents are likely to have much impact on the outcome of this dismal tumor. There is need for further research in the treatment of DIPG which is envisaged to be based on radiotherapy combined with newer agents, such as radiosensitizers or small molecules targeting specific pathways. Given the poor responses to conventional drugs and their grim prognosis, patients with DIPG represent an ideal population to assess novel treatments. The statistical design of these experimental treatments deserves specific consideration, as published prospective clinical studies done so far in children with DIPG show significant heterogeneity and even inconsistency in the statistical methodologies (historical controls, sequential analysis, etc.), statistical end point, stopping rules, response rates, and definition of time to progression (clinical, radiological). Based on available data, statistical design for these trials should be based on overall survival [21].

References

1. Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. J Natl Cancer Inst 1998;90:1269–77
2. Fisher PG, Breiter SN, Carson BS, et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocytic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000;89:1569–76
3. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP. Diagnosis and management of pediatric brain-stem gliomas. J Neurosurg 1986;65:745–50
4. Zimmerman RA. Neuroimaging of primary brainstem gliomas: diagnosis and course. Pediatr Neurosurg 1996;25:45–53
5. Hargrave D, Chuang N, Tariq N, Bouffet E. Can radiological characteristics predict length of survival in pontine glioma. Neuro-Oncology 2003;5:43 (abstract)
6. Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. Neurosurgery 1993;33:1026–30, 1993

7. Cartmill M, Punt J. Diffuse brain stem glioma. A review of stereotactic biopsies. Childs Nerv Syst 1999;15:235–7
8. Gilbertson RJ, Hill DA, Hernan R, Kocak M, Geyer R, Olson J, et al. ERBB1 is amplified and overexpressed in high-grade diffusely infiltrative pediatric brain stem glioma. Clin Cancer Res 2003;9:3620–4
9. Donahue B, Allen J, Siffert J, Rosovsky M, Pinto R. Patterns of recurrence in brain stem gliomas: evidence for craniospinal dissemination. Int J Radiat Oncol Biol Phys 1998;40:677–80
10. Kaplan AM, Albright AL, Zimmerman RA, Rorke LB, Li H, Boyett JM, et al. Brainstem gliomas in children. A Children's Cancer Group review of 119 cases. Ped Neurosurg 1996;24:185–92
11. Fisher PG, Donaldson SS. Hyperfractionated radiotherapy in the management of diffuse intrinsic brainstem tumors: when is enough enough? Int J Rad Oncol Biol Phys 1999;43:947–9
12. Mandell LR, Kadota R, Freeman C, Douglass EC, Fontanesi J, Cohen ME, et al. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys 1999;43:959–64
13. Freeman CR, Kepner J, Kun LE, Sanford RA, Kadota R, Mandell L, et al. A detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse intrinsic brain stem gliomas? Int J Radiat Oncol Biol Phys 2000;47:561–4
14. Jenkin RD, Boesel C, Ertel I, Evans A, Hittle R, Ortega J, et al. Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens Cancer Study Group. J Neurosurg 1987;66:227–33
15. Kretschmar CS, Tarbell NJ, Barnes PD, et al. Pre-irradiation chemotherapy and hyperfractionated radiation therapy 66 Gy for children with brain stem tumors. Cancer 1993;72:1404–13, 1993
16. Jennings MT, Sposto R, Boyett JM, et al. Preradiation chemotherapy in primary high-risk brainstem tumors: phase II study CCG-9941 of the Children's Cancer Group. J Clin Oncol 2002;20:3431–7
17. Freeman CR, Perilongo G. Chemotherapy for brain stem gliomas. Childs Nerv Syst 1999;15:545–53
18. Freeman CR, Bourgouin PM, Sanford RA, Cohen ME, Friedman HS, Kun LE. Long term survivors of childhood brain stem gliomas treated with hyperfractionated radiotherapy. Clinical characteristics and treatment related toxicities. The Pediatric Oncology Group. Cancer 1996;77:555–62
19. Walker DA, Punt JA, Sokal M. Clinical management of brain stem glioma. Arch Dis Child 1999;80:558–64
20. Shono T, Tofilon PJ, Bruner JM, Owolabi O, Lang FF. Cyclooxygenase-2 expression in human gliomas: prognostic significance and molecular correlations. Cancer Res 2001;61:4375–81
21. Bouffet E, Hargrave D, Baruchel S. Clinical trials for Brain stem Glioma patients (BSG): Critical review of statistical endpoints and results. Neuro-oncol 2003;5:29
22. Freeman CR, Krischer JP, Sanford RA, Cohen ME, Burger PC, del Carpio R, et al. Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study. Int J Radiat Oncol Biol Phys 1993;27:197–206
23. Packer RJ, Allen JC, Goldwein JL, Newall J, Zimmerman RA, Priest J, et al. Hyperfractionated radiotherapy for children with brainstem gliomas: a pilot study using 7,200 cGy. Ann Neurol 1990;27:167–73
24. Packer RJ, Littman PA, Sposto RM, D'Angio G, Priest JR, Heideman RL, et al. Results of a pilot study of hyperfractionated radiation therapy for children with brain stem gliomas. Int J Radiat Oncol Biol Phys 1987;13:1647–51
25. Prados MD, Wara WM, Edwards MS, Larson DA, Lamborn K, Levin VA. The treatment of brain stem and thalamic gliomas with 78 Gy of hyperfractionated radiation therapy. Int J Radiat Oncol Biol Phys 1995;32:85–91
26. Edwards MS, Wara WM, Urtasun RC, Prados M, Levin VA, Fulton D, et al. Hyperfractionated radiation therapy for brain-stem glioma: a phase I-II trial. J Neurosurg 1989;70:691–700

Dorsally Exophytic Brainstem Gliomas

29

Ian D. Kamaly-Asl, James M. Drake

Epidemiology – 416

Symptoms and Clinical Signs – 416

Diagnostics – 416
CT Scan Findings
MR Scan Findings

Staging and Classification – 417

Treatment – 417
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 419

Follow-up – 419

Future Perspectives – 419

References – 419

Various classification systems for brainstem gliomas have been described [1]. It has been recognized for some time that there is a subgroup of these lesions that are exophytic to the substance of the brainstem and have a very different biology to the diffusely infiltrating intrinsic brainstem lesions [2]. The histology of these lesions is usually pilocytic astrocytoma and outcome is generally good.

Epidemiology

Brainstem tumors account for 10%–20% of pediatric CNS tumors [1], with the dorsally exophytic subtype accounting for approximately 14%–24% of these lesions [2–4]. The average age of presentation for all brainstem gliomas is between 6–9 years of age in most studies [1, 5, 6]. Dorsally exophytic lesions age at presentation has been reported as being younger than this at 38 months [4] and over one quarter of patients present in the first year of life [2]. There is no gender or geographical predilection for these tumors [1].

Symptoms and Clinical Signs

Compared to diffuse brainstem gliomas, dorsally exophytic lesions tend to have a longer duration of symptoms which is generally over 6 months [2, 4, 5].

Children presenting at less than 1 year of age exhibit failure to thrive secondary to chronic vomiting and it is often the case that there is significant delay in diagnosis with exhaustive medical investigation prior to the tumor being diagnosed [2].

Older children generally present with headaches, vomiting and ataxia. Cranial nerve dysfunction (usually 6th or 7th) is evident in approximately 40% of children at presentation [2, 4].

Examination will usually reveal papilledema and ataxia with torticollis being common secondary to chronic tonsillar herniation [2, 4]. Long tract signs are unusual at presentation which distinguishes these lesions from other brainstem pathologies [2, 4].

Diagnostics

The determination of subtypes of brainstem gliomas has changed dramatically during the CT and MR scan eras. Accurate assessment of these lesions is paramount as distinguishing focal/exophytic from diffuse brainstem lesions has a significant impact on management. For this reason MR scanning has become the standard assessment for a brainstem lesion.

CT Scan Findings

By definition dorsally exophytic lesions protrude into and often fill the 4th ventricle, but occasionally they will be dorsolaterally exophytic, projecting into the cerebello-pontine angle [2–4] (Fig. 1). Hydrocephalus may be evident. The lesions are hypodense or isodense compared with grey matter and may contain cystic areas. There is generally bright enhancement following intravenous contrast administration.

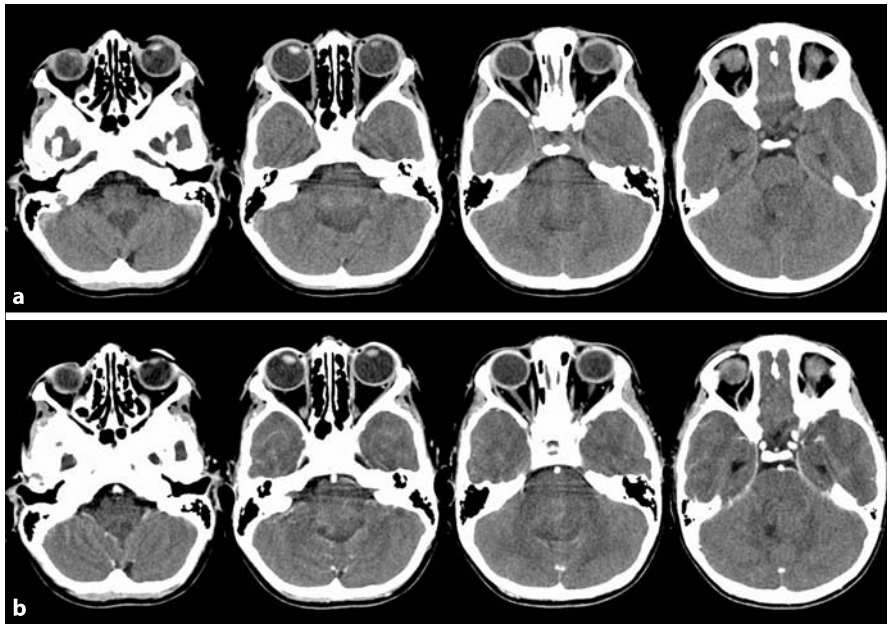


Fig. 1 CT scan of dorsally exophytic brainstem pilocytic astrocytoma (**a** precontrast; **b** post-contrast). There is an ill-defined mass arising from the brainstem and filling the 4th ventricle. Following contrast administration in this lesion there is some mild patchy enhancement

MR Scan Findings

MR scan is far superior than CT at defining the relationships of these lesions [2–4] (Fig. 2). As mentioned previously, the majority of the tumor will generally be within the 4th ventricle and a cap of surrounding CSF may be seen dorsolaterally. Ventrally the tumor will blend into the brainstem and the epicenter of this may be superficial on the floor of the 4th ventricle or deeper as a focal intrinsic lesion. Signal characteristics are of low signal on T1 with high signal on T2 sequences. The tumor edges will generally be consistent between T1 and T2 sequences as compared to diffuse intrinsic lesions where there usually is a larger area of T2 signal abnormality compared to T1. As with CT, there is usually bright enhancement following intravenous contrast administration.

Staging and Classification

Dorsally exophytic gliomas have been shown to be predominantly pilocytic astrocytomas although other histological types such as grade 2 and 3 fibrillary astrocytomas and gangliogliomas have been reported [1–4, 7]. The degree of invasion within the brainstem itself does vary between lesions; however, with most lesions being low grade, the majority of growth tends to be towards the path of least resistance, through the ependyma and into the 4th ventricle [3].

Treatment

Of all the brainstem glioma subtypes, dorsally exophytic lesions are the most surgically accessible. The mainstay of treatment is surgical debulking followed by close observation. Radiotherapy and chemotherapy are reserved for the recurrent lesions.

Surgery

Together with improvements in diagnosis, advances in microsurgical instruments and techniques allows surgery to be an option in tumors that would have previously been inoperable [1]. In addition neurophysiological monitoring during a procedure allows greater confidence when dissecting tumor within the brainstem and is standard procedure in most centers performing these operations. Both ultrasonic aspi-

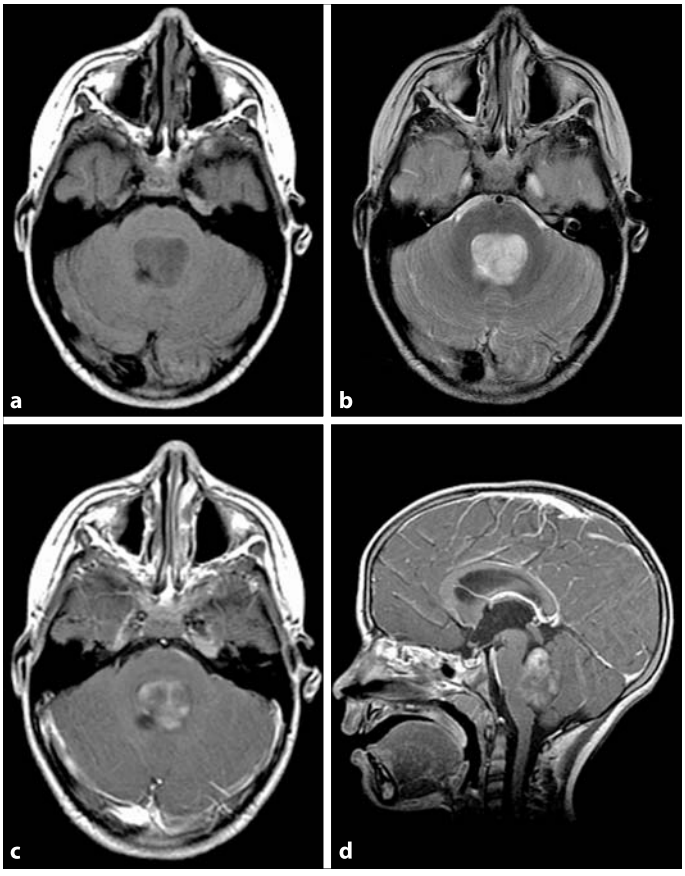


Fig. 2 MR scan of patient in Fig. 1 with a superficial dorsally exophytic brainstem pilocytic astrocytoma (**a**, T1 axial; **b**, T2 axial; **c**, T1 axial postcontrast; **d**, T1 sagittal postcontrast). The size of the lesion is consistent between T1 and T2 weighted sequences, distinguishing this from a diffuse pontine glioma

rators and operative lasers are helpful in the dissection of lesions within the brainstem. We have found that intraoperative ultrasound imaging has proved very valuable in assessing the extent of resection of the lesion.

Hydrocephalus requiring CSF diversion is reported in nearly 30% of patients [2]. Endoscopic third ventriculostomy would generally be the current preferred management for the hydrocephalus.

The patient is usually placed prone, although some surgeons prefer the sitting position. Surgical approach is through the midline with options of the telovelar approach or spitting of the vermis to expose the tumor within the 4th ventricle (Fig. 3). Immediate histological assessment is undertaken to guide the rest of the procedure. If the lesion is not low grade then there is no proven advantage to debulking within the brainstem. It is important early on to identify the level of the floor of the 4th ventricle as this should be the limit of the resection for tumors placed superficially within the brainstem. For tumors with a focal component in the brainstem (Fig. 4), the exophytic component is removed initially allowing broad access to the intrinsic component. The goal of surgery for the intrinsic component is debulking

Fig. 3 Dorsally exophytic brainstem glioma arising in the medulla and pons which fills the 4th ventricle

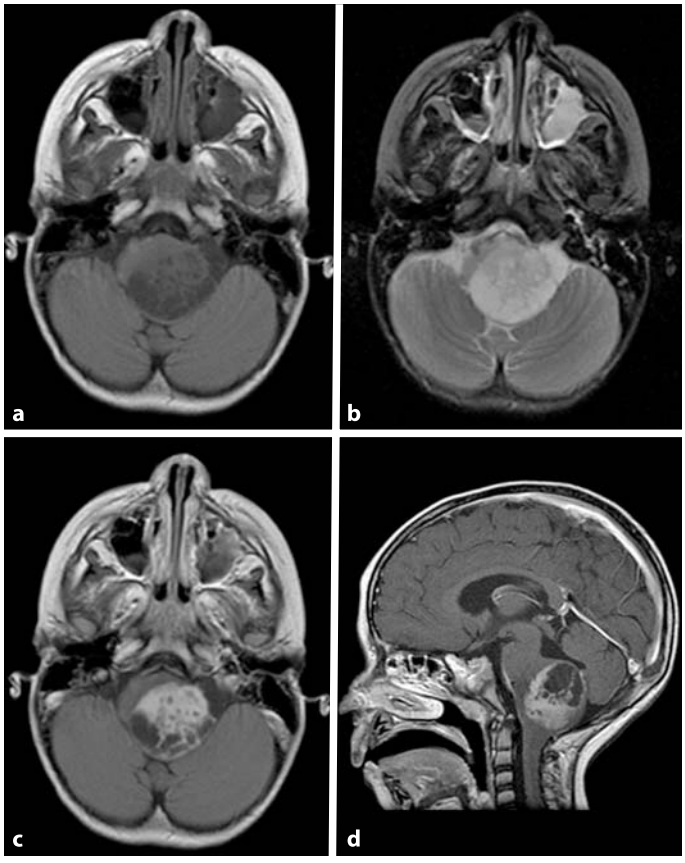


Fig. 4 MR scan of a patient with dorsally exophytic brainstem pilocytic astrocytoma with an intrinsic component (**a**, T1 axial; **b**, T2 axial; **c**, T1 axial postcontrast; **d**, T1 sagittal postcontrast). The lesion is exophytic backwards into the 4th ventricle and also laterally through the left foramen of Luschka

rather than a complete excision, given that surgical morbidity may be devastating and outcome appears favorable with subtotal resection [2].

For the dorsally exophytic brainstem gliomas surgical mortality is low with no surgical deaths in the reported series [2, 4, 5]. Most of the morbidity is transient with exacerbation of preoperative ataxia, dysmetria, nystagmus and cranial nerve dysfunction being described. Postoperative long tract signs are uncommon but have been reported [2, 4].

Radiotherapy

Given the low grade nature of the majority of the tumors, radiotherapy is usually not given as standard, even in the presence of residual disease [2, 4]. For tumors that have recurred the standard brainstem dose of 54 Gy delivered in 30 fractions over 6 weeks would often be given. This has provided tumor control in the small number of patients within the studies [2, 4, 5]. Stereotactic radiosurgery has been employed for brainstem tumors [8]. In nine patients with brainstem pilocytic astrocytoma where radiosurgery was given in an adjuvant fashion, tumor control was achieved in six patients with two patients having enlarging cysts and one enlarging solid tumor. Radiosurgery was also used on another nine patients when their brainstem pilocytic astrocytomas recurred. In four patients tumor control was achieved and in five progression was evident [8].

Chemotherapy

For brainstem gliomas in general there have been many trials of chemotherapeutic agents, none of which has shown any definite survival advantage and in general these studies have mostly recruited patients with diffuse pontine gliomas. A recent report, however, has investigated chemotherapy as the first line therapy for unresectable recurrent or progressive low-grade brainstem gliomas [9]. This study reported nine out of ten patients to be progression free at a median of 47 months after commencement of chemotherapy (carboplatin and vincristine for the majority of patients). Radiotherapy was avoided in all these patients.

Prognosis/Quality of Life

Overall 5-year survival for the dorsally exophytic pilocytic lesions is good with rates in most studies of about 95% [2, 4, 7]. Recurrence is recognized even with gross total excision [4], such that progression-free survival rates at 5 years are between 54% and 72% [2, 4, 7]. In brainstem gliomas in general, histological subtype is the primary determinant of survival with pilocytic astrocytomas having markedly improved overall survival compared to fibrillary astrocytomas (pilocytic 5 year survival 95%, standard error 5%; compared to fibrillary 1-year survival of 23%, standard error 11%) [7]. Other factors that worsen survival are cranial nerve (particularly abducens) dysfunction at presentation [7, 10] and symptom duration of less than 6 months [7]. Total or subtotal excision of low-grade brainstem lesions has been shown to have an improved outcome compared to partial (<50% of total tumor mass) excision (94% versus 52% at 5 years) [6]. Long-term neurological function following surgery for dorsally exophytic lesions is generally good with most patients being either at their presentation baseline or improved [2, 4].

Follow-up

Tumor recurrence is documented in cases between 2 and 84 months postoperation [2, 4, 5], with the majority being symptomatic at the time of recurrence. We would undertake follow-up imaging immediately postoperation, at 3, 6, and 12 months and then annually up to 5 years, then biennially up to about 10 years.

Future Perspectives

Although the outcome for the dorsally exophytic pilocytic gliomas is good, the rarer fibrillary gliomas still carry a very poor prognosis. Various novel modalities of treatment are being investigated including convection-enhanced and slow-flow delivery of chemotherapeutic agents, radio-sensitizing agents, gene therapy, and hyperbaric and interstitial radiotherapy [1]. Further research is required to fully understand the biology of these tumors in order to improve the success of treatment.

References

1. Jallo GI, Biser-Rohrbaugh A, Freed D. Brainstem gliomas. Childs Nerv Syst 2004;20:143–153
2. Pollack IF, Hoffman HJ, Humphreys RP, Becker L. The long-term outcome after surgical treatment of dorsally exophytic brain-stem gliomas. J Neurosurg 1993;78:859–863
3. Epstein FJ, Farmer JP. Brain-stem glioma growth patterns. J Neurosurg 1993;78:408–412
4. Khatib ZA, Heideman RL, Kovnar EH, Langston JA, Sanford RA, Douglas EC, et al. Predominance of pilocytic histology in dorsally exophytic brain stem tumors. Pediatr Neurosurg 1994;20:2–10

5. Farmer JP, Montes JL, Freeman CR, Meagher-Villemure K, Bond MC, O'Gorman AM. Brainstem gliomas. A 10-year institutional review. Pediatr Neurosurg 2001;34:206–214
6. Pierre-Kahn A, Hirsch JF, Vinchon M, Payan C, Sainte-Rose C, Renier D, et al. Surgical management of brain-stem tumors in children: results and statistical analysis of 75 cases. J Neurosurg 1993;79:845–852
7. Fisher PG, Breiter SN, Carson BS, Wharam MD, Williams JA, Weingart JD, et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000;89:1569–1576
8. Hadjipanayis CG, Kondziolka D, Gardner P, Niranjan A, Dagam S, Flickinger JC, et al. Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary. J Neurosurg 2002;97:56–64
9. Ronghe M, Hargrave D, Bartels U, Huang A, Vaida S, Kulkarni A, et al. Chemotherapy for low grade gliomas of the brainstem. Eur J Cancer 2005; (in press)
10. Albright AL, Guthkelch AN, Packer RJ, Price RA, Rourke LB. Prognostic factors in pediatric brain-stem gliomas. J Neurosurg 1986;65:751–755

Cervicomedullary Gliomas 30

Alexa L. Reeves, Richard G. Ellenbogen

Introduction – 422

Symptoms and Signs – 422

Radiologic Diagnosis – 423

Pathology and Growth Patterns – 423

Treatments and Their Indications – 424
Surgical Treatment
Radiotherapy
Chemotherapy

Outcome/Prognosis/Quality of Life – 427

Follow-up – 428

Summary – 428

References – 428

Introduction

Cervicomedullary gliomas are a unique group of tumors that originate in the brainstem, are primarily found in the pediatric population, appear quite infrequently in the adult population, and are amenable to surgical therapy [14]. The general class of tumors, referred to as brain stem gliomas, account for approximately 20% of all pediatric brain tumors [18]. However, "brainstem glioma" is a broad term that includes a spectrum of intra-axial tumors of the brainstem. It is becoming increasingly clear to neurosurgeons and oncologists that brain stem gliomas are also a heterogeneous group of tumors which are best treated according to clinical and radiological characteristics.

The majority of brainstem gliomas (60%–80%) are situated in the pons, are diffusely infiltrating, and are not amenable to surgical treatment. The median survival of patients with these diffuse pontine gliomas regardless of treatment, is quite poor, ranging from 6 to 15 months. Surgical biopsy or resection has no proven role in the treatment of these tumors. Unfortunately, we have not changed the natural history of this ominous tumor, in the past 50 years, despite significant advances in surgery and adjuvant therapy for other types of brain tumors [2, 3, 17].

Over the past two decades, it has become clear that there are distinct subsets of brainstem glioma based on prognosis, biological activity, and location. Classification of brainstem tumors based on MRI appearance, suspected histology, and thus prognosis has been adopted because it helps decide whether surgery or adjuvant therapy is indicated as the primary treatment [1, 4–7, 10, 19]. The subset of brainstem glioma called cervicomedullary gliomas appears to represent a group of tumors possessing benign histology and one in which an aggressive surgical approach may be warranted. The refinement in the treatment options for this subset of brainstem glioma has been based in part on the advent and developments in MRI technology. The subsequent outcome analysis of the aggressive surgical posture adopted by several pioneering investigators has changed our perspective on a tumor in which we thought death or disability was inevitable [5, 19].

Epstein et al. at NYU presented their initial novel surgical experience with cervicomedullary glioma in 1986 and then again in 1987 [4, 5]. At the same time, Stroink and the Toronto Sick Children's Hospital Neurosurgeons presented their parallel experience with brainstem gliomas and a classification based on CT characteristics, prognosis, and efficacy of surgical intervention [19].

Epstein's classification of brainstem tumors based on location and configuration on MRI, has been widely adopted. He classified brainstem tumors as diffuse, focal, and cervicomedullary. The diffuse pontine tumors demonstrated malignant histology (astrocytoma WHO Grades III, IV) with a poor prognosis. In contrast, most of the focal and all of the cervicomedullary tumors had a benign histology (astrocytoma WHO Grades I, II) and thus a better prognosis for progression-free survival [4, 10]. Preoperative deficits and deteriorating neurologic conditions were stabilized and often improved following radical excision of these cervicomedullary tumors. Epstein and his colleagues concluded that surgery of the brainstem could be justified and carried out with acceptable morbidity in those tumors that were both geographically isolated to the cervicomedullary junction and carried a benign histology [5].

Symptoms and Signs

Cervicomedullary gliomas in children tend to follow a relatively indolent clinical course. Protracted symptoms or signs of intermittent deterioration may permit several months or years of diagnostic delay before a neoplasm is identified on MRI. In Robertson's et al. series of 17 patients with cervicomedullary tumors, 80% of the patients had symptoms for at least 1 year. The symptoms prior to radiological diagnosis were present in some patients as short as 2 months and as long as 7.5 years [17]. Regardless, this prolonged course presumably reflects the slow-growing, relatively benign histology of the most frequent pathology found at this site, pilocytic astrocytoma. At our institution, the patients' symptoms were often confusing and intermittent requiring multiple visits to a primary care provider. In addition, headache was not a large component of the symptoms. A diagnostic study such as CT or MRI was performed only after progression of a cranial nerve paresis or extremity weakness.

Clinical manifestations can be classified into two overlapping groups of presentations based on their primary location in the medulla or the cervical cord. Patients with a primary medulla component present with lower cranial nerve dysfunction; patients with tumor primarily in the cervical cord present with motor and sensory symptoms representing frank spinal cord dysfunction. Cranial nerve dysfunction can include swallowing difficulties, speech difficulties, palate deviation and dysfunction, facial nerve palsy, head tilt, vomiting, nausea, and vertigo. The nausea and vomiting is often not associated with hydrocephalus and increased intracranial pressure, but instead direct involvement of the medulla. Young children can present with failure to thrive, apnea, and hypotonia [11, 17].

Spinal cord dysfunction manifests primarily as objective neurological dysfunction such has quadriparesis or hemiparesis. Patients also can exhibit lower motor neuron presentations with weakness associated with atrophy and hyporeflexia. In a small number of patients, sensory symptoms such as unremitting neck pain or facial pain from involvement of the trigeminal tract are prominent [9]. The neck pain, if investigated early can be the only complaint and not be accompanied by any neurological deficit. In our experience, the neck pain is often treated symptomatically and can precede objective neurological dysfunction by months or years.

More rarely, paresthesias, dysesthesias, clumsiness, hiccups, syncope, ataxia, and apnea may also be present at time of diagnosis. Symptoms and signs of hydrocephalus may appear when the tumor obstructs the IVth ventricle or its outlets, although this occurs only in the minority of patients [21].

Radiologic Diagnosis

MRI remains the gold standard for evaluation of brainstem gliomas. MRI provides an enormous amount of diagnostic information to the clinician, thus guiding subsequent therapy. The MRI helps assess the lesion in terms of location, focal versus diffuse configuration, infiltrative versus well-demarcated margins, the degree of brainstem invasion, expansion and extent, hemorrhage, necrosis, cyst formation, exophytic component, and degree of enhancement with gadolinium. CT scans may be the first diagnostic test performed in some patients but they can be misleading. The Boston Children's group found that the streak artifact through the brainstem caused distortion to the point that 75% of patients with MRI- and biopsy-proven cervicomedullary gliomas were missed on an initial CT scan. We employ the CT scan for a baseline estimate and rapid subsequent evaluation of hydrocephalus in patients with brainstem gliomas. In addition, CT is useful to determine if tumor calcification is present.

On T1 MRI images the majority of cervicomedullary gliomas are hypointense to white matter. On T2 and proton density images the lesions tend to be hyperintense to white matter. After gadolinium administration most lesions demonstrate enhancement, which is often homogeneous, but can be heterogeneous in some [21]. The cranial-caudal extent of the tumor can be assessed on sagittal images.

MRI can help differentiate between the different subsets of brainstem gliomas. The diffuse pontine gliomas demonstrate extensive involvement on all three planes (sagittal, coronal, and axial), as a result of its diffuse brainstem infiltration and subsequent expansion. The MRI appearance coupled with the clinical presentation of rapidly progressive decline can be pathognomonic for a typical pontine gliomas. As a result of "classic" MRI appearance of diffuse tumors, biopsy of this lesion is not indicated. Furthermore, the disease is infiltrative making biopsy treacherous as it is often difficult for the surgeon to choose a location in which further deficits are not created. Those diffuse pontine lesions which have an exophytic component lay in a grey zone in which a biopsy may be safely performed but may not provide information in which a treatment plan would be altered.

Dorsally exophytic tumors of the brainstem demonstrate less infiltration of the brainstem on MRI than either diffuse pontine or cervicomedullary tumors. The dorsally exophytic tumors are usually hyperintense on T2 images with a gadolinium-enhancing, dorsally exophytic component which grows into the IVth ventricle causing CSF obstruction and symptomatic hydrocephalus. The caudal extent of these tumors is often limited to the medulla and ventrally the tumor faintly blends into the brainstem [18].

A focal brainstem tumor has characteristic MRI appearance as well, and can be easily differentiated from a cervicomedullary tumor. The focal tumors can occur anywhere in the brainstem and are often under 2 cm in diameter. Tectal gliomas which cause hydrocephalus through blockage of the aqueduct are a prime example of a focal glioma of the brainstem. The focal tumors may be solid or cystic and the edges may be well demarcated on T1 or T2 images. Tectal plate gliomas are often solid with intense enhancement. They tend to exhibit a relatively benign natural history with an indolent growth rate [12].

Often, on sagittal MRI images, the cervicomedullary tumors extend from the caudal two thirds of the medulla to the rostral aspect of the cervical cord. In a series of 22 cervicomedullary tumors reported by Epstein et al,, eight patients had a nonneoplastic cyst in the region of the medulla [5].

Pathology and Growth Patterns

Consistent with the concept that cervicomedullary tumors are a clinically unique subset of brainstem tumors, the pathology is most often that of a low-grade glioma. Specific histopathologies including pilocytic astrocytoma, fibrillary astrocytoma, ganglioglioma, oligodendroglioma, ependymoma, and mixed glioma have been reported [5, 6, 10]. A minority of these patients will have a high-grade glioma such as an anaplastic glioma. However, the vast majority are low-grade astrocytomas, which can be further classified as either pilocytic (WHO Grade I) or fibrillary [10].

Cranial nerve monitoring was used to identify patterns of cranial motor nuclei displacement in 18 patients in Epstein's NYU series. The monitoring showed that diffuse pontine tumors tended to push the cranial nerve nuclei around the edge or left them in anatomical position on the floor of the IV ventricle. In contrast, tumors in the medulla tended to grow in an exophytic fashion and push the normal cranial nerve nuclei to a more ventral location [15]. This has significant implications for guiding the surgeon as he navigates the brainstem to attempt a safe resection. It also explains why resection or biopsy of pontine gliomas is fraught with danger.

Fisher and his group at Johns Hopkins and Stanford Hospitals reviewed the pathological specimens in 48 brainstem tumors [10]. The pathology specimens and MRI were reviewed by blinded independent observers. For all brainstem tumors, pilocytic tumors were most correlated with a location outside the pons such as cervicomedullary location, or dorsally exophytic. These patients showed a 5-year survival of 95% (SE = 5%) Fibrillary astrocytomas were associated with more rapid symptoms, cranial nerve palsy, pontine location, engulfment of the basilar artery and much worse survival (1-year survival 23%, (SE = 11%, $p<0.0001$). However, it should be noted that in the NYU series of 39 purely cervicomedullary tumors, 15 of the patients had a histological diagnosis of low-grade fibrillary astrocytoma, and most enjoyed a favorable outcome [20]. Thus, the fibrillary histology in that location does not confer a poor prognosis.

Traditionally, surgeons intuitively presumed neoplastic lesions found at the cervicomedullary junction expanded dorsally from the medulla down into the rostral cervical spine, typically to C1/2 but as far as T1. However, Epstein and Farmer in their retrospective MRI analysis of 88 brainstem gliomas, hypothesized that these tumors may actually derive from the cervical cord [8].

The authors supported their hypothesis with a sizeable series of MRI data on 44 cervicomedullary tumors. Thirty-two of these tumors were low-grade gliomas, the others were higher grade, including 4 anaplastic tumors. The authors hypothesized that there existed natural anatomical barriers of the brain which formed an obstruction to rostral growth of cervicomedullary tumors. They viewed brainstem tumors as spinal cord tumors which were limited by the pia, in the transverse plane, and exhibited rostral cylindrical growth until stopped by another anatomic barrier in the cranial caudal plane. The anatomical barriers in the cervicomedullary region in the medulla include the pyramidal decussating fibers, medial lemniscus, efferent fibers from the inferior olivary complex, and inferior cerebellar peduncle. These structures to some degree could deflect the rostral cylindrical growth of a cervical tumor. These barriers ultimately directed the tumor mass towards the obex, which appears the point of least resistance to tumor expansion. Subsequently, the lesion may enter the fourth ventricle at the level of the obex, because it appears to be the site of least resistance to rostral growth. The capacity for these anatomic structures to form a barrier is a relative one and may change over time. For example, the four anaplastic astrocytomas (WHO Grade III) in the cervicomedullary junction described in this series, broached the anatomically barriers and tumor invasion in these structures was observed. Although MR images confirm this cylindrical growth pattern for low-grade tumors, whether the growth begins at the medulla, expanding caudally or cervical cord expanding rostrally, to this day remains uncertain [8].

Surgical Treatment

The urgent, radical surgical treatment of cervicomedullary tumors is not a mandatory action as might be suggested by some. Consistent with all surgical procedures, the risk benefit ratio must be sufficiently in the patient's favor prior to embarking on the operation. Fortunately, in most patients the risks of surgical intervention are far outweighed by the risks of permanent deficit based on the natural history of tumor growth in this specific location.

Intraoperative judgment/experience, imaging, and monitoring is paramount in the safe resection of these lesions. These operations are best reserved for surgeons and centers that possess the intraoperative monitoring, ultrasound equipment, frameless navigation, and experience in removing intramedullary spinal cord tumors. The operation can be quite satisfying for the patient in the long run, but significant morbidity may be associated with the operation even in the most skilled hands. However, it is important for the surgeon to operate before the neurological sequelae irreversibly disable the patient [7]. The patients with the most long-standing and indolent course and benign pathology seem to fair the best under surgery. However, patients with progressive neurological deterioration and/or severe pain can receive stabilization and in some cases improvement with a judicious and timely surgical intervention. According to Epstein and colleagues these tumors are best conceptualized and approached by surgeons as intramedullary spinal cord tumors which extend rostrally to the medulla [20].

At our institution, we use a microscope with two sets of stereoscopic eyepieces situated 180° from each other, sometimes referred to as a "spine configuration." This configuration allows both the senior surgeon and the assistant to see precisely the same field

of view and permits the assistant to act in a true assistance role during the procedure. The patient is placed in the prone position with the head fixed in a Mayfield three point fixation head holder. For young children less than 3 years or patients with a very thin skull, a cerebellar head rest padded with soft gel rolls and a facial mask made from foam protect against pressure sores, venous hypertension, ocular compression, and abrasions. Newer head holders designed for young children have been utilized, which combine smaller skull pins and more gel rolls to hold and protect the skull. All other dependent parts of the body are padded.

We use intraoperative MRI guided frameless navigation and ultrasound during the resection of brainstem tumors. We have found real time navigation to be a useful in identifying the location of cysts and the extent of the tumor both in the cranial/caudal and ventral/dorsal direction. Intraoperative monitoring is performed by an experienced team of neurophysiologists and technicians. We prefer to use somatosensory evoked potentials, brainstem auditory evoked potentials, spontaneous EMG of the lower cranial nerves, and motor evoked potentials. Motor evoked potentials, when performed well are an integral adjuvant in the resection of spinal cord and brainstem tumors.

Transcranial stimulation evokes motor potentials by directly activating fast-conducting axons with a single electrical pulse. This potential, named a D-wave, provides an estimate of the percentage of functioning fast-conducting corticospinal fibers. For example, if the amplitude drops by 25%, a quarter of the fibers may have been injured. A series of short, high-frequency electrical pulses elicit muscle MEPs, which needle electrodes record from limb muscles with significant pyramidal innervation, such as thenar muscles or toe flexors. An on-off pattern indicates intact motor control, but their loss predicts only temporary loss of motor function. D-waves and muscle MEPs should be evaluated together. Although muscle MEP loss during resection predicts temporary disruption of motor function, if the D-wave amplitude stays above 50% the patient will have only a temporary motor deficit [7, 17].

Somatosensory evoked potentials (SEPs) can also be measured but do not correlate consistently with pre- and postoperative motor function. Our neurophysiologists also monitor the "H" reflex which in their hands seems to be more predicative of postoperative neurological deficits. Frequently, SSEPs are simply extinguished after the myelotomy. However, that does not predict a sensory deficit after the patient awakes. Almost all patients undergoing a radical resection will experience some deterioration of both evoked potentials and motor/sensory function. We use the monitoring as a guide, not as an "all or none" tool in which we halt resection and terminate the procedure, if there is a decrement in the signal. In addition, it is not uncommon that we will see transient cardiovascular instability (hypertension or bradycardia) or decrement in the monitoring during our resection. This is especially true as we get closer to the floor of the IV ventricle or chase tumor through the foramen of Luschka out to the ventral pial surface. During those periods we interrupt what we are doing and go to a different area of the tumor. The monitoring abnormalities and cardiovascular instability will often subside after awhile. If the decrement in the motor-evoked potential is persistent and significant, only then will we alter our procedure, but we do not uniformly terminate it.

A ventriculostomy is placed in the few patients who have preoperative hydrocephalus. A standard midline skin incision and approach is utilized. The only exception to that general approach is if the tumor is significantly eccentric the midline approach combined with a far lateral approach is employed. A cervical laminectomy, employing the high-speed drill is used to shave down the laminae bilaterally. If more than one laminectomy is needed we often resort to osteoplastic laminoplasties in which the laminae are replaced in situ at the end of the operation. Despite the increased surgical effort associated with osteoplastic laminoplasty there appears to be no Class I or II data which show that cervical kyphosis is less in those patients when compared to those who undergo laminectomies. A standard suboccipital craniectomy or craniotomy is performed and although there is no proven advantage of the craniotomy over the craniectomy, the craniotomy may permit a better cosmetic result, especially in older patients. We like to see the lateral sinus superiorly and a sufficient craniectomy at the foramen magnum, to provide full exposure, especially if any cysts are present at the rostral or caudal poles.

The frameless navigation provides the limits of the bone and dural opening as well as the location of cysts which may define the normal/tumor borders. Intraoperative ultrasound is performed after dural opening. The intraoperative ultrasound is performed by a neurosurgeon or a neurosurgeon with neuro-radiology support. After the dura is opened in the midline, the ultrasound is applied to help evaluate the extent of the tumor and where best to perform the myelotomy. Visual landmarks may be helpful but are not always present, so the fusion of the MRI-guided images and ultrasound give a more complete anatomical picture.

A significant amount of fragile blood vessels may be found on the surface of the posterior cervical cord and serve to obscure the surgical field at the site of the myelotomy. These can be coagulated if they are in the field of resection, as they are mostly small veins

and attempting to work around them increases the difficulty of the procedure. Obliterating this fine pial vasculature in this area is not associated with any neurological dysfunction in our experience.

The Nd:YAG or CO_2 laser system is a useful but not an indispensable tool in our hands for performing a satisfactory myelotomy, while minimizing neural injury. Alternatively, we perform the myelotomy with the same type of micro-blade we use for splitting a fissure. The myelotomy is usually placed in the midline over the central area of the tumor mass in a location where the tumor is closest to the pial surface. It is sometimes safest to start in the cervical region if the majority of the mass is noted to be there. The cervical cord may be rotated by the tumor mass so it is essential that the surgeon identify the dorsal root entry zone bilaterally and bisect the distance between the two dorsal root zones. The goal of the myelotomy is to get into the bulk of the tumor but to also avoid sacrificing one of the dorsal columns. If the tumor comes to the pial surface eccentric to the midline the myelotomy may be extended to that region without risk of damaging an entire dorsal column. If there is a cervical or medullary cyst, that cyst may serve as a target for myelotomy so that the normal/neoplastic interface is preserved at least initially. The myelotomy is then extended rostrally towards the medulla through the mass of the tumor. Often, we will perform stimulation using a hand-held cartouche, checking spontaneous EMG, over the dorsal surface of the medulla to ensure that we are visualizing tumor mass and not cranial nerve nuclei. We have found stimulation of the floor of the IVth ventricle and medulla useful primarily when we can see responsive EMG activity. Lack of stimulation often means that we have remained within the substance of the tumor and are not entering the cranial nerve nuclei or tracts.

The myelotomy is stopped proximal to the caudal pole of the tumor in the cervical cord. The goal is to stay within tumor and avoid microdissection through too much normal spinal cord in an ill-advised attempt to retrieve that last indistinguishable fragment of tumor. Extending the myelotomy further caudal or past the lowest extent of the tumor is unwise as it may cause normal cervical cord to be damaged. We do not view these operations as a curative in the surgical sense and often remind ourselves of this during the resection. While the goal is a safe radical excision of tumor, the difference between 90% tumor removal and less than 50% tumor removal in a particular patient does not always translate into an improved outcome or prolonged, progression-free survival, especially in patients with a more malignant histology. In contrast, a myelotomy extending over the bulge of the rostral pole of the tumor as it explodes through the obex and displaces or invades the medulla, seems to be safe in our hands. The tumor can often be visualized and carefully resected in a subpial plane using the cavitron. If present, a cyst "capping" the poles of the tumor alters the myelotomy placement or extent. The myelotomy can be started or extended to the tumor-cyst junction both rostrally and caudally. Then the incisions are continued over the solid part of the tumor until they meet in the middle.

The Cavitron ultrasonic aspirator (CUSA) is used to debulk the tumor. Microtips allow the surgeon to use the CUSA in these small spaces with greater ease. The surgeon begins debulking from the midportion of the tumor not the rostral or caudal poles, as these are the most hazardous areas to manipulate considering normal spinal tissue predominates in these areas. Gentle bipolar coagulation of residual tumor fragments with irrigating or nonstick microtips may also be useful at this stage of the procedure. Hemostasis is better achieved with gentle packing with gel foam or surgical rather than using micro-cautery. We are exceptionally careful and avoid incision into the floor of the IVth ventricle. Mapping has helped us understand the anatomy and in which direction the cranial nerves are deviated. Injury to areas around the stria medullaris is associated with significant morbidity and thus we avoid incisions in the floor of the IVth ventricle unless the tumor comes through the surface of the calamus scriptorius [15].

The determination of completion of the resection is clearly the most challenging part of the operation. It is a judgment issue based on surgical experience, configuration of the tumor, histopathology, accuracy of the monitoring, and utility of the intraoperative imaging. The extent of resection in a malignant cervicomedullary tumor does not appear to bear any correlation with progression-free survival [16]. In those patients a subtotal resection of tumor should be employed. A radical excision of a purely pilocytic cervicomedullary tumor with definable surgical planes and accurate monitoring and imaging may result in a near total excision of tumor and thus a better long-term outcome. It is for the subtotal resection, in which less than 50% of the tumor can be safely removed, that realistic limits must be established by judgment, real-time visualization of the tumor, and an understanding of the extent of infiltration of important anatomic structures.

We use pericranium or a manufactured dural substitute to close the dura watertight, but with a patulous graft. If an osteoplastic laminotomy is selected, we will replace the laminae and secure them with titanium or resorbable miniplates. A good fascial layer must be closed in a way to keep cerebrospinal fluid from leaking should it pass through the dural graft. The patient's history of previous surgery or radiotherapy must be taken into consideration in the closure as pa-

tients who received previous treatment or therapies may be at a higher risk of cerebrospinal fluid leak.

Radiotherapy

Radiation is most often deferred until after surgery because radical and even sometimes subtotal (<50%) surgical resection obviates the need for this therapeutic modality in the immediate postoperative period [16, 20]. In patients with a radical excision of a low-grade glioma in the cervicomedullary region, radiation should not be used until there is a recurrence [16]. The natural history of tumor growth in residual pilocytic astrocytomas of the cervicomedullary junction is quite slow. In patients older than 7 years, radiation therapy may be appropriate if only subtotal resection was possible, as in midline tumors, or if the tumor recurs or progresses. Radiation therapy may be withheld on younger patients unless they fail chemotherapy. Surgical treatment is preferable for all ages as a first-line treatment when indicated because of the numerous side effects of radiation therapy, including but not limited to neuro-cognitive deficits, developmental deficits, endocrine failure, vasculopathy, secondary neoplasms, and hearing loss. Should radiation therapy be required, radiation fields should include the T2-weighted abnormality as visualized by MRI.

Current methods to more effectively control radiation delivery being studied include conformal proton radiation therapy, gamma knife radiosurgery, stereotactic fractionated, and intensity-modulated radiotherapy. Proton radiation therapy (PRT) or Gamma Knife Radiosurgery may, in the future, prove to be a good option for progressive or recurrent low-grade astrocytomas of the brainstem. Hug et al. analyzed 27 pediatric patients in a 2002 study who were treated with PRT. Five of these patients' tumors were located in the brainstem. At a follow-up period of approximately 3 years, local control and survival was 60%. PRT is well tolerated, and children with local control maintain their performance status [13]. PRT seems a safe and efficacious 3-D conformal treatment modality that may be considered when radical surgical resection fails or can not be implemented [3]. As more efficient modes of irradiating brainstem gliomas prove beneficial, radiotherapy may play a broader role in their adjuvant treatment. Currently, surgery remains the most effective therapy for cervicomedullary tumors.

Chemotherapy

Opinions differ about the role of chemotherapy in treatment of cervicomedullary gliomas. Some argue that it should be used as the initial treatment for children under 10 years old or for older patients whose tumors have progressed after irradiation. Others recommend it only in children when surgery has failed or as an adjuvant therapy [21]. Single- and multidrug regimens have been tested. Actinomycin-D and vincristine allows deferment of radiotherapy in children younger than 5 years old. Alternatively, carboplatin, currently the most effective drug, can be used alone or in combination with vincristine [21]. The precise role of chemotherapy in the treatment of cervicomedullary tumors is yet to be defined.

Outcome/Prognosis/Quality of Life

Due to the low-grade nature of the majority of tumors in the cervicomedullary area, surgery provides, in general, an auspicious prognosis. However, this surgery is not performed without risks. The complications reported in this type of surgery are not minor. They include quadriparesis, sleep apnea, transient motor loss, cranial nerve palsy, impaired position sense, and spasticity [5]. The most common complication we have seen besides worsening cranial nerve paresis and motor loss include posterior fossa syndrome-associated supranuclear cranial nerve palsy, paresis, emotional lability, and mutism which may take weeks or months to resolve. This syndrome is known to occur with many types of posterior fossa tumor operations. The etiology is not clear, but injury to the vermis or cerebellar peduncles has been implicated in causing this not uncommon syndrome. Nevertheless, we have seen it with and without splitting the vermis to gain access to the brainstem. Diffusion MRI sequences often demonstrate involvement of the tracts from the cerebellum to the thalamus in this syndrome.

The most complete long-term analysis we have of this tumor was provided in 1997 by Weiner et al. from the NYU group [20]. They reviewed the experience with 39 consecutive patients with a cervicomedullary tumor in the MRI era. The male-to-female ratio was 26:13. Mean age of diagnosis was 14 years old and the mean duration of symptoms was 24 weeks, with a range of 1–168 weeks. In keeping with the two subsets of presentation, 20 patients presented with lower cranial nerve dysfunction and 19 presented with motor or spinal cord dysfunction. Twelve patients had a "gross" total resection, seven had a near total resection (90%), 15 had a subtotal resection (50%–90%), and 5 had a partial resection (<50%). The majority of the tumors (n = 18) were low-grade astrocytomas (WHO Grade I or II). The rest were mixed gliomas, ependymomas, gangliogliomas, and high-grade gliomas. The high-grade tumors experienced the most rapid and symptomatic tumor progression.

The 5-year progression-free survival was 60%, and at 5 years 89% of the patients were alive.

If the symptoms were present longer than 15 weeks, there was a longer progression-free survival. The better neurological grade predicted a better neurological outcome after surgery and at follow-up. The worse neurological grade often meant significant postoperative deficits. In summary, early surgical intervention in patients with good neurological grades and benign histology resulted in the best neurological outcomes and the longest progression-free survival [20].

Follow-up

Many patients will require extensive in-patient rehabilitation after radical excision of a cervicomedullary tumor even when the outcome appears good. Since surgery usually entails suboccipital craniotomies and cervical laminectomies/laminotomies, cervical kyphosis may become a problem for the young pediatric patient. This has been an uncommon observation at our institution unless subsequent adjuvant therapy was required. Also, serial surveillance MRI and neurological exams should be performed to monitor tumor recurrence, and spinal deformity, beginning immediately postoperatively and continuing on a yearly basis.

Summary

There has been a significant evolution of thought on radical surgery for intra-axial tumors of the cervicomedullary junction in the past two decades. In the past it was assumed that, like diffuse pontine gliomas, biopsy or resection of these tumors would result in unacceptable morbidity. However, it appears that cervicomedullary tumors represent a unique subset of intra-axial brainstem tumors. Cervicomedullary tumors are often histologically benign or low grade, possess some defined surgical planes, and an aggressive surgical posture is justified based on the satisfactory neurological outcome and improved progression-free survival. An aggressive surgical procedure can often result in neurological recovery or stability with long-term survival. The surgery is not risk free, and the resultant morbidity is not insignificant; nevertheless, surgery appears to afford an improvement on the natural history of this entity. Subtotal or radical resection of a pilocytic astrocytoma in the cervicomedullary junction improves the overall prognosis, long-term survival, and quality of life of patients with this tumor.

References

1. Bricolo A, Turazzi S, Cristofori L, Talacchi A. Direct surgery for brainstem tumours. Acta Neurochir Suppl (Wien) 1991;53:148–158
2. Chitnavis B, Phipps K, Harkness W, Hayward R. Intrinsic brainstem tumours in childhood: a report of 35 children followed for a minimum of 5 years. Br J Neurosurg 1997;11:206–209
3. Cohen KJ, Broniscer A, Glod J. Pediatric glial tumors. Curr Treat Options Oncol 2001;2:529–536
4. Epstein F, McCleary EL. Intrinsic brain-stem tumors of childhood: surgical indications. J Neurosurg 1986;64:11–15
5. Epstein F, Wisoff J. Intra-axial tumors of the cervicomedullary junction. J Neurosurg 1987;67:483–487
6. Epstein F, Wisoff JH. Intrinsic brainstem tumors in childhood: surgical indications. J Neurooncol 1988;6:309–317
7. Epstein F, Wisoff JH. Surgical management of brain stem tumors of childhood and adolescence. Neurosurg Clin N Am 1990;1:111–121
8. Epstein FJ, Farmer JP. Brain-stem glioma growth patterns. J Neurosurg 1993;78:408–412
9. Epstein N, Epstein F, Allen JC, Aleksic S. Intractable facial pain associated with a ganglioglioma of the cervicomedullary junction: report of a case. Neurosurgery 1982;10:612–616
10. Fisher PG, Breiter SN, Carson BS, Wharam MD, Williams JA, Weingart JD, et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000;89:1569–1576
11. Gilles FH, Leviton A, Hedley-Whyte ET, Sobel E, Tavare CJ, Sobel RS, et al. Childhood brain tumors that occupy more than one compartment at presentation. Multiple compartment tumors. J Neurooncol 1992;14:45–56
12. Grant GA, Avellino AM, Loeser JD, Ellenbogen RG, Berger MS, Roberts TS. Management of intrinsic gliomas of the tectal plate in children. A ten-year review. Pediatr Neurosurg 1999;31:170–176
13. Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredo LN, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlenther Onkol 2002;178:10–17
14. Landolfi JC, Thaler HT, DeAngelis LM. Adult brainstem gliomas. Neurology 1998;51:1136–1139
15. Morota N, Deletis V, Lee M, Epstein FJ. Functional anatomic relationship between brain-stem tumors and cranial motor nuclei. Neurosurgery 1996;39:787–793; discussion 793–784
16. Pierre-Kahn A, Hirsch JF, Vinchon M, Payan C, Sainte-Rose C, Renier D, et al. Surgical management of brain-stem tumors in children: results and statistical analysis of 75 cases. J Neurosurg 1993;79:845–852
17. Robertson PL, Allen JC, Abbott IR, Miller DC, Fidel J, Epstein FJ. Cervicomedullary tumors in children: a distinct subset of brainstem gliomas. Neurology 1994;44:1798–1803

18. Rubin G, Michowitz S, Horev G, Herscovici Z, Cohen IJ, Shuper A, et al. Pediatric brain stem gliomas: an update. Childs Nerv Syst 1998;14:167–173
19. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP. Diagnosis and management of pediatric brain-stem gliomas. J Neurosurg 1986;65:745–750
20. Weiner HL, Freed D, Woo HH, Rezai AR, Kim R, Epstein FJ. Intra-axial tumors of the cervicomedullary junction: surgical results and long-term outcome. Pediatr Neurosurg 1997;27:12–18
21. Young Poussaint T, Yousuf N, Barnes PD, Anthony DC, Zurakowski D, Scott RM, et al. Cervicomedullary astrocytomas of childhood: clinical and imaging follow-up. Pediatr Radiol 1999;29:662–668

Desmoplastic Infantile Gangliogliomas

31

Jeffrey P. Blount

Introduction – 432

Epidemiology – 432

Spectrum and Clinical Signs – 432

Diagnostics – 432
Imaging Characteristics: Synopsis
CT/MRI Characteristics

Staging and Classification – 432

Treatment – 433
Synopsis
Surgical Treatment
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 434

Follow-up/Specific Problems and Measures – 434

Future Perspectives – 434

References – 434

Introduction

Desmoplastic infantile gangliogliomas (DIGs) are rare, recently described typically large cystic, supratentorial tumors that occur predominantly in infants. It is important that they be recognized and properly diagnosed because they generally show a favorable response to surgical therapy in spite of malignant radiographic and histopathologic features.

Epidemiology

Desmoplastic infantile gangliogliomas are rare supratentorial cystic lesions [17, 18] They occur virtually uniformly in children under 2 years of age although a small number have been reported in teenage children [1, 5]. The nearly uniform early age of onset initially fostered speculation that DIGs were true prenatal or congenital neoplasms. This was later disproved when teenagers harboring DIGs were observed [1, 5]. The tumor was first described in 1987 by Vandenburg et al. and there are presently about 90 reviewed cases in the world literature [21]. The estimated incidence is 0.4% of all intracranial neoplasms and virtually all are described in children under 2 years of age [20, 22]. The largest single case series included 25 cases [4]. No sex or ethnic predilection is apparent.

Spectrum and Clinical Signs

DIGs are characteristically voluminous lesions at diagnosis [18]. The most common symptoms are macrocephaly (60%), hemiparesis, and signs of elevated intracranial pressure (distended fontanel, split sutures, sun setting) [16, 18]. Unlike dysembryoplastic neuroepithelial tumors (DNETs), which share some histological features, seizures are less common and occur in only about 20% [18]. Impairment of consciousness is conspicuously rare [1]. The large size with sparing of consciousness attests to the chronic nature of the lesion. The clinical history is however typically short which may suggest that the tumor grows slowly and asymptomatically for a long period until it crosses a critical threshold and becomes symptomatic.

Diagnostics

Imaging Characteristics: Synopsis

Imaging studies reveal large, dural based, cystic, supratentorial masses that demonstrate vigorous contrast enhancement [11, 17–19] on both CT and MRI images. There may be a moderate degree of edema. As such they share imaging characteristics with decidedly more malignant tumors [9, 11, 18].

CT/MRI Characteristics

The solid component of the tumor is hyperdense on nonenhanced CT and shows intense hyperdensity with administration of contrast [18, 19]. The adjacent leptomeninges also typically demonstrate vigorous contrast enhancement (which corresponds histologically with the vigorous desmoplastic reaction characteristic of these lesions; see below). Septations may be evident within the cystic component of the lesion and also typically enhance with contrast [18, 19]. At least one study has suggested that the tumor is initially solid and becomes more cystic with passing time [20].

On T1-weighted MRI sequences without contrast the cyst is hypodense and the solid portion is hypo- to isodense with surrounding brain [9, 14]. Administration of contrast material reveals bright enhancement of the solid portion of the tumor and cyst septations. On T2-weighted sequences the cyst is hyperdense while the solid component is usually hypodense but may show some heterogeneity [1, 19, 18]. Other glioneuronal tumors may be differentiated by MR characteristics: gangliogliomas and pleomorphic xanthoastrocytomas are usually hyperintense on T2-weighted sequences [20]. Dysembryoplastic neuroepithelial tumors (DNETs) also characteristically show minimal contrast enhancement [14].

Staging and Classification

Dysembryoplastic infantile gangliogliomas are too recently described for a staging or classification system to have been developed. There is however a characteristic histological appearance and significant controversy exists surrounding nosologic characterization of these lesions [12].They were initially described as superficial cerebral astrocytomas (SCA) or desmoplastic astrocytoma of infancy (DAI) but were later called desmoplastic infantile gangliogliomas when a ganglion cell component was recognized via immunohistochemistry [7].

The desmoplastic infantile ganglioglioma is histologically distinguished by a prominent desmoplasia, a mitotically active component, and positive immunostaining for neuronal elements (vimentin, neuron specific enolase or S-100) [7, 18]. Some authors have suggested that Microtubule-associated protein-2 (AP18) and neuron-specific B-tubulin (TUJ-1) were more sensitive in detecting neural elements

than synaptophysin [2]. MIB and p53 labeling are minimal [11]. Recognition of the desmoplasia and positive neuronal staining is important because the more cellular elements may suggest a markedly more malignant tumor [11]. Conventional ganglion cell tumors do not exhibit the pronounced desmoplastic reaction that characterizes the DIG [10]. The histological source of the fibrous elements remains controversial [11]. A number of theories have been advanced. One theory holds that the desmoplasia arises from neoplastic subpial astrocytes as a response to the environment adjacent to the dura [11]. Others suggest that the desmoplasia arises from pluripotential astrocytic cells capable of collagen synthesis or that the mesenchymal elements are under control of Schwann cells [12]. Clearly the etiology of the desmoplasia is not currently resolved. Identifying the neuronal elements allows the tumor to be distinguished from the earlier described, histologically similar desmoplastic astrocytoma of infancy (DAI). Immunostaining in DAI reveals extensive GFAP (+) staining but no evidence of neuronal lineage. Whether positive immunostaining (in the absence of histological evidence of neuronal hyperplasia) is sufficient to classify a tumor as to neuronal lineage has been questioned.

These difficulties and a shared benign clinical course have prompted some authors to suggest that all the desmoplastic tumors of infancy be combined under the broad classification of desmoplastic tumors of infancy [7]. Proliferation indices are usually low with Ki67 labeling indices ranging from 0.5% to 5%, which is consistent with the benign nature of these lesions [11].

Treatment

Synopsis

Maximal surgical resection is the treatment of choice for desmoplastic infantile gangliogliomas. The role of adjuvant therapy is incompletely resolved but there is an increasing trend that chemotherapy be reserved for patients with radiographic evidence of disease progression in whom no further surgical resection can be performed. Radiotherapy plays no significant role in the clinical management of the DIG.

Surgical Treatment

Although the natural history of the DIG is incompletely understood, the typically large size of the lesion with associated mass effect and reported favorable response to surgery mandate surgery as an initial therapy [8]. Long-term control is the rule following complete resection and has been multiply demonstrated following incomplete resection [1, 8, 16, 18]. Biopsy has little role and may lead to erroneous diagnosis and misguided adjunctive treatment [8]. The superficial location and cystic quality of the lesions may facilitate exposure and resection as the cyst is often filled with clear or xanthochromic fluid [18]. Difficulty can arise related to infiltration of eloquent cortex or rich vascular supply in small children (with associated small blood volumes) [4, 11]. A lack of cleavage plane between the tumor and surrounding normal brain can occasionally be problematic particularly when the lesion abuts eloquent cortex [18]. These characteristically large lesions in small children mandate careful surgical planning and compulsive attention to hemostasis [8]. Intraoperative deaths from exsanguination have been reported [8]. Some authors advocate staging the surgical resection to help reduce the risk of acute hemorrhage. Tumor size and degree of attachment to the deep vascular structures are further important considerations in determining whether gross total extirpation can be undertaken in a single setting [18]. If complete excision can be obtained, only follow-up imaging is necessary. If a complete resection cannot be obtained then consideration of a second or additional procedure should be entertained to obtain as complete a resection as possible.

Radiotherapy

Because DIGs occur in infants and are highly responsive to surgical treatment there is almost no role for radiotherapy in their treatment. Only those lesions showing progression after maximum possible surgical removal and adjuvant chemotherapy should be considered for radiotherapy as a salvage intervention [18].

Chemotherapy

Chemotherapy is typically reserved for DIGs that have been subtotally resected and have shown evidence of progression on follow-up imaging. The presence of residual disease on postoperative imaging is no longer an indication for adjuvant therapy per se because of multiple reports demonstrating either disease stability or spontaneous regression of residual disease following surgical resection without adjuvant therapy [1, 17, 18] An exception may be made for deeply seated lesions that may demonstrate a more serious prognosis [1, 4]. Others have proposed that residual disease in the presence of a high MIB labeling index should prompt a more aggressive approach to adjuvant therapy [17].

Prognosis/Quality of Life

In general the prognosis for desmoplastic infantile gangliogliomas is favorable following complete or even partial surgical resection [15]. Rare exceptions do occur and locally metastatic disease and fatal outcomes have been reported [3]. The overall favorable prognosis contrasts sharply with the anaplastic features often witnessed in the solid portion of the tumor [18]. One factor that appears very important in determining prognosis is the location of the lesion [6]. Characteristically, superficial lesions are amenable to surgical resection and demonstrate a favorable prognosis. Complete excision is not mandatory for a good outcome. Following subtotal resection [18] many lesions will remain stable or show spontaneous regression. Takeshima et al. demonstrated postoperative regression in two cases of DIG and provided immunohistochemical markers to support the hypothesis that the mechanism involved was increased apoptosis [17]. Poor outcomes have been rarely reported in DIGs and are usually associated with deep-seated or brain stem locations or those with high MIB labeling indices [13].

Follow-Up/Specific Problems and Measures

Serial imaging is appropriate for patients who have under gone craniotomy for removal of a DIG. An immediate postoperative MRI scan is typically repeated at 6-month intervals initially and then annually once disease stability has been established. Late recurrence has not been described, so long-term imaging over the course of a lifetime does not appear necessary following complete resection. Reoperation for further resection is indicated in the event of recurrent tumor or residual disease that shows progression on serial imaging. If reoperation is not an option due to recurrence in eloquent cortex then adjunctive chemotherapy is an appropriate consideration [1].

Future Perspectives

Further experience with desmoplastic infantile gangliogliomas may yield further insight into the nature and etiology of the intense desmoplasia that characterize these lesions. Relatively little is known about the genomic characteristics of these lesions at present. As molecular understanding of the glial-neuronal tumors increases it is likely that the full spectrum of these fascinating lesions will be more precisely defined. This may enable the evolution of a classification and staging system that accurately reflects the neurobiology and natural history of desmoplastic infantile gangliogliomas. An improved understanding of natural history may further guide rational utilization of adjuvant therapy.

References

1. Bachli H, Avoledo P, Gratzl O, et al. Therapeutic strategies and management of desmoplastic infantile ganglioglioma: two case reports and literature overview. Childs Nerv Syst 2003;19:359–366
2. Craver RD, Nadell J, Nelson JS. Desmoplastic infantile ganglioglioma. Pediatr Dev Pathol 1999;2:582–587
3. De Munnynck K, Van Gool S, Van Calenbergh F, et al. Desmoplastic infantile ganglioglioma: a potentially malignant tumor? Am J Surg Pathol 2002;26:1515–1522
4. Duffner PK, Burger PC, Cohen ME, et al. Desmoplastic infantile gangliogliomas: an approach to therapy. Neurosurgery 1994;34:583–589; discussion 589
5. Galatioto S, Gullotta F. Desmoplastic non-infantile ganglioglioma. J Neurosurg Sci 1996;40:235–238
6. Komori T, Scheithauer BW, Parisi JE, et al. Mixed conventional and desmoplastic infantile ganglioglioma: an autopsied case with 6-year follow-up. Mod Pathol 2001;14:720–726
7. Kros JM, Delwel EJ, de Jong TH, et al. Desmoplastic infantile astrocytoma and ganglioglioma: a search for genomic characteristics. Acta Neuropathol (Berl) 2002;104:144–148
8. Mallucci C, Lellouch-Tubiana A, Salazar C, et al. The management of desmoplastic neuroepithelial tumours in childhood. Childs Nerv Syst 2000;16:8–14
9. Martin DS, Levy B, Awwad EE, et al. Desmoplastic infantile ganglioglioma: CT and MR features. AJNR Am J Neuroradiol 1991;12:1195–1197
10. McLendon RE, Provenzale J. Glioneuronal tumors of the central nervous system. Brain Tumor Pathol 2002;19:51–58
11. Rout P, Santosh V, Mahadevan A, et al. Desmoplastic infantile ganglioglioma–clinicopathological and immunohistochemical study of four cases. Childs Nerv Syst 2002;18:463–467
12. Rushing EJ, Rorke LB, Sutton L. Problems in the nosology of desmoplastic tumors of childhood. Pediatr Neurosurg 1993;19:57–62
13. Setty SN, Miller DC, Camras L, et al. Desmoplastic infantile astrocytoma with metastases at presentation. Mod Pathol 1997;10:945–951
14. Shin JH, Lee HK, Khang SK, et al. Neuronal tumors of the central nervous system: radiologic findings and pathologic correlation. Radiographics 2002;22:1177–1189
15. Sperner J, Gottschalk J, Neumann K, et al. Clinical, radiological and histological findings in desmoplastic infantile ganglioglioma. Childs Nerv Syst 1994;10:458–462; discussion 462–453
16. Sugiyama K, Arita K, Shima T, et al. Good clinical course in infants with desmoplastic cerebral neuroepithelial tumor treated by surgery alone. J Neurooncol 2002;59:63–69

17. Takeshima H, Kawahara Y, Hirano H, et al. Postoperative regression of desmoplastic infantile gangliogliomas: report of two cases. Neurosurgery 2003;53:979–983; discussion 983–974
18. Tamburrini G, Colosimo C Jr, Giangaspero F, et al. Desmoplastic infantile ganglioglioma. Childs Nerv Syst 2003;19:292–297
19. Tenreiro-Picon OR, Kamath SV, Knorr JR, et al. Desmoplastic infantile ganglioglioma: CT and MRI features. Pediatr Radiol 1995;25:540–543
20. Tseng JH, Tseng MY, Kuo MF, et al. Chronological changes on magnetic resonance images in a case of desmoplastic infantile ganglioglioma. Pediatr Neurosurg 2002;36:29–32
21. Vandenberg SR, Herman MM, Rubinstein LJ. Embryonal central neuroepithelial tumors: current concepts and future challenges. Cancer Metastasis Rev 1987;5:343–365
22. VandenBerg SR, May EE, Rubinstein LJ, et al. Desmoplastic supratentorial neuroepithelial tumors of infancy with divergent differentiation potential ("desmoplastic infantile gangliogliomas"). Report on 11 cases of a distinctive embryonal tumor with favorable prognosis. J Neurosurg 1987;66:58–71

Pleomorphic Xanthoastrocytoma

32

Jean-Pierre Farmer, P. Daniel McNeely

Historical Background – 438

Epidemiology – 438

Symptoms and Clinical Signs – 438

Case Presentation – 438

Diagnostics – 439

Pathology – 439

Treatment – 440

Prognosis – 440

Future Perspectives – 441

References – 441

Historical Background

The pleomorphic xanthoastrocytoma (PXA) is a rare tumor type of astrocytic origin that was first described as a distinct neoplastic entity by Kepes and coauthors in 1979 [11]. The PXA was added as a separate diagnosis to the 1993 World Health Organization (WHO) classification of central nervous system tumors [12]. Prior to the advent of immunostaining, PXAs were thought to represent neoplasms of mesenchymal origin [10]. This was due to the abundant reticulin network often found in these tumors, and also due to the resemblance between the tumor's lipidized neoplastic glial cells and foamy histiocytes, or "xanthoma" cells. This resemblance explains why PXAs had been previously labeled as xanthomas or xanthosarcomas [9]. The PXAs superficial location with intense desmoplastic reaction causing adherence to adjacent dura no doubt contributed to the confusion concerning the origin of this neoplasm. These tumors were also occasionally designated giant cell glioblastomas due to the presence of aggressive histological features including bizarre multinucleated giant cells. In contrast to mesenchymal tumors and giant cell glioblastomas, PXAs are associated with an intermediate clinical course. Their pathological recognition therefore has important prognostic implications.

Epidemiology

Most reported cases of PXA are derived from isolated case reports and small-to-moderate sized series. The incidence of this neoplasm thus remains unknown. Pleomorphic xanthoastrocytomas are believed to account for less than 1% of all astrocytic neoplasms [10]. The largest published series consists of 71 cases reported by Giannini and coauthors [6] from the Mayo Clinic. In this series, mean age at diagnosis was 26 +/- 16 years, with a median age of 22 years and range of 5 to 82 years. No sex predilection has yet been identified. Since 1993, when PXAs were added to the WHO classification of central nervous system (CNS) tumors, only one such neoplasm out of 182 newly diagnosed pediatric CNS tumors has been identified at our institution. In the previous decade, one additional PXA, originally misdiagnosed as a gliosarcoma, could be derived from our archives.

Symptoms and Clinical Signs

Due to the lesion's superficial location involving the cerebral cortex, seizures are the most common mode of presentation for patients with PXAs [6]. Other neurological symptoms and signs depend on tumor localization within the CNS. PXAs are almost exclusively supratentorial, although cases have been reported in the retina [24], spinal cord [8], and cerebellum [13, 15, 22]. The most common location of these tumors is the temporal lobe, followed by the parietal, frontal, and occipital lobes. Approximately half of the tumors have a cystic component [6].

Case Presentation

This 6-year-old right-handed male initially presented with a complex partial seizure in April of 1999. An electroencephalogram (EEG) was done at this point and was normal. Imaging was not done initially. He experienced a second seizure in July, 1999. He was started on carbamazepine and did not have any further seizures. Neuroimaging done following the second seizure revealed a left medial temporal lobe tumor that was abutting the pial surface at the level of the tentorial incisura (Fig. 1). Incidental note was also made of low-lying cerebellar tonsils with a small asymptomatic syrinx in the cervical spinal cord (Fig. 2). He was followed initially at another center prior to being referred to our center. A neuropsychological assessment was completed and demonstrated average to above average cognitive abilities. Preoperative neurological examination was normal.

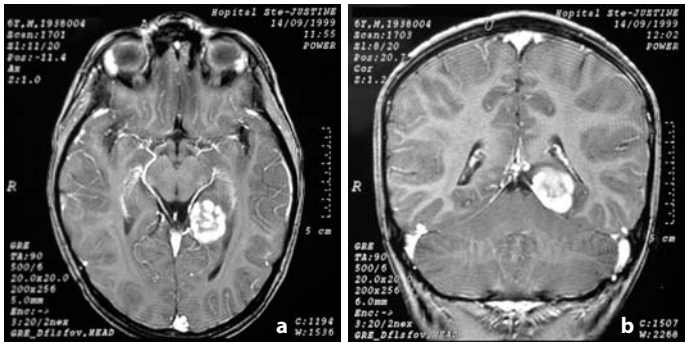


Fig. 1 **a** Axial T1-weighted gadolinium enhanced MRI scan demonstrating a left medial occipitotemporal pleomorphic xanthoastrocytoma with marked contrast enhancement and absence of a cystic component. **b** The lesion is intra-axial and abuts the pial surface medially, as seen on this coronal T1-weighted gadolinium enhanced MRI scan.

Fig. 2 Sagittal T1-weighted MRI scans demonstrating low lying cerebellar tonsils and a small syrinx in the lower cervical spinal cord

Surgical resection was carried out in January, 2000 using a posterior interhemispheric ("pineal-type") approach. Histopathology demonstrated this to be a PXA. Postoperative imaging revealed residual tumor, therefore a repeat resection (this time complete) was carried out in March, 2000. The patient has not experienced any further seizures. He has an incongruous right hemianopsia only detectable by formal Goldman perimetry, but is otherwise neurologically intact with a postoperative neuropsychological assessment identical to the preoperative one. Most recent imaging in September, 2003 did not show any evidence of residual or recurrent tumor (Fig. 3). He has not received any adjunctive therapy and will be followed with yearly magnetic resonance imaging (MRI) scans. The caudal excursion of his cerebellar tonsils, and the cervical spinal cord syrinx have both regressed on serial imaging, and he has remained asymptomatic as far as these lesions are concerned.

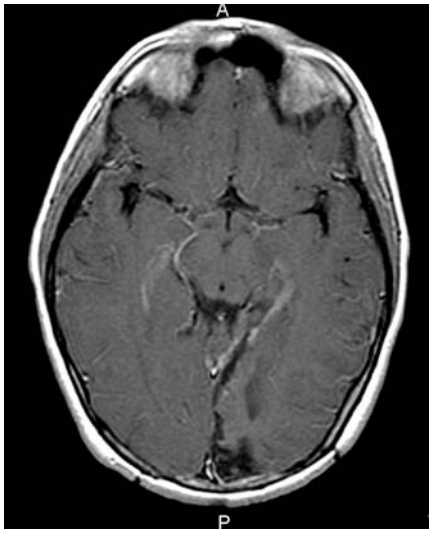


Fig. 3 Follow-up MRI scan obtained 3 years following a posterior interhemispheric approach for gross total resection of the lesion seen in Fig. 1. This axial T1-weighted gadolinium enhanced sequence does not show any evidence of residual or recurrent tumor.

Diagnostics

On computed tomography (CT), PXAs are typically hypodense with distinct borders. Calcification is not a common feature of these lesions. Approximately half of the tumors have a cystic component [6]. A mural nodule may be present. These tumors are usually hypo- or isointense to brain on T1-weighted MRI, and hyperintense on T2-weighted sequences. Marked contrast enhancement is usually noted on both CT and MRI.

Pathology

As suggested by its name, these tumors have a variable, or pleomorphic, histological appearance. Fibrillary neoplastic astrocytes are found amongst multinucleated giant cells with variable size and stain-

ing characteristics. Many cells in this neoplasm also contain intracellular accumulation of lipid droplets (Fig. 4). Other common features include the presence of eosinophilic granular bodies, lymphocyte collections, and a pericellular reticulin network [10]. Mitotic figures are present in approximately two thirds of cases. Necrosis is encountered in occasional cases, and endothelial proliferation is rare. Glial fibrillary acidic protein (GFAP) reactivity is usually present on immunostaining [7]. Pleomorphic xanthoastrocytomas correspond histologically to WHO Grade II [10]. The designation of "pleomorphic xanthoastrocytoma with anaplastic features" is suggested for tumors with elevated mitotic activity or necrosis.

Pleomorphic xanthoastrocytoma have also been described as occurring as part of combination tumors. One such example of this rare occurrence is the composite PXA-ganglioglioma [19, 23]. Neuronal differentiation of PXA tumor cells has been suggested as the possible explanation for this composite tumor [20].

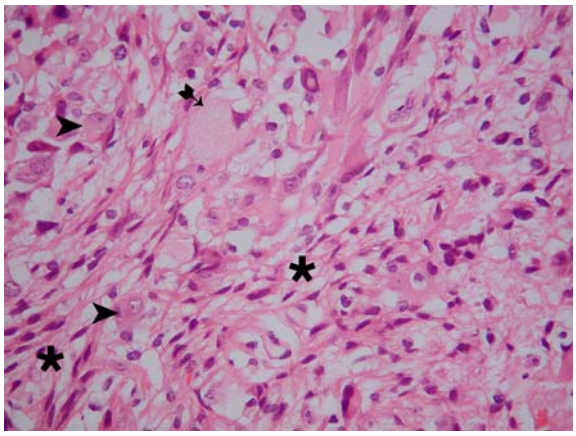


Fig. 4 Typical histological appearance of a PXA on a routine H&E stain. The tumor is composed of both spindled (*asterisks*) and epithelioid cells (*arrow heads*). They are very pleomorphic, but there is neither mitotic activity, nor microvascular proliferation, nor necrosis. One very large cell (*arrow*) has a finely vacuolated cytoplasm due to lipid accumulation. (Courtesy of Dr. S. Albrecht, Department of Pathology, Montreal Children's Hospital).

Treatment

Surgical resection is generally recommended as the primary diagnostic and therapeutic intervention. An incomplete resection has been associated with a higher recurrence rate [18]. The histology often progresses at the time of recurrence. For this reason, repeat surgery should be attempted for an incomplete resection, when feasible. The surgical approach must be tailored to the location of the lesion. Neuronavigation can be a particularly useful adjunct to the resection of PXAs. The superficial location of these tumors and their intimate relationship to fixed dural surfaces minimizes errors in accuracy of frameless stereotaxy which inevitably occur due to intraoperative shift. Intraoperative ultrasonography may also be helpful as these lesions are quite echogenic. Since these tumors often do not respect sulcal anatomy, "real-time" ultrasound guidance can help ascertain completeness of resection, which is believed to have important prognostic implications.

There is no consensus on the use of adjuvant treatment modalities. Carboplatin and vincristine chemotherapy has been used as an adjunct to surgical resection in one reported case [2]. Other authors have reported success with ACNU and VM 26 chemotherapy at the time of recurrence with successful remission for 2.5 and 5.5 years (in two separate cases) [21]. Temozolomide was used at recurrence in one reported case of an 11-year-old patient who eventually passed away as a result of disease progression [14]. Radiotherapy has been delivered in the immediate postoperative period in patients with PXAs with anaplastic features, and has also been reserved for use at the time of tumor recurrence [3, 4, 14, 21]. Tumor doses of 50–60 Gy have been reported [14, 21]. Stereotactic radiosurgery with a margin dose of 18 Gy delivered with a gamma knife unit has also been described following a subtotal resection [1].

Prognosis

Overall survival of patients who have PXAs is approximately 83% at 5 years with progression-free survival of 72% at 5 years and 61% at 10 years [6]. Most cases follow a benign clinical course, despite subtotal resection. This being said, extent of surgical resection is believed to correlate with recurrence-free survival [6, 18]. Furthermore, seizure control may be superior in patients who have undergone a complete lesionectomy, providing further impetus for obtaining a complete surgical resection of these tumors [17].

Histological features may also play a role in predicting the likelihood of recurrence. Specifically, an elevated mitotic index, and the presence of necrosis have been shown to reduce overall survival [6, 16]. Malignant progression of PXAs has been documented on numerous occasions [3–5, 14, 16]; therefore, careful follow-up is suggested for patients with these tumors, and repeat surgery, if feasible, should be recommended if the initial resection is incomplete.

Future Perspectives

Given the rarity of the PXA, pooled data from multiple centers is a potential strategy to help gain further insight into the natural history and optimal management of this neoplasm. Given the available literature, we consider that a complete resection, followed by serial clinical and MRI follow-up should be the preferred initial treatment strategy. The role of adjuvant chemotherapy and radiotherapy is unclear at present, and should likely be reserved for recurrent cases.

References

1. Arita K, Kurisu K, Tominaga A, et al. Intrasellar pleomorphic xanthoastrocytoma: case report. Neurosurgery 2002;51:1079–1082.
2. Cartmill M, Hewitt M, Walker D, et al. The use of chemotherapy to facilitate surgical resection in pleomorphic xanthoastrocytoma: experience in a single case. Childs Nerv Syst 2001;17:563–566.
3. Chakrabarty A, Mitchell P, Bridges LR, et al. Malignant transformation in pleomorphic xanthoastrocytoma–a report of two cases. Br J Neurosurg 1999;13:516–519.
4. Charbel FT. Pleomorphic xanthoastrocytoma with malignant progression. Surg Neurol 1998;50:385–386.
5. de Tella OI Jr, Herculano MA, Prandini MN, et al. Malignant transformation of pleomorphic xanthoastrocytoma: case report. Arq Neuropsiquiatr 2003;61:104–106.
6. Giannini C, Scheithauer BW, Burger PC, et al. Pleomorphic xanthoastrocytoma: what do we really know about it? Cancer 1999;85:2033–2045.
7. Giannini C, Scheithauer BW, Lopes MB, et al. Immunophenotype of pleomorphic xanthoastrocytoma. Am J Surg Pathol 2002;26:479–485.
8. Herpers MJ, Freling G, Beuls EA. Pleomorphic xanthoastrocytoma in the spinal cord. Case report. J Neurosurg 1994;80:564–569.
9. Kepes JJ, Kepes M, Slowik F. Fibrous xanthomas and xanthosarcomas of the meninges and the brain. Acta Neuropathol (Berl) 1973;23:187–199.
10. Kepes JJ, Louis DN, Giannini C, et al. Pleomorphic xanthoastrocytoma. In: Cavenee WK, editor. World Health Organization Classification of Tumours: Pathology and genetics of tumours of the nervous system. Lyon: International Agency for Research on Cancer Press; 2000. p. 52–54.
11. Kepes JJ, Rubinstein LJ, Eng LF. Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. A study of 12 cases. Cancer 1979;44:1839–1852.
12. Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumours of the central nervous system. World Health Organization, 2nd edn. New York: Springer-Verlag; 1993.
13. Kumar S, Retnam TM, Menon G, et al. Cerebellar hemisphere, an uncommon location for pleomorphic xanthoastrocytoma and lipidized glioblastoma multiformis. Neurol India 2003;51:246–247.
14. Leonard N, Alcutt DA, Farrell MA. Fatal pleomorphic xanthoastrocytoma with meningeal gliomatosis. Histopathology 1998;32:375–378.
15. Lim SC, Jang SJ, Kim YS. Cerebellar pleomorphic xanthoastrocytoma in an infant. Pathol Int 1999;49:811–815.
16. Macaulay RJ, Jay V, Hoffman HJ, et al. Increased mitotic activity as a negative prognostic indicator in pleomorphic xanthoastrocytoma. Case report. J Neurosurg 1993;79:761–768.
17. Montes JL, Rosenblatt B, Farmer JP, et al. Lesionectomy of MRI detected lesions in children with epilepsy. Pediatr Neurosurg 1995;22:167–173.
18. Pahapill PA, Ramsay DA, Del Maestro RF. Pleomorphic xanthoastrocytoma: case report and analysis of the literature concerning the efficacy of resection and the significance of necrosis. Neurosurgery 1996;38:822–828; discussion 828–829.
19. Perry A, Giannini C, Scheithauer BW, et al. Composite pleomorphic xanthoastrocytoma and ganglioglioma: report of four cases and review of the literature. Am J Surg Pathol 1997;21:763–771.
20. Powell SZ, Yachnis AT, Rorke LB, et al. Divergent differentiation in pleomorphic xanthoastrocytoma. Evidence for a neuronal element and possible relationship to ganglion cell tumors. Am J Surg Pathol 1996;20:80–85.
21. Tonn J.C., Paulus W, Warmuth-Metz M, et al. Pleomorphic xanthoastrocytoma: report of six cases with special consideration of diagnostic and therapeutic pitfalls. Surg Neurol 1997;47:162–169.
22. Wasdahl DA, Scheithauer BW, Andrews BT, et al. Cerebellar pleomorphic xanthoastrocytoma: case report. Neurosurgery 1994;35:947–950; discussion 950–941.
23. Yeh DJ, Hessler RB, Stevens EA, et al. Composite pleomorphic xanthoastrocytoma-ganglioglioma presenting as a suprasellar mass: case report. Neurosurgery 2003;52:1465–1468;discussion 1468–1469.
24. Zarate JO, Sampaolesi R. Pleomorphic xanthoastrocytoma of the retina. Am J Surg Pathol 1999;23:79–81.

Hypothalamic Hamartoma 33

Jeffrey V. Rosenfeld, A. Simon Harvey

Introduction – 444

Pathology – 444

Epidemiology – 445

Clinical Features – 445
Epilepsy Characteristics
Cognitive Impairment and Behavioral Disturbance
Endocrine Disturbance
Congenital Malformations Associated with HH

Preoperative Work-up and Diagnostics – 446
Staging and Classification
MRI Features
SPECT

Treatment – 446
Surgical Options for Patients with Intractable Epilepsy
The Anterior Transcallosal Transseptal Interforniceal Approach
Pterional or Fronto-Temporal Approach
Trans-Lamina Terminalis Approach
Endoscopic Resection or Disconnection
Stereotactic Radiofrequency Lesioning
Radiotherapy

Outcome of Surgery – 449
Extent of HH Resection
Seizure Outcome
Surgical Complications
Behavioral and Cognitive Improvements
Endocrine Complications
Weight and Appetite

Prognosis/Quality of Life (QOL) – 450

Precocious Puberty – 450

Follow-up/Specific Problems and Measures – 451

Future Perspectives – 451

References – 451

Introduction

Hypothalamic hamartoma (HH) is a rare developmental tumor which has a benign histology and does not progressively enlarge. Pedunculated HH attached to the tuber cinereum may cause precocious puberty whereas sessile HH which have intraventricular and intrahypothalamic components cause gelastic epilepsy and behavioral disorders. Large HH with involvement of both mammillary and tuberal regions tend to manifest with neurologic and endocrine problems [6, 7, 9]. Gelastic epilepsy is generally resistant to antiepileptic drugs (AED), ketogenic diet, and vagal nerve stimulation. The epilepsy syndrome that results may be progressive and devastating for the patient and their family. The localization of seizures can be deceptive, with some patients having had temporal lobectomy or frontal corticectomy without any effect on the seizures [3, 6, 17]. There is now good evidence that the epilepsy in these patients emanates from the HH [3].

HH vary in size considerably, ranging from a few millimeters to several centimeters in diameter (Fig. 1). Small HH are easily missed on brain imaging studies. The larger HH displace and distort the hypothalamus. It is often feasible to remove or disconnect the lesion from the adjacent hypothalamus in many patients without significant injury to the hypothalamus. The attachment to the mammillary body may be a principal route of spread of the seizures via the mammillo-thalamic tract to the thalamus and from the thalamus to the neocortex [8] (Fig. 2). It is probably important to disconnect the HH from the mammillary body and the rest of the hypothalamus to achieve control of the seizures.

Pathology

The histology of the HH resembles grey matter with some similarity to hypothalamic nuclei. Fully mature ganglion cells are scattered haphazardly within surrounding neuropil within which a variable number of reactive astrocytes are seen. Neurons may be clustered but show no lamination. There may be a variable degree of fibrillary gliosis, myelinated nerve fibers, and ependymal cell rests. There is rarely lipomatous differentiation or an appearance similar to tuberous sclerosis. The pathological differential diagnosis includes normal brain, ganglioglioma, gangliocytoma, and low-grade glioma (Fig. 3).

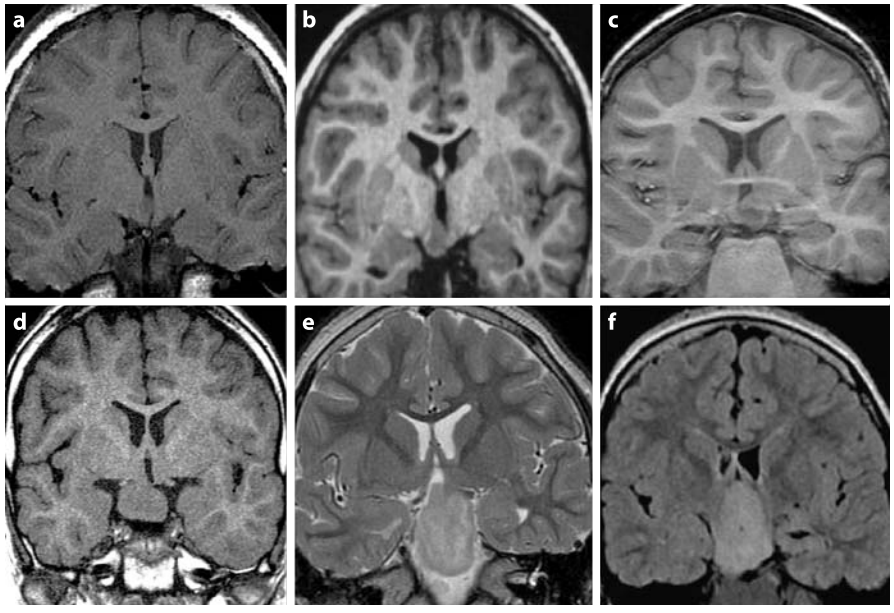


Fig. 1 Examples of sessile (nonpedunculated) hypothalamic hamartomas (HH) on magnetic resonance (MR) imaging demonstrating their great variety. **a** Small intraventricular HH with origin mainly from the right hypothalamus; **b** small partly intraventricular HH with origin mainly from the right hypothalamus and mild subventricular extension; **c** moderate-sized HH arising from the left hypothalamus; **d** moderate-sized HH with a wide origin at the base of the right hypothalamus extending inferiorly; **e** giant HH arising mainly from the left hypothalamus with inferior extension into the pre-pontine cistern; **f** giant HH virtually filling the third ventricle, arising from both sides of the hypothalamus displacing the walls of the third ventricle laterally and extending down into the suprasellar cistern

Epidemiology

The majority of HH are sporadic. Based on the numbers of known Australian patients with HH, we estimate the prevalence to be approximately 1–2 cases per million population. The prevalence may be slightly higher given that patients with small HH are often missed on routine neuro-imaging. HH may also be an incidental finding at necropsy.

Clinical Features

Epilepsy Characteristics

The seizures in individuals with HH often commence at birth and gelastic seizures usually commence by 2 years of age. Gelastic seizures appear as short bursts of laughter, sometimes described as a combination of a laugh and a cry and may occur every few minutes. The epilepsy may gradually evolve with the appearance of complex partial and generalized seizures over the years. The EEG may show abundant generalized inter-ictal spike wave activity in patients with mixed seizures. The severity of the epilepsy syndrome does not appear to correlate with the size of the hamartoma, although adults with small HH functioning at a normal or high intellectual level with mild and infrequent gelastic seizures are reported rarely. All seizure types may remit after HH surgery. Rarely, some cases are asymptomatic.

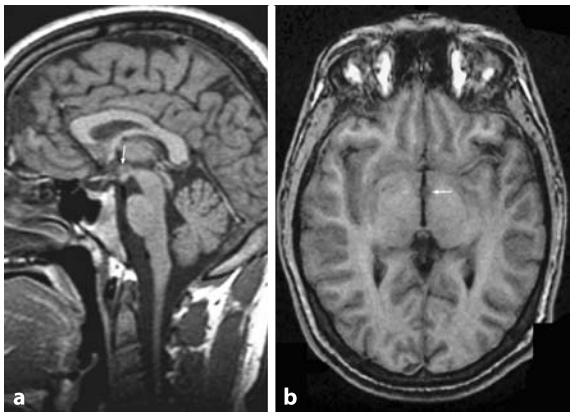


Fig. 2 Coronal and axial MR images showing a small HH arising from the left hypothalamus with attachment to the left mammillary body (*white arrows*)

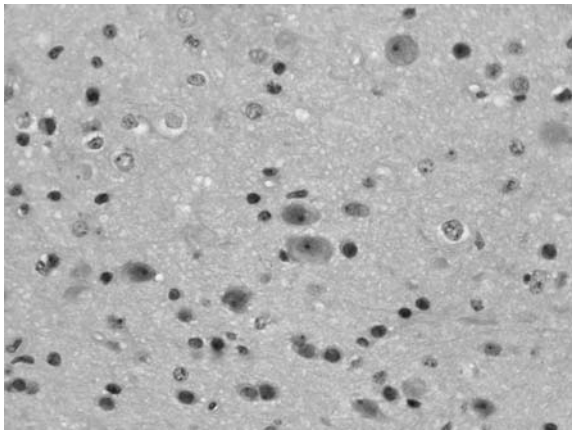


Fig. 3 Histology of hypothalamic hamartoma (HH). Hematoxylin and eosin ×400. This photomicrograph shows mature neurons and mature glial cells in a disorganized pattern

Cognitive Impairment and Behavioral Disturbance

Children with intractable and severe seizures often have significant behavioral disturbance with aggression, rage attacks, poor concentration, intellectual disability, and autistic features. There may be normal early development but a progressive decline in cognitive function and behavior occurs as the epilepsy continues and some patients with frequent seizures develop an epileptic encephalopathy [3].

Endocrine Disturbance

Forty-five percent of our patients with sessile HH had central precocious puberty (CPP) at presentation. The CPP is due to an oversecretion of GnRH which causes an excess production of luteinizing hormone (LH) and follicle-timulating hormone (FSH). This may be due to adjacent mechanical distortion of inhibitory pathways or direct secretion of GnRH or growth factors (transforming growth factor alpha) from the HH [11]. Disturbance of endocrine function may be clinically silent and should be routinely evaluated prior to HH surgery. Asymptomatic deficiencies in thyroid hormone, growth hormone, and cortisol response may be identified prior to surgery, and biochemical CPP may be present in clinically prepubertal children [7]. HH may rarely be associated with growth hormone secreting pituitary adenomas.

Congenital Malformations Associated with HH

Pallister-Hall syndrome is a rare autosomal disorder with wide phenotype associated with a mutation of the Gli 3 gene on chromosome locus 7p13. These patients have HH with gelastic epilepsy, variable de-

grees of pituitary insufficiency, various degrees of olfactory hypoplasia, polydactyly, Y-shaped metatarsals/metacarpals, airway anomalies varying from bifid epiglottis to laryngotracheal cleft, imperforate anus, and renal anomalies. The epilepsy in Pallister-Hall tends to be milder than in the sporadic cases. There is some phenotypic overlap with the Smith-Lemli-Opitz syndrome where there is a deficiency of cholesterol biosynthesis. The Gli 3 gene encodes a transcription factor in the sonic hedgehog pathway that has an essential role in embryogenesis [3].

Preoperative Work-up and Diagnostics

Neurology, including epilepsy work-up, radiology, neuropsychology, ophthalmology, and endocrinology assessments are performed.

The preoperative work-up should include a detailed neuropsychology assessment with memory function testing if they are old enough to cooperate, and a neurology and ophthalmology assessment with visual fields. The endocrine evaluation includes a detailed clinical assessment and biochemical testing of the hypothalamic-pituitary axis before and after resection of their HH which includes an evaluation of pubertal status, growth, weight, thyroid and adrenal function, and osmoregulation. They will also require a period of video-EEG monitoring and MRI scans (see the Sect. entitled "MRI Features" below), and preferably ictal and interictal Single Photon Emission Computed Tomography (SPECT) scans. Intracranial depth EEG recording is not generally required in the evaluation of the epilepsy.

Staging and Classification

MRI is used for anatomical conformation and surgical planning and the ictal SPECT scan is used to confirm the HH as the source of the seizures.

MRI Features

Fine with thin T1- and T2-weighted images in three orthogonal planes covering the hypothalamic region provides excellent anatomical detail of the HH to assist the surgeon in surgical planning, the HH usually being of slightly higher signal than cortical and hypothalamic grey matter, and being readily distinguished from the heavily myelinated fornices, mammillary bodies, and mammillo-thalamic tracts [9]. HH do not enhance following contrast administration. A careful examination of the MRI scans should be undertaken to identify other structural lesions such as cortical dysplasia, which are seen only rarely as in most cases the HH is the sole lesion. The intrahypothalamic HH are invariably attached to the mammillary region. In the cases with larger HH, the mammillary bodies are commonly distorted at the margins of the HH and may not be identified; the tuberal structures are displaced and the columns of the fornix displaced anterolaterally [9] (Fig. 1).

Several classification systems of HH have been proposed, based on the radiological appearance and the degree of intraventricular involvement [2, 4, 9, 20]. Pedunculated HH attach to the tuber cinereum and project into the suprasellar cistern. Sessile HH may have a unilateral or bilateral origin, a broad attachment to the hypothalamus, and varying degrees of extension below the third ventricle [9]. Larger HH may be colocated with an arachnoid cyst.

The differential diagnosis of the HH on the MR scan includes optic or hypothalamic glioma, suprasellar germinoma, and craniopharyngioma. Colloid cyst is easily excluded because of the different location.

SPECT

Ictal Single Photon Emission Computed Tomography (SPECT) may show a focus of hyperperfusion in the HH and is very helpful to confirm the origin of the seizures in the HH.

Treatment

The surgical options for patients with intractable epilepsy are:

1. Craniotomy and resection/disconnection
   - Trans-callosal (interhemispheric) approach
   - Pterional or fronto-temporal approach
   - Trans-lamina terminalis (subfrontal) approach
2. Endoscopic resection/disconnection
3. Stereotactic techniques
   - Radiofrequency thermocoagulation
   - Radiosurgery (gamma knife)
   - Interstitial radiosurgery (I-125 seeds)

The treatment of patients with HH causing precocious puberty is usually medical. Some young children with CPP and a pedunculated HH may be suitable for surgery, avoiding the need for prolonged hormonal therapy.

Surgical Options for Patients with Intractable Epilepsy

Excision or disconnection of the HH is feasible in many patients using several varied surgical tech-

niques which depend on the experience of the surgeon and the conformation and position of the hamartoma. Lesions which are predominantly intrahypothalamic and intraventricular are best approached from above, whereas those which are protruding beneath the floor of the third ventricle are approached via a trans-Sylvian/fronto-temporal approach. However, partial resection and disconnection of the intraventricular portion seems to be adequate for treatment of seizures. The complete resection of the HH may not be necessary. Disconnection of the HH may be the most effective element of the treatment, although this has not been confirmed.

The Anterior Transcallosal Transseptal Interforniceal Approach

The first five cases using this approach were reported in 2001 [17]. The series was expanded to 29 cases and was reported in 2003 [6]; there are now a total of 49 patients in the first author's personal series. The essentials of this approach are that it is a midline interhemispheric approach with a small corpus callosotomy (1.5–2 cm) just behind the genu, a midline transseptal dissection (between the leaves of the septum pellucidum), an interforniceal approach between the uppermost section of the columns before they converge to form the arches of the fornix, entering the anterior end of the roof of the third ventricle, and removing the hamartoma using the long, curved micro-tip of the ultrasonic aspirator. The consistency of the HH is tougher than normal cerebral tissue, slightly brown in color, relatively avascular, and can usually be differentiated from the surrounding normal cerebral tissue. The perforating arteries from the basilar apex demarcate the posterior limit of the dissection and for some large HH, the optic chiasm demarcates the most anterior extent of the resection. Frameless stereotactic navigation is helpful to choose the ideal trajectory and define the margins of the resection [16] (Fig. 4).

The advantage of this approach is the excellent view of the HH obtained from above and being able to debulk and/or disconnect the HH, and spare the mammillary bodies if they can be identified, the pituitary stalk and the optic chiasm. It is also possible to partially debulk and disconnect HH extending into the interpeduncular fossa and the pre-pontine cistern using the transcallosal approach (Fig. 5).

The avoidance of the blood vessels and cranial nerves which are encountered in the trans-sylvian approach may reduce the risk of stroke and oculomotor nerve palsy. There is a risk to short-term memory due to mammillary body or forniceal injury. There is also a risk of stroke from trauma to the thalamic perforators. A further disadvantage of this approach is the inability to extend the resection laterally if there is lateral extension and attachment of the HH, though this area may be less relevant to the genesis of seizures. If the perforating arteries are injured or diathermied, a stroke with hemiparesis may result.

Pterional or Fronto-Temporal Approach

This approach has been the most common approach used and provides the flexibility of subfrontal, transsylvian or subtemporal approaches. There is good access to the suprasellar cistern but there is restricted access into the third ventricle and the intraventricular component. It is feasible to debulk the HH which is protruding below the third ventricle and to disconnect it from the intraventricular component. However, we believe that it is more difficult to dissect the HH tissue off the mammillary body from below compared to the transcallosal approach. The third nerve and the internal carotid artery and its branches including perforating vessels are at risk if there is extensive dissection and retraction in this region. The addition of an orbito-zygomatic craniotomy may provide improved access to the subventricular HH with reduced brain retraction.

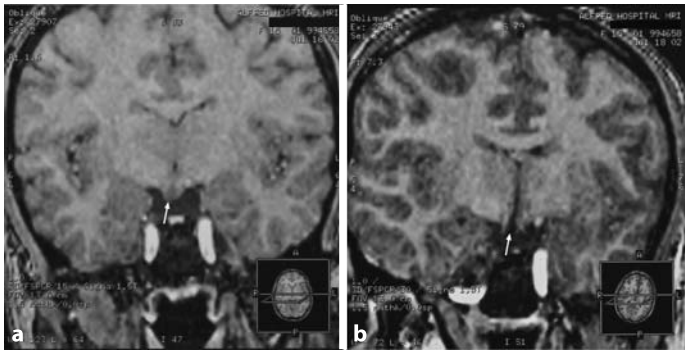


Fig. 4 **a** A small HH (*white arrow*) attached to both sides of the hypothalamus on coronal MR. **b** Complete excision of the HH (*white arrow*) with preservation of the adjacent hypothalamic tissue

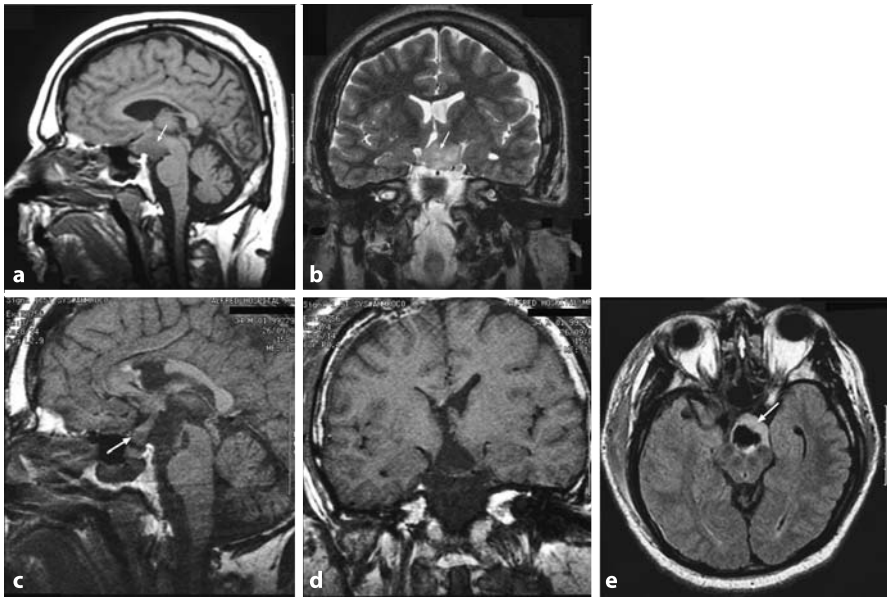


Fig. 5 A large HH (*white arrows*) on sagittal and coronal MR images **a** and **b** showing wide origin from the left hypothalamus, some right-sided attachment, distortion of the third ventricle and inferior extension over the dorsum sellae. Images **c, d**, and **e** are the postoperative appearances in sagittal, coronal, and axial MR images showing a subtotal excision with mainly an anterior rim of HH on the sagittal and axial images and a small lateral remnant on the coronal image (*white arrows*)

Trans-Lamina Terminalis Approach

This approach is sometimes used to remove the intraventricular component of a craniopharyngioma or other intraventricular tumor and enables access to the HH through the lamina terminalis. There are a number of disadvantages to this approach for resection of a HH. The approach requires a subfrontal or bifrontal interhemispheric approach which involves retraction and possible injury to one or both frontal lobes and possible olfactory tract and bulb injury. The anterior communicating artery complex is also in the line of the approach. It would be difficult to obtain as complete a clearance of a moderate- or larger-sized lesion through this approach and the view of the posterior aspect of the lesion would also be obscured.

Endoscopic Resection or Disconnection

Removal or disconnection of the intraventricular component of the HH can be achieved endoscopically, much like the approach to a third ventriculostomy. Delalande et al. advocate an endoscopic approach from above and a second stage fronto-temporal approach to remove or disconnect the remainder of the lesion if necessary [4]. The endoscope is passed transcortically, through the lateral ventricle and foramen of Monro and into the third ventricle. This approach would prove difficult for a larger lesion and may not permit as precise a removal as the open technique. The variable angling of the scope at the foramen of Monro sufficient to cover the entire lesion may also risk damage to the ipsilateral fornix. Normal- or small-sized ventricles would also create technical difficulties for the endoscopic approach.

Stereotactic Radiofrequency Lesioning

The stereotactic placement of a radiofrequency electrode into the HH and the thermal destruction of at least part of the HH may impact the epilepsy but there have been very few cases reported using this technique [10, 12]. The inability to remove or disconnect the lesion in most cases and the risk of thermal injury to surrounding structures discourage this technique. The advantage of the technique is the minimal invasion to reach the target.

Radiotherapy

Stereotactic radiosurgery—The Gamma Knife. Radiosurgery is an option for the treatment of HH. The series reported have been small. Regis et al. reported ten patients from seven different centers treated with the gamma knife. The mean follow-up was 35 months (12–71 months). The median margin-

al dose was 15.25 Gy (range, 12–20 Gy). All patients improved. Four patients were seizure free, two were markedly improved, and two improved. Two patients were treated twice to achieve seizure freedom. There was a correlation between dose and efficacy with a marginal dose of 17 Gy associated with all the patients in the successful group. Two patients had behavioral improvement. There were no significant side effects. Complete coverage of the HH did not seem to be mandatory [15]. There was a mean latency of 9 months to improvement. Unger et al. treated four children with HH with the gamma knife with 12–48 months of follow-up. A continuing decrease in seizure frequency and severity was noted. Three achieved Engel class IIa (rare disabling seizures) and one Engel class IIIa (worthwhile seizure reduction). The size of the lesions did not change [19]. Dunoyer et al. treated two HH patients with the gamma knife, one became seizure free, one had a >90% seizure reduction and both had behavioral improvement [5].

The concerns about radiosurgery are that there may be a significant risk of late recurrence of the epilepsy, that cerebral edema or radionecrosis may be problematic in the hypothalamic region, the potential injury to the hypothalamus, optic chiasm, and optic tract, that high dose radiation may be epileptogenic, and that there may be late cerebral tumor induction. The disadvantages of radiosurgery are that no tissue is obtained for pathology, the inability to eliminate or disconnect other than small HH, and the delay in therapeutic effect on the epilepsy. However, a subnecrotic dose of radiation may disrupt epileptogenic circuits and thus improve the epilepsy control.

Patient selection is unclear. Large lesions are preferably treated with surgery whereas small lesions may respond well to radiosurgery. Patients who are unsuitable for surgery, particularly those functioning in the normal or high cognitive range and whose memory is intact may be good candidates for radiosurgery or stereotactic radiofrequency lesioning. Patients who have failed to respond to radiosurgery may become candidates for surgery.

The stereotactic placement of I-125 seeds into six patients with HH resulted in two seizure-free patients and two with auras only [18]. There were no major complications. This technique is an alternative to stereotactic radiosurgery but is less attractive because it involves an open operation for the placement of the seeds.

There is no role for chemotherapy.

Outcome of Surgery

There have been 27 small case series of HH surgery reported from 1967 to 2000, with variable success, relatively short follow-up, and some serious complications [17]. Palmini et al. reported 13 patients from three centers in 2002; 12 had a fronto-temporal and one an endoscopic approach [14]. Delalande and Fohlen reported 17 patients in 2003. Sixteen had disconnection and one total removal. There were 14 open and nine endoscopic procedures [4].

Extent of HH Resection

The extent of resection depends on the size and position of the HH, the surgical approach, and the degree of disconnection as opposed to excision that the surgeon is planning. In the recent transcallosal series of Harvey et al., there was a near complete excision (95%–100%) in 18/29 patients, 75%–95% resection achieved in seven patients (four of these had near complete disconnection of residual HH) and less than 50% reduction was achieved in four [6]. In the series of Delalande and Fohlen there was total removal in 1/17 patients and disconnection in 16/17 [4]. We believe that excision and disconnection of the intraventricular HH is the goal of surgery and that attempts at complete excision may increase morbidity without improving seizure control unless the HH is small.

Seizure Outcome

The medium-term seizure outcome of HH resection via the transcallosal approach in 29 patients with a mean follow-up of 30 months (12–70 months) was as follows: 15 patients were seizure free (nine were off all antiepileptic medication), seven patients had >90% reduction in seizure frequency, three patients had 55%–80% reduction in seizure frequency, and four patients had <40% reduction in seizure frequency [6].

In the largely disconnection series of Delalande and Fohlen, 8/17 (47%) patients were seizure free, one patient had only brief gelastic seizures, and 8/17 (47%) patients were dramatically improved with a mean follow-up of 18.6 months (8 days to 43 months) [4].

Palmini et al. reported 2/13 (15.4%) seizure free, 11/13 (84.6%) >90% reduction of drop attacks and generalized tonic-clonic seizures. However, minor gelastic, complex partial and atypical absence seizures persisted in 11 patients with a follow-up of mean 2.8 years (1–5.5 years) [14].

Surgical Complications

The main surgical complications relate to hypothalamic disturbance which are discussed below in Sect. e,

third nerve paresis which occurred in 1/17 [4], transient in 1/29 [6], and 4/13 (three resolved fully) [14], and hemiparesis or hemiplegia due to perforator artery injury or internal carotid, anterior or middle cerebral artery injury, or vasospasm. This results in thalamic, capsular ,or cortical ischaemia or infarction. Harvey et al. reported 2/29 cases of temporary hemiparesis due to anterior thalamic infarcts [6], Delalande and Fohlen reported 1/17 hemiplegia, and 1/17 hemiparesis [4], and Palmini et al. reported 3/13 anterior thalamic infarcts and one capsular infarct with minimal long-term deficit [14].

Behavioral and Cognitive Improvements

There are often dramatic improvements in behavior following surgery, with decreased aggression, increased concentration and involvement in tasks, elevated mood, and greater speech output in many patients which is often seen in the first weeks postoperatively. These improvements require further careful evaluation to confirm. The improvement is generally associated with a reduction in interictal spike-wave activity and may relate to a reversal of the epileptic encephalopathy in some of these children [4, 6, 8, 14]. Short-term memory disturbance occurred in 14/29 patients and this resolved in all but four patients [6]. The disadvantage of the ongoing memory disturbance is outweighed by the improvements in seizures and behavior.

Endocrine Complications

Precocious puberty in patients with intrahypothalamic HH and gelastic epilepsy is not usually altered by HH surgery probably because the hypothalamus once primed remains switched on. Transient hypersomnolence, and hyperthermia may occur in the early postoperative period. Free thyroxine commonly falls after surgery, and some patients may require replacement therapy. Low growth hormone occurred in 6/29 (20.7%) patients following transcallosal surgery at our center [7].

Hypernatremia developed in most patients postoperatively with sodium >150 mmol/L seen in 16/29 (55%) patients at our center; however, this was asymptomatic and not often associated with polyuria. Four out of 29 patients (13.8%) developed transient diabetes insipidus and no patient required ongoing antidiuretic hormone replacement [6]. Prior, unsuccessful surgery may be a risk factor for endocrinopathy. Except for appetite stimulation and weight gain in some patients (see Sect. entitled "Weight and Appetite" below), postoperative endocrine disturbances appear to be transient, mild, or asymptomatic, and easily treated where necessary. Long-term follow-up of growth and sexual development in a larger series of patients is required [7].

Weight and Appetite

Appetite stimulation and early postoperative weight gain occurred in 45% of our patients having transcallosal surgery. This risk may be different in other surgical approaches. The weight gain tends to plateau but some dietary control is required. The causation of the weight gain is variable and multifactorial and may relate to ventromedial nucleus hypothalamic injury, dexamethasone therapy, physical inactivity in convalescence, psychosocial factors, psychiatric comorbidity with autism, depression, or anxiety, parental nurturing instinct, postoperative hypothyroidism, preoperative genetic/environmental effects and AEDs [7].

Prognosis/Quality of Life (QOL)

The control of postoperative seizures is variable and depends on the technique used and length of follow-up. Outcome ranges from 15.4% to 54% complete seizure control and 24% to 84.6% with >90% control of seizures. Improvements in QOL, behavior, and general functioning are common. The endocrine risks are small but there is a potential for appetite stimulation. There is a small risk of stroke and cranial nerve palsy. There is a small risk to short-term memory function with the transcallosal approach. Radiosurgery may also be a successful treatment but more experience is required to judge its role. QOL has been transformed in many patients following treatment for HH.

Precocious Puberty

Patients with CPP due to pedunculated HH are usually treated medically. GnRH analog is the treatment of choice. By flooding the GnRH receptor, hypothalamic switch-off and pubertal regression results. It is administered by subcutaneous injection as a long-acting preparation (1- and 3-month preparations are available). This treatment is usually effective in suppressing puberty and reducing the rate of bone age advancement, thus improving final height outcome. It is expensive, and usually needs to continue for several years. The young child with CPP and a pedunculated HH may be suitable for surgery via the pterional or subtemporal approach so as to avoid the problems of prolonged hormonal therapy [1, 13]. The orbito-zygomatic craniotomy may improve access to the pedunculated HH with reduced brain retrac-

tion. The risks of such surgery have been discussed. If normal hormonal balance is achieved, the pubertal changes may regress completely.

Follow-up/Specific Problems and Measures

Regular neurological and endocrine follow-up of the patient is recommended. Following hypothalamic surgery the patient must be observed closely over several weeks to detect hypernatremia, diabetes insipidus, and thirst dysregulation which may be delayed in onset. Ensuring a set daily volume of fluid intake should prevent the hypernatremia and dehydration. As with any epilepsy surgery, it is advisable to continue AEDs for 18 months to 2 years. The patient's weight must be closely monitored and a diet introduced if weight gain is a problem. Neuropsychology review should be continued postoperatively with an assessment of cognitive function including memory. Postoperative communicating hydrocephalus is unlikely but should be considered if there is a late cognitive decline.

Future Perspectives

There are several unanswered questions regarding treatment for HH. How much of the HH should be excised or disconnected to achieve seizure control? Which parts of the HH are critical to disconnect from the normal structures? Is the mammillary body/HH conjunction such a critical site? Is disconnection preferable to excision? Who are the best patients for gamma knife treatment?

As more experience is gained with the various treatment modalities, the selection of a treatment regimen will become clearer and more predictable for a particular patient with a particular type of HH. The ideal age for surgery is not yet well defined but it is probably better to operate earlier in the course of the epilepsy before the irreversible changes of secondary generalized epilepsy have become established and before intellectual development becomes irreversibly stunted by the effects of the frequent epilepsy. Which HH patients are suitable for surgery, versus radiosurgery or radiofrequency lesioning needs further clarification and has been discussed above in the Sect. entitled "Treatment." The long-term follow-up of seizures, cognitive function, behavior, growth, and development is required to better judge the place of the various treatments. This applies particularly in regard to seizure recurrence which should be assessed over at least 5 years.

HH is a rare condition which may cause devastating epilepsy and severe behavioral and cognitive problems which have been until recently resistant to treatment and where surgery has been feared and avoided. There are now several surgical techniques available for successfully treating sessile HH which are likely to become more refined over the next few years with respect to selection of cases and technique. Gamma knife radiosurgery is an alternative but the long-term safety and efficacy are uncertain. Precocious puberty is treated medically in most cases.

References

1. Albright AL, Lee PA. Neurosurgical treatment of hypothalamic hamartomas causing precocious puberty. J Neurosurg 1993;78:77–82
2. Arita K, Ikawa F, Kurisu K, et al. The relationship between magnetic resonance imaging findings and clinical manifestations of hypothalamic hamartoma. J Neurosurg 1999;91:212–220
3. Berkovic SF, Arzimanoglou A, Kuzniecky R, Harvey AS, Palmini A, Andermann F. Hypothalamic hamartoma and seizures: a treatable epileptic encephalopathy. Epilepsia 2003;44(7):969–73
4. Delalande O, Fohlen M. Disconnecting surgical treatment of hypothalamic hamartoma in children and adults with refractory epilepsy and proposal of a new classification. Neurol Med Chir (Tokyo) 2003;43:61–68
5. Dunoyer C, Raghab J, Resnick T, Jayaker P, Altman N, Wolf A, et al. The use of stereotactic radiosurgery to treat intractable epilepsy in childhood partial epilepsy. Epilepsia 2002;43:292–300
6. Harvey AS, Freeman JL, Berkovic SF, Rosenfeld JV. Transcallosal resection of hypothalamic hamartomas in patients with intractable epilepsy. Epileptic Disord 2003;5:527–265
7. Freeman JL, Zacharin M, Rosenfeld JV, Harvey AS. The endocrinology of transcallosal hypothalamic hamartoma resection for intractable epilepsy. Epileptic Disord 2003;5:239–247
8. Freeman JL, Harvey AS, Rosenfeld JV, Wrennall JA, Bailey CA, Berkovic SF. The evolution and postoperative resolution of symptomatic generalised epilepsy in hypothalamic hamartomas. Neurology 2003;60:762–767
9. Freeman JL, Coleman LT, Wellard RM, Kean MJ, Rosenfeld JV, Jackson GD, et al. MR imaging and spectroscopic study of epileptogenic hypothalamic hamartomas: analysis of 72 cases. Am J Neuroradiol 2004;25:450–462
10. Fukuda M, Kameyama S, Wachi M, Tanaka R. Stereotaxy for hypothalamic hamartoma with gelastic seizures: technical case report. Neurosurgery 1999;44:1347–1350
11. Jung H, Ojeda SR. Pathogenesis of precocious puberty in hypothalamic hamartoma. Horm Res 2002;57(Suppl 2):31–34
12. Kuzniecky R, Guthrie B, Mountz J, Bebin M, Faught E, Gilliam F, et al. Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. Ann Neurol 1997;42:60–67

13. Luo S, LiC, Ma Z, Zhang Y, Jia G, Cheng Y. Microsurgical treatment for hypothalamic hamartoma in children with precocious puberty. Surg Neurol 2002;57:356–362
14. Palmini A, Chandler C, Andermann F, Costa DC, Paglioli-Neto E, Polkey C, et al. Resection of the lesion in patients with hypothalamic hamartomas and catastrophic epilepsy. Neurology 2002;58:1338–1347
15. Regis J, Bartolomei F, de Toffol B, Genton P, Kobayashi T, Mori Y, et al. Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Neurosurgery 2000;47:1343–1351
16. Rosenfeld JV, Freeman JL, Harvey AS. Operative technique: the anterior transcallosal transseptal interforniceal approach to the third ventricle and the resection of hypothalamic hamartomas. J Clin Neurosci 2004;11(7):738–744
17. Rosenfeld JV, Harvey AS, Wrennall J, Zacharin M, Berkovic SF. Transcallosal resection of hypothalamic hamartomas, with control of seizures, in children with gelastic epilepsy. Neurosurgery 2001;48(1):108–118
18. Schulze-Bonhage A, Homberg V, Trippel M, Keimer R, Elger CE, Warnke PC, et al. Interstitial radiosurgery in the treatment of gelastic epilepsy due to hypothalamic hamartomas. Neurology 2004;62(4):644–647
19. Unger F, Schrottner O, Feichtinger M, Bone G, Haselsberger K, Sutter I. Stereotactic radiosurgery for hypothalamic hamartomas. Acta Neurochir 2002;84:57–63
20. Valdueza JM, Cristante L, Dammann O, et al. Hypothalamic hamartomas: with special reference to gelastic epilepsy and surgery. Neurosurgery 1994;34:949–958

Ependymomas 34

Nicholas Wetjen, Corey Raffel

Introduction – 454

Epidemiology – 454

Signs and Symptoms – 454

Diagnostics – 455
Magnetic Resonance Imaging
Computed Tomography
Pathology

Staging and Classification – 457

Treatment – 457
Surgery
Radiation Therapy
Chemotherapy
Radiosurgery

Prognosis/Quality of Life – 459

References – 460

Introduction

Ependymomas are the third most common pediatric brain tumor, following astrocytoma and medulloblastoma. They are thought to arise from ependymal cells lining the ventricles and central canal of the spinal cord.

The typical location of these tumors differs in adults and children. Most childhood ependymomas are intracranial while in adults they more commonly occur in the spinal cord. They occur infratentorially in 65% of pediatric cases, most often arising from the floor of the fourth ventricle. The remaining 35% of ependymomas occur equally divided between the spinal cord and cerebral hemispheres. Approximately 10%–12% of ependymomas disseminate through the cerebrospinal fluid pathways, often at the time of recurrence.

The main goal of therapy is surgical resection as gross total resection greatly enhances the chances for long-term survival. Radical surgical resection is often difficult, however, due to the tumor's origin from the floor of the fourth ventricle. The dilemma between achieving a gross total resection and risking significant neurological deficit makes the surgical resection of ependymoma difficult.

These tumors are typically resistant to chemotherapy and radiation and may recur even 10 to 20 years after initial resection. Radiation has typically been used to treat residual tumor but is generally not used in children less than 3 years old. The lack of progress in defining optimal treatment strategies relates to the relatively low incidence of these tumors. Multi-institutional studies organized through the Children's Oncology Group, the Italian Pediatric Neuro-oncology Group, the Australian and New Zealand Childhood Cancer Study Group, and International Society of Pediatric Oncology have been undertaken an effort to more effectively combine the collective experience of these institutions to better treat these patients.

Epidemiology

Intracranial ependymomas make up 7% of all glial neoplasms. In adults, 1.9% of all intracranial tumors are ependymomas but in children ependymomas comprise 6%–12% of all primary brain tumors. These tumor are intracranial in >90% of children. Intracranial ependymomas are the third most common histological types of tumor in children after astrocytomas and medulloblastoma. Fifty percent of ependymomas occur in children younger than 5 years old, and the majority (approximately 75%) is infratentorial, occurring in the region of the fourth ventricle. Approximately 20%–30% of all posterior fossa tumors in children are ependymomas. Typically, ependymomas present between 3 and 6 years of age with a peak at approximately 4 years of age. Younger patients are more likely to have infratentorial tumors. The incidence of ependymoma in children and adults combined is approximately 0.3/100,000 patient-years but three cases per 100,000 in children younger than 15 years. The reported incidence of intracranial ependymoma has increased 35% since 1973, perhaps resulting from improvements in diagnosis. They occur in males slightly more often than females (1.4:1).

The cause of these tumors is unknown. No environmental factor has been implicated. Reports that ependymomas contained DNA sequences similar to SV40 virus raised the question of whether polio vaccines in the 1950s may have been contaminated with SV40. Studies in Sweden and in the USA showed no significant increase in rate of incidence of ependymomas in patients receiving these vaccines.

Approximately 2%–5% of patients with neurofibromatosis type 2 harbor ependymomas, but these almost exclusively arise in the spinal cord. This has led to studies suggesting alterations in the NF2 gene in spinal, but not in intracranial, ependymomas. In a recent molecular genetic analysis of 18 sporadic pediatric intracranial ependymomas normal NF2 genes were found. Loss of the p53 locus on chromosome 17p or p53 gene mutations do not appear to play a significant role in the development of ependymomas in contrast to other gliomas. More malignant grades of ependymoma have increased proliferation indices, greater capacity to migrate, more matrix metalloprotease activity as well as greater expression of VEGF. In one family without NF2 who had a predisposition to ependymomas and meningiomas there was loss of a gene locus distinct from the region on chromosome 22 responsible for NF2.

Signs and Symptoms

The presenting signs and symptoms of ependymomas are dependent on age and location. Because these patients typically present in younger children it is not uncommon for the early manifestations to be nonspecific behavioral symptoms such as lethargy, irritability, and decreased social interaction. These symptoms are followed by headache and vomiting often in the absence of nausea. Frequent headaches that are worse in the morning, vomiting, lethargy, irritability, and decline in school or work performance combined with truncal or gait ataxia is sometimes referred to as the midline posterior fossa syndrome. This syndrome is not pathognomonic of ependy-

moma and may result from the presence of other posterior fossa tumors such as astrocytoma and medulloblastoma. Truncal ataxia as opposed to appendicular ataxia is more common with ependymomas due to their midline location. Intractable vomiting may be a prominent in the presentation of ependymomas due to mass effect upon or invasion into the floor of the inferior fourth ventricle. Often an extensive GI evaluation is performed prior to neuroimaging because of the strength of the GI complaints. Symptoms may become more persistent as the tumor gets larger. This tumor may cause symptoms for as long as 3 years before diagnosis and a longer symptomatic interval is associated with a more favorable prognosis.

Signs at presentation may include papilledema, nystagmus, and diplopia from 6th nerve palsy as well as changes in vision. In as many as 35% of patients, lower cranial nerve pareses are seen, often as a result of tumor extension through the foramen of Luschka into the lateral medullary cistern. Hydrocephalus is common in children with intracranial ependymomas due to obstruction of CSF flow through the fourth ventricle. Rarely, a head tilt and neck pain resulting from impaction of the cerebellar tonsils into the cervical spinal canal may be present.

Supratentorial tumors usually present as large masses with signs and symptoms of increased intracranial pressure. Focal signs and seizures are less common and have been reported to occur in about one third of patients. Younger patients with supratentorial tumors may present only with an abnormally rapid increase in head circumference. If these symptoms persist without treatment, increased pressure resulting in opisthotonos, bradycardia, and even apnea may result.

In adults, intracranial ependymomas most often arise in cerebral hemispheres or in relation to third ventricle symptoms. Thus, the most common symptoms are headache, diplopia, hemiparesis, and seizures. Tumors of the lateral ventricle may expand slowly and cause nonspecific symptoms, commonly cognitive impairment or memory difficulties.

Rarely, the patient may present with an acute spontaneous hemorrhage into the tumor or subarachnoid space, leading to an acute presentation of severe headache and alteration of consciousness.

Ependymomas may spread throughout the CSF pathways, although this is usually a feature of recurrence rather than presentation. Seeding of the CSF occurs in 9.6%–12% of intracranial ependymomas. Risk factors for dissemination are infratentorial tumors, high-grade tumors, younger age, and inability to achieve a gross total resection. Presenting symptoms referable to the spinal cord or nerve root from spinal drop metastases are extremely rare in ependymomas.

Diagnostics

Magnetic Resonance Imaging

The best imaging modality for the evaluation of posterior fossa tumors is MR scanning (MR). MR best defines the tumor and its relation to normal anatomy with high resolution in multiple image planes. The tumor's relationship to the brainstem, spinal cord, and cerebellopontine angle is well demonstrated and important for surgical planning. Ependymomas characteristically appear as an inhomogeneous mass arising from the inferior floor of the fourth ventricle and filling this chamber. They have a particular propensity to project through the foramen of Luschka into the cerebellopontine angle and through the foramen of Magendie into the cervical spinal canal. The vertebral or posterior inferior cerebellar arteries may be displaced or encased by the tumor.

Ependymomas have similar imaging characteristics regardless of intracranial location. The most common appearance on MR is of an inhomogeneous mass, isointense or hypointense on T1-weighted imaging (85%), isointense or hyperintense on T2-weighted imaging or proton density-weighted imaging and demonstrating inhomogeneous enhancement after administration of gadolinium contrast (Fig. 1).

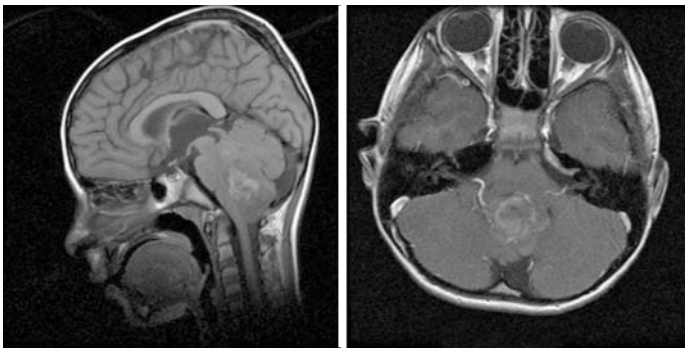


Fig. 1 MR image of an infratentorial ependymoma with heterogeneous, irregular contrast enhancement arising posterior to the brainstem closely associated with the floor of the fourth ventricle. The fourth ventricle appears expanded and causes obstruction of CSF outflow leading to hydrocephalus

As mentioned above, ependymomas rarely have dissemination at time of diagnosis. Nonetheless, preoperative determination of lack of dissemination can aid in surgical planning. Preoperative spinal imaging guides the surgeon with respect to how aggressive to be at surgery. If dissemination is present, a less aggressive surgical approach is warranted. A spinal MRI should be obtained preoperatively whenever possible. After posterior fossa surgery, artifacts from blood may make interpretation difficult.

Infants and small children are often very ill at presentation and sedation to obtain a spinal study may be unwise – staging MR in this condition may be deferred to after surgery. If a pre-op spinal scan is not obtained, waiting 2 weeks after surgery for a staging scan will allow for the disappearance of post-surgical artifact.

Computed Tomography

CT imaging was the first imaging modality to diagnose with accuracy the presence of posterior fossa tumors in pediatric patients. Ependymomas have the same or increased X-ray attenuation compared to cerebellar cortex (75%–80%) and are homogeneous in X-ray attenuation. Hemorrhage may present in 10%–13% of tumors. Calcification is present in ependymomas with a reported frequency of 25%–50% and is better defined with CT imaging than MR. Cysts and necrotic regions within (47%) or related to the tumor appear with low density. Fourth ventricular tumors are often (24%) surrounded by a halo of edema or CSF. This imaging finding is not specific to ependymoma and may be seen with other tumor types. Administration of contrast leads to at least partial heterogeneous and irregular contrast enhancement in virtually all ependymomas.

Supratentorial tumors, when they occur are frequently very large (>4 cm in 80%) at diagnosis. They are intraventricular in 24%, periventricular in 29%, parenchymal in 41%, and extra-axial in 6%. They appear heterogeneous with irregular enhancement similar to infratentorial tumors. Supratentorial ependymomas may have a low-density necrotic center (47%) mimicking a malignant glioma.

Imaging findings on MR and HCT are nonspecific. The sensitivity for correctly identifying an ependymoma on MR imaging is 0.5, the specificity 0.81. The differential diagnosis of a posterior fossa mass in a child includes medulloblastoma, choroid plexus papilloma, dorsally exophytic brain stem glioma, and pilocytic astrocytoma. There are, however, some imaging features more suggestive of ependymoma. The presence of desmoplastic development and a tumor-vermis cleavage plane in a posterior fossa tumor appearing isodense on CT is highly suggestive of ependymoma, as medulloblastomas more commonly originate at the roof of the fourth ventricle. Pilocytic astrocytomas more commonly are cystic with ring-enhancement occurring more laterally in the cerebellar hemispheres. Dorsally exophytic fibrillary astrocytomas may not enhance and more commonly distort the anatomy of the brainstem itself. Subependymomas are smaller (2.6 cm vs. 4 cm), less calcified, and noncystic compared to ependymoma and they typically occur in older patients.

Magnetic resonance spectroscopy has been used in attempts to improve diagnostic accuracy. Pediatric posterior fossa tumors have been shown to demonstrate different metabolic patterns. Astrocytomas have a decreased ratio of NAA/Cho ratio compared to normal brain, ependymomas have an even lower ratio than astrocytoma, and medulloblastoma have the lowest ratio. MRS has been shown to have a sensitivity of 0.75 and positive predictive value of 0.6. Neural network-based algorithms utilizing MRS in combination with standard MR imaging, patient age, and tumor size may predict histology with 95% accuracy.

Pathology

Grossly, ependymomas are soft, fleshy, reddish-gray, discrete tumors most often without a well-defined capsule. When calcified, they have whitish flecks of mineralization; rarely is there a large solid calcified mass. As on imaging, they are found commonly in the fourth ventricle extending into the lateral recesses and into the subarachnoid space of the lateral medullary cistern through the foramen of Luschka or into the cisterna magna and upper cervical spinal canal through the foramen of Magendie. Occasionally, ependymomas may invade brain tissue, exhibit cystic elements, necrotic regions, or hemorrhage.

On histologic examination, ependymomas are typically well-circumscribed, moderately cellular tumors with uniform cells. They exhibit little nuclear pleomorphism and rare mitoses. The tumors can exhibit a typical or classical morphology or they can show heterogeneous features. The diagnostic feature is the ependymal rosette, a ring of polygonal cells surrounding a central canal. Characteristic features include dichromatous patterns of small, epithelium-like cells merging with bipolar, fibrillated cells with perivascular pseudorosette formation. Combinations of perivascular pseudorosette, papillary clusters, calcification, and intranuclear inclusions may be identified in varying amounts in different regions of the tumor. Signs of malignancy can obscure the classical appearance of perivascular rosettes. Significant mitotic activity, nuclear polymorphism, and variations in the shape of the cell membranes generally charac-

terize high-grade tumors. The number of mitoses, labeling indices of proliferation markers, and cell density are considered good parameters for prognostic purposes.

A study by the Childhood Brain Tumor Consortium yielded 26 histological features and five factors that may provide a method for quantifying the histological heterogeneity of the tumor. Predicting behavior based on histology has been controversial because the microscopic pattern appears to be of limited value in establishing a prognosis.

On ultrastructural analysis, cilia in a 9 +2 arrangement, microlumina, microvilli, and long, interdigitating intercellular adhesive plaque-type junctions (zonula adherens) on the lateral surface are present on the cell membranes typical of ependymoma cells. Apical and lateral portions of these cells surrounding the microlumina are clearly different from the tight junctions (zona occludens) of epithelial tumors. Zonula adherens structures contain numerous 10-nm intermediate filaments occasionally forming thick bundles and resemble an ultrastructural correlate for GFAP (glial acidic fibrillary protein) in astrocytic tumors. These intermediate filaments positive for GFAP can be shown with colloidal gold immuno-electron microscopy. Rosette cell gatherings occur around small electron lucent lumina that are filled with numerous microvilli. Electron microscopy is not always required to make a diagnosis but can be used to confirm or establish a diagnosis when light microscopic appearance is atypical.

Immunostaining of ependymomas reveal cells are positive for GFAP and occasionally vimentin and EMA. Neuron-associated proteins such as synaptophysin are rarely seen.

Staging and Classification

Ependymomas are tumors composed of neoplastic ependymal cells that arise from ependymal or subependymal cell layers surrounding the ventricles and central canal of the spinal cord as described earlier. Embryological rests of ependymal cells may account for cases arising in the brain parenchyma and the myxopapillary ependymoma near the filum terminale-conus-cauda equina region.

The 2000 World Health (WHO) Organization classification classifies ependymomas into four broad categories. The classic or benign ependymoma (WHO Grade II) has four subtypes distinguished as cellular, papillary, clear cell, and tanycytic. The cellular variety of ependymomas are hypercellular with narrow perivascular pseudorosettes, uniform cellular appearance and low proliferative activity. Papillary ependymomas are rare and contain tubovillous architecture as their distinguishing feature. Clear cell ependymomas have clear cytoplasm with a perinuclear halo and closely mimic oligodendroglioma, neurocytoma, clear cell carcinoma, and hemangioblastoma. Immunoreactivity to GFAP and features on electron microscopy usually distinguishes it from these other tumor types. Tanycytic ependymomas consist of elongated cells arranged in fascicles with variable cell density. They resemble tanycytes, which are cells with elongated cytoplasmic process extending to ependymal surfaces. Rosettes and pseudorosettes are poorly delineated and these tumors must be distinguished from astrocytomas.

Anaplastic ependymomas are malignant tumors (WHO Grade III) and contain large numbers of mitotic figures, necrosis, and vascular proliferation. Anaplastic tumors show histological evidence of anaplasia, including high cellularity, nuclear atypia, hyperchromatism, and high mitotic activity. Vascular proliferation, necrosis, and CSF seeding are more common in these tumor types. Anaplastic ependymomas are estimated to occur in 30% of all ependymomas in more recent histologic reviews. These tumors will occasionally lose their structural features and exhibit necrosis and pseudopalisading making them difficult to distinguish from other malignant gliomas except by immunostaining and electron microscopy. The other two ependymomas categories, myxopapillary and subependymoma, are discussed in other chapters. Occasionally ependymoblastomas are grouped together in a series with ependymoma. The ependymoblastoma is a rare, malignant, embryonal brain tumor arising from periventricular neuroepithelial cells called an ependymoblast. WHO classifies them with the other primitive neuroectodermal tumors.

Treatment

Surgery is the mainstay of treatment for intracranial ependymoma. Radical resection has been shown to be the most important prognostic factor effecting survival in multiple studies. Total resection is typically achieved in around 50% and adjuvant therapy is often required.

Surgery

Surgical removal is the preferred initial treatment modality for posterior fossa ependymomas in children. Surgery provides tissue for diagnosis, reduces local mass effect, reduces tumor burden, and may open obstructed CSF pathways. Again, achieving a gross total resection (GTR) of an ependymoma is the most important determinant of patient outcome and the only prognostic factor for which there is a uni-

versal consensus. Five-year survival for a GTR is 88% compared to 53% for STR. Subtotal resection (STR) may extend symptom-free survival but it is clear that only GTR offers the best chance for a cure. Complete removal of the tumor decreases the rate of spinal seeding from 9.5% to 3.3% compared to subtotal removal, another reason for aggressive removal of the primary tumor at the first operation. Factors that prevent GTR include adherence to and invasion into the floor of the fourth ventricle, adherence to cranial nerves, and invasion of the surrounding brain. A total resection may only be achieved in only 50%–73% of cases. If a GTR was achieved at the initial operation, recurrence tumor most commonly occurs in region of prior surgery.

A postoperative MR should be obtained within 72 h to assess the extent of resection. Surgical impression agrees with radiographic assessment of tumor removal in only 68% of cases. Second-look surgery is justified for removal of residual tumor if it can be performed with low morbidity. Some authors advocate a second operation after a course of chemotherapy for residual or recurrent tumor, reasoning that chemotherapy makes subsequent surgery less difficult technically. This approach has not been investigated systematically with large numbers of patients.

Postoperative complications are related to tumor location and include cranial nerve palsies, increased ataxia, mutism, and rarely, death. Morbidity, primarily related to involvement of the brainstem and cranial nerves has decreased and ranges from 10% to 35%. Current mortality rates are less than 3%.

Cerebellar mutism and pseudobulbar palsy may develop within the first postoperative week but usually resolve over 1–3 months. For reasons that are not clear, this complication is far more common with resection of medulloblastoma than with resection of ependymoma.

Surgical approach is dependent on the location of the tumor. In young children, where tumors most commonly originate in the fourth ventricle, tumors can be resected through a midline suboccipital craniotomy or craniectomy in the prone or sitting position. Most authors report lower rates of GTR with tumors more laterally located into the lateral recess and cerebellopontine and cerebellomedullary cisterns involving cranial nerves. Multiple authors have noted that complete removal can more often be achieved in supratentorial (83%) than infratentorial (69%) cases. Supratentorial tumors are approached through a standard craniotomy with the exact nature of the approach determined by the location of the tumor. Lateral ventricular tumors and those in noneloquent regions have the highest likelihood of complete resection. Complication rates between patients receiving total and subtotal resection have been reported to be no different, implying that experience and intraoperative judgment are important in achieving a good postoperative outcome.

The use of preoperative CSF diversion procedures is almost always unnecessary, even with documented hydrocephalus at presentation. Hydrocephalus should be managed with preoperative steroids until the definitive surgical procedures. If the patient presents with acute neurological deterioration, an external ventricular drain should be placed to control hydrocephalus. There have been reported cases of upward herniation following placement of EVD and ventriculoperitoneal shunts (VPS) in patients presenting with acute hydrocephalus due to a posterior fossa mass. To prevent this complication, as little CSF should be removed as possible to achieve an improvement in clinical status. Resection of the tumor is the preferred means of re-establishing obstructed CSF pathways. Despite aggressive tumor removal, between 30% and 50% of patients will have persistent hydrocephalus, requiring the subsequent placement of a ventriculoperitoneal shunt.

Radiation Therapy

Intracranial ependymal tumors are relatively radiation resistant. Nonetheless, data from both single institutions and cooperative groups indicate that adjuvant radiation therapy has benefit in selected patients. At this time, controversy exists as to which patients should receive this therapy. Most studies suggest radiation for all patients with posterior fossa tumors, for all patients with subtotally resected tumors, for all patients with WHO Grade II tumors, and for all patients presenting with disseminated disease. Whether patients with gross total resection of supratentorial Grade II ependymomas, as defined by postoperative MR imaging, should receive irradiation is not clear. More studies are needed to clarify this question. Postoperative radiation has been shown in some studies to be effective in preventing regrowth following subtotal resection. Radiation doses of at least 5.4 Gy should be given over 5–6 weeks. The treatment fields should cover the tumor bed with a 1- to 2-cm margin to minimize long-term radiation damage. Craniospinal-axis fields offer survival advantage and are used only when spinal seeding is radiologically or pathologically evident. Radiation has deleterious effects on growth, endocrinologic function and CNS development when given to children. The deleterious effect is inversely proportional to the patient's age at the time of irradiation. In young children under the age of 3 years radiation therapy is avoided whenever possible. This needs to be balanced against the severity of the disease.

Chemotherapy

The deleterious effects of radiation, particularly on young patients, has led to the investigation of chemotherapeutic agents as adjuvant therapy in the treatment of intracranial ependymoma. Most chemotherapy regimens in retrospective studies have led to response rates on the order of 20%. Cisplatin and etoposide have been the most successful in allowing radiation to be delayed. Whether chemotherapy is effective in prolonging survival is not proven. More effective therapy is urgently needed to manage tumors in young children.

Radiosurgery

There has not been a large experience in treating ependymoma with stereotactic radiosurgery (SRS), although several recent series have been published supporting the use of SRS. There is considerable variation in the literature with respect to progression-free survival after SRS, with ranges from 22% to 32% being reported. Our experience suggests that local control of focally recurrent ependymoma is possible with SRS; patients often fail through the subsequent development of disseminated disease.

Prognosis/Quality of Life

A principle difficulty in assessing the efficacy of reported treatment strategies or prognostic factors in ependymoma relates to the lack of definitive classification of tumor biology and lack of uniformity in patient populations and selection criteria in various studies. In addition, advancements in microsurgery, anesthetic technique, neuroimaging, intensive care unit management, radiation therapy, chemotherapy, and nursing care have all played a role in altering the prognosis of patients harboring ependymomas to varying degrees. In reported series, one must be careful in considering these possible confounding factors.

As mentioned above, the most important prognostic factor effecting outcome in a patient with an ependymoma is the extent of surgical resection. Regardless of any other prognostic factor, such a resection increases the chance of progression-free survival at 5 years at least twofold.

Patient age at diagnosis plays role in determining survival; infants and children have more than twofold lower 5-year and 10-year PFS than adults. This may be related to undefined biologic difference in tumors affecting children versus adults or to location in surgically challenging areas in children. Ependymomas of the posterior fossa, particularly those extending or invading into the lateral recesses and brain parenchyma, are associated with a worse prognosis than ependymomas found elsewhere, likely reflecting increased difficulty of achieving a GTR in this location.

Poor outcome has been attributed to young age at presentation, extent of resection, spread beyond primary site, and histologic features suggestive of tumor anaplasia. The influence of histologic grade is among the most controversial of prognostic factors. Some series indicated a lack of correlation between pathologic features and outcome in childhood ependymoma while other clinical reports have identified a correlation between tumor grade and disease control. In a recent series from St. Jude's Children's Hospital in Memphis, patients with localized anaplastic ependymoma undergoing radiotherapy following total surgical resection had a progression-free survival of 28% at 3 years, compared with 84% in patients with more differentiated tumors. Anaplasia was defined as having one of the following three criteria: increased cellularity, atypia, and microvascular proliferation. These results remained significant after controlling for age at diagnosis (<3 years), preradiation therapy chemotherapy, and extent of resection. Anaplastic ependymoma was observed more frequently in supratentorial tumors and recurrence was restricted to these patients. The results were confirmed in another larger series of patients from Burdenko Neurological Institute in Moscow. Radiation was found to have a greater effect on patients with anaplastic lesions and 5-year overall survival rates were comparable to patients who had low-grade tumors.

Contemporary series report an overall 5-year survival of 60%–73% and a 10-year survival of approximately 50% [2, 3, 5, 10]. The median time to tumor recurrence is 22 months and almost all recurrences occur before 5 years. Ependymomas typically recur near the site of initial resection [1, 4, 6–9].

Surveillance scanning is always indicated following ependymoma resection and more frequent surveillance should be performed on children with deferred radiation treatment. Recurrent ependymomas should be considered for surgical re-resection unless this treatment is precluded by concerns of excessive morbidity.

Malignant progression of tumors is generally associated with accumulation of genetic aberrations in tumor cells. Several studies on ependymal tumors describe correlations between genetic alterations and tumor grade, localization, patient's age, and prognosis. Some of these studies suggest that increased genomic alterations be inversely related to the degree of anaplasia.

References

1. Duffner PK, Cohen ME, Myers MH, et al. Survival of children with brain tumors: SEER Program, 1973–1980. Neurology 1986;36:597–601
2. Duffner PK, Krischer JP, Sanford RA, et al. Prognostic factors in infants and very young children with intracranial ependymomas. Ped Neurosurg 1998;28:215–222
3. Healey EA, Barnes PD, Kupsky WJ, et al. The prognostic significance of postoperative residual tumor in ependymoma. Neurosurgery 1991;28:666–671; discussion 671–662
4. Lyons MK, Kelly PJ. Posterior fossa ependymomas: report of 30 cases and review of the literature. Neurosurgery 1991;28:659–664; discussion 664–655
5. McLaughlin MP, Marcus RB Jr, Buatti JM, et al. Ependymoma: results, prognostic factors and treatment recommendations. Int J Rad Oncol Biol Phys 1998;40:845–850
6. Nazar GB, Hoffman HJ, Becker LE, et al. Infratentorial ependymomas in childhood: prognostic factors and treatment. J Neurosurg 1990;72:408–417
7. Rawlings CE 3rd, Giangaspero F, Burger PC, et al. Ependymomas: a clinicopathologic study. Surg Neurol 1988;29:271–281
8. Robertson PL, Zeltzer PM, Boyett JM, et al. Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group.[see comment]. J Neurosurg 1998;88:695–703
9. Ross GW, Rubinstein LJ. Lack of histopathological correlation of malignant ependymomas with postoperative survival. J Neurosurg 1989;70:31–36
10. van Veelen-Vincent ML, Pierre-Kahn A, Kalifa C, et al. Ependymoma in childhood: prognostic factors, extent of surgery, and adjuvant therapy. J Neurosurg 2002;97:827–835

Medulloblastoma 35

Michael D. Taylor

Epidemiology – 462

Symptoms and Clinical Signs – 462

Diagnostics – 462

Staging and Classification – 464
Molecular Pathology

Treatment – 466
Synopsis
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 467

Future Perspectives – 468

References – 468

Epidemiology

While brain tumors are the most common solid malignancy seen in children, medulloblastoma is most common pediatric malignant brain tumor, accounting for up to 25% pediatric brain tumors [1]. Medulloblastoma has been diagnosed in all age groups, from fetuses in utero to octogenarians. However, most cases are diagnosed between 5 and 10 years of age with the peak age being 7 years [1, 2]. For unknown reasons, most case series report an excess of cases in males, with a male:female ratio of 1.8:1 often being reported [1]. Most cases occur sporadically due to unknown causes, although a small percentage of cases do occur as part of a recognizable familial tumor syndrome (see the Sect. entitled Molecular Pathology). Medulloblastoma was named, and originally described by Baily and Cushing in 1925, when they postulated that medulloblastoma cells resembled cells of the developing neural tube; 80 years later we are discovering that this original hypothesis was very insightful [3, 4].

Symptoms and Clinical Signs

The symptoms and signs at presentation are completely dependant on the age of the child at the time of presentation. In rare cases, medulloblastoma is diagnosed in utero on the basis of routine ultrasonography [2]. Babies and infants, where the sutures have not yet fused tend to present with an enlarging head circumference that is crossing growth curves. These young children may also manifest other symptoms of increased intracranial pressure including vomiting, lethargy, developmental delay, developmental regression, irritability, and loss of appetite. Signs seen in babies include macrocephaly, rapid head growth, bulging anterior fontanelle, splitting of the cranial sutures, sundowning (downward deviation of the eyes), irritability, and in later stages bradycardia and apneic spells. Most of the clinical signs and symptoms seen in very young children with medulloblastoma are secondary to increased intracranial pressure from supratentorial hydrocephalus, as the tumor is blocking the fourth ventricle. Older children have a much different presentation as their cranial sutures have fused (decreasing their tolerance for hydrocephalus), and because they can communicate with their parents. Older children often present with the classic midline triad of headache, lethargy, and vomiting [5]. Classically, the headache is present on awakening in morning, and improves after a bout of vomiting. The proposed pathophysiology for this sequence of events is that the child hyperventilates overnight, resulting in a rise in their pCO2, followed by cerebral vasodilation, resulting in a rise in intracranial pressure. The morning headache and vomiting are accompanied by hyperventilation that blows off the carbon dioxide, followed by vasoconstriction, resulting in a decrease in the intracranial pressure. Classically, patients will tell the physician that the vomiting is projectile, and/or that it is not accompanied by nausea. Many children, however, do not present in a classical, textbook manner, and many different sorts of headaches and vomiting are seen in clinical practice. Clinical signs complement the above history, with evidence of papilledema, and or sixth nerve palsy (secondary to increased ICP rather than brainstem invasion) recognized in many cases. In older children it may possible to elicit a history, or find an exam indicative of a cerebellar deficit including truncal ataxia (62% of patients), and/or limb ataxia/dysmetria (44%), and nystagmus [6].

There are no definitive signs or symptoms that allow the clinician to definitively differentiate medulloblastoma from ependymoma, or pilocytic astrocytoma, the other two common pediatric posterior fossa tumor types. Children with ependymoma are more likely to present with neck pain, neck stiffness, and head tilt due to extension of the ependymoma through the foramen magnum. Ependymoma patients are also more likely to present with intractable vomiting, due to involvement of the area postrema of the brainstem (vomiting center). Children who present with florid, lateralizing cerebellar signs may be more likely to harbor a lateral pilocytic astrocytoma.

Rarely, children will present acutely due to hemorrhage into a posterior fossa tumor, and all posterior fossa hemorrhages in children should be carefully investigated for an underlying neoplasm. Although up to 40% of pediatric medulloblastomas have undergone leptomeningeal dissemination at the time of diagnosis, very few such patients will present with symptoms or signs principally due to the metastases. However, children who present with intradural, extramedullary tumors, especially if they are multiple should undergo additional cranial imaging to rule out drop metastases from a primary brain tumor [1]. Symptomatic systemic metastases from a medulloblastoma are exceeding rare, and usually occur late in the course of the disease.

Diagnostics

Most children who present with a medulloblastoma, regardless of their age will be first investigated with a non-contrast-enhanced CT scan of the head. This study will reveal a hyperdense, well-defined lesion of the cerebellum, usually located in the cerebellar vermis (85%), but occasionally found in the cer-

ebellar hemispheres (Fig. 1) [1]. There is usually associated supratentorial hydrocephalus, often with transependymal edema. The finding of a hyperdense (as opposed to hypodense) tumor on a plain CT is thought to be due to the extremely high cellularity of medulloblastoma, and is an excellent indicator that this is indeed a medulloblastoma and not an ependymoma or a pilocytic astrocytoma. Calcifications are seen in 5%–10% of medulloblastomas, but are more common in ependymomas. Cysts can also be seen in medulloblastomas, but are far more common in pilocytic astrocytomas. With intravenous enhancement, most medulloblastomas will enhance brightly, and homogeneously. Surgeons must be aware however, that sometimes part of a medulloblastoma will not enhance, and only careful scrutiny of the preoperative films will allow the surgeon to recognize, and then resect this portion of the tumor.

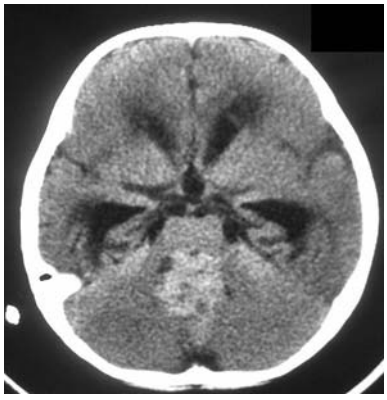


Fig. 1 Unenhanced CT scan of the head shows a hyperdense mass in the posterior fossa, with accompanying supratentorial hydrocephalus. Histology was medulloblastoma

The imaging modality of choice in cases of medulloblastoma is the MRI which provides a great deal more information about the anatomy, and extent of the tumor. Medulloblastoma shows low or intermediate signal on T1-weighted images as compared with white matter, and extremely variable signal on T2-weighted images (Fig. 2). MRI is excellent at helping the surgeon to determine if the tumor has invaded the floor of the fourth ventricle, or extended out through the outlets of the fourth ventricle. Enhanced MRI is the best test to look for leptomeningeal dissemination of the tumor in the intracranial subarachnoid spaces, as well as the ventricles. Any patient with a medulloblastoma should have a preoperative gadolinium-enhanced MRI of the entire spine in order to rule out leptomeningeal metastatic disease (Fig. 3). Leptomeningeal disease is much more common in medulloblastoma than in ependymoma or pilocytic astrocytoma; however, in a very young child with a posterior fossa tumor and widespread leptomeningeal disease, the possibility of an atypical teratoid/rhabdoid tumor should be considered. It is critical to perform the spinal MRI preoperatively, as intraoperative decisions will likely be less aggressive in the face of widely metastatic disease. Furthermore,

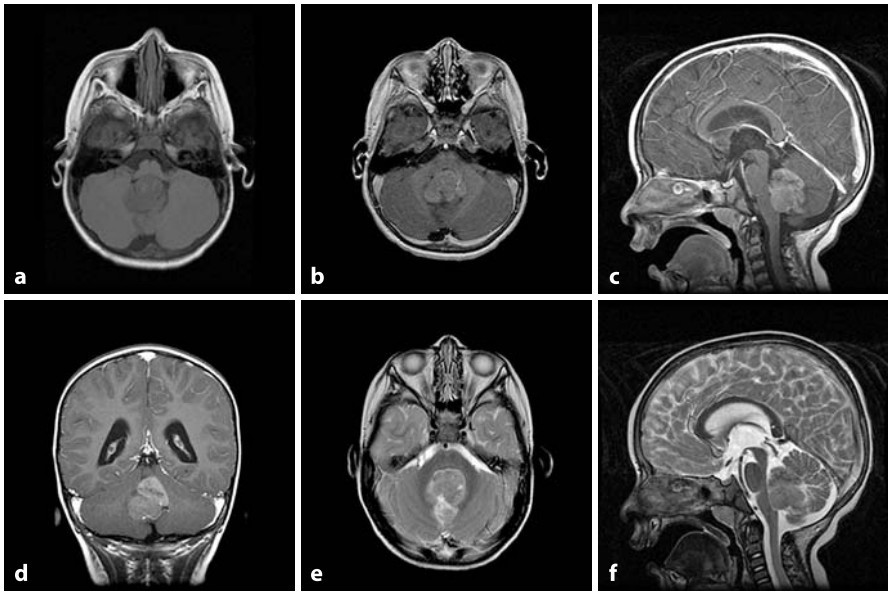


Fig. 2 MRI of the brain. (**a**) Axial T1 MRI shows a mass in the posterior fossa that moderately enhances with intravenous contrast (**b**). The mass largely occludes the fourth ventricle, but there appears to be a good plane between the tumor and the floor of the fourth ventricle. (**c, d**) Further demonstration of this midline, enhancing medulloblastoma. (**e, f**) The tumor is isointense to brain on T2 images

there is often spurious, artifactual enhancement of the spinal leptomeninges for up to 2–3 weeks post surgery. Currently, magnetic resonance spectroscopy is a research tool, but in the future it may be useful to differentiate different types of posterior fossa histologies. Postoperative imaging is also critical in the early postoperative period as reoperation may be indicated in the face of significant residual tumor. Once children have been treated for medulloblastoma, the role of periodic surveillance imaging to monitor for recurrence is controversial.

Staging and Classification

On routine histology medulloblastoma is a "small blue cell tumor" due to its high nuclear-to-cytoplasmic ratio. In the past, some authors suggested that medulloblastoma was the same biological entity as small blue cell tumors occurring elsewhere in the body, and that they all formed a family of primitive neuroectodermal tumors that arose from a common precursor cell found throughout the nervous system [i.e., pineoblastoma, supratentorial primitive neuroectodermal tumors (PNET)]. Currently this theory has fallen into disfavor, and most authors believe that medulloblastoma (PNET of the cerebellum) is a distinct biological entity that just happens to look similar to a number of other tumor types on histology. Most medulloblastomas occur in the cerebellar vermis (85%), but they may be seen in the cerebellar hemispheres, especially in older children and adults.

Fig. 3 T1 MRI with intravenous contrast of the posterior fossa and spine shows an enhancing mass in the posterior fossa (medulloblastoma). There are also nodular areas of enhancement along the spinal cord, and cauda equine, representative of leptomeningeal metastatic disease

At the time of surgery, the surgeon may find that the tumor has eroded through the cerebellar surface, or is protruding through the foramen of Magendie. The tumor appears as a pinkish gray to purple mass that has an obvious interface with the normal cerebellum. Medulloblastoma is often highly vascular, with its principle vascular supply arising from the posterior inferior cerebellar artery (PICA). Most commonly, the tumor arises from the medullary velum and does not invade the floor of the fourth ventricle. At the time of operation, it may be possible to see metastatic leptomeningeal disease which appears as a whitish coating that has been compared to sugar frosting.

Under the microscope the tumor is a highly cellular neoplasm, with large nuclei and not much cytoplasm ("high nucleo-cytoplasmic ratio"). The cells are round, with frequent mitoses (Fig. 4). Apoptotic bodies can often be recognized. Immunohistochemistry can be used to demonstrate differentiation along glial and neuronal lines, the presence of which is of uncertain significance. Several histological variants of medulloblastoma have been described; their recognition is usually possible on the basis of plain histology. Classic medulloblastoma is by far the most common variant (70% or more of cases); it consists of sheets of small blue cells. Desmoplastic medulloblastoma (10%–20% of cases) consist of paucicellular islands of well-differentiated cells surrounded by large amounts of reticulin and collagen, as well as more undifferentiated cells (Fig. 4). In some clinical series, desmoplastic medulloblastoma is associated with a better prognosis than other medulloblastoma variants. Large cell/anaplastic medulloblastoma (about 5% of cases) shows areas of large cells, and cells with anaplasia. The LCA subset of medulloblastomas are molecularly distinct from the rest of the medulloblastomas (see the Sect. entitled Molecular Pathology), and have a very poor prognosis. Medulloblastoma with extensive nodularity, and a high degree of neuronal differentiation has also been described as a separate variant, and it likely has a much better prognosis than the other medulloblastomas [7]. Molecular studies using expression array profiling are helping to refine the subdivision and classification of medulloblastomas; however, many of the afore-

mentioned histological variants are rare and therefore have not yet been well studied. Medulloblastoma must also be differentiated from another embryonal tumor that can occur in the cerebellum: the atypical teratoid/rhabdoid tumor (ATRT) [8]. This highly malignant, embryonal tumor can contain fields of small blue cells that are indistinguishable from medulloblastoma on light microscopy. Examination of larger specimens will reveal differentiation along numerous lines (hence the teratoid portion of the name), and will reveal rhabdoid cells that have a large pink cytoplasmic inclusion body made up of intermediate filaments. ATRTs were not well recognized until the 1990s, and have an extremely poor prognosis. As ATRTs largely occur in very young infants, their misdiagnosis likely accounts for some of the negative effects young age had on predicting prognosis in some of the older literature. ATRT can also be differentiated from medulloblastoma through molecular techniques as most of them will have mutations or deletions of the *hSNF5/INI1* gene on chromosome 22 [9]. Indeed, checking for deletions on chromosome 22 has entered the clinical arena, and makes up part of the standard pathological work-up of a posterior fossa small blue cell tumor in some centers.

Molecular Pathology

Little is known about the molecular biology of sporadic medulloblastoma. Characteristic chromosomal abnormalities are seen in medulloblastoma, and these chromosomal abnormalities are different than those seen in supratentorial PNET, or pineoblastoma. The most characteristic abnormality is isochromosome 17q, in which chromosome 17 breaks on the short arm (p arm), and two p arms stick together giving a chromosome with two copies of proximal 17p, two centromeres, and two complete copies of chromosome 17q (the long arm). Isochromosome 17q may be more common in cases of large cell anaplastic medulloblastoma, and may portend a poor prognosis. Large cell anaplastic medulloblastomas are also more likely to show amplification of the oncogenes *MYCC* or *MYCN*, and to have loss of function mutations of the tumor suppressor gene p53 [10, 11].

There are a number of hereditary tumor syndromes in which affected individuals are at increased risk to develop medulloblastoma [12]. Individuals with Gorlin Syndrome, or Nevoid Basal Cell Carcinoma Syndrome (NBCCS) have an increased incidence

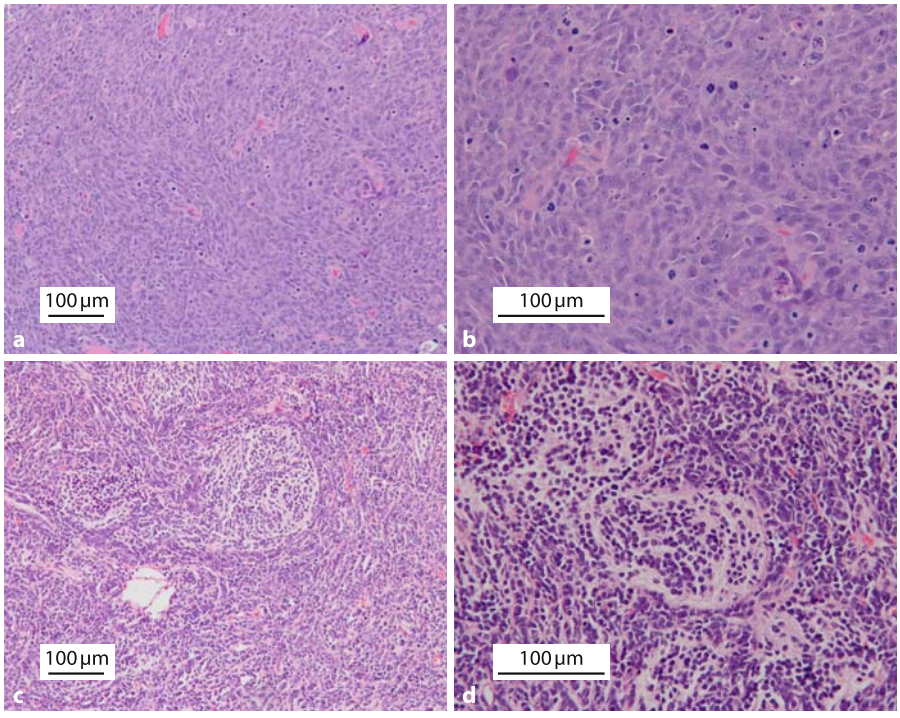


Fig. 4 Histology of Medulloblastoma. (**a**) Low power view of a classical medulloblastoma shows a typical small blue cell tumor with a high nuclear to cytoplasmic ratio. The tumor is very cellular. (**b**) Higher power view of a classical medulloblastoma showing frequent mitotic figures. (**c**) Low power view of a typical desmoplastic medulloblastoma showing nests or balls of lower cellularity mixed with areas of higher cellularity. (**d**) Higher power view of a desmoplastic medulloblastoma. (**e, f**) Reticulin stain of a desmoplastic medulloblastoma shows that the paucicellular nests are devoid of reticulin, a typical feature of desmoplastic medulloblastoma. (Histology figures courtesy of Dr. William Halliday, Hospital for Sick Children, Toronto, Canada.)

of developmental anomalies such as bifid ribs, wide set eyes, calcified dural folds, palmar and plantar pits, as well as an increased incidence of malignancies, especially basal cell carcinoma and desmoplastic medulloblastoma. It is important to recognize individuals with NBCCS as they will develop hundreds, or thousands of basal cell carcinomas in the radiation field if they are treated with craniospinal radiation. Most cases of NBCCS are secondary to germline mutations (a mutation in every cell of the body) in the *PTCH* gene on chromosome 9. PTCH is part of the Sonic Hedgehog signaling cascade, and loss of function of *PTCH* through mutation results in overactivity of the SHH cascade. Human Suppressor of Fused is another downstream member of the Sonic Hedgehog signaling cascade, and mutation of *HSUFU* in the germline predisposes children to develop desmoplastic medulloblastoma [13]. Somatic mutations of both *PTCH* and *HSUFU* have been found in sporadic desmoplastic medulloblastomas. The SHH signaling cascade is an extremely powerful mitogen for cells of the external granular cell layer of the cerebellum, the putative cell of origin for medulloblastoma.

Individuals with germline mutations of the *p53* tumor suppressor gene are predisposed to develop a wide variety of neoplasms; including leukemia, sarcomas, breast cancer, gliomas, and medulloblastoma. Any family with multiple cases of cancer should be suspected of harboring a germline *p53* mutation, which is called the Li-Fraumeni syndrome. Turcot syndrome is the clinical combination of colonic neoplasia and a brain tumor [14]. While Turcot syndrome is made up of a few different diseases, those individuals with germline mutations of the *APC* gene on chromosome 5 have an increased incidence of developmental anomalies, develop hundreds or thousands of colonic polyps that invariably progress to colorectal adenocarcinoma if the colon is not removed, and they are at increased risk to develop medulloblastoma. APC is a downstream inhibitor of the WNT signaling pathway, another powerful CNS mitogen. Other members of the WNT signaling cascade have been found to be somatically mutated in cases of sporadic medulloblastoma. Recognition of these rare syndromes is important as patients are at increased risk to develop other cancers, other family members may be at risk, and patients should receive appropriate genetic counseling before they decide to procreate. Furthermore, these syndromes have given us incredible insight into the molecular pathophysiology of medulloblastoma, and a basis to develop rational, targeted, nontoxic therapeutics in the future.

Treatment

Synopsis

Most children with medulloblastoma will be treated with a combination of maximal safe resection, treatment of associated hydrocephalus, craniospinal radiation, and chemotherapy.

Surgery

Most children with medulloblastoma will present with signs and symptoms of increased intracranial pressure. In most cases, a preoperative CSF diversion is unnecessary as treatment with intravenous corticosteroids will decrease the intracranial pressure enough to allow for resection on a semielective basis on the surgeon's next operative day. In those cases where children present in extremis (lethargy, bradycardia, respiratory collapse), CSF drainage through an external ventriculostomy is the preferred treatment. Insertion of a preoperative ventriculo-peritoneal shunt is not ideal, because it takes the amount and rate of drainage out of the physician's hands, and may allow for spread of tumor cells to the peritoneum. Endoscopic third ventriculostomy is used in some centers as an alternative to external ventriculostomy. Children may need to have their electrolyte disturbances and fluid balance corrected preoperatively due to prolonged vomiting.

The goals of surgery on a posterior fossa medulloblastoma are to unblock the CSF pathways, make a histological diagnosis, take the pressure off of critical structures such as the brainstem, and to obtain a complete, or near complete resection for the purpose of cytoreduction. The operation, posterior fossa craniotomy is done in the prone position with the head flexed. After dissecting through the soft tissue, the surgeon removes a portion of the occipital bone and the lamina of C1, following which the posterior fossa dura is opened. Many surgeons sample CSF from the cisterna magna to determine if there are malignant cells on cytology. The tumor is then dissected away from the normal cerebellum, and is removed piecemeal. It is crucial to visualize the floor of the fourth ventricle early in the operation so that the resection is not carried into the brainstem. In most cases, medulloblastoma will not invade the floor of the fourth ventricle, but in those cases in which it does, the surgeon should not chase the tumor into the brainstem or severe consequences will results (bilateral sixth, bilateral seventh nerve palsies, and worse). There is excellent evidence that children who receive a gross total resection (no tumor visible on the postoperative enhanced MRI), or a near

total resection (less than 1.5 cm3 of residual tumor) will have a better outcome than children who receive less complete resections. In fact, if there is a large residual tumor on the postoperative MRI, and the surgeon did not stop due to excessive vascularity, or the involvement of critical anatomic structures, then an early repeat resection is advisable in order to improve the child's prognosis. Overall, posterior fossa surgery is well tolerated in the current era. Death rates are low (less than 3%), and morbidity is tolerable (5%–10%). One complication that continues to plague neurosurgeons and their patients is the so-called posterior fossa syndrome or cerebellar mutism. Patients with posterior fossa syndrome (PFS) are initially fine after surgery, then around 72 h later they initially become irritable, then they become mute [15]. Focal deficits such as ataxia, and cranial nerve palsies can also be seen. The mutism will almost always improve over a period of days to weeks, but may never completely recover. Neither the anatomic basis, nor the pathophysiology of PFS is well understood, although several theories have been advanced. It seems to occur more often in children who have complete resections of very large tumors. There is no specific therapy for PFS.

Hydrocephalus may persist in up to 25% of children despite removal of the fourth ventricular mass and "unclogging" of the CSF pathways. In some cases this may be due to leptomeningeal metastatic disease, but in the majority of cases, the reason is cryptogenic. These children are usually treated with a ventriculoperitoneal shunt, although endoscopic third ventriculostomy has also been advocated.

Radiotherapy

Prior to the introduction of radiotherapy, medulloblastoma had a mortality rate of 100%. Current radiotherapy for medulloblastoma involves treating the entire craniospinal axis, with a boost to the site of the primary tumor. Children under the age of 3 years are not treated upfront with radiation, as craniospinal radiation in this age group is devastating to the developing brain, with no children so treated having a functional survival. Rather, these children are temporized with chemotherapy, and then treated with radiotherapy after the age of 3 years. The actual dose of radiation varies from center to center, and from protocol to protocol, but in our center it is 54 Gy in 30 fractions to the posterior fossa, and 36 Gy in 20 fractions to the rest of the craniospinal axis.

Although radiotherapy is the single most successful therapy for medulloblastoma, it is not without its cost. Side effects of radiation are seen in up to 56% of long-term survivors. Complications include cognitive impairment, loss of pituitary and thyroid function, radiation-induced neoplasms, sensorineural hearing loss, and moya moya syndrome (progressive occlusion of the intracranial carotid arteries) [16]. In a series from the Hospital for Sick Children in Toronto, there was an actuarial incidence of 10% of secondary malignancies [6]. Efforts are underway to identify patient subsets that can undergo reduced radiation dose, without decreasing the incidence of cure. The substitution of chemotherapy for a portion of the radiotherapy has also been suggested, but not proven as a way to reduce radiation doses.

Chemotherapy

The role of chemotherapy in the treatment of medulloblastoma is evolving [17]. Children less than 3 years of age at diagnosis will initially have chemotherapy instead of radiation as a temporizing agent, to allow their brains time to develop. Many authors divide medulloblastoma into standard risk and high risk groups. Standard risk children are greater than 3 years of age, have less than 1.5 cm^3 of residual disease, and have no evidence of distant metastases. Children with high risk disease are less than 3 years of age, have greater than 1.5 cm^3 of residual disease, and/or have disseminated disease. Most centers use chemotherapy in the setting of high risk disease. The actual chemotherapy regimen varies from protocol to protocol, and no one regimen has proven its overriding superiority. Chemotherapy has also been used in the setting of recurrence for salvage therapy. In these cases, high dose chemotherapy with autologous stem cell transplant has a high morbidity, but has resulted in some long-term survivors [18]. As our knowledge of the biology of medulloblastoma accumulates, novel, more effective, and less toxic chemotherapeutics will be introduced, and hopefully supplant cytoreductive surgery and radiotherapy.

Prognosis/Quality of Life

A number of clinical variables have been shown to correlate with a poor prognosis in medulloblastoma. Young age is associated with a negative prognosis, perhaps partially due to an unwillingness to irradiate the extremely young brain, but perhaps also due to a biological difference in medulloblastoma from babies and infants. In the older medulloblastoma literature, the population of young medulloblastoma patients is probably polluted with patients who really have ATRTs, but the difference in prognosis related to age persists after the ATRTs have been weeded out. The presence of disseminated disease is also a negative prognostic factor. Children with metastatic disease at presentation are less likely to respond to

therapy, and more likely to relapse early [1, 19]. Although there is no randomized trial of gross total resection versus a lesser resection, most surgeons, and most pediatric neuro-oncologists believe that the available evidence supports the value of gross total resection in improving the prognosis for children with medulloblastoma. Certain histological variants have been suggested to portend a favorable prognosis (i.e., desmoplastic medulloblastoma), while others may suggest a poor prognosis (large cell anaplastic medulloblastoma). A number of molecular markers of good and poor prognosis for medulloblastoma have been described. A poor prognosis has been associated with high levels of expression of the *Erb-B2* proto-oncogene, or the *MYCC* oncogene, while high levels of expression of the neurotrophin receptor *TrkC* have been associated with a good prognosis [20]. For example, in one recent study patients with average risk medulloblastoma, and low expression levels of *Erb-B2* had a 100% 5-year survival, while patients with average risk medulloblastoma, and high expression levels of *Erb-B2* had only a 54% 5-year survival. Future clinical trials will need to account for biomarkers such as these when they attempt to stratify disease. Recently, expression microarrays have been used to separate groups of medulloblastoma with a good prognosis, from those that had a poor outcome [21]. Methods such as this will eventually join classical, morphologic pathology in subclassifying medulloblastoma, as well as predicting its response to therapy, and overall prognosis.

Future Perspectives

There have been tremendous advances in the diagnosis and treatment of medulloblastoma since its description only 80 years ago. Survival rates of 70% or higher are described in many clinical trials, although they are probably lower in community-based studies that lack a referral bias. Our knowledge of the molecular biology of medulloblastoma is exploding, with one group recently publishing a paper outlining the successful treatment of medulloblastoma in a mouse model [22]. Currently however, children are still dying of medulloblastoma, and the majority of survivors have significant cognitive and physical impairments secondary to both the disease and its treatment.

References

1. Rutka JT. Medulloblastoma. Clin Neurosurg 1997;44: 571–585
2. Mitchell D, Rojiani AM, Richards D, Yachnis AT, Powell SZ. Congenital CNS primitive neuroectodermal tumor: case report and review of the literature. Pediatr Pathol Lab Med 1995;15:949–956
3. Rutka JT, Hoffman HJ. Medulloblastoma: a historical perspective and overview. J Neurooncol 1996;29:1–7
4. Wechsler-Reya R, Scott MP. The developmental biology of brain tumors. Annu Rev Neurosci 2001;24:385–428
5. Sutton LN, Phillips PC, Molloy PT. Surgical management of medulloblastoma. J Neurooncol 1996;29:9–21
6. Park TS, Hoffman HJ, Hendrick EB, Humphreys RP, Becker LE. Medulloblastoma: clinical presentation and management. Experience at the hospital for sick children. Toronto, 1950–1980. J Neurosurg 1983;58:543–552
7. Giangaspero F, Perilongo G, Fondelli MP, Brisigotti M, Carollo C, Burnelli R, et al. Medulloblastoma with extensive nodularity: a variant with favorable prognosis. J Neurosurg 1999;91:971–977
8. Packer RJ, Biegel JA, Blaney S, Finlay J, Geyer JR, Heideman R, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. J Pediatr Hematol Oncol 2002;24:337–342
9. Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 1999;59:74–79
10. Frank AJ, Hernan R, Hollander A, Lindsey JC, Lusher ME, Fuller CE, et al. The TP53-ARF tumor suppressor pathway is frequently disrupted in large/cell anaplastic medulloblastoma. Brain Res Mol Brain Res 2004;121:137–140
11. Bayani J, Zielenska M, Marrano P, Kwan Ng Y, Taylor MD, Jay V, et al. Molecular cytogenetic analysis of medulloblastomas and supratentorial primitive neuroectodermal tumors by using conventional banding, comparative genomic hybridization, and spectral karyotyping. J Neurosurg 2000;93:437–448
12. Taylor MD, Mainprize TG, Rutka JT. Molecular insight into medulloblastoma and central nervous system primitive neuroectodermal tumor biology from hereditary syndromes: a review. Neurosurgery 2000;47:888–901
13. Taylor MD, Liu L, Raffel C, Hui CC, Mainprize TG, Zhang X, et al. Mutations in SUFU predispose to medulloblastoma. Nat Genet 2002;31:306–310
14. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839–847
15. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery 1995;37:885–893
16. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004;5:399–408
17. Rood BR, Macdonald TJ, Packer RJ. Current treatment of medulloblastoma: recent advances and future challenges. Semin Oncol 2004;31:666–675
18. Mason WP, Grovas A, Halpern S, Dunkel IJ, Garvin J, Heller G, et al. Intensive chemotherapy and bone marrow rescue

for young children with newly diagnosed malignant brain tumors. J Clin Oncol 1998;16:210–221

19. Cohen BH, Packer RJ. Chemotherapy for medulloblastomas and primitive neuroectodermal tumors. J Neurooncol 1996;29:55–68
20. Gajjar A, Hernan R, Kocak M, Fuller C, Lee Y, McKinnon PJ, et al. Clinical, histopathologic, and molecular markers of prognosis: toward a new disease risk stratification system for medulloblastoma. J Clin Oncol 2004;22:984–993
21. Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, et al. Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature 2002;415:436–442
22. Romer JT, Kimura H, Magdaleno S, Sasai K, Fuller C, Baines H, et al. Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in Ptc1(+/–)p53(–/–) mice. Cancer Cell 2004;6:229–240

Supratentorial Primitive Neuroectodermal Tumors

36

Shahid Gul, Paul Steinbok

Epidemiology – 472

Symptoms and Clinical Signs – 472

Diagnostics – 473
Synopsis
Body

Pathology – 474

Staging and Classification – 475
Synopsis

Treatment – 475
Synopsis
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 476

Follow-Up/Specific Problems and Measures – 476

Future Perspectives – 477

References – 477

Epidemiology

Primitive neuroectodermal tumors (PNETs) are embryonal tumors composed of undifferentiated or poorly differentiated neuroepithelial cells. These tumors were first described in 1973 by Hart and Earle, who described PNETs as tumors which were morphologically similar to medulloblastomas but occurred outside the cerebellum. In 1993, the World Health Organization (WHO) recommended classifying medulloblastomas and PNETs under a single category, namely PNET. Those PNETs occurring in the cerebrum or suprasellar region are referred to as supratentorial PNETs (sPNETs). Pineal PNETs, otherwise known as pineoblastomas, are not considered by WHO to be sPNETs and have been excluded from discussion in this chapter. Within the group of sPNETs, tumors with a clear neuronal component have been subclassified as cerebral neuroblastoma, and those containing ganglion cells as ganglioneuroblastoma. All sPNETs are considered WHO tumor grade IV. More recently, it has become clear that the prognosis and molecular genetics of sPNETs are different from the infratentorial PNETs (medulloblastomas), and they should probably be classified separately from medulloblastoma (Table 1).

sPNETs are rare and represent less than 1% of primary central nervous system (CNS) brain tumors in children. The mean age at diagnosis for sPNETs is approximately 3 years, with two thirds of tumors diagnosed at less than 5 years of age. In contrast to pineoblastomas and medulloblastomas, which appear to have a slight male preponderance, there seems to be no sex predilection for sPNETs [1].

Symptoms and Clinical Signs

sPNETs most often present with clinical features of raised intracranial pressure. Intracranial hypertension may be related to the mass of the tumor alone or may be secondary to obstructive hydrocephalus resulting from tumor compromise of the intraventricular cerebrospinal fluid pathway. In infants, features of raised ICP may include vomiting, accelerated head growth, a bulging anterior fontanel, lethargy, papilledema, and abducens nerve palsy. In older children, intracranial hypertension can manifest as headache, nausea, vomiting, mental status change, papilledema, and abducens nerve palsy. The duration of symptoms prior to diagnosis rarely exceeds 3 months, which is what one might expect with a rapidly growing tumor.

As with other mass lesions of the central nervous system, the clinical presentation of sPNETs is influenced by the location of the mass and the regional neuroanatomy that is affected. Cerebral sPNETs typically grow from within the deep white matter and can involve corticospinal fibers and/or sensory fibers. As such, patients may present with contralateral weakness and/or sensory disturbances. Cerebral sP-

Table 1 Comparison between sPNETs and medulloblastomas

	sPNETs	Medulloblastomas
Prevalence	<1% of pediatric CNS tumors	About 20% of pediatric CNS tumors
Mean age of presentation	3 years	5 years
Sex	M=F	M>F
Imaging	Heterogeneous enhancement, distinct border	Homogeneous enhancement
Histopathology	Poorly differentiated neuroepithelial cells, small round nuclei	Same
Molecular biology	No specific chromosomal abnormalities	Deletion 17p and gain 17q
Metastasis	5%–39%	40%–60%
Treatment	Surgery + craniospinal radiotherapy + chemotherapy	Same
3-year progression-free survival	45%–47%	>80%

NETs may involve the cortex of the brain and cause seizures. Suprasellar sPNETs may compromise adjacent visual and neuro-endocrine structures.

Diagnostics

Synopsis

With CT and MRI, sPNETs appear heterogeneous due to the presence of calcification, necrosis, cysts, and hemorrhage. They are typically well-circumscribed lesions with moderate to intense enhancement and minimal surrounding edema. Spinal MRI should be obtained to assess for leptomeningeal spread to the spine.

Histologically, sPNETs are identical to medulloblastomas. Morphologically, features of sPNETs include poorly differentiated neuroepithelial cells with marked nuclear pleomorphism, variable mitotic activity and a high nuclear to cytoplasm ratio. The observed deletion of 17p and the gain of 17q in medulloblastomas have not been found in sPNETs.

Body

CT and MRI scanning are the most important tools in the diagnostic work-up of children with sPNETs. In infants with an open anterior fontanel, the initial diagnosis of the mass lesion can be made with transcranial ultrasound. In this situation, ultrasound may identify the appearance of an abnormal mass during the investigation of an enlarged head circumference and thus prompt CT and MRI scanning.

On CT imaging (Fig. 1a, b), sPNETs appear heterogeneous due to the variable presence of hemorrhage, necrosis, calcification, and cysts. Just over half of sPNETs demonstrate intratumoral calcification. CT scans are particularly useful at demonstrating the calcified component of these lesions. As with other hypercellular tumors, the solid component of sPNETs typically appears as a hyperdense mass. With contrast the tumor usually enhances brightly but inhomogeneously. Despite the malignant nature of these lesions, there is often minimal or no edema.

Although CT and MRI are both useful in characterizing sPNETs, MRI is clearly the imaging modality of choice for distinguishing these lesions from other tumors and delineating the anatomical confines of the mass lesion. The typical appearance of a sPNET on MRI is that of a heterogeneous mass with relatively well-defined margins, and moderate to intense enhancement (Figs. 2, 3). As with CT imaging, MRI may show areas of hemorrhage, necrosis, calcification, and cyst formation, with minimal associated surrounding edema. On T1-weighted MRI, sPNETs are typically heterogeneously low signal but may be high signal depending on the presence of blood. On T2-weighted MRI, PNETs generally appear isointense to cerebral cortex but may also appear hyperintense. MRI plays a key role in detection of intracranial or spinal leptomeningeal dissemination. This is of particular importance, since 20%–40% of sPNETs demonstrate evidence of such spread at presentation [1, 4].

Certain characteristics on MR imaging assist in differentiating PNETs from other tumors. Unlike other CNS neoplasms that can mimic PNETs, namely fibrillary astrocytomas, pilocytic astrocytomas, ependymomas, choroid plexus carcinoma, and gangliogliomas, PNETs are usually isointense to cortex on FLAIR sequence MR scans. In addition, the solid components of sPNETs were found to have a high signal on diffusion-weighted MR imaging [10].

In posterior fossa tumors, MR spectroscopy has been used to help distinguish medulloblastomas from posterior fossa astrocytomas and ependymomas. The role of MR spectroscopy in differentiating sPNETs from other tumors is currently not known.

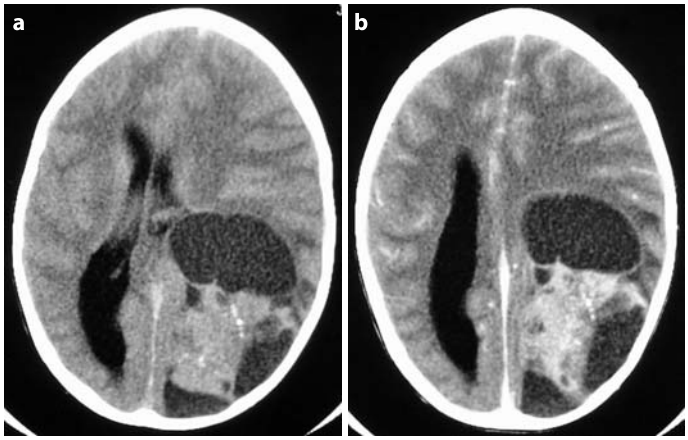


Fig. 1 Axial CT scan of sPNET: (**a**) without contrast and (**b**) with contrast

Pathology

On gross examination, sPNETs can have a variable appearance. Cerebral sPNETs are often large at the time of initial diagnosis. Suprasellar sPNETs tend to be smaller than those arising from the cerebrum. sPNETs can range from being well-demarcated lesions to having indistinct borders from the surrounding brain. sPNETs may have, in addition to the solid component of the tumor, areas of hemorrhage, calcification, necrosis, and cysts. The solid component is typically pink-red, soft, gelatinous, and highly vascular.

Histologically, sPNETs are very similar to medulloblastomas. sPNETs feature primitive, neuroepithelial cells that grow in dense sheets or cords. These cells are undifferentiated or poorly differentiated and demonstrate a high nuclear-to-cytoplasmic ratio with small, round basophilic nuclei that are rich in chromatin. There is usually marked nuclear pleomorphism with variable mitotic activity. There may be features of karyorrhexis or apoptosis. There may be Homer-Wright rosettes which are neuroblastic rosettes formed as a result of tumor cell nuclei arranged in a circular fashion about tangled cytoplasmic processes. Homer-Wright rosettes are typical but not essential for diagnosis. There may also be ependymal canals and Flexner-Wintersteiner rosettes. The histopathology may also reveal areas of calcification, necrosis, hemorrhage, and/or cyst formation.

sPNETs may also show some differentiation along neuronal, astrocytic, ependymal, muscular, or melanotic cell lines. Tumors that display neuronal differentiation can be called cerebral neuroblastoma. Tumors with ganglion cells can be called ganglioneuroblastoma. Rare examples of sPNETs may have smooth or striated muscle. Infrequently, tumor cells are found to contain melanin. Immunohistochemistry can be useful in identifying the poorly differentiated component of neoplastic cells that constitute sPNETs. Tumor cells may be reactive to synaptophysin, neuron-specific enolase (NSE), and glial fibrillary acid protein (GFAP).

The ultrastructural features of sPNETs highlight the primitive characteristics of this tumor. There is usually a paucity of cytoplasmic organelles. The presence of dense-core vesicles is diagnostic of neuroblastoma. The appearance of growth cones containing arrays of microtubules suggests ganglionic differentiation. The presence of synapses is rare. Glial differentiation is manifested by the appearance of cytoplasmic glial filaments.

Cytogenetic studies of sPNETs are relatively few. Although medulloblastomas and sPNETs appear morphologically similar, they are quite different on the basis of cytogenetics. Deletion of 17p and gain of 17q are the most frequently described chromosomal aberration in medulloblastomas. Molecular biology studies of sPNETs have failed to show any specific chromosomal abnormalities other than a deletion of 14q in 4/10 cases [7, 15]. The isochromosome 17q ab-

Fig. 2 Axial T1 postgadolinium MR scan of same patient

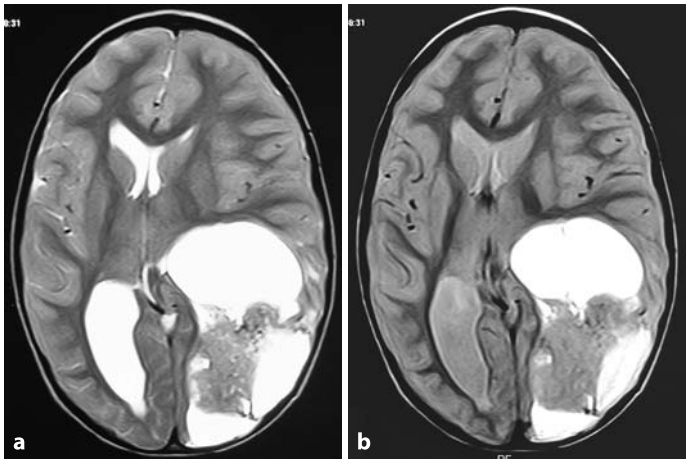


Fig. 3 Axial MR scan of same patient using (**a**) T2 and (**b**) FLAIR sequences

normality, which is found in 30%–50% of medulloblastomas, has been reported in only one sPNET [13].

Staging and Classification

Synopsis

Staging of sPNETs necessitates a spinal MRI to evaluate for the presence of leptomeningeal dissemination. This is ideally done preoperatively so as to avoid the postoperative study that may be obscured by blood and other tissue products. CSF for cytology obtained by lumbar puncture may be helpful in ruling out occult seeding of the neuraxis. Bone scan is useful for detecting extraneural spread of disease.

Staging the extent of disease in sPNET is critical in devising an appropriate treatment plan. Like medulloblastomas, sPNETs have the propensity to disseminate along cerebrospinal fluid (CSF) pathways. Metastatic dissemination of supratentorial embryonal tumors within the central nervous system is observed in 5%–39% of patients [3, 4, 12]. This is less frequent than the reported 40%–60% of patients with medulloblastoma who develop metastatic disease within the CNS. MR imaging is particularly helpful in determining the presence of metastatic deposits of tumor both within the brain and along the spinal cord. Spinal MRI is ideally performed at the time of the diagnosis of the supratentorial tumor and prior to any surgical intervention, since the immediate postoperative imaging may be obscured by the presence of blood and other tissue products. CSF for cytology obtained by lumbar puncture can be a useful method of determining the presence of metastases to the spinal cord, particularly when the spinal MRI findings are equivocal. In addition, postoperative cytology is useful in ruling out occult seeding to the spinal cord. Radionuclide bone scanning is useful for detecting extraneural dissemination to bone.

Staging of sPNETs can be done on the basis of the criteria proposed by Chang et al. [2] as follows: M0 (no tumor dissemination beyond the local site), M1 (positive CSF cytology), M2 (infratentorial or supratentorial seeding), M3 (intraspinal dissemination), and M4 (systemic dissemination, typically to bone).

Treatment

Synopsis

No single therapy is sufficient to treat sPNETs. In order to achieve maximal survival, sPNETs require a multimodality approach. A safe surgical resection of a maximal volume of tumor is the first line of treatment. This is typically followed by craniospinal irradiation for children over 3 years of age. There are currently no standard dosing regimens but the reported ranges include 4680–6000 cGy to the primary site and 2700–4000 cGy to the cranial and spinal fields. Currently there is no agreement on the use of chemotherapy for children with sPNETs. The effectiveness of adjuvant combination chemotherapy for medulloblastomas has led to a similar strategy for sPNETs.

Surgery

Surgical resection is the first line of treatment for sPNETs. The goals of surgery are (1) to obtain neoplastic tissue for histopathology, (2) to relieve symptoms caused by the mass effect of the tumor, and (3) to resect safely maximal tumor volume as a part of multimodal treatment to effect tumor control. Children with symptomatic raised intracranial pressure are managed with high-dose dexamethasone prior to surgery, and if emergent CSF diversion is required prior to resection of the tumor, a temporary external ventricular drain is preferred to a ventricular shunt. Later resection of the tumor may obviate the need for a permanent shunt.

Standard supratentorial craniotomies are used to approach both cerebral and suprasellar sPNETs. sPNETs are typically vascular and are best removed in a piecemeal fashion with either suction or ultrasonic aspiration. Some sPNETs allow the surgeon to take advantage of a defined interface between brain and tumor. In other sPNETs, the boundary between brain and tumor is indistinct and the surgeon is forced to create a dissection plane around the tumor or gradually debulk the tumor from within until a tumor brain interface is reached. The use of intraoperative computerized neuronavigational techniques can be helpful with planning the craniotomy as well as providing some guidance during the resection of deeper aspects of the tumor. Intraoperative ultrasound may be used to assist in identification of unintended residual disease at the site of tumor resection.

Imaging is usually performed on the first postoperative day to assess for residual tumor. If there is residual tumor and it is felt that it can be removed without significant risk of neurologic injury to the child, further resection of the residual mass is carried out. The goal is to resect the tumor completely, but there is no evidence of altered outcome with an almost total resection (less than 1.5 cc of residual tumor volume) compared to a total resection.

Radiotherapy

Most patients over 3 years of age with sPNETs receive postoperative radiotherapy to the tumor bed and to the craniospinal axis. The rationale for the use of radiotherapy is based on the intermediate radiosensitivity of embryonal tumors. Craniospinal radiotherapy is strongly recommended because of the propensity of sPNETs to disseminate along CSF pathways. Two trials, which studied children with supratentorial embryonal tumors, showed that the overall survival and event-free survival were lower when radiotherapy was delayed [5] or suppressed [3]. The radiation protocols for sPNETs are based on inferences from the medulloblastoma literature. The standard regimen for patients with sPNET is a radiation dose of 4680–6000 cGy to the primary site and 2700–4000 cGy to the cranial and spinal fields.

The drawbacks to radiotherapy in children are the well-known long-term sequelae. Depending on the portion of the CNS that is irradiated and the specific dosing regimen, the child who receives radiotherapy is at potential risk of radiation necrosis, neuroendocrinopathies, and cognitive impairments. The severity of the adverse effects associated with radiation is correlated with young age. The age below which the risks associated with radiotherapy become unacceptable is unknown. Most oncologists use 3 years of age as the lower limit, but others have suggested that craniospinal irradiation should not be considered in children below 5 years of age [11].

Chemotherapy

Currently there is no universal agreement regarding the standard or best therapy for sPNETs. Because of the rarity of the disease, the use of adjuvant combination chemotherapy, shown to be effective in medulloblastomas has been applied to sPNETs. The outcome using vincristine/nitrosourea combined with either prednisone or cisplatin has resulted in progression-free survivals (PFS) of 45% at 3 years [3, 14]. sPNETs arising from the pineal region appear to have a better prognosis (PFS 61%) when treated in a similar fashion [8]. Radiation combined with carboplatin as a radiosensitizing approach is being investigated by the Children's Oncology Group (COG). Alternative approaches, such as preirradiation chemotherapy with ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine increased the risk of early disease progression [17]. A French study used intensive cyclical drug couplets (carboplatin/procarbazine; etoposide/cisplatin; vincristine/cyclophosphamide) without irradiation in children <5 years with sPNETs, but 24/25 patients relapsed [11]. High-dose chemotherapy and stem-cell rescue using a combination of myeloablative drugs including thiotepa has had some success in recurrent medulloblastomas and is being evaluated for sPNETs in current clinical trials [6].

Prognosis/Quality of Life

Children with sPNETs are generally considered to have a poor prognosis. As with medulloblastomas, the aggressive biology of these tumors results in a high risk of local recurrence with the potential for leptomeningeal dissemination. Compared to medulloblastomas, sPNETs appear to be more aggressive and less chemosensitive. With aggressive surgical resection, radiotherapy, and chemotherapy, 3-year survival for children with sPNETs has been reported to be between 45% and 47% [3, 14]. The prognosis of sPNET is generally worse than that for medulloblastoma. Better outcomes for sPNETs have been reported with the use of high-dose chemotherapy with stem-cell support. Strother et al. obtained a 2-year progression-free survival of 94% for average-risk patients and 74% for high-risk patients [16]. Although the clinical and radiologic features of sPNETs seem to be similar between children and adults, there is suggestion that sPNETs in adults are associated with better outcomes [9].

In children with sPNETs, young age at diagnosis, tumor necrosis, and incomplete surgical resection may be poor prognosticators [11]. In part, the poor prognosis in younger children may reflect the reluctance to subject younger children to radiotherapy due to the potentially devastating late side effects of radiotherapy in this group of patients. The completeness of surgical resection needs to be correlated with better overall survival in children [11]. Event-free survival at 1 year was 50% for patients with complete resections compared with 8% for patients with incomplete resections [11], defined as all visible tumor resected on the basis of postoperative MRI. It is interesting to note that in adults with sPNETs, age, tumor necrosis, and the extent of surgical resection were not found to influence overall survival [9]. Patient sex and the particular location of the sPNET in a child do not seem to influence outcome [11, 14]. No histological or molecular genetic features have been shown to be associated with the overall outcome in children with sPNETs [3, 9, 11].

Follow-up/Specific Problems and Measures

Children who have undergone treatment of sPNETs require ongoing follow-up. Concerns relate to the aggressive nature of sPNETs, with a high risk of local recurrence and the potential for CSF dissemi-

nation of disease. Routine follow-up clinical assessments along with surveillance craniospinal imaging are used in identifying disease recurrence, dissemination or progression. The appropriate frequency of surveillance imaging has yet to be determined for sPNETs. Considering the probability of early recurrence, imaging every 3 months in the first 3 years and less frequent imaging thereafter seems appropriate. When there is question of disease progression on imaging, CSF cytology may be a useful adjunct. The sensitivity of CSF cytology for disease progression is unclear, but demonstration of malignant cells in the CSF indicates disease progression and dissemination.

The treatment of disease recurrence, progression, or dissemination has yet to be formally evaluated for sPNETs. The potential options for treatment include repeat surgery, local radiotherapy, and high-dose chemotherapy. A general consensus exists that local disease recurrence or progression should be treated aggressively. In these situations, it is reasonable to consider the option of repeat surgery for repeat resection of tumor. When sPNETs become disseminated after initial resection and adjuvant therapy, patients typically undergo progressive clinical decline. In the case of disease dissemination, current chemotherapeutic options are of limited beneficial effect, and patients are often considered for more experimental chemotherapy.

Future Perspectives

sPNETs in children continues to be a devastating disease. The roles of radiotherapy and chemotherapy are being reassessed. Failure in the form of local recurrence remains a formidable impediment to cure. Improved local control may be effected with higher doses of radiation to the tumor bed. It is still poorly understood whether higher doses of local radiation might improve tumor control without the unacceptable long-term side effects. The use of hyperfractionated radiotherapy may allow for higher doses of radiation without the untoward damage to normal brain. Newer and more aggressive chemotherapeutic regimens, with higher drug doses with or without bone marrow rescue, may lead to better outcomes. Ultimately, a better understanding of the molecular biology of sPNETs may hold future promise in providing more effective means of therapy for children with these tumors.

Acknowledgements. We wish to thank Chris Fryer (Oncology), Karen Goddard (radiation oncology) and Glenda Hendson (neuropathology) for their helpful comments and review.

References

1. Albright AL, Wisoff JH, Zeltzer P, et al. Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the Children's Cancer Group. Pediatr Neurosurg 1995;22:1–7
2. Chang CH, Housepian EM, Herbert C Jr. An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastomas. Radiology 1969;93:1351–1359
3. Cohen BH, Zeltzer PM, Boyett JM, et al. Prognostic factors and treatment results for supratentorial primitive neuroectodermal tumors in children using radiation and chemotherapy: a Childrens Cancer Group randomized trial. J Clin Oncol 1995;13:1687–1696
4. Dirks PB, Harris L, Hoffman HJ, et al. Supratentorial primitive neuroectodermal tumors in children. J Neuro-Oncol 1996;29:75–84
5. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. New Engl J Med 1993;328:1725–1731
6. Dunkel IJ, Finlay JL. High-dose chemotherapy with autologous stem cell rescue for brain tumors. Crit Rev Oncol-Hematol 2002;41:197–204
7. Girschick HJ, Klein R, Scheurlen WG, et al. Cytogenetic and histopathologic studies of congenital supratentorial primitive neuroectodermal tumors: a case report. Pathol Oncol Res 2001;7:67–71
8. Jakacki RI, Zeltzer PM, Boyett JM, et al. Survival and prognostic factors following radiation and/or chemotherapy for primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Childrens Cancer Group. J Clin Oncol 1995;13:1377–1383
9. Kim DG, Lee DY, Paek SH, et al. Supratentorial primitive neuroectodermal tumors in adults. J Neuro-Oncol 2002;60:43–52
10. Klisch J, Husstedt H, Hennings S, et al. Supratentorial primitive neuroectodermal tumors: diffusion-weighted MRI. Neuroradiology 2000;42:393–398
11. Marec-Berard P, Jouvet A, Thiesse P, et al. Supratentorial embryonal tumors in children under 5 years of age: an SFOP study of treatment with postoperative chemotherapy alone. Med Pediatr Oncol 2002;38:83–90
12. Mason WP, Grovas A, Halpern S, et al. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. J Clin Oncol 1998;16:210–221
13. Pruchon E, Chauveinc L, Sabatier L, et al. A cytogenetic study of 19 recurrent gliomas. Cancer Genet Cytogenetics 1994;76:85–92
14. Reddy AT, Janss AJ, Phillips PC, et al. Outcome for children with supratentorial primitive neuroectodermal tumors treated with surgery, radiation, and chemotherapy. Cancer 2000;88:2189–2193

15. Russo C, Pellarin M, Tingby O, et al. Comparative genomic hybridization in patients with supratentorial and infratentorial primitive neuroectodermal tumors. Cancer 1999;86:331–339
16. Strother D, Ashley D, Kellie SJ, et al. Feasibility of four consecutive high-dose chemotherapy cycles with stem-cell rescue for patients with newly diagnosed medulloblastoma or supratentorial primitive neuroectodermal tumor after craniospinal radiotherapy: results of a collaborative study. J Clin Oncol 2001;19:2696–2704
17. Timmermann B, Kortmann RD, Kuhl J, et al. Role of radiotherapy in the treatment of supratentorial primitive neuroectodermal tumors in childhood: results of the prospective German brain tumor trials HIT 88/89 and 91. J Clin Oncol 2002;20:842–849

Dysembryoplastic Neuroectodermal Tumors

37

Aurelia Peraud, Jörg-Christian Tonn, James T. Rutka

Epidemiology – 480

Symptoms and Clinical Signs – 480

Diagnostics – 480

Staging and Classification – 480

Treatment – 481
Surgery
Radiotherapy

Prognosis/Quality of Life – 481

Follow-up/Specific Problems and Measures – 482

References – 482

Epidemiology

Dysembryoplastic neuroectodermal or neuroepithelial tumor (DNET) was initially described by Daumas-Duport et al. [3] in 1988 as a mixed tumor with glial and neuronal elements, and has been included in the World Health Organization classification of brain tumors as a separate entity [9]. It is considered as hamartomatous, low-grade lesion (WHO grade I) due to the dysplastic appearance of the lesion and the surrounding cortex. It constitutes about 1.5% of all pediatric intracranial tumors. Macroscopically, DNETs are most of the time confined to the cerebral cortex, but may extend into the adjacent white matter. DNETs typically manifest during childhood or early adulthood with often medically refractory epileptic seizures. The seizure focus is frequently in temporal location, and the lesion most often found in the temporal lobe, followed by the frontal lobes, and only rarely located in other lobes. Associated cranial bone deformities with thinning of the overlying calvarium may be present. Histologically, DNETs are characterized by the presence of a specific element and by a nodular component. The specific elements consist of oligodendroglia-like cells which are distributed within a mucinous matrix, in which normal and dysplastic ganglion-like neurons appear to be floating ("floating neurons"). Although increased cellularity and some pleomorphism may be present, these lesions are devoid of anaplastic features. Based on the results of immunohistochemical studies, DNETs are considered to originate from progenitor cells with potential for glial and neuronal differentiation. The surgical outcome is excellent. Even after subtotal resection recurrences are rare.

Symptoms and Clinical Signs

By far the most common presenting symptom in patients with DNETs are seizures, followed by headache. The seizures usually begin before the age of 20 years, occasionally as infantile spasm. The type of seizures depends on location and age of the patient, but are most often partial seizures with or without secondary generalization. Patients with frontal lobe DNET may have psychosis as well as seizures. Focal neurological deficits are lacking. There are some reports describing an association with phakomatosis like neurofibromatosis type 1 [10]. Although DNET is commonly associated with cortical dysplasia, and some delay of early developmental milestones may be apparent, the involvement of the cortex is not severe enough to cause significant mental retardation [14].

Diagnostics

All imaging modalities show the cortical topography of the lesion, with MR images being superior for diagnosis. DNETs are typically well-circumscribed lesions with gyral or nodular configuration, hypointense on T1- and hyperintense on T2-weighted images relative to gray matter. They lead to an enlargement of the involved gyrus, but cause no mass effect. Cystic components can be seen in about 30% with focal enhancement in 16%–66% [4]. An extension into the white matter is noted in about 40%, and blurring of the gray-white matter interface has been contributed to invasion, cortical dysgenesis, and dysmyelination (Fig. 1). These tumors may be hypo- to isodense to gray matter on CT images, have cysts in up to 7.5% and calcifications in up to 36% [17]. Focal contrast enhancement is possible in around 20%. Erosion of the temporal fossa and calvarial scalloping are reported in 44%–60% of cortically based tumors [17]. DNETs are angiographically occult, occasionally avascular masses. They demonstrate an hypoperfused area on SPECT imaging with no thallium uptake and a low Methionine uptake on PET, unlike other low-grade gliomas [12].

Extraoperative electrocorticographic recordings from subdural electrodes demonstrated that the ictal onset zone in patients with temporal DNETs were more frequent in the adjacent tissues of the tumor (88.9%) than within the tumor or in mesial temporal area (66.7%) [16].

Staging and Classification

DNETs correspond histologically to WHO Grade I and are composed of a glial and neuronal components. Although they share some similarities with other mixed glioneuronal tumors like gangliolioma, glioneuronal hamartoma, or tuberous lesion, they lack so far known genetic alterations [5], and show typical histological criteria with a nodular architecture and the presence of a specific element. The specific glioneuronal element has a columnar appearance oriented perpendicular to the cortical surface. The columns are formed of axon bundles which are lined with oligodendrocyte-like cells. Neurons with normal cytology appear to float in an eosinophilic matrix between these columns ("floating neurons") [9, 2]. Despite the benign clinical course nuclear atypias, monstrous cells, foci of necrosis, and mitosis can be found [1]. Three different variants of DNET have been distinguished: the simple, the complex, and the so-called nonspecific form. These variants raise different problems in terms of their histological

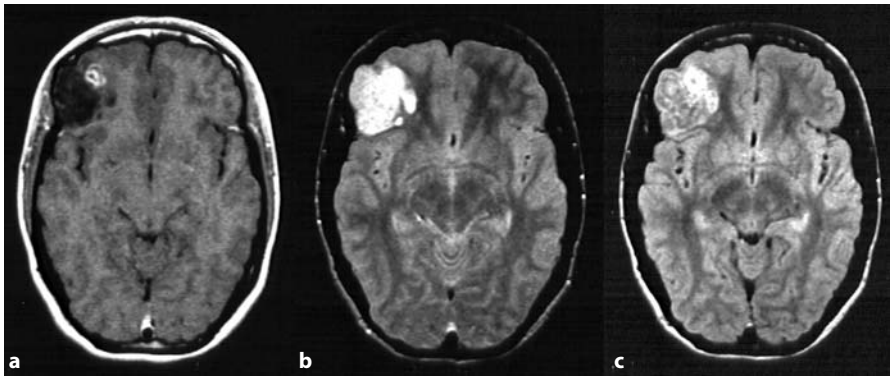


Fig. 1 DNET of a 15-year-old girl. Axial T1-weighted contrast enhanced image demonstrates a primary hypointense right frontal lesion with nodular gadolinium uptake at the mesial tumor aspect (**a**). The tumor led to an enlargement of the involved gyrus, exhibits a fairly sharp tumor margin, and is hyperintense on T2-weighted (**b**) and FLAIR (**c**) MR images

diagnosis; however, this histological subclassification has no clinical or therapeutic implication.

The simple form consists of the unique glioneuronal element, which may be surrounded by isolated neoplastic oligodendrocytes. In the complex form glial nodules are seen in association with the specific glioneuronal element and/or foci of cortical dysplasia. The glial component seen in the complex form have a highly variable appearance with a nodular or diffuse pattern, making a differentiation between conventional gliomas difficult. The nonspecific form lacks the diagnostic glioneuronal component and the multinodular architecture, but demonstrates similar clinical presentation, neuroradiological profile, and does not grow on long-term follow-up.

Treatment

Surgery

Surgical resection of the lesion is the sole reasonable therapeutic option in DNETs. Controversies exist whether the extent of resection has any impact on seizure outcome. Some authors believe that even with partial resection an improvement of seizure activity and of developmental delay can be achieved [14, 8], while others strongly recommend complete resection of the lesion including the epileptogenic area to obtain excellent seizure control [7, 16, 18]. Surgical planning and resection of lesions close to eloquent cortical areas can be facilitated with the use of neuronavigation (Fig. 2). Ictal SPECT investigations revealed hyperperfused areas of focal cortical dysplasia associated with DNET, indicating intrinsic epileptogenicity. Kameyama et al. therefore advocate excision of the DNET and the epileptogenic area of the focal cortical dysplasia [7]. But even with incomplete resection tumors remain stable over many years.

Radiotherapy

Before its description as a separate entity, DNET was usually diagnosed as low-grade astrocytoma, oligodendroglioma, mixed oligoastrocytoma, or ganglioglioma. As a result, patients were treated with radiotherapy and chemotherapy. The lesion is most likely curable by surgical excision alone; adjuvant therapy is not needed. But closed clinical and radiological follow-up is recommended because of the rare chance of tumor recurrence or even malignant transformation reported by some authors [6, 15]. The publication of Rushing et al. reports of a 14-year-old boy initially diagnosed with a mixed oligoastrocytoma who received combined radio- and chemotherapy and developed an anaplastic astrocytoma 3 years later. Review of the initial biopsy showed typical histological features of the complex form of a DNET [15].

Prognosis/Quality of Life

The overall prognosis for patients with DNETs is excellent and the lesion remains stable without progression over many years even after subtotal resection [3, 13]. Tumor recurrences or malignant transformation of the lesion are very unlikely, although single case reports exist [15]. Seizure outcome is best after early and complete resection of the lesion, and, if present, the epileptogenic area of focal cortical dysplasia [7]. Patients with a dual pathology of DNET and hippocampal sclerosis or focal cortical dysplasia seem to do worse with regard to seizure control [11].

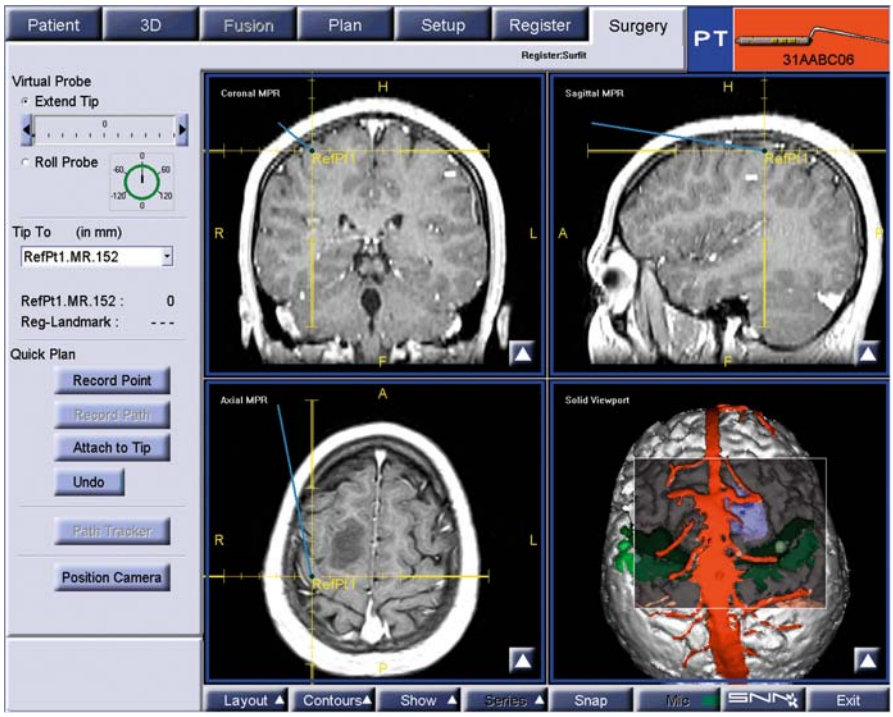


Fig. 2 Preoperative surgical planning with the help of neuronavigation. A precentral DNET of the right cerebral hemisphere is visualized on coronal, sagittal, and axial T1-weighted enhanced MR images for 3D planning and intraoperative control of the surgical procedure. The 3D reconstruction demonstrates the lesion (*blue*) in relationship to the primary motor cortex (*green*) and the superior sagittal sinus as well as the large draining veins (*red*)

Follow-up/Specific Problems and Measures

Irrespective of the extent of surgical resection, multiple reports confirm neither clinical nor radiological evidence of recurrence in any patient. Nevertheless, the outcome with regard to seizures is discussed controversially in the literature. Most authors recommend to resect not only the tumor but also the adjacent dysplastic cortex in order to obtain a seizure-free life for the patient, while some could not prove any benefit with extensive resection.

References

1. Cabiol J, Acebes JJ, Isamat F. Dysembryoplastic neuroepithelial tumor. Crit Rev Neurosurg 1999;9:116–125
2. Daumas-Duport C. Dysembryoplastic neuroepithelial tumours. Brain Pathol 1993;3:283–295
3. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER Jr, Vedrenne C. Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery 1988;23:545–556
4. Fernandez C, Girard N, Paz PA, Bouvier-Labit C, Lena G, Figarella-Branger D. The usefulness of MR imaging in the diagnosis of dysembryoplastic neuroepithelial tumor in children: a study of 14 cases. AJNR 2003;24:829–834
5. Fujisawa H, Marukawa K, Hasegawa M, Tohma Y, Hayashi Y, Uchiyama N, et al. Genetic differences between neurocytoma and dysembryoplastic neuroepithelial tumor and oligodendroglial tumors. J Neurosurg 2002;97:1350–1355
6. Hammond RR, Duggal N, Woulfe JM, Girvin JP. Malignant transformation of a dysembryoplastic neuroepithelial tumor. Case report. J Neurosurg 2000;92:722–725
7. Kameyama S, Fukuda M, Tomikawa M, Morota N, Oishi M, Wachi M, et al. Surgical strategy and outcomes for epileptic patients with focal cortical dysplasia or dysembryoplastic neuroepithelial tumor. Epilepsia 2001;42 (Suppl) 6:37–41
8. Kim SK, Wang KC, Hwang YS, Kim KJ, Cho BK. Intractable epilepsy associated with brain tumors in children: surgical modality and outcome. Childs Nerv Syst 2001;17:445–452
9. Kleihues P, Cavenee WK. Pathology and genetics of tumours of the nervous system. Lyon: IARC Press; 2000
10. Lellouch-Tubiana A, Bourgeois M, Vekemans M, Robain O. Dysembryoplastic neuroepithelial tumors in two children with neurofibromatosis type 1. Acta Neuropathol (Berl) 1995;90:319–322
11. Luyken C, Blumcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia 2003;44:822–830
12. Maehara T, Nariai T, Arai N, Kawai K, Shimizu H, Ishii K, et al. Usefulness of [11 C]Methionine PET in the diagnosis of dysembryoplastic neuroepithelial tumor with temporal lobe epilepsy. Epilepsia 2004;45:41–45
13. Markowska-Woyciechowska A, Zub L, Jarus-Dziedzic K, Rabczynski J, Paradowski B, Budrewicz S, et al. Dysembry-

oplastic neuroepithelial tumor (DNT)-case report and literature review. Neurol Neurochir Pol 2000;34:1031–1038
14. Raymond AA, Halpin SF, Alsanjari N, Cook MJ, Kitchen ND, Fish DR, et al. Dysembryoplastic neuroepithelial tumor. Features in 16 patients. Brain 1994;117 (Pt 3):461–475
15. Rushing EJ, Thompson LD, Mena H. Malignant transformation of a dysembryoplastic neuroepithelial tumor after radiation and chemotherapy. Ann Diagn Pathol 2003;7:240–244
16. Seo DW, Hong SB. Epileptogenic foci on subdural recording in intractable epilepsy patients with temporal dysembryoplastic neuroepithelial tumor. J Korean Med Sci 2003;18:559–565
17. Stanescu CR, Varlet P, Beuvon F, Daumas DC, Devaux B, Chassoux F, et al. Dysembryoplastic neuroepithelial tumors: CT, MR findings and imaging follow-up: a study of 53 cases. J Neuroradiol 2001;28:230–240
18. Zentner J, Hufnagel A, Wolf HK, Ostertun B, Behrens E, Campos MG, et al. Surgical treatment of neoplasms associated with medically intractable epilepsy. Neurosurgery 1997;41:378–386

Meningiomas 38

Abhaya V. Kulkarni, Patrick McDonald

Epidemiology – 486

Symptoms and Clinical Signs – 486

Diagnostics – 486
Synopsis

Staging and Classification – 487

Treatment – 487
Synopsis
Surgery
Radiotherapy
Conventional Radiotherapy
Stereotactic Radiosurgery

Prognosis/Quality of Life – 488

Follow-up – 489

Future Perspectives – 489

References – 489

As a group meningiomas represent a rare tumor in the pediatric age group. However, several published series in the literature provide some insight into the nature and prognosis of this tumor in children.

Epidemiology

While meningiomas are very common in adults, they are much rarer in children. Of all intracranial meningiomas, it is estimated that only 1%–3% are found in children [3, 14, 28]. As well, of all intracranial tumors in children, meningiomas account for only 1–3% [5, 8, 12–14, 22, 24, 27]. The population incidence of childhood meningiomas is estimated at 0.3 per 100,000 [7].

While in adults there is a well-described female prevalence, this is not uniformly so amongst children. In pediatric series, there appears to be a slight male predilection, with male:female ratios ranging from 1.1:1 to 3:1 [2, 8, 12, 14, 22, 26, 32]. It has been suggested that this male predilection is strongest amongst the youngest patients and skews toward a female predilection as patients age into adulthood [27].

Meningiomas can present in children of all ages, but the mean age tends to be between 9 to 13 years old [1, 12, 14, 22, 26, 34]. Rochat et al. have suggested that boys tend to present at relatively younger ages than girls [27]. Rarely, in up to 4% of cases, young infants can present with meningiomas and these tend to be large tumors at presentation [17, 32]. Meningiomas account for roughly 2% of intracranial tumors in infants under 12 months of age [7].

There is a well-documented association between meningiomas in children and the neurofibromatosis (NF). Amongst the pediatric series, NF is reported in between 5% and 24% of children with meningiomas [6, 12, 14, 22, 26, 27]. This is most commonly NF-2, but NF-1 cases are also seen. According to Deen et al., NF patients have a higher incidence of intraorbital and intraspinal meningiomas compared to the general population [6]. In some younger children, the more obvious manifestations of NF, e.g., skin stigmata in NF-1 or vestibular schwannomas in NF-2, might not manifest until years later.

Another important association with childhood meningiomas is previous cranial irradiation [15]. For example, there is a fourfold increase in the incidence of meningiomas in children who had radiation for tinea capitis [23]. In children with meningiomas, prior cranial radiation can be seen in as many as 7%–8% [9, 14]. The latency period between irradiation and tumor presentation is usually at least 8–15 years [2, 9]. There is a suggestion that meningiomas that arise from previous cranial radiation tend to be more aggressive and multifocal [30].

Symptoms and Clinical Signs

The presenting symptoms and signs of childhood meningioma vary with tumor location and age of the child. Amongst supratentorial tumors (80%–90%), common presenting symptoms include: seizures, hemiparesis/motor deficit, and symptoms of generally increased intracranial pressure [2, 12, 27, 32]. Amongst infratentorial tumors (usually cerebellopontine angle 10%–20%) the presentation could include cranial nerve palsies, especially involving nerves seven and eight [12, 32]. Children with orbital or sphenoidal meningiomas could present with visual disturbance or proptosis [6, 9, 22].

An unusual presentation seen more commonly among younger children is that of a cranial deformity (bulge) from the associated hyperostosis of the skull overlying the meningioma [2, 12].

Meningioma can present as an intradural spinal tumor in children, but this is less common, accounting for about 15%–20% of all pediatric meningiomas [6]. In this situation, the presentation is usually that of cord compression or pain [32].

Diagnostics

Synopsis

The best imaging for pediatric meningiomas is CT or MR which typically reveal large, brightly enhancing tumors, usually located in the supratentorial compartment. Unusual features of pediatric meningiomas compared to adults are: larger size of tumor, higher incidence of a cystic component, and a higher incidence of posterior fossa and intraventricular locations.

Plain X-ray images can reveal sometimes subtle abnormalities in some cases, including hyperostosis or bone erosion of the skull in 10%–30% [12, 17]. As well, a minority (around 10%–15%) might show evidence of calcification on plain X-rays [17].

In cases in which an angiogram is performed, this usually reveals a fairly vascular tumor, being fed by meningeal or sometimes choroidal arteries [12].

MRI and CT scanning are, by far, the most useful means of diagnosing a meningioma. Computed tomography typically shows a homogeneously enhancing extra-axial lesion, sometimes with calcification (see Fig. 1a) [32]. On MR imaging, meningiomas are typically iso- or hypointense on T1-weighted images and hyperintense on proton density and T2-weighted images [8, 14, 16, 26]. As with CT, these tumors tend to enhance homogeneously and brightly with MR contrast administration (see Fig. 1b, c) [16, 26]. Intracranial meningiomas can also demon-

Fig. 1 The imaging characteristics of typical intracranial meningioma in this 10-year-old girl. **a** A contrast-enhanced axial CT showing the homogeneous uptake of contrast by the very large tumor. **b, c** Axial and coronal T1-weighted MRI with gadolinium, showing again the very large size and uniform gadolinium enhancement

strate a variable amount of surrounding edema in the underlying brain matter and "tail" of dural enhancement beyond the boundaries of the main tumor mass [14, 18].

There are certain imaging features of pediatric meningiomas that are somewhat unique compared to adults. One characteristic feature is their large size at presentation, with most being greater than 5 cm in maximum dimension [8, 12, 19]. As well, there is a relatively high incidence of having a cystic component to the tumor (20%) and a similarly high incidence of multiple tumors (10%–20%) [4, 8, 13, 17, 19, 32].

Among unique features of pediatric meningiomas is their relative propensity for occurring within the posterior fossa (10%–20%), usually in the cerebellopontine angle, and within the ventricular system (10%–15%) [6, 12, 14, 27].

Staging and Classification

Classification and grading of pediatric meningiomas is the same as is used for adults. According to the World Health Organization (WHO) 2000 classification of tumors, most meningiomas are considered benign and graded as WHO Grade 1 [21]. There are some exceptions, as noted in Table 1. Within the larger pediatric series, the most common histological subtype of meningiomas are: meningothelial (25%–30%), transitional (15%–20%), fibroblastic (25%–30%), and psammomatous (1%–7%) [2, 12, 13, 32].

Atypical meningiomas have been reported with an incidence of 13%–30% in pediatric series with anaplastic meningiomas accounting for less than 10% [12–14, 22, 27, 34]. As well, chromosome 22 abnormalities are frequently found in these tumors [26, 34].

Table 1 World Health Organization (WHO) classification and grading of meningiomas [21]

WHO Grade I:	Meningothelial Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous Microcystic Secretory Lymphoplasmacyte-rich Metaplastic
WHO Grade II:	Clear cell Chordoid Atypical
WHO Grade III:	Papillary Rhabdoid Anaplastic meningioma

Treatment

Synopsis

As in adults, the mainstay of therapy in the treatment of meningiomas in children is surgical excision of the tumor, with the goal of total removal of the tumor including a generous dural margin where feasible. To date, chemotherapy has played little, if any, role in the treatment of pediatric meningioma. Conventional external beam radiotherapy may play a role in the treatment of malignant meningiomas in children, especially if there is only a partial excision. While there are no studies on the efficacy of stereotactic radiosurgery in the treatment of residual meningioma in the pediatric age group, based on its use in the adult

literature it may prove useful and further study is indicated before meaningful recommendations can be made on its use in children.

Surgery

Since Simpson published his landmark paper on the relation between extent of tumor resection and risk of recurrence [29], the goal of surgery for meningioma, whether in children or adults, has been complete resection of the tumor, and where feasible, a generous margin around its dural attachment. In the pediatric population, although the majority of meningiomas are located along the cerebral convexities, relative to adults, an increased number of pediatric meningiomas are located either intraventricularly or have no dural attachment [2, 7, 14]. In addition, pediatric meningiomas often reach a large size before coming to medical attention [19]. These factors can make complete resection of these tumors challenging.

Despite the difficulties associated with operating on large tumors in children, all major published series were able to achieve a gross total resection of tumor in the majority of cases [1, 12, 14, 19, 27, 32, 34]. The ability to achieve a total resection ranged from 60% [14] to 88% [1]. Given the potentially longer cumulative risk of growth after partial resection of meningiomas in children, total resection may be a greater imperative than in adults.

Cerebral angiography, once a mainstay in the diagnosis of meningioma, is now utilized mainly as an adjunct to surgery. Because of the relatively large tumor size seen in pediatric meningiomas, embolization of the major feeding vessels to the tumor should always be considered. This can serve to dramatically decrease the blood supply of the tumor and reduce blood loss during surgery—all the more important in small children with a smaller circulating blood volume.

Radiotherapy

Conventional Radiotherapy

Because of the ability to achieve a gross total resection in the majority of cases and a desire to avoid radiotherapy in young children, conventional external beam radiation is used infrequently in children with meningiomas. Indeed, prior radiotherapy is itself a risk factor for the development of a meningioma [20]. In general, conventional radiotherapy is reserved for older children, malignant pathology, or selected patients with surgically inaccessible residual or recurrent disease [14, 19].

Stereotactic Radiosurgery

Stereotactic radiosurgery has been shown to be a safe and effective way to treat appropriately selected meningiomas in adults (usually in surgically inaccessible areas) with control rates of up to 93% [10, 31]. Because of their rarity, there is minimal data on the use of stereotactic radiosurgery in children [11]. An Im et al. series of 11 pediatric meningiomas included three patients with either residual or recurrent tumor who went on to receive gamma knife radiosurgery [19]. Although all three have either no residual tumor or stable disease, at the present time there is insufficient evidence to make meaningful conclusions or recommendations regarding the use of stereotactic radiosurgery in children. Further study is necessary in children with surgically inaccessible residual or recurrent meningioma.

Prognosis/Quality of Life

Because of their rare occurrence, there is a paucity of large series with long follow-up of children treated for meningioma. As such, it is difficult to make definitive remarks regarding the risk of recurrence, prognosis, and quality of life in children found to harbor a meningioma. It has been suggested that children with meningiomas may have a short survival time relative to adults due to (1) the association with NF, (2) the increased size of tumors at presentation, and (3) a higher incidence of malignant changes. The literature itself is conflicting, with some studies suggesting a worse prognosis than in adults [27] and others suggesting results equal to the generally good results seen in the adult population [19].

A study of Danish children treated for meningioma between 1935 and 1984 revealed an overall survival rate of 35% [27] with mean follow-up of 16 years. The authors ascribe the poor survival rate to the size of the tumors at the time of diagnosis, and to the fact that the majority of the 22 patients in the study were treated prior to the modern neuro-imaging era. In one of the largest series in the literature, Erdlinger et al. [12] found an overall survival of 83%. All five deaths in their series of 29 patients were in children with NF, with a mortality rate of 42% in those children with NF.

In Zwerdling's report of 18 patients [34], survival was 88%. Both deaths in this study were in children with malignant histology.

Fortunately, most recent studies suggest a prognosis which parallels the one seen in adult patients. In Germano's 1994 study of 23 cases of meningioma in patients under 21 years of age [14], all patients were alive (despite a gross total resection in 60% of patients) with a mean follow-up of 10 years. Similarly, a

100% survival rate was seen in a study of 24 pediatric meningiomas in Iran [1] in which children with NF were excluded.

Although overall numbers are small, the presence of malignant histology and neurofibromatosis appear to be associated with a worse prognosis in children with meningiomas. In is unclear whether an inability to achieve a gross total resection is associated with a poor prognosis [34]. Clearly the risk of progression is greater in those who have undergone a partial resection [12, 34]. Even those who have undergone a gross total resection are at risk for recurrence [1]. When children with NF or with malignant histology are excluded, the overall prognosis in children with meningioma seems similar to that of adults.

There is a growing awareness that children treated for brain tumors suffer significant psychosocial and other morbidity relative to children treated for other forms of malignancy [25, 33, 34]. Most studies of children treated for meningioma do not directly refer to quality of life. Those that do suggest that significant neurological, neuropsychological, and endocrine morbidity is not uncommon [9, 19, 34].

Follow-up

Because of their potential years of life left to live, follow-up of children treated for meningioma is all the more critical. Similarly, because of a relatively high association with neurofibromatosis, all children found to have a meningioma should be screened for both NF-1 and NF-2. Development of bilateral vestibular schwannomas has been reported several years after treatment for a meningioma [12]; thus, even in those who do not present with other stigmata of NF, ongoing vigilance is required.

Children should undergo surveillance MRI or CT imaging on at least an annual basis for the first 4–5 years after treatment. In those who have had a complete resection, biannual MRI or CT scans can be considered.

Future Perspectives

As has been stated repeatedly in the previous paragraphs, given the rarity of meningiomas in the pediatric age group, it is difficult to infer meaningful conclusions regarding prognosis. In the future, large multicenter series may provide sufficient numbers and long-term follow-up information to determine risk of recurrence over the entire adult life span of these children.

References

1. Amirjamshidi A, Mehrazin M, Abbassioun K. Meningiomas of the central nervous system occurring below the age of 17: report of 24 cases not associated with neurofibromatosis and review of literature. Childs Nerv Syst 2000;16: 406–416
2. Baumgartner JE, Sorenson JM. Meningioma in the pediatric population. J Neurooncol 1996;29:223–228
3. Chan RC, Thompson GB. Intracranial meningiomas in childhood. Surg Neurol 1984;21:319–322
4. Darling CF, Byrd SE, Reyes-Mugica M, et al. MR of pediatric intracranial meningiomas. AJNR 1994;15:435–444
5. Davidson GS, Hope JK. Meningeal tumors of childhood. Cancer 1989;63:1205–1210
6. Deen HG Jr, Scheithauer BW, Ebersold MJ. Clinical and pathological study of meningiomas of the first two decades of life. J Neurosurg 1982;56:317–322
7. Di Rocco C, Di Rienzo A. Meningiomas in childhood. Crit Rev Neurosurg 1999;9:180–188
8. Doty JR, Schut L, Bruce DA, et al. Intracranial meningiomas of childhood and adolescence. Prog Exp Tumor Res 1987;30:247–254
9. Drake JM, Hendrick EB, Becker LE, et al. Intracranial meningiomas in children. Pediatr Neurosci 1985;12:134–139
10. Duma CM, Lunsford LD, Kondziolka D, et al. Stereotactic radiosurgery of cavernous sinus meningiomas as an addition or alternative to microsurgery. Neurosurgery 1993;32:699–704; discussion 704–695
11. Eder HG, Leber KA, Eustacchio S, et al. The role of gamma knife radiosurgery in children. Childs Nerv Syst 2001;17:341–346; discussion 347
12. Erdincler P, Lena G, Sarioglu AC, et al. Intracranial meningiomas in children: review of 29 cases. Surg Neurol 1998;49:136–140; discussion 140–131
13. Ferrante L, Acqui M, Artico M, et al. Cerebral meningiomas in children. Childs Nerv Syst 1989;5:83–86
14. Germano IM, Edwards MS, Davis RL, et al. Intracranial meningiomas of the first two decades of life. J Neurosurg 1994;80:447–453
15. Ghim TT, Seo JJ, O'Brien M, et al. Childhood intracranial meningiomas after high-dose irradiation. Cancer 1993;71:4091–4095
16. Glasier CM, Husain MM, Chadduck W, et al. Meningiomas in children: MR and histopathologic findings. AJNR 1993;14:237–241
17. Herz DA, Shapiro K, Shulman K. Intracranial meningiomas of infancy, childhood and adolescence. Review of the literature and addition of 9 case reports. Childs Brain 1980;7: 43–56
18. Hope JK, Armstrong DA, Babyn PS, et al. Primary meningeal tumors in children: correlation of clinical and CT findings with histologic type and prognosis. AJNR 1992;13:1353–1364

19. Im SH, Wang KC, Kim SK, et al. Childhood meningioma: unusual location, atypical radiological findings, and favorable treatment outcome. Childs Nerv Syst 2001;17:656–662
20. Kantar M, Cetingul N, Kansoy S, et al. Radiotherapy-induced secondary cranial neoplasms in children. Childs Nerv Syst 2004;20:46–49
21. Kleihues P, Cavenee W, eds. Pathology and genetics of tumors of the nervous system. World Health Organization classification of tumors. Lyon, France: IARC Press; 2000
22. Mallucci CL, Parkes SE, Barber P, et al. Paediatric meningeal tumors. Childs Nerv Syst 1996;12:582–588; discussion 589
23. Modan B, Baidatz D, Mart H, et al. Radiation-induced head and neck tumors. Lancet 1974;1:277–279
24. Nakamura Y, Becker LE. Meningeal tumors of infancy and childhood. Pediatr Pathol 1985;3:341–358
25. Noll RB, Gartstein MA, Vannatta K, et al. Social, emotional, and behavioral functioning of children with cancer. Pediatrics 1999;103:71–78
26. Perilongo G, Sutton LN, Goldwein JW, et al. Childhood meningiomas. Experience in the modern imaging era. Pediatr Neurosurg 1992;18:16–23
27. Rochat P, Johannesen HH, Gjerris F. Long-term follow up of children with meningiomas in Denmark: 1935 to 1984. J Neurosurg 2004;100:179–182
28. Sheikh BY, Siqueira E, Dayel F. Meningioma in children: a report of nine cases and a review of the literature. Surg Neurol 1996;45:328–335
29. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurochem 1957;20:22–39
30. Soffer D, Pittaluga S, Feiner M, et al. Intracranial meningiomas following low-dose irradiation to the head. J Neurosurg 1983;59:1048–1053
31. Subach BR, Lunsford LD, Kondziolka D, et al. Management of petroclival meningiomas by stereotactic radiosurgery. Neurosurgery 1998;42:437–443; discussion 443–435
32. Turgut M, Ozcan OE, Bertan V. Meningiomas in childhood and adolescence: a report of 13 cases and review of the literature. Br J Neurosurg 1997;11:501–507
33. Vannatta K, Gartstein MA, Short A, et al. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23:279–287
34. Zwerdling T, Dothage J. Meningiomas in children and adolescents. J Pediatr Hematol Oncol 2002;24:199–204

Pineal Region Tumors in Children

39

Anna J. Janss, Timothy Mapstone

Epidemiology – 492

Symptoms and Clinical Signs – 492

Diagnostics – 493

Pathology-Based Staging, Classification, Treatment, and Outcome – 494
Parenchymal Pineal Tumors
Pineal Cysts
Pineocytomas
Pineal Primitive Neuroectodermal Tumors/Pineoblastomas
Trilateral Retinoblastomas
Glial Pineal Tumors
Low-Grade Gliomas
High-Grade Gliomas
Ependymomas
Pineal Germ Cell Tumors
Germinomas
Teratomas
Nongerminomatous Germ Cell Tumors
Miscellaneous Pineal Tumors
Atypical Teratoid/Rhabdoid Tumors (AT/RT)
Vascular Lesions
Meningiomas

Follow-up/Specific Problems and Measures – 496
Follow-up
Ophthalmology
Sleep

Future Perspectives – 497

References – 497

This chapter will discuss common lesions that arise in the pineal gland in children. These include pineal cysts, pineocytomas, pineoblastomas (also classified as PNET), trilateral retinoblastomas, germ cell tumors including teratoma, germinoma, embryonal carcinoma, yolk sack tumor and choriocarcinoma, and astrocytomas, tectal plate gliomas, and ependymomas. They represent from 3% to 5% of all brain tumors in pediatric patients and are about one third as common in adults (i.e., about 1% of CNS tumors in adults). Pineal cysts will also be discussed as part of the neoplastic groups even though they are generally not neoplastic. Pineal cysts are being increasingly identified as MRI screening for other potential intracranial problems becomes more prevalent. The incidence of particular lesions varies based on ethnicity, with germ cell-based lesions, especially germinomas, being more common in Asian races. In North America and Europe, the incidence of intrinsic pineal tumors, glial tumors, and nongerminomatous mixed germ cell tumors predominate. Various lesions occur in the area of the pineal region, the majority of which are treated with a combination of surgery, radiation, and chemotherapy. However, some of these lesions are quite indolent and should be managed primarily with close serial observation. In general, management of the pineal lesions area in children remains relatively complex in part due to heterogeneity of lesions that arise in this location. However with modern neurosurgical and imaging techniques a reasonable cellular diagnosis can be made. Establishing the diagnosis is critical to appropriate staging and management. Management may include observation, surgery, and adjunctive radiation and/or chemotherapy therapy alone, or in combination. Appropriate follow-up is informed by the child's diagnosis and treatment.

Epidemiology

The pineal gland, located at the roof of the diencephalon, is a cone-shaped structure dorsal to the midbrain tectum. It is composed of a variety of cells including astrocytes, ganglion cells, blood vessels, and pineocytes. Pineocytes, the parenchymal cells of this organ, are specialized neurons rich in monoaminergic neuro-transmitters including serotonin, norepinephrine, and melatonin. While retinal proteins such as S-antigen are expressed on some pineocytes, the pineal gland is not photosensitive in humans and higher primates. Collateral projections from the retino-thalamic tract as well as sympathetic fibers from the superior cervical ganglion innervate the pineal gland [1]. Its role in human's higher primates is controversial, but likely related to synchronizing neuro-endocrine responses to sympathetic tone and circadian light-dark cycles [2].

Tumors of the pineal gland are rare, constituting 0.4%–1% of all CNS tumors and 3%–5% of primary pediatric brain tumors [3]. Classification of these tumors is almost as controversial as the function of the pineal itself, but for purposes of this chapter will be divided into four categories:

1. Tumors of pineal parenchyma—pineal cysts, pineocytomas, and primitive neuro-ectodermal tumors (PNETs) or pineoblastomas, including trilateral retinoblastomas
2. Glial tumors—low-grade gliomas primarily fibrillary astrocytomas, ependymomas, and higher grade gliomas such as anaplastic astrocytomas and glioblastoma multiforme;
3. Germ cell tumors—germinomas and nongerminomatous germ cell tumors such teratomas, embryonal carcinoma, yolk sack tumor, and choriocarcinoma and mixed germ cell tumors; and
4. Miscellaneous—exceedingly rare tumors such as atypical teratoid/rhabdoid tumors, vascular lesion, meningiomas, and even leukemic chloromas [4].

Reported incidence of different pineal tumors varies widely since these are rare heterogeneous tumors whose relative incidence depends on age and ethnicity. In European and North American series approximate incidence ranges are as follows: pineal parenchymal tumors, 25%–30%; glial tumors, 20%–25%; germ cell tumors, 20%–30%; and other miscellaneous tumors 10%–15% [5, 6]. In contrast, Asian series find over 70% of pineal lesions to be germ cell tumors while and parenchymal and glial tumors constitute approximately 15% each [7]. Since treatment and prognosis are dependent on tumor pathology, not location, survival statistics also depend on the ethnic make-up of a given series of patients.

Symptoms and Clinical Signs

Clinical presentation of pineal tumors, unlike outcome, is totally dependent on location. Symptoms of increased intracranial pressure (i.e., headache, nausea/vomiting, lethargy, visual disturbance) are the most common (70%) presentation of pineal tumors since they can easily obstruct the cerebral aqueduct or third ventricle resulting in hydrocephalus. Accordingly, macrocephaly, papilledema, optic atrophy, and sixth cranial nerve palsy are common signs in children with these tumors [8].

Diplopia, another common presenting symptom in children with pineal tumors (30%) may be due to abducens nerve palsy (above) or Parinaud's syndrome caused by compromise of the pupillary and oculomotor circuitry in the quadrigeminal plate and periaqueductal gray. Parinaud's syndrome is a triad: limited up-gaze, convergence-retraction nystagmus

(accommodative spasms), and light-near dissociation of pupils. Pupils will be round, mid-sized showing little or no reaction to light, but brisk constriction with attempted convergence [8].

Endocrinopathies, particularly diabetes insipidus (20%), precocious puberty (5%), or growth disturbance/short stature (5%) are important manifestations of pineal tumors in children since they most often precede obstructive hydrocephalus [9]. These are likely due to aberrant hypothalamic and pituitary function most often caused by tumor dissemination along the third ventricle, but may be due to mass effect on the hypothalamus.

Gait disturbance in children presenting with pineal tumor may be due to focal weakness (<5%), truncal ataxia (7%–10%) or Parkinsonian tremor and akinesia. [10]

Diagnostics

Determining the pathology and stage of a pineal tumor depends to a great extent on the neuro-imaging of the lesion, and may not require surgical pathology. A CT scan of the head is likely to identify hydrocephalus, a large pineal lesion or calcification of the pineal gland which is abnormal in children under 6 years of age [11]; an MRI (complete with diffusion weighted images, T1 with and without gadolinium and T2/FLARE), is important to clearly identify anatomy and focus the differential diagnosis [12, 13]. If hydrocephalus is present, decompression of ventricles is critical, and obtaining serum and CSF tumor markers is important (Fig. 1, Table 1). It is also advisable to perform a complete MRI of the spine with and without gadolinium for staging purposes since a significant number of germinomas, germ cell tumors, and pineal PNETs exhibit subarachnoid spread at presentation and the presence of tumor impacts prognosis and therapy. CSF collected from a lumbar puncture is preferable for examination of CSF cytology and should be performed following the spinal MRI

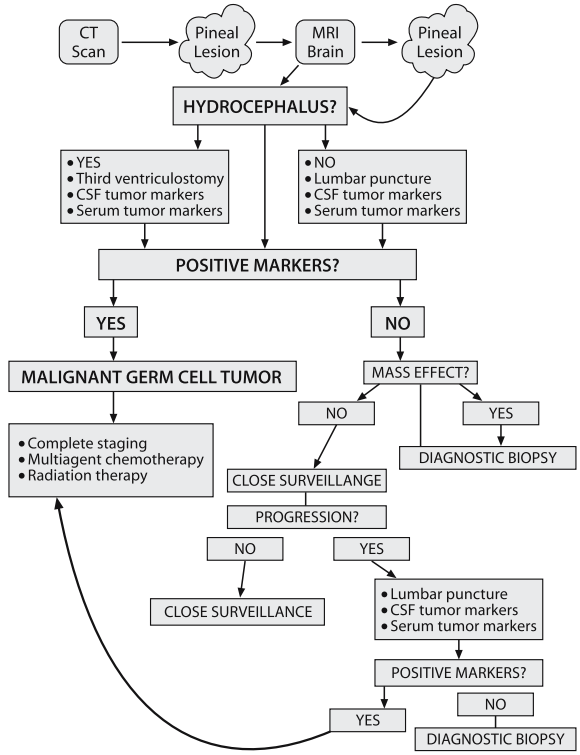


Fig. 1

Table 1 Tumor markers in patients with pineal tumors

Tumor type	α-Fetoprotein)	Chorionic gonadotropin	Placental alkaline phosphatase
Germinoma	–	±	+
Teratoma	–	–	±
Malignant teratoma	±	±	±
Undifferentiated germ cell tumor	±	±	±
Choriocarcinoma	–	+	±
Endodermal sinus tumor	+	–	±
Embryonal cell tumor	+	+	±
Pineocytoma	–	–	–
Pinealoblastoma (PNET)	–	–	–

to avoid imaging artifact that may be misinterpreted as tumor. If there is no hydrocephalus, tumor markers and CSF cytology should be obtained by lumbar puncture after the staging spine MRI. Any elevation in CSF α-fetoprotein, and CSF chorionic gonadotropin greater than 100 IU is diagnostic of a malignant germ cell tumor in most patients over 6 months of age [14–16].

If tumor markers are negative, the pineal lesion does not exhibit mass effect and the patient does not report progressive symptoms, close clinical and radiographic surveillance at intervals of 1–3 months is a reasonable course given that many pineal lesions (cysts, low-grade gliomas, and pineocytomas) have an indolent course and may not require therapy [6, 7, 17, 18]. If there is clear radiographic or clinical progression and tumor markers remain negative, a diagnostic biopsy is recommended. CSF cytology should be examined 10–14 days following surgical intervention to avoid cellular artifacts that may lead to false positive test results.

Pathology-Based Staging, Classification, Treatment, and Outcome

Parenchymal Pineal Tumors

Pineal Cysts

Pineal cysts are likely the most common mass lesion arising in or near the pineal gland. These tend to be well circumscribed but can be multiloculated and in general do not enhance. These cysts can at times be difficult to differentiate from a pineocytoma on neuroimaging and consequently close serial observation is warranted. Some authors [19] believe that evening levels of melatonin are elevated in patients with pineocytomas as opposed to a normal or diminished level in pineal cysts. If the cyst remains stable or asymptomatic, no intervention is warranted. If it enlarges and begins to cause neurological problems or compression of adjacent structures, surgical therapy with an attempt at excision is warranted since this lesion might be harboring a pineocytoma.

Pineocytomas

Pineocytomas are felt to be primarily benign lesions arising in the pineal gland although there remains some dispute as to the proper histological classification in the treatment and prognosis of these lesions. In general, it is felt that in the pineocytomas which have a more benign microscopic appearance, gross total resection and observation is all that is needed for treatment. However, evidence of malignant change or aggressive cell type or evidence of metastatic lesions suggests that one would be dealing with a more aggressive tumor and treatment should be tailored to represent that information. This treatment generally includes radiation therapy although there exist scattered reports of success using stereotactic radiosurgery. These mid-grade lesions have a median survival of about 60 months. A clarification has been described where tumors with dedifferentiated features, increased mitoses and diminished neurofilaments are considered midway between pineocytomas and pineoblastomas [5, 20].

Pineal Primitive Neuroectodermal Tumors/Pineoblastomas

Pineoblastoma is an older term used to describe primitive neuroectodermal tumors (PNETs) of the CNS located in the pineal gland. Pineal PNETs represent approximately half of the primary pineal parenchymal tumors in most large pediatric series. These tumors are treated relatively aggressively much like their infratentorial counterpart, medulloblastoma, but have higher rate of recurrence. Children with good resections and no evidence of subarachnoid dissemination at presentation, treated with combinations of craniospinal radiation and multiagent chemotherapy have 47% recurrence-free survival at 5 years [21]. The presence of metastatic spread, young age, and a large tumor with significant residual after resection portends a worse outcome for those unfortunate patients [22]. Staging of all PNETs should include a preoperative spine MRI when possible, and examination of CSF for tumor cytology. Biologic features of pineal and supratentorial tumors are likely the reason for differential response to treatment. We anticipate that with advances in understanding of molecular biology, signal transduction mechanisms in cancer, and experimental therapeutics more effective and targeted therapies will be available for these malignancies [23].

Trilateral Retinoblastomas

Children with retinoblastoma have increased risk for intracranial PNET, primarily of the pineal gland. The rate of this risk is 3% in all retinoblastoma, 5% in those with sporadic bilateral retinoblastoma and 8% in children with familial retinoblastoma. All children with retinoblastoma, and particularly those with the familial trait should undergo surveillance imaging for detection of the tumor in the "third eye," a folkloric term for the pineal gland [24]. Presence of pineal calcification demonstrated by CT prior to 6 years of age is suspicious for pineal tumor in

these children [11, 25] and deserves extensive evaluation and follow-up. Treatment of these tumors is similar to children with other pineal PNETs, but outcome seems to be worse [24, 26, 27]. New treatment protocols for unilateral and bilateral retinoblastoma may be reducing the incidence of intracranial PNET in these children [28], but due to the low incidence of this disease larger studies and extended observation periods may be necessary to confirm this report.

Glial Pineal Tumors

Low-Grade Gliomas

Glial tumors do not generally arise in the pineal gland itself but rather from the surrounding structures, in the tectum and in the posterior portions of the basal ganglia. Lesions in or near the tectum tend to be very low-grade gliomas which do not require any action other than to manage the hydrocephalus associated with the tumor. If the lesion involves more of the basal/ganglia posterior thalami, one might consider a stereotactic biopsy to document the histopathologic characteristics of these lesions. Nonetheless, in the absence of malignant changes on histopathology or significant growth on serial scanning, treatment is generally withheld except for the management of hydrocephalus.

High-Grade Gliomas

High-grade gliomas including anaplastic astrocytomas and glioblastoma multiforme are exceedingly rare in children overall and even less common in the pineal gland, accounting for only 2% of these tumors. Treatment is comparable to that of high-grade gliomas in other locations (see Chap. 25), and outcome in other locations is highly correlated to extent of resection [29]. This is unproven for pineal region tumors.

Ependymomas

Ependymomas will also occur in this area although they usually represent less than 1% of the pineal region tumors reported. They are treated in much the same way as supratentorial ependymomas with an attempt at aggressive resection with adjunctive therapy depending on the cell type and location [30]. There are some neuro-oncologists who feel total resection of supratentorial ependymoma does not warrant adjunctive therapy but simply close follow-up [31]. It has been taught that the presence of anaplasia in ependymoma was not a significant prognostic factor; however, recent articles have suggested that at least in infratentorial ependymomas the presence of anaplasia does portend a worse outcome and thus more aggressive adjunctive therapy for these lesions is warranted [32].

Pineal Germ Cell Tumors

Germinomas

Germ cell tumors continue to constitute the bulk of the neoplastic lesions which arise in the pineal region. These tumors are more common in children than adults with the majority arising between 11 and 15 years of age. There is a male predominance of approximately two to one. In most large series, the incidence of a pure germ cell tumor or germinoma is approximately 40%–50% in part depending upon the nationality of the group being studied, with Asian races tending toward the high end [6, 33, 34].

Staging for this tumor again should include preoperative MRI of the spine as well as examination of CSF cytology and tumor markers. Significant elevation of AFP and β-HCG (above) in the serum or CSF excludes the diagnosis of pure germinoma. Endoscopy has been shown to be useful in the management of attendant hydrocephalus, biopsy of the lesion, and identifying intraventricular metastasis not seen in neuro-imaging or CSF studies [9].

Germinomas are exquisitely treatment-sensitive tumors with overall survival exceeding 90% with local and ventricular volume radiation for children with localized disease, and 80% with craniospinal radiation in children with disseminated disease [16, 35]. Current multi-institution trials in the US, Asia, and Europe are adding chemotherapy to treatment of these tumors and attempting to reduce the dose and volume of radiation to reduce the toxic late radiation effects. It will be difficult to assess advantages of these trials due to the impressive efficacy of standard radiation and the fact that most patients with this disease are in the second decade of life, and thus less sensitive to the endocrinologic and cognitive late effects of radiation than younger children [35].

Poor prognostic factors for these patients include dissemination at presentation and any elevation in tumor marker (AFP and β-HCG). Unlike most CNS malignancies, tumor recurrence can be effectively treated with multiagent chemotherapy and/or reirradiation [36].

Teratomas

Both mature and immature teratomas respond best to aggressive surgical resection and even in the immature form this treatment can be curative.

Nongerminomatous Germ Cell Tumors

Nongerminomatous germ cell tumors (NGGCT) include embryonal cell carcinomas and endodermal sinus tumors at roughly 5%–9% incidence, teratoma both malignant and benign at 12%–18% incidence, choriocarcinoma 3%–5% incidence, and mixed germ cell tumors at 8%–20% incidence [37]. The role of surgery in these settings tends to be limited to obtaining a tissue diagnosis if a diagnosis cannot be obtained based on cytology or tumor markers in the CSF or blood.

These tumors are treated with multiagent chemotherapy and cranio-spinal radiation with additional boosts of radiation to lump tumor. The effect of a surgical resection on these malignant tumors on survival is minimal. Relapse-free survival 5 years from diagnosis in children with NGGCT ranges between 30% and 50% [6, 38]. Irradiation of tumor on neuroimaging in response to chemotherapy alone prior to radiation appears to improve outcome and may permit reduction of the dose of radiation. Trials to demonstrate this on a multi-institutional basis are ongoing. There are reports that should there be residual mass after aggressive adjunctive therapy, surgery to remove this portion of the lesion is warranted since it is likely to be a teratoma [16].

Miscellaneous Pineal Tumors

Atypical Teratoid/Rhabdoid Tumors (AT/RT)

AT/RT are highly malignant tumors of young children identified in the last 20 years. Half of these tumors occur supratentorially, and a significant number of these in the pineal. While rare in older patients, they account for 25% of embryonal tumors in patients under 12 months [39–40]. Staging of these tumors, like PNETs and germ cell tumors should include neuroimaging of the spine and examination of CSF cytology to exclude subarachnoid dissemination. In addition, imaging of the lungs and kidneys is warranted, as these tumors may be multifocal [41].

Early reports found that these tumors were universally fatal, but recent series suggest that some children with these tumors will survive if treated with aggressive chemotherapy and radiation. Novel immunostains may facilitate diagnosis of this tumor and children with this rare, highly morbid tumor should be referred for disease-specific treatment currently ongoing at multiple academic institutions [40].

Vascular Lesions

Despite confluence of major arteries and venous sinuses superior to the third ventricle, vascular anomalies of the pineal gland are exceedingly rare; however, they must be considered in the differential diagnosis in order to institute appropriate therapy. CT angiography or MR angiography may help establish this diagnosis [6, 20, 34, 42]. Treatment depends on the type of vascular lesion and the anatomy of the vasculature, a discussion not within the scope of this chapter.

Meningiomas

Incidence of meningiomas in pediatric populations is under 2% [43] and those in the pineal region vanishingly rare. When tissue diagnosis has been made, treatment and outcome is comparable to that of meningiomas of other brain regions (see Chap. 38).

Follow-up/Specific Problems and Measures

Follow-up

Follow-up for these tumors is dependent on the diagnosis and treatment. Obviously, a child who has had gross total resection of a cyst of benign tumor will require less intensive therapy than a child treated for a pineal malignancy. Guidelines for serial imaging for most brain tumors has not clearly been established, but in general is every 8–12 weeks while on therapy, every 12 weeks for a year after therapy, and every 6 months for 3–4 years after that. Annual neuro-imaging is standard for up to 10 years after diagnosis. Children with positive AFP or β-HCG prior to treatment of NGGCT may also benefit from serial monitoring of these markers in serum or CSF.

Children treated with radio- or chemotherapy need to be monitored regularly for late effects of their treatment. Guidelines for appropriate follow-up testing for specific drugs and radiation doses have been published and are available online (http://www.survivorshipguidelines.org).

Ophthalmology

Children who present with diplopia and/or visual impairment should be followed by ophthalmology and/or neuro-ophthalmology. Preservation of residual vision and correction of disconjugate gaze, either surgically or by use of prisms, are crucial to maintain quality of life in this patient population.

Sleep

There are no systematic studies of the impact of tumors, radiation, or surgery in the pineal on sleep architecture, despite the role of melatonin and the diencephalon in maintenance of circadian rhythms. Anecdotal reports suggest that melatonin may improve sleep in children after surgery to the pineal gland [44]. Additionally, pharmacologic management of sleep and arousal can be helpful for children with profound vision loss since light may regulate their circadian rhythm.

Future Perspectives

Use of third ventricular endoscopy for biopsy is a neuro-surgical technique available within the last decade. Visualization of metastatic tumor with this technology may have a role in staging of tumor as well as diagnosis ant therapy [45].

Advances in neuro-radiology have revolutionized management of children with pineal tumors. As indicated above serial imaging may be sufficient to manage some lesions of the pineal. MR spectroscopy is used clinically to demonstrate ratios of chemical species in the brain parenchyma and may suggest the cellularity or malignancy of a pineal lesion, but does not replace biopsy or demonstration of tumor markers as a diagnostic tool. There are some reports of single photon emission tomography being useful in the differential diagnosis of these tumors, but this technology is not universally available and its specificity and sensitivity is not established [46].

Basic research into differential gene expression in different tumors, particularly gliomas and embryonal tumors like PNETs and AT/RTs is informing new targeted therapy in pediatric neuro-oncology. Tumor tissue banking is a critical part of this work. The Children's Oncology Group pediatric clinical trial for infants will require tissue submission to a central bank prior to patient enrollment. The next generation of brain tumor trials, particularly in PNETs, will likely stratify treatment based on biologic markers as well as clinical prognostic factors [23]. Preservation of surgical specimens as snap frozen tissue, in fixatives that preserve RNA as well as classic fixatives should be a major concern for pediatric neuropathology and neurosurgery as it contributes greatly to understanding cancer biology and response to therapy.

The current strategy of avoiding biopsy of pineal tumors in children with elevated AFP or β-HCG may handicap progress in understanding and treatment of NGGCT. Similarly, small biopsy size makes banking of pineal germinomas and PNETs challenging. New techniques requiring small amounts of tumor tissue and isolation of DNA from paraffin imbedded specimens may overcome this problem, but participation in cooperative studies will be the only way that we can move understanding of pineal tumors forward and improve treatment and outcome of children with these relatively rare brain malignancies.

References

1. Carpenter MB. The diencephalon. In Carpenter MB, editor. Core text of neuro-anatomy. Baltimore: William and Wilkins; 1991. p. 20–21
2. Russell DS, Rubenstein LJ. Tumors of pineal parenchymal and glial cells. In L Rubenstein, editor. Pathology of tumours of the nervous system. Baltimore: William and Wilkins; 1990. p. 380–394
3. Yamada Y, Mena H, et al. Immunohistochemical characterization of pineal parenchymal tumors using novel monoclonal antibodies to the pineal body. Neuropathology 2002;22:66–76
4. Kudoh T, Otoi H, et al. Simultaneous development of pineal tumor and an intradural spinal mass during remission of acute lymphocytic leukemia. Jpn J Clin Oncol 2000;30:105–8
5. Fauchon F, Jouvet A, et al. Parenchymal pineal tumors: clinicopathological study of 76 cases. Int J Radiation Oncology Biol Phys 2000;46:959–68
6. Konovalov A, Pitskhelauri D. Principles of treatment of the pineal region tumors. Surg Neurol 2003;59:250–68
7. Kang J, Jeun S, et al. Experience with pineal region tumors. Childs Nerv Syst 1998;14:63–8
8. Glazer JS, Siatkowki RM. Intranuclear disorders of eye movement. In: Glazer JS, editor. Neuro-ophthalmology. Philadelphia: Lippincott Williams and Wilkins; 1999. p. 452–454
9. Reddy A, Wellons J, et al. Refining the staging evaluation of pineal region germinoma using neuroendoscopy and the presence of preoperative diabetes insipidus. Neuro-Oncology 2004;6:127–33
10. Dolendo M, Lin T, et al. Parkinsonism as an unusual presenting symptom of pineal gland teratoma. Pediatric Neurol 2003;28:310–2
11. Zimmerman R, Bilaniuk L. Age related incidence of pineal calcification detected by computer tomography. Radiology 1982;142:659–62
12. Zee C, Segall H, et al. MR imaging of pineal region neoplasms. J Comput Assist Tomogr 1991;15:56–63
13. Satoh H, Uozumi T, et al. MRI of pineal region tumours: relationship between tumours and adjacent structures. Neuroradiology 1995;37:624–30
14. Felix I, Becker L. Intracranial germ cell tumors in children: an immunohistochemical and electron microscopic study. Pediatr Neurosurg 1990–91;16:156–62
15. Herrmann H, Westphal M, et al. Treatment of nongerminomatous germ-cell tumors of the pineal region. Neurosurgery 1994;34:524–9

16. Friedman J, Lynch J, et al. Management of malignant pineal germ cell tumors with residual mature teratoma. Neurosurgery 2001;49:1271
17. Baumgartner J, Edwards M. Pineal tumors. Neurosurg Clin N Am 1992;3:853–62
18. Chandy M, Damaraju S. Benign tumours of the pineal region: a prospective study from 1983–1997. Br J Neurosurg 1998;12:288–33
19. Mandera M, Marcol W, et al. Pineal cysts in childhood. Childs Nerv Syst 2003;19:750–5
20. Jouvet A, Saint-Pierre G, et al. Pineal parenchymal tumors: a correlation on histological features. Brain Pathol 2000;10:49–60
21. Reddy A, Janss A, et al. Outcome for children with supratentorial primitive neuroectodermal tumors treated with surgery, radiation and chemotherapy. Cancer 2000;88:2189–93
22. Jakacki R, Zelzer P, et al. Survival and prognostic factors following radiation and/or chemotherapy of primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Childrens Cancer Group. J Clin Oncol 1995;13:1377–83
23. Grotzer M, Janss A, et al. TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors. J Clin Oncol 2000;18:1027–35
24. Bader JL, Meadows A, et al. Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. Cancer Genet Cytogenet 1982;5:203–13
25. Campo MD, Davis M. The role of CT in the diagnosis and management of childhood pineal region tumours. Australas Radiol 1991;35:336–9
26. Potter PD, Shields C, et al. Clinical variations of trilateral retinoblastoma: a report of 13 cases. J Pediatric Ophthalmol Strabismus 1994;31:26–31
27. Moll A, Imhof S, et al. Second primary tumors in patients with retinoblastoma. A review of the literature. Ophthalmic Genet 1997;18:27–34
28. Shield C, Meadows A, et al. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Arch Ophthalmol 2001;119:1269–72
29. Bucci M, Maity A, et al. Extent of surgical resection predicts a favorable outcome for children with malignant gliomas. 2004
30. Sutton L, Goldwein J, et al. Prognostic factors in childhood ependymomas. Pediatr Neurosurg 1991;16:57–65
31. Awaad Y, Allen J, et al. Deferring adjuvant therapy for totally resected intracranial ependymoma. Pediatric Neurol 1996;14:216–9
32. Merchant T, Haida T, et al. Anaplastic ependymoma: treatment of pediatric patients with or without craniospinal radiation therapy. J Neurosurg 1997;86:943–49
33. Schild S, Scheithauer B, et al. Histologically confirmed pineal tumors and other germ cell tumors of the brain. Cancer 1996;78:2564–71
34. Knierim D, Yamada S. Pineal tumors and associated lesions: the effect of ethnicity on tumor type and treatment. Pediatr Neurosurg 2003;38:307–23
35. Merchant T, Sherwood S, et al. CNS Germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation. Int J Radiat Onocol Biol Phys 2000;46:1171–6
36. Ono N, Isobe I, et al. Recurrence of primary intracranial germinomas after complete response with radiotherapy: recurrence patterns and therapy. Neurosurgery 1994;35:615–20
37. Bloom H. Primary intracranial germ cell tumors. Clin Oncol 1983;2:233–57
38. Robertson P, DaRosso R, et al. Improved prognosis of intracranial non-germitomoma germ cell tumors with multimodality therapy. J Neurooncol 1997;32:71–80
39. Burger P, Yu I, et al. Atypical teratoid/rhabdoid tumor of the central nervous system. A highly malignant tumor of infancy and childhood frequently mistaken for a medulloblastoma (A POG Study). Am J Surg Pathol 1998;22:1083–92
40. Hilden J, Meerbaum S, et al. Central Nervous System atypical teratoid/rhabdoid tumors: results of therapy in children enrolled in a registry. J Clin Oncol 2004;22:2877–84
41. Rorke L, Packer R, et al. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 1996;85:56–65
42. Linggood R, Chapman P. Pineal Tumors. J Neurooncol 1992;12:289–90
43. Surawicz T, McCarthy B, et al. Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990–1994. Neuro-Oncol 1999;1:14–25
44. Jan J, Tai J, et al. Melatonin replacement therapy in a child with a pineal tumor. J Child Neurology 2001;16:139–40
45. Oi S, Shibata M, et al. Efficacy of neuroendoscopic procedures in minimally invasive preferential management of pineal region tumors: a prospective study. J Neurosurg 2000;93:245–53
46. Plowman P, Saunders C, et al. On the usefulness of brain PET scanning to the paediatric neuro-oncologist. Br J Neurosurg 1997;1997:525–32

Pituitary Tumors in Children 40

Aaron S. Dumont, Jay Jagannathan, John A. Jane Jr

Epidemiology – 500

Symptoms and Clinical Signs – 500

Diagnostics – 500

Classification – 501

Treatment – 501
PRL-Secreting Adenomas
Cushing's Disease
GH-Secreting Adenomas

Prognosis – 503

Follow-up – 503

Future Perspectives – 503

References – 503

Epidemiology

Pituitary tumors are relatively uncommon in the pediatric population and most commonly present during adolescence. The average annual incidence has been estimated at 0.1 per million children, comprising about 1%–2% of all intracranial tumors of childhood [1, 2]. In contrast to adults, prolactin- (PRL-) and adrenocorticotropic- (ACTH-) secreting adenomas appear to be most common while nonfunctioning tumors appear to be rare [2, 3].

Symptoms and Clinical Signs

Symptoms and clinical signs of pituitary tumors in the pediatric patient depend upon the type and size of the tumor and age of the patient (Table 1). The patient may be asymptomatic and the lesion discovered during imaging for an unrelated condition (constituting a pituitary "incidentaloma").

Mass effect from the tumor may produce variable endocrinological and neurological manifestations. Diminished growth velocity or short stature is a common feature in many children harboring pituitary adenomas; this may be accompanied by delayed puberty or hypogonadism. The growing tumor can compress the pituitary stalk and cause galactorrhea from loss of tonic inhibition of prolactin ("stalk effect"). Visual changes, including diminished acuity or visual field deficits, may result from tumor compression of the optic apparatus. Mass effect producing increased intracranial pressure (ICP), although rare, may evoke headache, nausea, vomiting, and papilledema. Memory problems, behavioral changes, and a decline in school performance may also be seen.

As secreting adenomas predominate in this population, symptoms and clinical signs relate to the hypersecretion of a particular hormone. PRL-secreting tumors may produce galactorrhea, delayed growth, delayed or arrested puberty, hypogonadism, and potentially menstrual irregularity. Cushing's disease resulting from an ACTH-secreting adenoma results from cortisol excess. Many of the stigmata of cortisol excess seen in adult patients also occur in children such as obesity, striae, hypertension, thin skin, and glucose intolerance. Children also uniquely experience growth arrest, pubertal arrest, and virilization. In prepubertal children, GH-secreting tumors may produce gigantism with accompanying tall stature, enlarged hands and feet, thickened skin, and prognathism. In postpubertal patients, GH-secreting tumors produce typical stigmata of acromegaly including enlargement of the hands and feet, overgrowth of the skull and facial bones, macroglossia, sleep apnea, hypertension, glucose intolerance, arthritis, carpal tunnel syndrome, and hyperhidrosis.

Table 1 Presenting signs and symptoms

	Presenting signs/symptoms
Mass effect	Diminished growth velocity, short stature, delayed puberty, hypogonadism; visual changes; headache, nausea vomiting, papilledema (increased ICP); memory problems, behavioral changes, decline in school performance;
Hypersecretion	
i. Prolactin	Galactorrhea, delayed growth, delayed or arrested puberty, hypogonadism, menstrual irregularity
ii. ACTH	Obesity, striae, hypertension, thin skin, glucose intolerance, growth arrest, pubertal arrest, virilization
iii. GH	Prepubertal children—tall stature, enlarged hands/feet, thickened skin, prognathism Postpubertal children – enlargement of hands/feet, overgrowth of skull/facial bones, macroglossia, sleep apnea, hypertension, glucose intolerance, arthritis, carpal tunnel syndrome, hyperhidrosis

Diagnostics

All pediatric patients suspected of harboring a pituitary adenoma should undergo a complete neurological, ophthalmological, endocrinological, and radiological work-up (Table 2). A neurological examination is performed noting any focal neurological deficits including cranial neuropathies. All patients old enough to cooperate should undergo formal visual field testing, acuity testing, and dilated fundoscopic examination.

Each facet of the hypothalamic-pituitary-end organ axis is assessed. Diabetes insipidus is assessed with careful questioning of the parents and child where a classical history of polydipsia, polyuria, and nocturia may be ascertained. Serum electrolytes and

urinalysis may also provide confirmatory evidence; however, the sodium may be normal despite voluminous, dilute urine in the setting of intact thirst mechanisms and the ability to drink when desired. Serum prolactin levels should be evaluated in all patients with pituitary tumors. Mild elevation may be due to a "stalk effect" (loss of tonic inhibition) while levels greater than 200 μg/L support the presence of a prolactin-secreting adenoma. Thyroid function is evaluated by measuring free thyroxine, thyroxine, and thyroid-stimulating hormone. Adrenal function is assessed by a morning serum cortisol measurement. In the instance of suspected Cushing's disease, 24-h urine-free cortisol is evaluated (age permitting) and a dexamethasone suppression test can be performed. Rarely, inferior petrosal sinus sampling is performed in pediatric patients with suspected Cushing's disease. To evaluate for growth hormone status, serum GH and insulin-like growth factor-(IGF-)1 levels are measured. A radiograph can be obtained to assess bone age in comparison with chronological age. An oral glucose tolerance test can be performed when possible in cases of suspected growth-hormone secreting tumors. Serum gonadotropins should also be measured in older children and in those with signs of pubertal development.

Radiological evaluation is achieved with dedicated magnetic resonance (MR) imaging of the sellar region. At times, a computed tomographic (CT) scan may be useful to assess the degree of aeration of the sella, particularly in younger patients where the sella has not yet become fully pneumatized.

Classification

Pituitary tumors can be classified by size as microadenomas (<10 mm in diameter) or macroadenomas (>10 mm). Furthermore, tumors can be classified as nonsecreting (so-called nonfunctional tumors) or secreting tumors (Table 3). Secreting tumors are classified according to the hormone(s) produced. Specific secreting tumors produce characteristic syndromes such as Cushing's disease (ACTH-secreting tumor) and gigantism or acromegaly (GH-secreting tumor).

Treatment

In general, pediatric patients harboring pituitary tumors can be treated with observation, medical therapy, surgical therapy, radiation therapy, or combinations thereof. Medical therapy may be useful for prolactin-secreting microadenomas and macroadenomas without neurological deficit. Truly incidental microadenomas may be carefully observed and followed with serial clinical, radiological, and endocrinological evaluation.

Transsphenoidal surgery can be extremely effective in the treatment pediatric pituitary tumors. Technical issues pertinent to the pediatric popula-

Table 2 Patient evaluation

Neurological	Complete neurological examination including assessment of cranial nerve function
Ophthalmological	Formal visual field testing, acuity testing, dilated fundoscopic examination
Endocrinological	Clinical history supplemented by serum electrolytes and urinalysis (for DI); Radiograph to assess bone age in comparison to chronological age; Serum prolactin, free thyroxine, TSH, morning cortisol, GH, IGF-1, serum gonadotropins; Suspected Cushing's disease – 24-h urine-free cortisol, +/- dexamethasone suppression test, inferior petrosal sinus sampling Suspected GH-hypersecretion – oral glucose tolerance test
Radiological	Dedicated MR imaging of the sellar region (with and without contrast) CT scan in younger patients to assess aeration of sphenoid sinus

Table 3 Tumor classification

Size	
Microadenoma	Diameter ≤10 mm
Macroadenoma	Diameter >10 mm
Functional status	
Nonfunctioning adenoma	Null cell; gonadotroph immunoreactivity
Functioning adenoma	
Cushing's disease	ACTH immunoreactivity
Prolactinoma	PRL immunoreactivity
Gigantism or acromegaly	GH immunoreactivity
TSH-secreting	TSH immunoreactivity

tion include an age-dependent degree of pneumatization of the sphenoid sinus (Fig. 1) (which may necessitate drilling to afford access to the sella) and the smaller size of the nasal or sublabial apertures.

Radiation therapy has been utilized as an adjuvant treatment in the management of pediatric pituitary tumors [4–7]. Fractionated radiation therapy has been sparingly administered to pediatric patients with pituitary tumors because of the well-recognized possibility of radiation-induced hypopituitarism. Complications such as optic nerve damage, cranial nerve palsy, impaired memory, lethargy, and local tissue necrosis have been reduced due to improvements in targeting and dosing techniques. Stereotactic radiosurgery using the gamma knife, linear accelerator and proton beam have been shown to be a promising adjuvant for the treatment of Cushing's Disease, prolactinomas, and acromegaly in adults. The incidence of radiation-induced complications appears to be low. Further investigation with long-term follow-up to define the efficacy and risks of radiosurgery, as well as the risks for delayed endocrinopathies in the pediatric population must be performed before it becomes accepted as a standard treatment option.

Treatment of the most common specific secreting tumors are further discussed.

PRL-Secreting Adenomas

In the absence of complications necessitating immediate surgery, such as apoplexy, pharmacotherapy with dopamine-agonists should be considered as a first-line treatment approach. In children and adolescents, bromocriptine (BRC) and other dopamine agonists have been used successfully for tumor control and normalization of hypersecretion [8–10]. Selective dopamine receptor subtype-2 agonists, such as cabergoline and quinagolide, have excellent efficacy and may be better tolerated than BRC resulting in higher compliance [10].

Fig. 1 Sagittal cross-section depicting a nonpneumatized sphenoid sinus that may be seen in younger children. Often, this must be drilled to gain access to the sella for tumor resection

Transsphenoidal resection of prolactinomas is generally reserved for patients who prove to be refractory to or intolerant of medical therapy and in patients whose tumors produce significant deficit through extension or hemorrhage. Transsphenoidal surgery for prolactinomas can produce excellent results in experienced hands [2, 3, 11, 12].

Cushing's Disease

Transsphenoidal adenomectomy is the treatment of choice for ACTH-secreting adenomas. Surgical excision is successful in the majority of children as determined by resolution of signs and symptoms of hypercortisolism and normalization of biochemical indices (serum cortisol and 24-h urine-free cortisol) [13–17]. Patients must be followed long-term as recurrences can be seen more than 5 years following achievement of remission [13].

The approach to patients who relapse after transsphenoidal adenomectomy is still controversial. Repeat transsphenoidal surgery or radiation therapy/radiosurgery are the two primary treatment options. Radiation therapy may be associated with a high incidence of pituitary insufficiency in this patient population [16]. Bilateral adrenalectomy can be considered in patients who fail all prior treatment paradigms.

GH-Secreting Adenomas

The objectives of treatment of GH-secreting pituitary adenomas are to eliminate excess GH secretion and restore hormonal homeostasis, ameliorate mass effect, and prevent/reverse known complications of GH excess such as hypertension and glucose intolerance. The currently available treatment options for GH-secreting adenomas include transsphenoidal surgery, radiation therapy/radiosurgery, and pharmacological suppression of GH levels by means of DA-agonists or somatostatin (SS) analogues.

Currently, remission criteria include achievement of serum GH levels below 2.5 μg/L, glucose-suppressed GH levels below 1 μg/L, together with age-normalized IGF-I levels [18]. Transsphenoidal adenomectomy remains the first-line treatment for GH-secreting tumors. When treating macroadenomas,

particularly when they exhibit extrasellar growth, persistent postoperative hypersecretion of GH occurs frequently. In most surgical series, only about 60% of acromegalic patients achieve circulating GH levels below 5 μg/l, although this appears to be influenced by experience [19, 20]. In pediatric patients with gigantism, transsphenoidal surgery was found to be as safe as in adults [21]. Treatment with somatostatin analogues can be very effective in patients with GH hypersecretion [22], although few data in adolescent patients have been reported.

Prognosis

Prognosis for pediatric pituitary adenomas is dependent upon patient status, comorbid conditions, tumor size and extension, and functional status of the tumor.

For prolactinomas, medical therapy can be effective in achieving normalization of prolactin levels. In those patients that do require surgery, the size of the tumor, invasive characteristics and pretreatment prolactin levels appear to influence success [2, 3, 12]. Males often present with macroadenomas in the pubertal years and normalization of prolactin levels are achieved in less than 30% of patients [7]. In contrast, female patients often present with secondary amenorrhea and galactorrhea secondary to microadenomas and over 75% will achieve biochemical remission [7]. With combinations of therapy, tumor control can be achieved in the majority of patients.

Patients with Cushing's disease can achieve remission with transsphenoidal surgery in the majority of instances (70%–98%). However, late recurrences are known to occur and patients must be followed carefully. Retreatment, however, can result in enduring remission [2].

The reported experience with pediatric GH-secreting tumors is limited; however, a cure with surgery alone appears less likely in this population. Combinatorial therapy with transsphenoidal surgery, medical therapy (somatostatin analogues), and possibly radiation therapy appears to result in remission in the majority of patients.

Follow-up

Pediatric patients being treated for pituitary adenomas must be followed long-term, generally with serial clinical, ophthalmological, endocrinological, and radiological evaluations. In particular, height, weight, and pubertal status must be carefully monitored in relevant age groups. Serial visual field examinations and screening should be performed. Questioning directed at assessing hormonal status (screening for hypothyroidism, adrenal insufficiency, diabetes insipidus, etc.) should be directed to the patient and family. Serial testing of thyroid function and GH status (with IGF-1 levels and provocative testing when applicable) should be undertaken. Tanner staging, skeletal maturation, LH, FSH, and sex hormone levels should be performed serially. Patients with functioning tumors should be investigated as appropriate (for example, 24-h urine-free cortisol testing in patients with Cushing's disease). Patients already on hormonal replacement should have their replacement therapy adjusted as necessary. Finally, serial MR imaging should be performed to assess for tumor recurrence. Generally, an initial postoperative study is performed 6 weeks to 3 months following treatment and repeated yearly thereafter (or more frequently as indicated).

Future Perspectives

Minimally invasive techniques, such as endoscopic pituitary surgery, are being increasingly implemented. With proper adaptation for the pediatric population, these techniques will assume increasing importance in the management of pituitary adenomas in children [23]. Endoscopic surgery minimizes disruption of the nasal mucosa/normal anatomy and may decrease postoperative discomfort. Postoperative nasal packing is not necessary with this technique.

Molecular and cellular therapy may also play a role in the future treatment of pituitary adenomas. Rats harboring estrogen-induced prolactinomas were treated with a tetracycline-regulated adenovirus carrying the gene for tyrosine hydroxylase (the rate limiting enzyme in dopamine synthesis), and were found to have a reduction in tumor growth and plasma prolactin levels [24].

Tissue-specific promoters also are promising mechanisms to direct gene therapy. Culture experiments have indicated that tissue-specific promoters can selectively drive the expression of toxic gene therapy with excellent cytotoxicity to specific pituitary cell lines. Future in vivo studies evaluating the efficacy of tissue specific promoters that drive the expression of toxic gene therapy agents are anticipated.

References

1. Gold EB. Epidemiology of pituitary adenomas. Epidemiol Rev 1981;3:163–183
2. Partington MD, Davis DH, Laws ER Jr, Scheithauer BW. Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. J Neurosurg 1994;80(2):209–216
3. Mindermann T, Wilson CB. Pediatric pituitary adenomas. Neurosurgery 1995;36(2):259–268; discussion 269

4. Eder HG, Leber KA, Eustacchio S, Pendl G. The role of gamma knife radiosurgery in children. Childs Nerv Syst 2001;17(6):341–346; discussion 347
5. De Menis E, Visentin A, Billeci D, et al. Pituitary adenomas in childhood and adolescence. Clinical analysis of 10 cases. J Endocrinol Invest 2001;24(2):92–97
6. Damiani D, Aguiar CH, Crivellaro CE, Galvao JA, Dichtchekenian V, Setian N. Pituitary macroadenoma and Cushing's disease in pediatric patients: patient report and review of the literature. J Pediatr Endocrinol Metab 1998;11(5):665–669
7. Haddad SF, VanGilder JC, Menezes AH. Pediatric pituitary tumors. Neurosurgery 1991;29(4):509–514
8. Howlett TA, Wass JA, Grossman A, et al. Prolactinomas presenting as primary amenorrhoea and delayed or arrested puberty: response to medical therapy. Clin Endocrinol (Oxf) 1989;30(2):131–140
9. Colao A, Loche S, Cappa M, et al. Prolactinomas in children and adolescents. Clinical presentation and long-term follow-up. J Clin Endocrinol Metab 1998;83(8):2777–2780
10. Duntas LH. Prolactinomas in children and adolescents–consequences in adult life. J Pediatr Endocrinol Metab 2001;14(Suppl 5):1227–1232;discussion 1261–1222
11. Abe T, Ludecke DK. Transnasal surgery for prolactin-secreting pituitary adenomas in childhood and adolescence. Surg Neurol 2002;57(6):369–378; discussion 378–369
12. Kane LA, Leinung MC, Scheithauer BW, et al. Pituitary adenomas in childhood and adolescence. J Clin Endocrinol Metab 1994;79(4):1135–1140
13. Leinung MC, Kane LA, Scheithauer BW, Carpenter PC, Laws Jr ER, Zimmerman D. Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. J Clin Endocrinol Metab 1995;80(8):2475–2479
14. Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med 8 1994;331(10):629–636
15. Weber A, Trainer PJ, Grossman AB, et al. Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. Clin Endocrinol (Oxf) 1995;43(1):19–28
16. Devoe DJ, Miller WL, Conte FA, et al. Long-term outcome in children and adolescents after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 1997;82(10):3196–3202
17. Styne DM, Grumbach MM, Kaplan SL, Wilson CB, Conte FA. Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenomectomy. N Engl J Med 1984;310(14):889–893
18. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000;85(2):526–529
19. Lissett CA, Peacey SR, Laing I, Tetlow L, Davis JR, Shalet SM. The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone (GH) secreting adenoma. Clin Endocrinol (Oxf) 1998;49(5):653–657
20. Sheaves R, Jenkins P, Blackburn P, et al. Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol (Oxf) 1996;45(4):407–413
21. Abe T, Tara LA, Ludecke DK. Growth hormone-secreting pituitary adenomas in childhood and adolescence: features and results of transnasal surgery. Neurosurgery 1999;45(1):1–10
22. Paisley AN, Trainer PJ. Medical treatment in acromegaly. Curr Opin Pharmacol 2003;3(6):672–677
23. de Divitiis E, Cappabianca P, Gangemi M, Cavallo LM. The role of the endoscopic transsphenoidal approach in pediatric neurosurgery. Childs Nerv Syst 2000;16(10–11):692–696
24. Williams JC, Stone D, Smith-Arica JR, Morris ID, Lowenstein PR, Castro MG. Regulated, adenovirus-mediated delivery of tyrosine hydroxylase suppresses growth of estrogen-induced pituitary prolactinomas. Mol Ther 2001;4(6):593–602

Craniopharyngiomas 41

Rémy van Effenterre, Anne-Laure Boch

Introduction – 506

Epidemiology – 506
Prevalence
Age
Gender

Histogenesis and Pathology – 506
Histogenesis
Pathology

Symptoms and Signs – 506
Ophthalmologic Signs
Endocrine Signs
Neurological Signs

Diagnostics – 508
Plain Skull Radiography
CT Scan
Magnetic Resonance Imaging (MRI)
Angiography
Differential Diagnosis

Staging and Classification – 509
Classification in Relation to Sella Turcica and Diaphragma Sellae
Classification in Relation to Optic Chiasm
Relation to Third Ventricle

Treatment – 509
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 512
Extent of Tumor Resection
Operative Mortality
Tumor Recurrences
Functional Outcome

Future Perspectives – 514

References – 514

Introduction

Craniopharyngiomas are benign epithelial tumors, arising from the pituitary stalk or gland and developing in the sellar and suprasellar region. Their management is still controversial. Because it is an extracerebral benign lesion, the ideal goal of treatment should be complete tumor removal with improvement of altered visual functions, minimal deterioration of endocrinological function, and no neuropsychological impairment. But the situation of the tumor, its relationships with third ventricle, hypothalamus, optic tract, and vascular structures make its removal often difficult. Radical surgery has been criticized because of perceived poor functional outcome, especially in children. However, great progress has been made in surgical treatment, resulting in a dramatic improvement of the prognosis of craniopharyngiomas.

Epidemiology

Prevalence

Among all ages, craniopharyngiomas represent between 3% and 4% of intracranial tumors, that is, 0.5 to 2 new cases a year for one million inhabitants. More than half of these tumors are discovered in adults, but they are relatively more frequent in children. In children, they represent 10% of all intracranial tumors, 18% of supratentorial tumors, and 55% of suprasellar tumors. In adults, the rate in tumors of the suprasellar region is lower, pituitary adenomas and meningiomas being far more frequent.

Age

Developed from embryological remnants, craniopharyngiomas grow at different speeds, a fact which explains why they can be discovered at every age in life. They are exceptional before 2 years old, then their discovery is distributed quite regularly, with three peaks: between 7 and 13 years old, 20 and 25, and 60 and 65. Finally, 60% of craniopharyngiomas are discovered in adults, 40% in children or teenagers.

Gender

There is a small predominance in male gender (male: 55%, female: 45%).

Histogenesis and Pathology

Histogenesis

Since the first description by Erdheim (1904), it is widely accepted that the development of these tumors arise from remnants of the original Rathke's pouch (embryological theory). During embryonic development, the anterior wall of Rathke's pouch develops into a glandular, pseudostratified epithelium, normally representing the primordium of the adenohypophysis. If parts of the Rathke's pouch fail to develop into the normal adenohypophysis, their embryological remnants may differentiate into craniopharyngioma. Other authors think that craniopharyngiomas result from metaplastic transformation of adenohypophysis mature cells (metaplastic theory).

Pathology

Macroscopically, craniopharyngiomas are solid tumors with a variable, sometimes predominant, cystic component. In 15% of cases, it is entirely cystic, in 15% entirely solid, partially cystic and solid in 70%. Calcifications exist in 50% of cases (almost 100% in children). The cysts may contain a cholesterol-rich, machine oil-like, thick brownish-yellow fluid. The membranes are thick, often calcified ("eggshell calcifications"). The solid tumor has a crumbly appearance.

Microscopically, craniopharyngioma is a microcystic epithelial tumor. It is usually heterogeneous, with two main aspects: broad strands, cords, and bridges of a multistratified squamous epithelium with peripheral palisading of nuclei, nodules of "wet" keratin and dystrophic calcifications (adamantinous aspect); or sheets of squamous epithelium which separate to form pseudopapillae (papillary aspect). Depending on the predominance of one aspect or the other, the tumor is classified into adamantinous or papillary types. Both types are observed in adults. In children, all craniopharyngiomas are of adamantinous type. However, the evolution and prognosis are the same in both types. In periphery of tumor, the contact with nervous parenchyma produces a glial reaction, sometimes permeated with tumor digitations.

Symptoms and Signs

Clinical features essentially include visual disturbances, endocrine deficiencies, and neurological signs. Initial signs are often visual loss and increased intracranial pressure (ICP) in children, growth and

pubertal delay in teenagers, visual disturbances or cognitive impairment in adults.

Ophthalmologic Signs

Visual disturbances may be due to compression of the optic pathway or chronic raised intracranial pressure. The revealing sign is usually an impairment of visual acuity, impairment of visual field being rarely noticed by patients. In children, loss of vision is the first complain in 30% of cases, but, actually, most patients have a visual impairment at examination. Visual loss is often severe, because of the lack of complaint in preschool children. Even in occidental countries, all series demonstrate a rate of 5%–20% of children who are blind at presentation. In adults, 90% of patients have a visual impairment. Due to precocious complaint, visual loss is less profound than in children. However, it is severe (<1/20) in one eye in 30%, in both eyes in 10%.

Visual field impairment is usually asymmetrical, less systematized than in pituitary adenomas. It depends on the situation of tumor in relation to the optic pathway. In pre- and infrachiasmatic lesions, the impairment tends to be a bitemporal hemianopia. Retrochiasmatic tumors may cause any of the following: no visual disturbance, an enlargement of blind spot due to papilledema, homonymous lateral hemianopia, or bilateral central scotoma due to compression of macular fibers in their chiasmatic crossing.

Fundoscopy demonstrates uni- or bilateral papilledema in 30% of children and 10% of adults, optic atrophy in 40% of children and 30% of adults. It is normal in both eyes in 30%–50% of cases. Ocular palsies are infrequent, concerning less than 5% of patients. It may be an impairment of CN VI in chronic intracranial hypertension, or direct compression of CN III or IV.

Finally, ophthalmologic examination is entirely normal in 10% of adults, 30% of children presenting with craniopharyngioma.

Endocrine Signs

Except in purely endosellar craniopharyngioma exerting direct compression on the pituitary gland, endocrine deficiency is usually due to infundibulo-tuberian lesion, which perturb hypothalamic command to pituitary functions.

In children, endocrine deficiency is rarely the cause of consultation, for it is unrecognized. Nevertheless, it exists frequently before visual or neurological signs. According to different series, the frequency of endocrine signs at diagnosis vary from 20% to 60%. If full biological tests are performed, there are few children harboring complete normal pituitary functions: 6%–25%. Panhypopituitarism exists in 20%–50% of tested patients. Growth delay (more than 2 standard deviations above average) is obvious in one third of children. Examination of growth curves demonstrates that the slow down is usually very old. According to biological tests, deficiency in GH function is far more frequent: two thirds of children. This means that 1 child out of 2 is able to grow without growth hormone. Pubertal delay is relatively uncommon in pediatric series because the mean age is above 10 years old. However, when considering the teenager group, 50%–80% of patients have a pubertal delay. If bony age is over 11 years old in a girl, 13 years old in a boy, gonadic deficit may be affirmed if there is no secondary sexual characters, low rate of estradiol or testosterone, and no raised level of gonadotrophins during an LHRH test. Thyrotropic and corticotropic deficiencies are clinically uncommon. Biologically, it concerns one third of children. Polyuro-polydipsic syndrome, due to ADH deficiency, is observed in 18% of cases before treatment; obesity in 10%–25% of children; rarely, one may see other endocrine signs: adiposogenital syndrome, cachexia, or precocious puberty.

In adults, endocrine signs are presents in 30% of patients. Many young adults have a short stature, demonstrating a beginning of the disease during childhood. The most impaired function is the gonadotrope one, with amenorrhea in women, and loss of libido and impotence in men. Even in the absence of patent signs of endocrine deficiency, complete endocrine tests are often abnormal: less than 25% of patients are completely free of endocrine deficit.

Neurological Signs

Signs of increased ICP are common in children (70% of cases) and are often revealing. Intracranial hypertension may be due to hydrocephalus in blockade of Monro foramen or to the volume of the tumor itself, more particularly in giant cystic craniopharyngiomas. Isolated headaches, without any sign of increased ICP, may be observed in endosellar tumor, due to the distension of dura mater in the sella. Disturbances in memory and intellect may be related to some retrochiasmatic craniopharyngiomas, because of corpus mamillare compression. Depending on the development of tumor, one may observe frontal lobe disorders, epileptic seizures, or hemiparesis. Disturbances of sleep and thermoregulation may be related to lesions of hypothalamic nuclei.

Diagnostics

Plain Skull Radiography

Today, plain skull radiography is not yet performed commonly. If so, it may reveal indirect signs of sellar and intrasellar tumor (increasing of sella turcica volume, erosion of the edge of dorsum sellae), signs of intracranial hypertension (blunting of boney relief of skull base, thinning down of the calvarium, finger-like prints, disjunction of sutures), signs suggestive of craniopharyngioma (heap or egg-shell calcifications).

CT Scan

Thin axial and frontal CT scan acquisitions, with sagittal reconstruction, allow correct tumor visualization, but cannot give the diagnosis. The tissular part of the lesion appears isodense to normal cerebral parenchyma. The cystic part of the lesion appears hypodense when compared to normal cerebral parenchyma, but slightly hyperdense when compared to ventricular or cisternal CSF. Calcifications appear hyperdense and are more detectable on CT scan than on plain skull radiography. Injection possibly induces hyperdensity of the tissular part of the tumor, without any modification of the other tumor compartments. In addition, CT scan can show hydrocephalus, but also tumor contours and extensions, with tumor proximity from the Willis polygon and the third ventricle.

Some suprasellar craniopharyngiomas, mostly cystic with a thin and nonenhanced membrane, can be suspected by a suprasellar fulfillment hyperdensity, slightly denser to CSF density, or by a mass effect on intracranial arterial vessels. This configuration of craniopharyngiomas is far better diagnosed on MRI.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is the reference imaging exploration for craniopharyngiomas as for all midline pathologies. MRI should even be the first imaging exploration for opto-chiasmatic syndromes or pituitary deficiencies.

The tissular part usually appears in hyposignal on T1 sequences and in hypersignal on T2 sequences. Gadolinium enhancement is variable. The cystic part appears hyperintense on T2 sequences with a direct correlation between hyperintensity and cholesterol or methemoglobin concentration of the cyst liquid (some craniopharyngiomas can have hemorrhages). Calcifications are not visualized on MRI, but spots of signal absence usually indicate the presence of such calcifications.

MRI is sufficient to diagnose the tumor, to evaluate tumor proximity with vessels, suprasellar or hypothalamic region, and to define tumor limits in the three planes especially with 3D reconstructions. Angio MRI sequences allow a good visualization of the skull base vessels with their displacements, often in the same direction depending upon the craniopharyngioma development.

Finally, MRI can visualize the third ventricle, the chiasm, and their displacements. Sagittal slices can define the different types of tumor development, with an influence on surgical approach strategies.

Angiography

Since CT scan and MRI, most surgeons have lost interest in angiography. However some surgeons continue to perform a bicarotid angiography before radical intervention.

Differential Diagnosis

Clinically it is almost impossible to diagnose a craniopharyngioma since numerous other diagnoses can present similar symptoms. In children, growth delay associated with visual deficit and intracranial hypertension will evoke several diagnoses, such as hypothalamic gliomas, chiasmato-ventricular gliomas, or chronic hydrocephalus of various origins. Craniopharyngiomas are only one of all those possible diagnoses. Radiologically, it is exceptional to misdiagnose a glioma and a craniopharyngioma, especially on MRI. Hypothalamic gliomas, ectopic germinomas, and hamartomas are usually easily distinguishable. Pituitary adenomas, especially nonsecreting types with a cystic portion, can be sometimes difficult to differentiate from endo- and suprasellar noncalcified craniopharyngiomas. In adults, a partial pituitary deficiency associated with uni- or bilateral visual and campimetric deficits can indicate a craniopharyngioma, but this presentation can also exist in other suprasellar pathologies. With MRI sequences, diagnosis is easier with almost no confusion between craniopharyngiomas, pituitary adenomas, suprasellar meningiomas, or hypothalamic gliomas.

Three dimensional MRI imaging is a sufficient radiological exploration for craniopharyngiomas, since all useful details are present for the neurosurgeon. Unfortunately, the facility of tumor total resection is still unpredictable even on high-definition MRI. No radiological exam can evaluate if the brain tissue adjacent to the craniopharyngioma is ei-

ther displaced (with a cleavable space and a relational gliosis) or encrusted especially in the highly functional hypothalamus, making microscopically tumor resection almost impossible.

Staging and Classification

Craniopharyngiomas can be classified depending upon their locations from the sella, the diaphragma sellae, and upon their origins from the pituitary stalk or the infundibulum. They can also be classified depending upon the location from the optic chiasm and the third ventricle. This classification allows surgical series comparison which is of importance since developments and extensions of the tumor can explain surgical difficulties.

Classification in Relation to Sella Turcica and Diaphragma Sellae

- Purely intrasellar craniopharyngioma: Distending the dural walls of sella and compressing the pituitary gland, it is responsible for headache and progressive endocrine deficiency.
- Craniopharyngioma with sphenoid development: it is a skull base tumor with an intrasellar starting point.
- Infradiaphragmatic intra- and suprasellar craniopharyngioma: its starting point is intrasellar, and it develops to the suprasellar spaces in distending the diaphragma sellae, which commonly becomes inseparable from the tumor capsule. Clinically, it looks like a nonsecreting pituitary adenoma, with endocrine and/or visual signs. When superior extension goes up to the Monro foramen, it may cause hydrocephalus.
- Transdiaphragmatic intra- and suprasellar craniopharyngioma: it is a primitively infradiaphragmatic craniopharyngioma which has perforated the diaphragma sellae. Its superior extension is insinuated between nervous and vascular structures of suprasellar region, as seen in suprasellar craniopharyngioma.
- Supradiaphragmatic intra- and suprasellar craniopharyngioma: it is a suprasellar craniopharyngioma with a down development. The diaphragma sellae is depressed by the tumor. Radiologically, it looks like an infradiaphragmatic tumor. The true classification is established by the surgical procedure, discovering the tumor above the diaphragma.
- Suprasellar craniopharyngioma: from its starting point, on the pituitary stalk or infundibulum, the tumor develops free in the subarachnoid spaces. Due to an absence of dural plane between the tumor and neurovascular structures, adhesion may be very difficult to dissect.

Classification in Relation to Optic Chiasm

The repartition between pre-, infra-, or retrochiasmatic presentations is essential to evaluate the future surgical difficulties. Pre- or infrachiasmatic presentations are usually immediately accessible with a fronto-pterional approach. In those cases, optic nerves are generally long and don't block access to the tumor, whereas pure retrochiasmatic craniopharyngiomas are totally hidden by the chiasm which covers the tumor. Displaced anteriorly, the chiasm is then so-called prefixed, with short optic nerves and small interoptic space, offering a tiny corridor for surgical instruments. Tumor resection will then be more difficult in pure retrochiasmatic craniopharyngiomas and in cases where the tumor has an important retrochiasmatic component. In addition, those tumor locations usually imply a cerebral parenchyma invasion of the third ventricle floor.

Relation to Third Ventricle

Five to ten percent of craniopharyngiomas develop completely inside the third ventricle. Those craniopharyngiomas arise from the top part of the hypothalamo-pituitary tract, the so-called tuber cinereum. Such tumors are located on the third ventricle floor, which is distended downwards. Unfortunately, it is almost impossible to distinguish this tumor type from under third ventricle floor craniopharyngiomas types; except that this last location usually become invasive on cerebral tissue before getting inside the third ventricle. Such tumors with an intraventricular component indicate generally retrochiasmatic craniopharyngiomas types, frequently invading the floor of the third ventricle.

Treatment

Craniopharyngioma being a benign extracerebral tumor, radical surgery is the more logical treatment to provide a cure. When total removal is impossible, radiotherapy may reduce the risk of a poor evolution.

Surgery

Surgical procedure in craniopharyngioma has three goals. First, it should confirm the diagnosis, which is probable but not certain even with modern imag-

ing tools; second, it should decompress the nervous structures, cure raised intracranial pressure, and improve function, especially vision; third, it should prevent recurrences. As with most authors, we think that operative indication is definite in every symptomatic craniopharyngioma entirely or partially situated above the sella turcica. Because of fluctuation in the size of cysts, the neurological or visual aggravation may be rapid. Therefore, the surgical debulking shouldn't be delayed after discovery of a cystic tumor. The only craniopharyngiomas suitable for medical follow-up are the purely intrasellar ones. Many are progressive and they will need a surgical attempt. In case of hydrocephalus, we think that shunting must be avoided. External shunting causes exposure to infection; internal shunting is often not necessary after tumor removal and is vulnerable to shunt dysfunction. Both make the radical surgery more difficult, the tumor being more incarcerated in the brain. Active hydrocephalus (present in 20% of patients) is an indication for emergency debulking intervention.

Different surgical approaches have been described for craniopharyngioma resections and can be performed separately, concurrently, or perhaps successively. The surgical approach choice depends on the type of tumor development but also the neurosurgeon's habits and preferences. The correct approach is the one that allows a total tumor resection with the best functional outcome. The surgical approach can be correct only if the neurosurgeon controls it. What ever the surgical approach is, it is first necessary to obtain a good brain relaxation in order to dissect the tumor and its various extensions without retracting the brain. Retractors should just be placed to maintain the brain in place without any traction. Mannitol or diuretic drugs should not be used so that an eventual surgically induced insipid diabetes can be easier diagnosed without masking effect. An external lumbar drainage can be performed except in cases of hydrocephalus. Actually, with patience, it is always possible to obtain cerebrospinal fluid from cisterns even when they are filled by the tumor. As the tumor resection proceeds, more cerebrospinal fluid appears and the cerebral tissue collapses.

The subfrontal approach uses a frontal bone flap grazing the skull base. It provides tumor access via the interoptic and interopto-carotid spaces. It permits the control of the endosellar area and gives access to the suboptic membrane, which can be opened if necessary. The subfrontal approach is recommended for craniopharyngiomas with pre- or subchiasmatic development. In cases of associated retrochiasmic development, the opening of the suboptic membrane allows control of the third ventricle floor, in order to push it down, making the tumoral dome resection easier through the interoptic space. To our point of view, surgery should be performed on the minor hemisphere side and not on the side of the higher optic nerve compression. In cases of important intrafrontal tumoral extension, the surgery should be performed on the same side of this extension, whatever the hemispheric dominance is.

The subtemporal approach has been proposed for retrochiasmatic craniopharyngiomas. Various modifications have been described to enlarge this approach towards the skull base in order to minimize cerebral retraction during surgery. From this approach, the floor of the third ventricle and the interpeduncular space are deep. The access is hampered by the posterior communicating artery and the common oculomotor nerve. Tentorial edge incision is necessary if tumor resection has to be performed in the prepontine cisterns. There is here a danger for the pathetic nerve.

The transfrontal-transventricular approach and the transcallosal approach have been proposed for retrochiasmatic or false intraventricular craniopharyngiomas. If the floor of the third ventricle is intact, these approaches lead across this floor and so potentially induce deficits. Such approaches could be used in truly intraventricular craniopharyngiomas, but we don't recommend them since they don't allow a good control of the lower part of the third ventricle and the infundibulum where the tumor usually started. In addition, the transventricular approach can be responsible for postoperative epilepsy.

The pterional approach allows a good opening of the sylvian fissure. It gives access to the antero-lateral portion of the tumor, but the operating field contains the internal carotid, the carotid bifurcation, the posterior communicating artery, and the common oculomotor nerve. This pterional approach is commonly used nowadays for craniopharyngiomas or other suprasellar tumors, because neurosurgeons have learned to control it well for cerebral aneurysm surgery. To our point of view, this approach is not the best because it is a lateral approach with insufficient control of the midline and endosellar region.

Rhinoseptal transsphenoidal approach can be performed for purely intrasellar craniopharyngiomas or sphenoidal inferior developed craniopharyngiomas. It can allow a complete tumor resection of small endosellar or endopituitary craniopharyngiomas with respect to the adenohypophyseal. When the tumor is big with an adherent capsule to the pituitary chamber walls, such surgical approach is dangerous and tumor resection is often incomplete due to calcified lining of the tumor adherent to the cavernous sinus. Endosellar and endopituitary subdiaphragmatic craniopharyngiomas can effectively be resected from a rhinoseptal transsphenoidal approach, but total tumor removal is rare especially in suprasellar expansion types. Finally, if the diaphragma sellae is invaded by the tumor, rhinorrhea can occur after surgery.

The transpetrosal transtentorial approach has been proposed to resect purely retrochiasmatic craniopharyngiomas. It is a technically difficult approach with high functional risks for acoustico-facial nerves, pathetic nerve, etc., and appears to us controversial.

The frontopterional approach is the one that we recommend in all types of craniopharyngiomas (endo- and suprasellar, sub- or supradiaphragmatic, and even transdiaphragmatic ones) with any type of developments (pre-, sub-, retrochiasmatic or intraventricular). We perform the transsphenoidal approach only for endosellar craniopharyngiomas with no suprasellar extension. For elderly patients with contraindication for craniotomy, presenting with endo- and suprasellar craniopharyngiomas we perform a partial tumor resection through a transsphenoidal approach in order to decompress optic tracts. In all other cases, we think that a total tumor removal must be performed. This goal is more frequently reached using a fronto-pterional approach rather than other approach types.

The fronto-pterional approach consists of a large fronto-pterional bone flap grazing the skull base, the midline, and the orbital relief, with a large pterional exposition. This bone flap allows the surgeon to follow the posterior edge of the small sphenoidal wing, to open the sylvian fissure. Only the anterior and internal part of the temporal lobe is exposed. The uncus can be slightly retracted to expose the lateral face of the tumor. The approach is most of the time subfrontal, but the microscope axis can vary from the midline to 80° laterally. This approach allows a good control of the midline which is essential since the craniopharyngioma arises from the hypothalamo-pituitary tract located medially. The fronto-pterional approach permits the surgeon to work in the interoptic space and in the interopto-carotid space when it has been opened by the tumor or when it opens itself progressively during the case. This approach allows the surgeon to work in the retrocarotid space between the posterior face of the supraclinoidal carotid, the roof of the cavernous sinus, and the third cranial nerve, leaving the posterior communicating and choroidal arteries downwards or upwards. This approach allows the surgeon to work on top of the carotid bifurcation internal or external to lenticulostriate arteries. It gives access to interpeduncular and prepontine cisterns, permits the opening of the suboptic membrane, and gives control of the floor of the third ventricle.

By dissecting and fragmenting the tumor through those different spaces, it is possible to progress and to obtain the tumor resection of all craniopharyngioma types.

In the particular case of a purely retrochiasmatic craniopharyngioma with short optic nerves and prefixed chiasm, the tumor should be resected first on its lateral face, sometimes with difficulties. But progressively optic nerves and chiasm will get loose with a spontaneous opening of the interopto-carotid space through which tumor resection becomes feasible. The opening of the suboptic membrane will allow the surgeon to push down the floor of the third ventricle with the tumoral dome in order to grip the tumor.

In purely intraventricular craniopharyngiomas, resection can be performed through the suboptic membrane. It is the shorter way for it and the less traumatic since the approach stays extracerebral. This approach allows a perfect control of the infundibulum. If a tumor extension exists in the floor of the third ventricle, the adherence zone is better controlled with a fronto-pterional approach than with a transventricular or transcallosal approach.

Radiotherapy

Since Kramer and Backlund, numerous studies have demonstrated the efficacy of radiotherapy. However, the indications of radiotherapy remain controversial, particularly in children because still-developing brains are very sensitive to ionizing rays. Radiotherapy exposes the patient to radionecrosis risk (especially for visual pathways), to postradiation arteritis, to radio-induced tumors, and to cognitive deficits in children. Even if the pituitary function is preserved initially, in most cases a panhypopituitarism appears months or years after.

Radiotherapy has no indication when the tumor resection is total. In cases of partial tumor resection, some authors use radiotherapy systematically in order to limit or delay the risk of recurrence. To our point of view, we recognize radiotherapy only in cases where the tumor remnant shows a radiological or clinical evolution and only if a novel surgical procedure seems risky. Indeed, evolution of tumoral remnant in our purely surgical series happens in only 13% of apparent total tumor resection cases, 33% of subtotal tumor resection cases, and 69% of partial tumor resection cases.

Three main radiotherapeutic techniques are available:

- *Conventional radiotherapy* performed classically with 2–4 fields focused on the lesion, consisting of 5 sessions per week for 5–7 weeks. The total delivered dose being a minimal of 50 Gy, using cobalt therapy or a 6 to 10 MeV linear accelerator. Nowadays improvements have been performed mainly by multiplying beams, allowing a more precise dosimetry and a better protection of risky zones such as visual pathways (conformational radiotherapy).
- *Intracavitary irradiation:* It uses beta emitters (32P, 90Y, 198Au, 186Re) which are implanted into

cysts. Its goal is to stabilize cysts, not to treat solid tumors.

- *Stereotactic radiotherapy (radiosurgery)*. Reserved for small craniopharyngiomas or for tumoral remnants <2 cm diameter, radiosurgery is in plain extension. This technique is realized with either the gamma unit device or a linear accelerator delivering high energy photons. The spatial delimitation of the tumor target is defined in stereotaxic conditions. By multiplying the entry points of radiation, it is possible to focus the rays on the tumor with a high irradiation intensity on the lesion and a low irradiation on the adjacent parenchyma. For craniopharyngiomas, an important theoretical limitation is the proximity of the visual pathways. Indeed, the risk of chiasm radionecrosis (increased by the fact that fibers are already weakened by the mass effect), imposes a limit to irradiation doses in this area. Will radiosurgery be in the future an alternative to conventional radiotherapy and to surgical resections? A long-term evaluation will be necessary to figure out the role of this treatment.

Chemotherapy

General chemotherapy has never proven to be efficacious. Some authors used intracystic instillations of bleomycin, with a certain efficacy but a toxicity which remains to be evaluated.

In conclusion, two modalities of treatment are accepted nowadays: either radical surgery, without radiotherapy, radiotherapy being reserved for recurrences; or partial surgery, limited to biopsy and decompression of the optic pathway, associated with primary radiotherapy. Most modern authors favor the first type of management. Radiosurgery may modify this attitude if it would prove its efficacy and safety on the optic tract.

Prognosis/Quality of Life

Extent of Tumor Resection

In radical surgery, extent of tumor resection is the main factor governing risk of recurrences. It depends on three factors: invasion of the brain, localization of tumor, and consistency of tumor. Invasion of the brain is the main limiting factor for a complete removal, because it is usually impossible to dissect the invaded parenchyma. Removal in such conditions obliges the surgeon to sacrifice the parenchyma, a decision acceptable for the pituitary stalk and the infundibulum but not for the walls of third ventricle, optic tract, or brain stem. In agreement with other authors, we think that invasion can not be predicted preoperatively, even with excellent MRI studies. During surgical exploration, the surgeon, discovering the relationships between brain and tumors, should decide to resect a structure or not to complete the resection. In invasive craniopharyngiomas, the resection is total in only 50% of cases. In these cases, invasion concerned only the stalk and infundibulum, which can be removed. When the walls of third ventricle, optic tract, or brain stem are invaded, the resection can never be total. In contrast, in noninvasive tumors, resection can be total in most cases.

Localization of tumor in relation to the optic chiasm is another limiting factor of removal. When the tumor is purely retrochiasmatic, it is not visible in the interoptic space. This aspect of "prefixed" chiasm occurs in 30% of cases. The surgery of purely retrochiasmatic craniopharyngiomas is more difficult than other types. In these cases, some authors recommend drilling the jugum. This technique opens the sphenoid sinus, causing a risk of CSF leakage. Like others, we think it is possible to remove retrochiasmatic craniopharyngiomas with prefixed chiasm by beginning in the interopticocarotid or latero-carotid spaces. Opening of lamina terminalis is useful, not only in intraventricular tumor, but also in tumors developed under the floor of the third ventricle. In these cases, the surgeon may use a cottonoid. to push the tumor from up to down, in the axis of vision. Nevertheless, total removal is less often achieved in retrochiasmatic craniopharyngiomas: only 31% in our series, compared with 80% in other localizations. This may be the consequence of a frequent invasion of nervous parenchyma in retrochiasmatic tumors (85% in our series).

In agreement with many authors, we think the size of the tumor does not interfere with removal. Even in giant craniopharyngiomas, it is usually possible to debulk progressively the solid masses. Cysts are also frequent, helping the dissection.

Evaluation of the quality of removal is a very important point postoperatively. It is important for the patient, whose risk of recurrence depends greatly on this factor, and for the surgeon, who wants to compare his or her work with the literature data. It has been proposed for a while that an early CT scan would be the best indicator of the presence or absence or residual tumor. For many authors, the classification between "total" and "subtotal" removal is entirely based on postoperative CT scan. We think that this examination underestimates the microscopic tumor residues left by the surgeon in case of nonresected invaded parenchyma. Even postoperative MRI misses such a residue, being reliable only for macroscopic fragments of residual tumor. This is particularly true in the floor of the third ventricle. For us, the estimation of the surgeon himself is the best evalua-

tion of the quality of removal. "Total removal" means that no tumor is left under maximum optic magnification, with a clear-cut plane between the lesion and the brain, with resection of invaded parenchyma if necessary. When a doubt remains because of a blind area or an unclear cut plane (signifying interdigitations of craniopharyngioma cell rests into gliotic brain), it must not be termed "total" but rather "subtotal removal." For example in our series, all removals termed "total" by the surgeon had normal postoperative MRI; in the same way, all removals termed "partial" had residual tumor on the control; however, in the "subtotal" group, only one third of the control examinations were able to detect an abnormal image. If evaluated with the postoperative imaging, total removal would be 79%, though we assume only a 59% rate of "true" total removal! Actually, the only criterion for true total removal is the absence of recurrence after years of follow-up.

Operative Mortality

The postoperative mortality in major series of the literature is between 1% and 10%. The lower mortality rates are obtained in the transsphenoidal surgery series, were it can drop to 1%. However, it is questionable if the tumors operated on via this approach (small, intrasellar tumors) can be compared to the large suprasellar craniopharyngiomas, which can invade nervous structures and are far more difficult to remove. It is noticeable that minimal surgery (cyst puncture, biopsy, very partial removal) doesn't always have a lower rate of postoperative complications than radical surgery. The surgical mortality of these "minimal" procedures is underestimated in the publications of radiotherapy centers, where only the patients who survived the surgery are included.

Tumor Recurrences

Recurrence is the major risk in evolution of craniopharyngiomas. Good evaluation of the risk in term of recurrence demands a long follow-up, due to slow rate of growth. Five years follow-up is a minimum, ten years seems more correct to reassure the patient, even if most recurrences occur in the first 3 years after surgery. As a matter of fact, it is not a "true" recurrence but an evolution of tumor fragments, left by surgery because of microscopic invasion of nervous or vascular structures. In radical surgery, recurrence rate depends on the quality of removal, from 15% (mean value of literature data) in total removal to 75% in partial removal. Associated with partial removal, radiotherapy gives a risk of recurrence close to total removal surgery. However, radiotherapy carries its own complications (radionecrosis, dementia, tumors, etc.), and recurrence is not constant even in partial removal. Otherwise, radiotherapy is efficient when administered at recurrence. Because of these data, our position is to reserve radiotherapy for very partial removals and for treatment of recurrences. Considering the difficulty of a new operation on recurrences and its morbidity and mortality, we think that radiotherapy is the elective treatment at this stage, with a good result in the majority of cases and less risks than radical surgery. Thanks to close radiological follow-up, made possible by modern imaging tools, most recurrences must be discovered at a stage of small volume, which does not require new surgical debulking. Radiosurgery may be a promising treatment but needs further evaluation.

Functional Outcome

Quality of life is a main concern in patients treated for a benign tumor such as craniopharyngioma. Duff et al. propose that "Good outcome" should be evaluated thanks to eight inclusion criteria: (1) still alive at the follow-up examination, (2) no major motor deficit related to treatment or tumor progression, (3) functional vision, (4) a Katz grade of A, (5) a Karnofsky Performance Scale score of at least 80, (6) school status of no more than 1 year behind the expected grade for children and young adults, (7) employability for adults of working age, and (8) absence of debilitating psychological or emotional problems. Evaluated with these criteria, their series of 121 surgically treated patients achieved a good outcome in 60.3% of the cases. Our own series demonstrates a high rate of independent life with social integration and normal professional occupation (88% in adults, 74% in children), most patients returning to their pre-illness status (employment at the same level of responsibility in adults, no more than 2 years behind the age at school in children). These good results are due to a low rate of ophthalmologic and neuropsychological sequelae. Ophthalmologic condition is an important limitation of autonomy in the literature. Reviewing the available series, it seems that this point has not received the attention it deserves. The authors who focused on it agreed on four conclusions: (1) The probability of recuperation depends on the severity of preoperative impairment, optic atrophy (seen at fundoscopy) carrying the worst prognosis; (2) children are often more affected than adults, but at same impairment, the prognosis after optic decompression is the same at every age; (3) surgery offers better results than radiotherapy; and (4) recurrences are often responsible for definitive visual aggravation. In conclusion, ophthalmologic impairment is a frequent after-effect in craniopharyngiomas. The

handicap is severe in 10%–30% patients of the literature. Our series demonstrates that with close involvement in this problem, these results can be improved to less than 5%.

Anterior pituitary failure is common after treatment of a craniopharyngioma. It is constant and complete when the pituitary stalk has been divided for tumor removal. In 50% of cases, the stalk is not invaded by the tumor, and it is possible, by close dissection, to preserve it anatomically. This does not mean intact endocrine functions postoperatively in every case but we think that it is worth preserving the pituitary stalk when possible. A partial endocrine deficit allows better quality of life than a complete hypopituitarism, and some patients experience even a complete preservation of all hormonal functions. These patients have the best results, enjoying a normal life without any substitutive therapy. Interestingly, they usually have excellent neuropsychological outcome and absence of weight gain, all facts supporting the absence of hypothalamic injury. However, if any doubt remains on the quality of dissection between the stalk and the tumor, we recommend removing the parenchyma in order to complete the removal – hypopituitarism being far less serious than recurrence.

The neuropsychological prognosis of craniopharyngioma is diversely assessed in literature. In the 1970s, publications insisted on severe psychological disorders after treatment, especially in children. These patients were described as immature, impulsive, intolerant to frustration, with frequent impairment of cognitive functions. Social and professional life were compromised. The role of radiotherapy versus surgical lesions in such dysfunctions has been a great subject of debate. In recent series, it seems that intellectual and psychological results have been improved. Our results support these conclusions, most of our patients being able to return to normal active life after treatment. In children, the question of social prognosis remains, as some authors described severe impairment of school performance and latter autonomy. More than neurological deficits, these patients commonly experience behavioral disorders due to short stature, obesity, headache, emotional and sexual disturbances, which may cause a genuine handicap.

Future Perspectives

Nowadays, with the best prognosis of craniopharyngiomas being obtained with a total surgical tumor removal treatment, it is necessary to improve the functional outcome of the surgery. An earlier diagnosis is desirable and can be obtained by paying attention to discreet clinical symptoms in children and to complaints in adults. Also, faster execution of high quality radiological examinations should be performed for every suspect ophthalmologic or endocrine symptom. The surgical procedure being peculiarly delicate, dangerous, and having a direct influence on the functional outcome, it should be realized by specialized teams with extensive experience in this field. No medical treatment is in prospect for these benign tumors. Radiosurgery will perhaps show itself as an opportunity for the treatment of residual tumors distant to optic pathways.

Recommended Reading

1. Abrams LS, Repka MX. Visual outcome of craniopharyngioma in children. J Ped Ophthal Strab 1997;34:223–228
2. Bellhouse J, Holland A, Pickard J. Psychiatric, cognitive and behavioural outcomes following craniopharyngioma and pituitary adenoma surgery. Br J Neurosurg 2003;17:319–326
3. Carpentieri SC, Waber DP, Scott RM, Goumnerova LC, Kieran MW, Cohen LE, et al. Memory deficits among children with craniopharyngiomas. Neurosurg 2001;49:1053–1057
4. Chen C, Okera S, Davies PE, Selva D, Crompton JL. Craniopharyngioma: a review of long-term visual outcome. Clin Exp Ophthalmol 2003;31:220–228
5. Duff JM, Meyer FB, Ilstrup DM, Laws ER, Schleck CD, Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. Neurosurg 2000;46:291–305
6. Epstein FJ, Handler MH. Craniopharyngioma: the answer. Proc Symposium, New York, NY, December 17–19, 1993. Pediatr Neurosurg 1994;(Suppl 1) 21:1–132
7. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. J Neurosurg 1999;90:237–250
8. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al. The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. Int J Radiat Oncol Biol Phys 1999;44:255–263
9. Hasegawa T, Kondziolka D, Hadjipanayis C, Lunsford LD. Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. Neurosurg 2004;54:813–822
10. Honegger J, Barocka A, Sadri B, Fahlbusch R. Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. Surg Neurol 1998;50:19–29
11. Honegger J, Buchfelder M, Fahlbusch R. Surgical treatment of craniopharyngiomas: endocrinological results. J Neurosurg 1999;90:251–257
12. Maira G, Anile C, Albanese A, Cabezas D, Pardi F, Vignati A. The role of transsphenoidal surgery in the treatment of craniopharyngioms. J Neurosurg 2004;100:445–551
13. Muller HL, Faldum A, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R, et al. Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. Klin Padiatr 2003;215:310–314

14. Mutlukan E, Cullen JF. Visual outcome after craniopharyngioma. Ophthalmology 1990;97:539–540
15. Regine WF, Mohiuddin M, Kramer S. Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. Radiother Oncol 1993;27:13–21
16. Steno J, Malacek M, Bizik, I. Tumor-third ventricular relationships in supradiaphragmatic craniopharyngiomas: correlation of morphological, magnetic resonance imaging, and operative findings. Neurosurg 2004;54:1051–1060
17. Ulfarsson E, Lindquist C, Roberts M, Rahn T, Lindquist M, Thoren M, et al. Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. J Neurosurg 2002;97:613–622
18. Van Effenterre R, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. J Neurosurg 2002;97:3–11
19. Yasargil MG, Curcic M, Kis M, Siegenthaller G, Teddy PJ, Roth P. Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. J Neurosurg 1990;73:3–11
20. Zhang YQ, Wang CC, Ma ZY. Paediatric craniopharyngiomas: clinicomorphological study of 189 cases. Pediatr Neurosurg 2002;36:80–84

Intracranial Germ Cell Tumors 42

Kyu-Chang Wang, Seung-Ki Kim,
Sung-Hye Park, In-One Kim, Byung-Kyu Cho

Epidemiology – 518

Symptoms and Clinical Signs – 518

Diagnosis – 519
Synopsis

Staging and Classification – 524
Synopsis

Treatment – 524
Synopsis
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 526

Follow-Up/Specific Problems and Measures – 526

Future Perspectives – 526

References – 526

Epidemiology

Germ cell tumors originating from the gonads may also occur in the central nervous system (CNS). They arise from the primordial germ cells which were trapped within neural tissue during the process of migration at the time of early embryogenesis [16]. Intracranial germ cell tumors include six subtypes classified by the World Health Organization: germinoma, embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), choriocarcinoma, teratoma, and mixed germ cell tumor, representing diverse directions and various stages of differentiation of germ cells which proliferate and differentiate into various kinds of tissue during embryogenesis as Sano [12] has proposed. The exact correlation between each subtype and its normal counterpart cell type in embryogenesis, however, is unclear. Teratomas are classified into mature, immature, and teratoma with malignant transformation. Immature teratoma contains embryonal or fetal tissues and is graded by the immaturity and amount of the primitive neuroepithelial elements (glial cells of varying type, neurons, and choroid plexus). Teratoma with malignant transformation contains areas of frank conventional somatic type malignancy including adenocarcinoma, squamous carcinoma, or sarcoma. Rhabdomyosarcoma and undifferentiated sarcoma are the most commonly associated sarcomas. Teratoma mixed with other malignant subtypes of germ cell tumors was once called malignant teratoma, but the term is no longer in use to avoid confusion.

Intracranial germ cell tumors vary in their geographic incidence suggesting racial influence; in Western series, they constitute approximately 3%–5% of pediatric and adolescent primary brain tumors, while in series of Far Eastern Asian countries (Korea and Japan), the incidence of germ cell tumors is around 10% [4, 6, 15]. The difference is more prominent in the frequency of pure germinomas.

Germ cell tumors are frequent in children and adolescents. The ages of high prevalence are different according to the subtype of the tumors. Teratomas are more common in young children while germinomas and other tumors are frequent in teenagers suggesting an influence of puberty on the dormant primordial germ cells. Males are involved about twice more frequently than females. However, the male preponderance is not noted in the first decade and in suprasellar tumors, which show even gender distribution.

The pineal region is the most common site followed by the suprasellar area. Of the pineal tumors, more than 70% in Far Eastern Asia and 50%–70% in North America and Europe are germ cell tumors. The reason why the rostral end of the neural tube is the frequent site remains unknown. It is presumed that the migrating primordial germ cells accumulate at the ends of neural tube. Actually the sacrococcygeal area, the caudal end of the neural tube, is another frequent site of occurrence. But the predominance of teratomas and the presence of the primitive node and streak at that area in the embryonic period support another hypothesis for germ cell tumors of the caudal neuropore. Pure germinoma may present with double lesions at pineal and suprasellar regions comprising 5%–10% of germ cell tumors. Other regions include basal ganglia, thalamus, and cerebral hemisphere. The tumors rarely arise from the fourth ventricle and the spinal cord. Teratomas are not uncommon in the posterior fossa and the spinal canal of young infants.

The most common subtype is germinoma consisting of 50% or more in Far Eastern Asian countries and 41% in Western countries. Each subtype of nongerminomatous germ cell tumors are less common and frequently occur as a component of mixed germ cell tumors, which account for 10%–30% of all germ cell tumors. Teratoma is next to germinoma, accounting for about 15%–20% and choriocarcinoma is the least common, comprising less than 5% [6, 8, 12].

Symptoms and Clinical Signs

The symptoms and signs of intracranial germ cell tumors depend on the location of the lesion. It should be remembered that spontaneous hemorrhage from choriocarcinomas is common.

Pineal germ cell tumors are commonly associated with hydrocephalus causing increased intracranial pressure. Parinaud's syndrome is a characteristic localizing sign. Hypothalamic, midbrain, and cerebellar symptoms may also occur as a local effect according to the size and direction of the tumor growth.

Suprasellar germ cell tumors manifest with the triad of diabetes insipidus, visual disturbance, and pituitary hypofunction depending on the size of the tumor. Recently, small suprasellar germinomas can be diagnosed by the advances in neuroendocrinology and neuroimaging. Tumors of only a few millimeter diameter present with diabetes insipidus which is not reversible after treatment. These findings and the fact that some germinomas cause focal brain atrophy and Wallerian degeneration suggest destructive rather than compressive effects on the normal structures. Germ cell tumors of the basal ganglia, thalamus, or cerebral hemispheric lobes may cause seizures, hemiparesis, and dementia with local brain atrophy.

It is intriguing that some germinomas stay stable for up to several years before they grow rapidly at puberty. Such germinomas are usually small suprasellar tumors presenting with diabetes insipidus. Careful follow-up until late puberty is mandatory in such cases. Because small tumors at other sites

do not present symptoms, dormant tumors, if there is any, are not diagnosed in early stages.

About 10% of intracranial germ cell tumors have metastases within the CNS at presentation. Seeding along the ependymal lining and subarachnoid space may cause hydrocephalus. Rarely spinal cord dysfunction is the initial presentation.

Diagnosis

Synopsis

The diagnosis of germ cell tumors is made on the basis of clinical signs and symptoms, and advanced neuroimaging techniques. Certain germ cell tumors can be diagnosed on the basis of serum/cerebrospinal fluid (CSF) marker studies including: alpha fetoprotein (αFP), beta human chorionic gonadotropin (β-hCG), and placental alkaline phosphatase (PLAP). In many instances, CSF for cytology or surgery (biopsy, endoscopy, or craniotomy) may be required to establish a diagnosis.

Age at diagnosis, gender, duration of symptoms, and tumor location are useful in the differential diagnosis. Young age suggests teratomas. Teratoma, mature or immature, is the most common among congenital brain tumors. Females are less likely to have a germ cell tumor if the lesion is in the pineal region. Presence of overt diabetes insipidus at presentation, especially when the tumor is small, prefers germinoma to craniopharyngioma or optic pathway glioma. Histiocytosis also shows diabetes insipidus. Because mass usually does not reach a large size in histiocytosis, visual loss is uncommon whereas accompanying exophthalmos suggests histiocytosis rather than germinoma.

Computerized tomography (CT) and magnetic resonance imaging (MRI) are the radiological evaluation methods of choice. MRI demonstrates the details of the tumor and the spatial relationship to the surrounding normal structures including blood vessels. CT has advantage over MRI in detection of calcification and easy identification of fat tissue and fresh hematoma. Dense calcification and fat tissue suggest teratoma and hemorrhage supports the diagnosis of choriocarcinoma. Although not pathognomonic, some features are quite common in each subtype of germ cell tumors.

Germinomas are frequently solid with iso- or high density on CT, iso- or low signal intensity on T1-weighted MR images. Surrounding edema is absent or minimal and usually there is a strong homogeneous enhancement. Calcification is absent or minimal in extrapineal regions. Generally the neuroimaging features are close to the lymphomas. Some of them may have a small cystic portion. If surrounding brain shows evidence of atrophy or Wallerian degeneration, it favors germinoma. Double lesions involving the pineal gland and suprasellar region are almost pathognomonic of germinoma (Fig. 1).

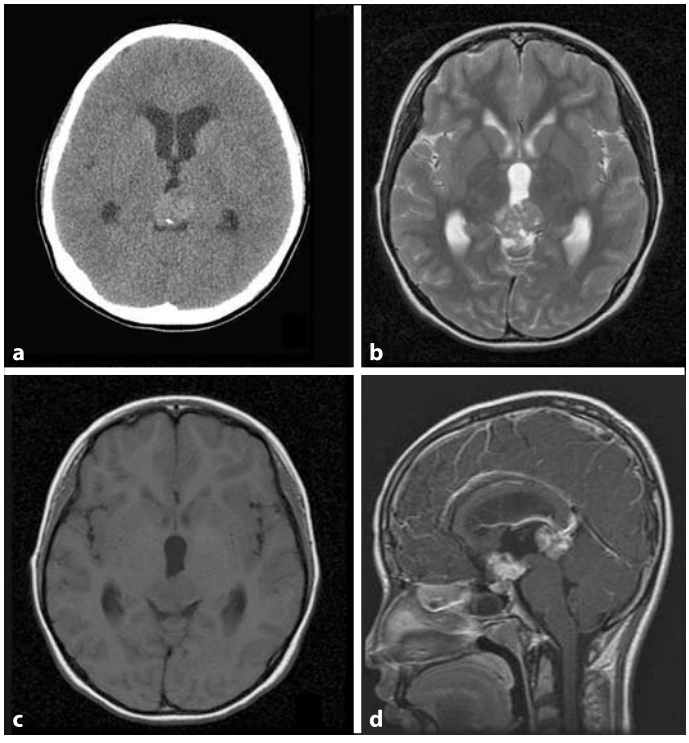


Fig. 1 An axial CT scan (**a**) of a "double lesion" germinoma in a 14-year-old boy shows a slightly high density mass with focal calcification in the region of pineal gland. The mass reveals isosignal intensities to the cortical tissue in T2 (**b**) and T1 (**c**) images. Masses in the pineal and suprasellar region are enhanced by gadolinium (**d**)

Nongerminomatous germ cell tumors tend to be more heterogeneous than germinomas. Surrounding edema is more prominent (Fig. 2). Teratomas are heterogeneous and the degree of enhancement is variable (Figs. 3, 4).

When a pineal tumor is detected by neuroimaging, lesions such as pineal parenchymal tumors, pineal cyst, dermoid or epidermoid cyst, gliomas, and cavernous malformation should be differentiated from the germ cell tumors. In children with suprasellar tumors, craniopharyngioma, optic pathway glioma, histiocytosis, and lymphocytic infundibuloneurohypophysitis should also be included in the differential diagnosis. In addition to the clinical findings, almost constant presence of discrete calcifications and large cysts in craniopharyngiomas, low density on CT, high signal intensity on T2- and low signal intensity on T1-weighted MR images in optic pathway gliomas are clues for radiological differentiation. Lymphocytic infundibuloneurohypophysitis is another lesion of differential diagnosis for a small infundibular germinoma. Follow-up neuroimaging every 6 months or less is helpful for differentiation in a lesion which is too small for biopsy.

Tumor markers have important roles in the diagnosis of intracranial germ cell tumors. αFP or β-hCG may be elevated in the serum and CSF according to the subtypes of germ cell tumors. Even though an

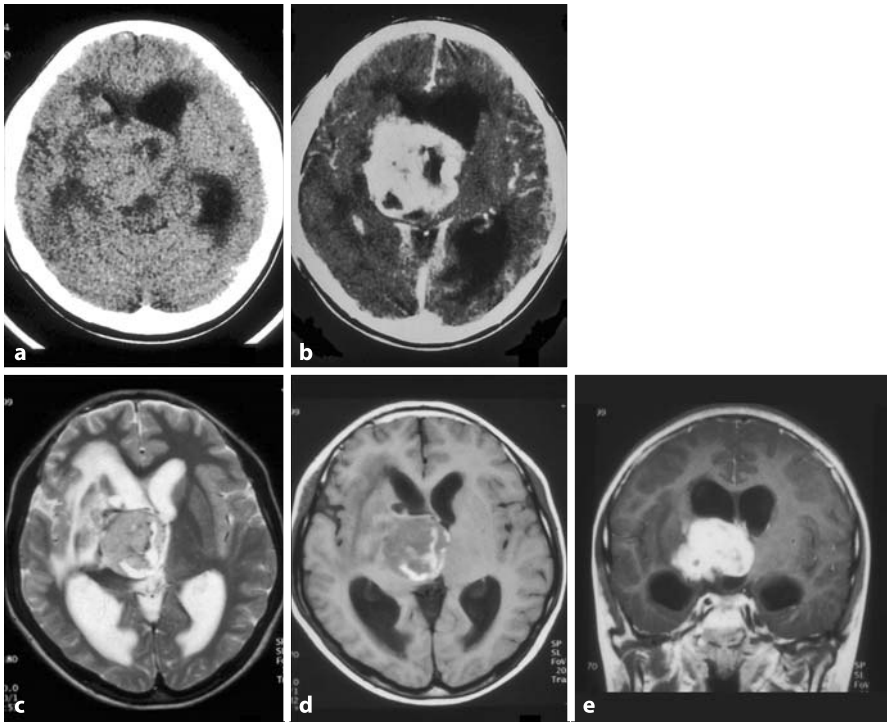


Fig. 2 CT scans (**a** before enhancement; **b** after enhancement) and MR images (**c** T2-weighted; **d** T1-weighted; **e** enhanced T1-weighted) of a mixed germ cell tumor in the right basal ganglia with elevated serum αFP and β-HCG levels in a 12-year-old boy demonstrate heterogeneous mass with remarkable surrounding edema (**c**), intratumoral hemorrhage (**d**), and enhancement (**b, e**)

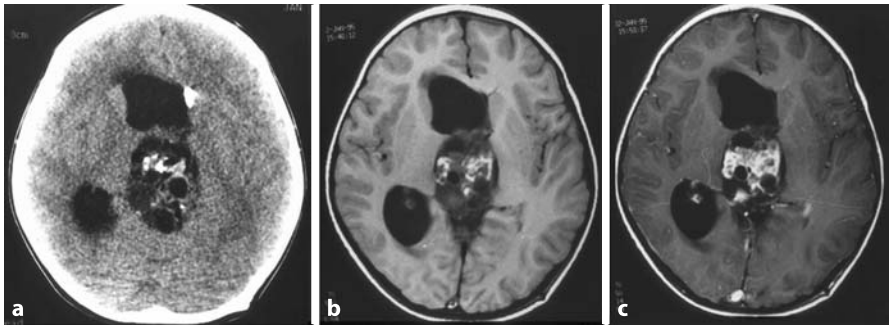


Fig. 3 A CT scan (**a** before enhancement) and MR images (**b** T1-weighted; **c** enhanced T1-weighted) of a mature teratoma in the pineal region in a 4-year-old boy show a heterogeneous mass with focal enhancement. The patient was previously shunted for associated hydrocephalus

exact correlation between tumor marker expression and pathological diagnosis is lacking, tumor markers, if positive, are very useful for planning treatment without tissue diagnosis. Mature teratoma and germinoma do not express αFP or β-hCG. Yolk sac tumor expresses αFP, choriocarcinoma expresses β-hCG, and embryonal carcinoma expresses both. Immature teratoma may secrete both. Some pure germinomas show mild elevation of β-hCG (<50 or 100 IU/L) secreted by harboring syncytiotrophoblasts. PLAP and lactic dehydrogenase may be elevated in germinomas. Limitations in tissue sampling, difficulties in complete histological evaluation of all parts of the tumor and small amount of secretion from the corresponding components may explain the discrepancies between tumor marker expression and histological diagnosis in some cases. The concentrations of tumor markers are usually higher in the CSF than in serum.

Cytologic examination of CSF may reveal tumor cells even though histological diagnosis is not always feasible.

Histological examination of germ cell tumors is still a major diagnostic tool. Representative sections are shown in Figures 5–9 and findings of immunohistochemical studies of germ cell tumors are summarized in Table 1, which may be required to delineate mixed germ cell tumors.

Germinoma is composed of monotonous primitive germ cells with varying amounts of lymphocytes and histiocytes. Granulomas are prominent in a quarter of cases. Occasionally, β-hCG secreting syncytiotrophoblasts are present without intervening cytotrophoblasts. Yolk sac tumors are histopathologically heterogeneous neoplasms. Reticular patterns are formed by a loose, basophilic, myxoid stroma harboring a meshwork of microcystic, labyrinthine spaces lined by clear or flattened epithelial cells with cytoplasmic PAS-positive, diastase-resistant hyaline globules. Papillary fibrovascular projections lined by epithelium, called Schiller-Duval bodies, are found. Embryonal carcinoma is composed of epithelial cells resembling those of embryonic disc and growing in one or more of several patterns, glandular, tubular,

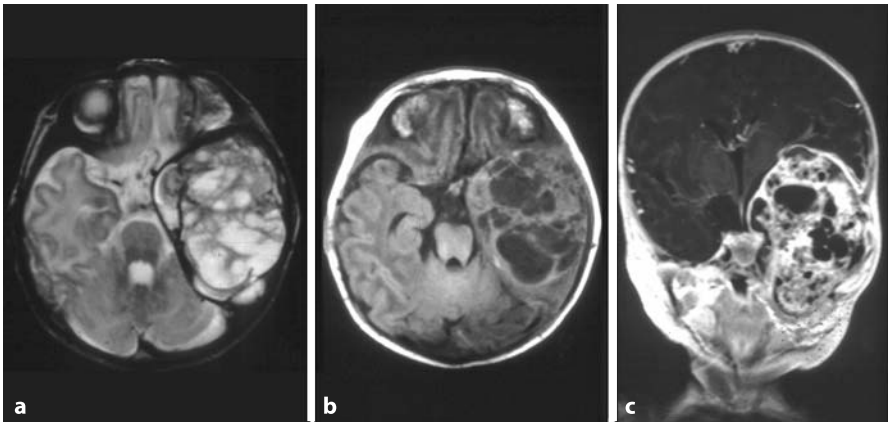


Fig. 4 MR images (**a** T2-weighted; **b** T1-weighted; **c** enhanced T1-weighted) of an immature teratoma in a 1-month-old boy reveal a huge multicystic heterogeneous mass at the base of the middle cranial fossa with strong enhancement of the solid portions

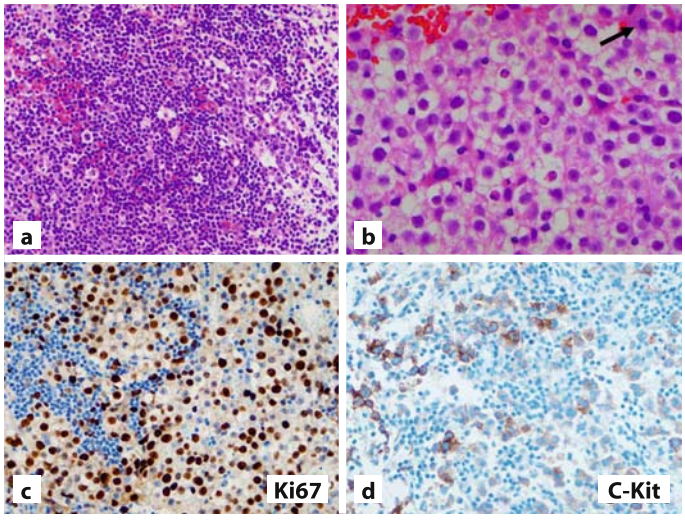


Fig. 5 (**a**) Low power view of germinoma shows malignant tumor cells with heavy lymphoplasma cell infiltration (×100). (**b**) The neoplastic cells show large vesicular nuclei and prominent cytoplasm. The cytoplasm is clear because of cytoplasmic glycogen and lipid. Apoptotic bodies are frequently seen and a mitosis (*arrow*) is noted (×200). (**c**) Ki 67 immunoreactive nuclei are numerous suggesting a high proliferation index (×200). (**d**) c-Kit immunostaining is positive in neoplastic germ cells (×200)

papillary, and solid. The neoplastic cells are large and primitive, which show αFP and CD30 reactivity. Choriocarcinoma shows an admixture of cytotrophoblast, syncytiotrophoblast, and extravillous trophoblast. Primary CNS choriocarcinoma is rare in pure form and is usually found associated with other germ cell components.

Teratoma is subdivided into mature, immature, and teratoma with malignant transformation. Mature teratoma is a cystic tumor, rarely a solid tumor, composed exclusively of mature, adult-type tissues derived from two or three embryonic germ layers. The most common ectodermal components are skin, brain, and choroid plexus. Mesenchymal derivatives

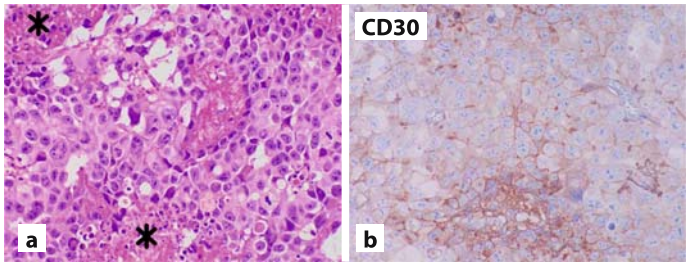


Fig. 6 (**a**) Solid sheets of embryonal carcinoma neoplastic cells with necrosis (*asterisk marks*) are seen. The neoplastic cells have large hyperchromatic nuclei and prominent nucleoli. The cytoplasm is amphophilic or eosinophilic (×200). (**b**) CD 30 is strongly positive in the neoplastic cell membrane (×200)

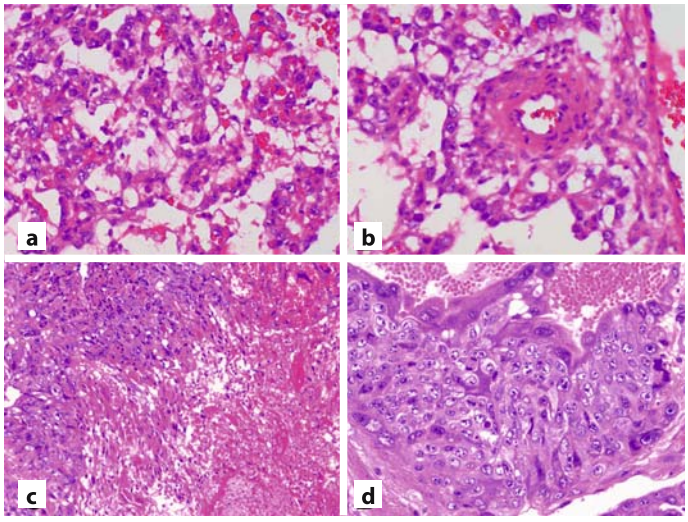


Fig. 7 (**a**) Endodermal sinus tumor shows a reticular pattern with numerous densely eosinophilic globules (×100). (**b**) Schiller-Duval body is composed of a central fibrovascular core with a covering single layer of cuboidal tumor cells (×400). (**c**) Choriocarcinoma shows sheets or nests of atypical tumor cells with extensive hemorrhagic necrosis (H&E: ×100). (**d**) The neoplastic cells are composed of an admixture of cytotrophoblasts, syncytiotrophoblastic giant cells and extravillous trophoblasts (H&E: ×400)

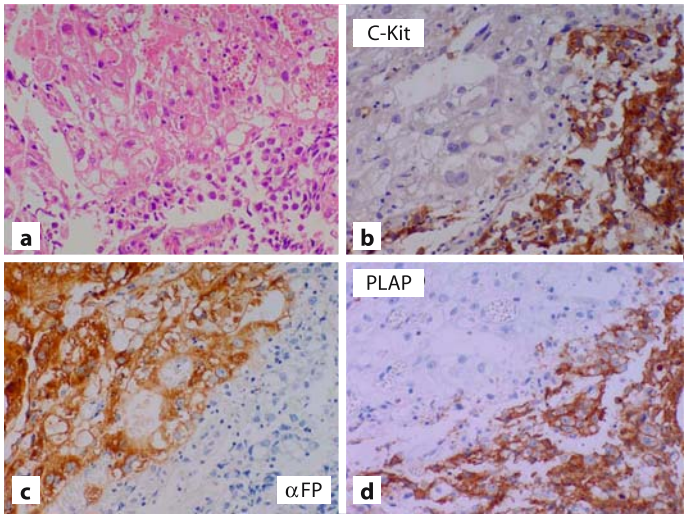


Fig. 8 (**a**) This mixed germ cell tumor is composed of endodermal sinus tumor (*upper*) and germinoma (*lower*) (×200). (**b-d**) The germinoma cells are immunoreactive for c-Kit and placental alkaline phosphatase (PLAP), while those of the yolk sac tumor are completely negative for both antibodies. α-fetoprotein (αFP) is immunoreactive in the neoplastic cells of endodermal sinus tumor, but negative in the germinoma cells. (**b**, c-Kit; **c**, αFP; **d**, PLAP immunostaining; **b-d**, ×200)

include cartilage, bone, adipose tissue, and muscles, both skeletal and smooth. Cysts lined by epithelia of enteric and respiratory types are the usual endodermal components. Mitotic activity is low or absent.

Immature teratoma contains a variable amount of immature, embryonal-type neuroectodermal (primitive neuroepithelial) tissue. Based on the quantity of the immature neuroepithelial component, immature teratomas are graded from 1 to 3 (Table 2). Two tiered grading into low grade (grade 1) and high grade (grade 2 and 3) for immature teratomas has been proposed to enhance reproducibility. Adequate sampling of the primary tumor and of all resected implants is crucial for histological grading. CNS immature teratomas have been reported to undergo spontaneous differentiation into fully mature somatic-type tissues over time [13].

Teratomas with malignant transformation are teratomas (usually mature) with various non-germ cell malignant tumors of epithelial and mesenchymal origin. The most common sarcoma is rhabdomyosarcoma and rarely undifferentiated sarcoma is present. For epithelial malignancies, most frequently squamous cell carcinoma and rarely adenosarcoma are also included.

Mixed germ cell tumors are composed of at least two different germ cell elements of which at least one is primitive. Although only the germinoma and immature or mature teratoma tend to occur as pure form, the most common association is also germinoma with teratoma, which has been estimated to occur in one fifth of all reported cases. Other mixtures of germinoma and yolk sac tumor, immature or mature teratoma with embryonal carcinoma, and/or choriocarcinoma may also be present. The relative percentage of each tumor type should be delineated.

The necessity of tissue diagnosis for planning treatment or for determining the prognosis is controversial, especially in the cases with positive tumor markers. Frequent heterogeneity of the tumor, relatively close correlation between the tumor marker expression and histology, sensitivity to chemotherapy and radiotherapy, and similar management schemes among the tumors with high levels of tumor markers argue against routine tissue diagnosis. Nonetheless, histological diagnosis is strongly recommended in cases with negative tumor markers because of possibilities of tumors other than germ cell tumors. The frequent occurrence of hydrocephalus in patients with germ cell tumors gives an opportunity to procure a histological specimen during shunting or endoscopic third ventriculostomy. Although stereotactic biopsy has difficulties in sampling representative tissues, it is valuable in differentiating germ cell tumors from other tumors in cases with negative tumor markers. The degree of clinical suspicion of a germ cell tumor may determine the method of tissue sampling: stereotactic or endoscopic biopsy versus open craniotomy for resection.

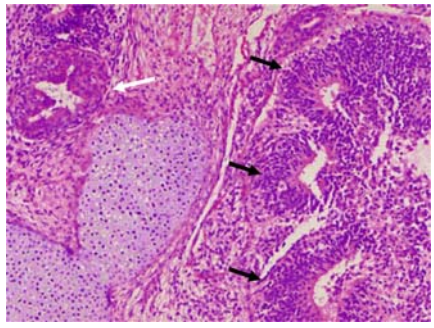


Fig. 9 Immature teratoma shows immature neuroepithelial tubules (*black arrows*), and mature teratoma components, such as cartilage islands, fibrous stroma, and a benign gland (*white arrow*) (×100)

Table 1 Immunohistochemical findings of the germ cell tumors

	PLAP	c-Kit	Pan-CK	EMA	αFP	β-hCG	CD30	CEA
Germinoma	+++	+++	–/+	–	–	–	–	–
Embryonal carcinoma	+++	+++	++++	–	+	+	+++	–
Yolk sac tumor	++	++	++++	–	+++	–	–	–/+
Choriocarcinoma	++	++	++++	++	–	++++	–	+

PLAP, placental alkaline phosphatase; c-Kit, CD117; pan-CK, pancytokeratin; EMA, epithelial membrane antigen; αFP, alpha fetoprotein; β-hCG, β-human chorionic gonadotropin; CEA, carcinoembryonic antigen

Table 2 Grading of immature teratoma

	Three-tiered grading system	Treatment modality
Grade 1	Tumors with rare foci of immature neuroepithelial tissue (INET <1 LPF/slide)	Surgical excision
Grade 2	Tumors with greater immature neuroepithelial tissue than grade 1 (1 LPF ≤INET ≤3 LPF/slide)	Surgical excision + adjuvant therapy
Grade 3	Tumor with large amount of immature neuroepithelial tissue (INET >3 LPF/slide)	Surgical excision + adjuvant therapy

INET, immature neuroepithelial tissue; LPF, low power field (×40)

Staging and Classification

Synopsis

Staging for germ cell tumors is largely accomplished by whole spine MRI and/or obtaining lumbar CSF for cytology.

Because of occasional metastases (about 10%) in the CNS, staging is necessary once the tumor is proven to be a germ cell tumor. The exception is a mature teratoma. Preoperative or postoperative whole spinal MRI and cytologic evaluation of the CSF by lumbar puncture should be performed before planning treatment. Preoperative studies are preferred to postoperative ones if not harmful. Postoperative studies should be performed 10–14 days after tumor debulking to avoid postoperative false positive artifacts. Staging work-up for extraneural metastasis is not recommended as a routine.

Treatment

Synopsis

Treatment for germ cell tumors depends on histological subtype and stage of disease. Treatment may consist of surgery, radiation therapy, and chemotherapy. Attempts are now being made to reduce the amount of craniospinal irradiation in efforts to preserve neurocognitive function, particularly in germinoma.

Surgery

The role of surgery in the management of germ cell tumors is both to alleviate the patient's symptoms and to provide tissue for diagnosis.

As many of these tumors occur in the midline, hydrocephalus is common. Options for the management of hydrocephalus are ventriculoperitoneal shunting, temporary external ventricular drain, and endoscopic third ventriculostomy. Shunting permits CSF sampling and provides safe CSF diversion with improved clinical status until the tumor burden resolves. However, ventriculoperitoneal shunting, in addition to the complications of shunting procedure, carries risk of tumor dissemination into the peritoneal cavity and occlusion of the shunt system by tumor debris. In addition, 80% of patients may not need a shunt once the tumor burden decreases [8]. External ventricular drainage followed by surgical resection of the tumor or emergent chemotherapy and/or radiotherapy may be a reasonable approach. It has the advantage of avoiding a permanent shunt and the risk of extracranial tumor spread. On the contrary, there is a slightly increased risk of infection while waiting for treatment to shrink the tumor and open CSF pathways. Recently, endoscopic third ventriculostomy has become the procedure of choice because it may relieve the hydrocephalus, avoids the complications of shunting and external ventricular drainage, and permits biopsy of the tumor.

Mature teratomas are best treated with radical resection, which is also curative. If other germ cell tumor components are mixed with mature teratoma, radiotherapy and/or chemotherapy should be administered according to the most malignant component of the tumor. For immature teratomas, radical resection is recommended as the initial treatment, usually followed by adjuvant radiotherapy and/or chemotherapy.

With current treatment modalities, cytoreductive surgery is not indicated in germinomas because of the sensitivity of these tumors to radiotherapy and chemotherapy.

Several investigators have suggested that radical resection in patients with nongerminomatous germ cell tumor have an improved chance at long-term survival [8, 11]; however, this has not been extensively confirmed. Others recommend chemotherapy as an initial treatment in cases with tumor marker positive nongerminomatous germ cell tumors. The residual lesion after neoadjuvant therapy may represent viable malignant tumor, benign teratoma, or simply nonneoplastic fibrosis. Although, there is no evidence that a second look surgery necessarily prolongs survival, it may be contemplated for the following reasons [2, 10, 14]. First, surgical management is less complex after neoadjuvant therapy. Second, the histological diagnosis of the residual lesion might influence treatment strategy. If malignant tumor is present, one might modify the extent of radiotherapy at the end of the initial chemotherapy or intensify the chemotherapy after radiotherapy. If the residual lesion is a benign teratoma, resection would be appropriate.

Radiotherapy

As germinomas are highly radiosensitive, a high cure rate with craniospinal irradiation (especially >40 Gy to the local tumor site) can be expected. However, the volume and dose of radiotherapy remain somewhat controversial.

In patients with disseminated germinomas, craniospinal radiotherapy is the preferred treatment, but for nondisseminated germinomas most studies support the use of limited field radiotherapy [8]. A higher radiation dose is recommended in patients with β-hCG secreting germinoma than in those with pure germinoma [1].

To reduce the deleterious side effects of radiation on intellectual, psychological, and hormonal development, modern series have evaluated the efficacy of low-dose radiation. In one study including 40 patients, high-dose radiotherapy was compared with low-dose radiotherapy, which was defined as ≤25.5 Gy to the whole brain, < 50 Gy to the tumor site, and <22 Gy to the spine [5]. The 5-year disease-free survival and overall survival for these patients were 97%. Outcome was not affected by the dose of radiation. More recent clinical trials have given chemotherapy followed by radiation treatment, thus reducing dose and volume for the treatment of pure germinomas [1].

In contrast to the treatment for germinoma, nongerminomatous germ cell tumors are infrequently cured by radiotherapy alone, even if craniospinal irradiation is administered [6]. Therefore, there seems to be little justification for reducing the dose of radiation in these patients. Current treatment strategies include the combination of high-dose craniospinal radiation and high-dose chemotherapy.

Recent studies adopting radiosurgery (26–28 Gy) as an adjuvant therapy for patients with germ cell tumor suggest encouraging treatment outcomes with minimizing the radiation dose to the surrounding normal tissue. However, longer follow-up is required to fully assess the long-term benefits and its own toxicity.

Chemotherapy

The rationale for the use of chemotherapy for intracranial germ cell tumors has been either to reduce the dose of radiation or to improve survival for patients with nongerminomatous germ cell tumor. Furthermore, chemotherapy has been explored as a way to delay radiotherapy in children younger than 3 years.

Platinum-based chemotherapy has been successful in the treatment of germinomas, with response rate over 80% [2]. But chemotherapy alone is not recommended for children with isolated or disseminated germinomas. Without addition of radiotherapy, more than 50% of patients, who achieved complete responses, showed relapse and the overall results were not as good as those obtained with radiation alone or with a combination of chemotherapy and radiation [2]. A combination of chemotherapy and focal radiotherapy, with a decreased dose of radiation, may maintain the excellent tumor control rates [1]. Currently, the standard neoadjuvant treatment consisted of four cycles of etoposide and cisplatin, followed by radiotherapy [3, 10]. The total radiation dose ranged from 30.6 to 50.4 Gy, depending on tumor histology, the response to chemotherapy, and the initial extent of disease. If patients have dissemination or multicentric disease at diagnosis, craniospinal radiation is given. With this regimen, a clinical response rate and 4-year survival of 100% has been reported [3].

Patients with nongerminomatous germ cell tumors are rarely cured by radiotherapy alone. Several studies suggest that chemotherapy can improve the overall duration and rate of survival when used in conjunction with craniospinal radiotherapy [9]. Two to four courses of chemotherapy are given and the response is assessed with a repeated CT or MRI, followed by craniospinal radiotherapy and then maintenance chemotherapy. The most active agents include cisplatin, carboplatin, etoposide, bleomycin, ifosfamide, and vinblastine. Radiation doses remain standard, and all patients receive craniospinal treatment. Partial or complete responses after 2–4 courses of this type of chemotherapy have been noted in 75% of cases and 4-year survivals have been reported as high as 67% [11].

Recent results indicate that complete excision of residual tumors after neoadjuvant therapy, consisting of combined chemo- and radiotherapy, is highly effective in patients with nongerminomatous germ cell tumors [7]: the 5-year progression-free survival rate was 91%. Long-term results are not available for this treatment protocol at present.

Prognosis/Quality of Life

The prognosis for germ cell tumors is highly dependent on the subtype [1].

In general, germinoma carries an excellent prognosis. Current treatment produces long-term survival rates over 90% [2, 5, 8]. β-hCG-secreting germinoma has a worse prognosis than pure germinoma, although this has not been found in all series: the 10-year survival rate is reported as around 80%. In addition, it is notable that patients with germinoma who developed recurrence can be successfully treated with salvage therapy and remain tumor free.

Teratomas represent a distinct histological entity that shows a significant diversity of the clinical course according to the histological grade of immaturity. In one study, the 10-year survival rates were 93% for patients with mature teratoma and 71% for patients with immature teratoma [8].

In contradistinction, nongerminomatous germ cell tumors have a poor prognosis, with reported survival rates ranging between 40% and 70% [6, 8]. Furthermore, pure-type tumor marker positive nongerminomatous germ cell tumors (embryonal carcinoma, yolk sac tumor, or choriocarcinoma) have dismal prognosis: the 5-year survival rates were less than 30%. Especially, choriocarcinoma show rapid disease progression and results in a poor clinical outcome. Therefore, aggressive treatment should be started without delay in this subtype. A 5-year survival was less than 40% for patients with biopsy-proven nongerminomatous germ cell tumor treated with radiotherapy alone. Recent series with the use of more aggressive multimodality therapy have suggested a better outcome for nongerminomatous germ cell tumor: 5-year survivals over 70% have been reported [7, 11].

Since intracranial germ cell tumors are highly curable, quality of life may be a great concern. Patients with intracranial germ cell tumors have usually received high doses of radiation for volumes as large as whole brain or whole ventricle, being vulnerable to late delayed radiation necrosis and secondary neoplasm [5]. In addition, the location, extent and biology of the tumor itself can cause remarkable permanent disabling endocrine, neurological, and neuro-ophthalmologic symptoms. Quality of life in long-term survivors with germinomas has been reported by several authors retrospectively and is suggested to be "acceptable" or "reasonable" [5, 8]. Less adverse effects of radiation in these patients than those with acute lymphocyte leukemia or medulloblastoma are explained by the fact that patients with intracranial germ cell tumors are usually older.

Follow-up/Specific Problems and Measures

Complete clinical remission is defined as normalization of tumor markers and the absence of residual tumors. Initial follow-up examinations after completion of chemotherapy must be performed in short intervals, including frequent evaluation of the tumor markers. Treatment response is evaluated by follow-up MRI scans every 6 months until the third year after diagnosis and then at 1-year intervals.

The high incidence of endocrine deficiencies and other late effects strongly suggests prospective evaluations, particularly of endocrine, neuropsychological and neuro-ophthalmologic dysfunctions. The fact that side effects may occur or worsen even years after therapy further emphasizes the need for long-term follow-up examinations. In children treated with cisplatin and/or ifosfamide, the renal function has to be monitored carefully for tubular nephropathy. Furthermore, permanent ototoxicity may occur and chemotherapy-related deaths have been reported in up to 10% of patients with platinum-based protocols for intracranial germ cell tumors [2]. Early recognition of tumor- or treatment-related side effects allows early therapy and may therefore reduce long-term morbidity.

Future Perspectives

Current protocols have enhanced dramatically the cure rates of intracranial germ cell tumors. However, much work remains in minimizing the late sequelae of adjuvant therapy in patients with a low risk of relapse and in improving the outcome for those with poorly responding tumors. In the near future, advances in our understanding of the molecular biology of germ cell tumors may lead to refinements in treatment and improved outcome.

References

1. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y. Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 2002;20(3):857–65
2. Balmaceda C, Heller G, Rosenblum M, Diez B, Villablanca JG, Kellie S, et al. Chemotherapy without irradiation – a

novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. J Clin Oncol 1996;14(11):2908–15
3. Buckner JC, Peethambaram PP, Smithson WA, Groover RV, Schomberg PJ, Kimmel DW, et al. Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. J Clin Oncol 1999;17(3):933–40
4. Cho KT, Wang KC, Kim SK, Shin SH, Chi JG, Cho BK. Pediatric brain tumors: statistics of SNUH, Korea (1959–2000). Childs Nerv Syst 2002;18(1–2);30–7
5. Hardenbergh PH, Golden J, Billet A, Scott RM, Shrieve DC, Silver B, et al. Intracranial germinoma: the case for lower dose radiation therapy. Int J Radiat Oncol Biol Phys 1997;39(2):419–26
6. Jennings MT, Gelman R, Hochberg F. Intracranial germcell tumors: natural history and pathogenesis. J Neurosurg 1985;63(2):155–67
7. Kochi M, Itoyama Y, Shiraishi S, Kitamura I, Marubayashi T, Ushio Y. Successful treatment of intracranial nongerminomatous malignant germ cell tumors by administering neoadjuvant chemotherapy and radiotherapy before excision of residual tumors. J Neurosurg 2003;99(1):106–14
8. Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, et al. Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 1997;86(3):446–55
9. Packer RJ, Cohen BH, Cooney K. Intracranial germ cell tumors. Oncologist 2000;5(4):312–20
10. Reddy AT, Mapstone TB. Intracranial germ cell tumors. In Winn HR, editor. Youmans neurological surgery, 5th ed. Philadelphia: W.B. Saunders; 2003. p. 3603–3611
11. Robertson PL, DaRosso RC, Allen JC. Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. J Neuro-oncol 1997;32(1):71–80
12. Sano K. Pathogenesis of intracranial germ cell tumors reconsidered. J Neurosurg 1999;90:258–64
13. Shaffrey ME, Lanzino G, Lopes MB, Hessler RB, Kassell NF, VandenBerg SR. Maturation of intracranial immature teratomas. Report of two cases. J Neurosurg 1996;85(4):672–6
14. Steinbok P, Cochrane DD. Pineal region and intracranial germ cell tumors. In McLone DG, editor. Pediatric neurosurgery, 4th ed. Philadelphia: W.B. Saunders, 2001. p. 711–724
15. Suh YL, Koo H, Kim TS, Chi JG, Park SH, Khang SK, et al. Tumors of the central nervous system in Korea: a multicenter study of 3221 cases. J Neurooncol 2002;56 (3):251–9
16. Teilum G. Classification of endodermal sinus tumour (mesoblatoma vitellinum) and so-called "embryonal carcinoma" of the ovary. Acta Pathol Microbiol Scand 1965;64(4):407–29

Choroid Plexus Tumors 43

Paul Kongkham, James T. Rutka

Epidemiology – 530

Symptoms and Clinical Signs – 530

Diagnostic Imaging – 531

Pathological Classification and Staging – 532

Treatment – 533
Surgery
Radiation Therapy
Chemotherapy
Angio-Embolization

Prognosis/Quality of Life – 535

References – 536

Epidemiology

Choroid plexus tumors (CPTs) are rare, primary brain tumors arising from the neuroepithelium of the choroid plexus. Although they may be found in patients of any age, the vast majority occur in the pediatric population. Up to 70% of these neoplasms occur in children, with over half arising in children under 2 years of age [35]. The annual incidence for CPTs is low, with 0.3 cases/million reported [57]. Despite this, the annual incidence in the pediatric age group is as high as 3%–5% [22], and up to 12% in those children under 2 years of age [23]. CPTs account for 0.4%–0.8% of all brain tumors [11], between 0.9%–3% of all primary pediatric brain tumors [9, 41], and up to 10%–20% of pediatric brain tumors during the first year of life [1]. Case reports exist describing in utero findings of CPTs by ultrasound, or of the diagnosis of CPTs in the neonate, suggesting that some of these lesions may occur congenitally [4, 32, 50].

CPTs are comprised of both the benign choroid plexus papilloma (CPP), as well as the malignant choroid plexus carcinoma (CPC). An intermediate group of tumors, labeled as atypical CPP, have also been described. There appears to be no difference between CPP and CPC in terms of sex predilection, age at presentation, symptoms, or location of lesion [16].

In children, approximately three-quarters of all CPTs are located within the lateral ventricles, in particular the atrium or trigone. Within the lateral ventricles, CPTs can also be seen in relation to the foramen of Monro, or in the temporal horn. This predilection for the lateral ventricle in children is in contrast with the adult population, in which the majority of CPTs are fourth ventricular in location. The next most common location in children is the fourth ventricle, followed by the third ventricle, and lastly extraventricular locations. Unusual locations in which CPTs have been described include the parenchyma of the brain, within the brainstem, in the cerebellopontine angle, or in relation to other basal cisterns [7, 37, 48]. In a study of 353 CPPs and 207 CPCs, Wolff et al. found that the older the patient, the more likely the tumor was to be located caudally within the neuraxis [54]. In their meta-analysis, they found mean ages of 1.5 years, 1.5 years, 22.5 years, and 35.5 years for tumors located within the lateral ventricles, third ventricle, fourth ventricle, and cerebellopontine angle, respectively. In addition, they found that 12% of patients exhibited metastatic disease at presentation, with metastasis more common among CPC than CPP. Up to 7% of cases may involve lesions in multiple locations synchronously, for example bilateral lateral ventricle CPTs [17, 29]. A portion of these cases, however, are likely to result from CSF seeding from a solitary primary lesion to a secondary site, as opposed to two synchronous primary lesions.

The majority of CPTs occur sporadically; however, case reports exist describing their occurrence in certain inherited syndromes. Patients with Li Fraumeni syndrome are predisposed to develop CPC. In addition, the presence of multiple CPPs has been described in patients with Aicardi syndrome [36, 47, 53].

Symptoms and Clinical Signs

Due to the predominantly intraventricular location of these tumors, patients may remain asymptomatic despite harboring large lesions. Symptoms usually begin with the development of hydrocephalus. Symptoms and signs heralding the presence of a CPT fall into five general categories: increased intracranial pressure (ICP), seizures, hemorrhage, focal neurologic deficits, and general/constitutional symptoms. In one series, the most common category of symptoms and signs were those of increased ICP [56]. Intracranial hypertension may be a result of mass effect from the tumor, or secondary to hydrocephalus. The hydrocephalus may be of the communicating type, resulting from CSF overproduction by the tumor. In addition, obstructive hydrocephalus may result from impairment of normal CSF drainage due to tumor mass effect, cellular debris, or products of prior hemorrhage. In Pencalet's series, 33 out of 38 children suffered from hydrocephalus at presentation [35]. As a result of this increased ICP, children may present with headache, irritability, gait abnormalities, nausea or vomiting, or visual disturbances. In infants and young children, one may find evidence of a tense fontanelle or frank macrocephaly on examination.

Less often, symptoms and signs of focal deficits may be present. These are partly related to tumor location and local mass effect. Among these findings are focal motor deficits, head tilt, titubation, cranial nerve dysfunction, or cerebellar dysfunction. Patients with third ventricular lesions may exhibit endocrinologic dysfunction, such as obesity, precocious puberty, diabetes insipidus, menstrual irregularity in the older child, bobble-head phenomenon, psychosis, or diencephalic disorder [8, 34, 38, 52].

General or constitutional symptoms and signs of CPTs include developmental delay, cognitive impairment, or regression of milestones, as well as general weakness, lethargy, or failure to thrive.

Patients with CPTs may present with metastatic disease at the time of diagnosis, and rarely the initial signs and symptoms may be due to the secondary metastatic deposit. For example, Sawaishi et al.

have reported on a 2-year-old female presenting with signs and symptoms of gait disturbance and dysuria, due to a lower spinal canal subarachnoid mass which proved to be a metastatic deposit originating from a primary CPC of the lateral ventricle [44].

Diagnostic Imaging

In general, the modern diagnostic armamentarium with respect to CPTs includes contrast-enhanced computed-tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and catheter-based cerebral angiography.

On CT scan, both CPPs and CPCs appear as spherical or multilobulated masses, hyperdense to cortex. Approximately 20% may contain calcifications, usually in older children. In addition, some may contain cystic regions. With intravenous contrast, both show strong, homogenous enhancement.

T1-weighted MRI scans display these tumors as iso- or slightly hypointense, while they appear hyperintense on T2-weighted images. The typical lobulated appearance is evident, and signal voids may be seen – attesting to the vascular nature of these tumors. Both CPPs and CPCs may be seen to compress adjacent brain parenchyma. Enhancement with an intravenous paramagnetic contrast agent shows intense, homogenous enhancement with CPPs (Fig. 1). For CPCs, the enhancement may be somewhat heterogeneous in nature. Additional features which are suggestive, although not diagnostic, of CPCs include evidence of parenchymal invasion, and associated edema [30, 49] (Fig. 2). These imaging studies help to distinguish CPTs from various other intracranial pathologies (Table 1). In addition to imaging of the brain, one should also image the spinal axis in order to rule out the presence of drop metastases at the time of diagnosis. Metastatic disease may present as a separate focal mass, or leptomeningeal enhance-

Table 1 Radiologic differential diagnosis for choroid plexus tumors

Ependymoma
Meningioma
Primitive neuroectodermal tumor
Astrocytoma
Germinoma
Teratoma
Choroid plexus metastasis
Other: xanthogranuloma, choroid plexus cyst

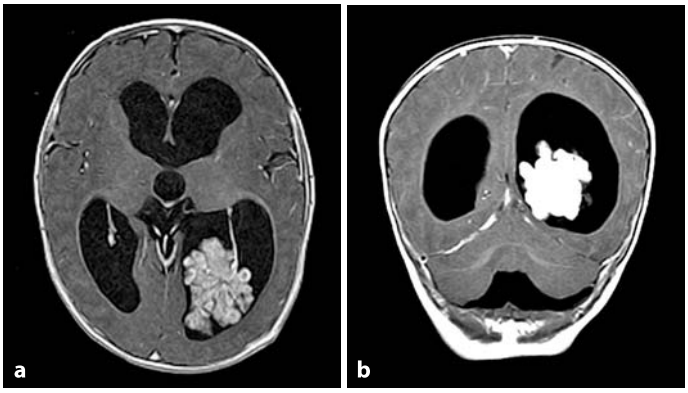


Fig. 1 T1-weighted axial (*left*) and coronal (*right*) MRI following administration of gadolinium in 8-month-old male with choroid plexus papilloma. A densely enhancing lesion is seen in the left lateral ventricle. The lesion is being fed by a vascular pedicle from the choroidal vessels

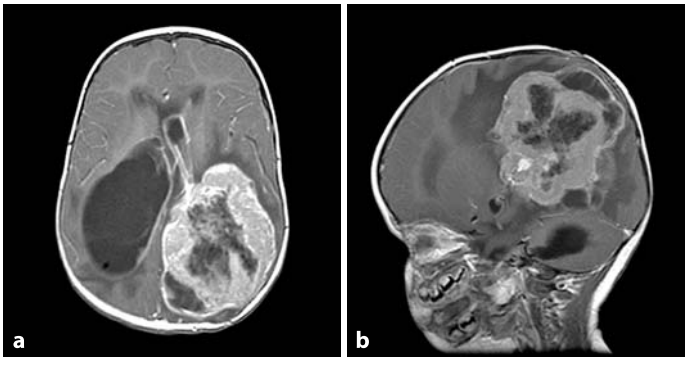


Fig. 2 T1-weighted axial (*left*) and sagittal (*right*) MRI following gadolinium administration showing a large inhomogeneously staining tumor of the left lateral ventricle with surrounding edema in a 7-month-old male. The presence of the edema, and the inhomogeneity of enhancement suggests a choroid plexus carcinoma, which the lesion proved to be on surgical resection

ment. Metastatic disease can also be sought by analysis of cerebral spinal fluid cytology, by lumbar puncture if not contraindicated, external ventricular drainage, or at the time of definitive surgery.

Supplementing the MRI with MRA may provide additional information regarding the arterial supply, and venous drainage, of these lesions, obviating the need for formal catheter angiography in most cases. With MRA, one may find enlarged, tortuous anterior or posterior choroidal arteries supplying the tumor. Such information is of use for surgical planning, in order to identify the tumor's primary blood supply and plan a surgical approach which facilitates early identification of this supply in order to minimize intraoperative blood loss.

Although not yet routine, magnetic resonance spectroscopy (MRS) may serve a role in aiding in the diagnosis of CPTs in the future. Horska et al. have studied both CPPs and CPCs with this technique, and have found that both lesions display high levels of choline-containing compounds, and an absence of creatine and N-acetyl aspartate. Compared to CPPs, CPCs showed a relatively higher level of choline, as well as a lactate peak [21]. Therefore, this imaging modality may be of utility in differentiating these tumors from other intraventricular lesions, as well as in distinguishing between papillomas and carcinomas.

Formal catheter-based cerebral angiography is of use in defining the vascular anatomy as it relates to the arterial supply and venous drainage of these lesions, as well as in aiding preoperative surgical planning (Fig. 3). Since the advent of MR angiography and venography, the role of catheter angiography strictly for diagnostic and planning purposes has diminished. This technique is still of use, however, in those cases where preoperative embolization of tumor feeders is considered, in an attempt to minimize subsequent intraoperative blood loss during tumor resection.

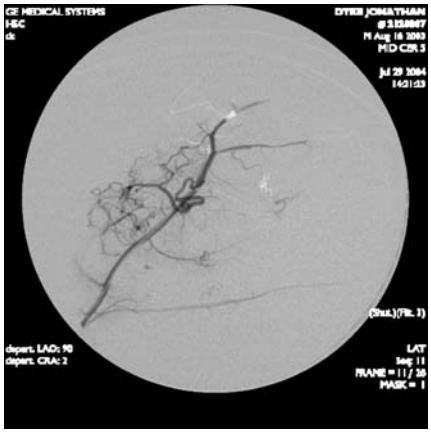


Fig. 3 Lateral subtraction angiogram of left middle cerebral artery depicting vascular nature of a choroid plexus carcinoma. It is wise to consider presurgical embolization of large feeding vessels prior to surgical removal of such complex vascular tumors

Pathological Classification and Staging

CPPs are categorized as World Health Organization (WHO) Grade I lesions. Grossly, these lesions have a purple, "cauliflower-like" appearance, with an irregular, frond-like surface. Most are soft, and vascular in nature, with variable calcification [31]. Microscopically, CPPs consist of a single layer of well-differentiated, cuboidal epithelial cells around a characteristic fibrovascular stalk. They exhibit finger-like projections, resulting in a papillary configuration. A well-formed basement membrane is present. The average MIB-1 labeling index for CPPs is around 3.7% [58]. An increase in MIB-1 labeling index may aid in differentiating CPP from an entity known as "villous hypertrophy", in which exuberant, yet nonneoplastic choroid plexus exists [1]. Atypical CPPs are those which exhibit increased cellularity, mitoses, and nuclear pleomorphism compared to typical CPPs, as well as poorly formed papillary structures. In addition, they may show a slightly higher MIB-1 labeling index.

CPCs are categorized as WHO Grade III lesions. Distinguishing CPC from CPP histologically can prove difficult, and in some cases the histologic features may correlate little with the tumor's biological behavior [9]. Controversy exists over the features required to label a tumor as a CPC, and various criteria exist. Among the features suggestive of carcinoma are cellular anaplasia, loss of normal papillary architecture, nuclear pleomorphism, necrosis, giant cell formation, and an increase in mitoses. The average MIB-1 labeling index seen in CPCs is 14% [58] (Fig. 4). An area of controversy is the need for brain invasion to make the diagnosis of CPC [46]. Some authors include those tumors with evidence of brain invasion in the category of CPC. Others, however, have described tumors with an otherwise benign appearance plus parenchymal invasion which behave in a benign fashion, responding to surgical treatment alone without the need for any adjuvant therapy [26]. These authors recommend classifying such lesions as papillomas, despite the presence of brain invasion. The presence or absence of metastatic disease is also unhelpful in making this distinction between CPP and CPC, as dissemination throughout the neuraxis has been associated with both pathologies [9, 60–62]. In addition, malignant evolution of CPP to CPC has been demonstrated [10].

Immunohistochemically and genetically, certain differences have been identified between CPPs and CPCs. CPPs have been found more often to express the markers transthyretin and S-100, seen in 80%–90% of cases [42]. CPCs more often express carcinoembryonic antigen (CEA) and CD44 than CPP [59]. Glial fibrillary acidic protein (GFAP) is seen in 25%–55% of CPPs, and 20% of CPCs [42]. Carlotti et al. showed that immunostains for certain cell cycle markers including the cyclins, cyclin-dependent kinases, and retinoblastoma protein, were upregulated in CPCs versus CPPs [6].

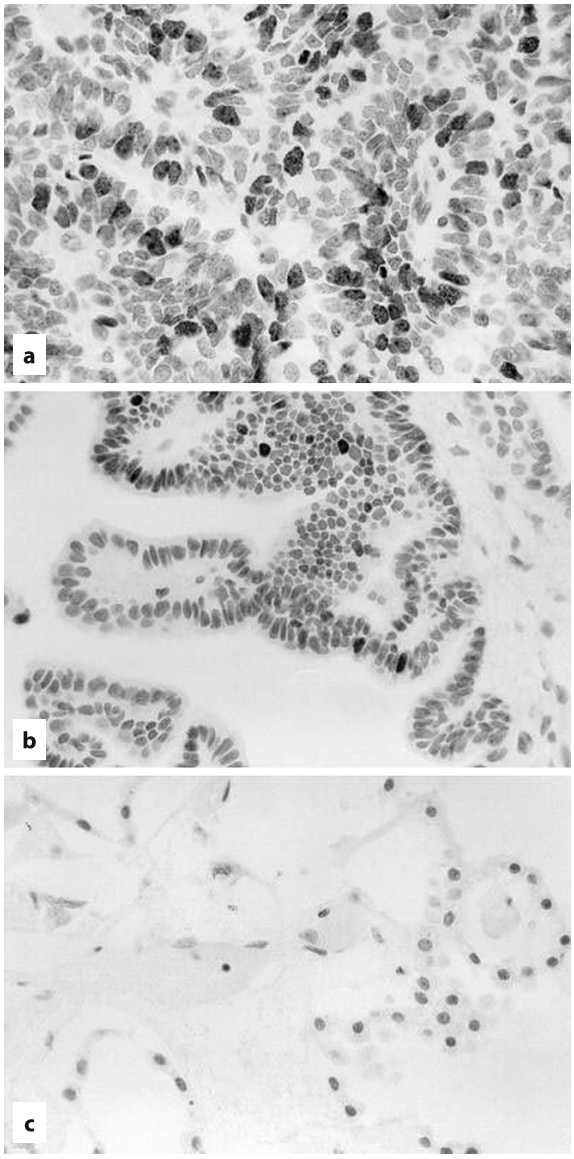


Fig. 4 Histopathology of choroid plexus tumors depicting MIB-1 labeling index of: (**a**) Choroid plexus carcinoma, 27.3 (**b**) choroid plexus papilloma, 4.1, and (**c**) normal choroid plexus, 0

In terms of chromosomal aberrations, CPPs displayed significantly greater gains of chromosomes 5q, 6q, 7q, 9q, and 15q, as well as loss of 21q, compared with CPCs [42]. CPCs, however, showed increased gains of chromosome 1, 4q, 10, 14q, 20q, and 21q, as well as loss of 5q and 18q [42].

Treatment

The treatment of children with CPTs remains a challenge, in part due to controversy surrounding the clinical and pathologic classification of these lesions, their relative rarity among brain tumors, and limited data on response to adjuvant therapies, combined with the young age of those afflicted with CPTs and potential treatment-related adverse events. The mainstay of treatment for both CPPs and CPCs remains gross total surgical excision. In the case of CPCs, adjuvant treatment may include pre- or postoperative chemotherapy, radiotherapy, or both.

Surgery

The goals of surgical intervention for patients with CPTs include gross total resection of the lesion itself, as well as addressing the associated hydrocephalus if present. Modern improvements in microneurosurgical technique, as well as the advent of neuroradiology, neuroanesthesia, neurointensive care, and dedicated nursing staff have all led to improved surgical outcomes for these patients [16, 51]. In addition, advances in shunt-related hardware have improved the prognosis for those with persistent hydrocephalus.

Basic surgical principles for the resection of CPTs are similar to those for intraventricular lesions in general, and a multitude of surgical approaches have been described. The choice of surgical approach is dictated by the location of the lesion, its arterial feeders, and surgeon experience and preference. In brief, the surgeon must plan a well-placed cortical incision, providing adequate access to the region of the ventricular system harboring the tumor and early identification of the vascular pedicle, followed by ligation of this pedicle and subsequent en bloc extirpation of the tumor (Fig. 5). Occasionally, obtaining access to the vascular stalk proves difficult due to the large size of the tumor. In these cases, careful use of the bipolar cautery to shrink the tumor, followed by piecemeal removal of the cauterized components, will bring the pedicle into view while minimizing intraoperative blood loss.

For patients with CPP, definitive treatment generally involves surgery alone, with the aim of a gross total resection. The prognosis for these patients following gross total resection is excellent, with 5-year

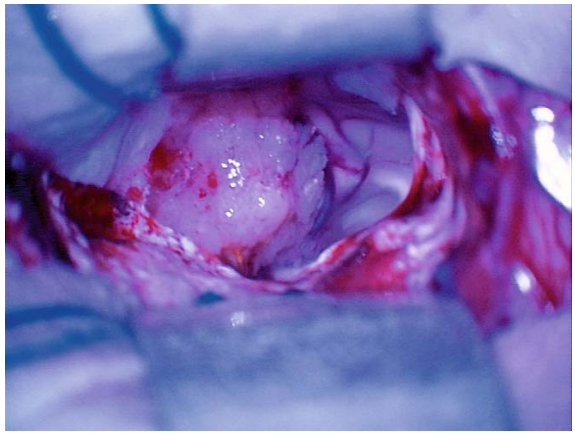


Fig. 5 Intraoperative image depicting cauliflower-like lesion in the lateral ventricle. With such operative exposure, the neurosurgical technique from here is to identify the main arterial feeders stepwise and coagulate them before removing the tumor

survival rates up to 100%, and 10-year survival rates up to 85% [16, 35, 54]. Fortunately, a complete resection is possible in the vast majority of CPPs. Carlotti et al., reporting on a series of 12 patients with CPP operated on during the period from 1982 to 1997, were able to achieve a complete resection in 100% of the cases [6]. In their series, Zuccaro et al. and McEvoy et al. also achieved complete resection in all CPPs reported [28, 56]. Pencalet et al. obtained a 96% gross total resection rate for their larger series of CPPs [35]. Results such as these have led many to conclude that complete resection of CPPs may be curative, and if obtained, further adjuvant therapy is not warranted [29, 35].

Krishnan et al. recently reviewed a large series of 41 patients with CPP, treated during the period from 1974 to 2000 at a single institution. Although their study population consisted of a greater proportion of adult patients, they also concluded that gross total resection is the treatment of choice for CPPs. Furthermore, in those patients with an initial subtotal resection, they observed that only half required further treatment by repeat resection, and that the addition of radiation therapy in this group added little to treatment outcome [24]. As such, they and others have recommended that patients with disease progression following initial subtotal resection undergo reoperation if feasible, as opposed to implementing chemotherapy or radiotherapy as adjuvant treatment [24, 54].

Similar to CPPs, the initial treatment of choice for patients with CPCs is generally surgical resection, in an attempt to obtain gross total excision. Two-year survival rates following complete excision are in the neighborhood of 72%, while the number with only a partial resection remaining alive at this time point is approximately 34% [54]. In their review of 75 reported cases of CPC, Fitzpatrick et al. found a survival rate of 84% versus 18% for CPC patients with gross total resection versus subtotal resection, respectively [18]. Due to their extreme vascularity, and potential for invasion, a complete resection can be more challenging in this subgroup of patients. In their series, Carlotti et al. were able to obtain a complete resection in only approximately half of their patients with CPCs [6]. Pencalet et al. were able to obtain a complete resection in 61.5% of their CPC patients [35]. Berger et al. undertook a retrospective review of their experience with 22 children diagnosed with CPC, between 1984 and 1995. All underwent surgical resection of the primary lesion, and 19/22 had further adjuvant therapy. Their overall 5-year survival was only 26%; however, in the subgroup of patients in whom a complete resection was attained, the 5-year survival was 86% [2]. The main prognostic factor in their series was the extent of surgical resection. They recommended that aggressive resection be attempted, and in children with an initial subtotal resection, a "second look" operation be considered if not limited by significant potential neurologic sequelae.

Despite complete removal of CPTs, a subset of patients continue to require permanent CSF diversion postoperatively. In one series, 9/38 children required a ventriculoperitoneal shunt following the removal of their tumor [35]. Other series have shown that between 30%–50% of patients may require a shunt for treatment of symptomatic hydrocephalus, despite complete tumor removal [16, 27, 39, 50]. In addition to postoperative hydrocephalus, another adverse surgical event seen in some children is the accumulation of subdural fluid collections (Fig. 6). Children with significant preoperative hydrocephalus, with thinning of the cortical mantle, appear to be at somewhat greater risk for this complication. On occasion, these collections require the placement of a shunt to facilitate their drainage. In order to minimize the chance of developing such a complication, some authors recommend filling the ventricles with saline prior to closure of the craniotomy, or using pial sutures or fibrin glue to close the corticotomy site, as well as temporary postoperative external ventricular drainage [31, 35].

Radiation Therapy

In general, the use of adjuvant radiation therapy for CPTs has been reserved for patients diagnosed with CPC. However, the radioresponsiveness of CPCs is the subject of ongoing debate. When employed, radiation therapy for CPCs is generally in the form

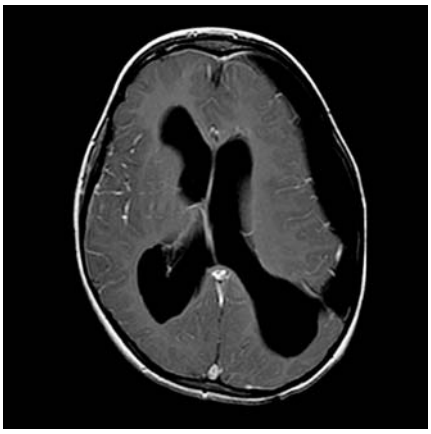


Fig. 6 Axial MRI scan 3 years after removal of a choroid plexus papilloma in a child now 4 years old. The scan shows a large subdural effusion which has resulted from the corticectomy and approach to the ventricle. On occasion, these large subdural effusions may need to be shunted. The child here is completely well without neurological symptoms or signs

of craniospinal irradiation, with a median dose of 35.2 Gy to the craniospinal axis, plus an additional boost to the tumor cavity (total dose 55.2 Gy) [9]. In those patients with presence of leptomeningeal metastatic disease, postoperative craniospinal irradiation may provide for better outcomes than adjuvant chemotherapy alone [9]. The role for adjuvant radiation therapy in the absence of metastatic disease or disease progression is more controversial, especially if initial gross total resection is achieved. Some favor withholding radiation therapy, in light of its well-known adverse cognitive and endocrine effects on the developing brain, especially in the youngest children. Radiation therapy is commonly withheld in those patients under 3 years of age. Others have commented on improved survival with adjuvant radiotherapy, even in those children in whom gross total resection was achieved. In their meta-analysis, Wolff et al. found that in both the gross total and subtotal resection groups, survival was better for the irradiated patients [54].

Chemotherapy

As with radiation therapy, the role of adjuvant chemotherapy has generally been restricted to the treatment of patients with CPCs. Chemotherapy regimens consist of combinations of cyclophosphamide, etoposide, vincristine, and a platinum agent [9]. Carlotti et al. used the "ICE" chemotherapy regimen for 2–6 cycles (ifosfamide, carboplatinum, etoposide) for the treatment of CPC patients in their series [6]. A subgroup of their patients received chemotherapy following initial biopsy or subtotal resection, and subsequently underwent a repeat attempt at gross total resection. In comparison of the initial biopsy/resection specimens with the subsequent postchemotherapy resection specimens, they found that expression of cell cycle proteins decreased following chemotherapy. A study by the Pediatric Oncology Group in 1995, examining 8 children with CPC, found that postoperative adjuvant chemotherapy was helpful in delaying the need for radiation therapy, even in those children with initial subtotal resection [13]. In addition to postoperative chemotherapy, some authors have suggested a role for preoperative chemotherapy in an attempt to reduce the size and vascularity of the tumor, thereby minimizing the risk of hemorrhage at surgery, along with its associated morbidity and mortality [19, 40, 45, 46].

Angio-Embolization

An additional therapeutic option for patients with CPTs is that of embolization of the feeding arteries, by interventional endovascular means. Though not a definitive treatment strategy, this may significantly minimize the blood loss incurred at the time of surgery. The technique is not without its risks, however, as the choroidal vessels supplying these tumors can be small in caliber and tortuous in nature, making them difficult to catheterize. In addition, there is the risk of arterial occlusion, due to embolus, thrombosis, or dissection.

Prognosis/Quality of Life

Due to the rarity of CPTs, and heterogeneity in how these lesions are treated, it is difficult to draw precise conclusions with respect to the overall prognosis and quality of life afforded these patients. Outcomes for these children span the entire spectrum – from intraoperative mortalities secondary to uncontrollable hemorrhage, variable degrees of postoperative and postradiation therapy neurologic sequelae, to the long-term difficulties associated with the need for permanent CSF diversion. In recent series, however, increasingly better outcomes are attained. Surgical cure from CPPs is the expected outcome, and long-term survival seems to be the rule. For patients with CPCs, the prognosis is less optimistic; however, long-term survival has been reported after aggressive surgical resection which can now be accomplished safely using presurgical chemotherapy and immediate preoperative embolization. Close follow-up with serial imaging of the craniospinal axis is recommended in this group of patients.

References

1. Aguzzi A, Weber T, Paulus W. Choroid Plexus Tumors. In: Kleihues P, Cavenee WK, editors. Pathology and genetics of tumors of the nervous system, 1st ed. Lyon: International Agency for Research on Cancer; 1997. p. 16–24
2. Berger C, Thiesse P, Lellouch-Tubiana A, Kalifa C, Pierre-Kahn A, Bouffet E. Choroid plexus carcinomas in childhood: clinical features and prognostic factors. Neurosurgery 1998;42(3):470–475
3. Bielschowsly M, Unger E. Kenntnis der primaren epithelgeschwulste der adergeflechte des gehirns. Arch Klin Chir 1906;81:61–82
4. Body G, Darnis E, Pourcelot D, Santini JJ, Gold F, Soutoul JH. Choroid plexus tumors: Antenatal diagnosis and follow-up. J Clin Ultrasound 1990;18:575–578
5. Boyd MC, Steinbok P. Choroid plexus tumors: problems in diagnosis and management. J Neurosurg 1987;66:800–805
6. Carlotti Jr CG, Salhia B, Weitzman S, Greenberg M, Dirks PB, Mason W, et al. Evaluation of proliferative index and cell cycle protein expression in choroid plexus tumors in children. Acta Neuropathol 2002;103:1–10
7. Carter AB, Price DL Jr, Tucci KA, Lewis GK, Mewborne J, Singh HK. Choroid plexus carcinoma presenting as an intraparenchymal mass. J Neurosurg 2001;95(6):1040–1044
8. Cassinari V. Tumori della parte anteriore del terzo ventricolo. Acta Neurochir 1963;11:236–271
9. Chow E, Reardon DA, Shah AB, Jenkins JJ, Langston J, Heideman RL, et al. Pediatric choroid plexus neoplasms. Int J Radiation Oncol Biol Phys 1999;44(2):249–254
10. Chow E, Jenkins JJ, Burger PC, Reardon DA, Langston JW, Sanford RA, et al. Malignant evolution of choroid plexus papilloma. Pediatr Neurosurg 1999;31(3):127–130
11. Cushing H. Intracranial tumors. Springfield, IL: Charles C Thomas; 1932
12. D'Ambrosio AL, O'Toole JE, Connolly ES Jr, Feldstein NA. Villous hypertrophy versus choroid plexus papilloma: a case report demonstrating a diagnostic role for the proliferation index. Pediatr Neurosurg 2003;39(2):91–96
13. Duffner PK, Kun LE, Burger PC, et al. Postoperative chemotherapy and delayed radiation in infants and very young children with choroid plexus carcinomas. The Pediatric Oncology Group. Pediatr Neurosurg 1995;22(4):189–196
14. Duke BJ, Kindt GW, Breeze RE. Pineal region choroid plexus papilloma treated with stereotactic radiosurgery: a case study. Comput Aided Surg 1997;2(2):135–138
15. Eder HG, Leber KA, Eustacchio S, Pendl G. The role of gamma knife radiosurgery in children. Childs Nerv Syst 2001;17(6):341–346
16. Ellenbogen RG, Winston KR, Kupsky WJ. Tumors of the choroid plexus in children. Neurosurgery 1989;25:327–335
17. Erman T, et al. Choroid plexus papilloma of bilateral lateral ventricle. Acta Neurochir (Wien) 2003;145(2):139–143
18. Fitzpatrick LK, Aronson LJ, Cohen KJ. Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected? J Neurooncol 2002;57(2):123–126
19. Greenberg ML. Chemotherapy of choroid plexus carcinoma. Childs Nerv Syst 1999;15(10):571–577
20. Hirano A. Some contributions of electron microscopy to the diagnosis of brain tumors. Acta Neuropathol (Berl) 1978;43:119–128
21. Horska A, et al. Proton magnetic resonance spectroscopy of choroid plexus tumors in children. J Magn Reson Imaging 2001;14(1):78–82
22. Humphreys RP, et al. Childhood choroid plexus tumors. Concepts Pediatr Neurosurg 1987;7:1–18
23. Jomaa R, Grant DN. Third ventricle choroid plexus papillomas. Childs Brain 1983;10:242–250
24. Krishnan S, et al. Choroid plexus papillomas: a single institutional experience. J Neurooncol 2004;68(1):49–55
25. Kubo S, et al. Immunocytochemical detection of insulin-like growth factor II (IGF-II) in choroid plexus papilloma: a possible marker for differential diagnosis. Clin Neuropathol 1999;18(2):74–79
26. Levy ML, et al. Choroid plexus tumors in children: significance of stromal invasion. Neurosurgery 2001;48(2): 303–309
27. McDonald J. Persistent hydrocephalus following the removal of papillomas of the choroid plexus of the lateral ventricles. J Neurosurg 1969;30:736–740
28. McEvoy AW, et al. Management of choroid plexus tumors in children: 20 years experience at a single neurosurgical centre. Pediatr Neurosurg 2000;32(4):192–199
29. McGirr SJ, et al. Choroid plexus papillomas: long-term follow-up results in a surgically treated series. J Neurosurg 1988;69:843–849
30. Morrison G, Sobel D, Kelly W, Norman D. Intraventricular mass lesions. Radiology 1984;153:435–442
31. Nagib MG, O'Fallon MT. Lateral ventricle choroid plexus papilloma in childhood: management and complications. Surg Neurol 2000;54:366–372
32. Noguchi A, et al. Choroid plexus papilloma of the third ventricle in the fetus. Case illustration. J Neursurg Spine 2004;100(2):224
33. Paulus W, Janisch W. Clinicopathologic correlations in epithelial choroid plexus neoplasms: a study of 52 cases. Acta Neuropathol 1990;80:635–641
34. Pecker J, Ferrand B, Javalet A. Tumeurs du troisieme ventricule. Neurochirurgie 1966;12:1–136
35. Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, et al. Papilomas and carcinomas of the choroid plexus in children. J Neurosurg 1998;88:521–528
36. Pianetti Filho G, Fonseca LF, da Silva MC. Choroid plexus papilloma and Aicardi syndrome: case report. Arq Neuropsiquiatr 2002;60(4)1008–1010
37. Pillai A, et al. Intrinsic brainstem choroid plexus papilloma. Case report. J Neurosurg 2004;100(6):1076–8
38. Pollack IF, Schor NF, Martinez JA, Towbin R. Bobble-head doll syndrome and drop attacks in a child with a cystic choroid plexus papilloma of the third ventricle. J Neurosurg 1995;83:729–732

39. Raimondi AJ, Gutierrez FA. Diagnosis and surgical treatment of choroid plexus papillomas. Childs Brain 1975;1: 81–115
40. Razzaq AA, Cohen AR. Neoadjuvant chemotherapy for hypervascular malignant brain tumors of childhood. Pediatr Neurosurg 1997;27(6):296–303
41. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Child's Nerv Syst 2001;17:503–511
42. Rickert CH, Paulus W. Tumors of the choroid plexus. Microsc Res Tech 2001;52(1):104–111
43. Rickert CH, Wiestler OD, Paulus W. Chromosomal imbalances in choroid plexus tumors. Am J Pathol 2002;160(3): 1105–1113
44. Sawaishi Y, et al. Choroid plexus carcinoma presented with spinal dysfunction caused by a drop metastasis: a case report. J Neurooncol 2003;63(1):75–79
45. Souweidane MM, et al. Volumetric reduction of a choroid plexus carcinoma using preoperative chemotherapy. J Neurooncol 1999;43:167–171
46. St. Clair SK, et al. Current management of choroid plexus carcinoma in children. Pediatr Neurosurg 1991;17(5): 225–233
47. Taggard DA, Menezes AH. Three choroid plexus papillomas in a patient with Aicardi syndrome. A case report. Pediatr Neurosurg 2000;33(4):219–223
48. Talacchi A, De Micheli E, Lombardo C, Turazzi S, Bricolo A. Choroid plexus papilloma of the cerebellopontine angle: a twelve patient series. Surg Neurol 1999;51:621–629
49. Taylor MB, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT. Magnetic resonance imaging in the diagnosis and management of choroid plexus carcinoma in children. Pediatr Radiol 2001;31(9):624–630
50. Tomita T, Naidich TP. Successful resection of choroid plexus papillomas diagnosed at birth: Report of two cases. Neurosurgery 1987;20:774–779
51. Tomita T, McLone DG, Flannery AM. Choroid plexus papillomas of neonates, infants and children. Pediatr Neurosci 1988;14:23–30
52. Turner O, Simon M. Malignant papillomas of the choroid plexus: Report of two cases with review of the literature. Am J Cancer 1937;30:289–297
53. Uchiyama CM, et al. Choroid plexus papilloma and cysts in the Aicardi syndrome: case reports. Pediatr Neurosurg 1997;27(2):100–104
54. Wolff JEA, Sajedi M, Coppes MJ, Anderson RA, Egeler RM. Radiation therapy and survival in choroid plexus carcinoma. Lancet 1999;353:2126
55. Wolff JEA, Sajedi M, Brant R, Coppes MJ, Egeler RM. Choroid plexus tumors. Br J Cancer 2002;87:1086–1091
56. Zuccaro, Sosa F, Cuccia V, Lubieniecky F, Monges J. Lateral ventricle tumors in children: a series of 54 cases. Child's Nerv Syst 1999;15:774–785
57. Janisch W, Staneczek W. Primary tumors of the choroid plexus. Frequency, localization and age. Zentralbl Allg Pathol 1989;135(3):235–240
58. Vajtai I, Varga Z, Aguzzi A. MIB-1 immunoreactivity reveals different labelling in low-grade and in malignant epithelial neoplasms of the choroid plexus. Histopathology 1996;29(2):147–151
59. Varga Z, Vajtai I, Aguzzi A. The standard isoform of CD44 is preferentially expressed in atypical papillomas and carcinomas of the choroid plexus. Pathol Res Pract 1996;192(12):1225–1231
60. Leys D, Pasquier F, Lejeune JP, Lesoin F, Petit H, Delandsheer JM. Benign choroid plexus papilloma. 2 local recurrences and intraventricular seeding. Neurochirurgie 1986;32(3):258–261
61. Domingues RC, Taveras JM, Reimer P, Rosen BR. Foramen magnum choroid plexus papilloma with drop metastases to the lumbar spine. AJNR 1991;12(3):564–565
62. Enomoto H, Mizuno M, Katsumata T, Doi T. Intracranial metastasis of a choroid plexus papilloma originating in the cerebellopontine angle region: a case report. Surg Neurol 1991;36(1):54–58

Malignant Rhabdoid Tumors of the CNS

44

Michael R. Carter

Epidemiology – 540
Incidence
Age and Sex Distribution
Location

Symptoms and Clinical Signs – 540

Diagnostics – 541
Radiological Features

Staging and Classification – 541
Molecular Genetics

Treatment – 542
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 543

Follow-Up/Specific Problems and Measures – 544

Future Perspectives – 544

References – 544

Rhabdoid tumors are a group of highly invasive neoplasms occurring predominantly in early childhood.

Malignant rhabdoid tumors (MRT) were first described in the kidney and were thought to represent a sarcomatous variant of Wilms tumor [1]. Similar tumors were subsequently identified at numerous extrarenal locations including the CNS, which remains the most frequent extrarenal location [2]. Although CNS MRT is now well recognized as a defined entity, there have historically been difficulties in making the diagnosis. The tumor may be largely composed of rhabdoid cells but may also contain mesenchymal and epithelial elements (termed atypical teratoid/rhabdoid tumors – AT/RT). Furthermore 70% of CNS malignant rhabdoid tumors contain fields of cells indistinguishable from primitive neuroectodermal tumor/medulloblastoma (PNET MB) [3]. Adding to the confusion is the fact that these two entities also share clinical and radiological features [4].

Epidemiology

Incidence

CNS MRT is an uncommon tumor. Fewer than 200 cases have been reported in the world literature and they are thought to account for around 2% of pediatric brain tumors [5]. The exact prevalence is difficult to ascertain because of previous difficulties with differentiation from PNET. However, it seems logical that the overall incidence will increase as this differentiation is increasingly recognized [6]. Although numbers are small, no striking racial or geographic relationships have yet been identified.

Age and Sex Distribution

CNS MRT is predominantly a tumor of young children, with 94% occurring in patients under 5 years of age [7]. Two prominent series found mean ages at diagnosis of 16.5 and 17 months [3, 6].

Most published series to date demonstrate a male predominance. This was reported to be a 1.4 to 1 ratio in childhood [7] but was also observed (and the ratio greater) in the small group of adults described with CNS MRT. Unpublished data from the UK Childhood Cancer Study Group register demonstrates a trend towards increasing male preponderance with age, even in childhood [8].

Data from the age group 0–1 year old are interesting in that a female preponderance is noted (5:3)

Location

Slightly more than half of all primary tumors occur in the posterior fossa (52%), 39% occur in the cerebral hemispheres, 5% in the pineal, and 2% in the spinal cord; 2% of tumors [7] are reported of multifocal origin. Again the situation with children of 12 months or less differs, with infratentorial tumors outnumbering supratentorial lesions by four to one [8]. In other age groups, the situation is reversed with supratentorial tumors being twice as common as infratentorial ones. The same data also demonstrates that primary spinal cord location (2 out of 36) occurred only in patients less than 4 years of age.

Several authors have observed that infratentorial MRTs commonly arise in the cerebello-pontine angle and invade adjacent structures.

Symptoms and Clinical Signs

General features of raised ICP in the under 3 years age group – failure to thrive, macrocrania, headache, vomiting – are the usual hallmarks of MRT. Head tilt and cranial nerve palsies (usually nerves 6 or 7) also may be obvious at presentation. In older children specific signs of cerebellar dysfunction may present

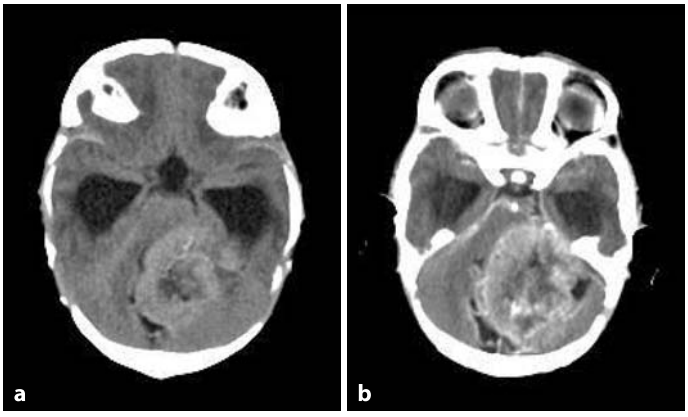


Fig. 1 **a** Noncontrast enhanced CT of MRT in a 6-week-old child. Irregular posterior fossa mass lesion occluding fourth ventricle and causing hydrocephalus. **b** The same tumor after contrast administration. Tumor has indistinct margins and is distorting brainstem, fourth ventricle, CP angle, and vermis

along with long tract signs and multiple lower cranial nerve palsies with brainstem involvement. Patients with supratentorial lesions may develop lateralizing signs and seizures in addition to intracranial hypertension. Patients with CSF dissemination may have signs of meningeal or spinal nerve root irritation although these may not be obvious in very small children.

Diagnostics

Radiological Features

CNS MRT demonstrate highly variable imaging characteristics, many of which overlap with other high-grade CNS tumors including PNET. Typically there are large, hyperdense, infiltrating lesions that demonstrate strong but heterogeneous contrast enhancement on both CT and MRI (Fig. 1) [6]. Lesions may be solid or partially cystic and commonly contain areas of hemorrhage and calcification, best seen on CT. They may appear partially intra- and partially extra-axial and invade adjacent structures such as dura. MRI imaging typically demonstrates hypodensity on T1 sequences with variable iso/hypodensity on T2 images. They enhance strongly with gadolinium and pathological vessels may be large enough to produce visible flow voids.

Meningeal involvement may be demonstrated by the presence of diffuse or nodular pial enhancement. MRTs typically exhibit much mass effect and in the posterior fossa may cause hydrocephalus.

Staging and Classification

Macroscopically MRTs are large, fleshy tumors, often reddish gray in color that in parts may appear defined from surrounding brain, while being clearly infiltrative in others. Brainstem/CPA tumors typically appear exophytic and distort and wrap around the stem, engulfing cranial nerves and brainstem vessels (Fig. 2).

Microscopically the tumor consists of rhabdoid cells with variable, additional elements of primitive neuroectodermal, mesenchymal, and epithelial origin. Approximately 15% of childhood MRT consist entirely of rhabdoid cells. These cells are medium sized, round/oval entities with eccentric nuclei and prominent nucleoli. Under the electron microscope, they typically contain bundles of intermediate filaments. Two thirds of MRTs will also contain small cell embryonal components, one third a mesenchymal component, and one quarter neoplastic epithelium. Homer-Wright or Flexner Wintersteiner rosettes may be present as may be ependymal canals. Neovascularity is not a feature, but necrosis and hemorrhages are frequent [7].

The immunohistochemistry of MRT is complex because of the disparate cellular components represented [7]. Rhabdoid cells generally express EMA and vimentin, but not desmin or any of the markers associated with germ cell tumors. Less frequently they may express smooth muscle actin, GFAP, NFP, and keratin.

The small cell embryonal components may express vimentin, GFAP, NFP, and desmin. Mesenchymal tissue expresses vimentin and occasionally SMA and desmin. Epithelial components typically express keratin and less commonly, vimentin or EMA. The histiogenic origin of rhabdoid cells is uncertain but may involve the other tissue types associated with MRT or possibly cells of histiocytic, meningeal, or germ cell lineage.

MRT demonstrate increased proliferative activity and Ki67/MIB-1 labeling indices indicate growth fractions of up to 80% [7]. Up to one third will have evidence of leptomeningeal dissemination at the time of diagnosis [7].

Molecular Genetics

Studies utilizing in situ hybridization and comparative genomic hybridization have demonstrated a high incidence of chromosome aberrations in MRT [9]. The most consistent normality is monosomy 22, detectable in up to 90% of cases [6, 7].The gene involved in MRT, hSNF5/INI 1 maps to locus 22 q11. INI 1 is a nine exon unit which is ubiquitously expressed. Its product, INI 1 protein, is a component of the mammalian SWI/SNF complex. This complex

Fig. 2 Postmortem specimen of the patient shown in Fig. 1. Irregular, lobulated tumor infiltrating and distorting the brainstem and cerebellar vermis with ependymal deposits in the third ventricle

acts in an ATP-dependant manner to modulate chromatin structure. In MRT, deletions/mutations in INI 1 occur specifically in exons 1 and 9 and inactivate the gene through production of novel stop codons. The exact function of INI 1 is unknown, but a role as a tumor suppressor gene has been postulated. Interestingly, this mutation is also associated with choroid plexus papillomas and carcinomas, although the nature of the relationship between these entities is unclear. This gene is constitutionally disordered in the Rhabdoid Syndrome wherein siblings are predisposed to synchronous Rhabdoid tumors (including CNS MRT) This possibility should be borne in mind when counseling families with a new diagnosis of MRT.

Treatment

Surgical resection remains the standard management although complete resection is rarely possible. In many cases, operation may be palliative or even merely diagnostic. Palliative CSF diversions may be undertaken and access devices sited to facilitate intrathecal chemotherapy. MRT s are highly invasive and local recurrence is usual even when removal seems to have been complete. Tumors have a tendency for dissemination through CNS pathways and 30% will have done so by diagnosis. Compared to medulloblastoma, MRT responds poorly to radio and chemotherapy [10]. Both treatments are commonly used despite the fact that response to either is unpredictable and many children show no objective signs of response at all [11].

Surgery

Gross total resection should be the goal of surgical treatment. The likelihood of this is dictated by location and is far more likely with tumors situated in the cerebral hemispheres and laterally in the cerebellum. Vascular, brainstem, and multiple cranial nerve involvement can preclude complete macroscopic removal and may contribute to operative morbidity. CT or MRI based neuronavigation is a useful adjunct in patients large enough to make its use practicable and is of undoubted benefit in terms of assessing the extent of resection and avoiding critical structures. The surgeon should always bear in mind that postregistration brain shift (particularly with larger tumors) may reduce the accuracy of image guidance systems. Intraoperative ultrasound has much to commend it for delineation of tumor mass/remnant and also planning corticotomy in a tumor concealed beneath the brain surface. Ultrasound has the great advantage providing real time information. It can also help with placement of ventriculostomy and the identification of unexpected hemorrhage. In Doppler mode, it allows identification of vascular structures. Most MRTs present as large masses with considerable intracranial hypertension. Patients should thus ideally be predosed with corticosteroids and anticonvulsants. Surgery is performed with endotracheal intubation and controlled ventilation. Intravenous mannitol can be administered prior to dural opening. Slight head-up positioning will help reduce venous engorgement, but the surgeon should bear in mind the risk of air embolism, particularly with suboccipital approaches. In the presence of hydrocephalus, placement of a ventricular drain may considerably facilitate dural opening and avoid the problems of brain herniation during the dissection. Longer-term control of hydrocephalus is afforded by endoscopic third ventriculostomy (where appropriate) or shunt placement. The risk of intra-abdominal seeding from shunts is unquantified. Tumors of the cerebellum are approached via a standard midline suboccipital approach, lateralized if necessary. Early identification of the fourth ventricular floor gives an important landmark and avoids inadvertent forays into the brainstem. Supratentorial tumors are approached via craniotomy, positioned so as to allow the most direct approach to the tumor bulk. In the case of a dominant tumor cyst, fluid can be aspirated at the beginning of the operation and the tumor then debulked from within. Most MRTs are highly infiltrative and are not surrounded by a distinct plane. In most cases however a tumor "edge" can be found and followed. Some CNS MRTs may behave intraoperatively in a similar fashion to choroid plexus carcinomas. Preparations should be made for rapid transfusion as these resections can be exceptionally hemorrhagic. The ultrasonic aspirator is highly effective in rapid debulking, aided by wide bore suction and irrigating bipolar electrocautery. Once resection has proceeded beyond the biopsy stage, one is committed and in a particularly vascular tumor, blood loss ceases only when the tumor is substantially removed. It is important to recognize that both surgeon and anesthetist benefit greatly from experienced assistance during major tumor resections in small children. We make a point of including this in preoperative planning for these cases. In recent months, this has allowed us to tackle difficult tumors that might otherwise have resulted in uncontrollable difficulties on the table. Patients benefit from a period of close observation in a high-dependency environment after surgery and families should be counseled about the very real risks of intraoperative mortality.

Preoperative measures such as chemotherapy and possibly embolization may have a role in the management of MRT. However, as most patients are young and present with acutely raised intracranial

pressure, the practicalities of such approaches have yet to be evaluated.

Radiotherapy

The majority of children presenting with MRT will be too young to benefit from irradiation. Despite the uncertain efficacy, most children older than 3 years with the disease will be offered radiotherapy. The literature describes palliative, local, and craniospinal regimens, utilizing doses of up to 55 Gy to the brain and 35 Gy to the spine [8, 11]. Recent interest has been shown in the use of radiosurgery in the management of local recurrences although the numbers are too small to generalize on the efficacy of this [12, 13]. The usefulness of brachytherapy or radiosensitizing agents in MRT is unknown.

Chemotherapy

A wide variety of chemotherapeutic options have been used to treat children with MRT [11]. These include the "baby POG protocol" (cyclophosphamide, vincristine, cisplatin, and VP-16), "augmented baby POG protocol"(higher dose cyclophosphamide and more intensive cisplatin), Infant PNET and PNET 111 regimes, St. Jude's protocol (vincristine, cyclophosphamide, and cisplatin) [8], eight drugs in 1-day therapy and other cisplatin- or carboplatin-based treatments. There may be an important role for chemotherapy in delaying irradiation in very young children, but the ability of chemotherapy to alter the natural history of the disease remains in doubt. Despite this, several recent studies have reported long-term survivors after surgery with the use of intensified treatment protocols combined with radiotherapy and autologous bone marrow transplant.

Olson et al. [14] reported disease-free survival at 60 and 24 months after intensified therapy (vincristine, dactinomycin, cyclophosphamide, doxorubicin, cisplatin, and etoposide). They also used triple intrathecal therapy comprising hydrocortisone, cytosine, and methotrexate. Hilde [12] reported disease-free survival at 46 months in a child treated with dose-intensive chemotherapy (cisplatin, etoposide, vincristine, ifosfamide, and doxorubicin) together with intrathecal thiotepa. High dose chemotherapy was then added (busulphan, melphalan, and thiotepa) together with stem cell rescue.

Most recently, Ronge et al. [11] reported disease-free survival at 52 and 65 months in two children (aged 14 months and 5 years respectively at diagnosis) who had subtotal tumor resections followed by treatment according to the current UKCCSG/SIOP protocol for childhood sarcoma. (MMT 953, arm B). This treatment utilizes six drugs and additional triple intrathecal therapy. The younger child had no radiotherapy but did go on to autologous marrow transplant. The older child had craniospinal irradiation. This child has the longest survival reported to date and it seems possible that systemic sarcoma protocols may have greater efficacy than other baby brain tumor regimens. This is currently under investigation in a multicenter collaboration [8]. The use of intrathecal treatment is a logical development as the incidence of CSF dissemination is high and may represent a substantial proportion of the tumor load. One study notes prolonged survival in a case treated with unintensified systemic therapy but triple intrathecal chemotherapy [15].

Prognosis/Quality of Life

In general terms the outlook with CNS malignant rhabdoid tumors remains dismal. Many children demonstrate no objective response to treatment and more than half demonstrate progression leading to death within a year from diagnosis [3, 6]. The median survival in most series is 6–8 months (range 1 week to 58 months) Overall 1- and 3-year survival approximates 49% and 19% [8].Most series do include individuals who achieve noticeably longer survival periods although they form quite a heterogeneous group [8, 11, 12, 14]. The low numbers preclude stratification of disease and the attribution of specific outcome indicators is dubious.

Total resection is uncommon with MRT and completeness of surgical excision has not consistently emerged in the literature as a factor in prognosis. Most of the long-term survivors reported underwent subtotal resections. Despite this, data are emerging to suggest that completeness of resection has a positive effect on survival times.(7 out of 9 children in The UKCCSG data summary, with survival greater than 12 months had undergone complete resections) (8). The overall numbers however are small and all reports must be interpreted in this light. The specific benefits of adjuvant chemo and radiotherapy are also difficult to ascertain, largely because the variety of treatment regimens undertaken precludes meaningful comparison.

Tumor location, and age at presentation have not reliably been shown to influence outcome, although both might reasonably be expected to affect operative morbidity at least.

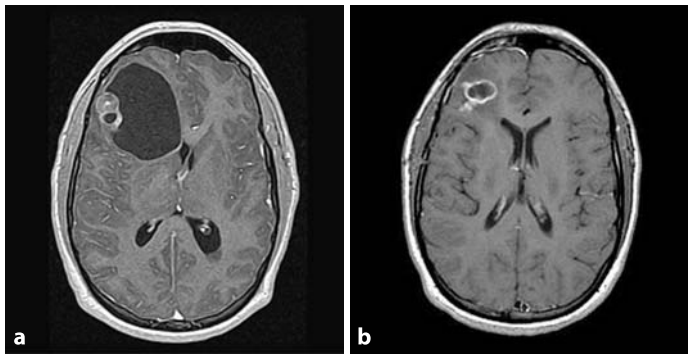


Fig. 3 **a** T2 gadolinium enhanced axial MRI showing a predominantly cystic right frontal supratentorial tumor in a teenage boy. This was completely resected yielding a diagnosis of classic ependymoma. **b** The same child 6 months later. Enhancing nodular recurrence was resected, yielding no evidence of ependymoma but a clear diagnosis of MRT

Follow-up/Specific Problems and Measures

Despite the classification of CNS MRT as a defined tumor entity, difficulties still exist in differentiating it from other tumor entities, notably PNET. This is an important problem because the outlook with MRT is significantly worse than PNET. The true prevalence of MRT has undoubtedly thus been underestimated It has been suggested [11] that misdiagnosis of CNS MRT as PNET/MB might account for the perception that children under 2 years with PNET/MB have a worse prognosis than older patients, as MRTs have significantly the worse outlook.

Furthermore, it is becoming clear that teratoid differentiation can occur in a number of other CNS tumors including, astrocytomas, meningioma, gangliogliomа, and ependymoma (Fig. 3) [16–18]. The molecular mechanisms underlying this and the prognosis significance of such transformation remain opaque. These cases present obvious diagnostic difficulties, but analysis of chromosomal and genetic markers in such circumstances can be important in determining tumor identity [9].

Future Perspectives

Technical advances in diagnostic imaging, surgery, the delivery of chemo- and radiotherapy will undoubtedly contribute to improved management of children with CNS MRT. However, as with most CNS tumors, major advances are critically dependant upon an increased understanding of cellular processes initiating and sustaining the neoplastic process. There is a huge need for cooperative biological studies which will aid in disease stratification and perhaps suggest targets for novel therapies. MRT is a rare tumor and the small number of cases reported have been managed according to various protocols. Presently it is impossible to define optimum therapy. The promotion of multicenter trials and international tumor registries will hopefully refine the world experience and eventually enable consensus as to what constitutes best treatment.

Most importantly of all, we should never forget that behind every diagnosis, every resection, and every actuarial survival curve, lies a sick child. And we, as neurosurgeons, should always be wary of recommending for others interventions that we would not wish for our own children.

References

1. Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms tumors: Results from the first National Wilms Tumor Study. Cancer 1978;41:1937–1948
2. Parham DM, Weeks DA, Beckwith JB. The clinicopathologic spectrum of putative extrarenal rhabdoid tumors: an analysis of 42 cases studied with immunohistochemistry or electron microscopy. Am J Surg Pathol 1994;18:1010–1029
3. Burger PC, Yu IT, Tihan T, et al. Atypical teratoid/rhabdoid tumors of the central nervous system: A highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: A Pediatric Oncology Group study. Am J Surg Pathol 1998;22:1083–1092
4. Zuccoli G, Izzi G, Bacchini E, et al. Central nervous system atypical teratoid/rhabdoid tumors of infancy. CT and MR findings. Clin Imaging 1999;23:356–360
5. Caldemeyer KS, Smith RR, Azzarelli B, et al. Primary central nervous system malignant Rhabdoid tumor. CT and MR appearance simulates a primitive neuroectodermal tumor. Pediatr Neurosurg 1994;21:232–236
6. Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical Teratoid/Rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 1996;85:56–65
7. Rorke LB, Biegel JA. Atypical teratoid/rhabdoid tumor. In: Kleihues P, WK Cavanee, editors. Pathology and genetics: tumors of the nervous system. Lyon: IARC Press; 2000. p. 145–8
8. Stiller C, UKCCSG Summary data. National Childhood Tumor Registry, Oxford, UK
9. Wharton SB, Wardle C, Ironside JW, et al. Comparative genomic hybridisation and pathological findings in atypi-

cal teratoid/rhabdoid tumor of the central nervous system. Neuropathol Appl Neurobiol 2003;29:254–261
10. Michalski A, Garre ML. Infant brain tumors. In: Walker DA, Perilongo G, Punt JAG, Taylor RE, editors. Brain and spinal tumors of childhood. London: Arnold; 2004. p. 359–369
11. Ronghe MD, Moss TH, Lowis SP. Treatment of CNS malignant rhabdoid tumors. Pediatr Blood Cancer 2004;42: 254–260
12. Hilden JM, Watterson J, Longee DC, et al. Central nervous system atypical teratoid/ Rhabdoid tumor: response to intensive therapy and review of the literature. J Neurooncol 1998;40:265–275
13. Hirth A, Pederson PH, Wester K, Mork S, Helgestad J. Cerebral atypical teratoid/rhabdoid tumor of infancy: long-term survival after multimodal treatment, also including triple intrathecal chemotherapy and gamma knife radiosurgery – a case report. Pediatr Hematol Oncol 2003;20(4):327–32
14. Olsen TA, Bayar E, Kosnik E, et al. Successful treatment of disseminated central nervous system malignant rhabdoid tumor. J Pediatr Hematol Oncol 1995;17:71–75
15. Weinblatt M, Kochen J. Rhabdoid tumor of the central nervous system. Med Pediatr Oncol 1992;27:87–98
16. Wyatt-Ashmead J, Kleinschmidt-DeMasters BK, et al. Rhabdoid glioblastoma. Clin Neuropathol 2001;20(6):248–55
17. Bannykh SI, Perry A, Powell HC, Hill A, Hansen LA. Malignant rhabdoid meningioma arising in the setting of preexisting ganglioglioma: a diagnosis supported by fluorescence in situ hybridisation. J Neurosurg 2002;97(6):1450–5
18. Hawkins CJ. Department of Neuropathology, Hospital for Sick Children, Toronto, Personal communication

Langerhans Cell Histiocytosis 45

Clare Gallagher, Walter J. Hader

Epidemiology – 548

Symptoms and Clinical Signs – 548

Diagnostics – 549

Staging and Classification – 551

Treatment – 551
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 552

Future Perspectives – 553

References – 553

Epidemiology

Langerhans cell histiocytosis (LCH) is a rare disorder of the mononuclear-phagocyte system, capable of producing a broad spectrum of clinical disease from a self-limiting focal skeletal lesion to a fulminant, sometimes fatal, multisystem disorder. The association of LCH with central nervous system disease dates back to the initial description by Hand in 1893, of a 3-year-old patient, who presented with exophthalmos, polyuria, and localized osteomalacia of the skull. Hand initially attributed the constellation of findings to tuberculosis, although he later suggested the disease likely had a different cause [1]. The unknown etiology of this disease led to the proliferation of names for the various clinical entities, including eosinophilic granuloma for localized skeletal lesions, Hand-Schüller-Christian disease for multifocal skull lesions and diabetes insipidus and (Abt-Letterer-Siwe disease for the disseminated form with multiple organ involvement. Lichenstein was the first to recognize the similarities that these clinical and pathological entities contained were due to one disease and coined the term histiocytosis X to encompass these histiocytic disorders of unknown etiology [2]. It was not until Nezelof, in 1973, described the resemblance between the ultrastructural elements of the normal Langerhans cell and those abnormal cells in histiocytosis X, that the common cell of origin was discovered [3]. As a consequence of that discovery, "Langerhans cell histiocytosis" was proposed to replace "histiocytosis X" and to unify the varied clinicopathological entities [4].

The incidence of LCH is estimated to be between 4 and 5.4 per million; however, its true incidence may be much higher due to the presence of asymptomatic disease [5]. While all age groups are affected, the peak incidence is in the pediatric group, specifically the 1- to 3-year-old range. Disseminated LCH is most prevalent in the under 2-years-old age group and half of single bony lesions occur under 5 years of age. Several case control studies have failed to identify any single risk factor for LCH; however, an association of thyroid disease and LCH was found in the largest study [5]. An association of LCH and childhood cancers, both solid tumors and leukemia, has been described. Secondary cancers developing after the diagnosis and treatment of LCH are well documented, but the occurrence of LCH after the diagnosis of a malignancy, suggests some patients may have a yet-undetermined predisposition to both conditions.

Symptoms and Clinical Signs

The presentation of LCH is variable, based on the organ affected by the disease. The most common sites of involvement include the skeleton, skin, lymph nodes, liver, and rarely the central nervous system. Solitary or multiple lesions of the bony skeleton, previously called eosinophilic granuloma, are very common in LCH and reported in 80%–100% of patients, with or without involvement of other organs. The majority of lesions involve the flat bones of the skull, mandible, ribs, and pelvis, less commonly the spine and long bone, but LCH can be found in any bone. Pain and swelling are usually the presenting symptoms with complications of bony involvement dependent on the area involved. Marrow infiltration is invariably present in patients with disseminated disease which is an expected finding given that is the site of origin of LCs [6].

Cutaneous lesions are common in the pediatric population and is seen in up to one third of cases. Rashes characterized by scaly, erythematous seborrheic-like red-to-brown papules are most prevalent in intertriginous zones. If this is the only site involved, regression is common. Lymph nodes may be involved due to local or systemic disease, but when enlarged this may signal a more aggressive disease. Involvement of the liver may be due to the direct infiltration by Langerhans cells or the secondary effects of cholestatic enlargement from nodal obstruction in the region of the porta hepatis, both of which can lead to severe liver dysfunction. The spleen is only involved in about 5% of cases. Pulmonary LCH may be seen in isolation or part of disseminated disease in which diffuse interstitial infiltrates may be evident on X-ray. Detection of Langerhans cells is possible on bronchioalveolar lavage. Respiratory failure is a complication in uncontrolled LCH with transplantation required for treatment [6].

Central nervous system (CNS) disease in LCH, usually part of a multisystem process, can be found in all parts of the CNS in all age groups [7, 8]. Neurological symptoms may antedate the diagnosis of LCH by up to 1 year in some cases; however, more commonly symptoms tend to occur long after the diagnosis of systemic LCH had been made. Clinical manifestations of CNS disease in LCH, outside of the hypothalamic–pituitary axis, occur in only 2%–4% of all cases. Isolated CNS lesions may also be seen but usually present outside of the pediatric population, most commonly in the 3rd or 4th decade. The clinical presentation of CNS LCH can be separated into disorders involving the hypothalamic–pituitary axis, secondary to space occupying lesions, neurodegeneration most commonly affecting the cerebellar-pontine pathways, and those with an overlap of the above symptoms [7]. Therapy-related CNS changes must be considered in the differential diagnosis of neurological symptoms in patients with prior chemotherapy or cranial radiotherapy treatment for skull lesions in infancy.

The most common presenting symptom of CNS-associated LCH is diabetes insipidus (DI) which develops in 10%–20% of all patients with LCH usually within 5 years of diagnosis [9]. Risk factors for the development of DI in LCH include multisystem disease with skull lesions, most in the temporal and orbital bones where intracranial tumor extension is possible. Isolated lesions of the hypothalamic-pituitary axis have been described in early reports as Ayala's disease or Gagel's granuloma. Dysfunction of the anterior pituitary is seen in up to 20% of LCH patients, commonly in association with DI and in patients with previous radiation treatment [7].

The second most common site of CNS involvement in LCH is the cerebellum; the true incidence is not known, but symptoms have been reported in 1%–12% of patients with LCH [7]. Symptoms may follow a pattern of cerebello-pontine progression from ataxia and nystagmus to dysarthria, dysphagia, and cranial nerve deficits indicative of brainstem involvement. In all cases neurological deterioration occurs with no correlation to the extent of disease outside the CNS. The true incidence of CNS space occupying lesions alone is also unknown. CNS lesions can arise from bone, meninges, or choroid plexus with symptoms due to focal neurological deficits or more generalized symptoms of increased ICP, including headaches, papilledema, and vomiting. Intra-axial lesions can occur anywhere in the CNS including the optic nerves, cerebral hemispheres, and spinal cord.

Diagnostics

The histiocytoses are diseases of proliferation of the mononuclear phagocyte or dendritic cell systems, and Langerhans cell histiocytosis is the most common of these disorders. The Langerhans cell (LC), a professional antigen presenting cell, is a precursor to the interdigitating dendritic cell and its distribution within tissue is limited to stratified squamous epithelium, thymic epithelium, lymph nodes, and bronchial mucosa. After antigen processing in the dermis, the LC migrates to lymph nodes to present antigen and initiate T-cell-mediated immunity [2]. Electron microscopy demonstrates cytoplasmic structures, unique to the Langerhans cell called Birbeck or Langerhans granules, the function of which is unknown. Immunopositivity for S-100 neuroprotein and CD1a antigen is a feature of the normal LC.

Histologically, the lesion seen in LCH is composed of pathologic Langerhans cells, indeterminate cells, interdigitating cells and macrophages, eosinophils, T cells, and multinucleated giant histiocytes. The pathologic Langerhans cell is not dendritic. Definitive diagnosis of LCH requires demonstration of histologic features on light microscopy, immunopositivity for S100 and CD1a in pathologic histiocytes and Birbeck granules on EM [2, 5]. Commonly, the expression of CD4 and both CD68 and HAM-56 (macrophage markers) consistent with activation can be demonstrated [2]. LCH in all its forms has been demonstrated to represent a monoclonal proliferation of CD1a-positive histiocytes which has led many to believe the disease has a genetic basis consistent with a neoplastic process [2]. The high probability of survival in LCH and frequency of spontaneous remissions together with the lack of identifiable genetic aberrations are not consistent with neoplasia and supports LCH as a reactive immune disorder [10].

The pathology of LCH is uniform regardless of severity although it may be influenced by location and age of the lesion. The lesions of LCH change over time from an initial cellular lesion with histiocytes to older lesions which are low in cell numbers, fibrotic with few macrophages and rare proliferative LCs. A large range of mitotic activity can be identified in LCH lesions but this is not correlated with prognosis [2]. The typical lesion varies with the tissue involved, with both CNS and lymph nodes showing different patterns to other regions. CNS disease may progress from an initial or hyperplastic-proliferative stage, demonstrating the characteristic phenotype of the LCH lesion, followed by maturation into a granulomatous, xanthomatous, and finally fibrotic stages, the latter in which the identifying features of LCH may not remain. The initiation of the disease is thought to proceed from the adventitial cell causing perivascular aggregates of histiocytes. This leads to granulomatous lesions with histiocytes, eosinophils, microglia, lymphocytes, and plasma cells [7]. Bony lesions include osteoclast-like multinucleated giant histiocytes, bone destruction, necrosis, hemorrhage, and eosinophilic abscesses. As the lesion ages it becomes more fibrotic and xanthomatous.

Patients suspected of harboring LCH require standard growth and developmental monitoring and baseline hormone studies including a water deprivation test to exclude diabetes insipidus. Skeletal survey may reveal osteolytic lesions of the skull without a sclerotic rim resulting in a "punched out" appearance, and although not diagnostic, is strongly suggestive of LCH. LCH in the spine most commonly involves the anterior elements and radiographic evidence of vertebral collapse or "vertebral plana" (Fig. 1) may signify a late stage in the process of spinal LCH. MRI of the brain with contrast (Gd-DTPA) is the procedure of choice for investigation and monitoring of CNS disease is suggested for all patients with LCH at baseline. Those with evidence of CNS involvement require in addition completion of an endocrine evaluation, cerebrospinal fluid analysis for lymphocyte markers, and formal neuropsychological evaluation.

Intracranial-associated LCH produces a wide spectrum of abnormalities on MR imaging (Fig. 2). These have been classified into four major groups: (1) craniofacial and skull base lesions with or without soft tissue extension; (2) intracranial and extra-axial disease in the hypothalamic-pituitary region, meninges and in association with other circumventricular organs; (3) intra-axial parenchymal disease of gray and white matter; and (4) localized or diffuse atrophy [11]. Craniofacial involvement, commonly with lesions in the orbits and calvaria represent is a long-known common feature of CNS-related LCH. Thickening and enhancement of the pituitary stalk accompanied by loss of the posterior pituitary "bright spot," which is normally present on T1-weighted MR imaging and reflects the presence of vasopressin-containing granules, is the most common early finding of CNS-LCH and may occasionally precede clinical evidence of diabetes insipidus [9]. The clinical course of patients appears to correlates poorly with stalk changes over the course of the disease and its treatment. The predisposition of LCH for extra-axial structures including the meninges, pineal gland, ependyma, and choroid plexus suggests LCH has a predilection for regions lacking a blood-brain barrier [11].

Intra-axial parenchymal MR changes of variable T1 and T2 intensity are frequent in the gray and white in patients with CNS-LCH and most often seen in the presence of other extra-axial disease [11]. Gray matter lesions are most common in the cerebellum and basal ganglia and are capable of producing clinical neurodegenerative syndromes with mild to severe impairments, the second most common presentation of CNS-related LCH. Brainstem involvement on MR imaging, particularly in the pons, usually was associated with severe neurological impairments. Rare biopsies of cerebellar lesions have revealed a combination of nonspecific demyelination, Purkinje cell loss, and reactive gliosis in the absence of active LCH.

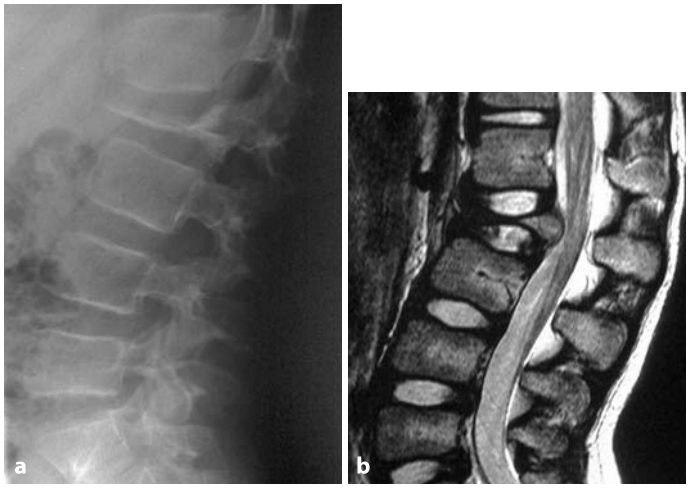


Fig. 1 Vertebral plana in a 12-year-old with back pain. Biopsy confirmed LCH. Patient was treated with back brace and is normal at 18-month follow-up. **a** Lateral lumbar spine X-ray **b** Sagittal T2-weighted MRI

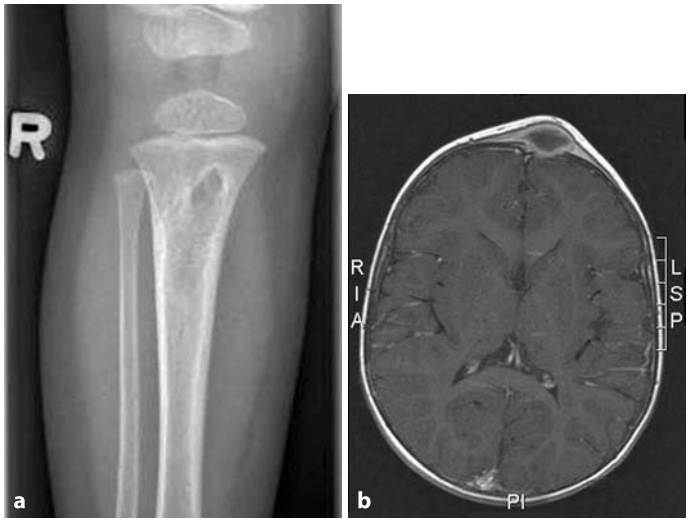


Fig. 2 2-year-old patient with leg pain and skull lesion. Pathological confirmation of LCH after complete resection of skull lesion. **a** Plain X-ray shows osteolytic lesion in tibia **b** Axial T1 MRI with gadolinium shows frontal skull lesion

The exact etiology of these lesions remains unclear. Changes restricted to periventricular white matter in a leukoencephalopathy-like pattern are common in patients with CNS-LCH and although resembling sequelae of prior cranial irradiation or chemotherapy are seen frequently prior to any treatment [11]. Parenchymal changes which are commonly found in patients with LCH, many of which are asymptomatic, suggest the actual incidence of CNS-LCH may be significantly higher than previously thought.

Staging and Classification

LCH is a disease characterized by extremely variable clinical manifestations as a result of single to multiple organ site involvement at presentation, each at varying degrees of severity. Classification based primarily on the sites of involvement, have described LCH as monostotic, polyostotic, disseminated, and unifocal extraskeletal. Monostotic or single osteolytic bone lesions previously known as eosinophilic granulomas (EG), represent the most common form of LCH. Polyostotic EG refers to multiple bony lesions with a frequent predilection for the skull. Disseminated LCH, most common in early infancy, in addition to bony lesions, involves the skin, liver, spleen, lymph nodes, bone marrow, and lungs to varying degrees. Unifocal extraskeletal LCH refers to isolated lesions at various sites including the lung, the skin, and the central nervous system, and while these sites are commonly involved in disseminated LCH, they rarely are affected alone.

Analysis of results of treatment have revealed that the functional status of the organs affected at the time of diagnosis appears to be more important than the number of sites involved for prognosis of LCH. Lahey was the first to propose criteria establishing objective evidence of a functional disorder specifically in three organs only, the liver, lungs, and bone marrow [12]. Further stratification of patients incorporating both the extent of disease as well as organ dysfunction was later suggested by Egeler and D'Angio [13], who defined staging of LCH as restricted or extensive and with or without organ dysfunction (Table 1). Patients were felt to have a progressively worse outlook with each subsequent level of staging, that is with increasing extent of disease and amount of organ dysfunction.

Treatment

LCH is a rare disorder, the optimal treatment of which remains unclear. No randomized double blind controlled trials of treatment are available for review and the majority of treatment recommendations are based only on large retrospective case series. The treatment of CNS-LCH is no different. Individual treatment strategies are based on the type and site of the intracranial lesions and the extent of LCH outside the CNS [7, 14]. In general, patients with localized or restricted disease carry an excellent prognosis, some of which require no treatment at all and others that are often cured by simple resection. Localized bony recurrences, when symptomatic, are successfully treated with anti-inflammatories alone, low dose radiotherapy, or intralesional injections of steroids. Conversely, patients with disseminated LCH may experience significant rates of morbidity and mortality and these patients frequently require an aggressive multimodality treatment strategy. Treatment may begin with mild, single-agent chemotherapy and progress to multiagent, high-dose chemotherapy regimens, sometimes in combination with radiation and bone marrow transplantation, for patients with recurrent or refractory disease [14].

Identification of effective strategies for the two most common CNS-related problems associated with LCH and its treatment, hypothalamic-pituitary

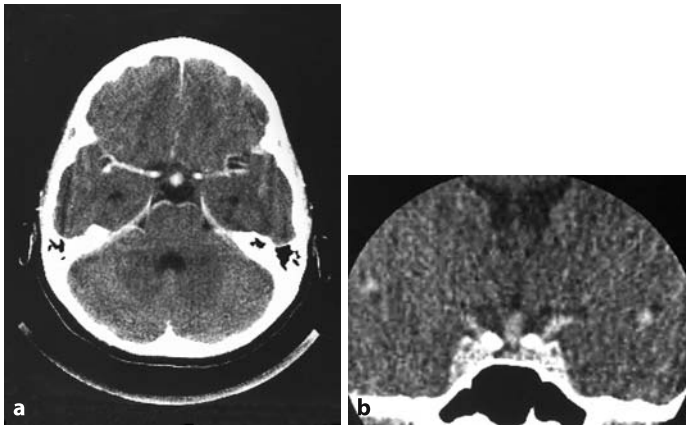


Fig. 3 14-year-old with diabetes insipidus, growth and thyroid hormone deficiencies. Biopsy of enhancing stalk lesion confirmed LCH. Treated with low dose radiotherapy. **a** Axial and **b** coronal CT scans

involvement with diabetes insipidus and progressive neurological deterioration, has been disappointing (Fig. 3). The decision to treat DI, apart from desmopressin replacement, is difficult, because once established DI is unlikely to be reversed with any treatment modality [7]. While little evidence exists to suggest any treatment for DI will result in a reversal of symptoms or even halt progression of disease to involve the anterior pituitary, there is a suggestion, in patients with multisystem disease and no DI at diagnosis, that treatment with chemotherapy may reduce the likelihood of patients developing DI during the course of their illness [7, 13]. Neurological impairment in LCH, secondary to a yet poorly defined neurodegenerative process, similarly does not respond to treatment and progresses in most cases [14].

Surgery

Complete surgical resection of accessible CNS-LCH-associated lesions remains the mainstay of treatment. However, when this is not possible, biopsy alone, with our without curettage in the case of bony lesions, is often sufficient for confirmation of LCH and to initiate healing of the lesion.

Radiotherapy

The use of radiotherapy for CNS-LCH lesions is rarely indicated. Low-dose radiotherapy of 300–600 cGy has been advocated for focal bony recurrences not accessible by surgical means. High-dose fractionated radiotherapy of 2000 cGy is an alternative for CNS-associated space-occupying lesions which are incompletely resected or symptomatic progressive hypothalamic-pituitary axis lesions.

Chemotherapy

The combination of vinblastine and single high-dose steroids appear to be the most effective conventional first-line treatments for reducing recurrent disease in multisystem LCH [15, 16]. Patients who have been identified as having a poor response to initial chemotherapy, as early as completion of a 6-week course of treatment, require an alternative multiple agent chemotherapy regimen. In patients with refractory disease, treatment with agents such as cyclophosphamide, methotrexate, mercaptopurine and cytosine arabinoside, vindesine, and anthracyclines have been assessed in several studies with favorable anecdotal responses [14]. The use of 2-chlorodeoxyadenosine, an agent with both cytotoxic and immunosuppressive effects, has also been utilized in the treatment of highly refractory LCH with an excellent overall response rate of 75% [14, 17].

Table 1 Categorization according to disease extent

Restricted Langerhans cell histiocytosis

a. Biopsy-proven skin rash, no other site of involvement
b. Monostotic lesion, with or without diabetes insipidus, adjacent lymph node involvement, or skin rash
c. Polyostotic lesions, consisting of several bones or more than two lesions in one bone, with or without diabetes insipidus, adjacent lymph node involvement, or skin rash

Extensive Langerhans cell histiocytosis

a. Visceral organ involvement with or without bone involvement, diabetes insipidus, adjacent lymph node involvement, and skin rash but without signs of organ dysfunction
b. Visceral involvement, with or without bone lesions, diabetes insipidus, adjacent lymph node involvement, and skin rash with signs of organ involvement of lung, liver, or hematopoietic system

Prognosis/Quality of Life

The natural history of LCH is variable from spontaneous resolution to rapid dissemination resulting in multiple organ failure and even death. Patients presenting with single system disease often have an excellent prognosis and may require no treatment at all. In the LCH-CNS study all patients who had space occupying lesions treated with surgery, steroids, or chemotherapy were free of disease [7]. When all forms of LCH are considered, short-term survival rates are high, better than 90% in most series [15, 16]. In patients with extensive disease, however, the survival rate drops to around 70%–80%.

The appropriate treatment for multisystem disease, with or without CNS involvement, remains unclear; however, it is evident that stratification of patients with disseminated LCH is possible. Initial response rates to chemotherapy regimens for patients with multisystem disease varies from 60%–75% and reactivation rates are as high as 50% [15]. Reactivations in patients with an initial complete response are likely to be mild and more limited in impact than the original manifestation of the disease. Several poor prognostic factors have been identified and these include age under 2 years old, number of organs in-

volved at diagnosis, and the initial response to chemotherapy [12, 15, 16]. Overall, patients with no negative prognostic factors, who are older than 2 years, and have no organ involvement, have a high chance of therapeutic response and low chance of mortality. Conversely, in those patients less than 2 years old with disseminated multiple system LCH, with both risk organ involvement, and a poor response to initial treatment, the 3-year probability of survival is low, less than 20% [16]. The significant negative impact of the initial response to chemotherapy on outcome in a large part results from the few effective alternative therapies which exist for use at the time of treatment failure.

Permanent consequences of LCH occur in up to half of patients and are the result of both disease manifestations as well as therapeutic approaches utilized in an attempt to limit disease progression. Long-term effects include intellectual impairment, endocrine abnormalities including diabetes insipidus and growth retardation, neurological and orthopedic disability, and rarely secondary treatment-related malignancies [13, 18]. Diabetes insipidus and hypothalamic-pituitary dysfunction as well as neurodegenerative symptoms respond poorly to any form of treatment. Progression of symptoms of neurological impairment to involve the brainstem, particularly the pons, is often associated with severe neurological disability and may be fatal. Identification of long-term quality of life issues associated with LCH and its treatment, apart from permanent physical consequences, has been limited due to the rarity of this condition.

Future Perspectives

The unclear biology of LCH and its rarity have contributed to the difficulty in identifying optimal treatment strategies. Considerable controversy remains as to whether LCH is a reactive or neoplastic process, leading some to believe that it may possibly be the result of a combination of oncogenesis and disordered immune regulation [19]. Successful treatment of LCH with a novel tumor necrosis factor-alpha inhibitory agent, in addition to conventional treatment, supports the idea that LCH may be a reactive process [20] and contributes to optimism that alternative therapies for LCH can be developed and contribute to improvements in outcome and reduction in permanent disability.

References

1. Leonidas JC, Guelfguat M, Valderrama E. Langerhans'cell histiocytosis. Lancet 2003;361:1293–1295
2. Schmitz L, Favara BE. Nosology and pathology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:221–246
3. Nezelof C, Basset F, Rousseau MF. Histiocytosis X: Histogenetic arguments for a Langerhans' cell origin. Biomedicine 1973;18:565–571
4. Chu T, DiAngio GJ, Favara B, Ladisch S, the Writing group of the Histiocyte Society. Histiocytosis syndromes in children. Lancet 1987;1:208–209
5. Nicholson HS, Egeler RM. The epidemiology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:379–384
6. Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:247–258
7. Grois NG, Favara BE, Mostbeck GH, Prayer D. Central nervous system disease in Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:287–305
8. Hund E, Steiner H-H, Jansen O, Sieverts H, Sohl G, Essig M. Treatment of cerebral Langerhans cell histiocytosis. J Neurol Sci 1999;171:145–152
9. Grois N, Prayer D, Prosch H, Minkow M, Potschger U, Gadner H. Course and clinical impact of magnetic resonance imaging findings in diabetes insipidus associated with Langerhans cell histiocytosis. Pediatr Blood Cancer 2004;43: 59–65
10. Fadeel B, Henter J-I. Langerhans cell histiocytosis: neoplasia or unbridled inflammation? Trends Immunol 2003;24: 409–411
11. Prayer D, Grois N, Prosch H, Gadner H, Barkovich AJ. MR imaging presentation of intracranial disease associated with Langerhans cell histiocytosis. AJNR 2004;25:880–891
12. Lahey, ME. Histiocytosis X – an analysis of prognostic factors. J Pediatr 1975;87:184–189
13. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. J Pediatr 1995;127:1–11
14. Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:339–357
15. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 1994;138:728–734
16. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans cell histiocytosis: 348 cases observed between 1983 and 1993. Arch Dis Child 1996;75:17–24
17. Goh NS, Mcdonald CF, Macgregor DP, Pretto JJ, Brodie GN. Successful treatment of Langerhans cell histiocytosis with 2-chlorodeoxyadenosine: Respirology 2003;8:91–94
18. Haupt R, Nanduri V, Grazia Calevo M, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in Langerhans cell histiocytosis patients: A pilot study from the

Histiocyte Society Late-Effects Study Group. Pediatr Blood Cancer 2004;42:436–444

19. Egeler RM, Annels NE, Hogendoorn PCW. Langerhans cell histiocytosis: A pathologic combination of oncogenesis and immune dysregulation. Pediatr Blood Cancer 2004;42:401–403

20. Henter J-I, Karlen J, Calming U, Bernstrand C, Andersson U, Fadeel B. Successful treatment of Langerhans' cell histiocytosis with Etanercept. N Engl J Med 2001;345:1577–78

Tumors of the Skull Base in Children

46

Eve C. Tsai, Gregy Hawryluk, James T. Rutka

Introduction – 556

Distinguishing Features of Pediatric Skull Base Tumors – 556

Tumors of the Anterior Cranial Base in Children – 556
Fibrous Dysplasia
Esthesioneuroblastoma

Neurosurgical Approaches to the Anterior Cranial Base in Children – 557

Tumors of the Middle Cranial Base in Children – 558
Juvenile Nasopharyngeal Angiofibromas

Schwannomas – 559

Neurosurgical Approaches to the Middle Cranial Base in Children – 560

Tumors of the Posterior Cranial Base in Children – 560
Chordomas and Chondrosarcomas

Neurosurgical Approaches to the Posterior Cranial Base in Children – 561

Complications and Outcomes – 562

Conclusions – 562

References – 563

Introduction

Tumors of the skull base have presented a difficult therapeutic challenge to the neurosurgeon due to the complexity involved in approaching these lesions. However, with recent technical advances and the development of specialized centers with teams of physicians interested in managing these patients, removal and cure of skull base tumors are now possible. While many of the surgical approaches developed to approach skull base tumors have been reported for adults, there have been few such reports in children. In general, children pose unique anatomical challenges for the skull base surgeon because of the constraints of the developing skull, and the small size of the patients.

There have now been a few published reports on skull base tumors in the pediatric population [3, 11, 18, 53, 95, 99]. In our review of skull base tumors, less than 5% of all surgeries performed with frameless stereotaxy were for skull base lesions [3]. In this chapter, we will review the presentation and treatment of some of the relevant tumors of the anterior, middle, and posterior skull base that occur in the pediatric population. We will also examine the common surgical approaches to these tumors with particular emphasis on the modifications and complications of these approaches as they apply to children.

Distinguishing Features of Pediatric Skull Base Tumors

Pediatric skull base tumors differ from adult tumors in many aspects. With respect to epidemiology, in the pediatric population, there are proportionately fewer skull base lesions in children, and there are more males (69%) than females with these lesions [95]. This sex difference may be due to the different tumor types that occur in children as there are many fewer meningiomas and more benign nerve sheath tumors [76, 95]. The surgical approaches must be considered carefully in children with respect to differing anatomy and involvement of growth centers. For example, anterior approaches in children are affected by the shallow anterior fossa floor and the immaturity of the sinuses. Approaches involving maxillotomy may need to be reconsidered as tooth buds may be compromised. Tissue planes have been reported to be better defined in children resulting in a higher percentage of complete resection in the initial attempt [95]. The higher frequency of complete resection, together with the high proportion of benign tumors, helps to explain why children with skull base lesions often have a better prognosis [95].

Tumors of the Anterior Cranial Base in Children

Clinical findings reported among patients with anterior cranial base lesions are related to the tumor location. The anterior cranial base can be divided into central and lateral regions. Central cranial base lesions can cause neurological deficits related to the olfactory nerve and frontal lobe (personality change), or can result in symptoms of increased intracranial pressure such as headache [3]. Local tumor effects may also cause symptoms such as nasal obstruction, discharge or bleeding [66], and hypertelorism [3]. Lateral cranial base lesions can result in vision changes, superior orbital fissure involvement [66], and proptosis [3]. While the most common anterior cranial base tumors in adults are nasal or paranasal malignancies and meningiomas, these tumors are relatively rare in children [77]. In our experience, the most common tumors of the anterior cranial base in children include fibrous dysplasia, and esthesioneuroblastomas.

Fibrous Dysplasia

Fibrous dysplasia is a developmental anomaly of bone-forming mesenchyme where the transformation of woven bone to lamellar bone does not occur and there is an overgrowth of a well-vascularized fibrous stroma surrounding the haphazardly arranged bony trabeculae [39]. It can occur in a monostotic form, or in a polyostotic form involving multiple bony sites, and as part of the McCune-Albright syndrome [39]. Aggressive surgical approaches for control of disease-related complications must be weighed against known difficulties associated with reconstructing large bony defects and the unpredictable clinical course of many patients [22]. Advocates for early surgery believe that conservative treatment during the "active" phase in children is unacceptable [13] as there is no indication that surgical procedures inhibit the growth rate of residual normal tissues [39] and progression of disease can continue into adulthood [46]. Therefore surgery at any age is indicated for the prevention of neurological deficit or substantial deformity. One of the most frequent and feared complications of fibrous dysplasia of the sphenoid wing is encroachment of the optic nerve and progressive visual loss. In such cases, decompression of the optic nerve with or without cranio-orbital reconstruction may be indicated. We have found that using frameless stereotaxic systems and intraoperative image guidance have been beneficial in unroofing the optic canal in the face of distorted anterior cranial base anatomy [3].

Although the incidence of recurrence associated with partial removal of the lesion has been reported to be as high as 25% [46], radiation has not been recommended due to risk of malignant transformation [67]. However, even without radiation, there have been reports of spontaneous malignant transformation [93].

Esthesioneuroblastoma

Esthesioneuroblastomas or olfactory neuroblastomas are tumors of neuroectodermal origin believed to arise from the mitotically active basal layer of the olfactory epithelium normally located within the superior one third of the nasal septum, cribriform plate, and superior turbinates [7]. They have been managed with surgical resection alone or with the addition of radiation and/or chemotherapy [43, 47, 65]. These tumors have been staged using the Kadish system [47] depending on the extent of disease. For group A, the tumor is limited to the nasal cavity; in group B, the tumor is localized to the nasal cavity and paranasal sinuses; and in group C, the tumor extends beyond the nasal cavity and paranasal sinuses. Five-year survivals for Stage A, B, and C disease has been reported to be 75%, 60%, and 41%, respectively [24].

In a series of 49 patients with esthesioneuroblastoma treated at the Mayo Clinic between 1951 and 1990, pathological grade was identified as the most important prognostic factor [65]. Their clinical manifestations and treatment results were reviewed to identify possible prognostic factors. While the overall 5-year survival rate for all patients was 69%, the 5-year survival rates for the low-grade and high-grade tumors were 80% and 40%, respectively. Surgical treatment alone was advocated for low-grade tumors if tumor-free margins can be obtained. Radiation was recommended for low-grade tumors when margins are close, for residual or recurrent disease, and for all high-grade cancers. The addition of chemotherapy was suggested for patients with high-grade tumors.

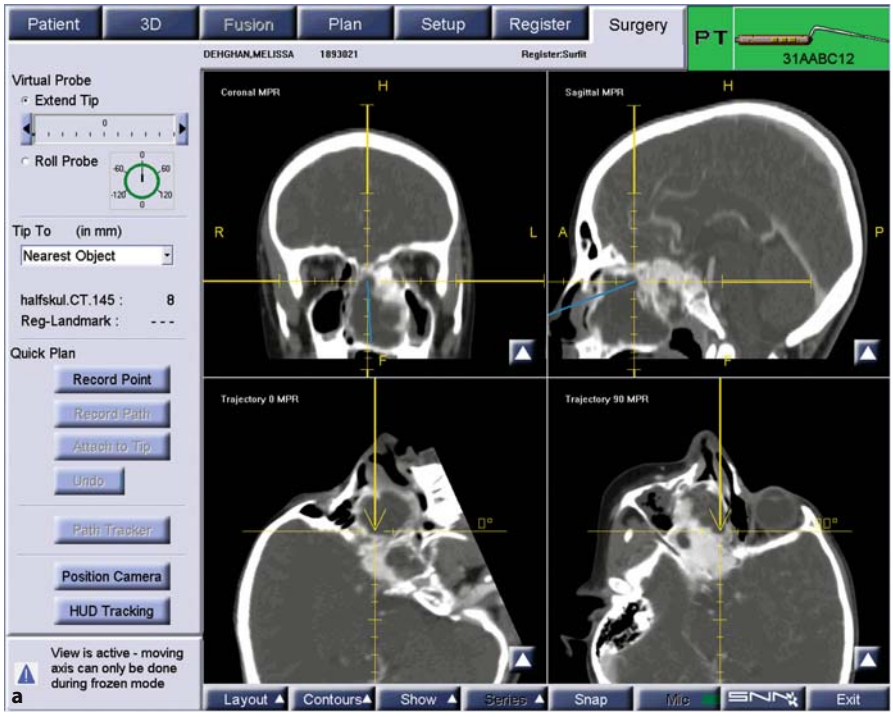
Chemotherapeutic agents have been utilized to treat mostly relapsed, metastatic, or inoperable disease. Single chemotherapeutic agents that have been used include thiotepa, doxorubicin, cyclophosphamide, vincristine, dacarbazine, and nitrogen mustard [43]. Consistent responses have been seen in combinations including cyclophosphamide with doses ranging from 600 to 1000 mg/m^2, doxorubicin at 40 mg/m^2 (IV bolus) with or without vincristine in a dose of 1.5 mg/m^2 usually given every 21 days, toxicity permitting [43]. Neoadjuvant combination therapies include cyclophosphamide/doxorubicin/vincristine [17], cisplatin/VP-16 [17], and cisplatin and 5 Fluorouracil by continuous infusions daily for 6 days, repeated every 21 days for 4 cycles followed by a surgical resection [71]. An alternating regimen of cyclophosphamide 600 mg/m^2 and vincristine 1.4 mg/m^2 with cisplatin 80 mg/m^2 and VP-16 120 mg/m^2 every 3 weeks has been used with a good palliative response. High-dose chemotherapy with autologous bone marrow transplantation has also been used in relapsed disease [70, 91].

Neurosurgical Approaches to the Anterior Cranial Base in Children

Surgical approaches to the anterior cranial base include transfacial, anterior craniofacial, craniotomy with orbital and/or zygomatic osteotomy, and transsphenoidal [66, 95]. The transfacial approaches can be categorized into transoral, transpalatal, lateral rhinotomy, Le Fort 1 osteotomy, and midfacial degloving [55]. While these approaches are used in adults, their use in the pediatric population frequently require modification. The transoral, and specifically the labial-mandibulotomy approach provides adequate exposure, but destroys the pediatric patient's central incisors, and may jeopardize other tooth buds in patients younger than 6 years [55] or 10 years of age [53]. The bulk of soft tissue that must be retracted with the transpalatal approach restricts exposure of the upper clival and sphenoidal regions [55]. The major concerns with respect to the transpalatal approach is the development of a palatal fistula or wound dehiscence [81]. The lateral rhinotomy and medial maxillotomy affords an excellent window of exposure for large skull base tumors such as fibrous dysplasia (Fig. 1).

Lewark et al. [55] report the use of the Le Fort 1 osteotomy in eleven children with complications attributed to the approach of loss of unerupted tooth buds and epiphora in one patient each. Disruption of facial growth was assumed to be unlikely as the osteotomy did not pass through growth centers [10]. While disruption of facial growth has been a source of concern, several groups report no disruption of facial growth with anterior (transzygomatic, orbital, transoral, transmandibular) and lateral (petrous, transcondylar, translabyrinthine, and transbasal) approaches [53, 72, 95]. Although formal morphometric studies were not performed on the facial bones of children with craniofacial procedures, Teo [95] reports normal facial skeletal growth in patients as young as 4 years with 20 months of follow-up.

Midfacial degloving provides good anterior exposure, and when combined with complete ethmoidectomy or medial maxillectomy, can provide central skull base exposure [55] without leaving external facial deformity. With endoscopic assistance, this ap-



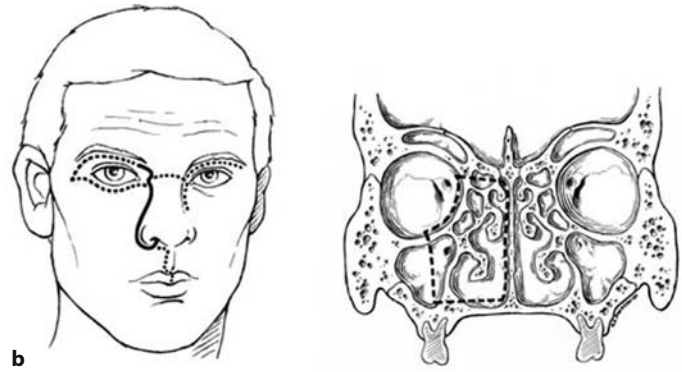


Fig. 1 **a** Artist's depiction of a lateral rhinotomy and medial maxillotomy approach to a large anterior skull base lesion. **b** Intraoperative neuronavigation approach to large cystic fibrous dysplasia lesion in 11-year-old female. Navigation is helpful in such cases to push the boundaries of tumor resection while respecting critical neurovascular elements

proach has been used in infants [96]. Drawbacks to midfacial degloving include sensory disturbances involving the teeth and infraorbital nerve distribution [55], oro-antral fistula, and epiphora [42]. The anterior craniofacial approach combines a conventional bifrontal craniotomy with a transfacial approach, thereby allowing excellent access to tumors of the anterior cranial base and sinuses and nasal cavities [55, 95].

Craniotomy, when combined with the orbital and/or zygomatic osteotomy, provides a lower trajectory approach and allows access to suprasellar and cavernous sinus lesions [87, 95]. In young children under age 6, the anterior cranial fossa is generally relatively shallow and the frontal sinuses have not developed fully. This makes anterior cranial approaches less difficult in children than in adults [53].

The transsphenoidal approach has many variations including a sublabial transnasal dissection, pernasal, transethmoid, pure transnasal, and endoscopic [57, 95, 97]. Transsphenoidal surgery in children may be limited by virtue of the small sella, and absence of a fully aerated sphenoid sinus. In such cases, image guidance may be invaluable in keeping the neurosurgeon directly on the midline in approaching the sella [3].

Tumors of the Middle Cranial Base in Children

Middle cranial base lesions in children can cause symptoms relating to the central (sphenoid sinus/sella turcica), paracentral (cavernous sinus), or lateral (sphenoid wing/infratemporal fossa) middle fossa [66]. Central middle fossa lesions result in pituitary and hypothalamic abnormalities such as panhypopituitarism, precocious puberty, secondary amenor-

rhea [3], and diabetes insipidus [66], or cause deficits relating to tumor mass effect on the optic nerve and chiasm [66]. With lesions of the paracentral middle fossa, patients can develop intractable facial pain and dysesthesia, and tumors can affect the optic nerve in the apex, cranial nerves III–VI, temporal and frontal lobes, and the cavernous carotid artery [66]. Lateral middle fossa lesions affect the divisions of the trigeminal nerve, lateral orbit, and infratemporal fossa and can cause facial deformity and oro-pharyngeal obstruction [66].

While in adults, meningiomas and schwannomas of the gasserian ganglion are the most common middle cranial base tumors to occur [58], astrocytomas, pituitary adenomas, craniopharyngiomas [3], hemangiomas, giant cell tumors, malignant fibrous histiocytomas, optic nerve gliomas, osteoblastomas [59], and juvenile nasopharyngeal angiofibromas [55] have been found in the pediatric population. We discuss the juvenile nasopharyngeal angiofibromas and schwannomas with respect to presentation, surgery, radiation, and chemotherapy below.

Juvenile Nasopharyngeal Angiofibromas

Juvenile nasopharyngeal angiofibromas are rare, histologically benign, locally invasive tumors [44], or vascular malformations [8] of the nasopharynx that are found primarily in the pubescent male. While usually localized to the nasopharyngeal regions, intracranial invasion can be as high as 36% [44]. Surgery and radiation therapy are the mainstays of treatment. Because of the increased intraoperative or postoperative hemorrhage associated with these lesions, preoperative embolization [69, 88] has been used to minimize blood loss. Common postoperative complications reported include eustachian tube dysfunction [25, 38], palatal dehiscence, and rhinolalia aperta [23].

Radiation therapy has been advocated as a primary treatment [20, 98] or as an adjunct to surgery [23, 37] for advanced disease. Long-term results of 15 patients treated with radiation alone found that two developed recurrences requiring salvage surgery [75]. While chemotherapeutic trials are difficult due to the rarity of the disease, chemotherapeutic agents have been used as adjuncts to surgery. A testosterone receptor blocker, flutamide, has been found to shrink tumors an average of 44%, while allowing patients to retain normal testosterone levels 2 or more years posttherapy [32]. Other agents that have been tried with varying success include: adriamycin and dacarbazine [82], doxorubicin, vincristine, dactinomycin, and cyclophosphamide [34].

Schwannomas

Although relatively rare in childhood, schwannomas of the cranial base can occur along several of the cranial nerves that involve both the middle and posterior fossae. The history of presentation of these lesions is usually protracted, and symptoms are typically referable to the nerve(s) that are affected. Because of the slow growth of these lesions, they can be quite large before they are detected (Fig. 2).

At times, combined skull base approaches are required as Schwannomas can travel from one intracranial compartment to another. The principles of neurosurgery relate to respecting the arachnoid planes that typically lie over the tumor, sweeping all critical uninvolved nerves and vessels out of the way contained within the layers of arachnoid, and inter-

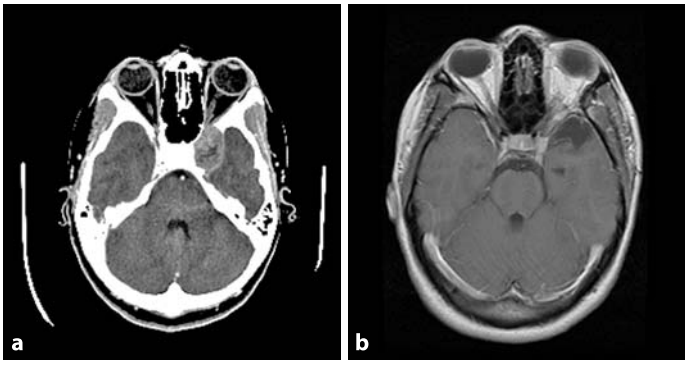


Fig. 2 **a** Axial CT from 12-year-old female with schwannoma affecting the trochlear nerve. The lesion occupies the medial aspect of the middle cranial fossa, and is expanding the superior orbital fissure. The lesion was approached via a unilateral orbitozygomatic skull base approach. The lesion was excised in toto without injury to the neurovascular structures of the cavernous sinus. **b** Postoperative axial MRI depicting removal of trochlear schwannoma. The patient is well, and free of tumor now 4 years after surgery

nal tumor decompression. In this way, a satisfactory tumor removal can be achieved, and children can be cured of these large and difficult tumors (Fig. 2). Skull base approaches have helped enormously in the neurosurgical removal of middle fossa schwannomas.

Neurosurgical Approaches to the Middle Cranial Base in Children

Middle cranial base approaches [50, 66] that have been used in the pediatric population include: (1) frontotemporal with orbital and/or zygomatic osteotomy [54, 62]; (2) temporal with zygomatic osteotomy and/or anterior petrosectomy [15, 28, 63, 89]; (3) preauricular infratemporal with or without mandibular dislocation or resection [1, 92]; and (4) transsphenoidal [36, 95]. Complications reported with the first anterolateral approach include death, pneumonia with septicemia, wound infection, meningitis, cerebrospinal fluid leakage, cranial nerve palsy [54], minimal transient complications (mild trismus, frontal branch paresis, serous effusion, and cheek hypesthesia) [12], and poor cosmetic result [62]. The temporal approach with petrosectomy was associated with new deterioration of facial nerve function [15], subdural temporal lobe hemorrhage, and cerebrospinal fluid rhinorrhea [89]. Complications associated with the infratemporal with or without mandibular manipulations include wound infections, cerebrospinal fluid leakage [92], temporary restriction of mandibular opening [1], conductive hearing loss, numbness of the lower lip, temporal depression caused by the use of the temporalis muscle flap, and facial paresis secondary to translocation of the facial nerve [27, 55]. As the effect of mandibular resection in the child is not well known, some advocate avoiding mandibular resection whenever possible [50].

Tumors of the Posterior Cranial Base in Children

Posterior cranial base lesions can present with symptoms relating to the upper central posterior fossa (petrous apex, clivus), lower central posterior fossa (foramen magnum), upper lateral posterior fossa (cerebellopontine angle), and the lower lateral posterior fossa (jugular foramen) [66]. Upper central posterior fossa tumors can affect cranial nerves (3–10), pons and cerebellum with resulting hydrocephalus, and vascular structures such as the carotid and basilar artery [66]. Lower central posterior fossa tumors typically can affect cranial nerves 11 and 12, and cause symptoms of neck pain. These tumors can also mimic signs and symptoms of syringomyelia or cervical spondylosis by causing varying degrees of sensorimotor long tract signs (weakness, astereognosis, cape shaped anesthesia, dysesthesia, and atrophy of hand) [66]. Upper lateral posterior fossa tumors typically affect the seventh and eighth cranial nerves and often involve the fifth and other lower cranial nerves, pons, and cerebellum, and lower lateral posterior fossa lesions can injure the ninth to eleventh cranial nerves [66]. If the retropharyngeal space or occipital condyle are involved, the twelfth cranial nerve can be harmed and if the cerebellopontine angle or temporal bone are involved, the seventh and eighth nerves can be affected [66]. Symptoms of dysphagia or nasal obstruction can occur with local tumor extension into the retropharynx or nasal cavity, and headaches or neck pain if the occipital condyle is involved and there is atlanto-occipital instability [85].

Patients most commonly present with headaches, diplopia, and are found to have an abducens paresis or palsy [58]. Additional symptoms of the posterior cranial base include other cranial nerve deficits such as hearing loss, dysphagia, dysarthria, facial numbness, and brainstem or cerebellar deficits such as ataxia, motor weakness, and memory problems. Local symptoms due to direct extension of tumor can also occur such as dysphagia or nasal obstruction if the retropharynx or nasal cavity is involved, and headaches and neck pain due to atlanto-occipital instability if the occipital condyle is involved [58].

While most pediatric posterior cranial base tumors such as meningiomas [4, 60], schwannomas [35, 40, 64], epidermoids [80, 83], cholesteatomas [31, 73], chordomas [11], and chondrosarcomas [30], are more common in adults, other rare tumors such as Ewing's sarcoma are more common in children [39]. We will review the current management strategies associated with chordomas and chondrosarcomas.

Chordomas and Chondrosarcomas

Chordomas and chondrosarcomas behave similarly with respect to biological behavior, location, and surgical treatment [85] and are typically slow-growing, locally-invasive tumors that occur at the cranial base [50]. Chordomas are dysontogenetic neoplasms that originate from the embryonic notochord and have the fairly consistent features of an overall lobular arrangement of cells, cells that grow in cords, irregular bands or pseudoacinar form, mucinous matrix, and large physaliphorous and vacuolated cells [79]. They are distinguished from chondrosarcomas on the basis of immunochemistry as chordomas stain positively for epithelial markers such as cytokeratin, epithelial membrane antigen, and α fetoprotein, while chondrosarcomas do not [85]. Chondrosarco-

mas which tend to occur in a paramedian location, have been classified as classic, mesenchymal, and dedifferentiated [52], with the latter two types being more aggressive the classic type [85]. Children tend to present with atypical chordomas [11].

Treatment generally consists of an attempt at complete surgical resection (Fig. 3) with postoperative radiation [16, 19, 94, 99]. These tumors are generally soft and cartilaginous or gelatinous; however, chondrosarcomas may be calcified [85]. The core of the tumor is removed piecemeal or with a drill and the margins are then removed until normal bone or venous channels within the bone are encountered [85]. The otic capsule remains relatively resistant to tumor invasion, compared to the clivus [85]. Ensuring complete removal of the tumor margins is difficult as quick sections of bone are not available [85]. Complete removal of any intradural extension of tumor is also attempted, taking care to avoid encased vessels, nerves, and brainstem [85]. Dural defects are grafted as required [85].

Radiation has been utilized as an adjunct to surgery [16, 19, 94, 99]. The radiation treatments that have been used include preoperative [19], postoperative conventional radiation therapy [2, 16], and postoperative stereotactic proton-photon beam therapy [2, 16]. While chondrosarcomas have been found to respond better to radiation therapy compared to chordomas [78], the neurotoxicity associated with the use of radiotherapy in young children must be considered and avoided if possible.

Chemotherapy has generally been disappointing and is used when other therapies have failed [43]. Vincristine has been used with symptomatic improvement in some [41, 74], but has failed in combination therapy with others [26, 84]. Single agent chemotherapy with carboplatin [29], cisplatin [29], and methotrexate [21] have been found to be ineffective in terms of tumor response and pain relief. Combination therapies with varying degrees of success include hydroxyurea with 5-fluorouracil [5]; cisplatin, vinblastine and bleomycin with concurrent radiation [6]; cyclophosphamide, vincristine, doxorubicin, dacarbazine preoperatively together with radiation [48]; vincristine and methotrexate with leucovorin rescue [29]; and ifosfamide and doxorubicin with intrathecal or intraventricular therapy with hydrocortisone, ARA-C, and methotrexate [84]. There was no benefit with the combination of actinomycin-D, cyclophosphamide, and vincristine, nor with cisplatin and 5-fluorouracil or high-dose methotrexate [84].

Neurosurgical Approaches to the Posterior Cranial Base in Children

The posterolateral approaches that have been used in the pediatric population can be categorized as transpetrosal approaches, retrosigmoid [56, 61], translabyrinthine [53], retrolabyrinthine [51], and partial labyrinthectomy [86], and transcochlear [33, 68, 90], far lateral/extreme lateral transcondylar approach [9, 50]; and extreme lateral, transjugular [49] approach [14, 66].

The transpetrosal approaches allow access to lesions centered on the petrous apex, with less access to supra- or infratentorial extensions, and involve mastoidectomy. Like the anterior sinuses, the mastoid air cells are also immature and less fully developed, and so these lateral approaches to the posterior fossa require less retraction of the neural structures in children than adults [53]. The labyrinth and facial nerve are skeletonized with the drill, thereby preserving hearing and facial nerve function. Although the superior petrosal sinus may be transected, the vein of Labbé and sigmoid sinus can be spared. Frequent complications associated with this approach

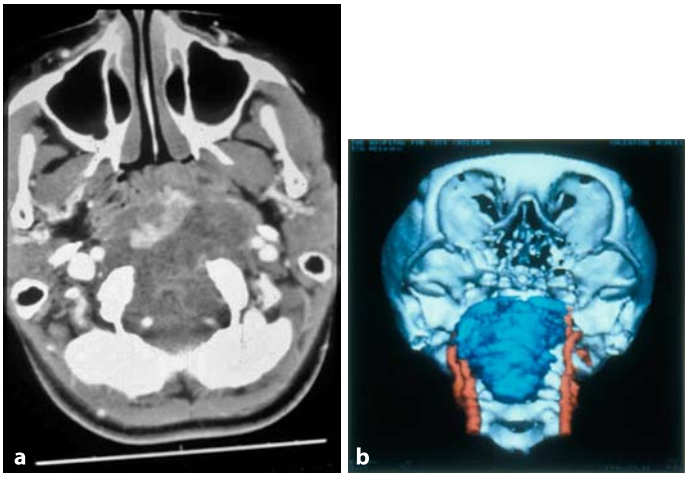


Fig. 3 **a** Axial CT from 14-year-old male with clival chordoma. **b** 3D reconstructed view of skull base showing massive lesion replacing the clivus

include cranial nerve deficits and cerebrospinal fluid leak [86]. The retrosigmoid approach involves a craniotomy in the angle of the sigmoid and transverse sinuses and when the labyrinth is removed, is called the translabyrinthine approach. Although facial nerve function can be preserved with these procedures in children, cerebrospinal fluid leak has also been reported in pediatric series [53]. The transcochlear approach, which allows access to lesions that are anteromedial to the internal auditory meatus and that are equally distributed within both the middle and posterior cranial fossae [95], offers only limited exposure to the lateral aspect of the clivus [55]. Facial nerve deficits may occur [68] as this approach requires facial nerve transposition. This approach also involves drilling of the temporal bone including the entire labyrinth, and thus, if hearing requires preservation, the transcochlear approach is not appropriate [95].

The transcondylar approach allows access to lower clival lesions, foramen magnum, and upper cervical spine. In this approach a low retromastoid craniotomy is performed and the medial two thirds of the mastoid process posterior to the facial nerve is resected. The sigmoid sinus and jugular bulb will be exposed and a C1 laminectomy is continued to expose the vertebral artery. With the mobilization of the vertebral artery, the ipsilateral occipital condyle is resected and the lateral process of C1 or C2 is necessary. The transjugular approach involves lateral suboccipital craniotomy with resection of the posterior third of the occipital condyle. The jugular foramen is opened by removing the posterior wall without mastoidectomy to preserve hearing and facial nerve function [49].

Complications and Outcomes

As there are few series of skull base procedures in pure pediatric populations, many of the complications that have been reported in the adult or mixed populations can be extrapolated to the pediatric population as a guide to the complications that are associated with skull base procedures. The complications associated with adult or mixed populations will not be reviewed here; rather we will describe some of the complications that have been described in pediatric skull base series [3, 53, 95].

In the Alshail series, 13 children with skull base lesions were treated using a variety of neurosurgical approaches including: transsphenoidal, pterional, frontal, transoral, subtemporal bifrontal, bifrontal midfacial, and transnasal [3]. There were several transient, but no permanent neurological deficits in this series. Lewark [55] reported an experience with eleven patients (mean age = 14.3 years) undergoing a Le Fort 1 osteotomy approach with the diagnoses of angiofibromas (n = 8), and one each of hemangioma, giant cell tumor, and malignant fibrous histiocytoma. After a mean follow-up period of 2.5 years (range 6 months to 2.5 years), they describe complications of loss of tooth buds, mild enophthalmos, and epiphora and state that disruption of facial growth is unlikely, as the osteotomy does not pass through growth centers.

In the large pediatric series of Lang et al. [53], the authors describe their results with 20 children ranging in age from 3 months to 14 years. The surgical approaches that they utilized include transzygomatic, translabyrinthine, craniofacial, transbasal, superior orbitotomy, transcondylar/suboccipital, Le Fort I maxillotomy, orbitozygomatic, transoral, transpetrous, and transmandibular and transzygomatic. Postoperative complications described include hypertrophic preauricular scar, temporal hollowing, nasal obstruction, ptosis, visual field defect, visual failure, facial nerve palsy, subarachnoid hemorrhage, diabetes insipidus, cerebrospinal fluid leak, meningitis, and hydrocephalus. No disruption in facial growth was noted in patients that had orbital or transmandibular access. No temporomandibular joint dysfunction was noted in those who underwent a transzygomatic approach. According to the Glasgow Outcome Scale [45] that they used, 18 of their children made a good recovery, one was moderately disabled, and one was severely disabled. They describe that in terms of their overall neurological condition, 14 improved, five were unchanged, and one was worse.

Conclusions

Tumors of the skull base in children pose unique challenges to the neurosurgeon. The differential diagnosis of a skull base tumor in the pediatric population differs from that of the adult population. With a working knowledge of skull base anatomy, and special considerations of the developing craniofacial skeleton, skull base lesions can be approached in children with acceptable morbidity and mortality. Outcomes for children with skull base tumors may be better than adults in part because of the benign histopathology that frequently affects the pediatric skull base, and the plasticity of the developing nervous system.

References

1. al-Mefty O, Anand VK. Zygomatic approach to skull-base lesions. J Neurosurg 1990;73:668–673
2. al-Mefty O, Borba LA. Skull base chordomas: a management challenge. J Neurosurg 1997;86:182–189
3. Alshail E, Rutka JT, Drake JM, et al. Utility of frameless stereotaxy in the resection of skull base and basal cerebral lesions in children. Skull Base Surgery 1998;8:29–38
4. Amirjamshidi A, Mehrazin M, Abbassioun K. Meningiomas of the central nervous system occurring below the age of 17: report of 24 cases not associated with neurofibromatosis and review of literature. Childs Nerv Syst 2000;16: 406–416
5. Ariel IM, Verdu C. Chordoma: an analysis of twenty cases treated over a twenty-year span. J Surg Oncol 1975;7:27–44
6. Azzarelli A, Quagliuolo V, Cerasoli S, et al. Chordoma: natural history and treatment results in 33 cases. J Surg Oncol 1988;37:185–191
7. Barnes L, Kapadia SB. The biology and pathology of selected skull base tumors. J Neurooncol 1994;20:213–240
8. Beham A, Beham-Schmid C, Regauer S, et al. Nasopharyngeal angiofibroma: true neoplasm or vascular malformation? Adv Anat Pathol 2000;7:36–46
9. Bejjani GK, Sekhar LN, Riedel CJ. Occipitocervical fusion following the extreme lateral transcondylar approach. Surg Neurol 2000;54:109–115; discussion 115–106
10. Belmont JR. The Le Fort I osteotomy approach for nasopharyngeal and nasal fossa tumors. Arch Otolaryngol Head Neck Surg 1988;114:751–754
11. Borba LA, Al-Mefty O, Mrak RE, et al. Cranial chordomas in children and adolescents. J Neurosurg 1996;84:584–591
12. Browne JD, Jacob SL. Temporal approach for resection of juvenile nasopharyngeal angiofibromas. Laryngoscope 2000;110:1287–1293
13. Camilleri AE. Craniofacial fibrous dysplasia. J Laryngol Otol 1991;105:662–666
14. Cass SP, Hirsch BE, Stechison MT. Evolution and advances of the lateral surgical approaches to cranial base neoplasms. J Neurooncol 1994;20:337–361
15. Cass SP, Sekhar LN, Pomeranz S, et al. Excision of petroclival tumors by a total petrosectomy approach. Am J Otol 1994;15:474–484
16. Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol 1996;41:67–72
17. Chao KS, Kaplan C, Simpson JR, et al. Esthesioneuroblastoma: the impact of treatment modality. Head Neck 2001;23:749–757
18. Coffin CM, Swanson PE, Wick MR, et al. Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 1993;117:927–933
19. Crockard A, Macaulay E, Plowman PN. Stereotactic radiosurgery. VI. Posterior displacement of the brainstem facilitates safer high dose radiosurgery for clival chordoma. Br J Neurosurg 1999;13:65–70
20. Cummings BJ, Blend R, Keane T, et al. Primary radiation therapy for juvenile nasopharyngeal angiofibroma. Laryngoscope 1984;94:1599–1605
21. Cummings BJ, Esses S, Harwood AR. The treatment of chordomas. Cancer Treat Rev 1982;9:299–311
22. Di Rocco C, Marchese E, Velardi F. Fibrous dysplasia of the skull in children. Pediatr Neurosurg 1992;18:117–126
23. Economou TS, Abemayor E, Ward PH. Juvenile nasopharyngeal angiofibroma: an update of the UCLA experience, 1960–1985. Laryngoscope 1988;98:170–175
24. Elkon D, Hightower SI, Lim ML, et al. Esthesioneuroblastoma. Cancer 1979;44:1087–1094
25. Fagan JJ, Snyderman CH, Carrau RL, et al. Nasopharyngeal angiofibromas: selecting a surgical approach. Head Neck 1997;19:391–399
26. Ferry AP, Haddad HM, Goldman JL. Orbital invasion by an intracranial chordoma. Am J Ophthalmol 1981;92:7–12
27. Fisch U, Pillsbury HC. Infratemporal fossa approach to lesions in the temporal bone and base of the skull. Arch Otolaryngol 1979;105:99–107
28. Fournier H, Mercier P. A limited anterior petrosectomy with preoperative embolization of the inferior petrosal sinus for ventral brainstem tumor removal. Surg Neurol 2000;54:10–17;discussion 17–18
29. Fuller DB, Bloom JG. Radiotherapy for chordoma. Int J Radiat Oncol Biol Phys 1988;15:331–339
30. Gadwal SR, Fanburg-Smith JC, Gannon FH, et al. Primary chondrosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 14 cases with a review of the literature. Cancer 2000;88:2181–2188
31. Garap JP, Dubey SP. Canal-down mastoidectomy: experience in 81 cases. Otol Neurotol 2001;22:451–456
32. Gates GA, Rice DH, Koopmann Jr CF, et al. Flutamide-induced regression of angiofibroma. Laryngoscope 1992;102:641–644
33. Glasscock 3rd ME, Woods 3rd CI, Poe DS, et al. Petrous apex cholesteatoma. Otolaryngol Clin North Am 1989;22: 981–1002
34. Goepfert H, Cangir A, Lee YY. Chemotherapy for aggressive juvenile nasopharyngeal angiofibroma. Arch Otolaryngol 1985;111:285–289
35. Gonzales-Pardo L, Brackett CE, Lansky LL. Facial nerve schwannoma in a 16-year-old girl. Childs Brain 1980;7: 220–224
36. Gsponer J, De Tribolet N, Deruaz JP, et al. Diagnosis, treatment, and outcome of pituitary tumors and other abnormal intrasellar masses. Retrospective analysis of 353 patients. Medicine (Baltimore) 1999;78:236–269
37. Gullane PJ, Davidson J, O'Dwyer T, et al. Juvenile angiofibroma: a review of the literature and a case series report. Laryngoscope 1992;102:928–933
38. Haines S, Duvall A. Transzygomatic and transpalatal excision of juvenile nasopharyngeal angiofibroma with intracranial extension. In: Sekhar LN, Janeck I, editors. Surgery of cranial base tumors. New York: Raven Press; 1993. p. 477–484

39. Hamilton HB, Voorhies RM. Tumors of the skull. In: Wilkins RH, Rengachary SS, editors. Neurosurgery. Vol 2. New York: McGraw-Hill; 1996. p. 1502–1528
40. Harada K, Nishizaki T, Adachi N, et al. Pediatric acoustic schwannoma showing rapid regrowth with high proliferative activity. Childs Nerv Syst 2000;16:134–137
41. Harwick RD, Miller AS. Craniocervical chordomas. Am J Surg 1979;138:512–516
42. Howard DJ, Lund VJ. The role of midfacial degloving in modern rhinological practice. J Laryngol Otol 1999;113: 885–887
43. Jacob HE. Chemotherapy for cranial base tumors. J Neurooncol 1994;20:327–335
44. Jafek BW, Krekorian EA, Kirsch WM, et al. Juvenile nasopharyngeal angiofibroma: management of intracranial extension. Head Neck Surg 1979;2:119–128
45. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–484
46. Jones NF, Schramm VL, Sekhar LN. Reconstruction of the cranial base following tumour resection. Br J Plast Surg 1987;40:155–162
47. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 1976;37:1571–1576
48. Karakousis CP, Park JJ, Fleminger R, et al. Chordomas: diagnosis and management. Am Surg 1981;47:497–501
49. Kawahara N, Sasaki T, Nibu K, et al. Dumbbell type jugular foramen meningioma extending both into the posterior cranial fossa and into the parapharyngeal space: report of 2 cases with vascular reconstruction. Acta Neurochir (Wien) 1998;140:323–330; discussion 330–321
50. Kennedy JD, Haines SJ. Review of skull base surgery approaches: with special reference to pediatric patients. J Neurooncol 1994;20:291–312
51. Kirazli T, Oner K, Ovul L, et al. Petrosal presigmoid approach to the petro-clival and anterior cerebellopontine region (extended retrolabyrinthine, transtentorial approach). Rev Laryngol Otol Rhinol (Bord) 2001;122:187–190
52. Kristensen IB, Sunde LM, Jensen OM. Chondrosarcoma. Increasing grade of malignancy in local recurrence. Acta Pathol Microbiol Immunol Scand 1986;(A)94:73–77
53. Lang DA, Neil-Dwyer G, Evans BT, et al. Craniofacial access in children. Acta Neurochir (Wien) 1998;140:33–40
54. Lee JP, Tsai MS, Chen YR. Orbitozygomatic infratemporal approach to lateral skull base tumors. Acta Neurol Scand 1993;87:403–409
55. Lewark TM, Allen GC, Chowdhury K, et al. Le Fort I osteotomy and skull base tumors: a pediatric experience. Arch Otolaryngol Head Neck Surg 2000;126:1004–1008
56. Lippman CR, Jallo GI, Feghali JG, et al. Aneurysmal bone cyst of the temporal bone. Pediatr Neurosurg 1999;31: 219–223
57. Locatelli D, Castelnuovo P, Santi L, et al. Endoscopic approaches to the cranial base: perspectives and realities. Childs Nerv Syst 2000;16:686–691
58. Long DM. Surgical approaches to tumors of the skull base: an overview. In: Wilkins RH, Rengachary SS, editors. Neurosurgery. Vol. 2. New York: McGraw Hill; 1996. p. 1573–1583
59. Low Y, Foo CL, Seow WT. Childhood temporal bone osteoblastoma: a case report. J Pediatr Surg 2000;35:1127–1129
60. Mandai K, Tamaki N, Kurata H, et al. The clinical analysis of pediatric meningioma: 5 cases. No Shinkei Geka 1997;25:131–136
61. Mazzoni A, Calabrese V, Danesi G. A modified retrosigmoid approach for direct exposure of the fundus of the internal auditory canal for hearing preservation in acoustic neuroma surgery. Am J Otol 2000;21:98–109
62. McDermott MW, Durity FA, Rootman J, et al. Combined frontotemporal-orbitozygomatic approach for tumors of the sphenoid wing and orbit. Neurosurgery 1990;26: 107–116
63. Megerian CA, Chiocca EA, McKenna MJ, et al. The subtemporal-transpetrous approach for excision of petroclival tumors. Am J Otol 1996;17:773–779
64. Mendel RC, Brumback RA, Leech RW, et al. Pediatric eighth cranial nerve schwannoma without evidence of neurofibromatosis. J Child Neurol 1999;14:67–69
65. Morita A, Ebersold MJ, Olsen KD, et al. Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993;32:706–714; discussion 714–705
66. Morita A, Sekhar LN. Skull base tumors. In: Bernstein M, Mitchel MS, editors. Neuro-oncology: the essentials. New York: Thieme Medical Publishers, Inc.; 2000. p. 420–433
67. Mortensen A, Bojsen-Moller M, Rasmussen P. Fibrous dysplasia of the skull with acromegaly and sarcomatous transformation. Two cases with a review of the literature. J Neurooncol 1989;7:25–29
68. Mortini P, Mandelli C, Franzin A, et al. Surgical excision of clival tumors via the enlarged transcochlear approach. Indications and results. J Neurosurg Sci 2001;45:127–139; discussion 140
69. Moulin G, Chagnaud C, Gras R, et al. Juvenile nasopharyngeal angiofibroma: comparison of blood loss during removal in embolized group versus nonembolized group. Cardiovasc Intervent Radiol 1995;18:158–161
70. O'Conor Jr GT, Drake CR, Johns ME, et al. Treatment of advanced esthesioneuroblastoma with high-dose chemotherapy and autologous bone marrow transplantation. A case report. Cancer 1985;55:347–349
71. Polonowski JM, Brasnu D, Roux FX, et al. Esthesioneuroblastoma. Complete tumor response after induction chemotherapy. Ear Nose Throat J 1990;69:743–746
72. Posnick JC, Goldstein JA, Armstrong D, et al. Reconstruction of skull defects in children and adolescents by the use of fixed cranial bone grafts: long-term results. Neurosurgery 1993;32:785–791;discussion 791
73. Prescott CA. Cholesteatoma in children – the experience at The Red Cross War Memorial Children's Hospital in South Africa 1988–1996. Int J Pediatr Otorhinolaryngol 1999;49:15–19
74. Razis DV, Tsatsaronis A, Kyriazides I, et al. Chordoma of the cervical spine treated with vincristine sulfate. J Med 1974;5:274–277

75. Reddy KA, Mendenhall WM, Amdur RJ, et al. Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. Am J Otolaryngol 2001;22:172–175
76. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 2001;17:503–511
77. Rickert CH, Scheithauer BW, Paulus W. Chromosomal aberrations in pituitary carcinoma metastases. Acta Neuropathol (Berl) 2001;102:117–120
78. Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol 1999;23:1370–1378
79. Ross DA, Sasaki CT. Pathology of tumors of the cranial base. Clin Plast Surg 1995;22:407–416
80. Salazar J, Vaquero J, Saucedo G, et al. Posterior fossa epidermoid cysts. Acta Neurochir (Wien) 1987;85:34–39
81. Sasaki CT, Lowlicht RA, Astrachan DI, et al. Le Fort I osteotomy approach to the skull base. Laryngoscope 1990;100:1073–1076
82. Schick B, Kahle G, Hassler R, et al. Chemotherapy of juvenile angiofibroma–an alternative? Hno 1996;44:148–152
83. Schijman E, Monges J, Cragnaz R. Congenital dermal sinuses, dermoid and epidermoid cysts of the posterior fossa. Childs Nerv Syst 1986;2:83–89
84. Scimeca PG, James-Herry AG, Black KS, et al. Chemotherapeutic treatment of malignant chordoma in children. J Pediatr Hematol Oncol 1996;18:237–240
85. Sekhar LN, Gay E, Wright DG. Chordomas and chondrosarcomas of the cranial base. In: Wilkins RH, Rengachary SS, editors. Neurosurgery. Vol. 2. New York: McGraw-Hill; 1996. p. 1529–1543
86. Sekhar LN, Schessel DA, Bucur SD, et al. Partial labyrinthectomy petrous apicectomy approach to neoplastic and vascular lesions of the petroclival area. Neurosurgery 1999;44:537–550; discussion 550–532
87. Sindou M, Emery E, Acevedo G, et al. Respective indications for orbital rim, zygomatic arch and orbito-zygomatic osteotomies in the surgical approach to central skull base lesions. Critical, retrospective review in 146 cases. Acta Neurochir (Wien) 2001;143:967–975
88. Siniluoto TM, Luotonen JP, Tikkakoski TA, et al. Value of pre-operative embolization in surgery for nasopharyngeal angiofibroma. J Laryngol Otol 1993;107:514–521
89. Slater PW, Welling DB, Goodman JH, et al. Middle fossa transpetrosal approach for petroclival and brainstem tumors. Laryngoscope 1998;108:1408–1412
90. Spetzler RF, Daspit CP, Pappas CT. The combined supra- and infratentorial approach for lesions of the petrous and clival regions: experience with 46 cases. J Neurosurg 1992;76:588–599
91. Stewart FM, Lazarus HM, Levine PA, et al. High-dose chemotherapy and autologous marrow transplantation for esthesioneuroblastoma and sinonasal undifferentiated carcinoma. Am J Clin Oncol 1989;12:217–221
92. Suarez C, Garcia LA, Fernandez de Leon R, et al. Infratemporal approaches to nasopharyngeal tumors. Eur Arch Otorhinolaryngol (Suppl)1997;1:S165–168
93. Taconis WK. Osteosarcoma in fibrous dysplasia. Skeletal Radiol 1988;17:163–170
94. Tai PT, Craighead P, Bagdon F. Optimization of radiotherapy for patients with cranial chordoma. A review of dose-response ratios for photon techniques. Cancer 1995;75: 749–756
95. Teo C, Dornhoffer J, Hanna E, et al. Application of skull base techniques to pediatric neurosurgery. Childs Nerv Syst 1999;15:103–109
96. Uretzky ID, Mair EA, Schoem SR. Endoscopically guided midfacial degloving in infants for removal of congenital and acquired midfacial masses. Int J Pediatr Otorhinolaryngol 1998;46:145–158
97. Van Den Abbeele T, Elmaleh M, Herman P, et al. Transnasal endoscopic repair of congenital defects of the skull base in children. Arch Otolaryngol Head Neck Surg 1999;125: 580–584
98. Wiatrak BJ, Koopmann CF, Turrisi AT. Radiation therapy as an alternative to surgery in the management of intracranial juvenile nasopharyngeal angiofibroma. Int J Pediatr Otorhinolaryngol 1993;28:51–61
99. Wold LE, Laws Jr ER. Cranial chordomas in children and young adults. J Neurosurg 1983;59:1043–1047

Calvarial Tumors in Children 47

Ganesh Rao, John R. W. Kestle

Introduction – 568

Epidemiology – 568

Symptoms and Clinical Signs – 568

Diagnostics – 568

Classification and Treatment – 568
Primary Benign Tumors
Malignant Tumors

Conclusions – 571

References – 572

Introduction

Calvarial tumors of children include a wide variety of lesions that are distinct from those forms commonly found in adults. They range from benign congenital masses to malignant erosive neoplasms, either primary or metastatic. These tumors may be encountered by a variety of clinicians. Calvarial tumors are rare, and the diagnosis and treatment of these lesions can vary significantly. In this chapter, we discuss common childhood calvarial tumors, their diagnosis, and treatment options.

Epidemiology

Primary neoplasms of the skull are estimated to account for only 0.8% of all bone tumors [23]. Most reported lesions in the literature are from case reports or small series, making it difficult to identify the frequency of the various lesions. In larger series, dermoid and epidermoid tumors account for 20%–59% of calvarial tumors in children, with a myriad of other lesions making up the remainder [16, 21].

Symptoms and Clinical Signs

Tumors of the skull in children usually present as painless bumps on the skull. Benign lesions grow very slowly and usually have a long history. Rapid growth or multiple lesions suggest a more aggressive histology. Local pain and/or tenderness is seen less commonly and may occur with eosinophilic granuloma or with lesions that have invaded the skull and involved the dura. Even with intracranial extension of tumors, it is uncommon for patients to present with signs and symptoms of neurologic compromise prior to the skull lesion being discovered.

Diagnostics

Imaging is recommended for most masses on the calvarium. The exception is the small lesion, with typical features of an epidermoid, which is located on a suture, away from the midline. Imaging may provide clues to the diagnosis, as well as the opportunity to evaluate for the possibility of intracranial extension. Plain radiographs of the skull are commonly used to evaluate calvarial tumors. Many lesions have characteristic features such as a lytic or "punched-out" appearance with sclerotic edges (e.g., dermoid or epidermoid tumor) or nonsclerotic edges (e.g., eosinophilic granuloma). Some lesions present with bony trabeculations (e.g., hemangioma).

CT scanning is the imaging modality of choice for bony lesions. It allows for better evaluation of bone erosion or invasion. The inner and outer skull tables and diploic spaces are clearly visualized. CT also provides information about the intracranial contents, but MRI is recommended when intracranial extension is suspected. MR venography is useful in lesions that may be in close proximity to a major venous sinus.

Definitive diagnosis of a calvarial tumor is often not possible from imaging alone. A lytic lesion with sclerotic margins is most commonly a benign tumor but may be mimicked by a metastatic tumor such as neuroblastoma. Thus, surgical excision or biopsy is warranted in most cases.

Classification and Treatment

Calvarial tumors may be classified as primary or metastatic. The primary calvarial tumors can be characterized as either benign or malignant. Some calvarial lesions are not neoplastic and are not discussed in this chapter. One should be aware of their existence as they often present as skull masses. They include atretic encephaloceles, calcified cephalohematomas, sarcoidosis, and fibrous dysplasia.

Primary Benign Tumors

Primary benign calvarial tumors include dermoid or epidermoid tumors, hemangiomas, osteomas, and ossifying fibromas. Although it is not neoplastic, eosinophilic granuloma (a lesion in the spectrum of Langerhans cell histiocytosis) should be included in a discussion of calvarial tumors.

Dermoid and epidermoid tumors are the most common calvarial tumors [21]. These are thought to arise from ectopic epithelial cell rests in bone. A continuous process of cell proliferation, senescence, and desquamation produces a cyst that enlarges to erode bone [3]. Clinically and radiographically, these lesions appear similar. Histologically, dermoid tumors have dermal elements (including skin, hair structures, and sebaceous glands) (Fig. 1), whereas epidermoids include only epidermal elements (keratinous debris). These lesions are most commonly located along the coronal and lambdoid sutures and near the anterior fontanelle. Dermoids can be quite large. Although either lesion may be associated with a sinus tract, as many as 20% of dermoid tumors, particularly those located in the occipital midline, will have extension of the dermal sinus tract to the dura mater [17, 21] (Fig. 2). On plain radiographs and CT, dermoids and epidermoids appear as lytic lesions with sclerotic margins (Fig. 3). MRI is recommended for

dermoid tumors occurring at the occipital midline to evaluate the possibility of a dermal sinus tract with intracranial extension [23]. Very rarely, these lesions have been reported to undergo malignant transformation [10, 14, 29].

Hemangiomas are benign lesions characterized by their dominant component of capillary, cavernous, or venous blood vessels. The cavernous type is the most common in the skull. They are commonly found in the frontal or parietal bone or the mandible and account for up to 10% of all cranial vault tumors [28]. Hemangiomas frequently present as small painless (or slightly tender) masses. These lesions are expansile and may grow outward to form a painful skull mass. They are most often unifocal, although multifocal hemangiomas have been reported [13]. Skull films will show a honeycomb or trabecular pattern. The classic "sunburst" appearance is seen in fewer than 15% of cases [23]. CT or MRI will show a well-defined bony rim with an interior that enhances [2]. These lesions will sometimes spontaneously involute. For expansive lesions that are symptomatic, surgical resection is recommended. Recurrence is very rare.

Osteomas are more common in adults than in children and account for the most common primary skull neoplasm of adults. In children, they are more common in females than males (a 3:1 ratio) [20]. A cranial vault lesion often manifests as a painless swelling. These lesions usually grow outward and generally do not compress the brain [7]. Calvarial osteomas are often found in the frontal area (in the parasagittal region near the suture) but may be found anywhere. They tend to be hard and fixed upon palpation. Most lesions are isolated. Multiple lesions, however, should alert the clinician to the autosomal dominant disorder Gardner's Syndrome, which includes multiple osteomas, colonic polyps, sebaceous cysts, and fibromas [23], and often results in colon cancer. CT is the most useful study for the evaluation of osteoma. The osteoma will show as a well-defined mass lesion, which will help distinguish osteoma from an intraosseous meningioma. There is also often a lack of vascularity on CT, which can further distinguish osteoma from meningiomas. Despite these imaging characteristics, histologic confirmation of the diagnosis is often necessary. Treatment is complete surgical excision of the osteoma, including possible cranioplasty. Smaller lesions may be treated with drilling and curettage. Outcome after resection is excellent [7].

Ossifying fibroma is a rare benign primary bone tumor often found in the mandible and maxilla in

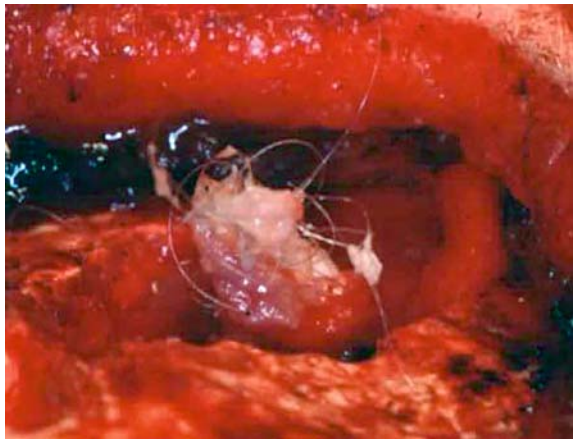


Fig. 1 Dermoid. The lesion has been opened and the contents including hair are visible

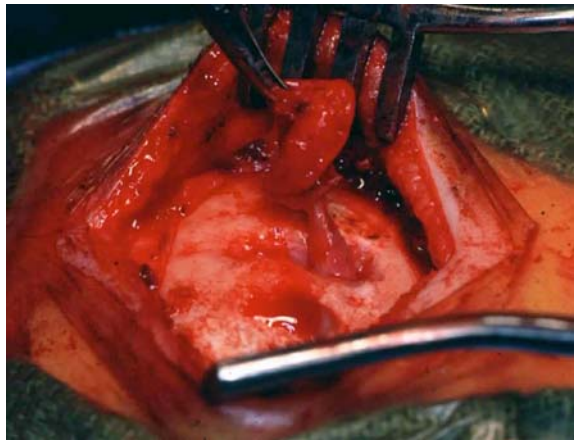


Fig. 2 Midline posterior fossa scalp dermoid with tract penetrating skull and terminating on dura

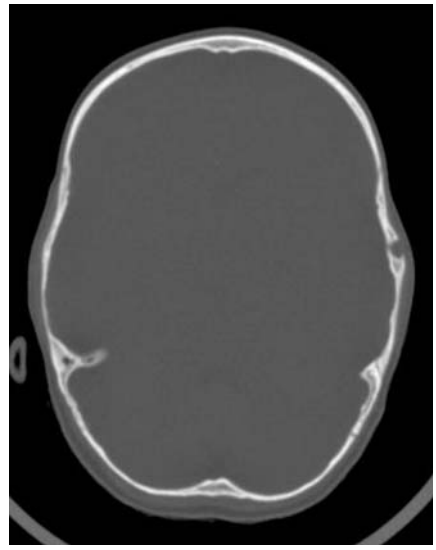


Fig. 3 Intradiploic epidermoid eroding outer table of the skull

childhood. Presentation is often with a small painless mass that may result in nasal obstruction, proptosis, or anosmia. Plain X-ray shows a radiolucent lesion with sclerotic edges. CT scan shows an expansile lesion with preservation of the inner and outer cortices. The treatment is en bloc resection, as partial excision will result in recurrence.

Eosinophilic granuloma (EG) is generally considered an inflammatory disease. Evidence of clonal expansion suggests a neoplastic basis for the disease [27]; however, the neoplastic nature of EG has not been corroborated with gene rearrangements [30]. EG refers to a solitary lesion in bone composed of histiocytes. It is the most common form of Langerhans cell histiocytosis, an idiopathic syndrome that includes Hand-Schüller-Christian disease and Letterer-Siwe syndrome [15]. EGs usually occur in the skull before age 20. The most common presenting symptom is a tender scalp mass. Plain X-ray reveals a solitary lytic lesion without sclerotic margins, sometimes referred to as a "justified" margin [3] (Fig. 4). CT will show an expansile, somewhat enhanced lesion with beveled edges (Fig. 5). MRI may reveal a focal, soft tissue mass sometimes with subgaleal or epidural extension. All EG patients should be evaluated for multiple lesions with a skeletal survey and bone scan. Various treatments have been advocated including curettage, complete resection, or intralesional injection of steroid. Some lesions may spontaneously regress but have been reported to recur several years later. Most commonly, an excisional biopsy is performed for diagnosis. Up to 30% of patients will develop recurrent lesions, and this is more common in children than adults [19]. For patients with multiple lesions, referral to an oncologist is warranted. Low-dose radiation and chemotherapy have been promoted. Multiple agents, including chlorambucil, vincristine, vinblastine, 6-mercaptopurine, cyclophosphamide, and methotrexate have been shown to have an efficacy rate from 30% to 60%. Patients with a solitary lesion are expected to have a 90% 5-year survival [23]. Factors associated with a poor prognosis are onset before 2 years of age, extensive visceral or extraosseous involvement [26], anemia, and thrombocytopenia [18].

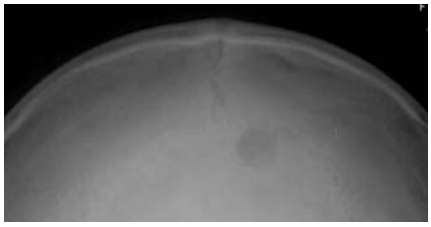


Fig. 4 Skull film of eosinophilic granuloma

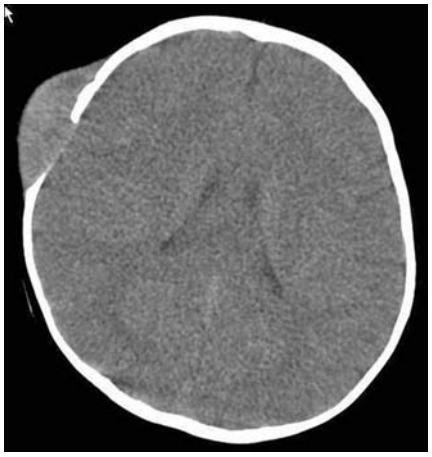


Fig. 5 Noncontrast axial CT scan of eosinophilic granuloma

Malignant Tumors

Malignant calvarial tumors include neuroblastoma, osteosarcoma, Ewing's sarcoma, fibrosarcoma, angiosarcoma, and lymphoma. Many malignancies are metastatic. Significant improvements in treatment techniques have led to better survival for patients with these lesions.

Neuroblastoma is a malignant tumor that arises from an aberration of development of neural crest cells during formation of the sympathetic ganglia or adrenal medulla. It is a common childhood tumor seen in children 5 years or younger with an abdominal mass and periorbital ecchymosis [23]. Neuroblastoma metastasizes to bone in as many as 50% of cases and is the most common metastasis to the skull in children [8]. Plain X-ray shows nodular lucencies with periosteal elevation. CT shows lucencies as well as spread into the sutures. Both CT and MRI show thick epidural or subdural enhancing soft tissue masses (Fig. 6). The appearance of neuroblastoma on CT and MR can mimic that of lymphoma. Treatment is with a combination of radiation or chemotherapy depending on the stage of the disease. Surgery is reserved for patients with significant intracranial extension and brain compression.

Osteosarcoma, or osteogenic sarcoma, is the most common primary malignant tumor of bone, but only 0.8%–2% of cases occur in the skull [11, 22, 23]. Four histologic types are recognized including osteoblastic (the most common), chondroblastic, fibroblastic, and telangiectatic. Osteosarcoma is a rapidly growing tumor, with pain and swelling being the primary symptoms. It generally destroys both the inner and outer tables of the skull, and intracranial extension

has been reported. Plain radiography reveals a destructive lesion involving the entire thickness of the skull. Contrast CT scan will show heterogeneous enhancement. Treatment of osteosarcoma involves surgical resection with tumor-free margins, combined with radiation and chemotherapy (usually including methotrexate). Subtotal resection with radiation and chemotherapy has also resulted in long-term survival in a limited number of patients. With this combination of therapy and without metastases, the long-term survival rate has been reported to be from 60% to 80% [24, 25].

Ewing's sarcoma is primarily a disease of children and young adults. It is a tumor of bone mesenchyme and is often metastatic to the calvarium. Primary skull tumors are rare (less than 4%), and a lesion in the skull should be considered a metastasis until proven otherwise [4]. Primary tumors may have significant intracranial extension (Fig. 7). Patients often present with intermittent pain that is worse at night. Indices consistent with infection (e.g., sedimentation rate, fever, white blood cell count) may be elevated. Skull radiographs show an irregular lytic lesion with periosteal reaction. Imaging may be consistent with neuroblastoma or lymphoma. Treatment includes surgical resection with radiation and chemotherapy. Subtotal resection with radiation is not as effective as complete resection. Failure of therapy is usually due to distant metastasis or local recurrence. At present, disease-free survival ranges from 50% to 80%, and patients with primary skull disease may have a better prognosis [5, 6].

Fibrosarcoma and angiosarcoma are very rare tumors, which may be found anywhere in the calvarium. Skull X-rays show irregular, radiolucent lesions. On CT, the appearance is similar to other malignant lesions. The treatment for most sarcomas is surgical resection. Fibrosarcomas may respond to chemotherapy, but radiation may not be of benefit. Angiosarcomas have been shown to be resistant to adjuvant chemotherapy.

Lymphomas originating in the sinuses, nasopharynx, or dura may extend to the skull or skull base. Although involvement of bone is common (up to 25% of patients will have some skeletal involvement), metastatic calvarial lesions are uncommon, and primary calvarial tumors are rare [9]. These lesions often mimic other types of tumors; however, their treatment differs from that of most other tumors. Patients will often present with a palpable, painless, scalp mass. In patients with concomitant dural involvement, headache may be a presenting symptom. Radiographs (Figs. 8a, b) show nonspecific, irregular lytic lesions. CT will often show a hyperdense enhancing mass. Surgical intervention is limited to biopsy only, and chemotherapy and radiation are the mainstays of treatment with the overall cure rate between 75% and 80% [1, 12].

Conclusions

Calvarial tumors in children run the gamut of benign to malignant disease. They often present with a palpable mass that may or may not be painful. CT is the imaging study of choice, but MRI may be necessary to identify an intracranial extension. Surgical excision is the primary treatment for most lesions.

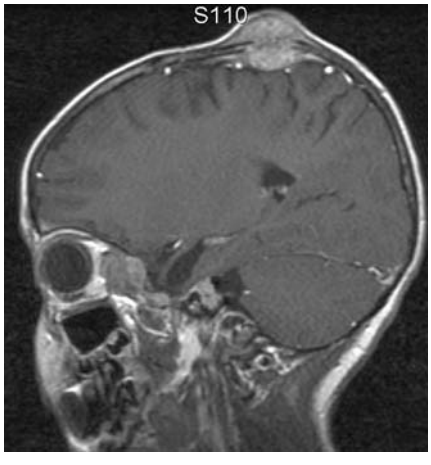


Fig. 6 Sagittal T1-weighted MRI with gadolinium enhancement of metastatic neuroblastoma

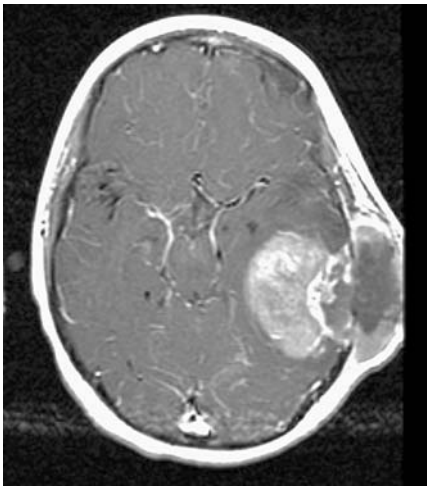


Fig. 7 Axial T1-weighted gadolinium enhanced MRI of Ewing's sarcoma with significant intracranial extension

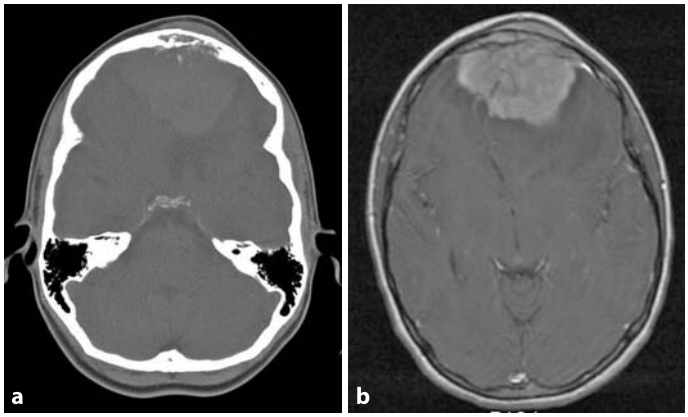


Fig. 8 CT bone windows (**a**) and T1-weighted MRI with gadolinium enhancement (**b**) of B-cell precursor lymphoma

References

1. Anderson JR, Wilson JF, Jenkin DT, et al. Childhood non-Hodgkin's lymphoma. The results of a randomized therapeutic trial comparing a 4-drug regimen (COMP) with a 10-drug regimen (LSA2-L2). N Engl J Med 1983;308: 559–565
2. Bastug D, Ortiz O, Schochet SS. Hemangiomas in the calvaria: imaging findings. AJR Am J Roentgenol 1995;164: 683–687
3. Burger PC, Sheithauer BW, Vogel FS. Surgical pathology of the nervous system and its coverings. 3rd ed. New York: Churchill Livingstone; 2002
4. Carlotti Jr CG, Drake JM, Hladky JP, et al. Primary Ewing's sarcoma of the skull in children. Utility of molecular diagnostics, surgery and adjuvant therapies. Pediatr Neurosurg 1999;31:307–315
5. Desai KI, Nadkarni TD, Goel A, et al. Primary Ewing's sarcoma of the cranium. Neurosurgery 2000;46:62–68; discussion 68–69
6. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348:694–701
7. Haddad FS, Haddad GF, Zaatari G. Cranial osteomas: their classification and management. Report on a giant osteoma and review of the literature. Surg Neurol 1997;48:143–147
8. Healy JF, Bishop J, Rosenkrantz H. Cranial computed tomography in the detection of dural, orbital, and skull involvement in metastatic neuroblastoma. J Comput Tomogr 1981;5:319–323
9. Herkes GK, Partington MD, O'Neill BP. Neurological features of cranial vault lymphomas: report of two cases. Neurosurgery 1991;29:898–901
10. Hoeffel C, Heldt N, Chelle C, et al. Malignant change in an intradiploic epidermoid cyst. Acta Neurol Belg 1997;97: 45–49
11. Huvos AG, Sundaresan N, Bretsky SS, et al. Osteogenic sarcoma of the skull. A clinicopathologic study of 19 patients. Cancer 1985;56:1214–1221
12. Jenkin RD, Anderson JR, Chilcote RR, et al. The treatment of localized non-Hodgkin's lymphoma in children: a report from the Children's Cancer Study Group. J Clin Oncol 1984;2:88–97
13. Kumar NA, Ranganadham P, Bhaskar G, et al. Multiple calvarial cavernous haemangiomas: case report and review of the literature. Neuroradiology 38(Suppl)1996;1:S83–85
14. Kveton JF, Glasscock 3rd ME, Christiansen SG. Malignant degeneration of an epidermoid of the temporal bone. Otolaryngol Head Neck Surg 1986;94:633–636
15. Lichtenstein L. Histiocytosis X;integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schuller-Christian disease as related manifestations of a single nosologic entity. AMA Arch Pathol 1953;56:84–102
16. Martinez-Lage JF, Capel A, Costa TR, et al. The child with a mass on its head: diagnostic and surgical strategies. Childs Nerv Syst 1992;8:247–252
17. Neblett CR, Caram PC, Morris R. Lateral congenital dermal sinus tract associated with an intradiploic dermoid tumor. Case report. J Neurosurg 1970;33:103–105
18. Nezelof C. Histiocytosis X: a histological and histogenetic study. Perspect Pediatr Pathol 1979;5:153–178
19. Rawlings 3rd CE, Wilkins RH. Solitary eosinophilic granuloma of the skull. Neurosurgery 1984;15:155–161
20. Ross DA, Sasaki CT. Pathology of tumors of the cranial base. Clin Plast Surg 1995;22:407–416
21. Ruge JR, Tomita T, Naidich TP, et al. Scalp and calvarial masses of infants and children. Neurosurgery 1988;22: 1037–1042
22. Salvati M, Ciappetta P, Raco A. Osteosarcomas of the skull. Clinical remarks on 19 cases. Cancer 1993;71:2210–2216
23. Shah MV, Haines SJ. Pediatric skull, skull base, and meningeal tumors. Neurosurg Clin N Am 1992;3:893–924
24. Sundaresan N, Galicich JH, Rosen G, et al. Primary osteogenic sarcoma of the skull. Five-year disease-free survival following surgery and high dose methotrexate therapy. N Y State J Med 1985;85:598–599

25. Sundaresan N, Huvos AG, Rosen G, et al. Combined-modality treatment of osteogenic sarcoma of the skull. J Neurosurg 1985;63:562–567
26. Williams JW, Dorfman RF. Lymphadenopathy as the initial manifestation of histiocytosis X. Am J Surg Pathol 1979;3:405–421
27. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X) – a clonal proliferative disease. N Engl J Med 1994;331:154–160
28. Winn HR, Youmans JR. Youmans neurological surgery. 5th ed. Philadelphia: W.B. Saunders; 2003
29. Yanai Y, Tsuji R, Ohmori S, et al. Malignant change in an intradiploic epidermoid: report of a case and review of the literature. Neurosurgery 1985;16:252–256
30. Yu RC, Chu AC. Lack of T-cell receptor gene rearrangements in cells involved in Langerhans cell histiocytosis. Cancer 1995;75:1162–1166

Epidural Spinal Tumors in Children

48

Colin Kazina, Patrick McDonald

Introduction – 576

Epidemiology – 576

Symptoms and Clinical Signs – 576

Diagnostics – 577
Synopsis

Staging and Classification – 577
Synopsis

Treatment – 578
Synopsis
Surgery
Radiotherapy
Chemotherapy
Neuroblastoma
Ewing's Sarcoma
Rhabdomyosarcoma
Lymphoma

Prognosis/Quality of Life – 579

Follow-up – 580

Future Perspectives – 580

References – 580

Introduction

Extradural spine tumors in the pediatric population are a relatively rare occurrence and constitute a heterogeneous group of pathologies. Management is dictated by both specific tumor pathology, as well as the severity of neurologic symptoms at presentation. Because of their rarity, management of spinal cord compression (SCC) secondary to epidural spinal tumors in children remains controversial and includes decompressive and resective surgery, radiotherapy, chemotherapy, or a combination of the three.

The management of epidural spine tumors in children can be significantly different from that of adults and care must be taken to avoid generalizations regarding prognosis for neurologic recovery based on adult data. The following chapter reviews the diagnosis and treatment of epidural spine tumors in children, with emphasis on the more common tumor pathologies. Primary bone tumors and nerve sheath tumors, while a potential cause of extradural SCC, are reviewed elsewhere and will not be covered in this chapter.

Epidemiology

Spinal tumors are commonly classified as intramedullary (within the spinal cord), extramedullary intradural, and extra- or epidural. Taken together, they account for 5%–10% of pediatric central nervous system tumors [1] with an annual incidence of approximately 1 per million population [2]. Epidural tumors represent roughly one third of spinal tumors and are distributed based on the relative size of the cervical, thoracic, lumbar, and sacral spine.

In a review of 112 spinal epidural tumors at St. Jude Children's Research Hospital in 1991 [3], neuroblastoma represented 28.6% of all tumors, Ewing's sarcoma 26.8%, osteogenic sarcoma 14.3%, rhabdomyosarcoma 12.5%, Hodgkin's lymphoma 7.1%, germ cell tumors 4.5%, and soft-tissue sarcoma 3.6%. A review of four of the larger series of pediatric epidural spine tumors [4] listed neuroblastoma as the most common at 26%, followed by Ewing's sarcoma (21%), rhabdomyosarcoma (13%), osteogenic sarcoma (12%), lymphoma (8%), other sarcoma (5%), germ cell tumors (5%), leukemia (3%), Wilms' tumor (2%), and other miscellaneous tumors (5%) (see Table 1).

Angiolipomas [5], chordomas [6], meningiomas [7], Langerhans cell histiocytosis, adrenal carcinoma, and hemangioendothelioma have also been described [8].

Table 1 Common epidural spine tumors in children [4]

Tumor	Frequency
Neuroblastoma	26%
Ewing's Sarcoma	21%
Rhabdomyosarcoma	13%
Osteogenic sarcoma	12%
Lymphoma	8%
Germ cell tumors	5%
Leukemia	3%
Other	12%

Symptoms and Clinical Signs

The clinical presentation of children with epidural spine tumors is marked by its variability, ranging from a slow, progressive onset of signs and symptoms over many months, to rapid deterioration over a period of days. Presentation varies with the age of the patient, the location of the tumor, and tumor histology. The duration of symptoms, from onset to diagnosis is quite variable, ranging from a mean of 17.4 months in all spinal tumors, to a shorter 2.4 months in malignant tumors [2].

Pain, either localized back pain or less commonly, radicular pain, is by far the most common presentation. In Ch'ien's review of epidural spine tumors [9], close to 60% of children complained of back pain. Specific features that may point to a more sinister etiology of back pain in children include night pain, pain associated with weight loss, and pain refractory to conventional analgesics.

After pain, weakness is the next most common sign of an epidural spine tumor, present in up to 50% of children. Depending on the location of the tumor, weakness can involve the lower extremities, or both upper and lower extremities. The majority present with upper motor neuron-type weakness, with hyperreflexia, increased tone, and a positive Babinski response. In tumors compressing the cauda equina or conus medullaris, or tumors isolated to the lower lumbar or sacral spine, lower motor neuron type weakness can be the presenting sign.

Sensory alterations are less common, usually manifesting as a sensory level rather than a dermatomal loss. In younger children, the patient or parents rarely recognize the loss of sensation themselves. On

more detailed testing, loss of position and vibration sense can be detected.

Bowel and bladder dysfunction occurs in roughly 50% of children [10], manifesting as periodic or frank incontinence in patients already toilet trained. Recurrent or persistent urinary tract infection may be the only clue to bladder dysfunction in children not yet toilet trained.

Scoliosis, especially a convex left-sided curve, can signal underlying neurologic-based spinal pathology. Although this is rarely the only manifestation of an epidural spine tumor, a left-sided, rapidly progressive curve should always be investigated. A kyphotic deformity is less common. Localized swelling, either directly over the spine or in the region of the paraspinal muscles can also be a sign of underlying pathology as can localized paraspinal muscle rigidity.

Because of their inability to communicate, the diagnosis of a spinal epidural tumor in infants and young children is especially difficult. Excessive irritability, recurrent bladder infections, crying with any movement, and failure to meet motor milestones, while not specific, can be manifestations of an epidural spine tumor. Regression of motor milestones, as seen in a young child previously ambulating who no longer ambulates, is often an ominous sign.

Diagnostics

Synopsis

The advent of modern neuroimaging with high resolution computed tomography (CT) and magnetic resonance (MR) imaging has dramatically increased our ability to diagnose spinal tumors, plan treatment, and follow children with epidural spinal pathology.

Plain radiographs have been largely supplanted by more sophisticated imaging modalities but still play a role as a preliminary investigation of children with suspected spine pathology. While up to half of plain films will be normal, the presence of a left-sided scoliosis, widened interpedicular distance, eroded pedicles, collapsed vertebral bodies, and pathologic fractures can all suggest an underlying neoplastic etiology.

For the purposes of delineating the lesion, its soft-tissue extension, possible metastatic spread, and to assist in operative planning, MR scanning, with and without contrast enhancement, is the imaging modality of choice. Axial, sagittal, coronal, and selected fat suppressed images will best delineate the lesion.

MR imaging of epidural spine tumors usually demonstrate a lesion hyperintense to CSF on T1-weighted images, but hypointense on T2-weighted images with heterogeneous contrast uptake. The degree of spinal cord compression, extension through neural foramina, and soft-tissue extension, as well as the presence of multiple lesions throughout the neuraxis can usually be delineated. We recommend simultaneous brain imaging with MR to rule out the rare instance of intracranial metastases. The ready availability of MR imaging has supplanted CT-myelography in the diagnosis of spinal lesions in all but those with a contraindication to MR scanning, or the presence of spinal instrumentation (which may result in poor quality images). This has made the risk of postmyelogram deterioration in those with spine lesions a rare occurrence.

CT scanning, with sagittal and coronal reconstructions, remains a useful modality for imaging the bony spine to look for bony invasion and the presence of instability, both pre- and postoperatively. A radionuclide bone scan may show an area of increased uptake when bony involvement is suspected.

For neuroblastoma, 123I meta-iodobenzylguanidine (MIBG) SPECT scanning reveals uptake in the vast majority of tumors and is useful in staging disease [11]. It is usually not utilized in the initial investigations of children presenting with SCC and an epidural tumor.

For selected patients, mainly those with slowly progressing or absent neurologic symptoms, tumor biopsy can play an important role and may obviate the need for more extensive surgical procedures in selected tumors. Image-guided biopsy to obtain a histologic diagnosis can be done safely [12] and in chemosensitive tumors such as neuroblastoma, may make surgery unnecessary.

Staging and Classification

Synopsis

Spinal tumors are classified as intramedullary (within the parenchyma of the spinal cord) or extramedullary. Extramedullary spinal tumors can be classified as intra- or extradural.

While there is no specific staging or classification system for pediatric epidural spine tumors, a number of factors impact on management and neurologic prognosis. The degree of spinal cord compression (SCC) and subsequent neurologic weakness can determine optimal management. Those presenting with para- or quadriparesis, or severe weakness are more likely to undergo decompressive/resective surgery rather than await the results of a biopsy and delay chemotherapy or radiotherapy. The presence of end-stage or disseminated disease or alternately a well-circumscribed, noninvasive lesion on imaging, may also influence how aggressive one may be when considering surgery. Specific tumor pathology may impact on initial treatment in that some tumors such

as neuroblastoma are chemosensitive, while others such as lymphoma are radiosensitive.

Of the common epidural spine tumors in children, neuroblastoma has the most widely accepted staging system – The International Neuroblastoma staging system [13] (see Table 2).

Treatment

Synopsis

The initial management of children presenting with epidural spinal tumors centers on obtaining an accurate diagnosis of tumor type (by obtaining tissue if necessary), preserving function or reversing neurologic weakness from spinal cord compression, and alleviating pain, whether due to tumor or spinal instability. The ultimate goal of treatment is eradication of disease with long-term survival and minimal morbidity. These goals may be achieved through surgery, chemotherapy, radiotherapy, or a combination of the three. Treatment requires a multidisciplinary approach with neurosurgeons, pediatric oncologists, physical and occupational therapists, psychologists and social workers.

At initial presentation, a quick decision is often needed regarding the need for surgical or medical management. In children presenting with any signs of spinal cord compression, high-dose corticosteroids are indicated as a temporizing measure to attempt to reverse neurologic deficits prior to definitive management. The next intervention, whether it be surgery, chemotherapy, or radiotherapy, remains controversial and depends on both the degree of neurologic impairment and the suspected tumor histology.

Table 2 International neuroblastoma staging system [13]

Stage 1	Localized tumor. Complete excision, with or without microscopic residual. Ipsilateral lymph nodes negative
Stage 2a	Localized unilateral tumor. Incomplete gross excision. Ipsilateral lymph nodes negative
Stage 2b	Localized unilateral tumor. Complete or incomplete excision. Ipsilateral and regional lymph nodes positive
Stage 3	Unresectable unilateral tumor infiltrating across midline, with or without lymph node involvement. Unilateral tumor with contralateral lymph node involvement. Midline tumor with bilateral infiltration or bilateral lymph node involvement
Stage 4	Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver or other organs
Stage 5	Localized primary tumor in patients <1 year with limited dissemination to liver, skin or bone marrow

Surgery

For asymptomatic patients, patients with a minimal amount of tumor in the epidural space or those with mild neurologic findings and a tumor known to be chemo- or radiosensitive, surgical intervention is usually not indicated. An evolving literature suggests that medical management alone is adequate for patients with neuroblastoma, germ cell tumors, and lymphoma (the so-called small cell tumors) [3, 4, 10, 14–16], even those with mild to moderate neurologic findings. Although controversial, it has been suggested that surgery is no better than medical management for patients with neuroblastoma, even those with severe weakness [16].

In contrast, patients with sarcomatous tumors (Ewing's, rhabdomyosarcoma, osteogenic sarcoma) are more likely to recover function with surgical debulking or resection, rather than medical management alone [3, 4, 10]. Similarly, although not consistent in the literature, children presenting with severe weakness such that they can no longer ambulate are more likely to recover function with surgical intervention rather than medical [3, 4, 9, 10]. Finally, a subset of medically treated patients continue to deteriorate while receiving chemo- or radiotherapy and should be considered for urgent surgical decompression.

Thus surgical decompression is recommended for patients who present with severe weakness from spinal cord compression, regardless of tumor type, those with symptomatic sarcomas, those in whom the diagnosis is unclear, and those who continue to deteriorate despite optimal medical therapy.

The majority of pediatric epidural spine tumors are not discrete, well-circumscribed lesions and as such complete resection is usually not possible. The goal of surgery is thus adequate decompression of the spinal cord and preservation of spinal stability as well as tissue diagnosis. This can usually be achieved through a posterior approach. In contrast to adults, the majority of epidural spine tumors in children compress the spinal cord dorsally after entering the

canal through neural foramina (see Fig. 1). Because of the high incidence of progressive kyphoscoliosis in children after laminectomy, laminoplasty is the preferred technique [17].

Radiotherapy

Although radiation plays an important adjuvant role in the treatment of epidural spinal malignancies, the dose should be limited whenever possible to avoid radiation-induced damage to an already vulnerable spinal cord. In neuroblastoma, radiation is reserved for those with progressive symptoms despite surgery and chemotherapy. For sarcomatous tumors, radiotherapy is necessary for local control [18] and is utilized as an adjuvant to surgery and/or chemotherapy. In hematologic malignancies, although lymphoma is radiosensitive, radiotherapy is reserved for those tumors unresponsive to chemotherapy and surgery.

Chemotherapy

Chemotherapy plays a crucial role in the treatment of pediatric epidural tumors, many of which are systemic tumors. The following paragraphs briefly review the use of chemotherapy in the more commonly encountered tumors.

Neuroblastoma

Arising from neural crest tissue, neuroblastoma is the most common solid malignant neoplasm in children and the most common epidural spine neoplasm. Chemotherapy to treat both epidural and extraspinal disease consists of combinations of agents including etoposide, carboplatin, cisplatin, cyclophosphamide, vincristine, and doxorubicin [19].

Ewing's Sarcoma

Also thought to arise from neural crest tissue, these tumors are thought to be in the same family as peripheral primitive neuroectodermal tumors (PNET). Combination chemotherapy usually consists of five agents: vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide [18].

Rhabdomyosarcoma

Rhabdomyosarcomas are thought to arise from mesenchymal skeletal muscle precursor tissue. Chemotherapy plays an adjuvant role to surgery where the goal is complete excision. Combinations of vincristine, cyclophosphamide, etoposide, topotecan, ifosfamide, and other agents are commonly used [20].

Lymphoma

Lymphomas are chemosensitive malignancies, usually responding rapidly to medical intervention. For lymphoma, adriamycin, vincristine, prednisone and cyclophosphamide, and bleomycin are used in combination.

Prognosis/Quality of Life

The two most important outcomes in children treated for epidural spine tumors are neurologic outcome and overall survival. Survival for the tumors commonly encountered is variable and related to the presence of systemic disease. Five-year survival of children with intraspinal neuroblastoma, based on the Pediatric Oncology Group (POG) experience [16], is 71%. Overall survival for Ewing's sarcoma is 70% for localized disease and 30% for those with me-

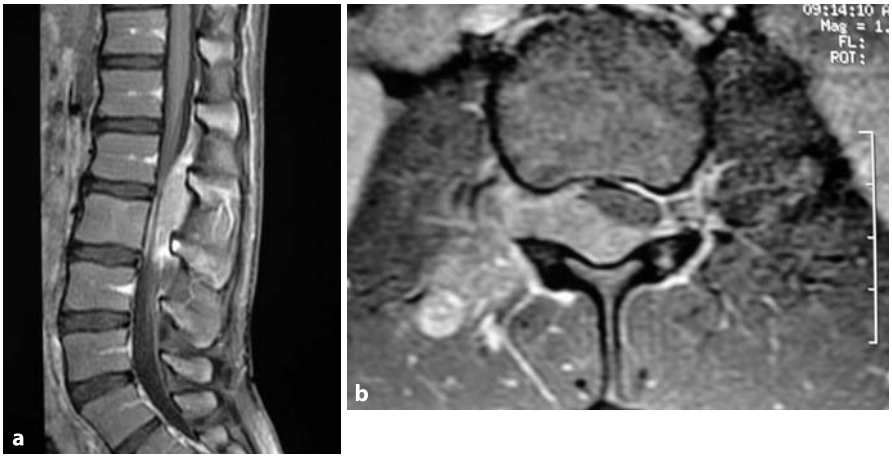


Fig. 1 Axial and sagittal gadolinium enhanced MR images of a 14-year-old boy with progressive lower extremity weakness and an enhancing epidural mass at the L2/3 level. The mass exits the right neural foramen. Pathologic analysis indicated a Ewing's sarcoma

tastases at the time of diagnosis [18]. Optimal treatment for sarcomas involves wide resection with adjuvant therapy. This is usually not possible when spinal involvement occurs and thus survival from osteosarcoma with spinal involvement is poor with a median survival of 23 months [21].

Neurologic outcome correlates with the severity of weakness at presentation [3, 9, 10, 16, 22]. Those who present with mild or moderate weakness are more likely to make a full functional recovery. In Katzenstein's review of the POG experience with neuroblastoma [16], 40% of those presenting with paralysis fully recovered function after treatment (four with chemotherapy and two with surgery), while 33% partially recovered and 27% remained paralyzed. In those with mild deficits at presentation, 77% made a complete recovery and the remaining 23% a partial recovery. Klein's review of the St. Jude's experience underscores that even in those presenting with complete paralysis, up to 50% eventually become ambulatory with treatment. This contrasts markedly with adults with epidural spinal cord compression where complete recovery in those presenting with paralysis is rare.

Quality of life clearly remains an issue for those who fail to make a complete neurologic recovery. Many will require assistive devices to ambulate and may never fully recover bowel and bladder function – a devastating effect of compression. Similarly, chemotherapy and radiotherapy carry risk of further morbidity and mortality and eventual second malignancy. There is growing awareness that children who survive cancer can have ongoing psychosocial issues [23]. This highlights the need for a multidisciplinary team including psychologists and social workers.

Follow-up

Since the majority of children with epidural spine tumors have malignant disease, close follow-up with surveillance spinal imaging, as well as ongoing surveillance of the primary malignancy is essential. Ideally this should be done in the context of a multidisciplinary pediatric neuro-oncology clinic, where available. Surveillance spine imaging with MR every 3 months for the first 2 years, followed by annual or semiannual imaging thereafter is recommended. If new symptoms develop, imaging should be done as soon as possible. For neuroblastoma, urinary levels of homovanillic or vanillylmandelic acid can be markers of recurrence.

Future Perspectives

Genetic markers for certain tumors such as n-myc amplification and TrkA expression in neuroblastoma and t(11,22)(q24;q12) translocation in Ewing's sarcoma are becoming increasingly important in tailoring therapy and determining prognosis. As the molecular and genetic basis for these tumors becomes better understood, individualized therapy may lower the incidence of treatment-related morbidity and increase the likelihood of tumor control and overall survival. Ongoing collaboration through the Children's Oncology Group, the International Society of Pediatric Oncology, and similar groups remains essential.

References

1. DeSousa AL, et al. Intraspinal tumors in children. A review of 81 cases. J Neurosurg 1979;51(4):437–45
2. Schick U, Marquardt G. Pediatric spinal tumors. Pediatr Neurosurg 2001;35(3):120–7
3. Klein SL, Sanford RA, Muhlbauer MS. Pediatric spinal epidural metastases. J Neurosurg 1991;74(1):70–5
4. Raffel C. Spinal cord compression by epidural tumors in childhood. Neurosurg Clin N Am 1992;3(4):925–30
5. Gelabert-Gonzalez M, Agulleiro-Diaz J, Reyes-Santias RM. Spinal extradural angiolipoma, with a literature review. Childs Nerv Syst 2002;18(12):725–8
6. Jallo J, et al. Chordoma: a case report. Surg Neurol 1997;48(1):46–8
7. Di Rocco C, Iannelli A, Colosimo Jr C. Spinal epidural meningiomas in childhood: a case report. J Neurosurg Sci 1994;38(4):251–4
8. Pollono D, et al. Spinal cord compression: a review of 70 pediatric patients. Pediatr Hematol Oncol 2003;20(6):457–66
9. Ch'ien LT, et al. Metastatic epidural tumors in children. Med Pediatr Oncol 1982;10(5):455–62
10. Raffel C, et al. Treatment of spinal cord compression by epidural malignancy in childhood. Neurosurgery 1991;28(3):349–52
11. Pirson AS, KB, Tuerlinckx D, Lacrosse M, Luyx D, Borght TV. Additional value of I-123 MIBG SPECT in neuroblastoma. Clin Nucl Med 2005;30(2):100–101
12. Hussain HK, KJ, Domizio P, Norton AJ, Reznek RH. Imaging-guided core biopsy for the diagnosis of malignant tumors in pediatric patients. Am J Roentgenol 2001;176(1):43–7
13. Henry MC, Tashjian DB, Breuer CK. Neuroblastoma update. Curr Opin Oncol 2005;17(1):19–23
14. Hayes FA, TE, Hvizdala E, O'Connor D, Green AA. Chemotherapy as an alternative to laminectomy and radiation in the management of epidural tumor. J Pediatr 1984;104(2):221–4
15. Sandberg DI, et al. Treatment of spinal involvement in neuroblastoma patients. Pediatr Neurosurg 2003;39(6):291–8
16. Katzenstein HM, et al. Treatment and outcome of 83 children with intraspinal neuroblastoma: the Pediatric Oncology Group experience. J Clin Oncol 2001;19(4):1047–55
17. Kehrli P, BR, Maitrot D. Open-door laminoplasty in pediatric spinal neurosurgery. Childs Nerv Syst 1996;12(9):551–2

18. Marec-Berard P, Philip T. Ewing sarcoma: the pediatrician's point of view. Pediatr Blood Cancer 2004;42(5):477–80
19. Kushner BH, KK, LaQuaglia MP, Modak S, Cheung NK. Neuroblastoma in adolescents and adults: the Memorial Sloan-Kettering experience. Med Pediatr Oncol 2003;41(6): 508–15
20. Van Winkle P, AA, Krailo M, Cheung YK, Anderson B, Davenport V, Reaman G, Cairo MS. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer 2005;44(4):338–47
21. Ozaki T, FS, Liljenqvist U, Hillmann A, Delling G, Salzer-Kuntschik M, Jurgens H, et al. Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. Cancer 2002;94(4):1069–77
22. De Bernardi B, et al. Neuroblastoma with symptomatic spinal cord compression at diagnosis: treatment and results with 76 cases. J Clin Oncol 2001;19(1):183–90
23. Noll RB GM, Vannatta K, Correll J, Bukowski WM, Davies WH. Social, emotional, and behavioral functioning of children with cancer. Pediatrics 1999;103(1):71–8

Spinal Column Tumors 49

William E. Whitehead, Anna Illner

Introduction – 584

Epidemiology – 584

Symptoms and Clinical Signs – 584

Diagnostics – 584

Staging, Classification, and Terminology – 585
Oncologic Staging
Benign Tumors
Malignant Tumors
Surgical Staging
Terminology

Benign Tumors – 586
Osteoid Osteoma
Osteoblastoma
Giant Cell Tumor
Aneurysmal Bone Cyst
Eosinophilic Granuloma

Malignant Tumors – 592
Ewing's Sarcoma
Osteogenic Sarcoma
Metastatic Tumors

Future Perspectives – 594

References – 594

Introduction

Spinal column tumors in the maturing spine are rare and diverse lesions. Most present with pain with or without neurologic deficit. When evaluating a child with persistent back pain, tumor should be considered in the differential diagnosis and investigated. When identified, common goals of treatment are removal of the lesion, preservation of neurologic function, and maintenance of spinal column stability.

Within this chapter, the most common tumor and tumor-like pathologies of the pediatric spine are reviewed (Table 1). Most of the information on treatment and management of these lesions comes from case reports and case series data; there are no well-designed prospective trials evaluating treatment options for these rare lesions.

Epidemiology

Tumors of the spinal column in children are uncommon. The incidence of spinal column tumors in major reported series of childhood spinal lesions ranges from 4% to 15% [1–8]. Age, sex, location in the spinal column (cervical, thoracic, lumbar, sacral), location within the vertebrae (posterior elements, vertebral body), and other epidemiological data vary with specific tumor type, and are useful in narrowing the differential diagnosis for a lesion. Tumors of the spinal column can occur throughout the spinal column from atlas to coccyx, and many of the pathologic processes common in the pediatric population can occur in adulthood.

Table 1 Common pediatric spinal column tumors

Benign	Osteoid osteoma
	Osteoblastoma
	Giant cell tumor
	Aneurysmal bone cyst
	Eosinophilic granuloma
Malignant	Osteosarcoma
	Ewing's sarcoma
Metastatic	Rhabdomyosarcoma
	Neuroblastoma
	Retinoblastoma
	Wilms' tumor
	Teratoma-teratocarcinoma
	Leukemia
	Ewing's sarcoma

Symptoms and Clinical Signs

Regardless of pathology, the most common presenting symptom of spinal column tumors is pain. Pain is usually at the site of the lesion, but may be radicular. Pain tends to be progressive and unrelenting. Usually it is not associated closely with activity. Pain associated with rest or sleep should increase the suspicion for underlying tumor. Tumors produce pain through local mass effect on or invasion of surrounding structures, expansion of the cortex of the vertebral body, pathologic fracture, compression of the nerve roots, and spinal deformity. In the small child pain is not always expressed verbally and can be manifested only as a change in personality, lethargy, instability, fever, limping, or bruising.

The duration of symptoms for benign lesions is typically several months to years before diagnosis. In a review of osteoid osteomas and osteoblastomas of the spine, the average duration of symptoms prior to diagnosis was 8.6 months for patients evaluated between 1990 and 1999 [9]. Malignant lesions typically present with a shorter duration of symptoms.

Neurologic deficits are not always present and are more common with aggressive or malignant disease. The severity of neurologic deficit ranges from mild radicular pain to complete loss of motor and sensory function including loss of bowel and bladder control. In patients with large lesions with posterior extension, a palpable back mass can be detected.

Diagnostics

Plain films of the spinal column are initial steps in the diagnostic work-up of back pain in a child. Flexion and extension views can be added to assess spinal stability as well as oblique views to improve visualization of the posterior elements. If a lesion is seen, imaging characteristics can help narrow the differential diagnosis and direct further diagnostic imaging to the involved site.

If no abnormalities are found on plain films, bone scintigraphy is obtained to exclude lesions which are too small or too subtle to be seen. When an abnormality is identified, cross-sectional imaging is obtained to further characterize the abnormality.

CT and MRI are valuable imaging techniques for narrowing the differential diagnosis and treatment planning. CT is superior for defining bony anatomy, and MR more precisely defines soft tissues and the relationship of the tumor to neural and vascular structures. With MRI and CT the location, size, invasiveness, vascularity, and tumor origin are defined. With this information the differential diagnosis is

narrowed, the lesion is staged, and plans for biopsy or resection are made.

Staging, Classification, and Terminology

A common system for the classification and staging of spinal column tumors has not been applied throughout the literature. As a result it is difficult to evaluate results, make comparisons across institutions, and apply information to individual patients. The oncologic staging system proposed by Enneking [10] for primary bone tumors has been applied to spinal column tumors in several recent reports [11–14].

Oncologic Staging

The Enneking system for classification is a system based on clinical features, radiographic pattern, and histologic findings [10]. Tumors are classified as benign or malignant.

Benign Tumors

Benign tumors are classified into three stages, S1, S2, and S3. S1 tumors are latent inactive tumors. They are asymptomatic lesions, bordered by a true capsule. These tumors do not grow or grow very slowly. No therapy is required unless palliative surgery is needed to decompress neural elements or stabilize the spine.

S2 tumors are active tumors. They grow slowly and cause mild symptoms. S2 tumors are bordered by a thin capsule and by a layer of reactive tissue. This is sometimes seen on plain X-rays as an enlargement of the tumor outline.

S3 tumors are aggressive. They are rapidly growing with a thin, often discontinuous capsule on imaging. These tumors invade neighboring compartments.

Malignant Tumors

Malignant tumors are divided into stages I, II, and III. Stage I lesions are low-grade malignant tumors. IA tumors are contained within the vertebra; IB tumors invade paravertebral compartments. There is no true capsule, but there can be a pseudocapsule of reactive tissue.

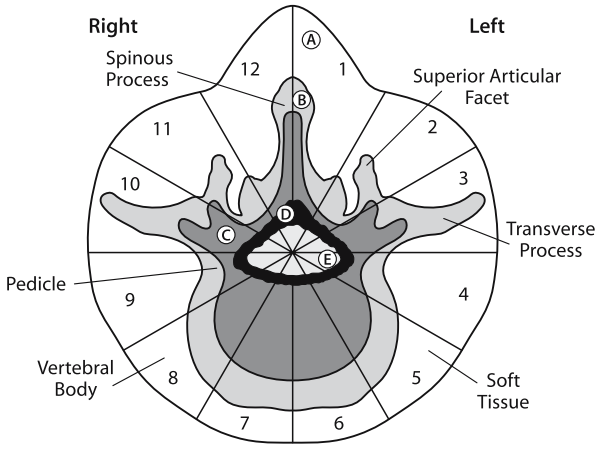
Stage II lesions are high grade. IIA tumors are contained within the vertebra; IIB tumors invade paravertebral compartments. There is no true capsule and no pseudocapsule of reactive tissue because growth is rapid. Satellite lesions around the border of the tumor can exist. On plain films these lesions are radiolucent and destructive; pathologic fractures are common.

Stage IIIA and IIIB describe the same lesions as IIA and IIB but with distant spread.

Surgical Staging

A staging system for surgical purposes has been created and applied to spinal column tumors. This system, the WBB (Weinstein-Boriani-Biagini), describes the anatomical extent of a lesion [12]. The system identifies the location and extensiveness of a lesion in a systematic fashion. It can be used to guide the surgeon in choosing a surgical approach for resection or biopsy.

The system is diagramed in Figure 1. On the transverse plane, the vertebra is divided into 12 radiating zones (1–12 clockwise) and into 5 layers (A to E from extravertebral to dural involvement).



A Extraosseous Soft Tissues
B Intraosseous (Superficial)
C Intraosseous (Deep)
D Extraosseous (Extradural)
E Extraosseous (Intradural)

M Metastasis

Fig. 1 WBB Surgical staging system for spinal column tumors. Numbered areas are arranged clockwise around the spinal canal. Letters indicate tissues involved

Terminology

Currently, there is a need to share a common terminology in reports on spinal column tumors when describing tumors and operations to remove them. The following definitions of terms to describe surgical interventions for spinal column tumors have been proposed [15].

Excision is a piecemeal removal of a tumor (curettage). This is an intralesional procedure.

Resection is an attempt to remove the tumor en bloc. The attempt should be confirmed by the pathologist through evaluation of the surgical margins. Based on the surgical margins, the pathologist should classify the resection as intralesional, marginal, or wide [11, 14, 16].

Radical resection is the en bloc removal of the tumor together with the complete compartment of origin. This is not possible in the spinal column without taking spinal cord and nerve roots.

Palliative procedures are all surgical procedures that are directed at a functional response (e.g., cord decompression and fracture stabilization) with or without partial removal of the tumor. Palliative procedures are done to make a diagnosis, decrease pain, and improve function.

Benign Tumors

Osteoid Osteoma

Osteoid osteoma is a benign, bone-forming tumor characterized by a nidus of bone surrounded by fibro-vascular tissue and a dense sclerotic margin of reactive bone. Histologically, it is almost identical to osteoblastoma and because of the similarity many use size (less than 1–2 cm) to distinguish the two [17–21]; however, radiology and natural history are also useful in separating the two pathologies.

Epidemiology – Osteoid osteomas occur in bones throughout the body and account for approximately 11% of all primary bone tumors; 10% of osteoid osteomas occur in the spinal column [17, 18, 20, 22]. They more commonly occur in the posterior elements (90%) than the vertebral body (10%) [9, 21, 23]. The most common location in the spinal column is the thoracic and lumbar spine followed by the cervical and sacral spine [21, 24]. They are most prevalent in ages 5–20 years, but they have been reported in patients ranging from 8 months to 72 years old [25, 26]. Of the benign spinal column tumors in the pediatric population, they are one of the most common.

Symptoms and Clinical Signs – The most common symptom at presentation is pain. It usually emanates from the site of the lesion. The pain is often constant, progressive, more noticeable at night, and classically is relieved with salicylates or nonsteroidal anti-inflammatory drugs, but this is not true in all cases (in some series only 30%–40% of patients gain significant relief) [20]. Approximately 5%–25% of patients will present with radicular symptoms [27]. It is the most common cause of painful scoliosis in adolescents [28]. The interval between symptom onset and diagnosis is frequently delayed several months to years, but this interval has been significantly decreased with the use of bone scintigraphy.

Diagnostics – Many osteoid osteomas are visible on plain radiographs as a radiolucent lesion with or without a calcified center and surrounded by a sclerotic margin of reactive bone. The lesion can be difficult to see within the posterior elements of the spine because of the complexity of the bony anatomy. They can also be difficult to visualize when there is a low level of calcification and reactive sclerosis. The most sensitive test for detection of these lesions is bone scintigraphy (Fig. 2 A); a negative bone scan in a patient with osteoid osteoma is almost unheard of and should be reported. Once the lesion is identified on bone scan, a CT scan best defines the extent of the lesion (Fig. 2B).

Treatment – Most reported osteoid osteomas of the spine have been treated with surgical excision. Complete surgical excision of the nidus results in relief of pain almost immediately in all patients. The surrounding reactive bone does not require resection and resolves with time. The difficulty with surgical excision can be accurate intraoperative localization of the nidus. A variety of techniques have been utilized intraoperatively to ensure complete resection – intraoperative bone scintigraphy, CT guided resection, tetracycline localization, and minimally invasive endoscopy [29, 30, 31, 35]. Spinal stability is a consideration with every resection and the indication for fusion is dictated by the location of the lesion and the extent of resection.

Persistent pain or recurrent pain is an indication of recurrence or incomplete resection and should prompt reimaging. In most cases scoliosis will resolve or improve after resection of the lesion. Case series data suggest that patients with a shorter duration of symptoms prior to treatment have a higher rate of improvement of their curve after treatment, but success is difficult to predict and patients should be closely followed until spinal maturity. Some curves do not improve after resection and require correction [9, 22, 25, 28, 32, 33].

Photocoagulation and radiofrequency ablation are minimally invasive techniques used to heat the nidus of the lesion and destroy the tumor cells. The

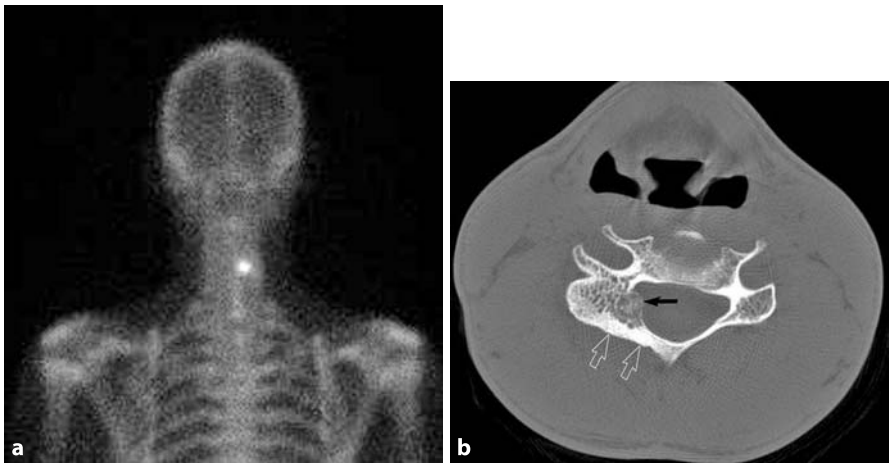


Fig. 2 Osteoid osteoma. Bone scintigraphy, (**a**) shows increased uptake in the midcervical spine. Axial CT, (**b**), demonstrates a small lucent lesion with a calcified central nidus (*arrow*) in the right neural arch. There is sclerosis of the surrounding bone (*open arrows*). Axial T1 W fat-saturated MRI with contrast, (**c**), demonstrates enhancement within the lesion and surrounding soft tissue

technique involves biopsy of the nidus followed by insertion of a probe into the lesion to deliver heat. It has been used extensively in osteoid osteomas outside of the spinal column but there is reluctance to use it in lesions located within 1 cm of neural tissue. There are a few reported cases of treatment of spinal column osteoid osteomas using this method. The reports have been successful [25, 34, 35]. Resection of bone is minimal and recovery time is shortened; long-term follow-up is necessary. No controlled trials comparing these two treatments exist.

Medical management of these lesions is a treatment option [25, 36]. This can be as effective as surgery without the morbidity in patients with pain and should be considered for patients in whom operative therapy would be complex and may lead to disability. Pain treated with NSAIDs has been reported to resolve in 30–40 months [36]. No reports of malignant transformation exist. Precautions must be taken with skeletally immature patients because this treatment strategy may have no effect on the development of scoliosis.

Prognosis/Quality of Life – Osteoid osteoma is a benign lesion with limited growth. No cases of malignant transformation have been reported. Mortality from this lesion is negligible, but quality of life can be severely affected by pain.

Follow-up/Specific Problems and Measures – After resection, pediatric patients with osteoid osteomas should be followed until they reach spinal maturity.

Osteoblastoma

Epidemiology – Osteoblastoma is a rare bone-producing tumor which accounts for less than 1% of all primary bone tumors [45, 51, 55]. Although they occur in any bone, they have a predilection for the spinal column; large case series report 30%–40% occur in this location [17,40]. Over 95% of spinal column osteoblastoma will involve the posterior elements. If a spinal column lesion primarily involves the vertebral body, it is unlikely to be osteoblastoma. Their distribution throughout the cervical, thoracic, lumbar, and sacral spine is roughly even [17, 22, 40, 41]. Most cases present in the second and third decade, but the lesion has been reported in a 6-month-old and a 75-year-old individual [42].

Symptoms and Signs – The most common symptom of spinal column osteoblastoma is pain [19, 24, 26, 40, 41, 43–46]. In general it is a dull progressive pain at the site of the lesion; it is not always nocturnal and not always relieved by salicylates or nonsteroidal anti-inflammatory drugs. The lesion may produce radicular symptoms and rarely myelopathy [20, 47, 48]. It can be responsible for acute paraplegia with loss of bowel and bladder control. Osteoblastoma is also a common cause of painful scoliosis and torticollis [17, 33, 49]. A palpable mass along the spinal column is sometimes found.

Diagnostic Tests – The most sensitive test for osteoblastoma is bone scintigraphy [17, 22, 26, 46]. An osteoblastoma of the spine with a negative bone scan should be reported. Many, but not all osteoblastoma

of the spine will be visible on plain radiographs. The typical appearance is that of a lytic lesion, with or without matrix calcification, surrounded by a narrow or broad zone of sclerosis or, if expansive, a thin bony shell [20, 24, 40]. A sclerotic rim is not always present. Older lesions tend to be more calcified [26]. Most lesions are between 1 and 8 cm but larger masses have been reported [45]. Osteoblastomas tend to form soft tissue masses which helps distinguish them from osteoid osteomas. The CT scan is very useful for defining the extent of the lesion for surgical planning. MR does not narrow the differential diagnosis but will show surrounding marrow and soft tissue edema as well as the lesion's relationship to critical neural and vascular structures [41]. The lesion usually will enhance (Fig. 3).

Staging and Classification – Most osteoblastomas are classified as benign, but an aggressive osteoblastoma has been described [19, 26, 48, 50]. Aggressive osteoblastomas have characteristics intermediate between osteosarcoma and osteoblastoma. This group is defined histologically and clinically. Clinically, the tumor does not metastasize but commonly recurs after treatment. The histological characteristics include epitheloid osteoblasts, stromal mitoses, areas of increased cellularity, and disordered matrix production; the group is distinguished from osteosarcoma by a relatively low mitotic rate and a lack of atypical mitoses and cartilaginous matrix often seen in osteosarcoma.

Treatment – Most reported cases of osteoblastoma in the spinal column are treated primarily by surgical removal [20, 22, 33, 40, 43, 51]. Complete resection is associated with the best clinical outcomes; however, total removal is not always possible due to hemorrhage and proximity of the lesion to critical vascular and neurologic structures [19, 51]. Multiple procedures from various approaches may be required to achieve marginal or wide resection [39, 47, 48, 52, 53]. If feasible, preoperative embolization should be considered to minimize the risk of hemorrhage during resection [26, 54].

In most series recurrence rates are 10%–15% after resection of nonaggressive lesions, but recurrence is higher after partial resection and after resection of aggressive lesions [40]. Radiation therapy and/or chemotherapy have been employed with some success for inoperable lesions and recurrent lesions [39, 38, 55]. Results of radiation therapy as the primary therapy after biopsy are limited and not encouraging [11].

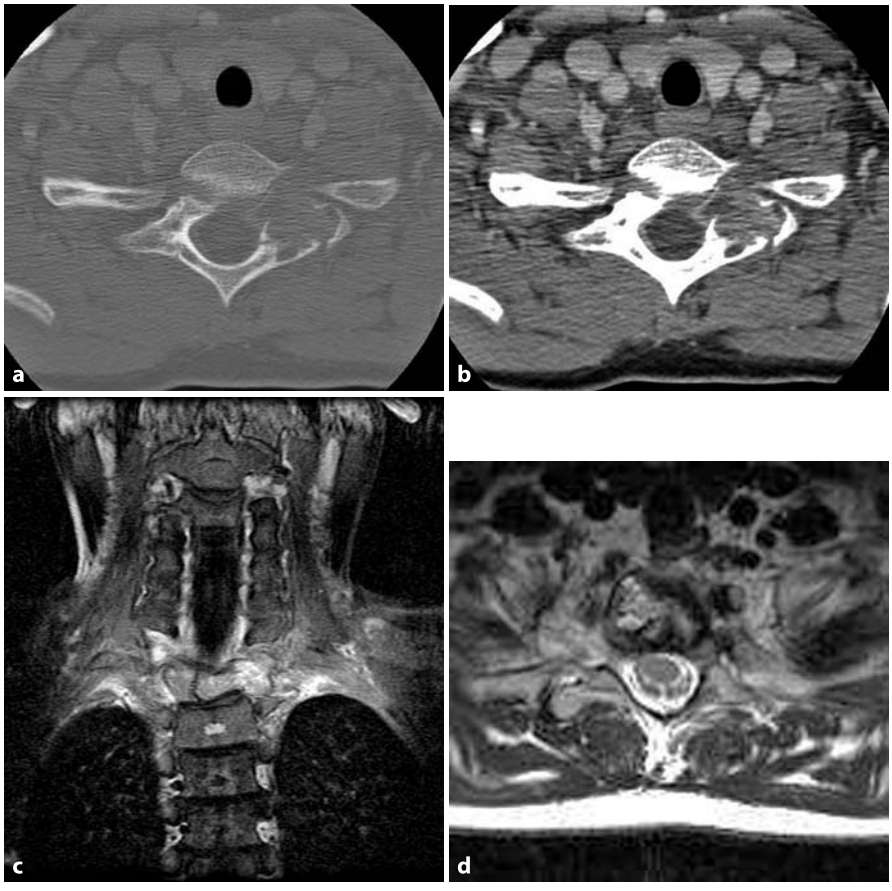


Fig. 3 Osteoblastoma. Axial CT in bone and soft tissue algorithm with contrast, (**a, b**), shows an expansile, lucent, enhancing lesion in the neural arch. There is no significant soft tissue component. Coronal T1 W fat-saturated MRI, (**c**), with contrast shows extension of the mass into the vertebral body. The lesion is heterogeneous and hyperintense on T2 W MRI, (**d**). (Courtesy of M. Shroff, MD)

Prognosis/Quality of Life – In the absence of recurrence, long-term survival after treatment is excellent [11, 57, 58]. Malignant transformation of osteoblastoma to osteosarcoma has been reported; many believe that misdiagnosis of osteoblastoma is responsible for most of these cases. It is difficult to be accurate because the pathologic appearance of these two lesions can be so similar [40, 43].

Follow-up and Specific Measures and Problems – Recurrence has been reported as late as 7 years after resection [56]. Long-term follow-up is necessary.

Giant Cell Tumors

Giant cell tumors are rare, but can occur throughout the body; approximately 5%–10% will occur in the vertebral body of the spine [42, 60, 61]. They are composed of osteoclastic giant cells with a spindle cell stroma. The vast majority of giant cell tumors are benign; however, 5%–10% are malignant and seen histologically as sarcomatous stroma.

Epidemiology – Most patients affected are in the third to fourth decade of life at diagnosis, but they can present in the second decade [24, 42]. There is a slight predilection for females [42]. The age range of reported cases is 11 to 69 years [62]. Giant cell tumors occur throughout the spine [61, 62–66]; The vast majority occur in the sacrum, followed by the cervical, thoracic, and lumbar segments [24]. They tend to occur in the vertebral body of the vertebra, but can be located in the posterior elements [42]. They range in size from 2 to 20 cm at the time of presentation [62].

Symptoms and Clinical Signs – The most common presenting symptoms are pain and neurologic deficit [24, 65]. There are reports of patients presenting with rapid onset of tetraplegia from cervical lesions [63]. A dramatic increase in size can occur after pregnancy due to hormonal stimulation.

Diagnostics – The appearance on plain film is typically of an expansile lesion with bone lysis, and no mineralization of the matrix. Lesions can cross the intervertebral disk space and the sacroiliac joint; they can produce vertebral body collapse. Bone scans typically will show increased uptake at the site of the lesion [42], but negative bone scans have been reported [67]. CT is valuable for precisely defining the extent of the tumor for therapy and follow-up. CT generally shows a lesion with soft tissue density and well-defined margins (Fig. 4). MR typically shows a lesion with heterogeneous signal intensity on all sequences. Generally, the tumor has low to intermediate signal intensity on T1- and T2-weighted images; low signal on T2 can be helpful in making the correct diagnosis [42]. The lesion can also contain fluid–fluid levels as seen in aneurysmal bone cysts and a low signal pseudo-capsule is a common finding [42].

Treatment – Adequate therapy for giant cell tumors of the spine is controversial and although various treatment options have been reported including surgical resection [58, 64], radical surgery (total spondylectomy or total sacrectomy with reconstruction) [68,69], primary radiation therapy [70, 71], surgical resection followed by radiation therapy [42, 63, 70–72], primary embolization [73], preoperative embolization followed by surgical resection [42, 66, 74], cryosurgery [75], and phenolization [76], no clinical trials have been done to compare these treatments. All information on treatment comes from case reports and case series. Complete surgical resection is the therapy recommended most in the literature [58, 61, 64, 66, 72]; however, size and location often limit the effectiveness of this approach. Giant cell tumors that cannot be completely resected are often treat-

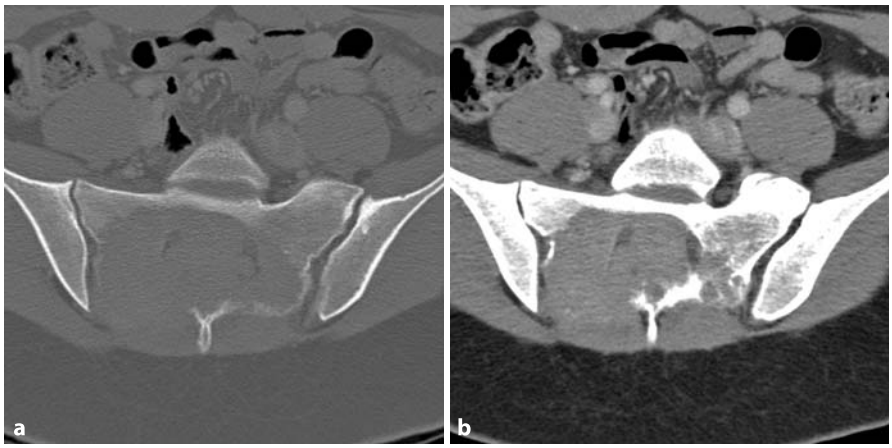


Fig. 4 Giant cell tumor. Axial CT in bone, (**a**), and soft tissue, (**b**), algorithm demonstrates a large lytic lesion involving the sacrum. Within the spinal column, the sacrum is the most common location for a giant cell tumor

ed with a combination of partial resection and radiation therapy [70, 71]. Selective arterial embolization has been employed prior to surgery to minimize bleeding [42, 73, 74].

Prognosis/Quality of Life – Prognosis is not as favorable compared to other benign lesions of the spine; recurrences are as high as 40%–60% and are seen radiographically as areas of new bone destruction [42].

Follow-up and Specific Measures and Problems – Because of the high recurrence rate, careful and long-term follow-up is necessary in patients with this tumor.

Aneurysmal Bone Cysts

An aneurysmal bone cyst is a benign, highly vascular lesion of the bone. It often consists of a soft tissue component and larger multiloculated blood-filled cystic component. The cystic component is not lined by epithelium so it is not a true vascular channel. Etiology of these lesions is unknown, but because of their association with trauma and other spinal neoplasms (especially giant cell tumors), they are believed to be due to local circulatory disturbances [42, 77].

Epidemiology – Aneurysmal bone cysts are uncommon lesions that occur primarily in the second decade of life, but occur in all ages. They have been reported throughout the body, but occur in the spinal column in 10%–30% of cases [24, 42, 78–81]. The most common location is the thoracic spine, followed by the lumbar, cervical, and sacral [24]. Almost all occur in the posterior elements, but extension into the vertebral body and adjacent spinal levels does occur [24]. In approximately one third of cases aneurysmal bone cysts occur with another tumor; most commonly a giant cell tumor, but they have been reported with fibrous dysplasia, fibroxanthoma (non-ossifying fibroma), chondromyxoid fibroma, solitary bone cyst, fibrous histiocytoma, eosinophilic granuloma, and even osteosarcoma [77, 82, 83].

Symptoms and Clinical Signs – The most common presenting signs and symptoms are pain, paraspinal mass, and neurologic deficit. Scoliosis is uncommon, but can occur. The onset of neurologic deficit can be sudden and complete [84, 85].

Diagnostics – Plain films usually show an expansile, osteolytic cavity with a "blown out" or "ballooned" bony contour; vertebra plana has also been reported for this lesion [86]. CT is excellent for defining bone involvement and usually reveals a thin bony shell completely around the lesion. The multiplanar images of MR are best at defining the relationship of the lesion to neural structures. Both MR and CT will show fluid–fluid levels within the cystic spaces of these lesions; while these are highly characteristic, they are not pathognomonic of the lesion and have also been reported in other tumors of the spinal column (Fig. 5) [24, 42].

Treatment – Because aneurysmal bone cysts respond to a variety of treatments, management varies. Treatment options are surgical excision, selective arterial embolization as an adjunct to surgical excision or as a primary therapy, radiation therapy as an adjunct to surgery or as a primary treatment, and injection of materials into the aneurysmal bone cyst to induce ossification of the lesion. Outcomes of reported cases are generally good even with a recurrence.

Surgical excision is a well-established treatment option, and is the only option in patients who require immediate decompression of neural elements. When considering surgery, the goals of the operation should be decompression of neural elements, complete excision of the lesion (especially the cyst wall lining) to avoid recurrence, and the maintenance of spinal stability. Surgical excision can be limited based on the proximity of the lesion to critical neural and vascular structures, the overall medical condition of the patient, and by the risk of intraoperative bleeding. Multiple approaches may be required for complete excision [80, 83, 87, 88]. Resection frequently leads to spinal instability and requires instrumentation and fusion [89, 90]. The recurrence rate after excision is approximately 10% [80, 84]. Most, if not all, recurrences occur after incomplete resection; however, not all incomplete resections lead to recurrence [78, 87, 91]. Some lesions will go on to ossify and resolve after partial excision. Most recurrences are within 6 months of treatment but recurrences have been reported as late as 2 years after therapy [78, 84]. Reported complications from surgical excision are death from hemorrhage, weakness from postoperative epidural hematoma, dural rents, and wound infection [84].

Selective embolization of feeding arteries to the lesion can be used preoperatively to minimize bleeding [92] or as a primary therapy for lesions that are difficult to approach surgically, for recurrent lesions, or for patients who do not want surgery [84, 92–98]. Embolization is not indicated as a primary therapy in patients who have symptomatic spinal cord compression. In approximately 25% of cases embolization is not possible due to a common vascular supply to the aneurysmal bone cyst and spinal cord or because of lack of a clearly identifiable feeding artery. Marked venous drainage has also been sited as a con-

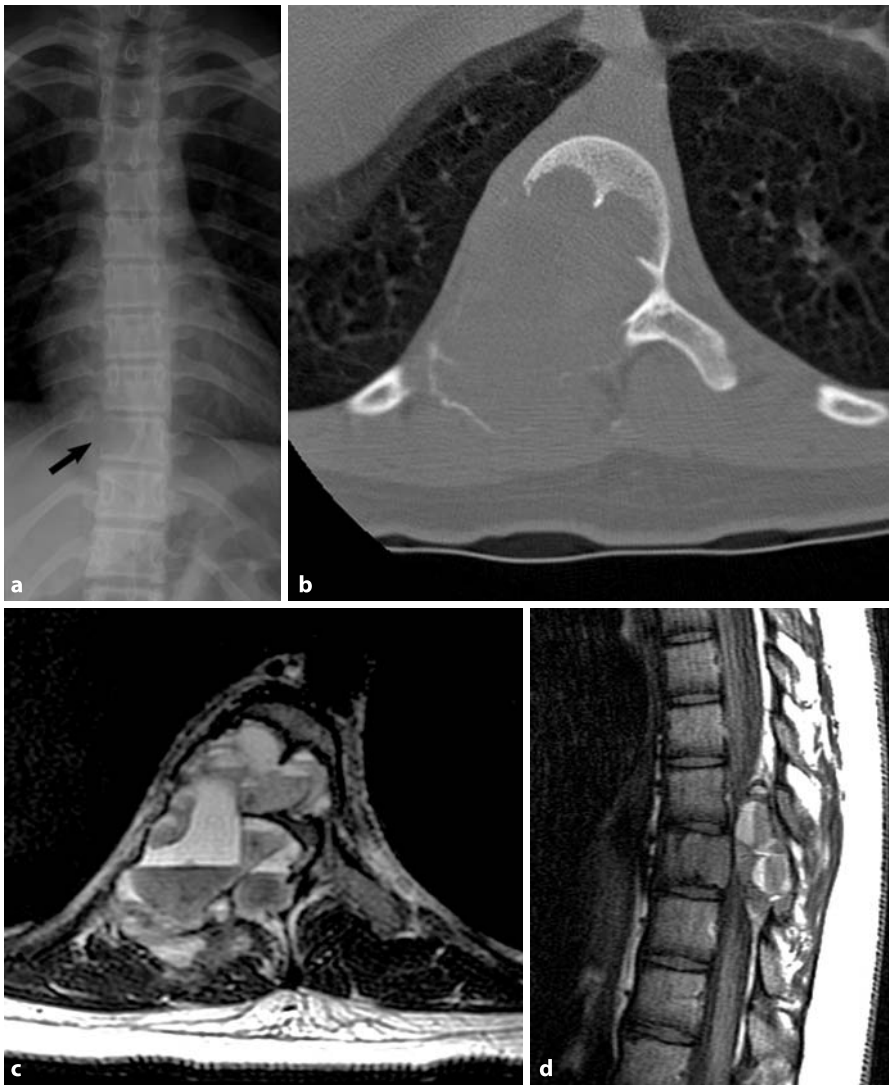


Fig. 5 Aneurysmal bone cyst. Plain film, (**a**), demonstrates loss of the right T9 pedicle (*arrow*). Axial CT, (**b**), shows a well-defined, lucent, expansile lesion centered in the right neural arch. The cortex is markedly thinned in several locations. Axial T2 W MRI, (**c**), and sagittal T1 W MRI, (**d**) show that the lesion is comprised of multiple locules containing hemorrhage levels, a classic feature of aneurysmal bone cyst. Note severe compression of the spinal cord

traindication for the procedure due to the risk of pulmonary infarction [97]. Many cases will require multiple embolizations for complete treatment [93, 95, 97]. After embolization, remission of pain can take days to weeks to occur. The lesion should go on to ossify within 1 year of treatment. Successful treatment has been defined as the resolution of symptoms with or without ossification of the lesion [93]. Long-term follow-up of cases treated with embolization is necessary; changes in the lesion after ossification have been reported as many as 4 years after treatment [98]. Embolization is effective with a comparable recurrence rate to surgery; recurrence rates of 10%–25% have been reported [78]. Because of the success of embolization, many are using it as the first-line therapy in patients without symptomatic spinal cord compression.

Radiation therapy is also an effective means of control for aneurysmal bone cysts. Modern doses of 26–30 Gy have been used successfully as either primary therapy, adjuvant therapy after incomplete resection, or treatment for recurrent disease [78, 82]. Patients should experience relief of symptoms within 2 weeks of completion of therapy [82]. Control rates of 75%–92% have been reported [99–105]. Radiation therapy is associated with delayed spinal instability and radiation-induced malignancy [78, 84]. Concerns over these complications have limited the use of this modality; however, the use of lower doses and improved delivery techniques have reduced the risk of these serious complications [82]. The recurrence rate after radiation therapy as primary therapy for aneurysmal bone cysts ranges from 14% to 50%; as an adjuvant therapy or for the treatment of recurrent disease the success rate is higher [78, 106, 107].

There are limited numbers of successful reports on the use of injectable agents into an aneurysmal bone cyst to induce healing. Agents such as deminer-

alized bone particles, calcitonin, methylprednisolone, and radioactive P32 have been used [108–111]. While these therapies have been successful, more data is needed before they can be recommended.

Follow-up/Specific Problems and Measures – Most recurrences occur within 6 months of treatment. Spinal instability after treatment can take 5 years to occur, thus, long-term follow-up is necessary [78]. Pediatric patients should be followed until spinal maturity.

Eosinophilic Granuloma

Eosinophilic granuloma describes the most benign form of Langerhans cell histiocytosis. It is the result of the pathologic proliferation of histiocytes within the bone associated with a mixed inflammatory infiltrate in which eosinophils are prominent. It may represent a disorder of the immune response rather than a true neoplasm, but clonality has been reported, and with it, the suggestion that the process is neoplastic [112].

Epidemiology – Eosinophilic granuloma presents primarily in the first or second decade of life, but lesions have been reported in patients up to 69 years of age [113]. They more commonly occur in the skull, femur, ribs, and pelvis; however, approximately 8% of cases will occur in the spine [114, 115]. Most spinal lesions involve the vertebral body and not the posterior elements.

Symptoms and Clinical Signs – Like most benign lesions of the spinal column, the most common presenting symptom is pain, focal or radicular. Very rarely patients will present with sensory change and weakness due to vertebral body collapse and neural compression [116, 117]. Solitary lesions are most common, but multiple lesions can occur.

Diagnostics – Radiography will show a lytic lesion of the bone. In approximately 40% of cases vertebra plana will be present [130]. MR will show mild T2 prolongation and enhancement of the involved vertebral body and any accompanying prevertebral or epidural mass (Fig. 6) [118].

Treatment – Management of eosinophilic granuloma of the spine should begin, if feasible, with needle biopsy to confirm the diagnosis. Surgery is indicated when biopsy results are nondiagnostic or when there is neurologic deficit from compression or spinal instability. In patients with single spinal lesions without neurologic deficit, management can be conservative with bracing and rest. The lesions are often self limiting and the vertebral body will frequently repair and reconstitute itself over time [115]. In cases were symptoms are severe, progressive, or in disseminated disease, radiation therapy or chemotherapy are indicated [119–121].

Fig. 6 Langerhans cell histiocytosis. Coronal, T1 W fat-saturated MRI with contrast demonstrates classic vertebra plana with enhancement of the collapsed vertebral body and a small paraspinous soft tissue component. Note the normal appearance of the adjacent discs. (Courtesy S. Blaser, MD)

Prognosis/Quality of Life – Outcomes generally are very good without persistent deficits or pain; recurrence is very rare.

Follow-up and Specific Measures and Problems – Close clinical follow-up is warranted to follow the remodeling process of the vertebral body, which can take up to a year to occur.

Malignant Tumors

Ewing's Sarcoma

Epidemiology – This is the most common malignant bone tumor in children age 5–15 years. Less than 10% of Ewing's sarcoma will originate in the vertebral column [42]. Of these, most will occur in the sacrum, but they can occur throughout the spinal column [122].

Symptoms and Clinical Signs – The most common presentation is pain. Acute onset of radiculopathy and/or myelopathy can occur in approximately 25% of cases [122, 123]. A palpable mass along the spinal column is frequently present.

Diagnostics – The classic presentation is that of a lytic lesion which often invades the surrounding soft tissue [24]. An associated soft tissue mass is common. Lesions can have areas of sclerosis and occasionally they are predominantly sclerotic. Complete collapse of the vertebral body, vertebra plana, can be seen (Fig. 7) [124].

Treatment – The mainstay of treatment is combination chemotherapy and local radiation. Surgery is indicated for tissue diagnosis, decompression of neural elements, and spinal instability [123, 125]. En bloc resection of the entire mass with margins is seldom feasible, but when possible the surgical literature suggests a fivefold decrease in the risk of local recurrence and an overall improvement in survival [126]. Metastasis can occur.

Prognosis/Quality of Life – Long-term survival is poor, but has markedly improved with advances in combination chemotherapy and radiation therapy. Five-year survival ranges from 33% to 60% [123, 127–129]. Sacral lesions tend to have a poor prognosis probably because they are able to achieve a larger size prior to presentation.

Osteogenic Sarcoma

Epidemiology – Osteogenic sarcoma is the most common primary malignant tumor of bone with the exception of myeloma [15]. Patients with spinal column lesions more commonly are older (fourth decade of life), but the lesion can occur in the pediatric population [24]. Osteosarcoma of the spine is very rare, accounting for less than 3% of all osteosarcoma cases [24, 130]. When it does occur in the spine, it is frequently seen in vertebrae previously affected by Paget's disease or radiation therapy [24, 40]. Approximately 90% arise in the vertebral body. Extension of the lesion into the posterior elements is common, but a primary posterior elements lesion is uncommon (occurs in 10% of cases) [24, 40]. The lesion can be polyostotic.

Fig. 7 Ewing's sarcoma. Sagittal T2 W MRI (**a**), and T1 W fat-saturated MRI with contrast (**b**), demonstrate an enhancing lesion involving the bony spinal canal extending into the prevertebral and epidural space. Note early vertebra plana deformity. Axial T1 W fat-saturated MRI with contrast, (**c**), demonstrates the extent of soft tissue involvement and spinal cord compression

Symptoms and Clinical Signs – The most common presenting signs and symptoms are pain, neurologic deficit, and palpable spinal mass. Neurologic deficit occurs in approximately two thirds of cases [131].

Diagnostics – The radiographic appearance of these lesions is variable. On plain films the lesion may be predominantly sclerotic, but most frequently has a mixed sclerotic and lytic appearance [24]. Loss of vertebral height and sparing of the adjacent disks are common; purely lytic lesions can occur but are rare [40]. Appearance can be similar to osteoblastoma, aneurysmal bone cysts, giant cell tumors, and metastasis. Bone scan is useful for identification of multiple lesions throughout the body.

Treatment – Patients with weakness and sensory loss require immediate surgical decompression which may include spinal fusion for instability. Attempts at en bloc resection should be pursued to improve outcome [126], but this is difficult to achieved due to the size, invasion of surrounding structures, and proximity to critical neural and vascular structures. Once the diagnosis is made, work-up should include a careful search for metastasis. Therapy includes combination chemotherapy and radiation.

Selected patients with large tumors and good neurologic function have been treated with chemotherapy prior to surgical resection. This approach has the advantages of decreasing the size of the tumor prior to resection making total removal more feasible and morbidity less likely. In addition, this approach may prevent more effectively the occurrence of metastasis because systemic chemotherapy is instituted earlier [132].

Prognosis/Quality of Life – Prognosis is dismal with this lesion. Death within 1 year is the norm. Few patients survive more than 2 years [40, 131].

Metastatic Tumors

Metastatic lesions do occur in the developing spinal column. Pathologies vary and are different from those seen in adults. Neuroblastoma, retinoblastoma, Wilms' tumor, embryonal carcinomas, Ewing's sarcoma, osteosarcoma, leukemia, teratoma-teratocarcinoma, and rhabdomyosarcoma can all metastasize to the spine in children. In general, these lesions are associated with a poor prognosis and treatment is nonsurgical unless there is a spinal instability or compression of neural elements.

Future Perspectives

Over the last 30 years important advances in the management of spinal column tumors have been made by advances in imaging, surgical techniques of resection, surgical instrumentation for stabilization of the spine, efficacy of multidrug and multicycle chemotherapy protocols, radiation therapy delivery, and methods of conducting clinical trials. Future advances will involve additional improvements in the delivery of radiation therapy and less toxic, higher efficacy chemotherapy. It is not unreasonable to expect molecular genetics to provide therapeutic and prognostic information from tumor histology. Tumor-specific information regarding the probability of distant metastasis, response to chemotherapeutic agents, and response to radiation could be predicted from genetic analysis [133].

References

1. Anderson FM, Carson MJ. Spinal cord tumors in children. A review of the subject and presentation of 21 cases. J Pediatr 1953;43:190–207
2. Beer, SJ, Menezes, AH. Primary tumors of the spine in children: natural history, management, and long-term follow-up. Spine 1997;6:649–659
3. Giuffre R, DiLorenzo N. Primary spinal column tumors in infancy and childhood: remarks on 53 operated cases. Mod Probl Paediatr 1977;18:231–5
4. Haft H, Ransohoff J, Carter S. Spinal cord tumors in children. Pediatrics 1959;23:1152–9
5. Hamby WB. Tumors in the spinal canal in childhood. J Neuropath Exp Neurol 1944;3:397–412
6. Huvos AG. Bone tumors: diagnosis, treatment, and prognosis. 2nd ed. Philadelphia: W.B. Saunders; 1991. p. 1–784
7. Matson DD. Primary intraspinal tumors. In: Matson DD, editor. Neurosurgery in infancy and childhood. Springfield: Thomas; 1969. p. 647–93
8. Price HI, Batnitzky S. The computed tomographic findings in benign diseases of the vertebral column. CRC Crit Rev Diagn Imaging 1985;24:39–89
9. Ozaki T, Liljenqvist U, Hillmann A, Halm H, Lindner N, Gosheger G, et al. Osteoid osteoma and osteoblastoma of the spine: experiences with 22 patients. Clin Orthop 2002;397:394–402
10. Enneking WF, Spanier SS, Goodman M. A system for surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106–120
11. Boriani S, Capanna R, Donati D, et al. Osteoblastoma of the spine. Clin Orthop 1992;278:37–45
12. Boriani S, Weinstein JN, Biagini R. Spine update. A surgical staging system for therapeutic planning of primary bone tumors of the spine. A contribution to a common terminology. Spine 1997;22:1036–1044

13. Campanacci M, Boriani S, Giunti A. Giant cell tumors of the spine. In: Sundaresan SN, Schmidek HH, Schiller AL, editors. Tumors of the spine: diagnosis and clinical management. Philadelphia: WB Saunders; 1990. p. 163–172
14. Hart RA, Boriani S, Biagini R, et al. A system for surgical staging and management of spine tumors. A clinical outcome study of giant cell tumors of the spine. Spine 1977;22:1773–1782
15. Weinstein JN, Boriani S, Campanacci. Spine neoplasms in pediatric spine. In: Weinstein SL, editor. Principles and practice. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 685–708
16. Campanacci M, Boriani S, Savini R. Staging, biopsy, surgical planning of primary spine tumors. Chir Org Mov 1983;75:99–103
17. Azouz EM, Kozlowski K, Marton D, Sprague P, Zerhouni A, Asselah F. Osteoid osteoma and osteoblastoma of the spine in children. Report of 22 cases with brief literature review. Pediatr Radiol 1986;16(1):25–31
18. Graham GN, Browne H. Primary bone tumors of the pediatric spine. Yale J Biol Med 2001;74:1–8
19. Healey JH, Ghelman B. Osteoid osteoma and osteoblastoma. Current concepts and recent advances. Clin Orthop 1986;204:76–85
20. Janin Y, Epstein JA, Carras R, Khan A. Osteoid osteomas and osteoblastomas of the spine. Neurosurgery 1981;8(1):31–8
21. Pettine KA, Klassen RA. Osteoid-osteoma and osteoblastoma of the spine. J Bone Joint Surg Am 1986;68(3):354–61
22. Aydinli U, Ozturk C, Ersozlu S, Filiz G. Results of surgical treatment of osteoid osteoma of the spine. Acta Orthop Belg 2003;69(4):350–4
23. Drevelegas A, Chourmouzi D, Boulogianni G, Sofroniadis I. Imaging of primary bone tumors of the spine. Eur Radiol 2003;13:1859–1871
24. Stella G, De Sanctis N, Boero S, Rondinella F. Benign tumors of the pediatric spine: statistical notes. Chir Organi Mov 1998;83 (1–2):15–21
25. Frassica FJ, Waltrip RL, Sponseller PD, Ma LD, McCarthy EF Jr. Clinicopathologic features and treatment of osteoid osteoma and osteoblastoma in children and adolescents. Orthop Clin North Am 1996;27(3):559–74
26. Habermann ET, Stern RE. Osteoid osteoma of the tibia in an 8 month old boy. J Bone Joint Surg Am 1974;56:633
27. Maiuri F, Signorelli C, Lavano A, Gambardella A, Simari R, D'Andrea F. Osteoid osteomas of the spine. Surg Neurol 1986;25(4):375–80
28. Ransford AO, Pozo JL, Hutton PA, Kirwan EO. The behaviour pattern of the scoliosis associated with osteoid osteoma or osteoblastoma of the spine. J Bone Joint Surg Br 1984;66(1):16–20
29. Ayala AG, Murray JA, Erling MA, et al. Osteoid osteoma: Intraoperative tetracycline-fluorescence demonstration of the nidus. J Bone Joint Surg Am 1986;68:747
30. Ghelman B, Thompson FM, Arnold WD. Intraoperative radioactive localization of an osteoid osteoma. J Bone Joint Surg Am 1981;63:826
31. Ziegler DN, Scheid DK. A method for location of an osteoid osteoma of the femur at operation. J Bone Joint Surg Am 1992;74:1549
32. Kirwan EO, Hutton PA, Pozo JL, Ransford AO. Osteoid osteoma and benign osteoblastoma of the spine. Clinical presentation and treatment. AO J Bone Joint Surg Br 1984;66(1):21–6
33. Saifuddin A, White J, Sherazi Z, Shaikh MI, Natali C, Ransford AO. Osteoid osteoma and osteoblastoma of the spine. Factors associated with the presence of scoliosis. Spine 1998;23(1):47–53
34. Cove JA, Taminiau AH, Obermann WR, Vanderschueren GM. Osteoid osteoma of the spine treated with percutaneous computed tomography-guided thermocoagulation. Spine 2000;25(10):1283–6
35. Hadjipavlou AG, Lander PH, Marchesi D, Katonis PG, Gaitanis IN. Minimally invasive surgery for ablation of osteoid osteoma of the spine. Spine 2003;28(22):E472–7
36. Ilyas I, Younge DA. Medical management of osteoid osteoma. Can J Surg 2002;45(6):435–7
37. Berberoglu S, Oguz A, Aribal E, Ataoglu O. Osteoblastoma response to radiotherapy and chemotherapy. Med Pediatr Oncol 1997;28(4):305–9
38. Obenberger J, Seidl Z, Plas J. Osteoblastoma in lumbar vertebral body. Neuroradiology 1999;41(4):279–82
39. Schneider M, Sabo D, Gerner HJ, Bernd L. Destructive osteoblastoma of the cervical spine with complete neurologic recovery. Spinal Cord 2002;40(5):248–52
40. Murphey, MD, Andrews CL, Flemming DJ, Temple HT, Smith WS, Smirniotopoulos JG. From the Archives of the AFIP – Primary tumors of the spine: radiographic-pathologic correlation. Radiographics 1996;16:1131–1158
41. Kroon HM, Schurmans J. Osteoblastoma: clinical and radiologic findings in 98 new cases. Radiology 1990;175(3): 783–90
42. Lucas DR, Unni KK, McLeod RA, et al. Osteoblastoma: clinicopathologic study of 306 cases. Hum Pathol 1994;25:117
43. Merryweather R, Middlemiss JH, Sanerkin NG. Malignant transformation of osteoblastoma. J Bone Joint Surg Br 1980;62(3):381–4
44. Myles ST, MacRae ME. Benign osteoblastoma of the spine in childhood. J Neurosurg 1988;68(6):884–8
45. Nemoto O, Moser Jr RP, Van Dam BE, Aoki J, Gilkey FW. Osteoblastoma of the spine. A review of 75 cases. Spine 1990;15(12):1272–80
46. Orbay T, Ataoglu O, Tali ET, Kaymaz M, Alp H. Vertebral osteoblastoma: are radiologic structural changes necessary for diagnosis? Surg Neurol 1999;51(4):426–9
47. Epstein N, Benjamin V, Pinto R, Budzilovich G. Benign osteoblastoma of a thoracic vertebra. Case report. J Neurosurg 1980;53(5):710–3
48. Shikata J, Yamamuro T, Iida H, Kotoura Y. Benign osteoblastoma of the cervical vertebra. Surg Neurol 1987;27(4): 381–5
49. Fakharani-Hein M, Griss P, Ludke A, Bittinger A. Rapidly developing scoliosis in an adolescent due to spinal os-

teoblastoma. A case report. Arch Orthop Trauma Surg 1988;107(4):259–62
50. Di Lorenzo N, Delfini R, Ciappetta P, Cantore G, Fortuna A. Primary tumors of the cervical spine: surgical experience with 38 cases. Surg Neurol 1992;38(1):12–8
51. Capanna R, Ayala A, Bertoni F, Picci P, Calderoni P, Gherlinzoni F, Bettelli G, Campanacci M. Sacral osteoid osteoma and osteoblastoma: a report of 13 cases. Arch Orthop Trauma Surg 1986;105(4):205–10
52. Weatherley CR, Jaffray D, O'Brien JP. Radical excision of an osteoblastoma of the cervical spine. A combined anterior and posterior approach. J Bone Joint Surg Br 1986;68(2):325–8
53. Faraj AA, O'Dowd J, Webb JK. Osteoblastoma of the vertebral body of the third lumbar vertebra. Eur Spine J 1998;7(3):249–51
54. Chew FS, Pena CS, Keel SB. Cervical spine osteoblastoma. AJR Am J Roentgenol 1998;171(5):1244
55. Camitta B, Wells R, Segura A, Unni KK, Murray K, Dunn D. Osteoblastoma response to chemotherapy. Cancer 1991;68:999–1003
56. Biagini R, Orsini U, Demitri S, Bibiloni J, Ruggieri P, Mercuri M, Capanna R, Majorana B, Bertoni F, Bacchini P, Briccoli A. Osteoid osteoma and osteoblastoma of the sacrum. Orthopedics 2001;24(11):1061–4
57. Seki T, Fukuda H, Ishii Y. Malignant transformation of a benign osteoblastoma: a case report. J Bone Joint Surg 1975;57:424–427
58. Mayer L. Malignant degeneration of so-called benign osteoblastoma. Bull Hosp Joint Dis 1967;28(1):4–13
59. Huvos AG. Bone tumors: diagnosis, treatment, and prognosis. Philadelphia: W.B. Saunders; 1979. p. 33–46
60. Bidwell JK, Young JW, Khalluff EJ. Giant cell tumor of the spine: computed tomography appearance and review of the literature. Comput Tomogr 1987;11(3):307–11
61. Shikata J, Yamamuro T, Shimizu K, Shimizu K, Kotoura Y. Surgical treatment of giant-cell tumors of the spine. Clin Orthop 1992;(278):29–36
62. Caudell JJ, Ballo MT, Zagars GK, Lewis VO, Weber KL, Lin PP, et al. Radiotherapy in the management of giant cell tumor of bone. Int J Radiat Oncol Biol Phys 2003;57(1): 158–65
63. Garcia-Bravo A, Sanchez-Enriquez J, Mendez-Suarez JL, Melian-Suarez A, Miranda-Calderin G. Secondary tetraplegia due to giant-cell tumors of the cervical spine. Neurochirurgie 2002;48(6):527–32
64. Honma G, Murota K, Shiba R, Kondo H. Mandible and tongue-splitting approach for giant cell tumor of axis. Spine 1989;14(11):1204–10
65. Ozaki T, Liljenqvist U, Halm H, Hillmann A, Gosheger G, Winkelmann W. Giant cell tumor of the spine. Clin Orthop 2002;401:194–201
66. Wajanavisit W, Laohacharoensombat W, Lektrakul S, Sirikulchayanonta V. Treatment of giant-cell tumor of the spine: report of four cases. J Med Assoc Thai 1995;78(10):565–72
67. Botsford DJ, Esses SI. Normal radionuclide scan in a giant cell tumor of the spine. Orthopedics 1991;14(7):790–2
68. Abe E, Sato K, Tazawa H, Murai H, Okada K, Shimada Y, Morita H. Total spondylectomy for primary tumor of the thoracolumbar spine. Spinal Cord 2000;38(3):146–52
69. Gokaslan ZL, Romsdahl MM, Kroll SS, Walsh GL, Gillis TA, Wildrick DM, et al. Total sacrectomy and Galveston L-rod reconstruction for malignant neoplasms. Technical note. J Neurosurg 1997;87(5):781–7
70. Khan DC, Malhotra S, Stevens RE, Steinfeld AD. Radiotherapy for the treatment of giant cell tumor of the spine: a report of six cases and review of the literature. Cancer Invest 1999;17(2):110–3
71. Malone S, O'Sullivan B, Catton C, Bell R, Fornasier V, Davis A. Long-term follow-up of efficacy and safety of megavoltage radiotherapy in high-risk giant cell tumors of bone. Int J Radiat Oncol Biol Phys 1995;33(3):689–94
72. Boriani S, Biagini R, Laus M, de Iure F, Campanacci L. Giant cell tumor of the vertebral column. Chir Organi Mov 1996;81(3):233–45
73. Eftekhari F, Wallace S, Chuang VP, Soo CS, Cangir A, Benjamin RS, et al. Intraarterial management of giant-cell tumors of the spine in children. Pediatr Radiol 1982;12(6):289–93
74. Misasi N, Sadile F. Selective arterial embolization in orthopaedic pathology. Analysis of long-term results. Chir Organi Mov 1991;(4):311-6
75. Marcove RC, Sheth DS, Brien EW, et al. Conservative surgery for giant cell tumors of the sacrum: the role of cryosurgery as a supplement to curettage and partial excision. Cancer 1994;74:1253–1260
76. Durr DC, Maier M, Jansson V, et al. Phenol as an adjuvant for local control in the treatment of giant cell tumour of the bone. Eur J Surg Oncol 1999;25:610–618
77. Kransdorf MJ, Sweet DE. Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging. AJR Am J Roentgenol 1995;164(3):573–80
78. Boriani S, De Iure F, Campanacci L, Gasbarrini A, Bandiera S, Biagini R, et al. Aneurysmal bone cyst of the mobile spine: report on 41 cases. Spine 2001;26(1):27–35
79. DiCaprio MR, Murphy MJ, Camp RL. Aneurysmal bone cyst of the spine with familial incidence. Spine 2000;25(12):1 589–92
80. Ozaki T, Halm H, Hillmann A, Blasius S, Winkelmann W. Aneurysmal bone cysts of the spine. Arch Orthop Trauma Surg 1999;119(3–4):159–62
81. Stiles RG, Spottswood SE, Jolgren DL, Stewart JR, DeVito DP, Schwartz HS. An unusual appearance of an aneurysmal bone cyst of the thoracic spine. J Spinal Disord 1991;4(1):104–9
82. Feigenberg SJ, Marcus Jr RB, Zlotecki RA, Scarborough MT, Berrey BH, Enneking WF. Megavoltage radiotherapy for aneurysmal bone cysts. Int J Radiat Oncol Biol Phys 2001;49(5):1243–7
83. Mehdian H, Weatherley C. Combined anterior and posterior resection and spinal stabilization for aneurysmal bone cyst. Eur Spine J 1995;4(2):123–5

84. Papagelopoulos PJ, Currier BL, Shaughnessy WJ, Sim FH, Ebersold MJ, Bond JR, et al. Aneurysmal bone cyst of the spine. Management and outcome. Spine 1998;23(5):621–8
85. Raftopoulos C, Hurrel A, Ticket L, Szliwowski HB, Brotchi J. Total recuperation in a case of sudden total paraplegia due to an aneurysmal bone cyst of the thoracic spine. Childs Nerv Syst 1994;10(7):464–7
86. Papagelopoulos PJ, Currier BL, Galanis EC, Sim FH. Vertebra plana of the lumbar spine caused by an aneurysmal bone cyst: a case report. Am J Orthop 1999;28(2):119–24
87. de Kleuver M, van der Heul RO, Veraart BE. Aneurysmal bone cyst of the spine: 31 cases and the importance of the surgical approach. J Pediatr Orthop B 1998;7(4):286–92
88. Chen SH, Huang TJ, Hsueh S, Lee YY, Hsu RW. Unusual bleeding of aneurysmal bone cyst in the upper thoracic spine. Chang Gung Med J 2002;25(3):183–9
89. Cybulski GR, Anson J, Gleason T, Homsi MF, Reyes MG. Aneurysmal bone cyst of the thoracic spine: treatment by excision and segmental stabilization with Luque rods. Neurosurgery 1989;24(2):273–6
90. Turker RJ, Mardjetko S, Lubicky J. Aneurysmal bone cysts of the spine: excision and stabilization. J Pediatr Orthop 1998;18(2):209–13
91. Poolos PN Jr, White RJ. Aneurysmal bone cyst of the cervical spine: a twelve-year follow-up after surgical treatment. Surg Neurol 1980;14(4):259–62
92. Meyer S, Reinhard H, Graf N, Kramann B, Schneider G. Arterial embolization of a secondary aneurysmatic bone cyst of the thoracic spine prior to surgical excision in a 15-year-old girl. Eur J Radiol 2002;43(1):79–81
93. De Cristofaro R, Biagini R, Boriani S, Ricci S, Ruggieri P, Rossi G, et al. Selective arterial embolization in the treatment of aneurysmal bone cyst and angioma of bone. Skeletal Radiol 1992;21(8):523–7
94. DeRosa GP, Graziano GP, Scott J. Arterial embolization of aneurysmal bone cyst of the lumbar spine. A report of two cases. J Bone Joint Surg Am 1990;72(5):777–80
95. Dubois J, Chigot V, Grimard G, Isler M, Garel L. Sclerotherapy in aneurysmal bone cysts in children: a review of 17 cases. Pediatr Radiol 2003;33(6):365–72. Epub 2003 Mar 22
96. Dysart SH, Swengel RM, van Dam BE. Aneurysmal bone cyst of a thoracic vertebra. Treatment by selective arterial embolization and excision. Spine 1992;17(7):846–8
97. Guibaud L, Herbreteau D, Dubois J, Stempfle N, Berard J, Pracros JP, et al. Aneurysmal bone cysts: percutaneous embolization with an alcoholic solution of zein–series of 18 cases. Radiology 1998;208(2):369–73
98. Koci TM, Mehringer CM, Yamagata N, Chiang F. Aneurysmal bone cyst of the thoracic spine: evolution after particulate embolization. AJNR Am J Neuroradiol 1995;16(4 Suppl):857–60
99. Biesecker JL, Marcove RC, Huvos AG, Mike V. Aneurysmal Bone cysts. A clinicopathologic study of 66 cases. Cancer 1970;26:615–625
100. Donaldson Jr WF. Aneurysmal bone cyst. J Bone Joint Surg Am 1962;4425–40
101. Tillman BP, Dahlin DC, Lipscomb PR, Stewart JR. Aneurysmal bone cyst: an analysis of ninety-five cases. Mayo Clin Proc 1968;43:478–495
102. Nobler MP, Higinbotham NL, Phillips RF. The cure of aneurysmal bone cysts. Irradiation superior to surgery in an analysis of 33 cases. Radiology 1968;90:1185–1195
103. Cruz M, Coley BL. Aneurysmal bone cyst. Surg Gynecol Obstet 1956;103:67–77
104. Dabska M, Buraczewski J. Aneurysmal bone cyst. Pathology, clinical course and radiographic appearances. Cancer 1969;23:371–389
105. Enneking WF. Musculoskeletal tumor surgery. New York: Churchill Livingstone; 1983. p. 1–741
106. Capanna R, Albisinni U, Picci P, et al. Aneurysmal bone cyst of the spine. J Bone Joint Surg 1985;67A:527–31
107. Nobler MP, Higinbotham NL, Phillips RF. The cure of aneurysmal bone cysts. Irradiation superior to surgery in an analysis of 33 cases. Radiology 1968;90:1185–1195
108. Bush CH, Drane WE. Treatment of an aneurysmal bone cyst of the spine by radionuclide ablation. AJNR Am J Neuroradiol 2000;21(3):592–4
109. Delloye C, De Nayer P, Malghem J, Noel H. Induced healing of aneurysmal bone cysts by demineralized bone particles. A report of two cases. Arch Orthop Trauma Surg 1996;115(3–4):141–5
110. Gladden Jr ML, Gillingham BL, Hennrikus W, Vaughan LM. Aneurysmal bone cyst of the first cervical vertebrae in a child treated with percutaneous intralesional injection of calcitonin and methylprednisolone. A case report. Spine 2000;25(4):527–30
111. Touzi M, Bergaoui N, Ben Hammouda M, Khalfallah B, Gannouni A, el May M. Sciatica secondary to an aneurysmal bone cyst treated with in situ calcitonin injections. Rev Rhum Engl Ed 1997;64(10):592–3
112. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X) – a clonal proliferative disease. N Eng J Med 1994;331:154–160
113. Islinger RB, Kuklo TR, Owens BD, Horan PJ, Choma TJ, Murphey MD, et al. Langerhans' cell histiocytosis in patients older than 21 years. Clin Orthop 2000;379:231–5
114. Bunch WH. Orthopedic and rehabilitation aspects of eosinophilic granuloma. Am J Pediatr Hematol Oncol 1981;3(2):151–6
115. Mammano S, Candiotto S, Balsano M. Cast and brace treatment of eosinophilic granuloma of the spine: long-term follow-up. J Pediatr Orthop 1997;17(6):821–7
116. Maggi G, de Sanctis N, Aliberti F, Nunziata-Rega A. Eosinophilic granuloma of C4 causing spinal cord compression. Childs Nerv Syst. 1996;12(10):630–2
117. Puertas EB, Milani C, Chagas JC, de Oliveira VM, dos Santos FP, Wajchenberg M, et al. Surgical treatment of eosinophilic granuloma in the thoracic spine in patients with neurological lesions. J Pediatr Orthop B 2003;12(5):303–6
118. Simanski C, Bouillon B, Brockmann M, Tiling T. The Langerhans' cell histiocytosis (eosinophilic granuloma) of the cervical spine: a rare diagnosis of cervical pain. Magn Reson Imaging. 2004;22(4):589–94

119. Bertram C, Madert J, Eggers C. Eosinophilic granuloma of the cervical spine. Spine 2002;27(13):1408–13
120. Levy EI, Scarrow A, Hamilton RC, Wollman MR, Fitz C, Pollack IF. Medical management of eosinophilic granuloma of the cervical spine. Pediatr Neurosurg 1999;31(3): 159–62
121. Raab P, Hohmann F, Kuhl J, Krauspe R. Vertebral remodeling in eosinophilic granuloma of the spine. A long-term follow-up. Spine 1998;23(12):1351–4
122. Venkateswaran L, Rodriguez-Galindo C, Merchant TE, Poquette CA, Rao BN, Pappo AS. Primary Ewing tumor of the vertebrae: clinical characteristics, prognostic factors, and outcome. Med Pediatr Oncol 2001;37(1):30–5
123. Grubb MR, Currier BL, Pritchard DJ, Ebersold MJ. Primary Ewing's sarcoma of the spine. Spine 1994;19(3):309–13
124. O'Donnell J, Brown L, Herkowitz H. Vertebra plana-like lesions in children: case report with special emphasis on the differential diagnosis and indications for biopsy. J Spinal Disord 1991;4(4):480–5
125. Sharafuddin MJ, Haddad FS, Hitchon PW, Haddad SF, el-Khoury GY. Treatment options in primary Ewing's sarcoma of the spine: report of seven cases and review of the literature. Neurosurgery 1992;30(4):610–8
126. Talac R, Yaszemski MJ, Currier BL, Fuchs B, Dekutoski MB, Kim CW, et al. Relationship between surgical margins and local recurrence in sarcomas of the spine. Clin Orthop 2002;397:127–32
127. Barbieri E, Chiaulon G, Bunkeila F, Putti C, Frezza G, Neri S, et al. Radiotherapy in vertebral tumors. Indications and limits: a report on 28 cases of Ewing's sarcoma of the spine. Chir Organi Mov 1998;83(1–2):105–11
128. Tasdemiroglu E, Bagatur E, Ayan I, Darendeliler E, Patchell RA. Primary spinal column sarcomas. Acta Neurochir (Wien) 1996;138(11):1261–6
129. Villas C, San Julian M. Ewing's tumor of the spine: report on seven cases including one with a 10-year follow-up. Eur Spine J 1996;5(6):412–7
130. Patel DV, Hammer RA, Levin B, Fisher MA. Primary osteogenic sarcoma of the spine. Skeletal Radiol 1984;12(4): 276–9
131. Sundaresan N, Rosen G, Huvos AG, Krol G. Combined treatment of osteosarcoma of the spine. Neurosurgery 1988;23(6):714–9
132. Sundaresan N, Rosen G, Fortner JG, Lane JM, Hilaris BS. Preoperative chemotherapy and surgical resection in the management of posterior paraspinal tumors. Report of three cases. J Neurosurg 1983;58(3):446–50
133. Regaud Lecture, Granada 1994. Tumors of the connective and supporting tissues; Suit H. Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston

Pediatric Spinal Intradural Extramedullary Tumors

50

Peter Dirks

Introduction – 600

Clinical Considerations – 600

Imaging – 601

Surgical Treatment – 601

Prognosis – 602

References – 602

Introduction

Intradural spinal cord tumors are uncommon childhood tumors and most series are comprised mainly of adult patients [1, 2]. Intradural extramedullary spinal tumors are estimated to represent less than one half of all intradural tumors in childhood [3–5]. Precise incidence figures are hard to come by for children. The main diagnostic considerations (Table 1) are schwannoma, neurofibroma, and metastatic spread from an undiagnosed intracranial tumor or primary metastatic disease, particularly PNET. In children, low-grade tumors such as low-grade astrocytomas and gangliogliomas can also disseminate in CSF pathways, and spinal dissemination appearing as extramedullary disease can very rarely be the presentation of primary intracranial tumors. Meningiomas may also occur but are exceedingly rare compared to adults. Developmental lesions such as lipomas and epidermoid/dermoid tumors are an important additional consideration as well but clinical clues and distinctive features on MRI imaging usually allow for a preoperative diagnosis. Neurenteric cysts, also very rare lesions, may be intramedullary or extramedullary and can be diagnosed by identification of particular imaging features. In the cauda equina region, myxopapillary ependymomas and the rare paraganglioma are particular considerations, but these tumors are also much more common in adults. Most intradural extramedullary tumors are benign and resectable so prognosis is often excellent.

Clinical Considerations

The most important clinical consideration first is whether the patient has neurofibromatosis (NF) type 1 or type 2 as these conditions are associated with nerve sheath tumors. NF1 can be difficult to diagnose in young children as clinical features are extremely variable and become more obvious with advancing age. A family history is very important but NF1 has a high frequency of new mutation, therefore presenting without family history. NF2 typically does not present until the late teenage years or early adulthood [6, 7]. NF1-associated tumors are can be multiple and management decisions rest on whether a lesion is causing symptoms or signs. Lesions that are asymptomatic but are enlarging or causing significant neural compression by imaging, especially cord compression, warrant consideration for surgical decompression.

Patients with intradural extramedullary spinal tumors typically present with a long history. Tumors can be surprisingly large and cause very little symptoms. These lesions can have local effects causing segmental root and cord dysfunction and distant effects effecting motor and sensory pathways. Pain is often prominent and is regional and radiating, and often unilateral in distribution as these tumors tend to be eccentric in location. Motor or sensory deficits occur in a clinical pattern consistent with location, again more typically unilateral segmental lower motor neuron disturbance or caudal ipsilateral upper motor neuron disturbance with ipsilateral dorsal column dysfunction and contralateral spinothalamic dysfunction (Brown-Sequard picture). Cauda equina lesions may have a long history of low back pain with radiation, mimicking sciatica. Often the pain is asymmetrical despite a large lesion occupying the entire dural tube. These lesions can be associated with surprisingly few neurological deficits as the cauda equina roots can withstand a substantial degree of compression if long standing. Bowel and bladder disturbances with tumors in this location are also very important clinical symptoms. Lesions at the foramen magnum can cause a disproportionate loss of position sensation in the upper limbs and can be associated with intrinsic hand muscle wasting and long tract signs. Suboccipital pain can also occur from disturbance of upper cervical roots. Gait abnormalities are also an important presenting feature in children. In children, it is also very important to look for evidence of scoliosis and for midline cutaneous stigmata of spinal dysraphism, such as a dermal sinus tract, subcutaneous mass or lipoma, cutaneous hemangioma, or hairy patch. Although some of the above clinical features suggest an extramedullary instead of an intramedullary tumor, the presentation may often be indistinguishable, and diagnosis is made based on MR imaging.

Table 1 Pediatric intradural extramedullary spinal tumors

Neoplasms	Schwannoma Neurofibroma Metastatic tumors – malignant and nonmalignant Myxopapillary ependymoma Paraganglioma Meningioma
Nonneoplastic masses	Dermoid/epidermoid tumors Neurenteric cyst Lipoma

Imaging

MRI clearly defines that these lesions are in the intradural extramedullary compartment in most cases, and a differential diagnosis is made based on lesion location and the particular MRI signal characteristics. A complete examination of the entire spinal axis is warranted for all intradural tumors and brain imaging may also be necessary in some cases.

Intradural extramedullary lesions are typically well defined. Schwannomas, neurofibromas, meningiomas, and ependymomas are typically isointense on T1 and hyperintense on T2 and enhance with gadolinium. Neurofibromas are often multiple and may have an intradural and extradural component causing enlargement of the neural foramen and an anterolateral paraspinal mass. Multiple intradural lesions demand imaging of the entire brain and spinal cord. Paragangliomas mimic myxopapillary ependymomas because of their predilection to occur in cauda equina.

Developmental lesions are diagnosed based on the signal characteristics of the tissues and associated regional congenital anomalies. CT may be particularly helpful to define bony anatomy in developmental lesions. Fat signal characteristics identify lipomas, which are typically lumbar in location. Neurenteric cysts occur in cervical or thoracic region, are associated with vertebral anomalies (such as butterfly vertebra) and have contents with signal characteristics of proteinaceous fluid [8–11]. The capsule of a neurenteric cyst may have an enhancing rim. Often a canal (of Kovalevsky) is visualized tracking from the cyst anteriorly causing a split in the vertebra, which is often better visualized on CT.

Surgical Treatment

Differential diagnosis is usually sharply narrowed down based on MR imaging. Surgery involves a posterior approach with laminectomy decompression and microsurgical tumor removal. The goal is complete removal for all pathologies. The unique consideration in children is the greater potential for postoperative spinal deformity with laminectomy alone. Preoperative steroids are often used. Level localization is obtained with a needle and a lateral X-ray after the patient is positioned or after exposure of the regional dorsal spine. Other essential adjuncts to surgery are the use of intraoperative ultrasound and monitoring somatosensory and motor-evoked potentials. Leads placed in segmental muscles and sphincters can be extremely useful for localization of particular roots and for detection of spontaneous nerve activity which can result from root manipulation.

In children, especially in the very young, laminoplasty is performed if greater than two levels will be removed for tumor removal, as this technique may reduce postoperative spinal deformities. There are several techniques that can be used to perform laminoplasty. Occasionally, a hemilaminectomy may be performed. For laminoplasty, after acquiring access

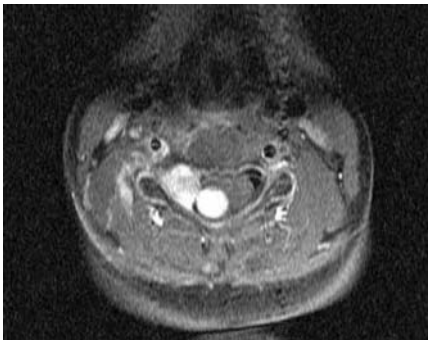


Fig. 1 4-year-old girl with café au lait spots and upper cervical and right arm pain. MRI shows intradural extramedullary tumor with extradural component involving right C6 nerve root. Total excision of intradural component with preservation of dorsal root and subtotal excision of extradural component by three level laminoplasty. No recurrence or growth and no spinal deformity at 3 years postoperatively

Fig. 2 17-year-old boy with back pain and bilateral leg pain and no abnormality on neurologic exam. Undergoes complete resection of myxopapillary ependymoma

to the extradural space, the high speed saw is used to make cuts in contiguous laminae just lateral to the spinous process. The laminae are removed with ligaments attached and are then reattached with sutures at each bony segment after tumor resection is completed.

For neurofibromas, more lateral exposure may be needed, and a facet joint, if extensively resected, may be compromised requiring consideration for contralateral segmental spinal fusion. When the dura is exposed, ultrasound is used to identify the lesion and plan the location of a midline dural opening. A T-extension of the dural opening may be needed for a neurofibroma which has an extradural component. Microsurgical removal is then performed and internal debulking is often initially required to decompress the cord in order to then allow safe capsule manipulation. Roots are identified and preserved, which is less important in the thoracic regions. For schwannoma, which arise from a posterior rootlet fascicle, the attached fascicle of the rootlet cannot be preserved and often is sacrificed. Dermoid/epidermoid tumors and neurenteric cysts may have a capsule that is adherent to surrounding nerve roots or to the spinal cord and it may not be completely excised; debulking/drainage of contents with resection of the majority of the capsule may be satisfactory surgical treatment providing symptomatic relief and preservation of root and cord function. Lipomas can be substantially debulked but cannot be totally excised due to their intimate adherence to the spinal cord tissue. Dura is closed post resection and anatomic layers restored.

Prognosis

As most of these lesions are benign, prognosis is good with surgical excision. Follow-up then occurs clinically and with MRI scans. The frequency of follow-up will depend on whether the lesion was completely or partially excised. Repeat excision may be justified as initial treatment of local recurrence. Chemotherapy is being investigated for neurofibromas involving inhibition of the molecular signaling pathways overactivated in these tumors. Subtotally resected or disseminated myxopapillary ependymomas may be treated with radiation. Recurrent ependymomas and meningiomas may be considered for radiation if not subsequently completely resectable.

References

1. el-Mahdy W, Kane PJ, Powell MP, Crockard HA. Spinal intradural tumours: Part I–extramedullary. Br J Neurosurg 1999;13:550–7
2. Wellons JC, Oakes WJ, editors. Pediatric intradural and extramedullary spinal cord tumors. Philadelphia: Elselvier Saunders; 2004
3. Constantini S, Epstein, F. In: Choux M, Di Rocco C, Hockley A, Walker M, editors. Pediatric neurosurgery. London: Churchill Livingstone; 1999. p. 601–616
4. DeSousa AL, Kalsbeck JE, Mealey Jr J, Campbell RL, Hockey A. Intraspinal tumors in children. A review of 81 cases. J Neurosurg 1979;51:437–45
5. Schick U, Marquardt G. Pediatric spinal tumors. Pediatr Neurosurg 2001;35:120–7
6. Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM. Neurofibromatosis 2 in the pediatric age group. Neurosurgery 1993;33:92–6
7. Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. J Child Neurol 2003;18:718–24
8. Blaser S, Illner A, Castillo M, Hedlund G, Osborn A. Pocket radiologist: Peds Neuro Top 100 diagnoses. Salt Lake City: Amirsys; 2003
9. Kim CY, et al. Neurenteric cyst: its various presentations. Childs Nerv Syst 1999;15:333–41
10. Kumar R, Jain R, Rao KM, Hussain N. Intraspinal neurenteric cysts – report of three paediatric cases. Childs Nerv Syst 2001;17:584–8
11. Paleologos TS, Thom M, Thomas DG. Spinal neurenteric cysts without associated malformations. Are they the same as those presenting in spinal dysraphism? Br J Neurosurg 2000;14:185–94

Intramedullary Spinal Tumors in Children

51

John S. Myseros

Epidemiology – 604

Symptoms and Clinical Signs – 604

Diagnostics – 604

Staging and Classification – 604

Treatment – 605
Surgery
Radiotherapy
Chemotherapy

Prognosis/Quality of Life – 608

Follow-Up/Specific Problems and Measures – 608

Future Perspectives – 608

References – 609

Epidemiology

Pediatric intramedullary spinal tumors (IMSTs) are generally uncommon, comprising 4%–6% of all central nervous system (CNS) tumors and 35%–40% of all intraspinal tumors in children [1, 2]. Of these, most are of glial origin. Astrocytomas are typically the most common, the majority being fibrillary. In children, the second most common IMSTs are gangliomas, followed by ependymomas [2]. Ependymomas become more prevalent in older patients. Many other histologic varieties including germ cell tumors, primitive neuroectodermal tumors, and intramedullary schwannomas have also been identified in the spinal cord [3, 4]. Hemangioblastomas are exceedingly rare in the spinal cord in children.

Despite the relative rarity of these tumors, they present a significant treatment and surgical challenge for the pediatric neurosurgeon. The treatment of children harboring IMSTs has changed over the last few decades. Where as trepidation permeated the surgeon's approach to the surgery of these lesions, seemingly involving the entire width of the spinal cord, complete excision of which would certainly lead to unacceptable morbidity, experience and innovation has allowed microneurosurgery to be the most effective upfront treatment for a majority of these lesions.

Symptoms and Clinical Signs

Identifying neurological signs and symptoms early significantly impacts the ultimate outcome of children with IMSTs. As with low-grade glial tumors of the brain, low-grade IMSTs may cause very subtle and slowly progressive symptoms. This insidious onset may be present for many months or even years. Conversely, high-grade lesions cause more dramatic and rapid symptoms [5].

Pain is the most common presenting sign in children with IMSTs [6]. In the thoracic spinal cord, this discomfort may be misinterpreted as rib or abdominal pain. Motor deficits and clumsiness and loss of bowel or bladder function may present later in the course. The younger child may present with delay or loss of developmental milestones. Occasionally dysesthesias will be present but go unrecognized. Scoliosis may result from IMSTs, particularly those in the thoracic cord associated with extensive cysts or syringohydromyelia.

Higher cervical lesions with invasion of or proximity to the brainstem medulla may present with torticollis, dysphagia, or even hydrocephalus secondary to disturbed CSF flow at the fourth ventricular outlet and across the foramen magnum. Diffuse IMSTs with leptomeningeal spread may also lead to a cerebrospinal fluid (CSF) absorptive deficit and subsequent hydrocephalus requiring diversionary shunt [7].

Diagnostics

Relative ease of accessibility to sophisticated imaging has aided in making earlier diagnosis in many children. Most pediatric healthcare facilities offer magnetic resonance (MR) imaging as even a primary imaging modality if the clinical suspicion for spinal cord pathology is high.

Isolated pain may lead to plain radiographs, which can be helpful in pursuing a diagnosis. Like their extramedullary and extradural counterparts, IMSTs may cause scalloping of the dorsal vertebral body. In addition, widening of the spinal canal and distortion of the pedicles from mass effect may be seen. Extensive long-standing tumors or those associated with large cysts may result in scoliosis.

Computed tomography (CT) is helpful in evaluating bony anatomy and concomitant spinal deformity. Myelography as an adjunct is rarely pursued unless there is a contraindication to MR imaging. MR is the diagnostic image of choice. Imaging with and without contrast may aid in preoperative diagnosis and certainly plays a role in surgical planning. Postoperative imaging helps verify the extent of surgical resection, evaluate postoperative complications, and serve as a monitoring tool for subsequent observation or the effects of adjuvant therapies. Although MR spectroscopy has been actively pursued in the preoperative evaluation of brain tumors, adequate voxel acquisition is problematic because of the limited size of the spinal cord.

Homogeneously enhancing lesions on T1-weighted MR images, such as the typical ependymoma and some astrocytomas, give the impression of a well-circumscribed tumor that may lend to complete resection (Fig. 1). Heterogeneously or nonenhancing lesions may translate intraoperatively into lesions indistinct from the normal spinal cord. Ependymomas are rarely nonenhancing [8]. If there is little or no enhancement, indicating a low-grade, slowly growing tumor, T2-weighted MR imaging may aid in distinguishing the extent of the tumor as well as the cystic components and their delineation from the normal cord (Fig. 2). In high-grade lesions, just as in the brain, T2-weighted images will demonstrate the extent of cord edema.

Staging and Classification

By definition, IMSTs are those whose location is in the parenchyma of the spinal cord. Although these

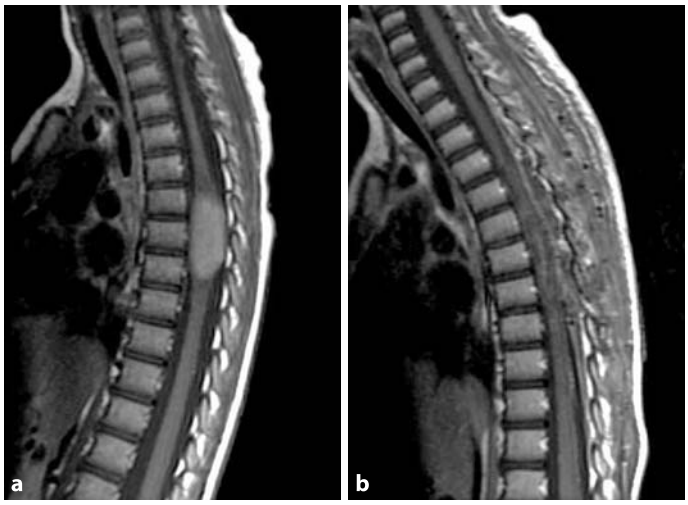


Fig. 1 MRI of a 2-year-old girl with radiating thoracic pain. Histologically this tumor was a pilocytic astrocytoma. **a** Sagittal postcontrast T1-weighted image shows a focal enhancing intramedullary thoracic mass. **b** Postoperative sagittal postcontrast T1-weighted image is helpful in evaluating the extent of resection

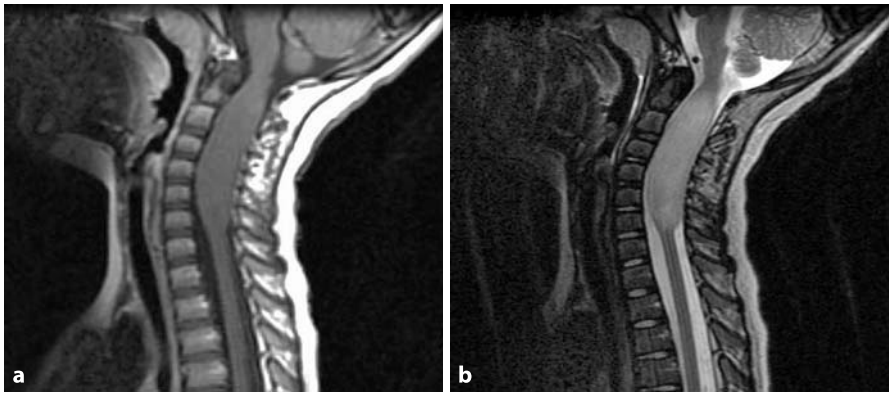


Fig. 2 MRI of a 5-year-old boy with longstanding bilateral proximal arm weakness. This was found to be a fibrillary astrocytoma. **a** Sagittal postcontrast T1-weighted image reveals no enhancement. **b** Sagittal T2-weighted image better defines the mass

tumors may be exophytic, their epicenter is in the cord. The more common filum terminale ependymoma, typically myxopapillary in nature, will be considered as an extramedullary tumor for these purposes. Children do, however, present with intramedullary ependymomas of the spinal cord 12% of the time [2, 9]. The most common histology is astrocytoma. As with parenchymal cerebellar astrocytoma of childhood, these IMSTs are also low-grade and fibrillary or pilocytic in nature. Higher-grade ependymomas and astrocytomas are less common.

Most IMSTs are isolated lesions. Astrocytomas may also have associated cysts as rostral or caudal caps. Although multifocal lesions within the spinal cord and brain have been noted and carry an understandably poorer prognosis, this presentation is not common. IMSTs may present at any level. As a group, cervical and cervico-medullary tumors are the most common, while in isolation, thoracic lesions are more common [9].

Conus lesions are quite rare, and cervico-medullary lesions may be considered brainstem tumors. Further staging depends on radiographic findings. Imaging at diagnosis should include brain MR to investigate multifocal disease. Concomitant lesions in the CNS and diffuse pial enhancement may impact the goal of surgery and also carries a poorer prognosis.

Treatment

Surgery represents the most valuable upfront intervention in the treatment of IMST and should be considered mandatory for children presenting with progressive symptoms. Present techniques have allowed for gross total resection of greater than 75% of these lesions, the majority of which are low grade [10]. Multifocal lesions, those associated with diffuse leptomeningeal enhancement, and IMSTs presenting with rapidly progressive symptoms forecasting a malignancy may not be amenable to complete surgical extirpation. In these cases, tissue biopsy or subtotal resection with or without canal decompression will allow for some symptomatic relief, with the subsequent need for radiation and chemotherapy. His-

torically, IMSTs of all histologic grade were biopsied and then treated with radiotherapy. The advent of microsurgical techniques, sensitive neurophysiological monitoring, and surgical experience now places the natural history of many of these tumors in the hands of the neurosurgeon. Depending on the histopathology, gross total or near total resection may be possible and preferable. Aggressive or highly undifferentiated tumors may not warrant complete resection, as certain neurological deficit in the face of imminent adjuvant therapy should be avoided.

Surgery

Unless deemed undesirable, all patients should be operated on in the prone position. A urinary catheter and appropriate venous and arterial lines should be established prior to turning the patient from the supine position. In addition, the neurophysiology team should place all necessary electrodes for intraoperative monitoring. For cervical or cervico-thoracic lesions, the head should be placed in a mildly flexed position, either on a well-padded horseshoe, or in rigid fixation. Active flexion and extension by the child preoperatively will ensure safe passive positioning of the head and neck in the operating room.

The operating table should accommodate the intraoperative radiography. This can prove helpful in isolating and verifying the desired levels of exposure. Needle localization using PA films for the thoracic spine or lateral radiographs in the cervical or lumbar spine will help limit the extent of the incision and subsequent laminotomy/laminectomy.

Perioperative antibiotics and steroids are given prior to incision. Routine exposure with care to clearly define the anatomic layers early will facilitate secure, multilayer closure at the end of the procedure. Although the electrocautery is judiciously utilized, the skin should be cut sharply to avoid a devascularizing injury that may lead to postoperative breakdown and potential spinal fluid leak. After exposure of the posterior elements, repeat radiographs or fluoroscopy should be used to verify the appropriate levels.

Unless contraindicated for other reasons, an osteoplastic laminoplasty should be performed with a high-speed craniotome or saw and a protective footplate. The lamina are cut sequentially through the rostral-most lamina. Care must be taken to keep the saw parallel to the spine in order to avoid a limiting exposure from a medial course or a nerve root injury from a lateral course. The caudal-most interspinous ligament is cut, and the surgeon may decide whether to sling the lamina rostrally, still attached by the rostral-most interspinous ligament, or cut this ligament to create a free laminectomy.

Hemostasis is obtained, and the intraoperative ultrasound is used to verify the location of the tumor. This is often obvious after dural exposure as the sac is distended. For tumors spanning a short distance, gentle palpation of the thecal sac may reveal the exact location of the lesion as well.

The dura is opened in the midline, preferably over a nondistended area. The durotomy is taken either to the edges of the laminectomy or until the spinal cord tapers to a more normal diameter. The dura is retracted, and the microscope is brought into the field. Ultrasound is again used to verify tumor and/or cyst location, and a midline myelotomy is planned directly over the tumor. Branches of the dorsal medullary vein typically run into the median sulcus; however, because the dorsal surface of the cord may be distorted, rotated, discolored, or expanded, finding the midline may be difficult. The dorsal route entry zones will reorient the surgeon and guide the myelotomy. This may be done sharply or with the laser. Care should be taken to avoid devascularizing the pial surface. Depending on the size of the lesion, the myelotomy may expose the tumor. If not, it is extended ventrally, perpendicular to the dorsal surface of the cord until the discoloration and altered texture of the tumor is encountered.

Low-grade astrocytomas may be difficult to discern from normal spinal cord. The presence of cysts, rostrally or caudally, typically demarcate the tumor margin in that area. In the axial plane, however, the plane is not clear. As such, circumferential dissection in hopes of en bloc resection is not advised. Debulking the lesion internally serves to decrease the size of the lesion and allow for systematic centripetal extirpation. As the edges of the myelotomy are released, pial retraction sutures will aid in visualization and decrease the amount of lateral manipulation of the cord. The glial margin separating the tumor from normal parenchyma may then be explored. Fine-tipped ultrasonic aspiration may aid in "painting" the tumor away. For softer tumors, gentle suction with the bipolar electrocautery is also effective. The microscope-mounted carbon dioxide laser offers the benefit of electrocautery as it evaporates the tumor with precision. Having established a baseline image prior to myelotomy with the ultrasound, serial ultrasounds during resection may prove helpful (Fig. 3). Although nonenhancing low-grade astrocytomas may be echogenically identical to the surrounding cord, the surgeon will have a real-time quantitative evaluation of the extent of resection.

Intramedullary ependymomas typically have a better-defined interface with the surrounding normal spinal cord. There is a temptation to remove these lesions en bloc without reducing their size. In large lesions, this may lead to undue manipulation of the cord with unexpected bleeding and preventable

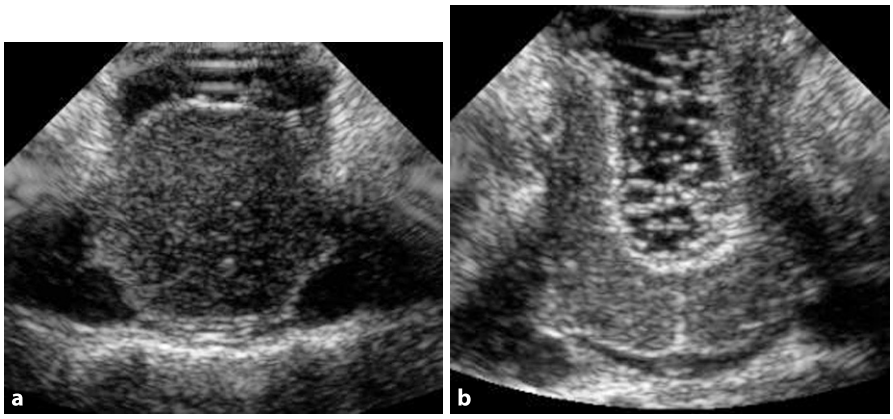


Fig. 3 Intraoperative ultrasound of the patient in **Figure 1. a** Axial image obtained prior to myelotomy reveals a large, expanded spinal cord. **b** Subsequent axial image shows progression of the resection

neurologic injury. Ependymomas should also be centrally debulked. This will then allow dissection of the tumor away from the normal cord. The residual peel of tumor, with its outer layer intact, may then be removed in one piece. There is risk for residual tumor and subsequent recurrence when these tumors are removed piece-meal. Ultrasound may again serve as an intraoperative guide.

Other more benign lesions may be approached with the same paradigm as that used with astrocytomas and ependymomas. Malignant IMSTs, however, should not undergo aggressive resection. These children have a poor prognosis and will certainly require adjuvant therapy regardless of extent of resection.

The use of intraoperative neurophysiologic monitoring is helpful in avoiding neurologic deficit in these children. Somatosensory-evoked potentials aid in monitoring dorsal column function. However, changes are commonly seen upon myelotomy and dissection. This will not typically dissuade further dissection as avoiding injury to the corticospinal tracts is paramount and takes precedence. Motor-evoked potentials (MEP) with epidural recording electrodes allow the surgeon to proceed with a more aggressive resection and are reliable predictors of neurological status after surgery [9, 11]. Loss of motor-evoked potentials should prompt immediate cessation of intervention until the potentials have recovered. If they should not improve, surgical judgment should dictate whether or not to proceed with resection.

When the resection is complete the pia should not be closed. Although doing so may reapproximate normal anatomy, the risk for intracavitary cyst formation would warrant leaving the myelotomy open. If the spinal cord has been decompressed, the dura is closed primarily with a running monofilament suture. If the cord is distended and primary closure is difficult, a graft is used. Positive pressure ventilation is then requested of the anesthesiologist to identify any potential CSF leak. The use of adhesive sealants may prove helpful in maintaining a dry epidural space. Antibiotic irrigation should be followed by reattachment of the removed lamina, either with titanium or absorbable microplates and screws, or with suture or wire through translaminar holes. Reapproximation of the rostral and caudal interspinous ligaments will aid in maintaining adequate coverage and fixation.

The incision is then closed in anatomic layers. The muscle can be reapproximated to reduce the potential dead space, but care should be taken to avoid necrosis. The fascial closure is deemed the most important and should be impermeable to CSF, even if the dura is left open. Lateral relaxing incisions in the fascia may be utilized if there is any tension and the integrity of the closure is in doubt. The subcutaneous layer may be intermittently tacked down to the fascia, and the skin is closed with a nylon suture. This will be less reactive and less likely to lead to superficial breakdown or infection in the child on steroids or postradiation, as well as help prevent an incisional CSF leak and infection should a pseudomeningocele develop.

Radiotherapy

Prior to the evolution of routine successful, aggressive surgical resection of IMSTs in children, the traditional approach for treatment was partial resection or biopsy and subsequent radiation therapy [12, 13]. Long-term control of astrocytomas and ependymomas in children has been shown even with minimal surgical resection followed by radiation therapy [14]. However, the detrimental effects to the bony spine and cord itself after irradiating the pediatric spine are well documented [15–17].

Postresection radiotherapy for the most common IMSTs in children, low-grade astrocytoma and ependymoma, should be reserved for specific indications. Children undergoing complete resection

should receive no further therapy [18]. These lesions may be observed even when subtotally resected if the histology is benign. Frequent serial MR imaging will detect any evidence of progression which, depending on the neurologic condition may provoke further resection, or subsequent radiotherapy. It is possible that residual low-grade tumors may show little or no progression. Malignant tumors, resected tumors that show rapid recurrence, and tumors that are deemed unresectable should be considered for radiation.

Chemotherapy

The role of chemotherapy in the treatment of children with IMSTs is not well established. Salvage chemotherapy may be used with some success in the treatment of recurrent intramedullary ependymoma [19]. It has also been used for high-grade astrocytomas and other malignancies, although effects on outcome and long-term survival are unclear [5].

Prognosis/Quality of Life

Although risk of mortality from surgery for IMSTs is not significant, the risk for neurologic dysfunction and paralysis is. Again, the extent of neurologic disability prior to surgery best predicts neurologic function after surgery. In experienced hands, there is approximately a 5% risk of paralysis in the child with no preoperative motor deficit [9]. This reinforces the need for early diagnosis and treatment. In a large series, comparing preoperative function to postoperative function, 60% of patients improved, 16% remained the same, and 23% were worse [10]. Those children operated on with little or no motor deficits had the best functional outcome. Sensory dysfunction, typically posterior column function involving position sense, can also be debilitating. For this as well as motor deficits, aggressive physical and rehabilitation therapy may prove helpful. Ultimately, the quality of life in these children is directly related to their functional outcome.

Prognosis and survival in children with IMSTs is most dependent on the histology grade of the tumor. There is strong evidence that radical surgical excision alone can achieve 5-year survival rates for low-grade tumors of 88%, very comparable to outcomes of children with similar tumors treated with radiotherapy [2]. As such, surgery alone may render the child cured. The long-term outcome of children with intramedullary spinal cord malignancies is poor. [18]

Follow-up/Specific Problems and Measures

Children treated for IMSTs require close multidisciplinary follow-up. Significant neurologic deficit may warrant rehabilitation. Frequent evaluation of neurologic function may lead to early diagnosis of recurrent tumor. Depending on tumor histology, degree of resection, new or progressive neurologic dysfunction, and the addition of adjuvant therapies, interval imaging with MR for tumor evaluation and plain radiographs for skeletal integrity are needed. Immediate postoperative MR imaging will establish a baseline against which further imaging can be compared.

A common concern in following these children after surgery is their propensity for acquired spinal deformities, particularly postlaminectomy kyphosis and scoliosis [20]. Progressive deformity may lead to compromise of the spinal canal and require surgical correction and fixation. Osteoplastic laminotomy certainly allows for bony union of the cut bone, and may contribute to spinal stability [21]. Although this is intended to decrease the rate of spinal deformity as well as protect to dorsal spinal canal, the development of kyphosis and/or scoliosis is still a problem. Vigilant orthopedic follow-up is necessary to address these deformities early. Cervical and thoracic orthosis postoperatively may help promote healing of the laminoplasty in a more anatomically correct fusion facilitating long-term stability, as these are typically the locations prone to deformity. Lumbar laminectomy is less likely to lead to future spinal alignment and stability problems.

Future Perspectives

Over the last two decades, the treatment of IMST has shifted from more conservative surgical philosophy and dependence on adjuvant therapies, to radical surgery aimed at gross total resection with little or no morbidity. With the increased precision of surgical techniques, sensitivity of neurophysiologic monitoring, improved high-powered microscopes, and the evolution of image-guidance in the spine and spinal cord, surgical outcomes and long-term survival will improve.

Radiotherapy to the pediatric spine, historically associated with potentially devastating bony and neurological sequelae, will also become more precise. Body stereotaxis and stereoscopic real-time fluoroscopy will enable the maximum dose of radiation to be focused to the involved tissue within 1–2 mm of the normal spinal cord above and below the tumor. Multiple beams from multiple directions will also de-

crease the insult to any normal spinal cord surrounding the tumor in the axial plane.

Because IMSTs in children are relatively uncommon, further breakthroughs in adjuvant chemotherapies will require multi-institutional clinical trials in order to determine safety and efficacy in a large population [22]. Genetic therapy holds promise for all tumors of the CNS, and the focal, well-circumscribed nature of IMSTs may allow for the utilization of convection delivery of therapeutic agents directly into the spinal cord [23].

References

1. Mottl H, Koutecky J. Treatment of spinal cord tumors in children. Med Pediatr Oncol 1997;29(4):293–5
2. Jallo GI, Freed D, Epstein F. Intramedullary spinal cord tumors in children. Childs Nerv Syst 2003;19(9):641–9
3. Miller DC. Surgical pathology of intramedullary spinal cord neoplasms. J Neuro-oncol 2000;47(3):189–94
4. Deme S, et al. Primary intramedullary primitive neuroectodermal tumor of the spinal cord: case report and review of the literature. Neurosurgery 1997;41(6):1417–20
5. Cohen AR, et al. Malignant astrocytomas of the spinal cord. J Neurosurg 1989;70(1):50–4
6. Constantini S, et al. Intramedullary spinal cord tumors in children under the age of 3 years. J Neurosurg 1996;85(6): 1036–43
7. Rifkinson-Mann S, Wisoff JH, Epstein F. The association of hydrocephalus with intramedullary spinal cord tumors: a series of 25 patients. Neurosurgery 1990;27(5):749–54; discussion 754
8. Lowe GM. Magnetic resonance imaging of intramedullary spinal cord tumors. J Neuro-oncol 2000;47(3):195–210
9. Muszynski CA, Constantini S, Epstein FJ. Intraspinal intramedullary neoplasms. In: Albright L, Pollack I, Adelson D, editors. Principles and practice of pediatric neurosurgery. New York: Thieme Medical Publishers; 1999. p. 697–709
10. Constantini S, et al. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 2000;93(2 Suppl):183–93
11. Kothbauer K, Deletis V, Epstein FJ. Intraoperative spinal cord monitoring for intramedullary surgery: an essential adjunct. Pediatr Neurosurg 1997;26(5):247–54
12. Garcia DM. Primary spinal cord tumors treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 1985;11(11):1933–9
13. Marsa GW, et al. Megavoltage irradiation in the treatment of gliomas of the brain and spinal cord. Cancer 1975;36(5):1681–9
14. O'Sullivan C, et al. Spinal cord tumors in children: long-term results of combined surgical and radiation treatment. J Neurosurg 1994;81(4):507–12
15. Clayton PE, Shalet SM. The evolution of spinal growth after irradiation. Clin Oncol (R Coll Radiol) 1991;3(4):220–2
16. Duffner PK, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 1993;328(24):1725–31
17. Sundaresan N,. Gutierrez FA, Larsen MB. Radiation myelopathy in children. Ann Neurol 1978;4(1):47–50
18. Nadkarni TD, Rekate HL. Pediatric intramedullary spinal cord tumors. Critical review of the literature. Childs Nerv Syst 1999;15(1):17–28
19. Chamberlain MC. Salvage chemotherapy for recurrent spinal cord ependymona. Cancer 2002;95(5):997–1002
20. Yasuoka S, Peterson HA, MacCarty CS. Incidence of spinal column deformity after multilevel laminectomy in children and adults. J Neurosurg 1982;57(4):441–5
21. Abbott R, et al. Osteoplastic laminotomy in children. Pediatr Neurosurg 1992;18(3):153–6
22. Balmaceda C. Chemotherapy for intramedullary spinal cord tumors. J Neuro-oncol 2000;47(3):293–307
23. Lonser RR, et al. Direct convective delivery of macromolecules to the spinal cord. J Neurosurg 1998;89(4):616–22

Peripheral Nerve Tumors in Children

52

W. Bradley Jacobs, Rajiv Midha

Epidemiology – 612

Symptoms and Clinical Signs – 612

Diagnostics – 612

Classification – 612

Treatment and Prognosis – 613
Tumors of Nerve Sheath Origin
Schwannoma
Neurofibroma
Perineurioma
Malignant Peripheral Nerve Sheath Tumors
Tumors of Neural Origin

References – 615

Epidemiology

Peripheral nerve tumors (PNTs) are uncommon lesions and occur with even less frequency in children than adults. Due to their uncommon nature, precise epidemiological data regarding pediatric PNTs is not readily available. Estimates suggest that 14% of all pediatric soft tissue tumors arise from the peripheral nervous system [4], with soft tissue tumors accounting for 6%–8% of all childhood malignancies (compared to <1% in adults) [7]. There are several key differences between the incidence of the various types of pediatric PNTs as compared with the adult distribution. For instance, while schwannomas and neurofibromas represent the vast majority of peripheral nerve neoplasms in the adult population, they account for less than 50% of childhood peripheral nerve neoplasms [4]. Furthermore, due to their embryonal nature, neuroblastic PNTs compose a relatively larger portion of childhood PNTs, with 99.5% of all peripheral neuroblastic tumors occurring in the first two decades of life [2], and accounting for about one third of childhood PNTs [4].

Symptoms and Clinical Signs

Pediatric PNTs most commonly present as a painless soft tissue mass in the abdomen or within an extremity, or as an incidental mass lesion on routine chest X-ray. The general differential diagnosis of a soft tissue mass is extensive and includes infectious/inflammatory lesions, vascular malformations, soft tissue neoplasia, and, in the case of abdominal or thoracic lesions, organ-specific neoplasia. Often, specific features of the clinical history, findings on physical examination, or diagnostic investigations can further direct the physician towards the correct diagnosis of a PNT. For instance, a family history or clinical stigmata of neurofibromatosis I (NF1) or neurofibromatosis II (NF2) raises suspicion of neurofibromas or schwannomas, respectively. Children may also complain of some degree of mild subjective sensory loss or paresthesias as a presenting sign of a PNT. Objective loss of function in the distribution of the affected nerve is relatively rare with benign PNTs, but does occur more commonly with neurofibromas than schwannomas [5]. Their extremely slow rate of growth, with subsequent gentle stretch and elongation of the involved fascicles accounts for the relatively well-preserved neural function that is observed, even in the context of large PNTs. Referred dysesthesia when percussing over the mass (Tinel's sign) is also a common finding. New onset pain, greatly increased pain, rapid increase in tumor size, or sudden, progressive loss of function along the involved nerve should raise suspicion of malignant degeneration of a previously benign neurofibroma or de novo formation of a malignant lesion, such as a malignant peripheral nerve sheath tumor (MPNST). Furthermore, due to the risk of malignant degeneration in children with NF1 [18], all PNTs of NF1 patients should be viewed with suspicion.

Peripheral neuroblastic lesions arise from the sympathetic nervous system and, accordingly, have a clinical presentation different from other peripheral nerve neoplasms. In addition to their presentation as abdominal, mediastinal, or thoracic mass lesions, this group of neoplasms may present with Horner's syndrome, owing to the involvement of cervical sympathetic nerves, or diarrhea, secondary to release of vasoactive intestinal polypeptide. Myelopathy secondary to spinal cord compression is also possible following infiltration of dumb-bell-shaped neuroblastic tumors through the neural foramina into the vertebral canal.

Diagnostics

The specific imaging characteristics of pediatric PNTs are similar to their adult counterparts. However, the diagnostic imaging investigation of PNTs can be a challenging proposition in the pediatric population, due to patient size and noncompliance. Magnetic resonance imaging (MRI) is the imaging modality of choice, as it is noninvasive, demonstrates proximal and distal lesions with equal efficacy, provides unparalleled image resolution, and can often definitively identify the nerve of origin. Nerve conduction studies and electromyography (NCS/EMG) may also be performed in the diagnostic work-up of a pediatric PNT. However, these studies are technically difficult in infants and young children and do not often contribute salient information to the specific diagnostic decision-making process, as there are no neurophysiological characteristics that differentiate among the peripheral nerve tumors and the studies are, in fact, often normal. As such, the role of NCS/EMG in the evaluation of pediatric PNTs is limited. NCS/EMG can, however, provide objective electrophysiological measures of baseline nerve function, and thus may be of use for documentation of baseline nerve function in cases where neurological function is to be monitored over time for deterioration or to evaluate treatment.

Classification

PNTs can arise from components of the nerve sheath (Schwann cells, perineurial fibroblasts) or from neuroectodermal cells. In addition, a number of rare tu-

mors with a non-nerve sheath/non-neural histogenesis may also infiltrate the peripheral nerves of children. The spectrum of PNTs is presented in Table 1 and represents a modification of Reed and Harkin's classic taxonomy of PNTs [14].

Treatment and Prognosis

Since PNTs encompass a diverse group of lesions (Table 1), the treatment of a specific PNT must be individualized on the basis of the presenting pathological entity. Similarly, due to the divergent pathobiology of PNTs, prognostication is also a function of the specific tumor.

Tumors of Nerve Sheath Origin

Schwannoma

While schwannomas are one of the most common PNTs in adults, they are relatively uncommon in the pediatric population. In one large series, only 3% of schwannoma presented in the first two decades of life [20], while another case series found that 5% of all pediatric peripheral nerve neoplasms were schwannomas [4]. Indeed, due to their relative rarity, pediatric patients harboring one or more confirmed schwannomas should be investigated for a possible NF2 mutation [11].

Table 1 Classification of peripheral nerve tumors

I.	**Nerve sheath origin**	
	A. Benign	
		Schwannoma
		Neurofibroma
		Perineurioma
	B. Malignant	
		Malignant peripheral nerve sheath tumor (MPNST)
II.	**Neural origin**	
		Neuroblastoma
		Ganglioneuroma
		Ganglioneuroblastoma
III.	**Non-neural origin**	
		Lipofibromatous hamartoma
		Intraneural lesions (lipoma, ganglion, hemangioma)
IV.	**Metastases to peripheral nerve**	

Pediatric schwannomas should be managed in a fashion identical to their adult counterparts. Surgical extirpation is the mainstay of therapy. As schwannomas are slow-growing benign lesions, complete resection provides a cure in practically all cases. While there is no outcome data that focuses solely on pediatric schwannomas, in the largest adult series to date, 90% of patients improved or remained clinically stable after surgical resection [5]. Given that the biological and clinical behavior of pediatric schwannomas appears identical to adult cases, a similar success rate should be achieved in pediatric cases.

Neurofibroma

The incidence of neurofibromas in the pediatric population, unlike schwannomas, more closely approximates that of the adult population. In a large series by Coffin et al. [4], neurofibromas accounted for 43% of all pediatric peripheral neurogenic tumors and due to the low incidence of schwannomas in children, 90% of all benign pediatric peripheral nerve sheath tumors. By way of comparison, in large adult surgical series, neurofibromas account for 40%–67% of benign peripheral nerve sheath tumors [1, 5]. The proportion of NF1-associated neurofibromas is approximately the same in pediatric and adult surgical series (around 30%) [4, 5], suggesting that an association with this phakomatosis does not account for the increased proportion of pediatric neurofibromas relative to schwannomas.

As with adult neurofibromas, two different morphological types of neurofibromas are found in the pediatric population. The first is the fusiform neurofibroma, which usually arises from a single nerve fascicle as an isolated proliferation of neoplastic cells within the sheath of an associated nerve. Fusiform neurofibromas develop as a nodular swelling on a nerve and are often solitary lesions, but may be multiple in the setting of NF1. A large portion of NF1 patients will develop cutaneous (dermal) neurofibromas throughout childhood. These lesions are fusiform neurofibromas of tiny cutaneous nerves. They are soft, discrete nodules, often with a violaceous color, that lie within the dermis and epidermis. They can occur on any cutaneous surface, are rarely painful, and exhibit a nonlinear growth pattern, with years of slow growth followed by periods of rapid expansion. These lesions rarely undergo malignant degeneration, but due to their usual occurrence in large numbers, can be severely disfiguring.

NF1-associated deep, fusiform neurofibromas are very uncommon in the first decade, but begin to appear thereafter, with a peak incidence late in the third decade [5]. Loss of function (motor and/or sensory) in the distribution of the involved nerve appears

more common among NF1-associated neurofibromas, with only about 20% of cases exhibiting normal preoperative function [5]. The treatment of choice of pediatric fusiform neurofibromas (non-NF1 and NF1-associated) is complete surgical resection and follows the same surgical principles as outlined elsewhere for adult neurofibromas.

Plexiform neurofibromas constitute the second type of neurofibroma. These tumors form a network-like growth, arise from multiple nerve fascicles, often involve multiple branches of a large nerve, and lead to a diffuse mass of thickened nerves. Plexiform neurofibromas do not necessarily involve a nerve plexus such as the brachial or lumbosacral plexus. These tumors are almost exclusively associated with NF1 and are the most common peripheral neoplasm in children with NF1 [12]. The prevalence of these lesions continues to increase as patients reach adulthood. Plexiform neurofibromas present as large, soft subcutaneous swellings with poorly defined margins starting in early childhood. Often the overlying skin is hyperpigmented and/or hypertrophied, with occasional hypertrichosis. While severe intractable pain may be associated with plexiform neurofibromas, this is the exception rather than the norm [10]. Motor and sensory abnormalities along the affected nerve are very common [5, 10].

Plexiform neurofibromas are recognized as a significant cause of morbidity and mortality in patients with NF1. Surgery remains the only viable option for patients in whom a tumor is causing intractable pain or disability, although results are often less than satisfactory. A recent large series of surgically treated pediatric plexiform neurofibromas noted that while severe neurological complications occurred in only 4.6% of patients, overall freedom from progression was only 54% at a median follow-up of 6.8 years [12]. Prognostic factors for tumor recurrence were: age less than 10 years at the time of initial surgery, presence of residual tumor after surgery, and location of the tumor on the head, neck, or face.

The risk of sarcomatous degeneration is high among nondermal NF1-associated neurofibromas, and is a particularly worrisome feature of plexiform neurofibromas. In general, NF1 patients have a 3%–5% risk of conversion of a plexiform neurofibroma to a MPNST, while non-NF1 plexiform neurofibromas undergo malignant degeneration in less than 1% of cases [19]. A recent report suggests that the relative risk of an NF1 patient developing a MPNST is 133 times greater in relation to the general population [9]. As such, given the potential long life span of pediatric patients with NF1, these children need careful long-term follow-up. Any hint of symptomatology that suggests malignant progression should trigger aggressive investigation and surgical therapy.

Perineurioma

The perineurioma is a benign tumor composed of neoplastic perineurial cells located throughout the endoneurium. The clinical presentation is most commonly due to progressive muscle weakness, with or without atrophy. Perineuriomas typically present during childhood and adolescence; however, this lesion is exceedingly rare in both the pediatric and adult populations, representing much less than 1% of all peripheral nerve neoplasms. Long-term follow-up indicates that they do not recur if resected and they do not metastasize. The treatment of choice consists only of diagnostic biopsy, followed by release of any entrapment points. Resection should be avoided, in order to retain neurological function for as long as possible, as nerve graft reconstruction after excision often does not result in recovery of nerve function.

Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNSTs) are nonrhabdomyosarcomatous soft tissue tumors that arise from the peripheral nerve sheath. Childhood and adolescent cases are uncommon and account for only 13% of all MPNSTs [6], and 12% of all peripheral neurogenic tumors of childhood [4]. The association of MPNST with NF1 is well established, with MPNSTs occurring in the setting of NF1 in 50% of cases [19]. Pediatric MPNST case series reveal that 29%–66% of pediatric MPNSTs arise in the setting of NF1 [3, 6, 13], comparable to the overall NF1-related incidence.

As with adult MPNSTs, radical surgical excision represents the treatment of choice for pediatric MPNSTs. Due to their malignant nature, MPNSTs grow within the nerve fascicles but commonly invade the epineurium and infiltrate the adjacent soft tissue, complicating surgical resection. Outcome appears to be closely related to the extent of surgical removal of the primary tumor, with survival rates ranging from 75% 3-year disease-free survival [13] to 80% 10-year survival [3] in cases of gross total tumor resection. This compares with a 14% 10-year survival rate for patients who undergo nonradical surgical therapy [3]. MPNSTs can metastasize to lung, liver, bone, and the CNS, but lack of local control appears to be the major cause of treatment failure [3, 13]. In the most recent series of pediatric MPNSTs, the 10-year survival rate was 41% [3].

Given the small numbers of patients in pediatric MPNST case series, it is difficult to definitively ascertain the role of radiotherapy and chemotherapy in the management of MPNSTs. Anecdotal evidence does suggest that radiation therapy decreases the rate of local recurrence in cases of nonradical

resection [3], but its role in cases of gross total resection remains ill-defined. The role of chemotherapy is even harder to define, as MPNSTs are considered a poorly responsive tumor. Chemotherapy response rates are unsatisfactory and appear to offer little efficacy, as patients with advanced disease have a poor outcome despite the use of chemotherapy regimens [3].

Tumors of Neural Origin

Neurogenic PNTs are embryonal tumors that arise from migrating neuroectodermal cells that arise in the neural crest and are destined for the sympathetic nervous system. Because of their embryonal nature, they are exceedingly rare in adulthood, but account for a significant portion of childhood PNTs. They are the most common solid extracranial malignant tumors of the first 2 years of life [15], with 96% occurring in the first decade [2]. There is no sex predilection. In one large pathological series, neuroblastic tumors comprised approximately one third of all childhood PNTs [4]. Neuroblastic tumors can arise from the abdominal (25%), thoracic (15%), cervical (5%), and pelvic (5%) sympathetic ganglia, as well as the adrenal medulla [8], and thus commonly present as a palpable abdominal mass, with hepatomegaly, or as a thoracic mass detected on routine chest X-ray. While all peripheral neuroblastic tumors have traditionally been placed under the rubric of neuroblastoma, current recommendations suggest that a distinction be made between four types of peripheral neuroblastic tumors, based on the degree and type of histological differentiation: neuroblastoma, ganglioneuroblastoma/intermixed, ganglioneuroblastoma/nodular, and ganglioneuroma [8].

Most neuroblastomas occur in the first 2 years of life. Neuroblastomas may present as a mass at the primary site of origin, and are often quite large at the time of diagnosis, or following metastatic spread to abdominal viscera, lymph nodes, liver, or bone. CNS metastases are rare in children, but when present are often dural based [17]. In general, if neuroblastomas are discovered before the development of metastases, complete surgical extirpation with negative margins should be the goal of treatment, where anatomically possible. Patients with stage 4 disease (distant metastases) are usually treated initially with chemotherapy, followed either by observation or delayed resection of tumor [16]. Recommendations for adjuvant therapy of nonmetastatic neuroblastoma depend on the stage, age, and degree of surgical resection. Those with only microscopic residual should be followed conservatively, while patients with gross residual disease would receive chemotherapy and radiotherapy (if older than 1 year of age) [16]. Despite aggressive therapy, overall prognosis is poor, and survival only approaches 20%–30% in cases with multiple negative prognostic indicators (i.e., N-myc amplification, 1*p* LOH, lack of TrkA expression, age greater than 1 year, abdominal location) [17].

Peripheral ganglioneuromas commonly arise in the retroperitoneal or retropleural space, often present much later than neuroblastomas, with a peak incidence in the second decade of life and usually present with symptoms secondary to mass effect. Metastases from ganglioneuromas are very uncommon, and this lesion essentially behaves in a benign nature. The treatment of choice is wide local excision and little evidence exists to support the use of adjuvant therapy [16]. Prognosis is excellent and long-term survival after successful surgical resection is good, except in the rare cases of metastases.

Ganglioneuroblastomas are biologically intermediate between ganglioneuromas and neuroblastomas. They most commonly occur in children less than 6 years of age and have a distribution similar to that of ganglioneuromas. The behavior of ganglioneuroblastomas is unpredictable, but the intermixed variant appears to have a more favorable prognosis than the nodular variant [8]. The goal of treatment should be complete surgical resection of the tumor where possible. Recommendations for adjuvant therapy follow that of neuroblastoma, as outlined above. Due to their aggressive nature, the prognosis of ganglioneuroblastomas is poor, and similar to that of neuroblastoma.

References

1. Artico M, Cervoni L, Wierzbicki V, et al. Benign neural sheath tumours of major nerves: characteristics in 119 surgical cases. Acta Neurochir (Wien) 1997;139:1108–1116
2. Brodeur GM, Castleberry RP. Neuroblastoma. In: Poplack DG, editor. Principles and practice of pediatric oncology. 2nd ed. Philadelphia: J. B. Lippincott; 1993. p. 739–767
3. Casanova M, Ferrari A, Spreafico F, et al. Malignant peripheral nerve sheath tumors in children: a single-institution twenty-year experience. J Pediatr Hematol Oncol 1999;21:509–513
4. Coffin CM, Dehner LP. Peripheral neurogenic tumors of the soft tissues in children and adolescents: a clinicopathologic study of 139 cases. Pediatr Pathol 1989;9:387–407
5. Donner TR, Voorhies RM, Kline DG. Neural sheath tumors of major nerves. J Neurosurg 1994;81:362–373
6. Ducatman BS, Scheithauer BW, Piepgras DG, et al. Malignant peripheral nerve sheath tumors in childhood. J Neurooncol 1984;2:241–248
7. Harms D. Soft tissue sarcomas in the Kiel Pediatric Tumor Registry. Curr Top Pathol 1995;89:31–45
8. Joshi VV. Peripheral neuroblastic tumors: pathologic classification based on recommendations of international neu-

roblastoma pathology committee (Modification of shimada classification). Pediatr Dev Pathol 2000;3:184–199
9. King AA, Debaun MR, Riccardi VM, et al. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. Am J Med Genet 2000;93:388–392
10. Korf BR. Plexiform neurofibromas. Am J Med Genet 1999;89:31–37
11. Mautner VF, Tatagiba M, Guthoff R, et al. Neurofibromatosis 2 in the pediatric age group. Neurosurgery 1993;33:92–96
12. Needle MN, Cnaan A, Dattilo J, et al. Prognostic signs in the surgical management of plexiform neurofibroma: the Children's Hospital of Philadelphia experience, 1974–1994. J Pediatr 1997;131:678–682
13. Raney B, Schnaufer L, Ziegler M, et al. Treatment of children with neurogenic sarcoma. Experience at the Children's Hospital of Philadelphia, 1958–1984. Cancer 1987;59:1–5
14. Reed RJ, Harkin JC. Tumors of the peripheral nervous system. Washington, D.C.: Armed Forces Institute of Pathology; 1983
15. Ross JA, Severson RK, Pollock BH, et al. Childhood cancer in the United States. A geographical analysis of cases from the Pediatric Cooperative Clinical Trials groups. Cancer 1996;77:201–207
16. Saenz NC, Schnitzer JJ, Eraklis AE, et al. Posterior mediastinal masses. J Pediatr Surg 1993;28:172–176
17. Schwab M, Shimada H, Joshi VV, et al. Neuroblastic tumours of adrenal gland and sympathetic nervous system. In: Cavenee WK, editor. Pathology & genetics: tumours of the nervous system. Lyon: IARC Press; 2000. p. 153–161
18. Shearer P, Parham D, Kovnar E, et al. Neurofibromatosis type I and malignancy: review of 32 pediatric cases treated at a single institution. Med Pediatr Oncol 1994;22:78–83
19. Sorensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. N Engl J Med 1986;314:1010–1015
20. Woodruff JM, Kourea HP, Louis DN, et al. Schwannoma. In: Cavenee WK, editor. Pathology & genetics: tumours of the nervous system. Lyon: IARC Press; 2000. p. 164–166

Spinal Neuro-Oncology III

Organised by Jörg-Christian Tonn

53 Intramedullary Tumors – 619
Manfred Westphal

54 Intradural Extramedullary Tumors – 635
Roland Goldbrunner

55 Epidural Tumors and Metastases – 645
Carlos A. Bagley, Zima L. Gokaslan

Intramedullary Tumors 53

Manfred Westphal

Definition – 620

Epidemiology and Etiology – 620

Histology and Molecular Genetics – 620

Diagnostics – 620

Differential Diagnosis – 626

Treatment and Prevention – 628

Prognosis – 631

References – 632

Definition

Intramedullary tumors may arise in the spinal cord from the intrinsic cell types therein (intra-axial lesions) or get into the spinal cord as metastases from systemic cancer (extra-axial lesion). Intra-axial intramedullary tumors are gliomas and are classified like the intrinsic brain tumors according to the WHO grading system [21]. Corresponding to the intracranial compartment, ependymomas, astrocytomas, oligodendrogliomas, and glioneuronal tumors are found also in the intramedullary segment of the central nervous system. Hemangioblastomas are frequently also found in the spinal cord and are truly intramedullary but as they arise from the surface they are almost an invagination into the cord, displacing and compressing the fiber tracts rather than dissecting them. Tumors are called purely intramedullary from the level of C1 downwards to the end of the cord at the level of the conus. Interestingly, when extending from the cervical cord into the medulla oblongata, a tumor is called cervico-medullary, "cervico" in this case referring to the intramedullary part in the spinal cord. Tumors of the filum terminale will in this context not be considered intramedullary.

Depending on their location, tumors are cervical, cervicothoracic, thoracic, thoracolumbar, and conal.

Upward extensions into the medulla oblongata will be called cervicomedullary and further extension into the pons will lead to a tumor being classified as pontomedullary.

Epidemiology and Etiology

Intramedullary tumors affect all ages and races. They are mostly spontaneous and not associated with specific syndromes. There is a higher incidence of intramedullary ependymomas with patients with neurofibromatosis type 2 [31] and with multiple hemangioblastomas and von Hippel Lindau disease, both hereditary syndromes. In general, the majority of the adult patients are between 20 and 50 years of age.

Intramedullary tumors reflect the whole histological spectrum of intracranial neuropathology. Likewise, there is no associated etiology for any of the tumors as there is not for the cerebral tumors.

Histology and Molecular Genetics

The relative proportions of the different histologies within the spectrum of tumors occurring in the spinal cord tissue is slightly different from the brain tissue. In contrast to the brain, ependymomas are the major group, followed by astrocytomas and gangliocytomas and hemangioblastomas. Lipomas are not really considered neoplastic but are still slowly expanding lesions and need to be discussed in the context of management of spinal cord lesions. This spectrum is reflected by our own departmental series which is very similar to other large series (Table 1).

There is no report on fundamental, specific molecular genetic differences between spinal cord tumors and cerebral tumors. Only spinal cord ependymomas have been compared to the less frequent cranial tumors and it was found that there are some differences which, however, do not indicate a different etiology or cell lineage [23]. Hemangioblastomas in the spinal cord are known to carry mutations of the VHL gene as do the other tumors elsewhere in the central nervous system [34].

Diagnostics

The onset of neurological symptoms is usually very slow and the symptoms may erroneously be seen in the context of fatigue or exhaustion so that they are not taken seriously. The feeling of heaviness in the legs, some tingling in one extremity, the sensation as if a cuff is inflated around an arm or a leg and occasional numbness are not considered severe enough to be aggressively pursued because there are many other transient indispositions which may cause the same symptoms. Only with progressive loss of neurological function and the gradual development of a transverse syndrome will patients be subjected to more aggressive diagnostics. The field of intramedullary pathologies has been revolutionized since the routine availability of the MRI in the late 1980s. Since

Table 1. Spectrum of intramedullary lesions (1984–2004) (n = 260)

Neoplastic	
Ependymoma	97 (36%)
Subependymoma	2 (1%)
Astrocytoma I–II	43 (17%)
Astrocytoma III/IV	18 (8%)
Oligodendroglioma	4 (2%)
Ganglioglioma/-cytoma	10 (4%)
Lipoma	9 (4%)
Metastasis	2
Vascular	
Cavernoma	28 (9%)
Angioblastoma	45 (19%)

then, diagnosis and differential diagnosis has become much more rapid and definitive and can safely guide the appropriate therapy. Imaging can be supported by electrophysiology which can provide an estimate of how severely some fiber tracts might already be damaged. The analysis of cerebrospinal fluid may also be of help when as a differential diagnosis an inflammatory process needs to be considered.

As a rule of thumb, all tumorous lesions show a considerable mass effect and distend the medulla to an extent easily seen on sagittal MRI because of narrowing of the perimedullary CSF space, best depicted in a T2-weighted series.

Ependymomas show a very diverse appearance [5, 26, 37]. Because of their origin from the central canal, they are usually centrally located and displace the medulla in a concentric pattern which is best seen on axial images. Rarely can they break their coat of fiber tracts and protrude dorsally or ventrally through the dorsal midline sulcus (Fig. 1). That, however, is a rather unusual presentation and other differential diagnoses (i.e., amelanotic melanocytoma) have to be considered and evaluated by exhaustive immunohistochemistry (Fig. 2). Usually they are contained within the cord and are either solid and homogeneously enhancing with gadolinium (Fig. 3) or as in most cases there will be polar cysts which can extend three to four levels beyond the tumor poles (Fig. 4). The syringomyelia, which may appear septate, is usually communicating. In addition, some tumors may show regressive changes within themselves like degenerative cysts or signs of older hemorrhages (Fig. 5). Whatever the appearance of an ependymoma is, it will most likely be relatively easy to remove it completely (see below). Therefore that diagnosis should not be missed in order to not delay or withhold treatment. Under no circumstance should patients be told by therapists who are not dealing with these lesions

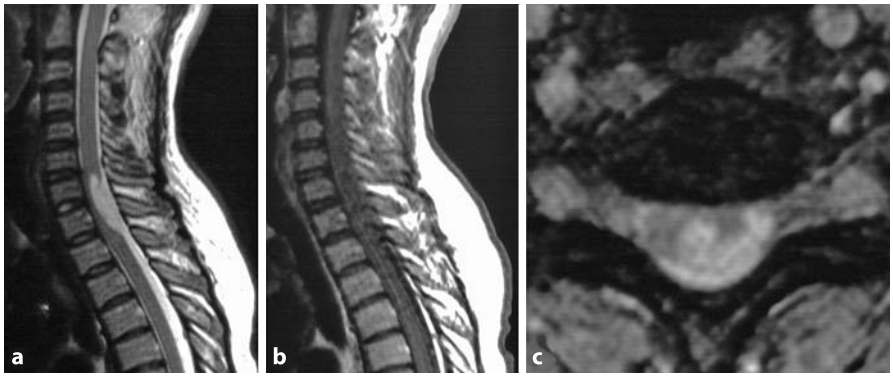


Fig. 1. Sagittal MR scans (**a, b**) of an atypical cervicothoracic ependymoma which shows homogeneous contrast enhancement and can be seen to be exophytic in the axial scans (**c**). The tumor part which covers the surface of the cord could be completely lifted up and showed no sign of infiltration

Fig. 2. Very similar MRI appearance of a tumor of the lower thoracic cord in a 74-year-old male which upon scrutiny by immunohistochemistry turned out to be an amelanotic melanocytoma

on a regular basis, that because of the dramatic neuroradiological presentation they have an untreatable lesion. It should be a standard, that MR images from intramedullary lesions are sent for consultation to experienced neuroradiologists especially because of the very heterogeneous spectrum of appearances.

Astrocytomas are also heterogeneous in their appearance [5, 12, 15] but in contrast to ependymomas, they are asymmetrical and located off-center which is in agreement with symptoms of more laterality than in the mostly central ependymomas. Pilocytic astrocytomas (WHO I) can enhance homogeneously with contrast media, have some patchy enhancement, or no enhancement at all (Fig. 6–8). The nature of their growth is hard to predict from the MRI where the axial images as far as definitive mar-

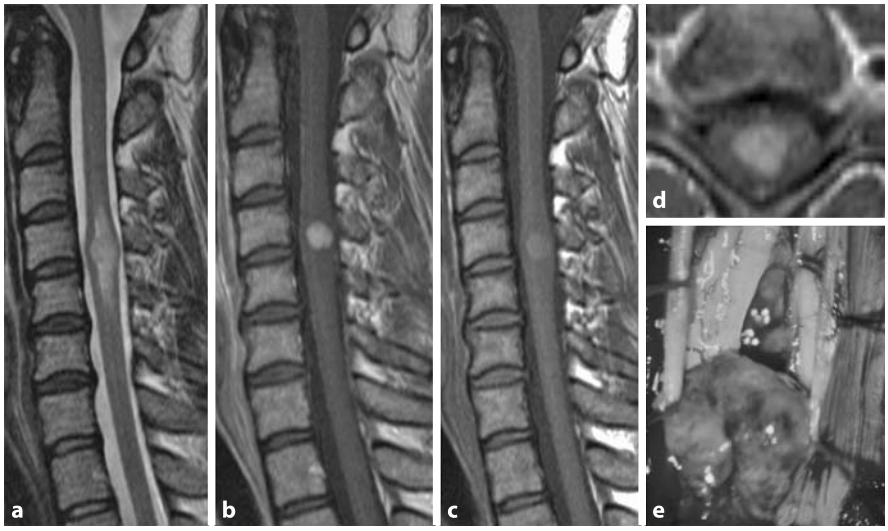


Fig. 3. Typical small intramedullary ependymoma showing again the uniform enhancement, central location, focal distension of the cord, polar edema. These tumors are very well delineated and can be usually removed in toto (**E**)

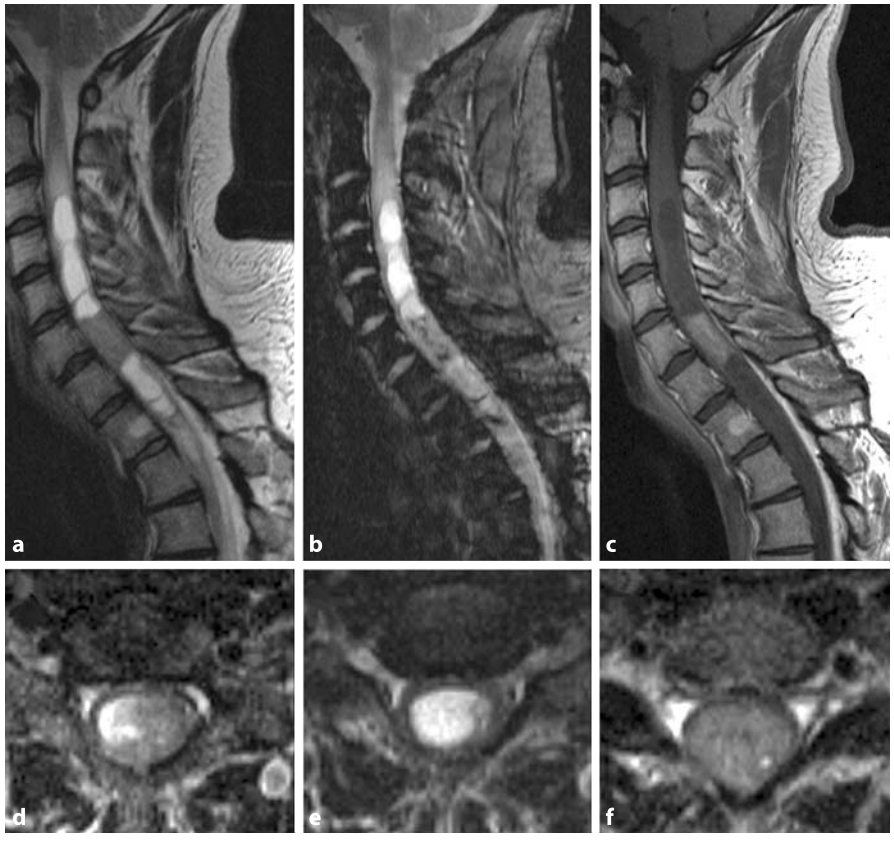


Fig. 4. Typical intramedullary ependymoma with inhomogeneous, polar cysts which make a similar impression to septate syringomyelia (**a, b**). The tumor itself is a contrast-enhancing mass which appears to be taking up the whole transverse diameter of the cord with no proper cord tissue (**d-f**)

gins are concerned can be just the opposite intraoperatively as what is seen in the images. In cases which are endophytic, a clean resection might be accomplished but in other cases, despite suggestive axial images no dissection plane can be found and only a debulking is possible. In cases in which very diffuse growth with Gd enhancement is seen, only a biopsy may be possible. A biopsy is, however, definitely indicated to exclude other lesions which might have other treatment options.

Diffuse astrocytomas (WHO II) regularly do not enhance, show diffuse growth in all MRI sequences, and show some kind of edema (T2 abnormality) extending far beyond the main tumor mass. Like in the intrinsic lesions of the brain, this could be indicative of continuous tumor spread and these tumors are known to extend eventually far upwards into the medulla oblongata or the pons where they cause terminal problems [35].

Anaplastic astrocytomas are rare (Fig. 9). They are suspected in the presence of a relative short and progressing history of neurological defects, affecting one side more than the other and an MRI with diffuse distension, no polar cysts, patchy but strong contrast enhancement, T2 changes much beyond the distended part of the medulla, and signs of necroses as in intracerebral glioblastoma. Because of the rarity of these lesions and their heterogeneous imaging nature, the differential diagnosis has to rely heavily on the inclusion of the clinical picture but definitive certainty can only be obtained from histological evaluation.

Glioneuronal tumors are nodular, inhomogeneously enhancing lesions which may have a cyst [32] (Fig. 10). They can cause very pronounced distension of the medulla and even enlargement of the spinal canal which already indicates their dysontogenic nature and long presence. They can go along with hemiatrophy of the whole body when located in the

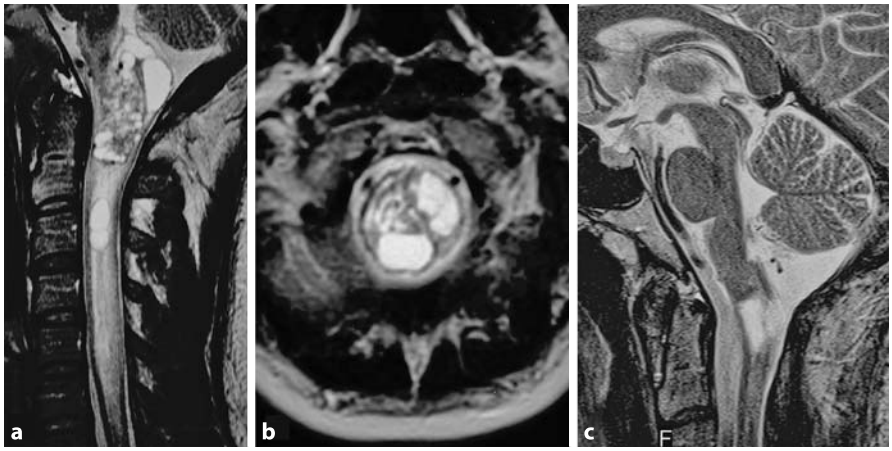


Fig. 5. Ependymoma of the craniocervical junction (**a**) which is associated with polar as well as intratumoral cysts. Despite the impressive size, even such lesions can be removed without neurological deficits (**c**). The inhomogeneous appearance in such cases is indicative of regressive changes which allow for optimal distinction between tumor and the proper cord tissue during microsurgical dissection

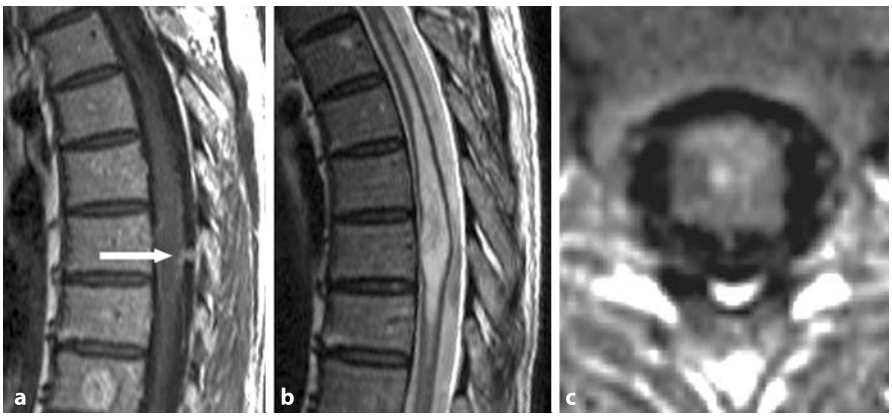


Fig. 6. Very atypical, biopsy-proven pilocytic astrocytoma which has profusely infiltrated through the whole cord with only minimal affection of the fiber tracts. At several points the tumor has broken out of the cord forming little solid nodules on the surface

upper cervical region or of the legs when located in the thoracic region (Fig. 11).

Intramedullary hemangioblastomas are nearly always associated with a cystic component which can extend over many levels, while the angioblastoma is only the size of a small pea or a grain of rice [11, 28] (Fig. 12). When located at the surface, they can grow within a cyst which indents the medulla (Fig. 13) but

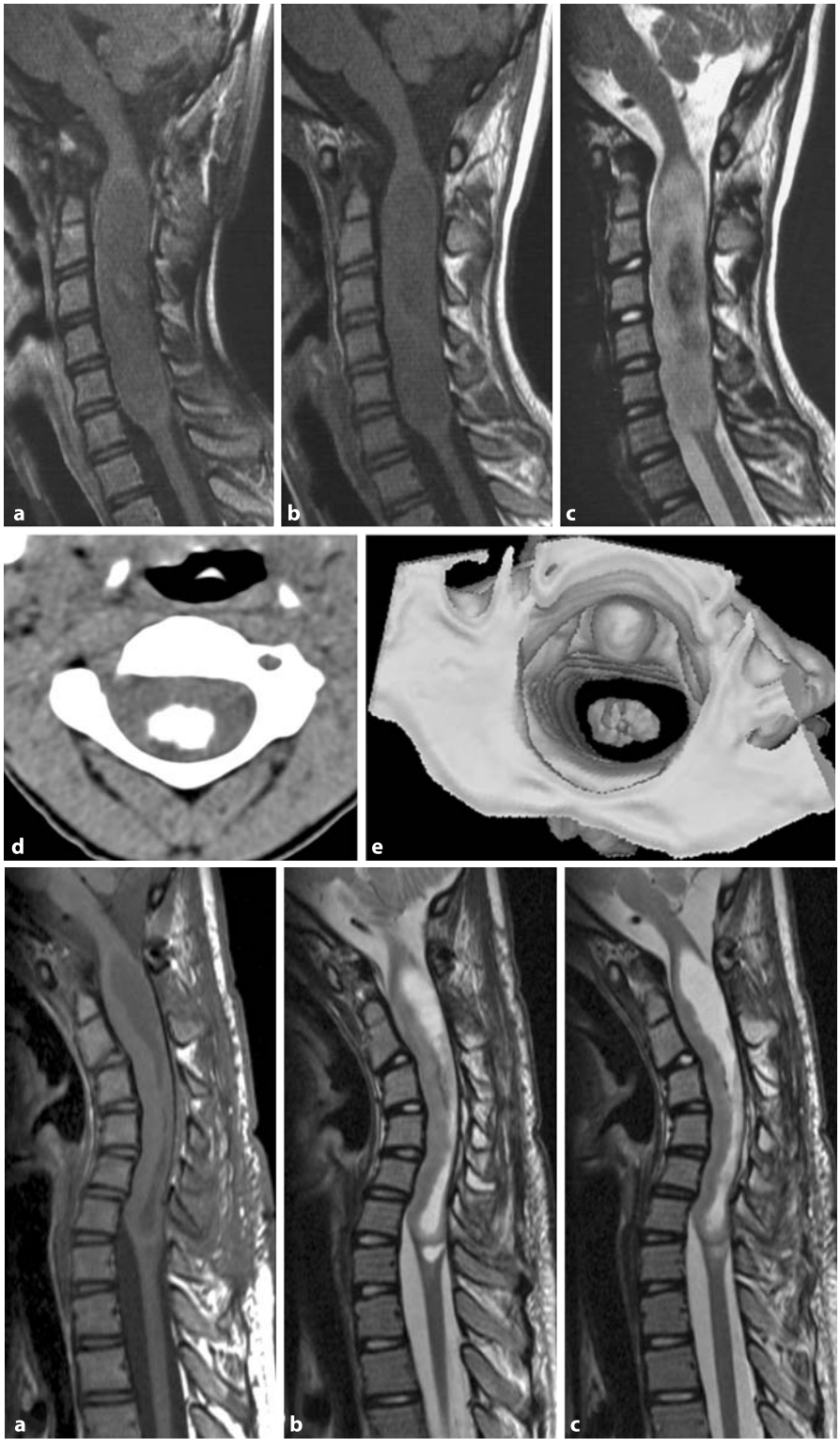


Fig. 7. Extensive cervical pilocytic astrocytoma of a 14-year-old boy which showed a long calcified nucleus as seen as a hypointense area in the MRI (**c**), and on axial (**d**) as well as spiral (**e**) CT. In contrast to the more endophytic, very well-delineated growth of the young boy shown earlier (Fig. 14), this case could only be extensively debulked in the absence of a clear dissection plane. The long exposure led to the development of a swan neck already within 1 year postoperatively despite laminotomy, requiring eventual stabilization

can also be without a cystic component. Upon gadolinium application they stain intensely. In the T2-weighted sequences it may be possible to see distended vessels on the surface of the medulla which are usually the draining veins. Angiography can confirm the diagnosis but should only be performed mainly if there is an attempt to do a preoperative embolization (see below). To make the diagnosis is easy in most cases even for sporadic cases, but most cases are associated with a known von Hippel-Lindau disease.

Intramedullary metastases are rare. They are typically associated with a known systemic cancer and can be truly intramedullary from hematogenous metastases as well as invading the medulla from the surface after breaking the pial membrane in the context of meningeal carcinomatosis. They have no typical neuroimaging characteristics and the diagnosis is based on the context of the systemic disease. Primary intramedullary melanoma has been reported but it is unresolved whether this is truly a primary lesion

Fig. 8. Recurrent pilocytic astrocytoma which had be gross totally resected 8 years prior to the shown scans. The lesion appears also homogeneously contrast enhancing but lacks polar cysts. Upon reoperation by the same surgeon, the whole interface between tumor and residual cord was found to be an area of broad invasion, not allowing radical resection

Fig. 9. Recurrent anaplastic astrocytoma in a 56-year-old woman. A diffuse enlargement of the cervical cord is seen as well as inhomogeneous contrast enhancement (**a, b**). Without further option for resection or radiation, the patient underwent chemotherapy but still progressed to a picture which is consistent with glioblastoma (**c, d**)

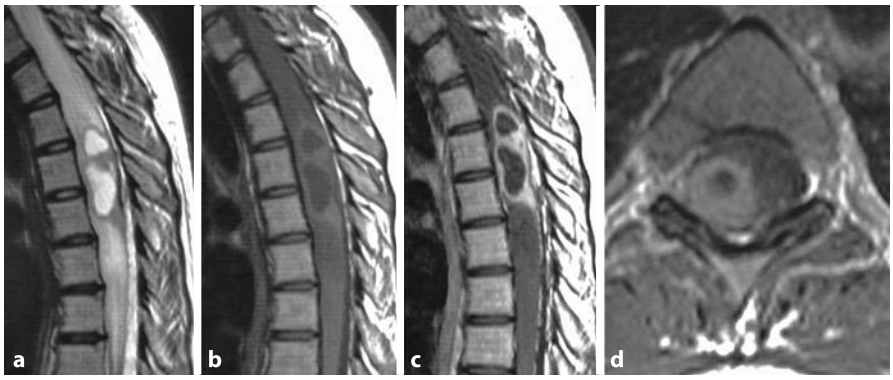


Fig. 10. Eccentric, cystic intramedullary lesion with contrast enhancement in a massively distended cord (**a-c**). In the presence of very slowly progressing symptoms which retrospectively had a history of years, only a well-differentiated process is to be suspected and in this case the histology turned out to be gangliocytoma. Intraoperatively the lesion turned out to be gangliocytoma and could only be debulked as the lesion is isomorphic with the tissue of the cord and offers no dissection plane despite the sharp demarcation in the axial MRI (**d**)

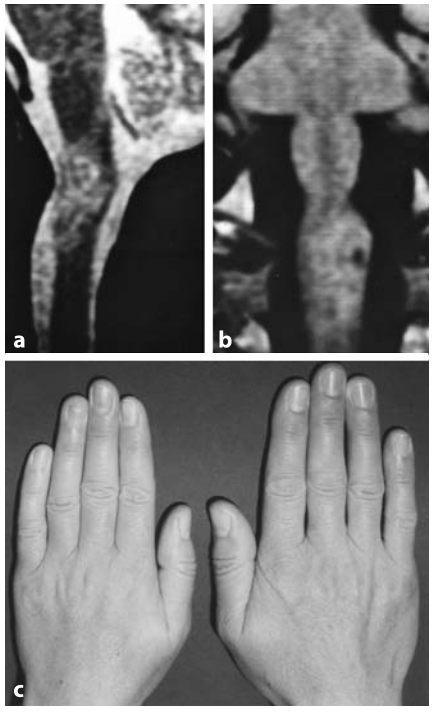


Fig. 11. Incidental finding of an intramedullary lesion in a 40-year-old woman. Retrospectively she reported that all her life her left side was somewhat weaker and upon physical examination she revealed a marked hemihypotrophy which can be seen in direct comparison of the hands. The lesion was never biopsied but a glioneuronal dysontogenic lesion is the most likely histology

or cancer with unknown primary, which is not infrequently found in melanoma due to the postulated immunogenicity outside the CNS.

Intramedullary lipomas show a characteristic pattern of signal intensities in T1 and T2 which allow the diagnosis without histology [19, 25]. In most cases, the lipoma is exophytic as a very intense mass in T1 but it may also be intramedullary, mimicking syringomyelia on some sequences (Fig. 14).

Differential Diagnosis

The most important differential diagnoses are inflammation and arteriovenous fistula [8, 24, 43].

Inflammatory lesions are mostly eccentric, have diffuse margins, weak contrast enhancement and most often a spindle-shaped extension rather than a nodular appearance (Fig. 15). They may be most easily mistaken for an anaplastic astrocytoma. Very frequently there is only a relatively short history of clinical symptoms which is disproportional to the usually limited extent of the lesion when compared to the ratio of size to symptoms in tumorous lesions. Apart from the case history, the next clue is the complete absence or only negligible extent of mass effect. CSF examination may be normal.

The other very important differential diagnosis is that of a congestive myelopathy due to an arteriovenous malformation. Spinal dural AV-fistula may cause such congestion and if left undiagnosed and untreated will result in gliotic changes in the medulla which may even become necrotic, which is why the disease, before the elucidation of its cause, was known as necrotizing myelitis. The neuroradiological signs are clear because there are distended blood vessels on the surface of the medulla and a homogeneous central edema on T2 which may affect almost the whole spinal cord (Fig. 16). When this is not recognized and erroneously biopsied the wrong diagno-

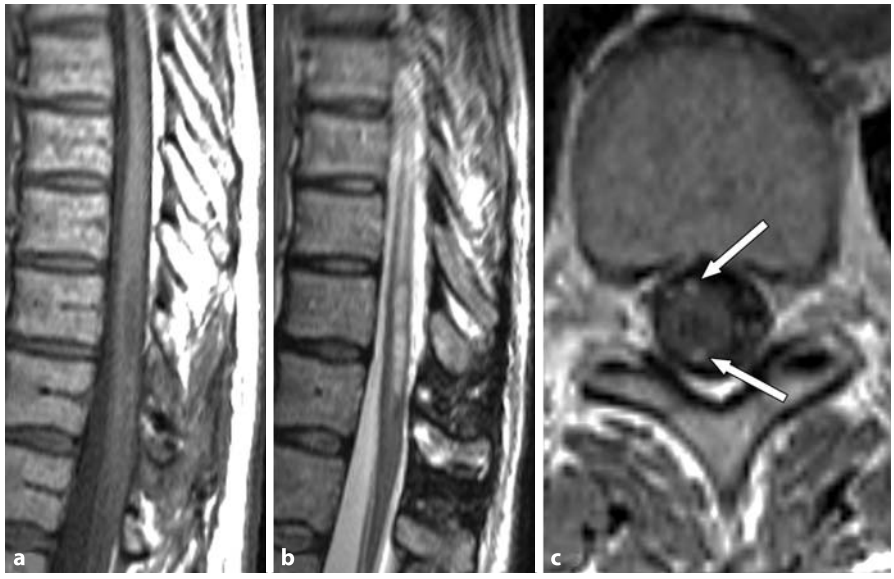


Fig. 12. A patient with von Hippel-Lindau disease and repeated operations for spinal hemangioblastomas. On this occasion, a severe neurological symptomatology with dysesthesias, pain and urinary incontinence were attributable to a lower thoracic syringomyelia (**a, b**) caused by a hemangioblastoma of only 4 mm in diameter

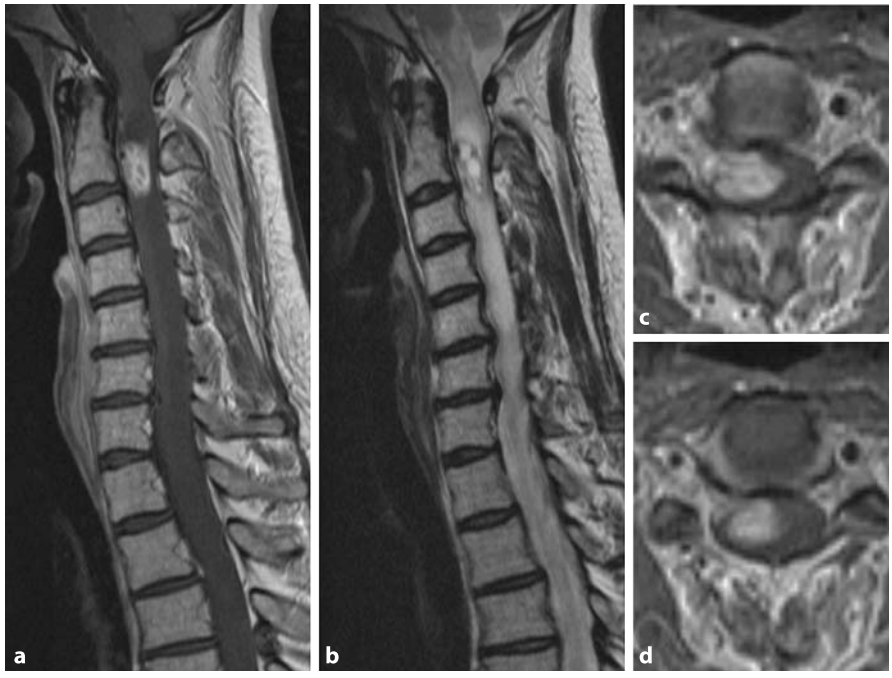


Fig. 13. Contrast-enhancing, presumably intramedullary tumor with a polar cyst which was thought to be an ependymoma. Intraoperatively it was found to be a hemangioblastoma which needed to be approached from a far lateral exposure with transection of the dentate ligament. No prominent blood vessels were seen and the only clue to the possible differential diagnosis was the broad attachment to the surface of the cord

sis may even become consolidated histologically because of the truly present gliotic changes which can resemble low-grade glioma.

Finally, it has to be mentioned that the spinal cord is considered to be less tolerant to radiation than other tissues and that therefore there is a considerable risk for radiation-induced myelopathy [27]. When radiation for thyroid cancer or lesions in the mediastinum require high-dose radiation and a considerable amount of dose is going through the spinal canal, radiation necrosis may be produced. In imaging it imposes like malignant glioma and there is also a relatively short history of progressive neurological deficit. However, the case history and the analysis of the radiation plans should clear the situation [1]. Often the fatty degeneration of the vertebral bodies is seen right in the area of medullary pathology. Induction of a secondary malignancy should be ruled out because of the time course which is much more rapid for radiation necrosis than for a radiation-induced malignancy. This diagnosis becomes much less frequent due to the improved conformal radiation techniques.

Treatment and Prevention

Treatment of spinal cord tumors is mostly surgical but may for some subgroups involve also radiation and/or chemotherapy, especially in lymphomas.

Ependymomas can be completely removed by established and refined microsurgical approaches [6, 9, 10, 36]. There is a well-demarcated dissection plane and the ends are frequently delineated by cysts. There is a tapering sleeve of gliosis around the cysts at the ends which extends into the central ca-

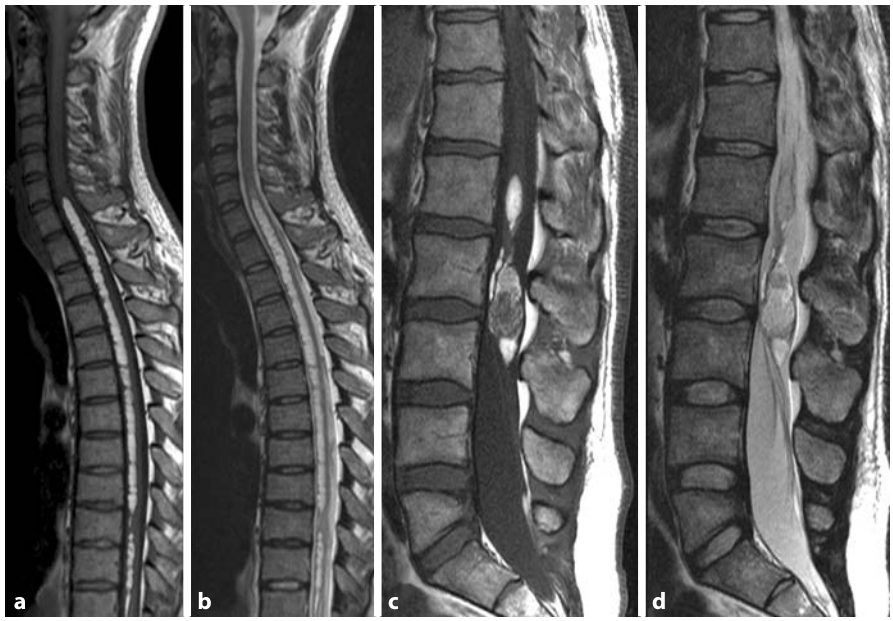


Fig. 14. Extensive holocord lipoma associated with a tethered cord malformation and a possibly teratomatous component at or below the level of the conus. The symptoms of dysesthesias and pain in the legs in the absence of any genitourinary symptoms cannot be associated with a specific location of this very extensive lesion so that no exposure was felt to be indicated and the patient is managed conservatively

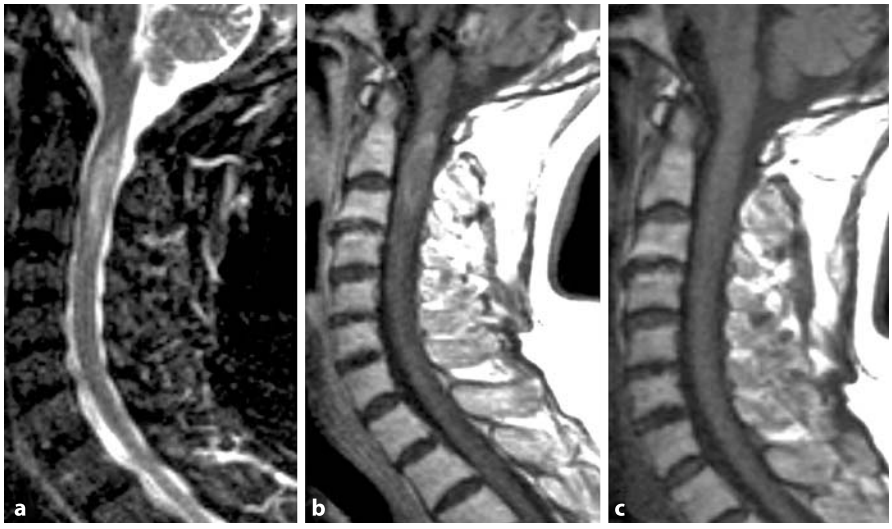


Fig. 15. Male patient with a diffusely-enhancing, ill-defined lesion in the cervical spinal cord and a rapid onset of symptoms. The absence of a cord distension together with the rapid onset of the neurological problems is characteristic for an inflammatory lesion. This proved to be the case and the lesion resolved over the course of a year

nal which is coagulated and cut, thereby preventing any upward or downward spread. The approach is through a midline incision and then dissection along the surface from pole to pole which in most cases of ependymoma allows for an en bloc resection (Fig. 17). The vascular supply comes from the anterior spinal artery from the ventral side and injury to that vessel is the major pitfall for surgery. The tolerance to disturbances of the vascular supply also varies at different levels of the cord. The cervical region is rich in supply from above and below because of feeders to the anterior spinal artery from different

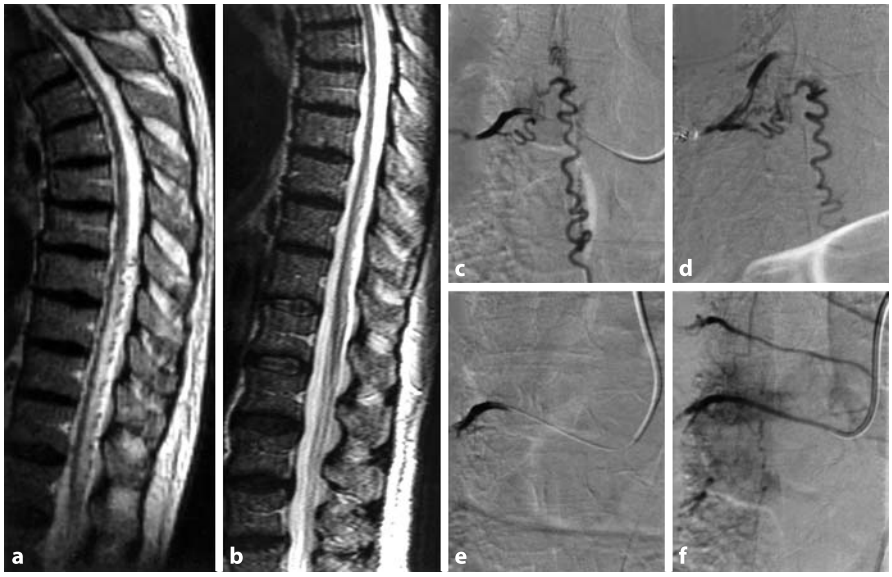


Fig. 16. A patient with the typical features of a spinal dural arteriovenous fistula. There is an edema in most of the thoracic cord but only very little mass effect (**a**). In this case, there is a very pronounced venous congestion which should lead to the correct diagnosis already on MRI. Angiography identifies the fistulous point (**c, d**), whereupon the fistula can be eliminated by transection (**e, f**), whereupon the edema resolves (**b**)

Fig. 17. Extensive, typical cervical ependymoma (**a**). Developing the lesion from the polar cysts along a dissection plane to the fiber tracts, the lesion can be developed in one piece (**b**). Postoperative stability is optimized by reinsertion of the en bloc laminotomy (**c**). Postoperatively the cysts are usually completely collapsed (**d**) and also the alignment is highly satisfactory

levels. The midthoracic region in contrast is less rich and therefore much more vulnerable (Westphal et al., unpublished observation). Dissection as with all other medullary pathologies is monitored by intraoperative electrophysiology of the motor and somatosensory evoked potentials, making the complete resection safer [22, 29]. For Grade II lesions there is a high cure rate after complete removal.

For anaplastic lesions, the rate of recurrence is considerable [14, 33]. The anaplastic lesions should also receive other therapies such as radiation [16] and/or chemotherapy [4, 7], although no standardized regimen has been established.

Follow-up with MRI is done for Grade II in yearly intervals up to 6 years, then biannually thereafter. Recurrence after 10 years is extremely unlikely. For Grade III lesions follow-up is in 6-month intervals for the first 2 years and then annually until year 6, and then as in the Grade II lesions. Should there be a recurrence, a reoperation should be considered as well as a new regimen for chemotherapy, incorporating a spectrum of agents not used in the first episode.

The removal of pilocytic astrocytomas may be attempted but sometimes only a debulking is possible (Fig. 7) or a dural expansion after biopsy. Additional therapies can be extrapolated from the supratentorial lesions where radiation and chemotherapy have been introduced [3]. Radiation therapy should, however, be withheld because of the vulnerability of the cord to doses exceeding 50 Gy. The patients are regularly followed as for low-grade ependymomas, and whenever there is progression repeated decompressions may be reconsidered. Upward extension is possible but usually the distension at the original level causing eventually a complete transverse syndrome is more typical. Although there may be a complete removal, recurrence is more likely because of the more infiltrative nature of the tumors compared to ependymomas (Fig. 8). Histological progression has not been reported in intramedullary tumors and also there is no case yet of an "anaplastic" intramedullary pilocytic which recently has been recognized intracranially.

Astrocytomas of all grades are removed as far as possible to gain time and secure the diagnosis [12, 15]. There are no series for adjuvant therapies for low-grade tumors which allow conclusions [13]. Patients are followed up and redecompression is carried out when necessary and permissible. Upward extension with progressive involvement of additional levels is common. As with the intracerebral astrocytomas there is progression to higher grades (II to III, or IV and III to IV) and then chemotherapy and radiation may be given as a palliative therapy. The postoperative course of Grade II patients may be stable for several years, whereas the course of the anaplastic tumors is rapidly progressive [20] leading eventually to lower brain stem dysfunction due to upward extension.

Oligodendrogliomas are very rare [39] and so there is no series which reports on the efficacy of procarbazine/CCNU/vincristine chemotherapy which has proven to be highly successful in the treatment of cranial oligodendrogliomas [40].

Glioneuronal tumors when found accidentally and suspected because of absence of any symptoms or dynamics of neurological deficits may be observed. When symptoms and clinical course justify intervention, surgery is the only option and when gross total resection is achieved, may lead to a long-term remission [9, 18, 32]. The surgeon has to be prepared for an isomorphic lesion which has no gliotic boundaries, is only slightly off-color from the fiber tracts, and without distinct change in consistency as it is really glioneuronal and very similar to the original tissue matrix of the cord. Therefore, decompression may only be possible in some cases. In this respect, these lesions are very different from the supratentorial compartment where they can be resected within a safety boundary of normal white matter in most cases, guided by intraoperative imaging like ultrasound or MRI. Such tolerance does not exist because in the spinal cord because the fiber tracts are certain to be contained somewhere in the tissue, which in MRI or in the intraoperative ultrasound appears abnormal in its signal characteristics.

Hemangioblastomas are surgically removed, with or without prior embolization [38, 41, 42]. The symptoms, which are more frequently from the syringomyelia-like cyst [30] than from the tumor, usually reverse after removal. Especially for the multiple hemangiomas found in the patients with von Hippel Lindau, great consideration has to be used to only treat the symptomatic lesions and not any which are present on the scans [34, 41]. The dynamics are very asynchronous and some lesions may be silent for many years whereas others suddenly appear and become symptomatic. The cause of this is unknown.

Lipomas may become symptomatic but are difficult to treat. They have a very tough interface with the cord and cannot be dissected in most cases. Because of progressive symptoms, sometimes a partial resection of up to 70% of the mass or dural expansion is performed [19].

Teratomas are a very rare pathology and are mature in the vast majority of the cases. When symptomatic due to a growing cystic compartment, they will be partially resected, but when very adherent to the cord or the conus/filum interface where they tend to occur more often then elsewhere, remnants may be left behind without any future necessity for other kinds of therapy.

Surgical treatment of spinal cord lesion has to follow some general rules. Whenever possible, an en bloc laminotomy with reinsertion of the segment (laminoplasty) is to be preferred to laminectomy, and in multilevel exposures it is mandatory. In cervical exposures, the farther the exposure is extended laterally, the more muscles are detached and the more danger there is for a swan neck deformity [2, 17]. This sometimes needs to be corrected with later stabilization but can sometimes be prevented with immediate and consequent physiotherapy which has to be closely watched by the physicians who take care of the patients in between follow-up visits (Fig. 18). Development of a swan neck deformity is more frequent in children [44], and more frequent when the lesion itself causes muscular weakness like an infiltrative glioma and when the exposure is long, involving three or more levels (Fig. 7).

After removal of an intramedullary lesion, care should be taken to close the arachnoid. We have observed a case in which adhesions formed to the dura which led to a "suspended" or tethered appearance of the myelon in the area of exposure. Within years this led to posture-dependent pain and required a revision. (Fig. 19).

Prognosis

The prognosis of intramedullary tumors depends very much on the histology but also on the time of diagnosis. Ependymomas Grade II tumors have

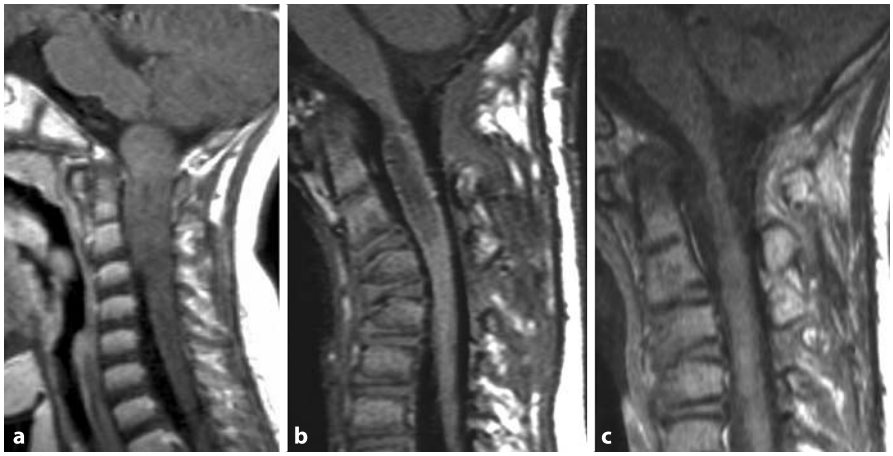


Fig. 18. Large pilocytic astrocytoma in the cervicomedullary junction of a 4-year-old child (**a**) which could be completely removed because of a favorable dissection plane (**b**). As seen more frequently in young children, there was, however, misalignment of the cervical spine and the indication of a developing swan neck (**b**). Before surgical intervention, specific and intensive physiotherapy was administered, leading to lasting stabilization and realignment

Fig. 19. Postoperative MRI of a patient with a midthoracic ependymoma. Although an attempt was made to close the arachnoid, it has to be postulated that "sticky surfaces" remained which adhered to the dural opening and suture so that eventually the surface of the exposure became adherent. Because of segmental movement associated pain, a revision was performed 8 years after the initial surgery where the cord was dissected from tight scar adhesions to the dura

the best prognosis, especially when they are detected early. Patients can expect to be cured with minor sensory deficits or dysesthesias which can originate from the manipulation of the dorsal columns. Glioblastoma has the worst prognosis, no matter what is done therapeutically.

The prognosis is mixed for anaplastic ependymomas, nonresectable pilocytic astrocytomas, and slowly progressive glioneuronal tumors. Regular follow-up is warranted to determine possible time points for repeated intervention.

The functional prognosis of the patients depends also on the tolerance of the spinal cord for therapeutic interventions at the time of diagnosis and that is greatly reduced when the patients are in poor grade according to Cooper and Epstein. Once a patient through a long history of misconceptions about his condition has become wheelchair bound before the diagnosis is established, the chances for the patient to get out of it are almost nil. For other patients who even in the most optimized clinical setting suffer from a deterioration from a surgical procedure, advice has to be given that regeneration takes place over a period of about 2 years and that for that time at least there should be intense physiotherapy to get to the best possible postoperative result which may be much better than the preoperative status.

References

1. Allison R, Vaughan J, Thurber A, Rajecki M, Vongtama V, Barry T. Spinal cord dose is higher than expected in head and neck radiation. Med Dosim 1999;24:135–139
2. Alvisi C, Borromei A, Cerisoli M, Giulioni M. Long-term evaluation of cervical spine disorders following laminectomy. J Neurosurg Sci 1988;32:109–112
3. Aryan HE, Meltzer HS, Lu DC, Ozgur BM, Levy ML, Bruce DA. Management of pilocytic astrocytoma with diffuse leptomeningeal spread: two cases and review of the literature. Childs Nerv Syst 2004 Sep 15; [Epub ahead of print]
4. Balmaceda C. Chemotherapy for intramedullary spinal cord tumors. J Neuro-oncol 2000;47:293–307
5. Bourgouin PM, Lesage J, Fontaine S, Konan A, Roy D, Bard C, et al. A pattern approach to the differential diagnosis of intramedullary spinal cord lesions on MR imaging. AJR Am J Roentgenol 1998;170:1645–1649
6. Brotchi J. Intrinsic spinal cord tumor resection. Neurosurgery 2002;50:1059–1063
7. Chamberlain MC. Salvage chemotherapy for recurrent spinal cord ependymoma. Cancer 2002;95:997–1002
8. Choi KH, Lee KS, Chung SO, Park JM, Kim YJ, Kim HS, et al. Idiopathic transverse myelitis: MR characteristics. AJNR Am J Neuroradiol 1996;17:1151–1160
9. Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg Spine 2000;93:183–193
10. Cristante L, Herrmann HD. Surgical management of intramedullary spinal cord tumors: functional outcome and sources of morbidity. Neurosurgery 1994;35:69–74; discussion 74–66
11. Cristante L, Herrmann HD. Surgical management of intramedullary hemangioblastoma of the spinal cord. Acta Neurochir (Wien) 1999;141:333–339; discussion 339–340
12. Epstein FJ, Farmer JP, Freed D. Adult intramedullary astrocytomas of the spinal cord. J Neurosurg 1992;77:355–359
13. Hassall TE, Mitchell AE, Ashley DM. Carboplatin chemotherapy for progressive intramedullary spinal cord low-grade gliomas in children: three case studies and a review of the literature. Neuro-Oncol 2001;3:251–257
14. Hoshimaru M, Koyama T, Hashimoto N, Kikuchi H. Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. Neurosurgery 1999;44:264–269
15. Houten JK, Cooper PR. Spinal cord astrocytomas: presentation, management and outcome. J Neuro-oncol 2000;47:219–224
16. Isaacson SR. Radiation therapy and the management of intramedullary spinal cord tumors. J Neuro-oncol 2000;47:231–238
17. Ishida Y, Suzuki K, Ohmori K, Kikata Y, Hattori Y. Critical analysis of extensive cervical laminectomy. Neurosurgery 1989;24:215–222
18. Jallo GI, Freed D, Epstein FJ. Spinal cord gangliogliomas: a review of 56 patients. J Neuro-oncol 2004;68:71–77
19. Kim CH, Wang KC, Kim SK, Chung YN, Choi YL, Chi JG, et al. Spinal intramedullary lipoma: report of three cases. Spinal Cord 2003;41:310–315
20. Kim MS, Chung CK, Choe G, Kim IH, Kim HJ. Intramedullary spinal cord astrocytoma in adults: postoperative outcome. J Neuro-oncol 2001;52:85–94
21. Kleihues P, WC. Pathology and genetics of tumors of the nervous system. Lyon: IARC; 2000
22. Kothbauer K, Deletis V, Epstein FJ. Intraoperative spinal cord monitoring for intramedullary surgery: an essential adjunct. Pediatr Neurosurg 1997;26:247–254
23. Lamszus K, Lachenmayer L, Heinemann U, Kluwe L, Finckh U, Hoppner W, et al. Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 2001;91:803–808
24. Lee M, Epstein FJ, Rezai AR, Zagzag D. Nonneoplastic intramedullary spinal cord lesions mimicking tumors. Neurosurgery 1998;43:788–794; discussion 794–785
25. Lee M, Rezai AR, Abbott R, Coelho DH, Epstein FJ. Intramedullary spinal cord lipomas. J Neurosurg 1995;82:394–400
26. Lowe GM. Magnetic resonance imaging of intramedullary spinal cord tumors. J Neuro-oncol 2000;47:195–210
27. Macbeth FR, Wheldon TE, Girling DJ, Stephens RJ, Machin D, Bleehen NM, et al. Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of pallia-

tive radiotherapy for non-small cell lung cancer. The Medical Research Council Lung Cancer Working Party. Clin Oncol (R Coll Radiol) 1996;8:176–181
28. Miller DC. Surgical pathology of intramedullary spinal cord neoplasms. J Neuro-oncol 2000;47:189–194
29. Morota N, Deletis V, Constantini S, Kofler M, Cohen H, Epstein FJ. The role of motor evoked potentials during surgery for intramedullary spinal cord tumors. Neurosurgery 1997;41:1327–1336
30. Pai SB, Krishna KN. Secondary holocord syringomyelia with spinal hemangioblastoma: a report of two cases. Neurol India 2003;51:67–68
31. Parsa AT, Fiore AJ, McCormick PC, Bruce JN. Genetic basis of intramedullary spinal cord tumors and therapeutic implications. J Neuro-oncol 2000;47:239–251
32. Patel U, Pinto RS, Miller DC, Handler MS, Rorke LB, Epstein FJ, et al. MR of spinal cord ganglioglioma. AJNR Am J Neuroradiol 1998;19:879–887
33. Prayson RA. Clinicopathologic study of 61 patients with ependymoma including MIB-1 immunohistochemistry. Ann Diagn Pathol 1999;3:11–18
34. Richard S, Campello C, Taillandier L, Parker F, Resche F. Haemangioblastoma of the central nervous system in von Hippel-Lindau disease. French VHL Study Group. J Intern Med 1998;243:547–553
35. Saleh J, Afshar F. Spinal cord astrocytoma with intracranial spread: detection by magnetic resonance imaging. Br J Neurosurg 1987;1:503–508
36. Schwartz TH, McCormick PC. Intramedullary ependymomas: clinical presentation, surgical treatment strategies and prognosis. J Neuro-oncol 2000;47:211–218
37. Sun B, Wang C, Wang J, Liu A. MRI features of intramedullary spinal cord ependymomas. J Neuroimaging 2003;13:346–351
38. Tampieri D, Leblanc R, TerBrugge K. Preoperative embolization of brain and spinal hemangioblastomas. Neurosurgery 1993;33:502–505; discussion 505
39. Ushida T, Sonobe H, Mizobuchi H, Toda M, Tani T, Yamamoto H. Oligodendroglioma of the "widespread" type in the spinal cord. Childs Nerv Syst 1998;14:751–755
40. van den Bent MJ. Diagnosis and management of oligodendroglioma. Semin Oncol 2004;31:645–652
41. Van Velthoven V, Reinacher PC, Klisch J, Neumann HP, Glasker S. Treatment of intramedullary hemangioblastomas, with special attention to von Hippel-Lindau disease. Neurosurgery 2003;53:1306–1313; discussion 1313–1304
42. Wang C, Zhang J, Liu A, Sun B. Surgical management of medullary hemangioblastoma. Report of 47 cases. Surg Neurol 2001;56:218–226; discussion 226–217
43. Westphal M, Koch C. Management of spinal dural arteriovenous fistulae using an interdisciplinary neuroradiological/neurosurgical approach: experience with 47 cases. Neurosurgery 1999;45:451–457; discussion 457–458
44. Yeh JS, Sgouros S, Walsh AR, Hockley AD. Spinal sagittal malalignment following surgery for primary intramedullary tumours in children. Pediatr Neurosurg 2001;35:318–324

Intradural Extramedullary Tumors

54

Roland Goldbrunner

Epidemiology – 636

Symptoms and Clinical Signs – 636

Diagnostics – 636
Synopsis
Meningiomas:
Nerve Sheath Tumors

Staging and Classification – 638
Synopsis

Treatment – 639
Synopsis
Surgery
Preparation and Positioning
Monitoring
Approach
Ultrasonography
Tumor Resection

Radiotherapy and Chemotherapy – 642

Prognosis and Functional Outcome – 642

Follow-up/Specific Problems and Measures – 643

Future Perspectives – 643

References – 643

Epidemiology

Spinal intradural tumors are uncommon lesions with a five-fold smaller incidence than intracranial neoplasms. The total incidence of spinal intradural tumors varies from 3 to 10 per 100,000 population [20, 22]. In adults, about one third of these lesions is located within the spinal cord itself, two thirds are found extramedullary. In children, the ratio of intra-/extramedullary tumors is approximately 50% [22]. Respecting the intramedullary location, astrocytomas and ependymomas are the most common entities, whereas nerve sheath tumors (NST) like schwannomas and neurofibromas as well as meningiomas are the most frequent extramedullary tumors. The incidence of meningiomas and NST is about equal in the Western population [25%–35% of all intraspinal tumors]; however, in Asian populations spinal schwannomas are much more frequent than meningiomas with ratios of almost 4:1 in China and Japan [2].

Within the vertebral canal, intradural extramedullary tumors generally are most often encountered in the thoracic region, followed by the cervical section. Accordingly, 80% of meningiomas are thoracic; meningioma growth caudal to the level of the conus medullaris is very uncommon. Also, NST predominantly grow in the thoracic area. In contrast to meningiomas, the lumbosacral region seems to be affected with a similar incidence as the cervical section.

There is a strong female predominance in spinal meningiomas with 75%–85% of meningiomas arising in women. They are found in any age group, but most occur between the fifth and eighth decades of life. In spinal nerve sheath tumors, there is no sex predilection in contrast to intracranial NST having a female/male ratio of 2:1. All ages are affected, but a peak incidence can be evaluated between the fourth and sixth decades of life.

Symptoms and Clinical Signs

Pain is the most common and usually the first symptom produced by extramedullary spinal tumors. It may precede the diagnosis of the (usually benign) tumor by about 2 years. Particularly in schwannomas affecting single nerve roots, the pain has a radicular character and my be indicative for the site of the lesion. Many intraspinal tumors create signs and symptoms with a combination of segmental and distant features. Segmental signs and symptoms comprise motor neuron defects one level lower by affection of the anterior roots or compression of the anterior horn cells as well as specific sensory losses by involvement of the dorsal roots. Distant signs and symptoms are caused by affection of the ascending or descending longitudinal tracts, interrupting function below the level of the lesion. In case of the corticospinal tract, upper motor neuron deficits with spastic paresis may occur; in case of compression of the spinothalamic tract, pain and temperature sensation are decreased. If the dorsal tracts are affected, positional sense and vibration are disturbed resulting in gait ataxia as a very common symptom. In case of extramedullary tumors, the affection of longitudinal tracts is caused by external compression, which often is unilateral. This explains the higher incidence of Brown-Sequard-like signs in extramedullary tumors compared to intramedullary tumors. Sympathetic and parasympathetic signs, which are caused by involvement of descending autonomic pathways, are more uncommon in extramedullary tumors compared to intramedullary lesions. However, large lumbar schwannomas or other mass lesions compressing the conus medullaris may present with bladder or bowel dysfunction as a first symptom.

Interpretation of the symptoms and clinical signs which may be produced by extradural mass lesions has to take into consideration that not every symptom is indicative for the level of spinal cord or root compression. An important factor to be deliberated is a potential vascular affection. Compression of radicular arteries or the anterior spinal artery may produce complex and unexpected signs and symptoms. Spinal cord regions located in the watershed zone between the large radicular arteries usually are the first regions to suffer when the vascular supply is compromised. These watershed-related symptoms may precede the symptoms of direct root or cord affection for months leading to an incorrect clinical diagnosis. A third factor which might cause or aggravate unexpected signs and symptoms is tethering of the spinal cord or nerve roots by the tumor. The main symptom of tethering in adults is pain. Tethering as a primary symptom is a rare feature in extramedullary tumors; however, it might play a role if a recurrence is suspected and postoperative alterations of the arachnoid have to be differentiated from a real tumor recurrence.

Diagnostics

Synopsis

Magnetic resonance imaging (MRI) is the method of choice for visualization of intradural tumors. Contrast-enhanced T1-weighted images, T2-weighted images, and particularly constructive interference in steady state (CISS) sequences provide data about exact localization, size, and relations to adjacent structures. Therefore, MRI offers clues for differential di-

agnosis of the most common extramedullary tumors (NST and meningiomas) and presents information needed for surgical planning.

Imaging of the spinal canal has been performed by myelography and computed tomography (CT) for many years; since the late 1980s MRI has become the method of choice. Detailed MRI of the spine requires the use of dedicated surface coils, which improve signal to noise ratio, provide greater tissue contrast resolution and greater spatial resolution, and make thinner slices possible. The sagittal plane provides the most diagnostic information and presents an overview over large areas of the spinal canal. Axial slices, more than coronal slices, offer additional anatomical information which might be necessary for surgical planning.

From the almost infinite number of options MRI offers to the investigator, several sequences have proven to be the most valuable in providing information about the tumor of interest. Routinely, T1-weighted (with and without application of the contrast medium gadolinium) and T2-weighted images are obtained. At many institutions, CISS sequences are also employed. CISS sequences have ultra short repetition times (TR) and echo times (TE) times providing the best contrast resolution of all sequences available. Therefore, these sequences contribute information about intratumoral cysts and involvement of nerve roots or even denticulate ligaments within the tumor mass. Additionally, they can display CSF signal between well-demarcated tumors and the cord parenchyma allowing proper surgical planning.

There are very few indications for myelography or CT scanning in the diagnostics of spinal tumors. In patients with contraindications for MRI, e.g., electronic implants like pacemakers, contrast-enhanced, high-resolution CT, in some cases also postmyelographic CT, are used to determine the level and the size of the tumor. CT scanning may also be useful in intra/extradural tumors with erosion of bony structures to provide additional information for surgical planning (e.g., dumbbell nerve sheath tumors).

Meningiomas

Spinal meningiomas are slightly hyperintense on T2-weighted imaging and iso- or hypointense on T1-weighted images. They have a broad contact to the dura and characteristically display a strong and homogeneous enhancement with gadolinium. Similar to intracranial meningiomas, contrast uptake may be seen beyond the solid tumor along the dural adhesion site, which is known as the "dural tail." These tumors are well circumscribed and delineated from the spinal cord. Calcified areas are dark on all MRI sequences and lack any contrast uptake. These calcified areas also can be detected by high resolution CT scanning (Fig. 1).

Nerve Sheath Tumors

Schwannomas are the most common nerve sheath tumors, followed by neurofibromas. Malignant NST are very rare entities within the spinal canal. Schwannomas are usually diagnosed as solitary. Since neurofibromas are associated with neurofibromato-

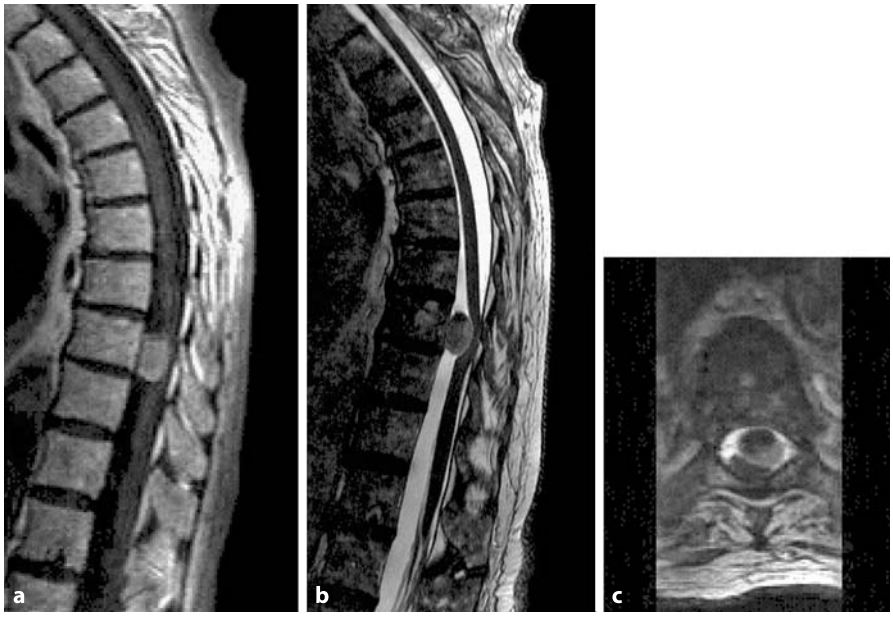


Fig. 1 (**a**) sagittal T1-weighted MRI showing homogeneous contrast uptake and broad contact to the ventral dura. (**b**) Sagittal CISS sequence and (**c**) axial CISS sequence revealing clear demarcation between tumor and myelon

sis type I (von Recklinghausen's disease), these tumors are often found to be multiple. Similar to meningiomas, both NST entities are isointense on T1-weighted images and hyperintense on T2-weighted imaging. Contrast enhancement is variable and can be very intense and homogeneous—like in meningiomas—while others display inhomogeneous or only faint enhancement at the periphery of the tumor (Fig. 2). Neurofibromas occasionally show low signal areas within the tumor mass representing dense areas of collagenous stroma. However, a clear distinction between schwannoma and neurofibroma is not reliable by neuroradiological means.

Staging and Classification

Synopsis

Nerve sheath tumors, comprising schwannomas and neurofibromas, and meningiomas are the most common intradural extramedullary tumors. These tumors are benign except rare cases of malignant NST or anaplastic meningioma. There are a few malignant entities found in the intradural extramedullary, e.g., drop metastases. There is a significant correlation of NST with neurofibromatosis type I, type II, or spinal schwannomatosis.

In 2002, the World Health Organization's (WHO) classification of tumors of the nervous system was updated [9]. This WHO classification and grading should be the basis for description and grading of intradural extramedullary tumors. As stated above, meningiomas and NST, comprising schwannomas and neurofibromas, are the most common entities having a very similar incidence. These entities are benign (WHO Grade I) in most cases. Other tumor entities found within the intradural extramedullary space are lipomas, dermoids, epidermoids, teratomas, hemangioblastomas, and paragangliomas. All these entities are very uncommon; there are only few case reports in the literature (reviewed in [23]). Also, these rare entities are benign; the only malignant tumor types in the intradural extramedullary space are malignant nerve sheath tumors (WHO Grades III or IV), anaplastic meningiomas (WHO Grade III), hematogenous metastases or drop metastases, e.g., from medulloblastomas (WHO Grade IV).

Meningiomas arise from arachnoid cluster cells and therefore are located preferably at the exit zones of nerve roots or entry zones of arteries in the spinal canal. They have a rubbery or firm consistency and are rounded or lobulated in most cases. In almost any case, they have a broad attachment to the dura which can be used for diagnostics (see the Sect. entitled "Diagnostics" above). Most meningiomas are purely intradural, but they also may grow intra- and extradurally. There are also reports about purely extradural spinal meningiomas as well as intramedullary meningioma growth [22]. Meningiomas usually are well vascularized and may show intense calcifications which can be visible on CT scans. These calcifications may increase the consistency of the tumor and could influence the surgical strategy in case of a ventrally located, large, highly calcified meningioma, which can not be debulked due to its consistency. Atypical meningiomas (WHO Grade II) constitute between 4.7% and 7.2% of all meningiomas; anaplastic meningiomas (WHO Grade III) account for 1.0%–2.8% of all meningiomas [12]. There are no valid data about the rate of Grade II or III meningiomas in the spinal canal; however, the percentage of these grades seems to be lower than among the intracranial meningiomas.

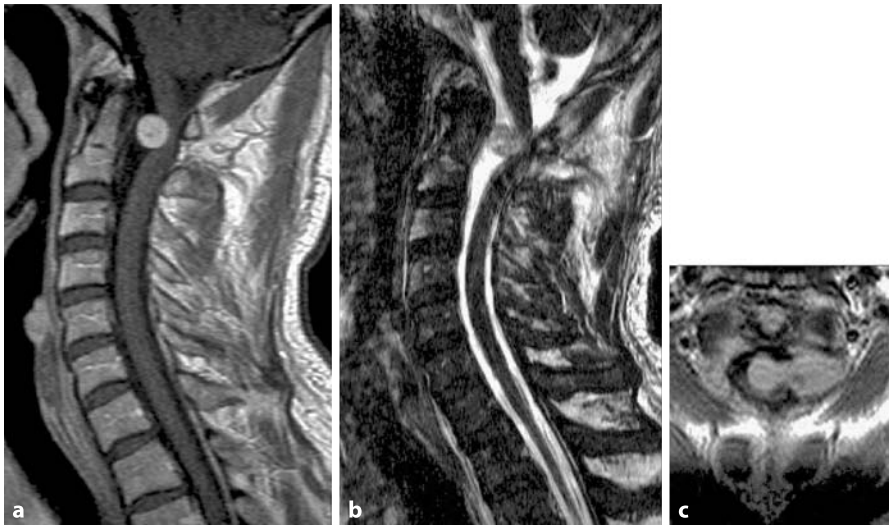


Fig. 2 (**a**) T1-weighted MRI showing a round, well-demarcated tumor with intense contrast uptake. (**b**) Sagittal CISS sequences imaging the compression of the myelon by the well-confined tumor. (**c**) Contrast-enhanced, axial T1 images displaying the typical dumbbell shape

Schwannomas are derived from differentiated neoplastic Schwann cells; neurofibromas are composed of Schwann cells, perineurial-like cells, fibroblasts, and cells with intermediate features. Schwannomas are globoid, encapsulated masses with thick-walled, hyalinized tumor vessels and a lack of necrosis or calcifications. They are composed of Antoni A areas with closely packed tumor cells presenting nuclear palisades, and Antoni B areas with loosely arranged tumor cells and clusters of lipid laden cells. In both areas so-called Verocay bodies can be found formed by roughly parallel arrays of tumor cell nuclei separated by dense, hypereosinophilic tissue. Neurofibromas have a firm consistency and often present a plexiform or multinodular shape. They may or may not be confined to a single nerve, surrounded by thickened epineurium. Typically the cells are surrounded by collagen fibers and a myxoid matrix; this is the reason for the firm consistency. Neurofibromas may contain atypical nuclei and show increased cellularity and mitotic figures which can be interpreted as the basis for malignant progression [24]. However, in contrast to peripheral nerves, where malignant peripheral nerve sheath tumors (MPNST, WHO Grade III or IV) are a well-defined entity representing 5% of all soft tissue tumors, malignant NST in the spinal canal are extremely rare. Most NST grow within the intradural extramedullary space, but may extend via the intervertebrate foramen into the extraspinal region (e.g., as dumbbell tumors) where they can reach enormous sizes. There are also reports about intramedullary schwannomas or neurofibromas which can be explained by tumor growth originating from aberrant nerve roots. In case of association with neurofibromatosis type 1 or 2 (NF1 or NF2), multiple tumors may be present at different levels of the spinal cord. Neurofibromas are more common in NF1, schwannomas are typical for NF2 [14]. However, the presence of multiple NST is not automatically indicative for the classical neurofibromatosis variants NF1 or NF2. Patients with multiple spinal schwannomas without vestibular neoplasms may have schwannomatosis, a syndrome of yet unclear etiology. In schwannomatosis, loss of heterozygosity and mutations of the NF 2 gene regularly can be demonstrated in tumor specimens. However, there are no systemic alterations of the NF-2 gene on chromosome 22 excluding a germline mutation [7, 11, 13, 19]. On the other hand, some families with spinal schwannomatosis without any intracranial neoplasm have been shown to present an autosomal dominant inheritance of this disorder which leads to the interpretation of schwannomatosis as a NF2 variant [5]. Altogether, the discussion as to whether schwannomatosis is a mosaic form or variant of NF2 or a distinct entity among the neurofibromatoses is still open.

Treatment

Synopsis

Surgery is the method of choice for treatment of intradural extramedullary tumors. The uppermost cases of these tumors can be removed totally by surgical means and do not need further treatment. Electrophysiological monitoring of motor and sensory functions increases safety of intraoperative procedures. Ultrasonography allows intraoperative imaging for exact approaching and provides information about tumor morphology transdurally. The approaches through the bony structures considering appropriate exposure and postoperative stability (laminectomy, laminoplasty) are discussed. Finally, the most advantageous ways of incision and closure of the dura and the techniques for debulking and complete resection of these tumors are shown.

Surgery

Since the vast majority of intradural extramedullary tumors are benign and since most of them are well circumscribed and show a clear demarcation to spinal cord tissue, surgery offers excellent chances for total removal and therefore is the therapy of choice for these lesions.

Preparation and Positioning

Patients should be informed about the high probability of a benign nature of these lesions once diagnosed by MRI. On the other hand, the risk of paraparesis or paraplegia during surgery by vascular irritation or direct affection of the spinal cord has to be discussed. This risk may be significant in elderly patients or patients with a severe neurological deficit preoperatively. To minimize the risk of intramedullary edema and consequent neurological deterioration, patients routinely are prepared with steroids (dexamethasone 8–16 mg) preoperatively. In case of intraoperative irritation of the spinal cord, additional steroid doses, up to 1000 mg methyl-prednisolone, are applied.

In thoracic and lumbosacral tumor locations, patients are positioned in a prone position. In cervical locations, also the sitting position may be chosen with the head fixed in the Mayfield clamp. Sitting positioning has the advantage of increased venous drainage to minimize congestion in the operated area. On the other hand, extensive CSF drainage possibly leading to intracranial subdural hematoma and the risk of air embolism are significant disadvantages of the sitting position. Additionally, in the

prone position the assistant, who is standing opposite to the surgeon, can work much more effectively than in the sitting position, which usually only allows one-hand assistance.

Monitoring

To assess neurological functions during surgery, electrophysiological monitoring is a standard procedure in intramedullary tumors. In extramedullary neoplasms, surgery for small and dorsally located tumors does not need electrophysiologic monitoring since the risk of harming the spinal cord is minimal. However, in large or ventrally located tumors, electrophysiologic monitoring may be very useful for intraoperative decision making and for the prediction of neurologic outcome. The function of the dorsal columns is easily monitored by somatosensory-evoked potentials (SSEP), which are bilaterally induced at the tibial nerve. In case of cervical tumors, these potentials also can be evoked by stimulation of the median nerve, which leads to more stable responses with shorter latencies. Motor-evoked potentials (MEP) by transcranial electrical or magnetic stimulation of the motor cortex allow monitoring of the function of the corticospinal tract. However, since MEP monitoring leads to mass movements of the stimulated musculature, it only can be applied discontinuously, in contrast to SSEP. In extramedullary tumors, MEP monitoring may be helpful in ventral locations. An important method for monitoring nerve root function during surgery of a cervical or cauda equina NST is electromyographic (EMG) recording by single muscle electrodes, which allows (1) identification of single nerve roots and (2) monitoring of the current functional status of the nerve. Analogous to intramedullary tumors, special care is taken in tumors compressing the conus medullaris. In these cases, any of the electrophysiological methods could be very helpful. An overview of the monitoring strategy for large tumors dependent on the tumor location is stated in Table 1.

Approach

Most intradural extramedullary tumors can be operated via the standard postero- or posterolateral approach. Before skin incision, the level of the lesion is marked under fluoroscopy. A midline skin incision is performed and the lamina covering the spinal canal are exposed at the level of the pathologic process. Choosing the appropriate approach through the bony structures, optimal exposure of the tumor and spinal stability are the most important concerns. The dural exposure should encompass the area of the tumor, leaving a space of some millimeters at the cranial and caudal margin of the process to allow for tumor mobilization and a watertight dural suture after the removal. For most tumor sizes and locations, one- or two-level laminectomy, which also may be partial laminotomy, is sufficient. In case of small lateral tumors, a hemilaminectomy is performed. If an intraforaminal NST is operated on, hemilaminectomy or laminectomy is combined with partial or total facetectomy. This approach also allows exposure of large, cervical dumbbell schwannomas reaching several centimeters lateral the level of the dura. In some cases of large lateroventral or ventral NST, an even more lateral approach may be necessary. This strategy requires a long midline or paramedian incision. The muscle masses are dissected far laterally and maintained by a retractor. The patient is tilted to the contralateral side to expose the posterolateral side of the spinal canal to the surgeon. After hemilaminectomy, one or two pedicles are drilled off subtotally providing adequate exposure of the ventrally located tumor. If this lateral approach is not sufficient for safe removal of large, ventral, cervical tumors without traction of the spinal cord, a ventral approach performing a corpectomy with reconstruction is the safest choice [17]. Large dumbbell schwannomas may require a combined or a two-stage procedure. Thoracic or thoracolumbar dumbbell tumors are best exposed via the lateral extracavitary approach, which allows a combination of posterior midline access to the spinal canal and lateral access to the spine after complete

Table 1

	Cervical	Thoracic	Lumbosacral	Conus medullaris
SEP	++	++	(+)	++
EMG	++	–	++	++
MEP (ventral locations)	+	+	(+)	++

++, important; +, helpful; –, unnecessary

mobilization of the paravertebral muscle mass [15]. The pleura is not opened during this approach; ribs do not have to be resected necessarily. Alternatively, a two-stage procedure may be chosen with resection of the intraspinal part via a posterior or posterolateral approach at the first and resection of the extraspinal part via a lateral approach at the second stage. Large ventrally located tumors, e.g., meningiomas, are best and safest exposed via a transthoracic approach with vertebrectomy and reconstruction. The risk of procedure-related paraparesis is least using this approach. In large cervical dumbbell schwannomas, which cannot be resected by a posterolateral approach alone, an anterolateral cervicotomy via the lateral aspect of the carotid sheath is performed which permits wide exposure of the extraspinal portion of the spinal roots.

If a multilevel approach is necessary (laminectomy over more than two levels), we prefer to perform a laminoplasty with refixation of the incised lamina by nonresorbable sutures. This has been proven to avoid kyphosis and subluxation in children [1, 18]. Since instability is a common problem after multiple laminectomies in adults, this procedure has been introduced as a standard in our institution.

Ultrasonography

Ultrasonography has been employed for spinal diseases like dysraphism in infants for many years. Intraoperative sonography during spinal procedures – particularly during surgery of spinal tumors – is a relatively new indication. Transdural ultrasonography allows localization of the pathologic process precisely and in real time. Particularly cauda equina tumors might migrate cranially depending on the position of the patient [6]. Therefore, surgical planning with preoperative scans alone might not be sufficient. When the dura is exposed, ultrasound scanning of the myelon and the adjacent tumor is performed in sagittal and transversal plane. Transdural visualization of the tumor makes sure that the exposure is sufficient and that there is enough space left rostrally and caudally of the tumor (see the Sect. entitled "Approach" above). Further removal of bone or ligaments after opening of the dura, usually leading to bleeding into the intradural space, is avoided. Ultrasonography also provides anatomical data of the tumor itself (cysts, hyperechoic areas) in real time and permits resection control; however, this information is much more valuable in intramedullary than in extramedullary processes.

Tumor Resection

In contrast to intramedullary lesions, where a median durotomy is the by far most frequent approach, in extramedullary tumors dura incision has to be modified depending on the anatomical relation of the tumor and the myelon. In lateral tumors, the durotomy should be lateralized or slightly curved to choose the shortest way to the tumor without unnecessary exposure of the myelon. In ventrally located tumors, which have to be approached from a dorsolateral or ventrolateral direction, transverse cutting of the dura may be combined with a median or paramedian longitudinal incision. In NST extending into the intervertebrate foramen, the transverse dura incision parallels the dural root sleeve.

The vast majority of extramedullary tumors possesses a clear demarcation towards the spinal cord which facilitates preparation. Small tumors can be removed in toto after preparation of the tumor surface with standard microsurgical techniques. Large tumors have to be debulked first to avoid traction or pressure to the medulla. The safest way to perform debulking is the use of an ultrasonic aspirator. After that, the tumor surface can be prepared and the tumor mass removed as in smaller tumors.

In meningiomas, which may be strongly vascularized, the same strategy is used as in intracranial locations: The first step is to identify and dissect the area of dural attachment and primary vascular supply in order to avoid bleeding into the intradural and subarachnoidal space during further preparation. To keep the intradural space free of blood is one of the major concerns of the surgeon and one of the major tasks for the assistant.

The strategy in NST is to identify the nerve root of origin first (Fig. 3). In large tumor masses, debulking may be necessary to get sufficient overview. Preservation of the motor root and most sensory fascicles is usually possible with dorsal root NST. When the intraspinal tumor mass is removed, the dural sleeve

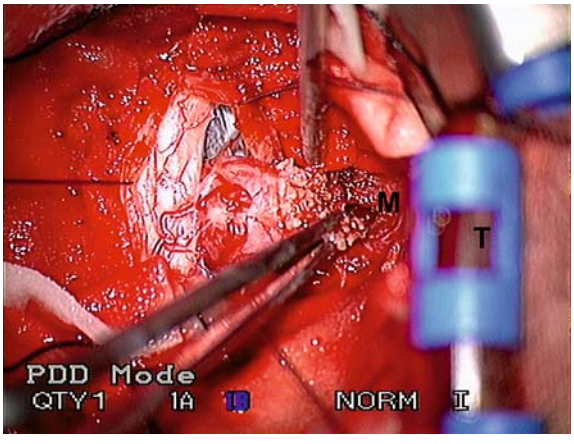


Fig. 3 Dumbbell schwannoma of the right C2 dorsal nerve root. The dura has been opened in a T-shaped fashion to expose the myelon (*M*) as well as the tumor (*T*) along the root

of the root is opened. In nearly all cases of NST, the tumor originates from a dorsal root; therefore, motor function can be preserved (with valuable aid of EMG monitoring). If root preservation seems possible, an intrafascicular tumor dissection has to be performed. However, if the tumor extends into the nerve root sleeve beyond the dorsal root ganglion, total extirpation is only possible if the entire nerve is sacrificed. Therefore, this situation has to be discussed with the patient and the decision of radical resection versus preservation of function has to be made prior to the procedure. If the nerve root is dissected, a complete separation of all nerve root and dural tissue from the intraspinal dura has to be carried out to make a watertight closure of the dura possible using autologous grafts, lyophilized fascia lata, or artificial compounds containing fibrin. If the root is preserved, the use of fibrin glue or analogous compounds is encouraged, since a complete dural reconstruction by suture is difficult to perform intraforaminally.

There are no additional considerations for surgery of benign extramedullary neoplasms other than meningioma or NST. Lipomas, dermoids, epidermoids, or teratomas may occur in combination with dysraphism. In these cases, aspect, clinical investigation, and X-ray of the spine may provide additional information. Surgery usually is not the first option for systemic metastases or drop metastases of medulloblastomas. In these cases, radiotherapy and/or chemotherapy are the first choice.

Radiotherapy and Chemotherapy

Since the vast majority of intradural extramedullary tumors are benign and can be removed completely by surgical means, radio- and chemotherapy only play a marginal role in these entities. Recurrent meningiomas or NST usually occur in case of subtotal removal. In these tumors, repeated surgery offers a good chance of total or subtotal resection without adding to the patient's neurological deficit. In case of anaplastic meningiomatosis or malignant NST, adjuvant irradiation of the spine may be indicated after surgery. The role of spinal radiosurgery, an upcoming technique, still has to be determined. Many patients suffering from medulloblastoma present with spinal tumor manifestation. In these patients, irradiation and chemotherapy within a therapeutic concept (e.g., HIT regimen) is performed.

Prognosis and Functional Outcome

The overall prognosis of patients with intradural extramedullary tumors is excellent. The majority of these tumors is benign and if the tumor has been removed thoroughly, the patient is cured from the oncological point of view. Total removal is accomplished in 89%–98% of patients in larger series [3, 8, 10, 21]. Data about recurrence rates are differing widely from 1%–14.4% in the same series; there is no significant difference between meningiomas and NST.

The functional outcome is dependent on the preoperative neurological status. Thus, surgery performed at an early stage of the disease provides best results. In our recent series of 40 intradural extramedullary tumors, operated within 2 years, patients were graded according to the McCormick score (Table 2 [16]) preoperatively and 6 months after surgery. Of 35 patients with Grades I and II preoperatively, 27 showed improvement of the neurological status for at least 1 grade with 14 patients remaining without any neurological deficit (Grade 0) 6 months postoperatively. There was no deterioration to Grades III and IV in these patients. Among the small group of preoperative Grade III and IV patients, three patients improved to Grades 0 and I, two patients stayed unchanged at Grade IV. Similar data are presented in other series [3, 8, 10, 21] with even better outcome at later follow-up stages. It has to be kept in mind that in patients with a poor neurological status recovery might take 2 years or even longer and that intense physiotherapeutic effort can be regarded as very beneficial for these patients [4].

Table 2 Functional classification scheme [16]

Grade	Definition
0	No deficit
1	Mild focal deficit not significantly affecting function of involved limb; mild spasticity or reflex abnormality; normal gait
2	Presence of sensorimotor deficit affecting function of involved limb; mild to moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; still functions and ambulates independently
3	More severe neurological deficit; requires cane/brace for ambulation; may or may not function independently
4	Severe deficit; major sensorimotor deficit of more than one limb; patient functionally fully dependent

Follow-up/Specific Problems and Measures

In benign extramedullary tumors without suspected neurofibromatosis there is no need for a regular follow-up during life time. If the tumor is resected completely, we recommend a clinical and MRI control 1 year after surgery with another follow-up after 3 years. In case of incomplete resection or malignancies, a follow-up dependent on the histology and growth characteristics of the tumor is performed. In patients with different types of neurofibromatosis or schwannomatosis, MRI is performed annually. In these patients, we recommend a conservative attitude operating only on progressive or symptomatic lesions.

Future Perspectives

Surgery at early stages of the disease provides the best outcomes. Since fist symptoms usually precede the diagnosis by about 2 years, efforts have to be made to perform MRI as the most sensitive diagnostic tool as soon as possible. Significant progress has been made within recent years in improving surgical approaches to the spine. However, further optimization of small-sized approaches and more refined surgical techniques may allow better function preservation rates despite radical tumor resection. Further development of spinal radiosurgery using linear accelerators or the so-called gamma knife may lead to a valuable addition to the treatment options for complex intradural, extramedullary tumors.

References

1. Abbott R, Feldstein N, Wisoff JH, Epstein FJ. Osteoplastic laminotomy in children. Pediatr Neurosurg 1992;18:153–156
2. Cheng MK. Spinal cord tumors in the People's Republic of China: a statistical review. Neurosurgery 1982;10:22–24
3. Conti P, Pansini G, Mouchaty H, Capuano C, Conti R. Spinal neurinomas: retrospective analysis and long-term outcome of 179 consecutively operated cases and review of the literature. Surg Neurol 2004;61:34–43
4. Eriks IE, Angenot EL, Lankhorst GJ. Epidural metastatic spinal cord compression: functional outcome and survival after inpatient rehabilitation. Spinal Cord 2004;42:235–239
5. Evans DG, Mason S, Huson SM, Ponder M, Harding AE, Strachan T. Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis: a clinical and molecular study. J Neurol Neurosurg Psychiatry 1997;62:361–366
6. Friedman JA, Wetjen NM, Atkinson JL. Utility of intraoperative ultrasound for tumors of the cauda equina. Spine 2003;28:288–290
7. Kaufman DL, Heinrich BS, Willett C, Perry A, Finseth F, Sobel RA, et al. Somatic instability of the NF2 gene in schwannomatosis. Arch Neurol 2003;60:1317–1320
8. King AT, Sharr MM, Gullan RW, Bartlett JR. Spinal meningiomas: a 20-year review. Br J Neurosurg 1998;12:521–526
9. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, et al. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 2002;61(3):215–25; discussion 226–9 61:215–225
10. Klekamp J,Samii M. Surgical results for spinal meningiomas. Surg Neurol 1999;52:552–562
11. Leverkus M, Kluwe L, Roll EM, Becker G, Brocker EB, Mautner VF, et al. Multiple unilateral schwannomas: segmental neurofibromatosis type 2 or schwannomatosis? Br J Dermatol 2003;148:804–809
12. Louis DN, Budka H, von Deimling A. Meningeal tumours. In: Kleihues P, Cavenee WK, editors. Tumours of the nervous system. Lyon; International Agency for Research on Cancer (IARC); 2000. p. 133–152
13. MacCollin M, Willett C, Heinrich B, Jacoby LB, Acierno Jr JS, Perry A, et al. Familial schwannomatosis: exclusion of the NF2 locus as the germline event. Neurology 2003;60:1968–1974
14. Mautner VF, Schroder S, Pulst SM, Ostertag H, Kluwe L. Neurofibromatosis versus schwannomatosis. Fortschr Neurol Psychiatr 1998;66:271–277
15. McCormick PC. Surgical management of dumbbell and paraspinal tumors of the thoracic and lumbar spine. Neurosurgery 1996;38:67–74
16. McCormick PC, Torres R, Post KD, Stein BM. Intramedullary ependymoma of the spinal cord. J Neurosurg 1990;72:523–532
17. O'Toole JE, McCormick PC. Midline ventral intradural schwannoma of the cervical spinal cord resected via anterior corpectomy with reconstruction: technical case report and review of the literature. Neurosurgery 2003;52:1482–1485
18. Raimondi AJ, Gutierrez FA, Di Rocco C. Laminotomy and total reconstruction of the posterior spinal arch for spinal canal surgery in childhood. J Neurosurg 1976;45:555–560
19. Seppala MT, Sainio MA, Haltia MJ, Kinnunen JJ, Setala KH, Jaaskelainen JE. Multiple schwannomas: schwannomatosis or neurofibromatosis type 2? J Neurosurg 1998;89:36–41
20. Sloof JL, Kernohan JW, MacCarthy CS. Primary intramedullary tumors of the spinal cord and filum terminale. Philadelphia: Saunders; 1964
21. Solero CL, Fornari M, Giombini S, Lasio G, Oliveri G, Cimino C, et al. Spinal meningiomas: review of 174 operated cases. Neurosurgery 1989;25:153–160
22. Stein BM, McCormick PC. Spinal intradural tumors. In: Wilkins RH, Rengachary SS, editors. Neurosurgery. New York: McGraw-Hill; 1996. p. 1769–1781
23. Van Goethem JW, van den HL, Ozsarlak O, De Schepper AM, Parizel PM. Spinal tumors. Eur J Radiol 2004;50:159–176
24. Woodruff JM, Kourea HP, Louis DN. Tumours of cranial and peripheral nerves. In: Kleihues P, Cavenee WK, editors. Tumours of the nervous system. Lyon: International Agency for Research on Cancer (IARC); 2000. p. 125–132

Epidural Tumors and Metastases 55

Carlos A. Bagley, Zima L. Gokaslan

Epidemiology – 646

Symptoms and Clinical Signs – 648

Diagnostics – 649

Staging and Classification – 651

Treatment – 652
Surgery
Radiotherapy
Chemotherapy
Other

Prognosis/Quality of Life – 658

Follow-Up/Specific Problems and Measures – 659

Future Perspectives – 660

References – 660

Epidemiology

Cancer affects approximately 1.4 million Americans every year. Despite recent advancements and improvements in the care or these patents, approximately half will eventually succumb to their disease, a rate that has remained relatively unchanged over the last half century. In 2001, cancer ranked second to only heart disease in terms of mortality in the USA, accounting for approximately 23% of all deaths. The most common causes of death in oncology patients are complications related to metastasis of their primary disease [42]. The skeletal system is the third most common site for metastases, behind the lung and liver. Within the skeletal system, the spinal column is the most commonly affected site [6]. In fact, metastases are the most common type of neoplastic lesion found in the spinal column, comprising up to 90% of all spinal tumors in some series. Autopsy studies also demonstrate that upwards of 90% of cancer patients will have spinal metastatic deposits at the time of death. Of those with spinal metastases, up to 50% will require some form of treatment for their spinal metastasis and 5%–10% will require surgery [3, 5, 42, 43].

The lungs are the most common source of neoplasia in men and women, accounting for 32 and 25% of all cases respectively, followed by breast/prostate (10%/15%) and colon/rectal cancer (10%). A 30-year review of the literature published in 1988 by Brihaye found that in nearly 1,500 patients with symptomatic metastatic disease to the spine, 16.5% arose from breast cancer, 15.6% arose from lung cancer, 9.2% from prostate cancer, and 6.5% for kidney cancer [10, 42]. Overall, these four tumor types account for over 50% of all spinal metastases. Furthermore, 10%–20% of metastases to the spine will have no known primary [12].

Breast cancer is by far the most common source of metastatic tumor deposits to the spine. In fact, as many as 85% of women with breast cancer will develop skeletal metastases during the course of their disease [12]. The clinical course of these metastatic deposits may vary greatly between patients. Lesions may behave rather indolently in some, whereas the behavior may be much more aggressive in others. Breast cancer cells typically spread to the spine via the azygous venous system, most commonly to the thoracic region [3 ,12]. Although solitary lesions do occur, multiple, often noncontiguous levels are most often involved.

Lung cancer, as mentioned above, is the second most common source of metastatic disease to the spine and the most common type of cancer in adults. Spinal lesions are often times multiple and usually present late in the overall disease course. Of the different lung cancer subtypes, the adenocarcinomas are the most common type to present with symptomatic spinal metastases warranting therapeutic intervention [12]. Other subtypes, such as squamous cell, are far more aggressive and often have massive lung and liver involvement by the time symptomatic spinal metastasis develops. Lung cancer cells may enter the pulmonary venous system, subsequently reaching the heart after which they may spread to the entire skeletal system [3]. In addition, spinal involvement may result from direct tumor invasion of the anterior elements.

Prostate cancer is generally considered a disease of the elderly with many cases being diagnosed after the age of 70. Prostate cancer may spread to the lumbosacral spine by entering the pelvic venous system [3]. Although spinal metastases may occur at any point during the disease process, it is uncommon for these to become symptomatic until very late.

Renal cell carcinoma represents a significant portion of the spinal metastases that come to clinical attention. As mentioned above, it is the forth most common source of spinal metastases. In addition, renal cell carcinoma will often times present initially with spinal metastases [27]. These lesions, unlike breast or lung carcinomas, will most often times have a single level of spinal involvement in addition to the renal mass. This fact has tremendous implications in the development of the surgical treatment plan for these patients (see the Sect. below entitled “Surgery”).

Most patients with spinal metastases will be found to have to have multilevel disease. In most cases, however, only one level is symptomatic at the time of clinical presentation. The thoracolumbar spine is the most common region of the spine to be affected by both primary and metastatic disease. In fact, between 70% and 80% of symptomatic primary and metastatic tumors occur in the thoracolumbar region [1, 42, 45]. This may be due in part to the small size of the vertebral body and small size of the spinal canal in the thoracic region in addition to the typical routes by which the most common metastatic tumors spread as discussed above.

Primary spinal neoplasms make up less than 10% of all tumors seen in the spinal column [3, 45]. As with metastatic lesions, the age of the patient at presentation has significant implications regarding the possible aggressiveness of the primary spinal tumor. In the case of primary tumors, however, the age cut off occurs much earlier. In patients older than 21 years, 70% of primary lesions prove to be malignant [7]. The mean age at diagnosis for benign lesions is approximately 21 years, whereas that for malignant lesions is approximately 49 [45]. As with metastatic lesions, the thoracolumbar spine is most commonly involved, followed by the sacrum and lastly the cervical spine [45].

The most common of the benign primary tumors are osteoid osteomas and osteoblastomas. These tumors are similar histologically and are differentiated mainly by size. These lesions have a propensity for spinal involvement and usually involve the posterior elements. Patients harboring an osteoid osteoma or osteoblastoma usually present in the second or third decade of life complaining of nocturnal back pain. This back pain classically responds very well to aspirin, although a lack of a response does not preclude the diagnosis. Patients may also present with progressive scoliosis. In these cases the lesion is usually found at the apex of the concave surface of the scoliotic curve. The scoliosis improves in nearly all of these cases after treatment, the exception being disease processes that were treated late in the course, usually later than 15 months after onset [7].

Aneurysmal bone cysts are pseudotumoral lesions that have an affinity for the thoracic spine [7]. The lesion consists of unclotted venous blood under pressure filling communicating bone spaces, causing expansion and ballooning of the affected bone [2]. These lesions comprise 1.4% of all bone tumors and 20% of aneurysmal bone cysts occurring in the spine. Aneurysmal bone cysts typically affect young individuals, with upwards of 90% occurring before 20 years of age [2, 7]. There is no sex predilection with these lesions.

Hemangiomas are benign lesions that are found incidentally in the spinal column in approximately 11% of spines at autopsy [16]. These lesions are aggregates of thin-walled vessels with qualities that are more hamartomatous than neoplastic [11]. These lesions are usually asymptomatic, but may occasionally cause symptoms of local pain and tenderness or nerve root or spinal cord compression (<1%) [11]. They have a very distinctive radiographic appearance and seldom require any intervention.

Eosinophilic granuloma is a benign process evolving of unclear etiology. Its benign course in its solitary form suggests that it is an inflammatory rather than a true neoplastic process. However, clonality has been reported with this lesion and with it the suggestion that it is a neoplastic process [11]. Most lesions occur in the first decade or two of life. Lesions most commonly occur in the skull, but vertebral involvement occurs in 10%–15% of cases [7]. The thoracolumbar spine is the most common region involved with spine eosinophilic granuloma. Bony destruction by this process may result in complete vertebral body collapse with maintenance of the dense cortical bone end plates, known as "vertebra plana." Eosinophilic granuloma is the most common cause of the classic finding in children and young adults.

Giant cell tumors are benign tumors of the spinal column that have a predilection for the thoracolumbar and sacral regions. Patients with spinal involvement usually present in the third and forth decades of life [7]. Only approximately 7% of giant cell tumors occur in the spine and they represent approximately 5% of all primary vertebral column tumors. It is the second most common primary sacral tumor after chordomas [15]. There is a slight female predominance for giant cell tumors involving the spine and the peak incidence for these tumors is in the third to fourth decades [7, 15, 28, 31].

Giant cell tumors are locally aggressive and destroy local bone. These tumors typically progress through the vertebral cortex, but rarely through the periosteum. Histologically they contain sinusoidal vessels with hypervascular stroma. The giant cells, which are multinucleated macrophages, are not specific for giant cell tumors, and may occur as a reaction to foreign tissue [15]. Although they are histologically benign, approximately 5%–10% of giant cell tumors may undergo malignant degeneration and assume a more aggressive course [3, 31].

The most common primary malignant neoplasm of the spinal column is a solitary plasmacytoma. In a review of 51 malignant primary spinal tumors treated at the University of Iowa over a 50-year period, 15 (29%) were found to be solitary plasmacytomas [45]. Plasmacytomas of the spine have a peak incidence in the fifth and sixth decades, have a predilection for the thoracic spine, and affect men slightly more commonly than females [11, 12]. This tumor may be an underlying cause of a collapsed vertebrae (vertebra plana) in this age group.

Plasmacytomas may occur as an isolated spinal lesion, or more commonly as prodrome to multiple myeloma. Multiple myeloma, which is much more common, affects 2–3 people per 100,000 [12]. This form of the disease likewise has a predilection for spinal column involvement. Even if the systemic work-up proves negative at the time of initial presentation, the diagnosis of a plasmacytoma should be viewed with a degree of skepticism until proven with long-term follow-up, as the majority of these patients will eventually present with additional lesions consistent with multiple myeloma.

Chordoma is a low-grade malignant tumor commonly found in the spinal column. They are thought to arise from the remnants of the primitive notochord in the vertebral column. In the spine, the most common locations for this slow growing, aggressive tumors are the sacrum and coccyx followed by the clival/upper cervical region. Chordomas account for 2%–4% of malignant primary osseous neoplasms and is the most common primary sacral neoplasm and second most common primary osseous behind plasmacytomas [15, 31]. They occur most commonly in the fifth and sixth decades with a 2:1 male predominance [41].

Chordomas are locally invasive, lobulated masses with a gelatinous texture. Two subsets of this tumor exist: typical chordomas and chondroid chordomas. In the typical variant, variable amounts of intracellular mucin are embedded in pools of extracellular mucin. In the chondroid variant this gelatinous mucinous matrix is replaced by cartilaginous foci. Microscopically, the hallmark of chordomas is the vacuolated, "bubble bearing" cell know as a physaliphorous cell [11].

Chondrosarcoma is another very rare, malignant neoplasm that may involve the spinal elements. Approximately 10% of chondrosarcomas arise in the vertebral column and they account for approximately 10% of all malignant primary spinal tumors [7, 12]. There are several subtypes of this tumor and they range from almost benign-appearing round cell tumors to the much more malignant-appearing spindle cell sarcomas. York et al. reported the MD Anderson Cancer Center experience with 21 cases of spinal chondrosarcoma over a 43-year period [40]. They found a median age of these patients to be approximately 45 years and no sex predilection. In addition, they found a predilection for the thoracic spine for these malignant lesions. Given the small number of patients in this and other series reported in the literature, firm conclusions regarding the epidemiology and demographics of this tumor subtype are difficult to make at this time.

Osteosarcoma is a very rare, malignant primary neoplasm of bone. It is most commonly seen in the metaphyses of long bones. The reported incidence of spinal osteogenic sarcoma ranges from 0.85%–2% in the literature [7, 13]. Many series report lesions that are secondary to spinal irradiation for Paget's disease, therefore the incidence of true primary osteogenic sarcoma is likely much less. Patients with secondary lesions tend to be much older than those with primary tumors. In fact, 60% of osteogenic sarcomas in patients over 60 years prove to be secondary lesions. Overall, 30% of all osteogenic sarcomas of the spine are secondary tumors [7, 12].

Symptoms and Clinical Signs

Patients with spinal column tumors may present differently depending on the extent of the systemic disease, extent of the bony involvement and integrity, rate of tumor growth, and degree of neural compression. Patients with extensive systemic disease may first present with signs and symptoms related to other organ dysfunction (i.e., liver dysfunction in the case of extensive liver metastases). In these cases, spinal metastases may be an incidental finding during the overall work-up. Patients may also present with nonspecific symptoms of anorexia and unexplained weight loss. Furthermore, on physical examination a palpable mass may be present. Depending on the tumor location, this may be paraspinal or even rectal as in the case of large sacral lesion [45].

Patients may present with variable amounts of neurologic dysfunction depending on the location of the tumor and the degree of cord or root impingement. Nerve root compression may occur secondary to the loss of foraminal height that occurs with collapse of the vertebral body or from direct impingement by the tumor mass. This may result in variable amounts of upper or lower extremity weakness in the case of cervical or lumbar lesions, respectively. In the case of a thoracic radiculopathy, a band-like region of numbness or pain in the chest or abdominal area may be found. Findings consistent with myelopathy from spinal compression include sensory deficits, loss of temperature sensation, gait imbalance and poor coordination, Hoffman's sign, Babinski's sign, clonus, painless urinary retention, urinary and or bowel incontinence, and progressive weakness. The cord compression may be from soft tissue elements, such as the tumor, or may occur secondary to bony impingement due to collapse of the vertebral body and retropulsion of bone a fragment.

Progression of symptoms may also vary with the aggressiveness of the tumor. Low-grade, benign lesions tend to grow very slowly as they impinge on neural structures. This allows the body to compensate for the compression slowly and therefore the size of these lesions may be quite impressive at the time of diagnosis. More aggressive lesions, on the other hand, tend to grow and progress very rapidly, therefore not allowing for these compensatory mechanisms. Rapid onset and progression of symptoms therefore is a harbinger of a more aggressive lesion and poorer prognosis.

Patients with metastatic lesions often times have a previous history of cancer. Back pain is the most common initial complaint in patients with metastases to bone of the epidural space [42, 45]. These back pain complaints may precede the development of neurologic symptoms by weeks or months and should therefore be taken very seriously in patients with a previous history of cancer or disorders that predispose them to the development of neoplasms. The back pain in this situation may be due to inflammatory mediators or tumor stretching of the periosteum of the vertebral body, or from mechanical instability of the spinal column secondary to extensive bony destruction by the tumor.

This first type of back pain, commonly referred to as tumor-related pain, is predominately nocturnal, unrelenting, and improves with activity over the course of the day. This category of pain generally responds to anti-inflammatories or steroids and improves significantly following definitive tumor treat-

ment. In addition, patients harboring radiosensitive tumors may have significant relief of their pain following radiation therapy. This is presumed to be due to reduction of the tumor mass by the radiation and thus relief of the periosteal stretching [42].

The second category of back pain seen in these patients, that which is due to mechanical instability of the spinal column, differs significantly in its character from tumor-related pain. The instability is caused by the loss of bony integrity by tumor invasion with resultant pathologic spine fractures. Pain due to mechanical instability is generally posturally related. This pain is exacerbated by movement and by axial loading of the spine while sitting or standing. The discomfort also tends to worsen as the day progresses. Mechanical back pain does not respond to antiinflammatories or steroids. Relief may be obtained by changes in position such as lying supine or with external bracing.

Diagnostics

The work-up of any patient with a suspected spinal lesion begins with a thorough medical history and physical examination. Red flags in the review of systems, as mentioned in the previous section, include progressive, unremitting, nocturnal back pain, unexplained weight loss, hematuria, melena or bright red blood per rectum, changes in bowel habits, hemoptysis, and new lumps on a woman's routine self breast examination. It is important to know how closely the patient is followed medically with routine cancer screening examinations and if they have any conditions that may predispose them to malignancy such as human immunodeficiency virus (HIV), inflammatory bowel disease (IBD), or carcinoma in situ of the breast or cervix. Exposures to potential carcinogens and smoking history are also important aspects of the medical history that clinicians should know. Laboratory work-up includes routine blood chemistries, routine blood cell counts and hematocrit, prostate specific antigen (PSA) in men, and serum and urine protein electrophoresis should multiple myeloma be suspected.

Advances in radiographic techniques have greatly improved our ability to detect spinal metastases. The armamentarium of possible studies includes plain radiographs, bone scans, computerized tomography (CT) with and without myelography, magnetic resonance imaging (MRI), as well as positron emission tomography (PET scans). Differentiating tumor from other lesions such as osteomyelitis can sometimes be difficult based on imaging findings alone.

Assumptions regarding the aggressiveness of a tumor may be made based on its location within the vertebrae. Aggressive primary spinal tumors, such as chordomas, tend to involve the vertebral body or anterior elements primarily. To contrast this, benign primary spinal lesions such as osteoid osteomas, osteoblastomas, and aneurismal bone cysts tend to be confined to the posterior elements. Weinstein et al. found in their review of primary spinal tumors that two thirds of all vertebral body tumors were malignant whereas only one third of those found in the posterior elements were [5, 45]. Metastatic lesions to the spinal column also occur most commonly in the vertebral body. The vertebral body is involved in upwards of 85% of cases and is affected seven times more commonly than the posterior elements.

Diagnostic evaluation in a patient with a suspected spinal lesion usually begins in a set of plain X-rays of the spine. This test is relatively inexpensive and available in virtually all centers. Compression fractures and sagittal (kyphotic) and coronal (scoliosis) plane deformities may be readily detected. In addition, scalloping of the vertebral body, widening of the interpedicular distance, and loss of a pedicle on AP films may be found on plain X-rays when there is a spinal tumor present. One of the classic findings on an AP radiograph is due to the destruction of the pedicle cortical bone by tumor. This loss of the pedicle on an AP film is known as the "winking owl" sign.

Plain radiographs reveal vertebral lesions in upwards of 85% of patients with symptomatic epidural compression [42]. Furthermore, dynamic X-rays (flexion and extension or standing films) may give further information regarding the mechanical stability of the spinal column. Plain radiographs, however, are relatively poor screening tools for spinal bony lesions. Visualization of a radiolucent defect on X-rays requires at least 50% destruction of the vertebral body [5]. In addition, lesions confirmed to the vertebral body marrow, without significant cortical involvement, may remain undetected by this technique.

Technetium-99 bone scans are very sensitive in detecting neoplastic processes involving the skeletal system and is the current standard of practice for the detecting of osseous metastases. It is an excellent screening tool in that entire skeletal systems can be imaged at one time. This study detects regions of increased osteoblast activity and will detect lesions as small as 2 mm [42]. Tc-99 accumulate preferably in regions of higher bone turnover, which is the case with most osseous metastases. Multiple regions of increased uptake throughout the skeletal system, referred to as "hot spots," are consistent with metastatic disease. The two disease processes that tend to be exceptions to this pattern are the plasma cell malignancies. Both plasmacytomas and multiple myeloma may not be evident on bone scans due to the minimal osteoblastic reaction that these lesions pro-

duce. In addition, bone scans lack specificity in detecting neoplastic processes and cannot differentiate benign from malignant lesions. The differential diagnosis for an isolated lesion on a bone scintigraphy includes neoplasm (both primary and metastatic), infection, trauma, osteoarthritis, or local soft tissue inflammation. Furthermore, since bone scans rely on the osteoblastic activity, early lesions may be missed since this activity may be limited. The overall sensitivity of Tc-99 bone scans has been reported to be 62%–89% [33].

Positron emission tomography (PET) is a relatively newly developed tool for the detection of metastatic disease. This technique relies on the detection of metabolic activity and has become the standard for such detection [17, 33]. High cost and limited availability, however, have limited its widespread clinical use in the past. A recent resurgence in interest in PET has led to increased availability with resultant decreased cost. PET scans rely on the metabolism of fluorine-18 deoxyglucose by metabolically active tissue. The amount of tracer accumulation within a tissue directly reflects its metabolic activity. Higher-grade lesions have a much higher metabolic rate than do lower-grade lesions and may readily be differentiated using this technique. This technique has been shown to be superior to bone scintigraphy in the detection of spinal metastases. Furthermore, lesions may be detected earlier since this technique directly measures the metabolic activity of the tumor rather than indirect markers such as bone remodeling [33].

An additional benefit of PET is the ability to determine the most metabolically active portion of a lesion, which may be very important information in the case of cystic, necrotic, or previously irradiated tumors. The information obtained may be used in the planning of biopsy procedures to potentially increase the rate of diagnosis. At this time, however, due to its limited availability and the lack of familiarity amongst many clinicians, the role of PET in the overall diagnosis and management of cancer patients is to be determined.

Computerized tomography (CT) scans are excellent in assessing the bony integrity of the vertebral body and, in cases of spinal cord compression, determining whether the compression is due to bone or soft tissue/tumor. In addition, osseous lesions may be detected at a much earlier stage of bony destruction than with conventional X-rays. For patients with metal hardware in place at the level of interest, with severe claustrophobia, or with pacemaker or other metal implants, CT scans safely provide good resolution without significant hardware artifact. The addition of sagittal and coronal reconstructions provides further information regarding the sagittal and coronal alignment of the spinal column.

Myelography, with the introduction of intrathecal contrast, may be performed in conjunction with the CT scan to provide further information regarding the spinal cord. Accessing the thecal sac for the myelogram additionally allows cerebrospinal fluid sampling for analysis for cytology, protein, glucose, and cell count. The resolution of CT and CT myelograms, however, remains inferior to that of MRI (discussed below) when assessing the spinal cord and the sort of tissue elements (ligament, tumor, etc.). Myelography, in addition to being invasive, carries the addition risk of acute neurologic decompensation in high-grade blocks [29, 44]. Furthermore, surveillance of the entire spinal column for evidence of occult metastases is not practical with CT given that it is time consuming, cumbersome, and involves very high total radiation doses.

In addition to CT scans of the affected spinal regions, every patient that is suspected of having a metastatic lesion should have CT scans of the chest, abdomen, and pelvis to search for a primary source. This is of critical importance in the therapeutic decision-making process and the staging of the neoplastic process. In addition, choices regarding the most accessible lesion for biopsy purposes (discussed below) may be made with this additional information in mind.

Magnetic resonance imaging (MRI) is the most sensitive and specific technique for detecting spinal metastases. It offers the advantage of relatively quickly sagittally surveying the entire spinal column, which is important when metastatic disease is suspected. In addition, it allows the assessment of the entire extent of the tumor mass, including the epidural and paraspinal components.

The typical sequences used in the detection of spinal lesions are T1- and T2-weighted. With the additional administration of gadolinium contrast, the sensitivity of MRI in detecting spinal metastases is further increased. The typical appearance and enhancement patterns vary according to the tumor type. In terms of primary spinal tumors, hemangiomas tend to have high signal intensity on T1-weighted images, whereas most other primary tumors, including osteoid osteomas, osteoblastomas, giant cell tumors, and chordomas, tend to have variable signal intensity on T1-weighted scans [31]. On T2-weighted sequences the signal is likewise variable with most primary lesions. Metastatic lesions appear relatively hypointense to the marrow signal on T1-weighted and hyperintense on T2-weighted sequences [5, 31]. The appearance on T2-weighted images produces a “myelogram” like effect with the bright CSF. The exceptions to this are melanoma metastases and metastases with a high fat content, which may appear bright on T1 scans.

As sensitive as MRI is in detecting spinal tumors, it cannot always help in differentiating between metastases and osteomyelitis, osteoporotic compression fractures and previously treated, nonviable tumor. In general, however, the intervertebral disk tends to be very resistant to neoplastic invasion, even with significant bony involvement and destruction. To the contrary, the disk space is virtually always involved with severe spinal column infections and in many cases is the nidus for infection. Therefore, sparing of the disk space by a destructive spinal process is highly suggestive of a neoplastic process.

Biopsy is an often times integral part of the diagnosis and staging of spinal tumors. The indications for a biopsy of a spinal lesion include the need for a diagnosis, as in the case of an unknown primary disease, and cases in which the lesion must be differentiated from infection. It is important to note that if, in the process of the patients work-up, another, more accessible lesion is found, consideration should be given to a biopsy of that site rather than the spinal lesion.

In order to adhere to sound, fundamental surgical principles, the biopsy tract and site should be planned such that they may be excised through the same surgical incision should a definitive surgical procedure be required. Failure to adhere to this basic principle can have disastrous consequences for the patient's long-term prognosis. It is therefore preferable in these cases that the treating spine surgeon be intimately involved with the planning and execution of the biopsy procedure.

Three types of biopsy procedures are available for lesions of the spinal column: excisional, incisional, and needle biopsy. Excisional biopsy is best utilized in cases of a solitary, posteriorly situated lesion such as an osteoid osteoma. The majority of lesions of the spine require either needle or incisional biopsies. Needle biopsies yield small samples for analysis and may suffer from sampling error. The yield may be increased with the use of a trocar to increase the sample size and with CT guidance. Despite the best attempts, however, the nondiagnostic rate for these biopsy specimens is as high as 30–40% [1]. Incisional biopsies may be performed as the last step in staging the patient, just prior to definitive surgery. In fact, both procedures may be performed under the same anesthetic if the preoperative work-up has been completed and the intraoperative frozen section is clearly diagnostic. It cannot be overemphasized, however, the importance of a complete and thorough work-up prior to performing a biopsy. In some cases the laboratory work-up or CSF analysis may yield a diagnosis, therefore sparing the patients the need for an additional invasive procedure.

Staging and Classification

No single staging system exists for metastatic spinal tumors. These lesions are staged independently based on the primary tumor type and the extent to which it has spread. The TNM classification takes into account the size and extent of the primary tumor (T), regional lymph node involvement (N), and distant metastases (M). The clinical stage for the tumor is determined by the physical findings as well as the results of radiographic and laboratory testing. The pathologic stage of the tumor is determined by histological examination of the tumor specimens obtained at the time of biopsy or surgery. In most cases the pathologic stage most accurately predicts the prognosis.

Enneking proposed a system for the oncologic staging of primary spinal tumors based on their biological behavior, which has been shown to be useful clinically [8]. This system divides benign primary and malignant tumors into three categories: S1, S2, and S3 for benign tumors and Grades I, II, and III for malignant primary lesions. The classification is based on a complete preoperative work-up and includes the clinical features, the radiographic patterns on CT and MRI scans describing the extension of the tumor, the particular imaging pattern and relationship to surrounding tissues, the results of an isotope scan, and the histological findings at biopsy [8].

Stage 1 benign tumors (S1, inactive) do not display considerable growth and produce few clinical symptoms. These tumors possess a true capsule and are surrounded by a thin layer of reactive tissue [1, 8]. A well-defined margin between the tumor and the normal tissue is seen even on plain radiographs. Tumors in this category rarely require treatment and include lesions such as hemangiomas.

Stage 2 (S2, active) lesions are benign tumors that exhibit slow growth and may present with mild symptoms. In addition, these lesions demonstrate increased tracer uptake on bone scans. These tumors also have a thin layer of capsule surrounded by a thin layer of reactive tissue. S2 lesions remain confined to the bony compartment and do not invade adjacent tissues. Examples of primary, benign neoplasms that fall into this category are osteoblastomas and giant cell tumors.

S3 benign lesions (aggressive) are more active than stage I and II lesions are do not possess a true tumor capsule. There are regions of tumor that protrude into and beyond the surrounding thick layer of hypervascular reactive tissue. These tumors are not confined to the vertebral compartment and may extend to involve neighboring tissues. Bone scans are also positive with these lesions and will often dem-

onstrate a hazy border to the tumor mass. Some cases of giant cell tumors and aneurysmal bone cysts may fall into this category.

Grade I, low-grade malignant lesions are divided into A and B subcategories. Grade IA neoplasms remain confined to the vertebral body, whereas IB lesions extend into the paravertebral compartments. No true capsule is present with these lesions; however, a thick, reactive pseudocapsule may be present. Tumor cells, however, extend well beyond the confines of this pseudocapsule [1].

Grade II malignant lesions are more aggressive and rapidly growing than the Grade I tumors. Grade IIA lesions again remain confined to the vertebral compartments, whereas the IIB lesions exhibit paravertebral extension. Due to the aggressiveness and the rapid-growing nature of the lesions, there is little time for a contiguous reactive tissue layer to form. There are satellite and skip lesions present with Grade II lesions that may be present at some distance from the parent tumor site.

Grade IIIA and IIIB malignant, primary lesions possess many of the same features of Grade I and II lesions. The distinguishing feature with these lesions is that there are tumor metastases present at great distances away from the original tumor.

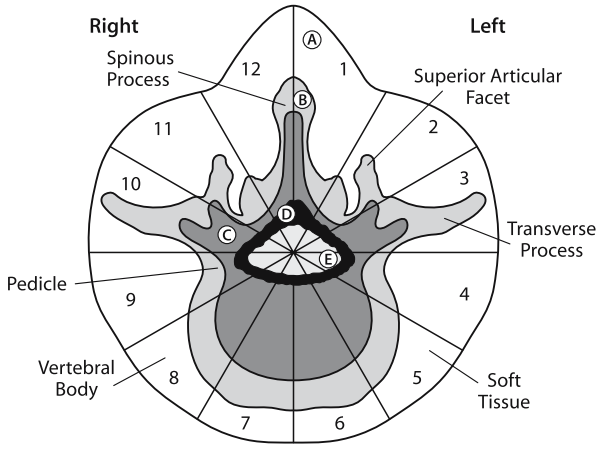
After the diagnosis and the oncologic stage of the primary spinal tumor have been established, the tumor may then be staged surgically. Tomita et al. reported on their adaptation of the Enneking oncologic staging system to a surgical staging system for primary spinal tumors. They incorporated a description of the affected anatomic site as well as the extent of the tumor. The vertebral body was divided into 5 anatomic sites: (1) the vertebral body, (2) the pedicle, (3) the lamina and spinous process, (4) the epidural canal, and (5) the epidural area. This system was developed in an attempt to determine which tumors are amenable to various surgical techniques.

Another commonly used surgical staging system was initially introduced by Weinstein and subsequently modified by the surgical group at the Rizzoli Institute in Bologna, Italy. This staging system, known as the WBB staging system, has been the subject of numerous clinical evaluations and has proven to be beneficial in surgical planning [45]. This system divides the vertebra into 12 radial zones, numbered 1–12 in clockwise order, and 5 layers labeled A to E from the paravertebral soft tissue to the dural region (Fig. 1). An additional layer, layer F, is added in the cervical spine to take into account the vertebral artery canal 1. The tumor can therefore accurately be described in three dimensions and all critical anatomic structures are taken into account. This added information allows for more refined surgical approach planning in addition to facilitating communication between centers in comparing results.

Treatment

Surgery

The approach to patients with spinal column tumors varies depending on whether the tumor is primary or secondary. In the setting of metastases, the goals of surgery are the preservation of neurologic function, pain control, and immediate stabilization of the spine. In addition, for a minority of patients with a single, intraosseous metastasis, the potential to cure or significantly alter the overall prognosis exists [37]. The generally agreed upon indications for surgical intervention for osseous vertebral neoplasms are (1) radioresistant tumor, (2) severe neurologic compromise, (3) evidence of spinal instability or bony compression, and (4) tumor recurrence despite maximum previous radiation treatment.



A Extraosseous Soft Tissues
B Intraosseous (Superficial)
C Intraosseous (Deep)
D Extraosseous (Extradural)
E Extraosseous (Intradural)

M Metastasis

Fig. 1 WBB (Weinstein, Boriani, Biagini) surgical staging system. The transverse extension of the vertebral tumor is described with reference to 12 radiating zones (numbered 1 to 12 in a clockwise order) and to five concentric layers (A to E, from the paravertebral extraosseous compartments to the dural involvement). The longitudinal extent of the tumor is recorded according to the levels involved. (Reprinted with permission from Lippincott, Williams, & Wilkins [8])

When considering surgical interventions a number of patient factors must be taken into account. The first is the expected survival for the patients. There does not exist a consensus in the literature in regarding the expected length of survival of patients who may benefit from surgical intervention. In addition, survival is something that is extremely difficult to predict for the individual patients despite out best attempts. Some authors have proposed requirements of 3- to 6-month expected survival; however, this is not universally agreed upon. Therefore, each patient's prognosis must be assessed individually when considering surgical intervention.

The overall nutritional status of the patient is another important factor to consider preoperatively. Poor nutritional status leads to poor woundhealing and increased risk of infections. Many patients in this population may be further predisposed to these complications by other treatments they have received such as radiation and chemotherapy. The hematologic effects of these treatments, along with a poor nutritional baseline may result in the disastrous consequences of wound breakdowns and deep surgical wound infections. The nutritional status should be assessed and optimized whenever possible. Some advocate parental nutrition for a limited period of time perioperatively in order to address this issue. In addition, whenever there is a concern regarding wound healing, consideration should be given to consultation of a plastic and reconstructive surgeon. Numerous techniques have been described to obtain adequate wound coverage and closure in these often times complex cases. This may prove vital to the successful outcome in these cases.

Defining spinal instability in the setting of neoplasia remains somewhat controversial in the literature. For the occipitocervical junction, ligamentous structures and bony articulations are critical for stability of this region. The cruciate ligament, along with the apical and alar ligaments, provide the bulk of the stability at C1 and C2. In the thoracic and lumbar spinal regions, the biomechanics of stability are quite different. A significant body of literature has been devoted to these issues in the setting of trauma, whereas very little exists solely in the context of neoplasia. Denis' three-column model for spinal instability is widely accepted as a biomechanical model for thoracolumbar trauma and has applications to neoplastic processes that involve this region of the spine [14, 32]. This model divides the spinal column into three columns. The anterior column consists of the ventral one half of the vertebral body, the ventral annulus fibrosus, and the anterior longitudinal ligament; the middle column consists of the dorsal one half of the vertebral body, dorsal annulus fibrosus and posterior longitudinal ligament; the posterior column consists of the pedicles, laminae, ligamentum flavum, and interspinous and supraspinous ligaments.

Based on this Denis model, the criteria for defining spinal instability in the setting of trauma are (1) two or more column injury, (2) >50% loss of vertebral body height, (3) >20° to 30° of kyphotic angulation, or (4) involvement of the same column in two or more adjacent levels [14]. In addition to these factors, the quality of the surrounding bone must be taken into consideration in patients with neoplastic disease of the thoracic and lumbar spines. Furthermore, the cervicothoracic and thoracolumbar regions are very high stress regions of the spine. This is due in part to the rather abrupt transition from the mobile cervical spine to the rigid thoracic spine to the mobile lumbar spine. These abrupt transitions increase the risk of developing fractures and instability in the regions, especially in the setting of neoplastic invasion. These factors must be taken into account when considering surgical intervention on the spine.

The overall surgical goal varies depending on the histology and stage of the tumor. For patients with primary spinal tumors, the goal should be complete en bloc resection as complete removal of the tumor and its microscopic residua significantly affects the patient's likelihood of recurrence and overall survival. The importance of remaining outside of the tumor margins during the resection cannot be overemphasized. Violation of this principle leads to a much higher tumor recurrence rate and decreased long-term patient survival.

Patients with a solitary spinal metastasis likewise have the potential for long-term survival and therefore the goal of surgery should be complete en bloc tumor removal with negative margins. For some extremely aggressive tumors, such as sarcomas, a wide, compartmental resection is required to remove more remote microscopic deposits.

Patients with widely metastatic disease and a symptomatic metastasis, the goal should be to restore spinal stability and relieve neurologic compression. In these patients with widespread disease cure is not possible, so the goal of surgery is palliative and an intralesional resection is a more reasonable option.

The question of which patients with metastatic disease to the spine are most appropriate for surgical intervention is one that remains without a consensual answer at this time. To address this issue, several preoperative evaluation schemes have been devised to select out those patients likely to benefit from surgery. Tokuhasi et al. proposed a prognostic scoring system that takes into account six variables: general medical condition, number of extraspinal metastases, number of vertebral metastases, visceral metastases, primary tumor type, and presence of neurologic deficit [38]. Each parameter is evaluated with

a score of 0 to 2 points, with a maximum score of 12. They recommend excisional surgery for patients with a score of 9 or more, whereas palliative surgery is recommended for those with a score of less than 5. The criticisms of this scoring method are the "gray area" patients with scores of 6 to 8 and that the authors did not provide any statistical background of points 0, 1, and 2 for each factor [39].

To address the weaknesses of the Tokuhasi scoring system and to guide the selection of the type of surgery, Tomita et al. developed and evaluated a prognostic scoring system in which only three variables are taken into account: grade of the primary malignancy (slow growth, 1 point; moderate growth, 2 points; and rapid growth, 4 points), visceral metastases to vital organs (no metastases, 0 points; treatable metastases, 2 points; untreatable metastases, 4 points), and bone metastases (solitary, 1 point; multiple 2 points) [39]. The maximum possible score in this system was 10 points. The difference in mean patient survival was found to be statistically significant when comparing any two of the three groups in a retrospective review of 67 patients. These authors then applied this system prospectively in a series of patients to determine the treatment strategy in addition to the treatment goal based on their prognostic score. For patients with a prognostic score of 2–3, the goal is long-term local control with an expected survival of more than 2 years. The most appropriate surgical option for these patients is to suggest wide excision to reduce the possibility of local recurrence. Patients with prognostic scores of 4–5 have an intermediate expected survival of 1–2 years. For these patients marginal or intralesional resection is an appropriate option; however, wide marginal excision should be considered if technically feasible. Prognostic scores of 6–7 justified palliative surgery, with an expected patient survival of approximately 1 year. Scores of 8–10 were consistent with a patient survival of less than 6 months and these authors felt that these patients were most appropriate for nonoperative, supportive care. Even though these prognostic systems serve as a guide for deciding the best candidates for surgery, the final decision must be made with each patient individually.

Numerous surgical approaches have been described to deal with neoplastic processes of the vertebral column. Some benign lesions, such as osteoid osteomas and osteoblastomas, may involve solely the posterior elements. These lesions are therefore best approached dorsally via a limited laminectomy and resection. In addition, anterior laterally placed lesions may be approached through dorsolateral approaches in the thoracic and lumbar spine. These include both costotransversectomies and transpedicular approaches. Although this provides a less direct route to the pathologic area, certain situations may call for such an approach. These include patients that medically are unable to tolerate a more ventral approach and cases in which anatomic structures may provide a formidable obstacle, as in the case of the innominate vessels and the aortic arch at the second and third thoracic vertebral levels.

As mentioned previously, the bulk of spinal tumors involve the vertebral body, therefore anterior approaches provide the most direct route to these lesions. Because the posterior elements are the only remaining anatomic structure that is intact, their removal by laminectomy may actually make the patient worse by leading to progressive kyphosis. Numerous options have been described for ventral approaches to the spine. In the occipitocervical junction, options include transoral, extended "open door" maxillotomy, and transmandibular circumglossal approaches. Each affords its own unique view of the clivus and C1/C2 region anteriorly. Due to the intricate anatomy of these transoral and transfacial approaches, an access surgeon should likely be involved in these cases. In addition, issues such as the need for a tracheostomy and gastrostomy tube postoperative for a period of time should be discussed with the patient during preoperative counseling. The mid and lower cervical regions may be approached via a standard anterior lateral approach. Care must be taken during this approach to avoid injury to the trachea and esophagus as well as the recurrent laryngeal nerve.

Several ventral approaches to the cervicothoracic, thoracic and thoracolumbar regions have been described in the literature [20, 24, 35, 43] (Fig. 2). High cervical vertebrectomies may be approached through a median sternotomy. The trap door exposure, described by Nazzaro, Arbit, and Burt is a ventral method for exposing high thoracic region lesions that involve T3 and T4 levels [30]. This exposure combines a standard ventral approach to the cervical spine, with both a partial median sternotomy and a ventrolateral thoracotomy. Lower level thoracic lesions may be effectively approached through a dorsolateral thoracotomy [24], whereas a thoracoabdominal approach provides exposure for decompression and stabilization of the thoracolumbar spine.

The lumbosacral spine may likewise be exposed via a myriad of ventral and dorsal approaches. Retroperitoneal and transperitoneal approaches may be used for direct ventral exposure of the spine at this level. Dorsolaterally, the transpedicular route allows for both dorsal and ventral decompression. Large sacral lesions may require a more extensive approach in which both ventral and dorsal exposure and decompression is required. This may require a multidisciplinary team approach to expose the ventral spine, protect the abdominal visceral, and close the large defect left from the tumor resection. In addition, because of the biomechanics of the lumbosacral

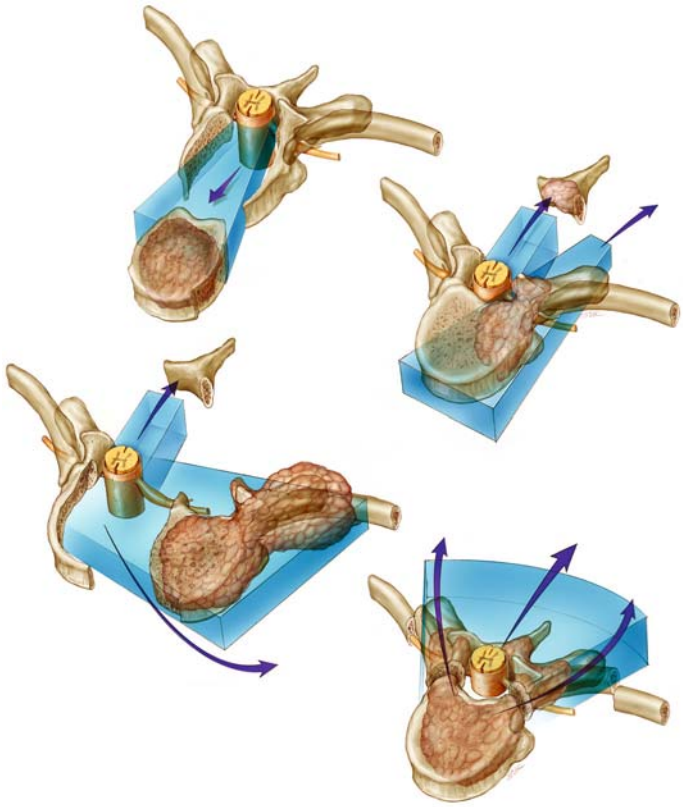


Fig. 2 Artist's illustration of various approaches to the spine depending on the location of metastatic lesion within a given spinal segment

region, additional fixation involving the pelvis may be required [23, 26].

The type of anterior column reconstruction performed after a vertebral body resection depends on the anticipated survival of the patient. When a reasonable survival is expected, reconstruction with a biological material is preferred. Graft options include autologous and cadaveric strut grafts (usually fibula or rib) as well as metallic cage implants that are packed with either autologous harvested bone or cancellous allograft bone chips. The use of bone graft for anterior reconstruction requires that postoperative radiation be delayed in order to prevent fusion failure (see below).

Patients in whom there is a relatively limited life expectancy may be more suitable for anterior column reconstruction with polymethylmethacrylate (PMMA). The advantage of this technique is that it provides immediate stability of the spinal column. In addition, there is no convincing evidence in the literature that the presence of PMMA interferes with local radiation therapy, nor that radiation affects the compressibility, shear strength, of durability of methylmethacrylate [42]. Therefore, it is the author's view that radiation therapy may be delivered without delay when PMMA is used for anterior reconstruction.

Various methods have been proposed to anchor the PMMA to the rostral and caudal vertebral bodies of the vertebrectomy defect. These include chest tube techniques, Steinmann pins, and fixation screws. It is the authors' preference to use the chest tube technique describe by Errico and Cooper due to its excellent stability and because Steinmann pins or screws are not required, as they may cause significant artifact on postoperative MRI scans.

In addition to the reconstruction of the anterior column, posterior instrumentation is often required to supplement the anterior construct. This may be done in a single session through a single or double approach, as well as in a staged fashion [20]. Cases involving reconstruction of the cervicothoracic and thoracolumbar regions are under particularly high stress, as discussed above. Furthermore, severe kyphotic deformity from anterior column failure may be indicative of posterior column incompetence. This often necessitates both ventral and dorsal rigid internal fixation in order to provide durable stability (Fig. 3). Options of dorsal fixation include hooks, rods, wires, cables, or plates with lateral mass and or pedicle screws. In the occipitocervical region, combinations of occipital screws and wires along with cervical lateral mass and pedicle screws have been demonstrated to provide adequate stability in

the face of neoplastic processes [22, 25]. In addition, pedicle screw fixation has been shown to provide excellent result in terms of pain relief and restoration or preservation of mobility in patients with neoplastic spinal lesions [19].

Radiotherapy

Radiation therapy has long been the treatment of choice for spinal metastases and for certain primary lesions. In fact, numerous studies from the 1960s and 1970s demonstrated no difference in outcome between patients treated with radiation therapy alone and those treated with laminectomy with or without radiation treatment. The major criticism of these studies, however, was that laminectomy alone, given that spinal metastases are usually ventral, was an inappropriate surgical choice as the sole operative procedure in the majority of these cases. Nonetheless, radiation therapy has been shown to improve pain control in 50%–90% of patients, and to improve neurologic function in approximately 40% of patients with metastatic cord compression. Those patients in whom the neoplastic process was diagnosed earlier fared the best. In fact, in those patients treated early, the tumor histology had very little influence on the treatment outcome whereas it had a much more profound effect when patients were treated late in their course [42]. Metastatic tumors such as breast, prostate, and small cell ("oat cell") lung cancer along with primary tumors such as plasmacytomas and hemangiomas, are very radiation sensitive and therefore excellent candidates for this treatment option. Radiation-resistant tumors such as renal cell carcinoma and sarcomas respond relatively poorly to radiation treatment alone and are best treated with a combination of surgical resection and radiation.

When evaluating patients with possible neoplastic cord compression for radiation therapy, it is im-

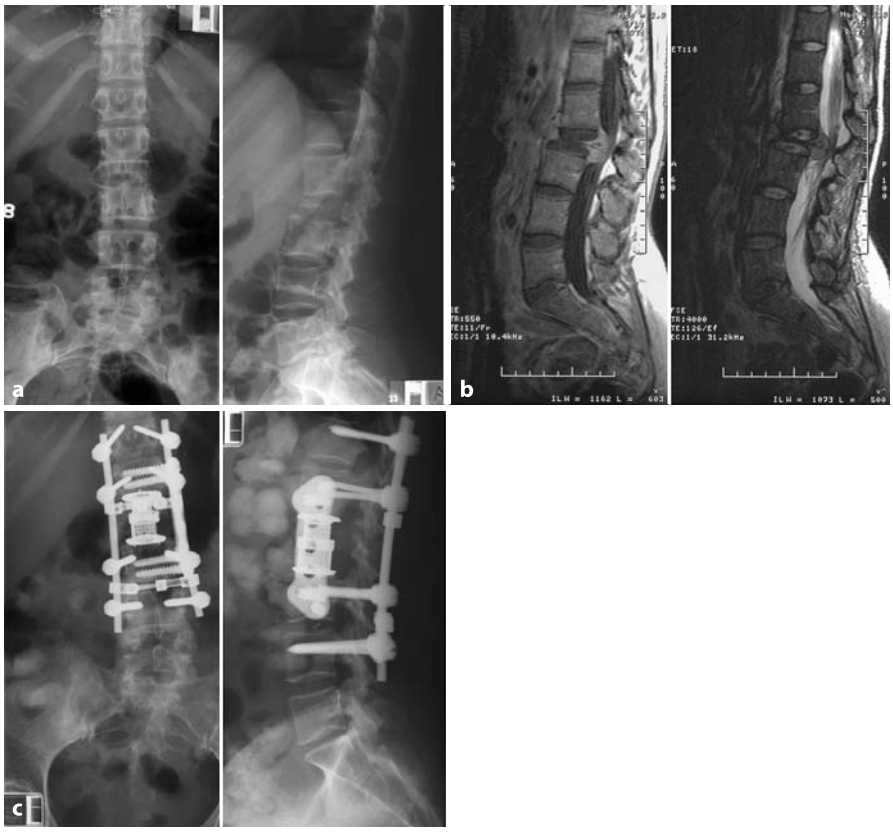


Fig. 3 Preoperative AP and lateral plain radiographs (**a**) and MRI scans (**b**) of a 39-year-old female with history of breast carcinoma. The patient presented with acute onset low back pain, bilateral lower extremity weakness, bowel and bladder dysfunction. Plain X-rays show complete collapse of L2 vertebra while MRI reveals severe compression of cauda equina. The patient underwent a two-stage procedure: I. Retroperitoneal approach, L2 corpectomy, reconstruction with distractable cage, correction of kyphotic deformity, fixation with plate/screws and fusion. II. Posterior thoracolumbar pedicle screw fixation and fusion. Postoperative plain X-rays show the final construct (**c**). One year later, following additional XRT locally, the patient was neurologically intact and pain free

portant to determine if the source of compression is from the tumor mass or if it is from bony fragments. Patients with significant neoplastic bony destruction will often times have concomitant pathologic vertebral fractures. In a significant proportion of these cases there will be retropulsion of vertebral body fragments into the spinal canal that may impinge on the spinal cord. Radiation therapy has no chance of relieving the compression in these cases. In addition, the bony destruction may result in destabilization of the spinal column, which may predispose the patient to future neurologic injury. These patients are best managed with surgical decompression and stabilization (if needed) should their overall medical condition permit.

The standard radiation treatment protocol for palliation of spinal metastases is 300-cGy daily fractions to a total dose of 3,000 cGy. A single posterior field or opposed fields are used to encompass the involved segments plus 1–2 spinal levels above and below [5]. The tolerance of the spinal cord and cauda equina to radiation therapy is the major limiting factor in treating with higher doses of radiation. Higher doses increase the risk of developing radiation-induced myelopathy with resultant loss of spinal cord function. A recent review of the Mayo Clinic's experience with patients requiring reirradiation for recurrence of malignant spinal lesions found that at a median follow-up period of 4.2 months, nearly 70% of the patients remained ambulatory [36]. The median total radiation dose in the reirradiated segment was 5,425 cGy. This study demonstrates that in select patients, with limited life expectancy, reirradiation may still have a role.

After the decision to proceed with radiation therapy has been made, the timing must still be carefully considered. Several studies have shown that radiation therapy has deleterious effects on wound healing as well as bone healing and graft incorporation [9, 18]. The negative effects that radiation has on skin healing have been well documented. The operative incision must be taken into account when developing a radiation treatment plan to prevent potentially disastrous wound dehiscence and infection. In addition, there is a great deal of literature from animal models that points to preoperative and immediate postoperative radiation as having the most significant negative effects on bony fusions. Delayed radiation therapy (>21 days), however, has not been shown to have this same negative effect. The negative effects of radiation also appear to be more profound with posterior than anterior graft fusions. This is presumably due to the increased blood supply of the anterior column and the reliance of posterior grafts on adjacent tissues (which are also negatively affected by the radiation treatment) for fusion. The authors advocate a 3- to 4-week delay following surgical intervention before initiating radiation therapy when a bone graft has been placed.

Chemotherapy

Chemotherapeutic options can be divided into antitumoral drugs and drugs that prevent or ameliorate the effects of the tumor. Antitumor chemotherapy has a relatively limited role in the treatment of spine metastases. A few primary tumors, such as Ewing's sarcoma, osteogenic sarcomas (both primary and secondary), and germ cells tumors, are very chemosensitive and therefore these agents have a role in the treatment of patients harboring these lesions. Systemic chemotherapy is often the first line of treatment for these patients, even in the face of epidural spinal cord compression.

A small number of metastatic tumors, namely breast and prostate cancer, have variable numbers of hormone receptors. This makes these lesions susceptible to chemotherapeutic agents that act to block these receptors. Agents such as tamoxifen have been used systemically with fair clinical results. Spinal metastatic lesions from these tumors may or may not possess the same concentration of hormone receptors. Therefore, primary lesions in the breast or prostate may respond, whereas the metastatic lesion does not to the same degree.

Dexamethasone has been shown to reduce the spinal cord edema and pain associated with some spinal column tumors. Dosage schemes range from low dose (16 mg per day in divided doses) to very high dose (96 mg per day in divided doses) [5]. The optimal dose that is necessary to treat patients with acute spinal cord compression is somewhat controversial. In addition, it is unclear whether high doses are associated with improved neurologic outcomes when compared to low to moderate doses. High dose steroids are associated with significantly higher complication rates such as hyperglycemia, gastrointestinal ulceration and perforation, and avascular necrosis of the hip. In addition, steroids may affect the yield of biopsy specimens of undiagnosed spinal masses. Lymphoma and thymomas are particularly sensitive to this oncolytic steroid effect and thus may prevent or delay their diagnosis.

Bisphosphonates are a class of drugs that act to inhibit osteoclast activity and therefore suppress bone resorption. They have been shown to be quite effective at treating malignancy-associated hypercalcemia. Pamidronate, the most commonly used drug in this class, has been shown to reduce or delay the onset of pathologic fracture in cancer patients when used in combination with systemic antitumoral therapy. This has been shown to be effective for breast cancer, multiple myeloma, and osteolytic metastases [4, 5].

Other

Endovascular embolization plays a critical role in the management of certain spinal tumors. Some primary tumors, such as hemangioma and aneurysmal bone cysts, as well as metastatic lesions, such as renal cell and thyroid cancer, are extremely hypervascular, which may result in tremendous intraoperative blood loss. Preoperative angiography and embolization offer a means of reducing the blood supply to the tumor mass and thus significantly reducing the morbidity associated with surgical resections.

The tumor histology as well as signs of hypervascularity on MRI images may determine the need for preoperative embolization. Prabhu et al. reported a series of 41 patients with spinal neoplasms who underwent preoperative embolization and tumor resections over a 5-year period [34]. They found a positive predictive value of MRI signs of vascularity (bright contrast enhancement, large signal flow voids, or intratumoral hemorrhage) of 77% and a negative predictive value of 21%. They were able to achieve 80% or greater angiographic embolization in 80% of their patient population. In their report the surgical procedure was performed within 48 h of the embolization procedure. They had asymptomatic neurologic complications in two patients and no patients died as a result of the embolization or the surgical procedure. Strong consideration should be given to preoperative embolization for tumor histological types associated with hypervascularity and for lesions with MRI imaging which indicates a concern regarding increased vascularity.

Vertebroplasty is a relatively new technique that has been added to the armamentarium of treatment options for cancer patients with vertebral body lesions. This technique was developed in France in the late 1980s and involves the percutaneous injection of polymethylmethacrylate (PMMA) into a fracture vertebral body. This acts to reinforce the vertebral body and therefore alleviate the pain associated with these destructive processes. Percutaneous, balloon kyphoplasty is a recent modification to this technique that involves inflation of a balloon within a collapsed vertebral body in order to restore vertebral body height and reduce the degree of kyphotic deformity prior to the injection of the PMMA. These techniques have been used extensively in recent years for the treatment of painful primary and metastatic, osteolytic vertebral processes. Fourney et al. reported on a series of 56 consecutive cancer patients undergoing vertebro- and kyphoplasty at the M.D. Anderson Cancer Center over a 2-year period. They noted improvement or complete relief of pain in 84% of their patients within 72 h of the procedure [21]. They found that this pain relief was quite durable and maintained statistical significance through the follow-up period of 1 year. They did not report any deaths from complications associated with these procedures during the study period. Although not a direct treatment for the tumor, these results demonstrate a clear palliative role for both vertebro- and kyphoplasty in the treatment of cancer patients (Fig. 4).

Prognosis/Quality of Life

The prognosis for patients affected by primary spinal column tumors varies depending on the tumor histology and the oncologic stage of the tumor. For benign neoplasms such as hemangioblastomas and osteoid osteomas, surgical cure is the rule. Other benign histologic tumors such as chordomas have a high likelihood of recurrence with subtotal resections. The prognosis in these cases depends in large part on the stage of the disease at presentation and the ability of the tumor to be removed en bloc. For more malignant primary tumors like chondrosarcomas, the overall survival and recurrence risk likewise depend in large part on the extent of surgical resection in addition to the tumor response to radiation treatment. Lesions that remain confined to the vertebral body (stage IA or IIA) and that are amenable to en bloc resection carry a favorable prognosis with surgical intervention.

The prognosis for patients with metastatic spinal lesions depends on several factors. As discussed above, three factors that have been found to have a statistically significant effect on patient survival: grade of the primary tumor, status of visceral metastases, and number of bony metastases. In addition, the response of the tumor to chemo- and radiation therapy is of prognostic importance. For example, some breast cancers respond exquisitely well to radiation and chemotherapy regimens whereas others do not respond at all.

Regarding tumor histology, there is a tremendous difference in the expected 1-year survival for various primary lesions. Prostate and breast cancer have the highest 1-year survival rates at 83% and 77%, respectively. Rectal and uterine cancer patients have an intermediate 1-year survival (approximately 50%), whereas patients with sarcoma, lung, and gastrointestinal cancers have a less than 20% 1-year survival rate [39].

It is widely reported in the literature that patients with visceral metastases fare much poorer than those without. This is due in large part to the impact on the patients' overall clinical condition that these metastases have. Patients with a poorer clinical status at the time of presentation with spinal metastases fare much worse than those who are in good clinical condition at presentation. Their poor clinical condition

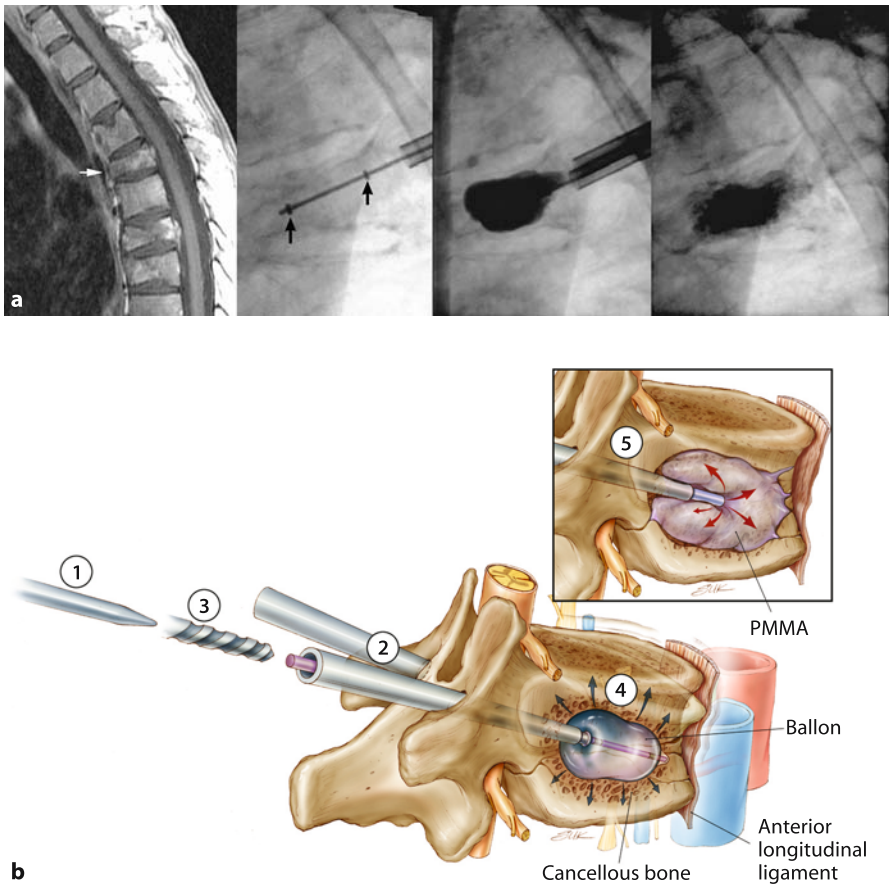


Fig. 4. **a** Kyphoplasty was performed at T-6 in a patient with multiple myeloma. *Left*: Preoperative sagittal MR image revealing T-6 osteolytic compression fracture (*white arrow*). *Center left, center right, and right*: Sequential lateral fluoroscopic images demonstrating the trajectory of the IBTs, inflation of the balloons, and filling of the osseous voids with PMMA. Two markers identify the balloon position for accurate placement (*black arrows*). **b** Artist's rendering of the kyphoplasty technique. Using a bilateral transpedicular approach, bone biopsy needles are directed into the posterior third of the VB. Guide pins (K-wires) are used to exchange the biopsy needles for blunt cannulated obturators (*1*). Working cannulas (*2*) are then advanced, and the obturators and K-wires are removed. A hand-mounted drill (*3*) creates bilateral channels within the anterior aspect of the VB for placement of the IBTs (*4*). Balloon inflation allows restoration of VB height. *Inset*: The IBTs are removed and the osseous void is filled with PMMA displaced from bone cement cannulas (*5*). (Reprinted with permission from *Journal of Neurosurgery* [21])

affects their ability to tolerate various treatment options such as chemotherapy and surgery.

With the improvement in surgical instrumentation and techniques, as well as improved radiation protocols, the quality of life for patients with spinal column neoplasms has improved significantly. New, more aggressive approaches to local tumor resection have led to decreased local recurrence rates and prolonged survival for many patients. In addition, the rate of pain control among patients undergoing radiation treatment or surgery is well above 85% in most clinical series. Improvements in spinal instrumentation have decreased the failure rate and improved our ability to help restore neurologic function and ambulatory ability for many. Even in the absence of an increase in longevity, these improvements in the quality of the patients' lives should not be underappreciated.

Follow-Up/Specific Problems and Measures

Patients treated for primary or secondary spinal column tumors must be followed very closely for signs of tumor recurrence. Some benign lesions that may be cured surgically need not be followed as closely as those that are prone to recurrence. New complaints of worsening back pain or new neurologic complaints must be taken very seriously and investigat-

ed thoroughly. MRI scans are typically obtained every 3–6 months for at least the first 2 years after treatment. If there are no signs of recurrence and all imaging studies have been stable over that period, then these studies may be spaced out to annually. It is imperative to keep an open line of communication with these patients so that possible signs of recurrence are detected early when intervention has the highest chance of success.

Future Perspectives

A cure for cancer remains elusive at this time. Extensive research and resources are being dedicated to the search for a cure and the development of new treatments appear annually. Future directions include improving our ability to detect spinal metastases at an earlier stage. In addition, the development of new local therapies (radio-sanitizers, drug delivery systems, etc.) for the treatment of these neoplastic processes offers a new route through which we may address these lesions.

References

1. Abdu WA, Provencher M. Primary bone and metastatic tumors of the cervical spine. Spine 1998;23:2767–2777
2. Ameli NO, Abbassioun K, Saleh H, Eslamdoost A. Aneurysmal bone cysts of the spine. Report of 17 cases. J Neurosurg 1985;63:685–690
3. Bell GR. Surgical treatment of spinal tumors. Clin Orthop 1997;(335):54–63
4. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med 1996;334:488–93
5. Bilsky MH, Lis E, Raizer J, Lee H, Boland P. The diagnosis and treatment of metastatic spinal tumor. Oncologist 1999;4:459–469
6. Black P. Spinal metastasis: current status and recommended guidelines for management. Neurosurgery 1979;5:726–46
7. Boriani S, Weinstein JN. Differential diagnosis and surgical treatment of primary benign and malignant neoplasms. The adult spine: principles and practice In: Frymoyer JW, editor. The adult spine: principles and practice. Philadelphia: Lippincott-Raven; 1997. p. 951–987
8. Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. Spine 1997;22:1036–1044
9. Bouchard JA, Koka A, Bensusan JS, Stevenson S, Emery SE. Effects of irradiation on posterior spinal fusions. A rabbit model. Spine 1994;19:1836–1841
10. Brihaye J, Ectors P, Lemort M, Van Houtte P. The management of spinal epidural metastases. Adv Tech Stand Neurosurg 1988;16:121–176
11. Burger PC, Scheithauer BW, Vogel FS. Surgical pathology of the nervous system and its coverings. Philadelphia: Churchill Livingstone; 2002. p. 540–543
12. Cahill DW. Surgical management of malignant tumors of the adult bony spine. South Med J 1996;89:653–65
13. Cohen ZR, Fourney DR, Marco RA, Rhines LD, Gokaslan ZL. Total cervical spondylectomy for primary osteogenic sarcoma. Case report and description of operative technique. J Neurosurg Spine 2002;97:386–392
14. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine 1983;8:817–31
15. Diel J, Ortiz O, Losada RA, Price DB, Hayt MW, Katz DS. The sacrum: pathologic spectrum, multimodality imaging, and subspecialty approach. Radiographics 2001;1:83–104
16. Doppman JL, Oldfield EH, Heiss JD. Symptomatic vertebral hemangiomas: treatment by means of direct intralesional injection of ethanol. Radiology 2000;214:341–348
17. Eary JF. Nuclear medicine in cancer diagnosis. Lancet 1999;354:853–857
18. Emery SE, Brazinski MS, Koka A, Bensusan JS, Stevenson S. The biological and biomechanical effects of irradiation on anterior spinal bone grafts in a canine model. J Bone Joint Surg Am 1994;76:540–8
19. Fourney DR, Abi-Said D, Lang FF, McCutcheon IE, Gokaslan ZL. Use of pedicle screw fixation in the management of malignant spinal disease: experience in 100 consecutive procedures. J Neurosurg Spine 2001;94:25–37
20. Fourney DR, Abi-Said D, Rhines LD, Walsh GL, Lang FF, McCutcheon IE, et al. Simultaneous anterior-posterior approach to the thoracic and lumbar spine for the radical resection of tumors followed by reconstruction and stabilization. J Neurosurg Spine 2001;94:232–44
21. Fourney DR, Schomer DF, Nader R, Chlan-Fourney J, Suki D, Ahrar K, et al. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg Spine 2003;98:21–30
22. Fourney DR, York JE, Cohen ZR, Suki D, Rhines LD, Gokaslan ZL. Management of atlantoaxial metastases with posterior occipitocervical stabilization. J Neurosurg Spine 2003;98:165–170
23. Gokaslan ZL, Romsdahl MM, Kroll SS, Walsh GL, Gillis TA, Wildrick DM, et al. Total sacrectomy and Galveston L-rod reconstruction for malignant neoplasms. Technical note. J Neurosurg 1997;87:781–787
24. Gokaslan ZL, York JE, Walsh GL, McCutcheon IE, Lang FF, Putnam Jr JB, et al. Transthoracic vertebrectomy for metastatic spinal tumors. J Neurosurg 1998;89:599–609
25. Jackson RJ, Gokaslan ZL. Occipitocervicothoracic fixation for spinal instability in patients with neoplastic processes. J Neurosurg Spine 1999;91:81–89
26. Jackson RJ, Gokaslan ZL. Spinal-pelvic fixation in patients with lumbosacral neoplasms. J Neurosurg Spine 2000;92:61–70

27. Jackson RJ, Loh SC, Gokaslan ZL. Metastatic renal cell carcinoma of the spine: surgical treatment and results. J Neurosurg Spine 2001;94:18–24
28. Kleihues Paul, Cavenee, Webster K. Pathology and genetics: tumours of the nervous system. Lyon: IARC Press; 2000. p. 78–79
29. Mullan J, Evans JP. Neoplastic disease of the spinal extradural space; a review of fifty cases. AMA Arch Surg 1957;74:900–907
30. Nazzaro JM, Arbit E, Burt M. "Trap door" exposure of the cervicothoracic junction. Technical note. J Neurosurg 1994;80:338–341
31. Osborn, Anne G. Diagnostic Neuroradiology. Philadelphia: Mosby, Inc.; 1994. p. 906–910
32. Panjabi MM, Oxland TR, Kifune M, Arand M, Wen L, Chen A. Validity of the three-column theory of thoracolumbar fractures. A biomechanic investigation. Spine 1995;20:1122–7
33. Peterson JJ, Kransdorf MJ, O'Connor MI. Diagnosis of occult bone metastases: positron emission tomography. Clin Orthop 2003;415:S120–S128
34. Prabhu VC, Bilsky MH, Jambhekar K, Panageas KS, Boland PJ, Lis E, et al. Results of preoperative embolization for metastatic spinal neoplasms. J Neurosurg Spine 2003;98:156–64
35. Seol HJ, Chung CK, Kim HJ. Surgical approach to anterior compression in the upper thoracic spine. J Neurosurg Spine 2002;97(3 Suppl):337–342
36. Schiff D, Shaw EG, Cascino TL. Outcome after spinal reirradiation for malignant epidural spinal cord compression. Ann Neurol 1995;37:583–589
37. Sundaresan N, Galicich JH, Lane JM, Bains MS, McCormack P. Treatment of neoplastic epidural cord compression by vertebral body resection and stabilization. J Neurosurg 1985;63:676–684
38. Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine 1990;15:1110–1113
39. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. Spine 2001;26:298–306
40. York JE, Berk RH, Fuller GN, Rao JS, Abi-Said D, Wildrick DM, et al. Chondrosarcoma of the spine: 1954 to 1997. J Neurosurg Spine 1999;90:73–78
41. York JE, Kaczaraj A, Abi-Said D, Fuller GN, Skibber JM, Janjan NA, et al. Sacral chordoma: 40-year experience at a major cancer center. Neurosurgery 1999;44:74–79
42. York JE, Wildrick DM, Gokaslan ZL. Metastatic tumors. In: Benzel EC, Stillerman CB, editors. The thoracic spine. St. Louis: Quality Medical Publishing; 1999. p. 392–411.
43. Walsh GL, Gokaslan ZL, McCutcheon IE, Mineo MT, Yasko AW, Swisher SG, et al. Anterior approaches to the thoracic spine in patients with cancer: indications and results. Ann Thorac Surg 1997;64:1611–1618
44. Wild WO, Porter RW. Metastatic epidural tumor of the spine. A study of 45 case. Arch Surg 1963;87:825–830
45. Weinstein JN, McLain RF. Primary tumors of the spine. Spine 1987;12:843–851

Peripheral Nerve Tumors IV

Organised by Abhijit Guha

56 Peripheral Nerve Tumors – 665
Joseph Wiley, Asis Kumar Bhattacharyya, Gelareh Zadeh, Patrick Shannon, Abhijit Guha

Peripheral Nerve Tumors 56

Joseph Wiley, Asis Kumar Bhattacharyya, Gelareh Zadeh, Patrick Shannon, Abhijit Guha

Overview and Epidemiology – 666

Symptoms and Clinical Signs – 666

Diagnostics – 666

Staging and Classification – 670

Associated PNT Predisposition Syndromes – 673

Treatment – 674
Overall Comments
Specific Comments
Benign Neural PNTs
Benign Nonneural PNTs
Malignant Neural PNTs
Malignant Nonneural PNTs

Conclusions – 682

References – 683

Overview and Epidemiology

Peripheral nerve tumors (PNTs) are rare soft tissue lesions that can arise anywhere on the body and as a result have a wide differential diagnosis, which is often confirmed to be a PNT only at surgery. PNTs occur both sporadically and within the context of genetically predisposing syndromes, hence a thorough history of the mass and associated symptoms, with a focused family history for neurofibromatosis (NF) or other known predisposition syndromes, combined with a local plus systemic examination is crucial. The low frequency of PNTs and incomplete understanding of the molecular etiology and cell of origin of the various subtypes has led to lack of a rigorous classification of PNTs, though one is proposed by the World Health Organization (WHO) [1], with several others such as the one used at our institute (Fig. 1). MRI imaging is the preoperative imaging modality of choice of PNTs, though it is not pathognomonic for the diagnosis or differentiation of the various subtypes of PNTs.

While these tumors may initially be seen by a wide variety of surgeons, the rarity and presence of several subtypes necessitates an individualized approach to case management. Optimal management involves specialized centers, employing the collective expertise of neurosurgeons, radiologists, neuropathologists, and medical oncologists with expertise in PNTs. Among the most essential aspects for optimal management of PNTs is the clear definition of preoperative goals, which in many instances, depending on patient and tumor characteristics, may be just clinical and/or radiological follow-up. Where surgery is indicated, the goals may be to obtain biopsy only, subtotal debulking to decrease mass effect of the tumor, or complete tumor excision. The choice of the optimal surgical goal, although often suggested by the preoperative MRI, is most often conclusively undertaken intraoperatively depending on the evaluation of the risks of tumor removal versus associated neurological deficits. Magnification, use of intraoperative electrophysiological recordings, and knowledge of the gross and microscopic pathology are important for maximizing tumor removal with minimal morbidity.

In general, schwannomas, the most common of all PNTs in non-NF-1 patients, can be completely resected without added permanent neurological deficits in over 95% of patients, due to the extrafascicular growth pattern. In contrast, the majority of neurofibromas, the second most common PNT and the tumor type most prevalent in NF-1 patients, cannot be completely resected due to its intrafascicular growth. However, even in these neurofibromas, safe radical debulking is achievable with microneurosurgical techniques and selective fascicular electrophysiological monitoring. Malignant peripheral nerve sheath tumors (MPNST) or neurogenic sarcomas require special mention. The preoperative goal is first to confirm the diagnosis, due to lack of any pathognomonic imaging studies, followed usually at a separate setting by radical oncological surgery, with removal of the nerve and adjacent fascial planes to obtain tumor-free margins and minimize the chance of systemic metastasis. Many of the other PNTs, arising from the nerve or adjacent structures, have their own optimal management strategy based on the biology of the lesion and our ability to resect with minimal morbidity. These will be discussed further on an individual basis for each tumor type.

Symptoms and Clinical Signs

A focused history of a patient suspected to harbor a PNT should be directed towards the onset, duration, and growth alterations of the mass. Presence or absence of neurological and nonneurological symptoms such as pain, numbness, and weakness and any associated systemic complaints suggestive of an underlying cancer is of importance. A family history suggestive of NF-1 or NF-2 or other predisposition syndromes is of special importance, since almost half of all PNTs are linked with these syndromes. The physical exam should be directed towards the mass including comments on whether the mass is firm versus soft, pulsatile versus nonpulsatile, mobile versus adhered to the soft tissues, and if mobile does it move perpendicular to but not along the long-axis of a known peripheral nerve, which is highly suggestive of a PNT. Although the majority of PNTs will not have any fixed sensory or motor deficits on presentation, the presence or absence of a Tinel's sign may give a clue towards nerve of origin or one that is juxtaposed to the PNT. The physical examination is not complete without examination of local structures such as vessels, joints that may be compressed by the PNT, and a systemic examination with a focus on absence or presence of clinical signs associated with NF-1, NF-2, or the much more rare Schwannomatosis predisposition syndromes, as listed in Table 1.

Diagnostics

In addition to physical examination, additional investigations are also warranted. Preoperative electrophysiological examination is not normally performed as it is not diagnostic nor does it help in the management decision. However, intraoperative electrophysiology is crucial as discussed below in the Sect. entitled "Treatment." CT scans are occasionally

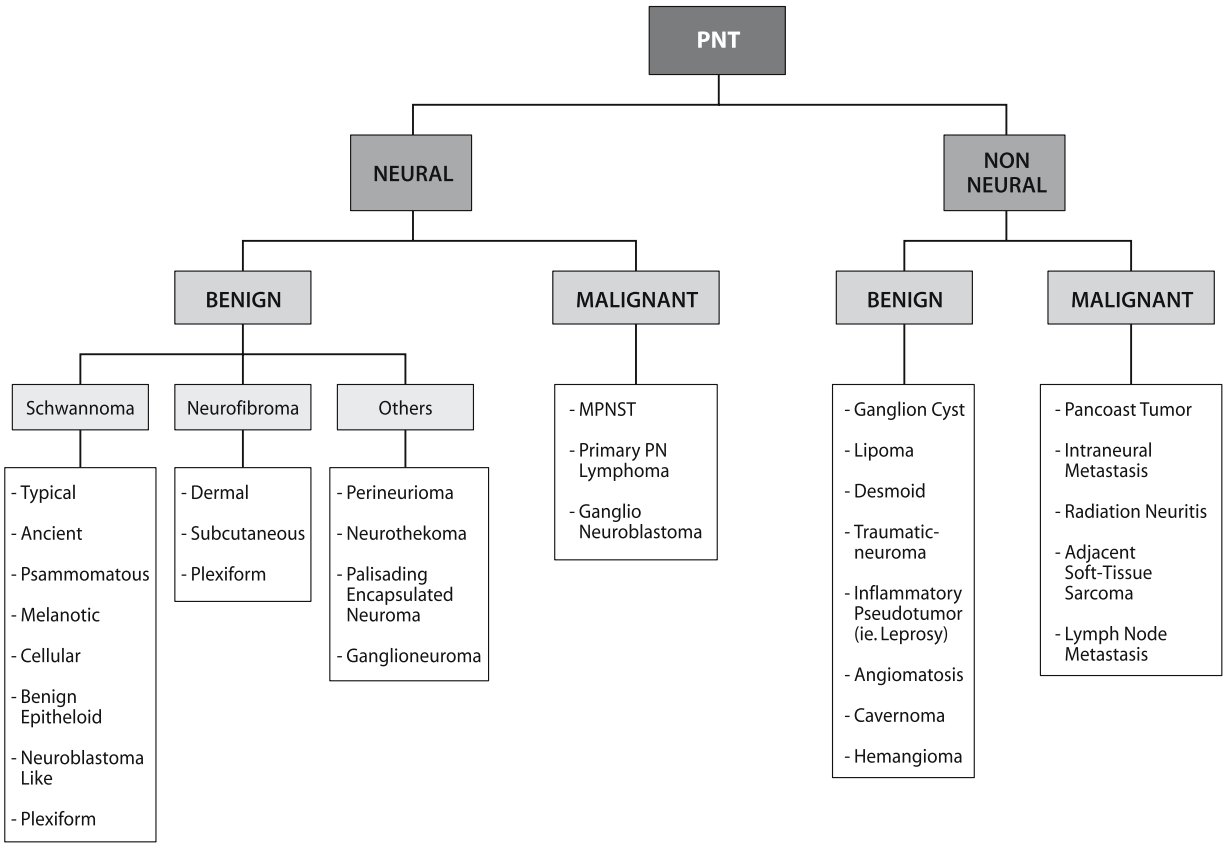


Fig. 1. Classification of peripheral nerve tu-

helpful, especially to demonstrate remodeling of adjacent bony structures such as the neural foramina or spinal canal. Angiography or MR angiography is rarely required, and restricted to large PNTs at the base of the neck, chest, or retroperitoneum, where close proximity and/or rarely vascular invasion may be present. MRI imaging is the most versatile tool, though it is often not definitive that a mass is arising from a peripheral nerve versus the much more common soft tissue masses which may be adjacent to the nerve. Furthermore, MRI imaging may be highly suggestive but not diagnostic of the subtype of PNT, with elements of the history and physical examination often superior in predicting whether the lesion is benign versus malignant and the likely subtype of PNT to be present. A well-defined tumor, displaying low T1, high T2 signal with homogeneous contrast enhancement, is highly suggestive of a schwannoma (Figs. 2A, 3A). Occasionally, there is MRI demonstration of the nerves of origin or exit, and displaced passerby fascicles around the capsule, all consistent with a schwannoma and its typical extrafascicular growth. In contrast, neurofibromas are more fusiform (i.e., spindle) or multinodal, suggestive of their typical intrafascicular growth (Figs. 2B, 3C). Of note, a PNT in the context of an NF-1 patient will most certainly be a neurofibroma versus an NF-2 patient who likely harbors a schwanno-

Table 1. NIH Diagnostic criteria for neurofibromatosis type 1 and type 2 and schwannomatosis

Neurofibromatosis type 1 (~incidence)
- Six or more CAL spots (98%)
- Two or more neurofibromas of any type or one plexiform neurofibroma (95%)
- Axillary freckling (88%)
- Optic nerve gliomas (20%)
- Two or more lisch nodules
- Osseous lesions with or without pseudoarthrosis
- First degree relative with NF-1
- * Two or more gives the clinical diagnosis of NF-1

Neurofibromatosis type 2
- Definitive criteria:
  - Bilateral vestibular schwannomas (BANF)
  - or
  - A family history of neurofibromatosis type 2 in a first degree relative, and:
    - Unilateral vestibular schwannoma diagnosed at an age less than 30 years, or
    - Two or more of the following—meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
- Presumptive criteria:
  - Unilateral vestibular schwannoma at age less than 30 years and:
    - One of the following—meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
  - Multiple meningiomas and unilateral vestibular schwannoma at age less than 30 years
  - or
  - One of the following—glioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

Schwannomatosis
- Definitive criteria:
  - Two or more pathologically proved schwannomas and
  - Lack of radiographic evidences of vestibular nerve tumors at an age of over 18 years
- Presumptive criteria:
  - Two or more pathologically proven schwannomas, without symptoms of eighth-nerve dysfunction, at age of over 30 years
  - or
  - Two or more pathologically proven schwannomas in an anatomically limited distribution (single limb or segment of the spine), without symptoms of eighth-nerve dysfunction, at any age

ma. Lipomas and ganglion cysts, which arise mainly but not always from outside the nerve sheath, have a characteristic and almost diagnostic MRI picture (Figs. 2C, D). Lipomas have the characteristic bright on T1 and T2 signal, while ganglion cysts are bright on T2 with the origin traced to joint capsule in proximity to the nerve.

MRI of PNTs may demonstrate nonhomogeneous enhancement, indicating intratumoral hemorrhage, necrosis, or cystic degeneration; however, cor-

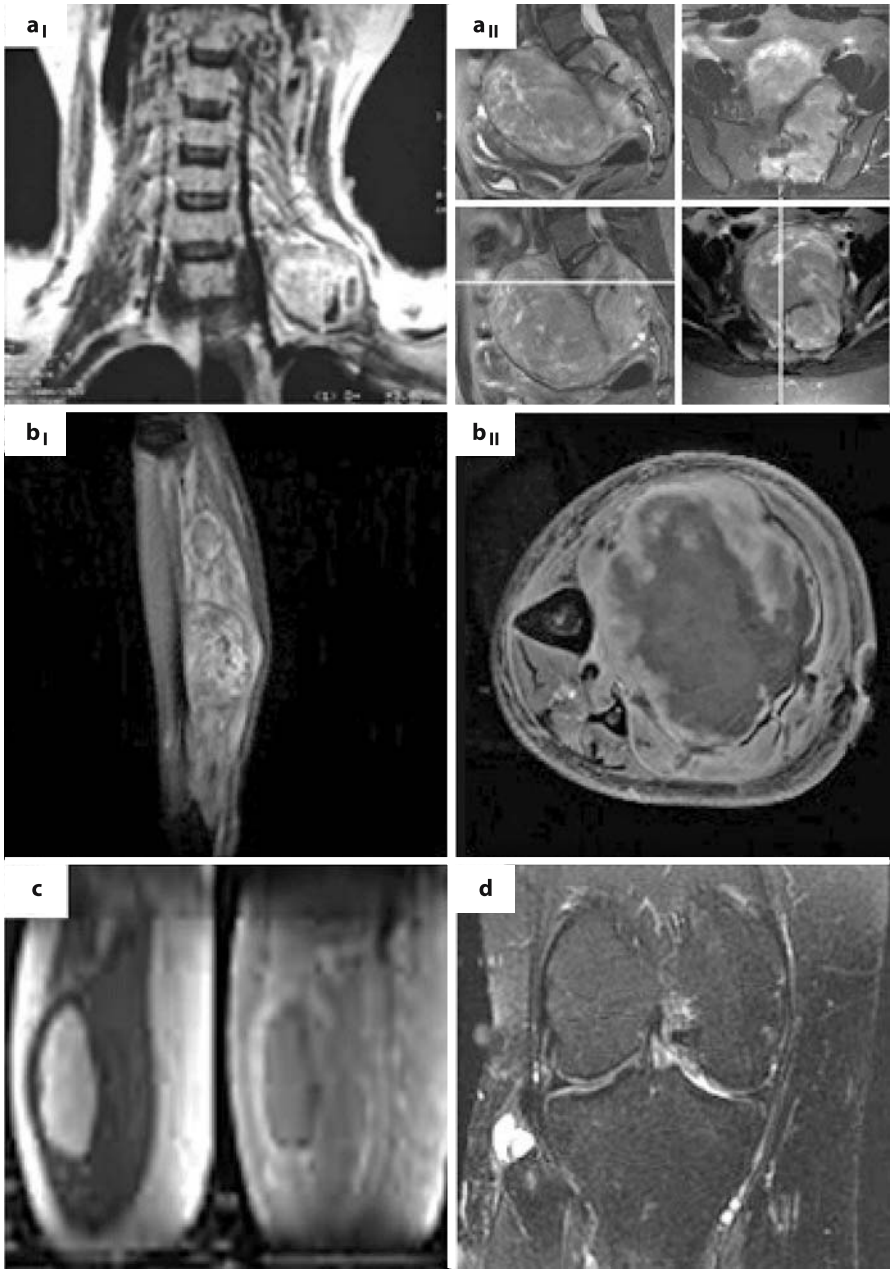


Fig. 2. MRI of PNTs. **a** Schwannoma, $\mathbf{a}_{\mathbf{I}}$ brachial plexus schwannoma arising from middle trunk, demonstrating extrafascicular growth with passerby fascicles and regions of heterogeneity (T1+gad); $\mathbf{a}_{\mathbf{II}}$ giant pelvic schwannoma arising from lower sacral roots with distortion of the bladder, managed with a transabdominal approach (T2); $\mathbf{b}_{\mathbf{I},\ \mathbf{II}}$ Neurofibroma in a NF-1 patient, demonstrating the fusiform intrafascicular involvement of the nerve, with large central regions of heterogenous enhancement, suggestive but not diagnostic of malignant transformation to MPNST; **c** lipoma in the region of the femoral nerve (T2 and fat suppression sequences); **d** ganglion cyst arising from the tibial-fibular joint causing compression of the common peroneal nerve (T2)

relation to malignancy is poor. In fact, there are no definitive radiological features of an MPNST, a diagnosis mainly suspected on rapid clinical and radiological growth, progressive neurological deterioration, and most importantly pain. Use of 18FDG PET scanning, a developing technique for dynamic imaging of glucose metabolism [2], is of potential promise in distinguishing MPNSTs from benign PNTs, though further clinical verification is required. Initial studies have shown that 18FDG-PET can be used to identify soft tissue sarcomas, metastases, histological grade, and potentially malignant transformation of a benign plexiform neurofibroma to an MPNST [2]. In those instances where malignant transformation is probable but not yet confirmed, biopsy of the lesion before surgery is essential. The Tru-Cut biopsy can be performed in the outpatient clinic under local anesthetic, though due to pathological heterogeneity of MPNSTs, the requirement of adequate and good quality tissue for diagnosis, and potential of induction of severe neuropathic pain, we advocate open four quadrant biopsy at our institute as demonstrated in Figure 7B.

Staging and Classification

The pathological diagnosis of the varying subtypes of PNTs are often challenging due to their rarity and overlapping immunohistochemical (IHC) profiles. In a simplistic manner, there are two broad categories of PNTs (Fig. 1). First are the PNTs arising from a neural sheath origin, which in itself is composed of a variety of cell types, sometimes requiring detailed IHC and electron microscopy characterization. Within this category are benign or malignant, with the most common benign group composed mainly of schwannomas and neurofibromas, with others including perineuromas, etc., composing a distant third group. In the malignant category the most common are MPNSTs or neurogenic sarcomas, which themselves are extremely rare but highly

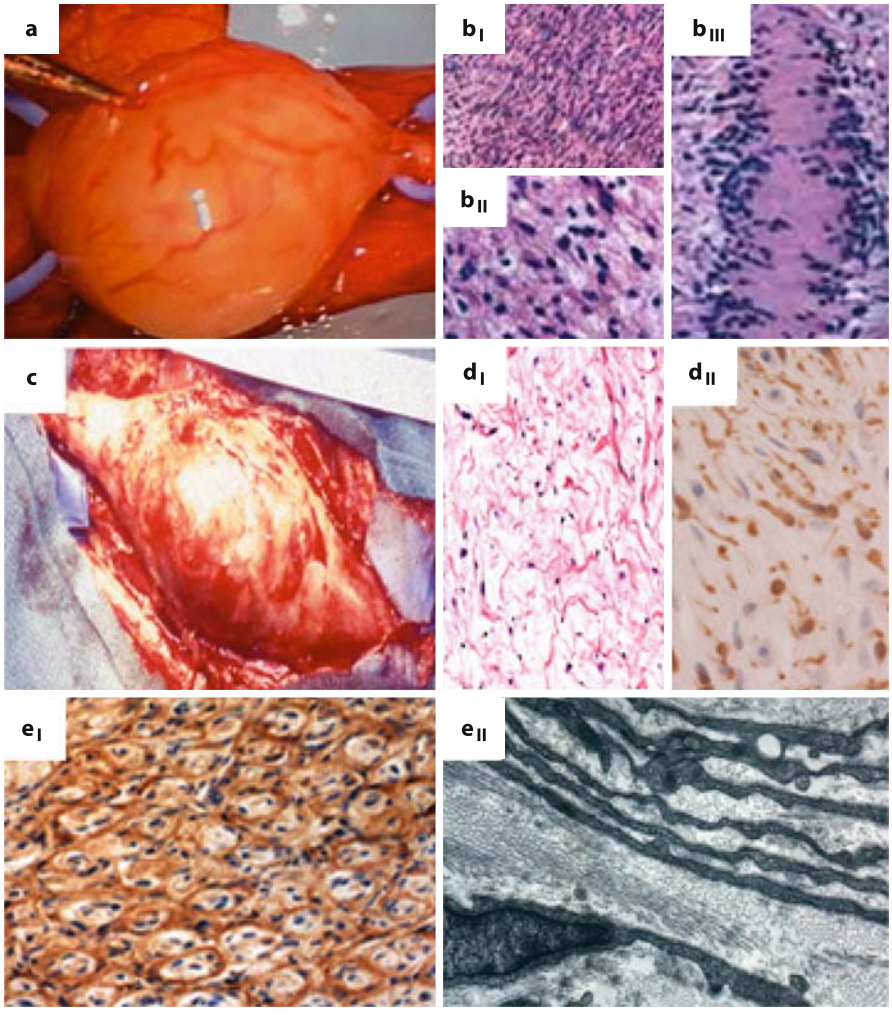


Fig. 3. Gross and microscopic pathology of PNTs: **a** schwannoma isolated from passerby fascicles; **B_{I-III}** (H&E schwannoma): **I**, Antoni-A; **II**, Antoni-B; **III**, Verocay body; **c** neurofibroma incorporating the nerve in a fusiform manner; **d_I** (H&E) dermal neurofibroma with intrafascicular growth; **d_{II}** (S-100) plexiform neurofibroma; **e** perineurioma: **e_I**, EMA+'ve & S-100-'ve; **e_{II}**, electron microscopy demonstrating incomplete basal lamina and abundant pinocytic vesicles

aggressive tumors. Second are PNTs arising from a nonneural sheath origin, which again are subdivided further into benign and malignant lesions (Fig. 1). Benign, but sometimes locally aggressive nonneural PNTs include ganglion cysts, lipomas, desmoids, neuromas, pseudotumors, and a variety of vascular malformations. Malignant nonneural PNTs include Pancoast lung cancers, intraneural invasion of carcinoma or from adjacent soft tissue sarcomas. In addition, treatment for a primary nonneural cancer can lead to secondary involvement of the associated nerve, such as radiation plexitis or rarely radiation-induced PNTs.

The rarity, multiple cell types in a normal peripheral nerve and the resulting wide variety of PNTs, has led to widely disputed and multiple classification and nomenclature schemes, as outlined below in the Sect. entitled "Staging and Classification" for historical purposes. First is the controversy centering on the cell of origin. Do these tumors arise from myelin-producing Schwann cells, pericytes, or from the fibroblasts that are responsible for producing the endoneurium and epineurium of nerves? Virchow, in 1847 [3], coined the term "neuroma fibrillare amyelinicum" for the tumor subsequently described by von Recklinghausen [4], but it is Verocay, in 1910, who is first credited with the description of a nerve tumor as a special entity [5]. Verocay referred to the origin as being from fibrous neural sheaths and introduced the term "neurinoma" which translates to "nerve tumor" [5]. This term is usually not advocated by neuropathologists, as it fails to specify and implicate the transformed cell type. Mallory did implicate the fibroblast as the transformed cell type and thereby coined the term "perineurial fibroblastoma" in 1930, a term strongly supported by Penfield [6]. However, with more detailed cellular characterization and differentiation, it has been recognized that the fibroblast was not the transformed cell type in the majority of PNTs. Stout, in 1935, introduced the term "neurilemoma," indicating the neuroectodermal origin of these tumors, in the first Armed Forces Institute of Pathology fascicle on PNTs [7]. However, as pointed out by Russell and Rubinstein, the term neurilemoma refers to membranes and not the specific transformed cell type, which has resulted in the PNT [8]. The cell-specific term "schwannoma" was put forth by Ehrlich and Martin in 1943 and subsequently verified by electron microscopy (EM), which has been vital in the detailed definition of normal and pathological nerves, including PNTs [9]. Using EM, Fisher and Veuzesvski demonstrated, in 1968, the distinctive basement lamella that clearly differentiates Schwann cells within the endoneurium from fibroblasts, the latter being the main cellular element of the epineurium [10]. The perineurial layer investing each nerve fascicle are composed of fibroblast-looking cells under light microscopy. However, unlike fibroblasts, but similar to Schwann cells, these perineurocytes possess basement membranes, but differ in formation of tight junctions leading to formation of the blood-nerve barrier. In addition, these perineurocytes contain abundant pinocytic vesicles, a characteristic feature also found in the derivative benign tumors from these cells called perineuriomas (Fig. 3 E).

The complexity of neuropathological evaluation of PNTs is not just due to the origin of the transformed cell type, but augmented by the growth pattern of the tumor. For example, in both schwannomas and neurofibromas, it is agreed that the primary transformed cell type is the Schwann cell, based on EM and genetic analysis [11]. However, the pathology and subsequent management vastly differs due to the distinctive extrafascicular versus intrafascicular growth of schwannomas versus neurofibromas, respectively (Figs. 3A–D). Schwannomas are characterized by cellular Antoni-A regions, with abundant spindle-shaped cells which form palisading structures called Verocay bodies (Fig. 3B). These cellular regions are sometimes accompanied by sparsely cellular Antoni-B regions, which stain poorly for mucopolysaccharides; however, intratumoral axons are not seen due to their extrafascicular growth. The biological basis for these two regions remains conjectural, with the hypothesis that perhaps Antoni-B may represent degenerated Antoni-A regions. In contrast to the usual compact array of Schwann cells in schwannomas, neurofibromas are characterized by an abundant myxomatous collagenous mucopolysaccharide and reticulum-positive matrix, within which are a relatively smaller number of transformed Schwann cells plus a variety of nontransformed cell types including fibroblasts, pericytes, and mast cells, all encompassing traversing myelinated and unmyelinated axons, reflective of their intrafascicular growth (Fig. 3D) [12].

The reason for this differing growth pattern in the Schwann cells of these two most common benign neural sheath origin PNTs is not clear. It may reflect differences in the biological subtype of Schwann cell that is transformed in the two tumors, with perhaps a more embryologically primitive Schwann cell giving rise to the invasive neurofibromas and a more mature Schwann cell in schwannomas. However, the most likely answer is the differences of the primary molecular alterations that lead to transformation of the Schwann cells in neurofibromas and schwannomas, which in turn triggers secondary differences in their biological growth patterns. In neurofibromas, both sporadic and those associated with NF-1, the primary molecular transformation event in the Schwann cells is loss of neurofibromin expression, encoded by the Nf1 gene (Fig. 4A) [13]. However, clinical and biological dif-

ferences exists between subtypes of neurofibromas, as discussed below in the Sect. entitled "Benign Neural PNTs", suggesting that molecular alterations in addition to loss of neurofibromin and perhaps interactions with other nontransformed cell types present contributes to the biology of neurofibromas. In schwannomas, both sporadic and those associated with NF-2, the primary molecular event is loss of MERLIN/Schwannomin expression, encoded by the Nf2 gene (Fig 4B) [14]. Again, clinical and biological variations between subtypes of schwannomas, such as those associated with schwannomatosis (Fig. 4C), are suggestive of the presence of additional molecular alterations.

The terminology for MPNSTs has also been equally confusing. Some neuropathologists have categorized them as either malignant schwannomas or malignant neurofibromas. Histologically, the usual characteristics of a malignant solid tumor, such as hypercellularity, cellular and nuclear pleomorphism, and mitotic figures serve to differentiate these tumors from their benign counterparts (Figs. 7B,C). However, many of these features are seen to varying extents in subtypes of totally benign schwannomas and neurofibromas, requiring interpretation of the pathology by trained neuropathologists taking into account a history of rapid growth and pain suggestive of malignancy. For example, distinction between ancient and cellular schwannomas and MPNSTs is not obvious, as many of the malignant features described above are present in all three PNTs to varying extents, though the first two are totally benign, while MPNSTs are lethal sarcomas. To further complicate matters, there is a lack of any specific IHC marker for MPNSTs, which in ~50% are dedifferentiated to the point of losing expression of classical Schwann cell markers such as S-100. There is no separate grading scheme for MPNSTs, due to their rarity. The 3-tier WHO classification scheme for the more common soft tissue sarcomas is routinely used and has demonstrated prognostic relevance in MPNST, though their clinical behavior is distinct from other sarcomas.

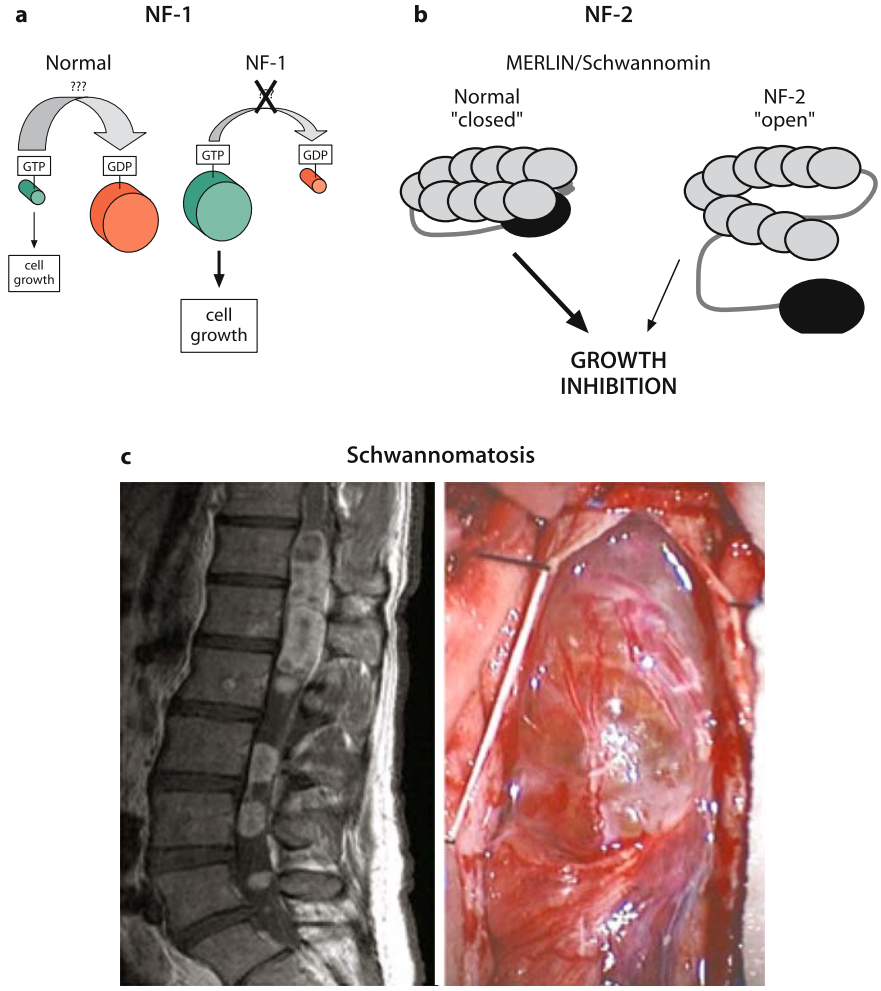


Fig. 4. a Neurofibromatosis-1 gene product, neurofibromin, normally inactivates the cell growth promoting intracellular signaling molecule Ras-GTP to Ras-GDP, a function which is lost in NF-1 tumors; **b** neurofibromatosis-2 gene product, MERLIN/Schwannomin, normally is in a closed position by interaction of its N- and C-terminal to inhibit yet-unknown growth promoting signals, a confirmation and function which is lost in NF-2 tumors; **c** schwannomatosis, with multiple spinal and PNTs, but not acoustic neuromas, is also a tumor-suppressor gene syndrome, with its gene near but distinct from NF-2

Associated PNT Predisposition Syndromes

As mentioned above in the Sect. entitled "Overview and Epidemiology", PNTs can occur sporadically or in the context of predisposing genetic syndromes. These syndromes include NF-1, NF-2, and Schwannomatosis, all examples of classical tumor-suppressor gene syndromes, where one mutated nonfunctional allele of the implicated gene is accompanied by somatic loss or mutation of the second normal allele, leading to transformation. Identification of these syndromes was pioneered by Knudson's two-hit hypothesis, first observed in retinoblastoma [15]. Although rare, having a cohort of genetically defined patients, whose tumors share similar molecular biological profiles with the much more common sporadic tumors, provides much insight into the biology of their sporadic counterparts. In addition to this benefit, special considerations come into play in the surveillance and surgical management of a patient with predisposition syndromes, where the tumors are often multiple and appear at an earlier age.

NF-1 is the most common heritable disorder in humans that has as one of its symptoms a predisposition toward the development of neoplasms of tissues derived from the neuroectoderm. These include neurofibromas, MPNSTs, gliomas, and pheochromocytomas, among other tumors in NF-1 patients. NF-1 has a prevalence of 1:4000, with approximately half of these arising from de novo germline mutations [16], representing an extremely high mutation rate, reasons for which are not fully understood but may relate to the large size of the gene. Once in the germline, NF-1 is transmitted in an autosomal dominant pattern, with 50% of children of an NF-1 parent affected. Presence of the single mutated *Nf1* allele, either through germline or familial transmission, leads to the NF-1 syndrome in all patients who acquire the mutation (100% penetrance), though the clinical degree to which one is affected is extremely variable, even with siblings that share the same *Nf1* mutation. Diagnosis of the syndrome as based on the criteria outlined by the NIH in 1987 [17] (Table 1) facilitated cloning of the responsible gene in 1990, which was localized to the pericentromeric region of the long arm of chromosome 17 at 17q11.2 [18]. The *Nf1* gene is extremely large at 350 Kb and encodes a ubiquitously expressed protein which is 2818 amino acids in length and ~240 KDa molecular weight, called neurofibromin. Due to the large size of the *Nf1* gene and the absence of any mutational hotspots, molecular screening is not yet clinically practical, hence the diagnosis for the most part is still reliant on the NIH criteria. The main but not likely the only function of neurofibromin was quickly ascertained, since it shared homology in a region called the GAP Related Domain (GRD) [19] to several proteins of known function including the Ira proteins in yeast and p120Ras-GAPin mammals. This observation led to the discovery of neurofibromin's main function as a Ras GTPase Activating Protein (Ras-GAP). The somatic loss or mutation of the second *Nf1* allele leads to loss of neurofibromin for reasons unknown especially in Schwann cells, leading to elevated levels of the active Ras-GTP, a potent mitogenic signal transducer resulting in transformation, as schematized in Figure 4 A [20].

NF-2 is about one tenth as less common as NF-1, with an incidence of approximately 1:40,000 livebirths. Similar to NF-1, the syndrome demonstrates an autosomal dominant pattern of inheritance, with 50% of cases resulting from de novo germline mutation [21]. The syndrome can have two separate clinical presentations, which can be present in the same family: (1) Wishart: the more aggressive subtype, characterized by early onset multiple intracranial and spinal tumors; and (2) Gardner: subtype characterized by late onset bilateral acoustic schwannomas. The *Nf2* gene has been localized at 22q12.2 and encodes a much smaller 595-amino-acid protein, termed MERLIN or Schwannomin, the function of which is not as well defined as neurofibromin, but involves linking membrane-bound glycoproteins to the cytoskeleton [22]. MERLIN is an acronym for moesin-ezrin-radixin-like-protein, due to its homology with members of the protein 4.1 B family [22]. Loss of functional MERLIN/Schwannomin results in alterations of intracellular signaling pathways implicated in cellular proliferation and migration (Fig. 4B). Like other tumor suppressor gene syndromes, there is a predilection towards developing a number of different tumors besides the most common bilateral acoustic schwannomas, including astrocytomas, meningiomas and ependymomas (Table 1). Due to the higher prevalence of CNS tumors, especially those in the posterior fossa and intramedullary spinal cord, the morbidity and mortality encountered by NF-2 patients is higher than in NF-1 patients.

Schwannomatosis, previously believed to be an attenuated type of NF-2, since patients do not harbor bilateral acoustic schwannomas, is now recognized as a distinct individual genetic disorder [23]. The characteristic tumor is the benign schwannoma of cranial, spinal and/or peripheral nerves (Table 1, Fig. 4C). While the disease segregates with chromosome 22, it has been shown that the locus is separate from that responsible for NF-2 on 22q12.2. Tumors associated with Schwannomatosis often have loss of MERLIN/Schwannomin expression; however, they do not harbor germline *Nf2* mutations [24]. Due to the multiple schwannomas, neurogenic pain is often very disabling, with permanent neurological deficit less fre-

quent compared to their NF-1 and NF-2 counterparts. While surgery is extremely effective in reducing symptoms of pain, when total resection is feasible, referral to a pain management clinic is often required when surgical removal carries too much risk.

Treatment

Overall Comments

Not all patients with a suspected PNT require surgical management. For example, a long-standing, slowly growing, minimally symptomatic mass, with all the classical MRI features of a schwannoma in an elderly or medically compromised patient is best left alone. Similarly, multiple dermal or plexiform neurofibromas in a NF-1 patient are best watched with routine clinical and radiological follow-up, unless local compressive symptoms or malignant conversion in the latter is suspected. For those in whom surgery is warranted, the preoperative goals, which may vary between total excision, subtotal excision, or biopsy, need to be clearly understood between the surgeon and patient. Several surgical principles germane to all PNTs exists (Fig. 5): (1) in all instances, microsurgical techniques and intraoperative electrophysiological monitoring are required; (2) the affected limb should be positioned and draped so that evaluation of the muscles innervated by the nerve in question can be achieved by palpation and/or direct audible EMG recordings; (3) short-acting or no neuromuscular paralysis should be used to allow intraoperative electrophysiological evaluation; (4) the incision should extend proximal-distal to the tumor to allow for isolation of nerve fiber of origin and exit, and to commence surgery from normal to abnormal pathology (Fig. 5A) and; (5) incisions are made along flex-

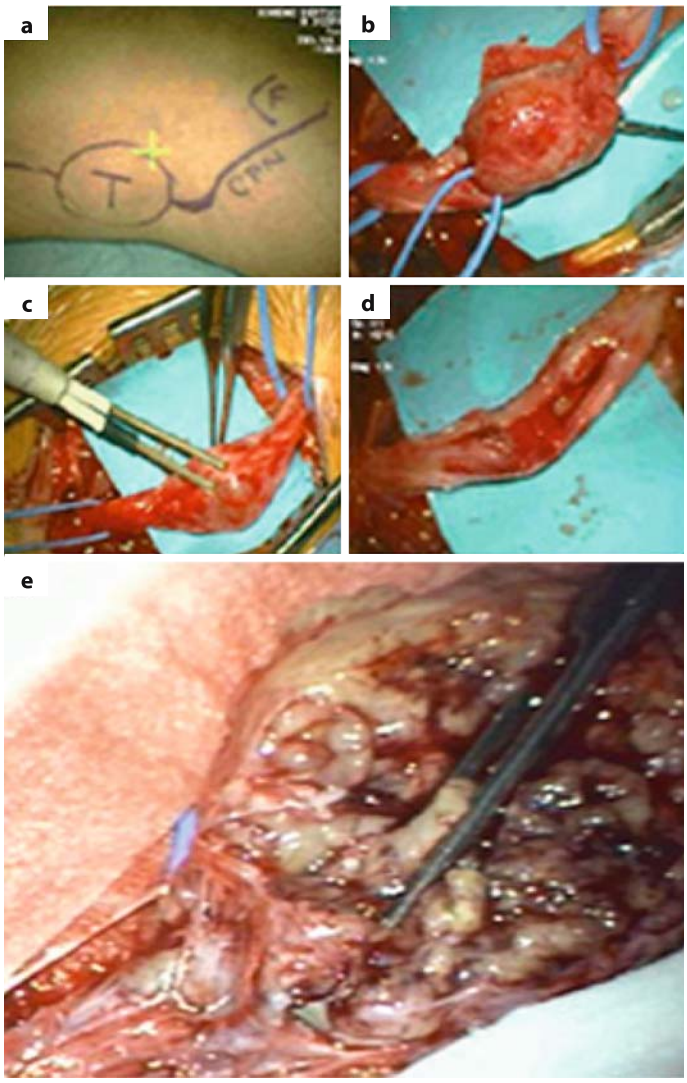


Fig. 5. General intraoperative microneurosurgical principles for removal of PNTs: A: incision above and below the tumor (T), with decompression of adjacent naturally occurring compression sites such as the common peroneal nerve (*CPN*) below the fibular (*F*) head; **b** isolation of nerve of origin and exit using the microscope; **c** identification and isolation of splayed passerby fascicles with electrophysiological stimulation; **d** removal of the schwannoma, leaving passerby fascicles and thereby neurological function intact; **e** large schwannomas may require first internal subcapsular decompression followed by tumor capsule removal

or or extensor creases rather than across, with nearby naturally occurring adjacent entrapment points such as the carpal tunnel or fibular-head, decompressed prophylactically to prevent delayed compression syndromes (Fig. 5A).

The first step is to isolate the proximal and distal segments of the main nerve trunk from the adjacent neurovascular structures, followed by nerve fascicle of origin and exit which is usually feasible in schwannomas with the aid of magnified vision (Fig. 5B). The capsule is carefully examined for passerby fascicles, which may be quite attenuated and splayed, though quite functional as ascertained on direct electrical stimulation (Fig. 5C). Presence of these fascicles is suggestive of the extrafascicular growth typical of a schwannoma. The majority of small-medium sized PNTs can be removed in total (Fig. 5D); however, in larger tumors tissue from an electrically silent region of the tumor is obtained for quick section. Often the exact differentiation of the PNT subtype cannot be made on the quick section, requiring use of good clinical judgment to maximize tumor removal with minimal deficits. If preoperative imaging and the quick section diagnosis is consistent with a schwannoma, then this opening can serve as a portico for undertaking an internal radical subcapsular decompression, often using the ultrasonic aspirator, to facilitate bulk tumor removal prior to microneurosurgical dissection and preservation of the passerby fascicles (Fig. 5E). If a major, functionally relevant fascicle is involved by the tumor and a significant deficit is apprehended after total resection, the outcome of subtotal removal versus total resection and nerve grafting should be considered. This scenario is one that luckily is rare in schwannomas, where the nerve of origin is already nonfunctional with usually little clinical sequelae when resected with the tumor. As discussed below in the Sect. entitled "Benign Neural PNTs", if the suspected pre- and intraoperative diagnosis is that of a plexiform neurofibroma, the aim of surgery is to achieve subtotal removal with maximal preservation of nerve function. Due to the size of the tumor, presence of intratumoral functioning fascicles, and longitudinal extension of the tumor along the course of the nerve, total removal and nerve grafting is rarely an option. Management of the MPNST is considered below in the Sect. entitled "Malignant Neural PNTs", along with specific considerations for the different types of benign and malignant lesions.

Specific Comments

Benign Neural PNTs

Schwannoma: Also known as neurilemomas, these tumors are the most commonly encountered peripheral nerve tumor in adults (Figs. 2A, 3A,B) arising in any nerve beyond the oligodendroglial-Schwann cell junction. Most lesions are incidentally diagnosed, slow growing, in middle-aged patients, with equal rates of occurrence in males and females. Paraspinal tumors present as dumbbell tumors with myeloradiculopathy, while large space-occupying schwannomas in the retroperitoneum and mediastinum are occasionally observed (Fig. 2A) [25], without malignant transformation [26]. The S-100 and Leu-7 expressing Schwann cell is the transformed cell, giving rise to a well-encapsulated tumor with extrafascicular growth, with the surgical objective of isolating the single fascicle of origin and exit and removal of the tumor with preservation of the passerby fascicles (Fig. 5). As discussed, histologically schwannomas typically consist of areas of densely cellular Antoni-A and diffuse Antoni-B regions, with Verocay bodies, which are palisading nuclear structures (Fig. 3B). Electron microscopy is useful in confirming Schwann cell composition, as evidenced by a completely surrounding basal lamina, of a suspected PNT when in doubt, but it is usually not required for most typical schwannomas. However, there are several atypical schwannoma variants (Fig. 1), which although having aggressive pathological features, for the most part run a totally benign course. These atypical variants include: (1) ancient schwannomas with presence of calcifications, necrosis, degenerated and hemorrhagic cysts, large multinucleated pleomorphic giant cells, though entirely benign as evidenced by a low mitotic rate [27]; (2) psammomatous melanotic schwannoma are packed with melanin and lamellated calcospherules and may occur sporadically or in the context of the tumor predisposition Carney Syndrome, with a small but yet indeterminate risk of malignant degeneration [28]; (3) epitheloid schwannoma characterized by epitheloid cells arranged in cords or nests with degenerative features occasionally appearing [29]; (4) cellular schwannoma characterized by large number of spindle cells with occasional mitotic figures, which are usually less than 10/high-power-field, however, not harboring necrosis [30]; (5) neuroblastoma-like schwannoma characterized by giant rosettes, with a histological similarity to neuroblastoma [31]; and (6) plexiform schwannoma which are often but not always associated with NF-2 or Schwannomatosis, where the tumor is histologically similar to a typical schwannoma though having an intrafascicular growth pattern of a neurofibroma [32].

Neurofibroma: Neurofibromas occur sporadically but in approximately half of the patients they are part of the defining neoplasm of NF-1 syndrome. In relation to schwannomas, patients presenting with neurofibromas have a slightly higher incidence of pain, itching, and fixed neurological deficits. Several sub-

types of neurofibromas are commonly present, with differing clinical and biological behavior (Fig. 1). There are three common subtypes of the neurofibromas: dermal, subcutaneous, and plexiform. Dermal are the most common, with many of these soft pedunculated tumors present in NF-1 patients. Dermal neurofibromas do not become malignant, hence require surgical removal in only selected cases where they pose significant cosmetic deformity, persistent pain, or maceration due to repeated abrasion to clothing or moving joints. Subcutaneous neurofibromas have a similar clinical course to dermal neurofibromas, except not being pedunculated due to their deeper origin. Occasionally they do require decompression for superficial mass effects, requiring collaboration with plastic surgeons. Plexiform neurofibromas typically appear as an intrafascicular diffuse growth along multiple branches of more proximal nerves, resulting in a "string of onion" appearance (Fig. 2B, 3C) [33]. Although they can occur sporadically, the presence of multiple plexiform neurofibromas, especially those presenting within the first decade of life, is strongly indicative of a diagnosis of NF-1 [34]. Pathologically, neurofibromas are composed of elongated, wavy, interlacing hyperchromatic cells, with spindle-shaped nuclei in a loose and disordered mucoid background with collagenous fibrils (Fig. 3D). As mentioned, neurofibromas, in addition to the transformed Schwann cells, are also composed of multiple cell types including perineural cells, fibroblasts, lymphocytes, mast cells, and axons, with presence of axons within the tumors.

Common sites of plexiform neurofibromas are the trunk and paraspinal regions (~43%); head and neck, including the brachial plexus (18%–42%); and limbs (15%–18%) [35]. Compression of visceral structures resulting in significant clinical morbidity can occur, with plexiform neurofibromas of the larynx [36], gastrointestinal tract [37], retroperitoneum [38], and pelvis [39]. Slow progressive growth is the usual course, although accelerated growth can occur without biological transformation as in early childhood, puberty, pregnancy, and rarely after trauma causing intratumoral hemorrhage [40]. However, accelerated growth, especially with spontaneous onset of unremitting pain, requires determination of whether malignant transformation to MPNST has occurred or not, as discussed below in the Sect. entitled "Malignant Neural PNTs." For those plexiform neurofibromas not suspected to have undergone malignant transformation, surgery is usually not indicated, with yearly clinical review, supplemented by MRI evaluation at 2- to 3-year intervals. Surgical interventions are sometimes required for cosmetic purposes, relief of pain, progressive growth causing pressure effects on adjacent structures, and increasing neurological deficits. The aim of surgery is to debulk the tumor while minimizing neurological morbidity, an aim that can be achieved in a majority of cases with microneurosurgical techniques and intraoperative electrophysiological monitoring. Total excision of the tumor with reconstructive nerve grafting is not an option, with subtotal debulking to relieve mass effect and analysis of the tumor thoroughly for any chance of malignant transformation being the preferred strategy.

Perineurioma: These are benign, encapsulated tumors that clinically mimic schwannomas, but originate from transformed pericytes. They stain for epithelial membrane antigen (EMA) but are negative for S-100, Leu-7, and neurofilaments (Fig. 3E). Electron microscopy reveals pericytes, lacking the characteristic complete basement membrane of a Schwann cell, with abundant pinocytic vesicles. Like schwannomas, surgical excision with preservation of passerby fascicles is the treatment of choice [41].
<heading5>Neurothekoma: These are benign tumors that primarily arise in the face, neck, shoulder, and arm of young women. Neurothekomas appear as one of two subtypes, myxomatous and cellular. The myxomatous type is of Schwann cell origin and the cellular type may have atypical histological features [42]. Complete excision, where indicated due to cosmetic reasons or enlargement, is the management of choice.

Palisading Encapsulated Neuroma: These are benign, solitary, dome-shaped tumors, commonly appearing on the face of middle-aged men or women. The tumors are well encapsulated, usually do not grow to any significant extent, and are composed of Schwann cells, perineural cells, and small axons. Conservative surgical excision shows good results, with recurrence a rare event [43].

Benign Nonneural PNTs

Ganglion Cyst: These nonneural tumors arise from joints or tendon sheaths, leading usually to extraneural compression (Fig. 2D, 6A). Reports of intraneural involvement in long-standing cases especially of the common perineal nerve from the tibia-fibular joint have been noted, where the cysts can track along small articular nerve sheaths toward their distal terminus. Ganglion cysts frequently appear around the wrist, knee, elbow, and hip joints. Often these patients present after repeated aspirations, which alleviate the neurological symptoms temporarily until cyst reaccumulation occurs. Although definitive treatment is not required in all cases, especially in the elderly and/or where neurological symptoms is absent, it is recommended in most. Definitive treat-

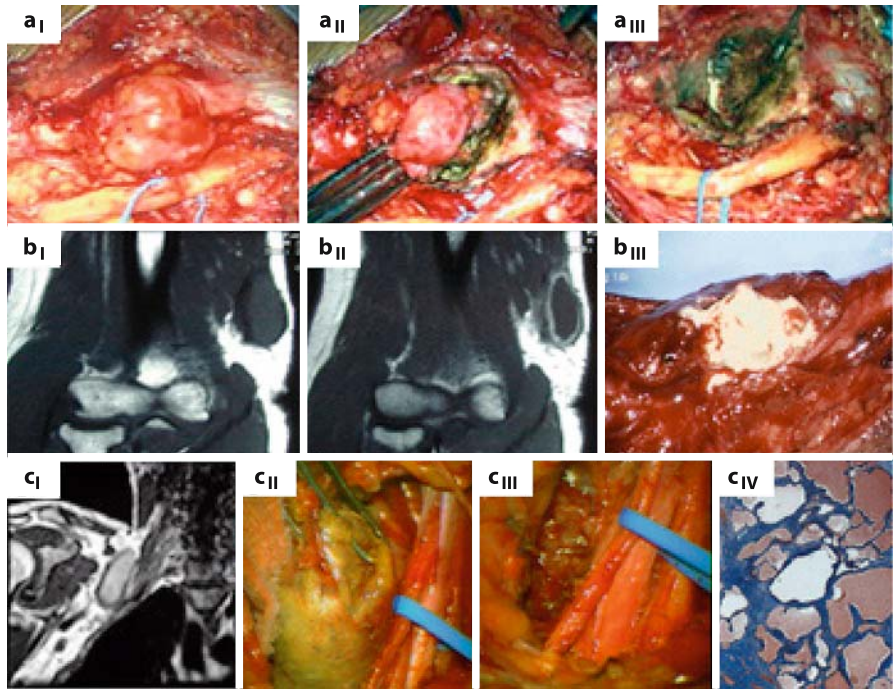


Fig. 6. A: Ganglion cyst: $\mathbf{a}_{I}$, isolation of cyst from common peroneal nerve; $\mathbf{a}_{II}$, dissection of cyst from tibial-fibular joint; Resection and cauterization of cyst from joint and decompression of nerve from anterior-tibial muscle fascia distally; **b** pseudotumor of ulnar nerve (likely sarcoids). $\mathbf{b}_{I, II}$ T1 +/-gad MRI demonstrating peripheral enhancement of the lesion behind the medial elbow joint; $\mathbf{b}_{III}$ granulomatous inflammatory exudates consistent with sarcoidosis; **c** cavernoma from posterior aspect of the brachial plexus; $\mathbf{c}_{I}$ T2 MRI; $\mathbf{c}_{II–III}$ pre- and postremoval of the cavernoma arising from the long-thoracic nerve traversing posterior to the plexus along belly of scalene-medius; $\mathbf{c}_{IV}$ trichrome staining demonstrating the numerous dilated vascular channels of the cavernoma

ment involves not only decompression of the affected nerve, but extraction of the cyst from the joint of origin, usually involving removal or cauterization of the articulating cartilage (Fig. 6A).

Lipoma: These tumors may arise from adipocytes outside or within the nerve. MRI characteristics are diagnostic and often help to differentiate from the extrinsic versus intrinsic origin of the lipoma, which is crucial in pre- and intraoperative management decisions (Fig. 2C). Lipomas commonly affect median nerve and present clinically as carpal tunnel syndrome and macrodactyly. Surgical intervention is required when there is only progressive neurological symptoms, which may vary with pregnancy, work, etc. In cases of extrinsic lipomas, which can only be determined conclusively intraoperatively, total removal with sparing of the nerve can be achieved. However, in intrinsic lipomas, care must be taken for neurological preservation. This may be achieved by just undertaking release of the entrapment point, such as the carpal tunnel and/or limited removal of the lipoma using microneurosurgical techniques with electrophysiology [44].

Desmoids: These are locally aggressive tumors of fascial and musculo-aponeurotic structures. They may arise from the supraclavicular fossa or the chest wall and subsequently invade the brachial plexus. Desmoids can also arise in other body cavities and be multiple in some patients. While resection with clear margins is the optimal goal, this is not often achievable due to infiltration into the soft tissue structures such as the nerves and adjacent blood vessels. The goals of surgery include establishment of the diagnosis and decompression of neural structures, with minimization of neurological morbidity. The first attempt at this is often the best chance of achieving these goals, fully recognizing that often it is a subtotal removal that can be best achieved. Adjuvant therapies such as postoperative radiation and chemotherapy are used, though with limited efficacy and their own toxicities [45].

Traumatic Neuroma: These are not tumors but a hyperproliferative cellular response composed of fibroblasts and Schwann cells. Often pain is the main issue, especially those that are superficial and subject to repeated irritation. Medical management

including desensitization and other forms of psychosomatic treatments including acupuncture are often helpful, through the supervision of a pain clinic. Occasionally surgical removal is the best option;, there is a large body of literature on this difficult subject, which is outside of the mandate of this chapter.

Pseudotumors: These, like neuromas, are also not neoplastic lesions, but rather chronic inflammatory in nature. The origin and travel history, coupled with a relatively subacute presentation and systemic symptoms and findings, are often helpful. Among these granulomatous lesions, leprosy and sarcoids are common (Fig. 6B). In an endemic region of these inflammatory diseases, or a patient of high suspect, appropriate medical therapy is warranted, perhaps with a percutaneous aspirate to obtain microbiological diagnosis as indicated. However, one often is faced without a clear-cut picture as to the nature of the lesion in the context of significant pain and neurological symptoms, requiring surgery with the goals of ascertaining diagnosis and decompression to improve function. The principles of peripheral nerve microneurosurgery outlined above in the Sect. entitled "Overall Comments," including quick section and microbial diagnosis, is of paramount importance. Minimal manipulation of the nerve required to achieve these goals should be undertaken [46].

Angiomas: Vascular abnormalities of the peripheral nerves are rare, but like the CNS can be of several forms. Benign angiomatosis results from widespread abnormal proliferation of the intrinsic vascular bed of the nerve, which may cause slow and progressive neurological decline in function. These intraneural masses rarely present with hemorrhage and are usually composed of an increased number of relatively normal, matured small vessels. Benign hemangiomas are a more localized collection of prolific and abnormal vessels, which although being rare, do have an increased propensity of intraneural hemorrhage. Cavernomas and AVMs of peripheral nerves, or adjacent structures, can present with acute hemorrhage, pain, and neurological symptoms. MRI characteristics of hemorrhage are suggestive, but not diagnostic in ruling out intratumoral hemorrhage into more common PNTs, such as schwannomas and neurofibromas. Microneurosurgical general management principles for PNTs, as previously discussed, are applicable (Fig. 6C).

Malignant Neural PNTs

Malignant Peripheral Nerve Sheath Tumor (MPNST, Neurogenic Sarcoma): MPNSTs account for 3%–10% of all soft tissue sarcomas, with half of these cases originating in an earlier age group in NF-1 patients [47]. Incidence of MPNST in NF-1 patients is 2%–5% compared with 0.001% in the general population [47]. In NF-1 patients, the dermal or subcutaneous neurofibromas do not become malignant, while plexiform neurofibromas harbor a lifetime risk of ~10% of malignant conversion [48]. Progressive enlargement, incapacitating pain, and increasing neurological deficit in a previously known plexiform neurofibroma are highly suggestive of malignant transformation, requiring further investigation and pathological evaluation. MRI characteristics, such as heterogeneous contrast enhancement suggestive of necrosis or hemorrhage are worrisome, but not pathognomonic of malignant transformation. Rarely, invasion into adjacent soft tissues or distant metastasis especially to the lungs have already occurred at presentation, making it more likely that one is dealing with an MPNST. The potential for biological imaging modalities such as ^{18}FDG PET, pioneered in preliminary studies in the UK, is of promise in radiologically distinguishing benign plexiform neurofibromas from low- and high-grade MPNST, hence directing management strategies [2].

The ideal management of rare MPNSTs remains problematic, with our institute recommending a multidisciplinary management strategy, as outlined in Fig. 7A. Clinical suspicion, with enlargement and pain being key features, is followed by biopsy. We advocate a four-quadrant open biopsy rather than fine needle or percutaneous Tru-Cut biopsy, since these MPNSTs can be heterogeneous and these biopsies tend to cause more pain and potential neurological deficit as they are not taken from an electrically silent region. Heterogeneity of MPNSTs is illustrated in Figure 7B, where the top of this tumor harbors pathological features of an atypical but benign plexiform neurofibroma, while other regions such as the middle or lateral components represent sarcomatous transformation of varying degrees, from low-grade to a highly malignant dedifferentiated MPNST. In addition to heterogeneity, the diagnosis of MPNST and differentiation from the more common soft tissue sarcomas or atypical variants of schwannomas on quick section is difficult, even to the most experienced neuropathologists. Adequate tissue for specialized immunohistochemical stains, electron microscopy, and molecular profiles associated with certain subtypes of sarcomas may be required to reach the ultimate diagnosis. The diagnostic challenge is eased by the fact that there is no specific immunohistochemical marker for MPNSTs and ~50% of the tumors have dedifferentiated to lose the Schwann cell associated S-100 expression. For example in Figure 7B, the MPNST in one portion has undergone rhabdomyoblastic dedifferentiation to a Triton tumor, a subtype of MPNST which is associated in two thirds of the cases with

NF-1 [49]. Triton tumors have a spindle cell morphology with interspersed large rounded strap cells, with eosinophilic, fibrillar cytoplasm harboring cross-striations in the cytoplasm [49]. Electron microscopy and muscle specific antigens further confirm the rhabdomyoblastic dedifferentiation. Classification of MPNST is based on those used for the much more common soft tissue sarcomas, from Grades 1–3, depending on the number of mitotic figures and degree of nuclear and cellular atypia, with Triton tumors such as in Figure 7B being Grade 3 sarcomas [50]. These diagnostic challenges and the implications of MPNST on the subsequent management, require definitive pathological confirmation and thereby staged surgery, with the second oncological stage aimed at local and systemic control.

After pathological confirmation, the proposed management strategy requires a thorough discussion with the patient, as the objective is not to spare the nerve, but rather oncological local control, by obtaining tumor-free margins (Fig. 7A). We undertake a metastatic survey with CT/MRI of the chest and abdomen, preoperative radiation in many but not all cases, and then follow with definitive oncological surgery, if systemic metastasis is not already present. In theory, preoperative radiation has the potential of decreasing the local tumor burden, thereby facilitating tumor-free margin resection and better overall prognosis; however, this has not been proven with randomized clinical trials in soft tissue sarcomas. Other reasons to advocate preoperative radiation includes those MPNSTs where the location and size would prove postoperative radiation to be difficult, where dissection is anticipated along a major neurovascular bundle, and where skin or tissue grafts are planned for reconstruction. The role of preoperative chemotherapy with Adriamycin-based agents is another unresolved issue for soft tissue sarcomas and MPNSTs. Certainly if systemic disease is already present, radiation and chemotherapy are undertaken as the first line of therapy, though overall the prognosis is poor.

As mentioned, the overall goal of surgery is to achieve an en block removal with tumor-free mar-

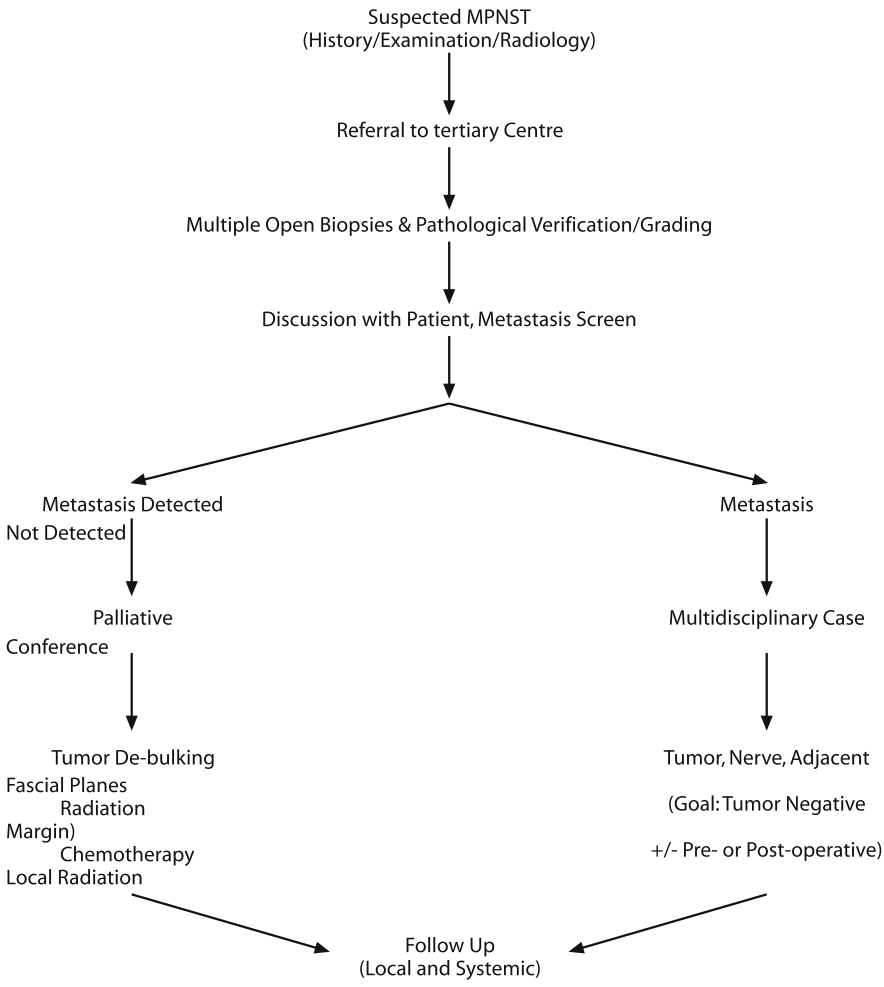


Fig. 7. a Management Strategy for Malignant Peripheral Nerve Sheath Tumor (University of Toronto Multidisciplinary Sarcoma Group)

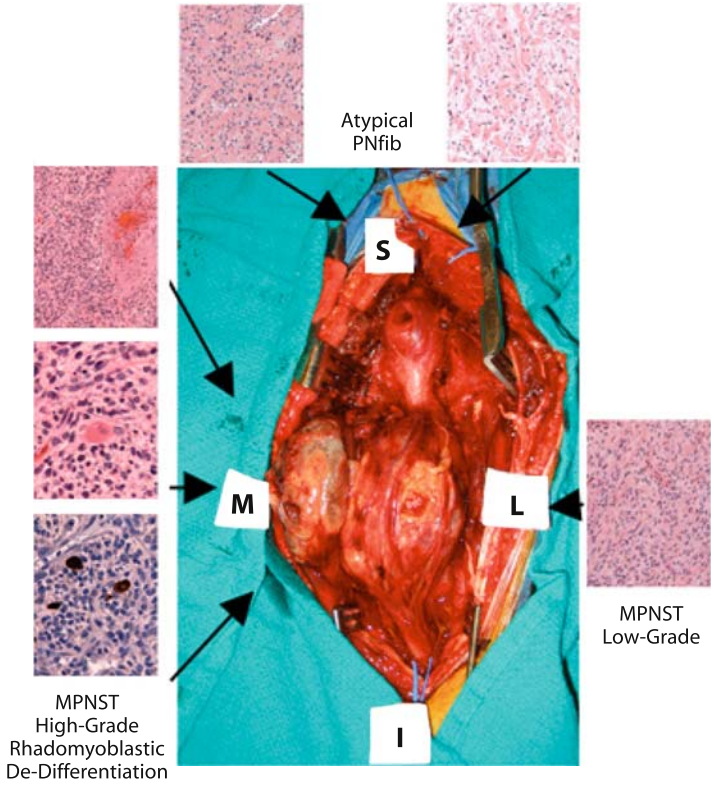


Fig. 7. b MPNST heterogeneity, arising from transformation of a known plexiform neurofibroma in the posttibial nerve of a NF-1 patient, supportive of our recommendation to undertake multiple biopsies to obtain confirmatory pathological and grading verification. Superior (*S*) pole of the tumor shows atypical but benign neurofibroma (the prior site of a percutaneous biopsy), lateral (*L*) pole shows a low-grade 1 MPNST, while the medial (*M*) pole is a high-grade III MPNST with rhabdomyoblastic dedifferentiation

gins, even at the cost of major nerves and adjacent soft tissue structures, hence requiring collaboration with orthopedic oncology colleagues and physiotherapy and occupational therapists (Fig. 7C). Nerve grafting is not considered because more proximal nerves are not amenable to reinnervation with grafting or adjuvant radiation therapy, and the natural history of MPNST is often not long enough for effective reinnervation. Adverse prognostic factors include: size (>5 cm), higher tumor grade, advanced histology, nontumor-free surgical margin, and association of NF-1. Systemic spread, especially pulmonary metastasis, is the terminal event, when despite limited efficacy chemotherapy is usually administered. The 5-year survival rate of MPNST is worse than other soft tissue sarcomas and is generally ~34%–51%, with our management strategy resulting in a 64% 5-year survival [48]. Large-scale, randomized studies to address some of these issues on treatment options and evaluation of novel biological therapies is extremely hard to achieve, given the few numbers of these patients, whom are often managed outside of a multidisciplinary academic centers. Biological therapies, based on our evolving molecular understanding of MPNSTs, include those which target p21-Ras (such as farnesyl-transferase inhibitors, FTS), the overexpressed epidermal growth factor receptors (EGFRs), and angiogenic molecules such as vascular endothelial growth factor (VEGF), among others. Detailed discussions of these topics are beyond the scope of this chapter and the reader is referred to several review articles [51, 52].

Primary Lymphoma of Peripheral Nerve: These are extremely rare tumors with only approximately ten cases reported in the literature, the majority of which are B-cell lymphomas of the sciatic nerve [53]. These primary PNTs need to be differentiated from the more common neuro-lymphomatosis, in the setting of systemic lymphoma. Management after diagnosis is a combination of radiation and chemotherapy.

Malignant Nonneural PNTs

Pancoast Tumor: With recent trends advocating an aggressive surgical approach to lung cancers after undertaking radiation and chemotherapy, where 15%–50% 5-year survival have been noted [54], there has been an increasing collaboration with thoracic surgeons and neurosurgeons towards gross total removal of Pancoast tumors (Fig. 8A). Preoperative evaluation with both CT and MRI scans and MRA is helpful to denote the extent of spinal column, brachial plexus, and vascular involvement. This body of information allows a more informative preoperative consultation with the patient to better plan for expected morbidity, and also plan for reconstructive

spinal and vascular surgery as indicated. These are long, intensive procedures, with the goal of achieving tumor-free resection, with significant morbidity, many of which are anticipated based on the preoperative clinical and radiological information. Several approaches can be used to allow access to the tumor and brachial plexus and control of the vessels. We have found a combined supraclavicular exposure with sternotomy and thoracotomy to provide an excellent exposure to the tumor, early proximal and distal control of the great vessels, as well as delineation of the tumor to the brachial plexus. Like the vessels, the plexus may be pushed aside, rather than invaded, with intraoperative pathological confirmation by sampling the epineurium. If actual invasion is present or predicted preoperatively, sacrifice of

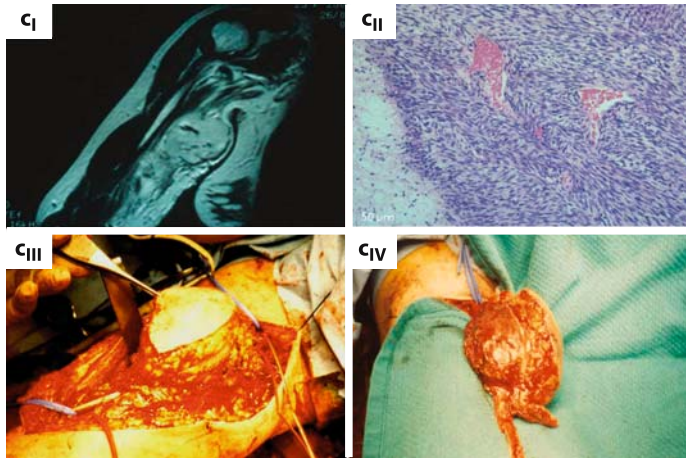


Fig. 7. Compartmental resection of MPNST arising from the musculocutaneous nerve of an NF-1 patient. $\mathbf{c_I}$ MRI (T2); $\mathbf{c_{II}}$ H&E transition of plexiform neurofibroma (*left*) to Grade III MPNST (*right*), confirmed with open biopsies at first surgery; $\mathbf{c_{III}}$ Pedicle of tumor, overlying and surrounding tissues including the biceps muscle and isolated proximal-distal musculocutaneous nerve, at second surgery with preoperative radiation; $\mathbf{c_{IV}}$ resected en bloc tumor with surrounding fascial and soft tissues with intraoperative verified tumor-free margins

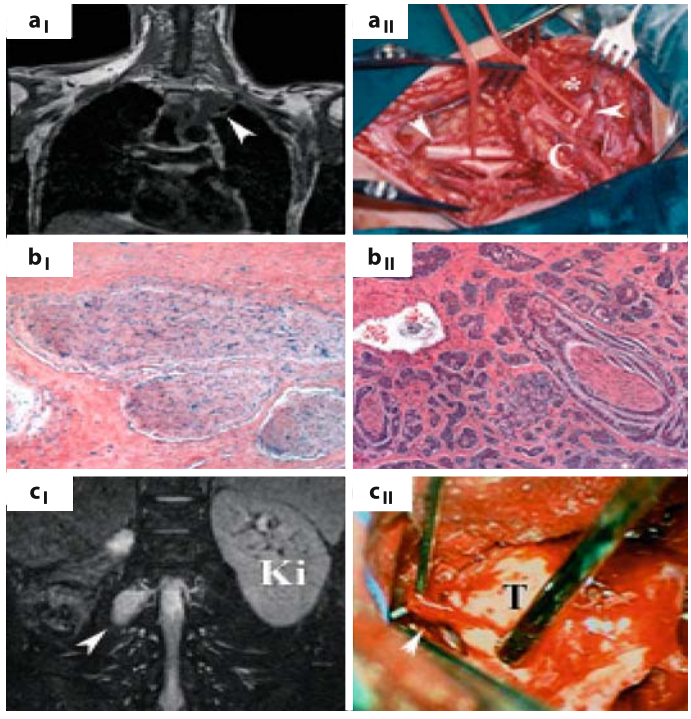


Fig. 8. **a** Pancoast tumor: $\mathbf{a_I}$- Left apical carcinoma pushing against lower trunk (*arrowhead*); $\mathbf{a_{II}}$ supra- plus infraclavicular (*C*) exposure of brachial plexus with control of subclavian artery (*arrowhead*) and isolation of lower trunk (*) can be combined with sternal split and trap-door thoracotomy; $\mathbf{b_I}$ radiation plexitis with intraneural fibrosis; $\mathbf{b_{II}}$ rare primary intraneural carcinoma infiltration; **c** radiation-induced PNT; $\mathbf{c_I}$ right paraspinal radiation-induced PNT, several years postnephrectomy (*Ki*) and radiation for Wilm's Tumor; $\mathbf{c_{II}}$ resection of atypical neurofibroma (*T*), with lumbar root isolated but intrinsically associated with tumor

the nerve roots may be required; a discussion needs to have been undertaken with the patient preoperatively. Preoperative imaging will also delineate the amount of neural canal and direct spinal column involvement, which after removal may require stabilization through anterior and posterior approaches. Postoperative physiotherapy, occupational rehabilitation, and pain management is of paramount importance to allow maximization of function.

Intraneural Metastasis and Radiation Neuritis: The diagnosis of radiation necrosis versus direct intraneural metastasis as a cause of brachial plexopathy, in the context of stable breast or lung cancer, is one that is hard to differentiate preoperatively. MRI imaging usually demonstrates "matted" nerves, but doesn't differentiate between the two entities; however, it does serve to rule out large focal tumor recurrence or lymph node involvement. Where prior radiation is not a potential variable, only a few cases of presenting intraneural metastasis arising from carcinoma of the breast [55], malignant melanoma [56], and carcinoid [57] have been described (Fig. 8B). Immediate [58] or delayed onset radiation-induced brachial plexopathy is relatively common, occurring in 1.5%–35% of breast cancer patients. The acute presentations are rare and directly related to swelling and demyelination effects of radiation. The delayed and more common effects likely arise from focal compression by fibrosis and obliteration of the vasonervosum leading to chronic ischemia (Fig. 8B) [59]. In our experience, about half of the patients presenting with progressive plexopathy and a remote history of a prior tumor and radiation without systemic recurrence have a mixture of radiation plexopathy with intraneural tumor recurrence. Determination of whether intraneural tumor recurrence has occurred or not is of importance regarding oncological management and institution of additional chemotherapy; hence, this is a main indication for surgical exploration of the nerves. Restoration of motor power and wasting is not an achievable goal, hence not an indication for surgery. However, if systemic pain control is not effective, then a limited external neurolysis, taking precaution to minimize the disturbance to the precarious blood supply to the nerve, does help in about half of our patients. Various other surgical approaches, including omentoplasty and muscle pedicle flap, aimed at revascularization of the nerves have been attempted, with inconclusive results [60].

Radiation Induced PNTs: Radiation-induced PNTs are a rare but known complication of radiotherapy, though it is commonly believed that peripheral nerves are relatively resistant to the effects of radiation and the complication of radiation-induced tumors. Histological changes in peripheral nerves following exposure to radiation include a decrease in nerve fibers, and an increase in microtubule density suggestive of hypoxia, neuropathy, nerve root degeneration, fibrosis, and vasculopathy [61]. An emerging body of clinical evidence implicates radiation in the genesis of PNTs. In a retrospective study of 10,080 patients treated with low-level (1–2 Gy) radiotherapy for tinea capitis, there was a dose-dependent relative risk of 18.8-fold for the development of intracranial schwannomas [62]. Survivors of Hiroshima and Nagasaki had an elevated risk of developing schwannomas [63], with increased incidence of PNTs also in patients receiving radiotherapy for benign tonsillar disease [64]. These and other epidemiological studies and our own experience with five patients, do demonstrate the carcinogenic potential of radiation resulting in PNTs. Secondary-radiation-induced PNTs do require fulfillment of Cahan's criteria [65], which includes a pathologically proven secondary neoplasm of increased natural expectancy, different from the primary and occurring within the field of radiation after several years delay. Based on our experience, surgery is required for most of these radiation-induced PNTs, to first establish the etiology of the lesion and to distinguish from local tumor recurrence, though the preoperative clinical and MRI findings are often highly suggestive (Fig. 8C). These PNTs, the majority of which have been diagnosed as atypical neurofibromas in our experience, differ somewhat from spontaneous neurofibromas in that they are more aggressive clinically, but not to the extent of an MPNST. The dissection often does not allow full resection, due to intrafascicular involvement of the tumor and radiation-induced fibrosis, resulting in local recurrence requiring long-term follow-up. In our limited experience, we have not yet had a radiation-induced PNT that has further transformed to a full MPNST.

Conclusions

Tumors of the peripheral nerve present a wide range of pathological subtypes, with differing clinical and biological behavior, hence requiring different management strategies. A thorough history, including a family history and physical examination and supplemented by MRI-based radiological investigation, is of importance. Not all PNTs require surgery; with the cases where indicated, the preoperative goals need to be fully clarified with the patient. Intraoperative microneurosurgical techniques with electrophysiological monitoring by an experienced surgeon allow achievement of the desired goal with minimal morbidity. Total removal is achievable in most schwannomas, while subtotal but radical decompression is the usual course in large benign plexiform neurofibro-

mas. In suspected MPNSTs, staged surgery, with the first stage being diagnostic, followed by radical oncological resection and obtaining tumor-free margins in specialized centers, is the desirable management. The clinical diversity of peripheral nerve tumors necessitates a multidisciplinary approach to treatment. Current research into the molecular pathologies of predisposing syndromes is yielding insight into the etiology of sporadic disease. In addition, this research provides potential targets for novel therapies in the treatment of these lesions. Until such time as these developing modalities become clinically useful, the surgical and radiological tools outlined above are the gold standard for the management of these highly complex tumors.

References

1. Lopes MBS, VandenBerg SR, Scheithauer BW. The World Health Organization classification of nervous system tumors in experimental neuro-oncology. In: Levine AJ, Schmidek HH, editors. Molecular genetics of nervous system tumors. New York: Wiley-Liss; 1993. p. 1–36
2. Ferner RE, Lucas JD, et al. Evaluation of 18fluorodeoxyglucose positron emission tomography (18FDG Pet) in the detection of malignant peripheral nerve sheath tumours arising from within plexiform neurofibromas. J Neurol Neurosurg Psychiatry2000;68:353–357
3. Ahn MS, Jackler RK, Lustig LR. The early history of the neurofibromatosis evolution of the concept of neurofibromatosis type 2. Arch Otolaryngol Head Neck Surg 1996;122:1240–1249
4. von Recklinghausen FD. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen.(On multiple fibromas in the skin and their relationship to multiple neuromas.) Title page, translated from German: Festschrift in commemoration of the 25th anniversary of the founding of the Pathological Institute of Berlin, presented to Professor Rudolf Virchow by F. von Recklinghausen, professor in Strasbourg. Berlin, A. Hirschwald, 1882
5. Verocay J. Zur Kenntnis der Neurofibrome. Beitrage Zur Pathologischen Anatomie und zur Allgemeinen Pathologie 1910;48:1
6. Penfield W. The encapsulated tumors of the nervous system: Meningeal fibroblastomata, perineurial fibroblastomata and neurofibromata of von Recklinghausen. Surg Gyn Ob 1927;45:178–188
7. Stout AP, Lattes R. Atlas of tumor pathology, second series, fascicle I: Tumors of the soft tissues. Washington, D.C.: American Forces Institute of Pathology; 1967
8. Russell DS, Rubinstein LJ. Pathology of tumours of the nervous system. London: Edward Arnold; 1989
9. Ehrlich HE, Martin H. Schwannomas (neurilemomas) in the head and neck. Surg Gyn Ob 1943;76:577–583
10. Fisher ER, Veuzesvski VD. Cytogenesis of schwannoma (neurilemoma), neurofibroma, dermatofibroma, and dermatofibrosarcoma as revealed by electron microscopy. Am J Clin Pathol 1968;49(2):141–54
11. Letson GD, Muro-Cacho CA. Genetic and molecular abnormalities in tumors of the bone and soft tissues. Cancer Control 2001;8(3):239–251
12. Peltonen J, et al. Cellular differentiation and expression of matrix genes in type 1 neurofibromatosis. Lab Invest 1998;59:760–771
13. Perry A, et al. NF1 deletions in S-100 protein-positive and negative cells of sporadic and neurofibromatosis 1 (NF1)-associated plexiform neurofibromas and malignant peripheral nerve sheath tumors. Am J Pathol 2001;159(1):57–61
14. Hung G, et al. Immunohistochemistry study of human vestibular nerve schwannoma differentiation. Glia 2002;38(4):363–70
15. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci 1997;68:820–823
16. Huson SM, et al. A genetic study of von Recklinghausen neurofibromatosis in South East Wales. Prevalence, fitness, mutation rate and effect of parental transmission on severity. J Med Genet 1989;26(11):704–711
17. National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis. Bethseda, MD: July 13–15, 1987. Neurofibromatosis; 1988;1(3):172–178 (Review)
18. Li Y, et al. Genomic organization of the neurofibromatosis 1 gene (NF1) Genomics 1995;25(1):9–18
19. Gutmann DH, et al. Identification of the neurofibromatosis type 1 gene product. Proc Natl Acad Sci 1991;88(21):9658–9662
20. Guha A, et al. Ras-GTP levels are elevated in human NF1 peripheral nerve tumors. Oncogene 1996;12:507–513
21. Roleau GA, et al. Genetic linkage of bilateral acoustic neurofibromatosis to DNA marker on chromosome 22. Nature 1987;329:246–248
22. Trofalter JA, et al. A novel moesin-ezrin-radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell 1993;75:826–829
23. Purcell SM, Dixon SL. Schwannomatosis. An unusual variant of neurofibromatosis or a distinct clinical entity? Arch Dermatol 1989;125(3):390–393
24. Kaufman DL, et al. Somatic Instability of the NF2 gene in schwannomatosis. Arch Neurol 2003;60:1317–13–20
25. Micali S, et al. Benign schwannoma surrounding and obstructing the uteropelvic junction. First case report. Eur Urol 1997;32:121–123
26. Woodruff JM, et al. Schwannoma (neurilemoma) with malignant transformation. A rare, distinctive peripheral nerve tumor. Am J Surg Pathol 1994;18:882–95 (Review)
27. Guha A, Bilbao J, Kline D, Hudson A. Peripheral nerve tumors: In: Youmans J, editor. Neurological surgery, 4th edn. Philadelphia:W.B. Saunders; 1996
28. Carney JA. Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing Syndrome. Am J Surg Pathol 1990;14:206–222

29. Kindblom LG, et al. Benign epitheloid schwannoma. Am J Surg Pathol 1998;22(6):762–770
30. Henke AC, et al. Cellular schwannoma mimics a sarcoma: an example of a potential pitfall in aspiration cytodiagnosis. Diagn Cytopathol 1999;20:312–316
31. Somerhausen Nde S, et al. Neuroblastoma-like schwannoma: a case report and review of the literature. Am J Dermatopathol 2003;25(1):32–34
32. Ishida T, et al. Phenotypic diversity of neurofibromatosis 2: association with plexiform schwannoma. Histopathology 1998;32(3):264–270
33. Korf BR, et al. Report of the working group on neurofibroma. The National Neurofibromatosis Foundation, Inc. 1997;4–27
34. Waggoner DJ, et al. Clinic based study of plexiform neurofibromas in neurofibromatosis type 1. AM J Med Genet 2000;92(2):132–135
35. Richardson RR, et al. Neurogenic tumors of the brachial plexus: report of two cases. Neurosurgery 1979;4(1):66–70
36. Yucel EA, et al. Plexiform neurofibroma of the larynx in a child. J Laryngol Otol 2002;116(1):49–51
37. Malagari K, et al. Plexiform neurofibroma of the liver: findings on MR imaging, angiography, and CT tomography. AJR Am J Roentgentgenol 2001;176(2):493–495
38. Bass JC, et al. Reetroperitoneal plexiform neurofibromas: CT findings. AJR Am J Roentgenol 1994;163(3):617–620
39. Maio A, et al. Ultrasound evaluation of unusual pelvic cystic masses. J Clin Ultrasound 1993;21(9):651–655
40. Krueger W, et al. Plexiform neurofibroma of the head and neck. Am J Surg 1979;138(4):517–520
41. Bilbao JM, et al. Perineuroma (localized hypertrophic neuropathy). Arch Pathol Lab Med 1984;108(7):557–560
42. Kleinschmidt-DeMasters BK, Lillehei KO. Intraneural neurothekoma: case report. Neurosurgery 1995;37(2):333–334
43. Megahed M. Pallisaded encapsulated neuroma (solitary circumscribed neuroma). A clinicopathological and immunohistochemical study. Am J Dermatopathol 1994;16(2): 120–125
44. Kameh DS, et al. Lipofibromatous hamartoma and related peripheral nerve lesions. South Med J 2000;93(8):800–802
45. Gaposchkin CG, et al. Function sparing surgery for desmoid tumors and other low-grade fibrosarcomas involving the brachial plexus. Neurosurgery 1998;42(6):1297–1301; discussion 1301–1303
46. Perez-Lopez C, Gutierrez M, Isla A. Inflammatory pseudotumor of the median nerve. Case report and review of the literature. J Neurosurg 2001;95(1):124–128 (Review)
47. King AA, et al. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. AM J Med Genet 2000;93:388–392
48. Bhattacharyya A, Perrin R, Guha A. Management of peripheral nerve tumors. J Neuro-oncol 2004;69:335–349
49. Velagaleti G. Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation (malignant triton tumor) with balanced t(7;9)(q11.2;p24) and unbalanced translocation der(16)t(1;16)(q23;q13). Cancer Genet Cytogenet 2004;149(1): 23–27
50. Costa J, Glatstein WE, Rosenberg SA. The grading of soft tissue sarcomas. Results of a clinicopathologic correlation in a series of 163 cases. Cancer 1984;53:530–541
51. Ferner R, Gutmann D, Coffin C, Grimer R, Guha A, Judson I, et al. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis 1. Cancer Res 2002;62:1573–1577
52. Angelov L, Salhia B, Roncari L, Guha A. Inhibition of angiogenesis by blocking activation of the VEGFR-2 leads to decreased growth of neurogenic sarcomas. Cancer Res 1999;59:5536–5541
53. Misdraji J, et al. Primary lymphoma of peripheral nerve: report of four cases. Am J Surg Pathol 2000;24(9):1257–1265
54. Detterbeck FC. Pancoast (superior sulcus) tumors. Ann Thorac Surg 1997;63(6):1810–1818
55. Artico M, et al. Late intraneural metastasis of the brachial plexus from mammary carcinoma. Report of a case. J Neurosurg Sci 1991;35(1):51–53
56. Cantone G, et al. Intraneural metastasis in a peripheral nerve. Acta Neurochir (Wien) 2000;142(6):719–720
57. Griswold W, et al. Intraneural nerve metastasis with multiple mononeuropathies. J Peripher Nerv Syst 2000;5(3): 163–167
58. Olsen NK, et al. Radiation-induced brachial plexus neuropathy in breast cancer patients. Acta Oncol 1990;29(7): 885–890
59. Stoll BA, Andrew JT. Radiation-induced peripheral neuropathy. BMJ 1966;1:834–837
60. Schierle C, Winograd JM. Radiation-induced brachial plexopathy: review. Complication without a cure. J Reconstr Microsurg 2004;20(2):149–52
61. Dini M, et al. Malignant tumors of the peripheral nerve sheath (MPNST) after irradiation. Pathologica 1997;89(4):441–5
62. Ron E, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 1988;319(16): 1033–9
63. Preston DL, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst 2002;94(20):1555–63
64. Shore-Freedman E, Abrahams C, Recant W, et al. Neurilemomas and salivary gland tumors of the head and neck following childhood irradiation. Cancer 1983;51:259–2163
65. Cahan G, Woodward Q, Higinbothan NL, et al. Sarcoma arising in the irradiated bone: report of eleven cases. Cancer 1948;1:3–29

Systemic and General Aspects of Neuro-Oncology V

57 General Care of Patients with Cancer Involving the Central Nervous System – 687
Stuart A. Grossman

General Care of Patients with Cancer Involving the Central Nervous System

57

Stuart A. Grossman

Antineoplastic Therapy for Patients with CNS Malignancies – 688
Adjuvant Chemotherapy
Chemotherapy for Recurrent Brain Tumors
Judging the Efficacy of Therapy
Delivery of Chemotherapy to the Tumor
Clinical Trials

Seizures – 692

Brain Edema – 692

Thromboembolic Disease – 693

Psychosocial Issues – 693

Care of the Dying Patient – 693

Conclusions – 694

References – 694

The management of patients with malignancies involving the central nervous system (CNS) involves health care professionals from many disciplines. Physicians delivering primary care and emergency medicine are often the first consulted when patients present with signs and symptoms of increased intracranial pressure, change in mental status, focal deficits, or seizures. Thereafter, neuroradiologists, neurologists, neurosurgeons, neuropathologists, radiation oncologists, medical oncologists, specialists in rehabilitation medicine, social workers, and nurses work together to determine an accurate diagnosis, initiate appropriate therapies, and provide optimal care. Unfortunately, despite aggressive therapies, most of these cancers prove fatal in a relatively short period of time. This requires that high quality palliative and pastoral care play an important role of the management of these patients and their families.

In many respects, the general principles of caring for patients with neuro-oncologic disorders are similar to those for patients with other malignancies. An initial evaluation provides critical information to determine if the intent of therapy is curative or palliative. A curative approach might be considered for patients with some intra-axial malignancies, such as medulloblastoma, primary CNS lymphoma, germinoma, and ependymoma. In contrast, the goals for patients with glioblastoma multiforme (GBM) center on prolonging survival and maintaining quality of life. Just as observation is indicated in selected patients with systemic malignancies (i.e., asymptomatic, stable follicular lymphoma or prostate cancer), some patients with low-grade gliomas are followed without therapy for years without compromising survival. However, most patients with cancer involving the CNS require active interventions. These frequently include surgery, radiation, and chemotherapy. Surgery may range from a needle biopsy for diagnostic purposes to an attempt to resect all visible cancer. Radiation can be provided to the entire brain, involved regions of the brain, or small, precise fields in well-circumscribed tumors. Similarly, chemotherapy can be administered as adjuvant therapy in newly diagnosed patients or in the setting of recurrent disease.

The care of patients with CNS malignancies differs from patients with systemic malignancies in several important ways. Tumor responses and progression are often difficult to assess despite the availability of excellent imaging modalities. The presence of the blood-brain barrier (BBB) and the use of anticonvulsants can markedly reduce the efficacy of systemically administered chemotherapy. Clinical trials in patients with brain tumors pose special challenges. Chronic glucocorticoid administration to control peritumoral brain edema predisposes patients to serious and debilitating side effects. Thromboembolic disease is common. The progressive loss of independence and cognitive ability in this patient population places an extraordinary burden on patients and their families. Finally, caring for patients dying of brain tumors requires special consideration.

Antineoplastic Therapy for Patients with CNS Malignancies

The indications, agents, doses, preferred routes of delivery, and expected benefits of chemotherapy depend on the specific CNS neoplasm being treated. As a result, these discussions are found in the relevant chapters of this book. However, it is important to note that the overall impact of chemotherapy in the treatment of common CNS malignancies remains modest. Most patients with brain metastases have relatively chemotherapy-resistant tumors, many have progressed through chemotherapy by the time they develop CNS metastases, and effective agents may not penetrate the blood brain barrier [15, 48, 57]. The efficacy of intrathecal chemotherapy for patients with leptomeningeal metastases remains controversial [4, 49]. Although intrathecal methotrexate is commonly administered to these patients, there are no controlled studies documenting its benefit in patients with solid tumors. In addition, CSF flow abnormalities interfere with the uniform distribution of intrathecally administered chemotherapy and devices placed to facilitate intrathecal therapy can result in complications [11–14, 29, 39, 56]. In patients with low-grade gliomas no convincing data exists to suggest that adjuvant chemotherapy prolongs survival [7, 45, 50]. Similarly, recent results in patients with anaplastic oligodendrogliomas, anaplastic astrocytoma, and GBM suggest that the addition of procarbazine, CCNU, and vincristine (PCV) to radiation therapy does not prolong survival [1, 10].

However, there are several recent examples where chemotherapy has been of significant benefit in the management of patients with primary brain tumors. Randomized, prospective, blinded studies have documented that BCNU embedded in biodegradable wafers slightly prolongs survival in patients with newly diagnosed and recurrent high-grade gliomas [6, 61]. Another large randomized study has recently documented that temozolomide during and after radiation therapy significantly extends survival compared to radiation alone in patients with newly diagnosed GBM [54]. In addition, high-dose methotrexate administered as a single agent has been shown to produce long-term, disease-free remissions in patients with primary CNS lymphomas, thus avoiding the serious neurotoxicity of whole brain radiation [19]. These findings are changing the standard of care for these patient populations.

Adjuvant Chemotherapy

Decades of experience in a wide variety of systemic cancers have established prerequisites for successful adjuvant chemotherapy. First, all visible tumor must be surgically removed. Thus, patients with bulky residual lymph nodes or distant metastases are not entered on adjuvant chemotherapy protocols. Second, effective chemotherapeutic agents must be available. For this purpose, "effective" is defined as an agent or regimen with substantial complete and partial response rates in patients with recurrent disease. Third, chemotherapy should be administered after surgery, at the maximally tolerated dose, and for a limited time to minimize toxicities. Even when these conditions are met, the benefits from adjuvant chemotherapy in solid tumors are modest. For example, in 55 trials involving over 37,000 women with estrogen-receptor-positive breast cancer and positive axillary lymph nodes, a 10.9% survival advantage was noted at 10 years (P = <.00001) with tamoxifen treatment [30]. Similarly, women with large primary breast cancers and negative axillary lymph nodes were randomized to receive adjuvant chemotherapy or observation [38]. The overall survival at 10 years was 81% in patients who received chemotherapy and 71% in the observation group ($P = .02$). Despite these relatively modest differences between treated and control patients, a significant number of lives were saved because of the large number of affected patients.

In clinical trials in brain tumors, patients with anaplastic astrocytoma and GBM routinely enter studies of "adjuvant" chemotherapy after undergoing only needle biopsies or partial resections of their tumor. If this occurred in the breast cancer trials cited above, the modest gains seen with adjuvant chemotherapy might well have been diluted by the patients with bulky residual disease. In addition, it is unrealistic to expect chemotherapy to prevent recurrences in the adjuvant setting if it does not have a substantial response rate in advanced disease. The most active chemotherapeutic agents in patients with recurrent anaplastic astrocytoma and GBM are carmustine (BCNU), the PCV (procarbazine, lomustine [CCNU], and vincristine) regimen, and temozolomide. Complete responses to these regimens are rare, and partial responses are expected in 20%–40% of patients [20, 21]. These factors may contribute to the poor results reported in adjuvant trials in primary brain tumors. They also highlight the remarkable results of the recently reported EORTC study where the addition of temozolomide to radiation provided a significant survival advantage in patients with glioblastoma multiforme [54]. This occurred even though this agent has modest single-agent efficacy in patients with recurrent GBM and only 40% of the patients on this study had gross total resection of their tumors.

Chemotherapy for Recurrent Brain Tumors

Chemotherapy for patients with recurrent disease in the CNS is virtually always palliative. In general, a CT or MRI scan, to establish the dimensions of the tumor, and baseline measurements of the white blood cells, red blood cells, and platelet counts are obtained prior to initiating chemotherapy. The selected agent or regimen is administered and toxicity is carefully monitored. After two cycles of chemotherapy, the neuroimaging study is repeated. If the scan is stable or improved and the treatment was well tolerated, another two cycles are administered and the results are similarly re-examined. This therapy might continue for as long as 1 year. Longer treatment durations are unlikely to provide significantly more tumor kill but may further compromise the immune status, bone marrow reserve, and overall quality of life. If at any time, the scan shows evidence of progressive disease or the patient's neurologic status declines secondary to tumor growth, treatment is discontinued. The situation is then re-evaluated to determine if there are other suitable treatment options of if supportive care would be most likely to benefit the patient. There is an inverse relationship between the number of prior chemotherapy regimens the patient has received and the likelihood of response to future chemotherapy.

The most common toxicity seen with nitrosourea or temozolomide-based therapy is myelosuppression. The nadir counts with the nitrosoureas occur 3–6 weeks after therapy and deepen with each subsequent therapy. As a result, doses need to be reduced or therapy discontinued if the white count or platelet count trend is worrisome. Prolonged dosing of the nitrosoureas may also result in severe pulmonary toxicity and pulmonary function tests are suggested if long-term treatment is anticipated. Temozolomide appears less myelosuppressive than the nitrosoureas. Approximately 90% of patients tolerate the EORTC dosing schedule of 75 mg/m^2/day during radiation therapy without significant myelosuppression [54]. However, counts must be followed closely as some patients develop life-threatening myelosuppression. Nausea with these agents is modest and is usually well controlled with modern antiemetics.

Judging the Efficacy of Therapy

Assessment of tumor progression and response relies on information from the history, physical examination, and radiologic studies [22]. Progression in patients with CNS malignancies is obvious when the patient and family report worsening neurologic function, the history and physical examination document progressive deficits, and neuroimaging studies

reveal interval tumor growth. However, a reduction in the glucocorticoid dose can produce the same constellation of findings. This exaggerates BBB dysfunction resulting in increased local edema, worsening neurologic signs and symptoms, and a scan which reveals increased contrast enhancement, edema, and mass effect even though the volume of cancer cells in the brain remains unchanged [60]. Contrast-enhanced CT and MRI scans do not delineate the margins of the tumor, but instead provide an assessment of BBB integrity. When the BBB is intact, intravenously administered contrast dye remains intravascular and plasma proteins do not leak across the barrier. However, when the barrier is disrupted, plasma proteins, water, and intravenously administered contrast escape the vessels, producing an increase in "contrast enhancement," edema, and mass effect.

Similarly, therapies that disrupt the integrity of the BBB, such as external beam radiation therapy, placement of intracranial radiation implants or chemotherapy wafers, or the use of highly focused radiation beams may cause patients to develop neurologic signs and symptoms, findings of increased intracranial pressure, and a scan compatible with tumor "progression." These findings are clinically indistinguishable from tumor progression and often respond to an increase in glucocorticoids. Positron emission tomography or magnetic resonance spectroscopy attempt to distinguish tumor progression from radiation necrosis, but surgical intervention to debulk the "mass" and provide tissue for pathological review is often required to correctly identify the etiology of the patient's decline [42, 51]. The injury from standard external beam radiation gradually diminishes about 3 months after the completion of the radiation.

Tumor response can be as difficult to assess as tumor progression. The physical examination can be an unreliable determinant of response as neurologic injuries often result in permanent neurologic disabilities. Thus, a patient's clinical status may not improve even if a tumor completely disappears following resection or the administration of effective radiation or chemotherapy. For this reason, neuro-imaging studies provide a more accurate reflection of the status of the tumor than the history and physical examination. As noted above, contrast-enhanced CT and MR imaging rely on disruption of the BBB to provide indirect information regarding the size of the tumor. Thus, the appearance of the scan can be improved by increasing the glucocorticoid dose which repairs BBB dysfunction thereby reducing the size of the contrast-enhancing mass and the associated edema, and mass effect without truly changing the size of the tumor.

The difficulties in assessing tumor progression and response highlight the challenges facing clinicians when decisions have to be made regarding the efficacy of a therapeutic regimen. The currently available criteria to assess "tumor response" account for changes in glucocorticoid dosing, but do not adequately address the effect of therapies that disrupt the BBB [36].

Delivery of Chemotherapy to the Tumor

Therapeutic concentrations of systemically administered chemotherapy must reach the tumor cells if they are to have the desired effect. Two significant barriers make it difficult for many drugs to reach cancer cells within the brain in adequate concentrations. The first relates to an interaction between hepatic P450 enzyme-inducing antiepileptic drugs (EIAED) and chemotherapy [58, 59]. This was initially described in patients with newly diagnosed GBM who were treated with paclitaxel at a dose and schedule that caused alopecia, mucositis, and myelosuppression in patients with lymphomas and breast cancer [16]. None of the brain tumor patients treated with this regimen developed the expected toxicities and serum paclitaxel levels were noted to be one sixth of that seen in patients with systemic cancers. This finding was explained when it was noted that all of the brain tumor patients were taking phenytoin, a potent p450 hepatic enzyme inducer, and that paclitaxel is metabolized by the hepatic p450 system. Subsequent studies with a variety of other antineoplastic agents have demonstrated the importance of this observation. Doses of chemotherapeutic agents such as CPT-11 may need to be four times higher in patients on EIAED to achieve the desired serum concentrations and clinical effects [18, 47]. These observations are not restricted to classic antineoplastic agents. The same has been noted with differentiating agents (phenylbutyrate), antiangiogenesis agents (CAI), and signal transduction inhibitors (R115777) [46, 58]. Some chemotherapeutic agents that were not thought to be metabolized by the P450 system (9-aminocamptothecin) are affected by the concurrent EIAED administration, while others known to be hepatically metabolized (procarbazine) remain unchanged in the presence of EIAED [24, 28]. These data suggest that much of the previously conducted clinical research on chemotherapy in patients with brain tumors may be invalid as the doses of chemotherapy used were determined in patients with systemic malignancies who were not taking EIAED.

The other known barrier restricting the entry of drugs into the central nervous system is the BBB. The BBB is an anatomic and physiologic barrier that is usually disrupted in patients with high grade astrocytomas, primary CNS lymphomas, and brain metastases. This observation has been exploited for radio-

logic studies as the contrast agents administered for MRI and CT scans do not penetrate an intact BBB. As a result, the normal brain does not enhance while the tumor, with its local BBB disruption, does. Detailed studies of the integrity of the BBB within brain tumors have demonstrated that that it can be porous in some regions of the tumor and relatively intact in others. It has been clearly shown that glioma and PCNSL cells are frequently found at considerable distances from the contrast-enhancing tumor [9, 31]. Thus, even if large or water soluble chemotherapeutic agents reach the enhancing portions of the tumor, many neoplastic cells in nonenhancing regions may remain untreated. In addition to constraints on molecular weight, charge, and lipid solubility, there are physiologic components to the BBB, such as P-glycoprotein, that probably play a significant role restricting the penetration of agents such as vincristine, paclitaxel, or anthracyclines.

If drug does not reach the tumor in therapeutic concentrations, there is little chance that a meaningful response can occur. Vincristine has been used for decades in the treatment of primary brain tumors, yet recent studies document that it probably never reaches the tumor [5]. Microdialysis catheters are used to measure glucose, lactate, pyruvate, and glutamate levels in patients with traumatic brain injury to predict brain at risk for dying [2, 32, 41]. These catheters have been used in animal experiments to document how methotrexate reaches the cerebrospinal fluid [3]. Based on these studies, investigators within The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium have initiated a study in patients with recurrent GBM who require a biopsy or partial tumor debulking. A microdialysis catheter is placed in residual contrast-enhancing tumor at the time of surgery and postoperatively high-dose methotrexate is administered. Methotrexate concentrations in the serum and extracellular fluid of the tumor are measured. Preliminary data suggests that the concentrations of methotrexate within contrast-enhancing GBM are higher than plasma levels 24 h after the methotrexate infusion is completed [44]. This study suggests that microdialysis techniques may help to determine which agents and schedules should be used in clinical trials to determine the efficacy of a novel agent or approach. If sufficient drug does not reach the tumor after intravenous administration, other approaches, such as local infusion into the tumor bed, might prove more likely to yield the desired result.

Even when interstitial chemotherapy is delivered directly to the tumor using convection-enhanced delivery or implantation of a chemotherapy-embedded polymer, the delivery of drug to the entire tumor volume is far from certain. Preliminary data on drug distribution from catheters suggests that a substantial amount of the drug tracks back along the catheter. Studies of the distribution of BCNU from implanted biodegradable wafers note that much of the drug is released as a "burst" during the first few days after implantation [17, 26, 52]. Furthermore, the volume of distribution is unlikely to reach all of the tumor cells. Intraventricularly administered drugs have also been shown to have very limited penetration into brain and spinal cord parenchyma and will not effectively reach an intraparenchymal tumor [8, 33]. Furthermore, the distribution of drug throughout the subarachnoid space following administration through an Ommaya reservoir in patients with leptomeningeal carcinomatosis is uneven as illustrated by the high rate of CSF flow abnormalities in this patient population [11, 29].

These reports suggest that it is naïve to assume that drugs administered systemically, directly to the tumor, or into the cerebrospinal fluid will reach tumor in therapeutic concentrations. They also emphasize the importance of documenting adequate drug concentrations in the tumor before declaring an agent ineffective.

Clinical Trials

The survival of patients with primary brain tumors has changed little during the past three decades despite advances in neuro-imaging, neurosurgery, radiation, and chemotherapy. As a result, clinical research remains a high priority in this patient population. Novel therapies are usually evaluated through a series of clinical studies referred to as Phase I, Phase II, and Phase III trials. Phase I trials are designed to determine the dose-limiting toxicities (DLT), the maximum-tolerated dose (MTD), and the pharmacology of a novel agent. These are usually small trials where sequential cohorts of patients receive higher doses of the new agent until prohibitive toxicity is seen. In Phase II studies, the agent is administered at the MTD to determine if clinically significant activity tumor is detected. If the agent appears sufficiently active, a randomized Phase III trial may be conducted where the outcome from novel therapy is compared to a standard therapy. Phase III trials are generally required for new drugs to receive approval to enter the marketplace.

Several deficiencies in the design of brain tumor trials conducted in the past have been described above. These include inaccuracies in determining tumor response and progression, the underdosing of drugs affected by concomitant EIAED administration, the inability of some agents to penetrate the BBB, and the suboptimal distribution of locally administered agents. Other studies inadvertently undermined the chance for a novel agent to succeed.

As noted above, adjuvant chemotherapy trials in patients with high-grade gliomas routinely allow the entry of patients with bulky residual disease. This minimizes the possibility of a positive outcome from the adjuvant therapy. Overly optimistic designs have also been used for noncytotoxic agents. For example, novel antiangiogenesis agents have been studied in patients with rapidly recurring GBMs which are already highly vascularized [25]. Unfortunately, these patients may not live long enough to permit a determination of the efficacy of this new class of potentially important agents. Alternatively, these agents could be administered with standard therapy in newly diagnosed patients and survival, rather than response, could serve as the primary endpoint [23, 35].

Obtaining informed consent in this patient population is also more difficult than in patients with systemic cancers. Patients with primary brain tumors often have difficulty with cognition, expressive or receptive language, compliance, or a low performance status which often preclude participation in clinical trials. This patient population is also vulnerable to situations where "informed" consent may be compromised. Consider a patient presenting with a seizure and an MRI that suggests the diagnosis of GBM. Although this patient might be a candidate for a research trial that involved placement of a novel radiation therapy device, chemotherapy-embedded wafer, or an immunotoxin or gene therapy trial, the patient has yet to receive a cancer diagnosis. In addition, the patient has no time to consider standard or experimental therapeutic options and is likely to worry about offending a neurosurgeon preparing for the operating room.

Vaccine or other immunologic-based strategies are most likely to work in patients who are immunocompetent. Most patients with malignant brain tumors receive high doses of glucocorticoids to control peritumoral brain edema, as well as radiation and chemotherapy that clearly affect the immune system. Pneumocystis pneumonia has been reported in patients with glioblastoma multiforme and primary CNS lymphoma [37, 40]. A new study suggests that 28% of patients with GBM reach a CD4 count of less than 200 during their 6 weeks of radiation therapy [34]. Much as a chemotherapy trial should not seek to evaluate a drug that does not reach the brain tumor in therapeutic concentrations, the efficacy of a vaccine should not be assessed in immunosuppressed patients.

Seizures

It is estimated that 20%–40% of all brain tumor patients experience a seizure by the time their brain tumor is diagnosed and at least another 20%–45% ultimately develop seizures [19]. Seizures are also common in patients with brain or leptomeningeal metastases. Virtually all patients with primary brain tumors are placed on anticonvulsants during their initial evaluation. Some present with seizures or were thought to be at high risk for them and the remainder receive them prior to the surgical procedure that provides their diagnosis. Many patients remain on these agents for the rest of their lives. Allergic reactions are relatively frequent and can be severe. Carbamazepine is myelosuppressive and makes it more difficult to administer full doses of chemotherapy. Anticonvulsants that induce hepatic P450 enzymes, such as phenytoin, phenobarbital, and carbamazepine, can dramatically affect the pharmacology of many chemotherapeutic agents [58, 59]. As noted above, this often significantly reduces the serum levels of these antineoplastic agents rendering them less effective. In addition, some chemotherapeutic agents alter the pharmacology of anticonvulsants. For example, cisplatin can reduce phenytoin levels and make it more likely that susceptible patients have seizures [27]. Some patients require twice as much phenytoin to maintain therapeutic levels shortly after receiving cisplatin. In addition, these agents may cause sedation and affect cognition and memory. Current data suggests that the use of prophylactic anticonvulsants is not beneficial [19]. As a result, anticonvulsants can be cautiously withdrawn from patients without a prior history of seizures. Newer anticonvulsants, which are not hepatic P450 inducers, are being prescribed to these patients with increasing frequency as they are better tolerated and minimize the risk of important drug interactions with chemotherapy.

Brain Edema

Peritumoral brain edema is common in patients with primary or metastatic brain tumors. The extent of the edema may be assessed using a T2-weighted MRI scan. The exact mechanism by which glucocorticoids repair the leaky BBB remains unknown. However, since the 1960s these agents have been essential to reducing perioperative morbidity and mortality and to improving neurologic signs and symptoms caused by peritumoral edema. Glucocorticoids are usually administered at presentation, in the postoperative period, during radiation, and at the time of tumor recurrence. However, many patients remain dependent on these agents for long periods of time. The side effects associated with the glucocorticoids are often more troublesome to patients than the toxicities of chemotherapy. The immunosuppressive and antipyretic effects of these agents may lead to serious infectious complications. Special care must be

exercised in neutropenic patients taking glucocorticoids as they can be septic without rigors, fevers, or localizing signs of infections. Pneumocystis carinii pneumonia (PCP) also occurs in patients receiving or being tapered off these agents [37, 40]. This often begins with fever, cough, and dyspnea and rapidly progresses to hypoxia and respiratory failure. Even with appropriate therapy, it is associated with a mortality rate that approaches 50%. Glucocorticoids and radiation can dramatically reduce CD4 counts in patients with GBM. Approximately 28% of these patients will develop CD4 counts below 200, which is similar to patients with advanced AIDS [34]. This may explain their susceptibility to PCP. Furthermore, patients with primary brain tumors who receive temozolomide and glucocorticoids also have an unusually high incidence of PCP [53, 54]. As a result, PCP prophylaxis should be considered in patients receiving prolonged glucocorticoid therapy, temozolomide, or where monitoring demonstrates a CD4 count below 200.

Other glucocorticoid toxicities significantly affect quality of life in this patient population [55]. Patients may experience a voracious appetite, weight gain, fluid retention, and the typical changes in body habitus associated with Cushing's disease. In addition, emotional lability, sleep disturbances, hyperglycemia, gastric hyperacidity, osteoporosis, skin and capillary fragility, joint pains, visual changes, and an acneiform rash are common. One of the most disabling complications is a proximal myopathy that usually begins with the proximal muscles of the lower and upper extremities but can spread to the pelvic and respiratory muscles. Early symptoms include difficulty rising from a low chair. This commonly progresses to unexpected falls and inactivity.

Thromboembolic Disease

Thromboembolic disease represents a major cause of morbidity and mortality in this patient population [43]. It has been estimated that approximately one third of patients with glioblastoma multiforme develop clinically apparent deep venous thromboses and pulmonary emboli. This figure is probably substantially higher in elderly, immobile patients with multiple other medical problems. The administration of chemotherapy may further increase the incidence of thromboembolic events as it does in other malignancies. Physicians are frequently hesitant to anticoagulate patients with brain tumors fearing that this may precipitate intracranial bleeding. A baseline noncontrast CT scan of the brain can be helpful. If blood is not present, careful monitoring and conservative heparin-loading doses followed full anticoagulation with heparin and warfarin are usually well tolerated by these patients. Many drugs prescribed to patients with brain tumors are known to potentiate (phenytoin) or diminish (glucocorticoids, phenobarbital, carbamazepine) the anticoagulant effect of warfarin. The platelet count should be maintained above 50,000/uL while anticoagulants are administered and the concomitant administration of aspirin-containing drugs and nonsteroidal anti-inflammatory agents should be avoided. Thrombolytics are contraindicated and vena caval filters are rarely required.

Psychosocial Issues

The natural history of most primary brain tumors heralds devastating changes for patients and their families. Many patients present with seizures or visual impairment and are unable to drive a car from the time they are diagnosed with this illness. Others cannot dress, walk, eat, or bathe independently. Cognitive deficits, expressive and receptive aphasias, short-term memory deficits, motor deficits, and a propensity to fall can make it impossible for some patients to remain unsupervised even for short periods of time. The sudden and extreme dependence on family and friends, along with the potential loss of mental function and communicative capacity place great stresses on patients and their families. In addition, the changes in body habitus, acne, and proximal myopathy that occur with glucocorticoids can affect a patient's self-image. Patients are frequently unable to return to work and caregivers often need to adjust their work schedules to provide care. These circumstances often lead to significant financial hardships. As a result, patients and families must have access to a broad range of medical and social support services.

Care of the Dying Patient

As the vast majority of patients with CNS malignancies can not be cured by available therapies, maximizing the quality of life and allowing these patients to die comfortably and with dignity are important goals [55]. The end of life can be difficult for this patient population. Patients may be physically unable to communicate their needs or feelings. Progressive confusion, disorientation, and somnolence are common and many patients are distraught by their extraordinary dependence. Many patients become increasingly lethargic and die peacefully. However, headaches, nausea, and vomiting from increased intracranial pressure, seizures, bedsores, and *Candida* mucositis or esophagitis are not infrequent. Controlling the symptoms of increased intracranial pressure

and preventing seizures are paramount during this phase of the illness. Increasing doses of glucocorticoids may transiently reduce intracranial pressure but could also prolong the illness. Alternatively, opioids can be administered to reduce the intensity of the headaches. With increasing sedation, patients may have more difficulty taking oral medications. This may require glucocorticoids, opioids, and anticonvulsants to be administered rectally, parenterally, transdermally, or via a small flexible nasogastric feeding or a gastrostomy tube. Many of these changes must be made thoughtfully. Converting a patient with a known seizure disorder to a new anticonvulsant or a new route of administration is hazardous and can precipitate seizure activity. The physical and emotional toll on caregivers is not to be underestimated.

Conclusions

The optimal management of patients with primary brain tumors involves more than providing state-of-the-art surgery, radiation, and chemotherapy. Unfortunately, the outcome of these therapies remains inadequate for the vast majority of patients with malignant neoplasms of the central nervous system. Novel therapies and approaches are needed if progress is to be made. This requires that investigators construct trials paying particular attention to the difficulties in assessing response and delivering drugs to these tumors. Furthermore, clinicians must be committed to placing patients on clinical trials that answer important questions rather than treating them with relatively inactive, but available, drugs. Until real progress is made in curing these cancers, significant effort should be directed towards improving the quality of life for these patients and their families. Knowledge of the unique aspects regarding anticonvulsants, glucocorticoids, thromboembolic disease, psychosocial issues, and terminal care in this patient population is a first step. However, enormous gaps in our knowledge remain in each of these supportive care areas. Additional studies on these important topics will provide better care to patients with CNS malignancies.

References

1. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. J Clin Oncol 2001;19: 509–518
2. Bellander BM, Cantais E, Enblad P, Hutchinson P, Nordstrom CH, Robertson C, et al. Consensus meeting on microdialysis in neurointensive care. Intensive Care Med 2004;30:2166–2169
3. Benjamin RK, Hochberg FH, Fox E, Bungay PM, Elmquist WF, Stewart CF, et al. Review of microdialysis in brain tumors, from concept to application: first annual Carolyn Frye-Halloran symposium. Neuro-Oncol 2004;6:65–74
4. Bokstein F, Lossos A, Siegal T. Leptomeningeal metastases from solid tumors: a comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. Cancer 1998;82:1756–1763
5. Boyle FM, Eller SL, Grossman SA. Penetration of intra-arterially administered vincristine in experimental brain tumor. Neuro-Oncol 2004;6:300–305
6. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet 1995;345:1008–1012
7. Buckner JC, Gesme Jr D, O'Fallon JR, Hammack JE, Stafford S, Brown PD, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol 2003;21:251–255
8. Burch PA, Grossman SA, Reinhard CS. Spinal cord penetration of intrathecally administered cytarabine and methotrexate: a quantitative autoradiographic study. J Natl Cancer Inst 1988;80:1211–1216
9. Burger PC, Vogel FS, Green SB, Strike TA. Glioblastoma multiforme and anaplastic astrocytoma. Pathologic criteria and prognostic implications. Cancer 1985;56:1106–1111
10. Cairncross G, Seiferheld W, Shaw E, Jenkins R, Scheithauer B, Brachman D, et al. An intergroup randomized controlled clinical trial (RCT) of chemotherapy plus radiation (RT) versus RT alone for pure and mixed anaplastic oligodendrogliomas: Initial report of RTOG 94–02. J Clin Oncol 2004;22:1500
11. Chamberlain MC, Corey-Bloom J. Leptomeningeal metastases: 111indium-DTPA CSF flow studies. Neurology 1991;41:1765–1769
12. Chamberlain MC, Kormanik P, Jaeckle KA, Glantz M. 111Indium-diethylenetriamine pentaacetic acid CSF flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 1999;52:216–217
13. Chamberlain MC, Kormanik PA. Prognostic significance of 111indium-DTPA CSF flow studies in leptomeningeal metastases. Neurology 1996;46:1674–1677
14. Chamberlain MC, Kormanik PA, Barba D. Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases. J Neurosurg 1997;87: 694–699
15. Fenner MH, Possinger K. Chemotherapy for breast cancer brain metastases. Onkologie 2002;25:474–479
16. Fetell MR, Grossman SA, Fisher JD, Erlanger B, Rowinsky E, Stockel J, et al. Preirradiation paclitaxel in glioblastoma multiforme: efficacy, pharmacology, and drug interactions.

New Approaches to Brain Tumor Therapy Central Nervous System Consortium. J Clin Oncol 1997;15:3121–3128
17. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. Clin Pharmacokinet 2002;41:403–419
18. Gilbert MR, Supko JG, Batchelor T, Lesser G, Fisher JD, Piantadosi S, et al. Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. Clin Cancer Res 2003;9:2940–2949
19. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54:1886–1893
20. Grossman SA. Arguments against the routine use of currently available adjuvant chemotherapy in high-grade gliomas. Semin Oncol 2003;30:19–22
21. Grossman SA, Batara JF. Current management of glioblastoma multiforme. Semin Oncol 2004;31:635–644
22. Grossman SA, Burch PA. Quantitation of tumor response to anti-neoplastic therapy. Semin Oncol 1988;15:441–454
23. Grossman SA, Fisher JD, Piantadosi S, Brem H. The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium: Organization, Objectives, and Activities. Cancer Control 1998;5:107–114
24. Grossman SA, Hochberg F, Fisher J, Chen TL, Kim L, Gregory R, et al. Increased 9-aminocamptothecin dose requirements in patients on anticonvulsants. NABTT CNS Consortium. The New Approaches to Brain Tumor Therapy. Cancer Chemother Pharmacol 1998;42:118–126
25. Grossman SA, Phuphanich S, Lesser G, Rozental J, Grochow LB, Fisher J, et al. Toxicity, efficacy, and pharmacology of suramin in adults with recurrent high-grade gliomas. J Clin Oncol 2001;19:3260–3266
26. Grossman SA, Reinhard C, Colvin OM, Chasin M, Brundrett R, Tamargo RJ, et al. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. J Neurosurg 1992;76:640–647
27. Grossman SA, Sheidler VR, Gilbert MR. Decreased phenytoin levels in patients receiving chemotherapy. Am J Med 1989;87:505–510
28. Grossman SA, Phupanich S, Batchelor T, Mikkelson T, Powers P, Carson K, et al. Phase I/II of oral procarbazine in the treatment of recurrent high grade astrocytomas. Neuro-Oncology 2001;3:358–359
29. Grossman SA, Trump DL, Chen DC, Thompson G, Camargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. An evaluation using 111indium-DTPA ventriculography. Am J Med 1982;73:641–647
30. EBCTC. Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet1998;351:1451–1467
31. Halperin EC, Burger PC, Bullard DE. The fallacy of the localized supratentorial malignant glioma. Int J Radiat Oncol Biol Phys 1988;15:505–509
32. Hlatky R, Valadka AB, Goodman JC, Contant CF, Robertson CS. Patterns of energy substrates during ischemia measured in the brain by microdialysis. J Neurotrauma 2004;21:894–906
33. Huang TY, Arita N, Ushio Y, Hayakawa T, Nagatani M, Mogami H. [Distribution of ACNU in the rat brain after intracisternal injection–macroscopical autoradiographic study]. No To Shinkei 1987;39:263–266
34. Hughes MA, Grossman SA, Kleinberg L. Primary brain tumors treated with steroids and radiation: low CD4 counts and PCP prophylaxis. Int J Rad Bio Physics 2005 (in press)
35. Laterra JJ, Grossman SA, Carson KA, Lesser GJ, Hochberg FH, Gilbert MR. Suramin and radiotherapy in newly diagnosed glioblastoma: phase 2 NABTT CNS Consortium study. Neuro-oncol 2004;6:15–20
36. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;21:1277–1280
37. Mahindra AK, Grossman SA. Pneumocystis carinii pneumonia in HIV negative patients with primary brain tumors. J Neurooncol 2003;63:263–270
38. Mansour EG, Gray R, Shatila AH, et al. Survival advantage of adjuvant chemotherapy in high-risk node-negative breast cancer: ten-year analysis–an intergroup study. J Clin Oncol 1998;16:3486–3492
39. Mason WP, Yeh SD, DeAngelis LM. 111Indium-diethylenetriamine pentaacetic acid cerebrospinal fluid flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 1998;50:438–444
40. Mathew BS, Grossman SA. Pneumocystis carinii pneumonia prophylaxis in HIV negative patients with primary CNS lymphoma. Cancer Treat Rev 2003;29:105–119
41. Nelson DW, Bellander BM, Maccallum RM, Axelsson J, Alm M, Wallin M, et al. Cerebral microdialysis of patients with severe traumatic brain injury exhibits highly individualistic patterns as visualized by cluster analysis with self-organizing maps. Crit Care Med 2004;32:2428–2436
42. Nelson SJ, Vigneron DB, Dillon WP. Serial evaluation of patients with brain tumors using volume MRI and 3D 1H MRSI. NMR Biomed 1999;12:123–138
43. Norris LK, Grossman SA. Treatment of thromboembolic complications in patients with brain tumors. J Neurooncol 1994;22:127–137
44. Olson JJ SJ, Phuphanich S, McKenzie E, Grossman SA. Intratumoral pharmacokinetics determined with microdialysis in a patient with glioblastoma multiforme following systemic administration of high dose methotrexate. Neurooncology (in press)
45. Pace A, Vidiri A, Galie E, Carosi M, Telera S, Cianciulli AM, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann Oncol 2003;14:1722–1726
46. Phuphanich SB, Baker SD, Grossman SA, Gilbert MR, Fisher JD, Carson KA, et al. Oral Sodium Phenylbutyrate in Patients with Recurrent Malignant Gliomas: A Dose Escalation and Pharmacologic Study. Neurooncol 2005;in press
47. Reardon DA, Quinn JA, Rich JN, Gururangan S, Vredenburgh J, Sampson JH, et al. Phase 2 trial of BCNU plus irinotecan in adults with malignant glioma. Neuro-oncol 2004;6:134–144

48. Schuette W. Treatment of brain metastases from lung cancer: chemotherapy. Lung Cancer 45(Suppl)2004;2: S253–S257
49. Siegal T. Leptomeningeal metastases: rationale for systemic chemotherapy or what is the role of intra-CSF-chemotherapy? J Neurooncol 1998;38:151–157
50. Stieber VW. Low-grade gliomas. Curr Treat Options Oncol 2001;2:495–506
51. Stokkel M, Stevens H, Taphoorn M, Van Rijk P. Differentiation between recurrent brain tumour and post-radiation necrosis: the value of 201Tl SPET versus 18F-FDG PET using a dual-headed coincidence camera–a pilot study. Nucl Med Commun 1999;20:411–417
52. Strasser JF, Fung LK, Eller S, Grossman SA, Saltzman WM. Distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea and tracers in the rabbit brain after interstitial delivery by biodegradable polymer implants. J Pharmacol Exp Ther 1995;275:1647–1655
53. Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 2002;20:1375–1382
54. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn M, et al. Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized phase III trial by the EORTC Brain & RT Groups and NCIC Clinical Trials Group. J Clin Oncol 2004;22:2
55. Taillibert S, Laigle-Donadey F, Sanson M. Palliative care in patients with primary brain tumors. Curr Opin Oncol 2004;16:587–592
56. Trump DL, Grossman SA, Thompson G, Murray K. CSF infections complicating the management of neoplastic meningitis. Clinical features and results of therapy. Arch Intern Med 1982;142:583–586
57. van den Bent MJ. The role of chemotherapy in brain metastases. Eur J Cancer 2003;39:2114–2120
58. Vecht CJ, Wagner GL, Wilms EB. Interactions between antiepileptic and chemotherapeutic drugs. Lancet Neurol 2003;2:404–409
59. Vecht CJ, Wagner GL, Wilms EB. Treating seizures in patients with brain tumors: Drug interactions between antiepileptic and chemotherapeutic agents. Semin Oncol 2003;30:49–52
60. Watling CJ, Lee DH, Macdonald DR, Cairncross. Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. J Clin Oncol 1994;12:1886–1889
61. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro-Oncol 2003;5:79–88

Subject Index

A

Abt-Letterer Siwe disease 54, 548
acanthosis nigricans 196
acidophil stem cell adenoma 193
acoustic neuroma 223, 332
acromegaly 191, 196, 502
actinomycin 351, 427
acute myeloid leukaemia 284
adamantinomatous craniopharyngioma 61
adenohypophysis mature cell 506
adenoma
– GH-secreting 502
– pituitary 61, 171, 182, 184, 191, 197, 198, 203, 503
adrenalectomy, bilateral 204
adrenocorticotrophic hormone (ACTH) 337
– cell hyperplasia 203
Aicardi syndrome 530
AIDS 292, 298
Alexander's disease 403
alkylating agent 297
alpha-fetoprotein (AFP) 209, 214, 495
5-aminolevulinic acid fluorescence 371, 372
anaplastic
– astrocytoma 15, 128, 132, 390, 623, 689
– ependymoma 26, 162
– ganglioglioma 33, 397, 398
– medulloblastoma 468
– meningioma 85, 95
– oligodendroglioma 22
anesthesia 129
aneurysmal bone cyst 590, 591, 647
angio-embolization 535
angiofibroma, juvenile nasopharyngeal 559
angiogenic activity 151
angiography 252, 532
– bicarotid 508
– cerebral 488
angioma 678
angiosarcoma 571
anterior orbitotomy 287
antiangiogenic therapy 241
antiestrogen 261
antineoplastic therapy 688
aphasia 129
apoplexy, pituitary 186
apoptosis 474
appetite stimulation 450
Ara-C 298
arachnoid membrane of Liliequist 257
astroblastoma 29
astrocytes 9
astrocytic
– brain tumor 133
– glioma 11, 12, 142
– tumor 208
astrocytoma 19, 23, 104, 131, 335, 604, 605, 620, 622
– anaplastic 15, 128, 132, 390, 623, 689
– bilateral thalamic 366
– cerebellar 402
– diffuse 12, 17, 623
– fibrillary 12, 132, 347, 349, 403, 417, 424
– – infiltrative 366
– gemistocytic 12
– infiltrating 104
– malignant 128
– pilocytic 20, 366, 403, 416, 422, 605, 622
– – juvenile 369, 402
– – of the pulvinar 365
– pilomyxoid 20, 66
– protoplasmic 12
– small-cell 18
– superficial cerebral (SCA) 432
astrocytosis, reactive 308
astrogliosis 30
ataxia 394, 416, 419
atypical meningioma 85
Ayala's disease 549
aziridinylbenzoquinone (AZQ) 380

B

Babinski's sign 648
baby POG protocol 543
B-cell
– marker 294
– precursor lymphoma 572
benzodiazepine 337
betadine solution 404
beta-HCG 495
bicarotid angiography 508
bilateral
– adrenalectomy 204
– thalamic astrocytoma 366
– thalamic glioma 369
– thalamic tumor 367
– vestibular schwannoma 332
biopsy 513, 651
– stereotactic 371, 409
bipolar angiocentric astrocytoma 105
Birbeck granules 549
bisphosphonate 657
bitemporal hemianopia 507
bladder dysfunction 577
bleomycin 512
bowel dysfunction 577
brachytherapy 120, 240
– interstitial 205
– intracavitary 135
brain
– biopsy 308
– edema 692
– metastases 304

– – radiation therapy 310
– – stereotactic radiosurgery 312
– – surgery 311, 313
– parenchyma 531
– tumor
– – classification 5
– – molecular genetics 11
– – recurrence 689
brainstem
– glioma 416
– tumor 378, 408
breast cancer 646
Broca's area 109
bromocriptine 193, 194, 198, 502
bromodeoxyuridine (BrdU) 311
bronchial adenocarcinoma 17
Brown-Sequard picture 600
Burkitt's lymphoma 53

C

C1 laminectomy 260, 562
C2 laminectomy 260
cabergoline 194, 198, 199
café-au-lait macule 329
callosotomy 447
calvarian tumor 74
– of children 568
capillary
– hemangioblastoma 57
– hemangioma 280
carbamazepine 438, 693
carboplatin 113, 142, 351, 358, 373, 405, 419, 440, 535
carcinoembryonic antigen (CEA) 247
carcinoid syndrome 262
carcinoma
– choroid plexus 28
– embryonal 56
– pituitary 62
cardiac rhabdomyoma 335
carmustine 298
Carney complex 42
catecholamine 267
β-catenin 61
catheter angiography 263, 532
cavernous
– hemangioma 281
– sinus 182
– – meningioma 252, 257
Cavitron ultrasonic aspirator (CUSA) 426
CDKN2 15
central nervous system
– disease 548
– malignancy 688
– tumor 386
central neurocytoma 34, 175
central precocious puberty 445
cerebellar
– astrocytoma 402
– ataxia 209
– liponeurocytoma 35, 176
– mutism 467
– tonsils 439
cerebellopontine angle 226
cerebral
– angiography 488
– edema 449
– neoplasm 128
– neuroblastoma 160, 472
– parenchyma 508
cervical
– ependymoma 629
– kyphosis 428
– laminectomy 425
– spondylosis 560
cervicomedullary
– glioma 422
– tumor 620
cervicothoracic ganglioglioma 399
chiasma syndrome 252
chiasmatic-hypothalamic glioma 358
2-chlorodeoxyadenosine 552
cholesteatoma 219
choline 532
chondroblastoma 75
chondroid
– chordoma 247, 249
– metaplasia 106
– pattern 106
chondroma 75, 244
chondrosarcoma 75, 244, 246, 249, 560, 648
chordoid
– glioma 30
– meningioma 253
chordoma 47, 244, 246, 560, 647
– clival 561
choriocarcinoma 56, 495, 519, 522, 526
choroid plexus 55
– tumor 26, 27, 530
– carcinoma 28
– papilloma 149
– – atypical 28
chromatin 39, 105, 474
chromogranin 62
– A 36
chromosomal aberration 465, 533
chromosome 22 25
cilengitide 390
circadian rhythm 496
cisplatin 136, 459, 525, 526
claustrophobia 650
clinoidal meningioma 252, 257
clival
– chordoma 561
– meningioma 258
colon polyp 196
comparative genomic hybridization (CGH) 20
computer-assisted stereotaxy 316
congenital aqueductal stenosis 378
corpus callosotomy 336
cortical
– brain mapping 315
– dysplasia 171, 175, 446
– tuber 335, 336
corticosteroid 298, 309, 411
corticotomy 542
cortisol 184, 186
costotransversectomy 654
Cowden syndrome 58, 61, 173
cox model 120
cranial
– base lesion 556
– deformity 486
– irradiation 486
– motor nuclei displacement 424
– nerve
– – dysfunction 422
– – palsy 458
– – paresis 244, 262
– – schwannoma 218
– – tumor 228
– neuropathy 245
craniectomy 293, 425, 458
cranio-orbitotomy 287
craniopharyngioma 61, 154, 183, 448, 506
– papillary 61
– retrochiasmatic 510
craniospinal
– axis 467, 476
– irradiation 213, 475, 525, 535
– radiotherapy 142
craniotomy 209, 211, 316, 371, 425, 434, 458, 523, 534, 558, 562, 606
– orbito-zygomatic 447, 450
– restromastoid 562
– supratentorial 475
creatine 532

cryosurgery 589
CSF
– a-fetoprotein 493
– chorionic gonadotropin 493
– cytology 477, 493
Cushing's disease 42, 191, 202, 500, 501, 503, 693
cyclo-oxygenase inhibitor (COX) 411
cyclophosphamide 296, 297, 405
cystic
– brain metastasis 308
– puncture 513
– tumor 351
cytarabine 297
cytokeratin 28, 30, 64, 247
cytoreduction 357

D

Denis' three column model 653
dermoid tumor 568
dermolipoma 280
desmin 541
desmoid 677
desmoplastic
– infantile astrocytoma 33, 172
– infantile ganglioglioma (DIG) 33, 172, 348, 432
– medulloblastoma 160, 468
– stroma 172
dexamethasone 122, 125, 136, 296, 298, 309, 411, 475, 639, 657
diabetes insipidus (DI) 204, 500, 549, 553
diaphragma sella 509
diathermy 288
diencephalic syndrome 354
diffuse
– astrocytoma 623
– intrinsic pontine glioma (DIPG) 408
– large B-cell lymphoma 53
– melanocytosis 51
– pontine glioma 423
diffusion-weighted (DWI) image 292
digital subtraction angiography (DSA) 239
diplopia 408, 455, 492
DNT-like tumor of the septum pellucidum and caudate nucleus area 65
dopamine
– agonist (DA) 185, 193, 198
– antagonist 502
dorsally exophytic tumor 423
dose-limiting toxicities 691
doxorubicin 296, 297
dumbbell 42
– schwannoma 640, 641
dural
– lymphoma 98
– metastases 99
durotomy 641
D-wave 425
dysembryoblastic
– neuroepithelial tumor (DNET) 34, 173, 347, 480
– neuroectodermal tumor 480
dysesthesias 129
dysfunction, pituitary 182
dysmetria 394, 419
dysphagia 604
dysphasia 129
dysplasia
– cortical 446
– focal cortical 481
dysplastic
– cerebellar gangliocytoma 173
– gangliocytoma of the cerebellum 60

E

EBV 54
ecchordosis 244
eccondrosis physaliphora 244
EGFR 11, 19
electrocautery 404, 606
electroencephalography (EEG) 266
electrophysiological examination 666
elephantiasis neuromatosa 44
EMA 49, 541
embolization 590
– endovascular 658
– preoperative 88, 91
embryonal
– carcinoma 56
– tumor 37
– – with abundant neurophil and true rosettes 66
endocrine deficiency 507
endoscopic third ventriculostomy (ETV) 378, 406, 418, 523, 524
endovascular embolization 658
enzyme-inducing antiepileptic drug 690
eosinophilic granuloma 75, 551, 570, 592, 647
ependymal tumor 25, 27
ependymoblastoma 26, 37, 160
ependymoma 17, 146, 333, 454, 462, 495, 604, 607, 620, 621
– anaplastic 25, 26, 162
– cervical 629
– intracranial 454
– myxopapillary 26
– tanycytic 457
epidermal growth factor receptor (EGFR) 19, 388
epidermoid tumor 568
epilepsy 350, 398
– gelastic 444, 445
– surgery 169, 175, 336, 451
epileptic encephalopathy 445, 450
epithelial membrane antigen 247
Epstein-Barr virus (EBV) 54
Erdheim-Chester disease 54, 55
esthesioneuroblastoma 218, 220, 227, 556, 557
estrogen 251
etoposide 142, 298, 405, 459, 525, 535
Ewing's sarcoma 571, 579, 592, 593
exophthalmometer 275
exophthalmos 282
exsanguination 433
external
– beam radiotherapy 410
– granular cell 162
– ventricular drain (EVD) 403
extraconal space 273
extradural spine tumor 576
extraneural metastasis 152
extraventricular (parenchymal) neurocytoma 64

F

familial
– hemophagocytic lymphohistiocytosis 55
– tumor syndrome 57
fascicular electrophysiological monitoring 666
^{18}FDG PET 670
fibrillary
– astrocytoma 132, 347, 349, 403, 417, 424
– glioma 131
– neoplastic astrocytes 439
fibroma, ossifying 569
fibrosarcoma 571
fibrous dysplasia 75, 556

FLAIR image 378
Flexner-Winterstein rosettes 474, 541
floating neurons 480
fluorescein angiography (FA) 239
fluorine-18 deoxyglucose 650
flutamide 559
focal cortical dysplasia 481
follicle-stimulating hormone (FSH) 445
foramen
– magnum meningioma 260
– of Luschka 456
– of Magendie 456, 464
Foster Kennedy syndrome 252
fronto-orbital meningioma 90
functional prognosis 632
fusiform neurofibroma 613

G

Gagel's granuloma 549
galenic venous system 211
gamma knife 199, 223
– radiosurgery 224, 226, 261, 427, 448
– surgery 176
ganglioblastoma 397, 398
gangliocytoma 17, 31, 171, 444
ganglioglioma 31, 107, 348, 394, 417, 444
– anaplastic 33, 397, 398
– cervicothoracic 399
– desmoplastic infantile 432
– low-grade 397
– neuroblastomatous 398
– occipital 395
– of the brainstem 399
– of the cerebral hemisphere 399
– of the spinal cord 399
– spinal 396
ganglioma 170
ganglion cyst 669, 676
ganglioneuroblastoma 472, 615
ganglioneurocytoma 34
ganglioneuroma 615
Gardner's syndrome 74, 569
gastrostomy 412, 654
gelastic epilepsy 444, 445
gemistocytic astrocytoma 106
germ cell tumor 55, 210, 214, 518, 578
– mixed type 56
germinoma 55, 210, 495, 518
– thalamic 369
GH, see growth hormone
GH-secreting
– adenoma 502
– tumor 500, 503
giant cell
– glioblastoma 5
– tumor 589, 647, 651
gliadel 137
– wafer 134
glial fibrillary acidic protein (GFAP) 13, 308, 347, 440, 457, 533
glial tumor 494
gliasite balloon 133, 134, 135
glioblastoma 12, 15, 19, 135, 140
– giant-cell 17
– MR spectroscopy 131
– multiforma (GBM) 128, 132, 688
– small-cell 18
– with oligodendroglial component 17, 24
glioma 281
– astrocytic 11, 12, 142
– bilateral thalamic 369
– cervicomedullary 422
– diffuse intrinsic pontine (DIPG) 408
– diffuse pontine 423
– fibrillary 131
– high-grade 495
– low-grade 368, 373, 444, 394
– mixed 21
– of the brainstem 416
– optic 20
– tectal 378, 423
gliomatosis cerebri 30, 143
glioneuronal
– hamartias 170
– neoplasm 32
– tumor 620, 623
– – with neurophil-like islands or rosetted glioneuronal tumor 65
gliosarcoma 17, 19, 438
Glivec 332
glomus
– jugulare 265
– – tumor 261
– tumor 264
– – embolization 267
– tympanicum 265
– – tumor 219, 261
glucocorticoid 693
Goldman perimetry 276, 439
gonadotroph adenoma 183
Gorlin syndrome 40, 58, 465
granular cell
– astrocytoma 66, 106
– tumor of the neurohypophysis 62
Grave's
– disease 275
– ophthalmopathy 271
gross total resection (GTR) 457, 488, 533
growth hormone 185,196
– antagonist 198

H

H. pylori infection 295
hamartin 334
hamartoma, hypothalamic 444
Hand-Schüller-Christian disease 54, 75, 548, 570
HCG-beta 209, 214
head trauma 251
hemangioblastoma 60, 151, 236, 337, 338, 604
– capillary 57
– intramedullary 624
– of the midbrain 380
– of the posterior fossa 237
– of the retina 237, 239
hemangioma 76, 569, 647, 651, 656
– capillary 280
hemangiopericytoma 50, 98, 283
hemianesthesia 129
hemianopsia 339
hemilaminectomy 601
hemiparesis 129, 432, 447, 450
hemorrhage 209, 456
hemostasis 433, 606
hepatic p450 system 690
Her2/Erbb2 9
high-grade glioma 495
histiocytic lesion 54
histiocytosis 75, 519
HIV infection 298
Hodgkin lymphoma 53
Hoffman's sign 648
Homer-Wright rosettes 474, 541
homovanillic acid 580
honeycomb appearance 22
Horner's syndrome 262, 612
hourglass schwannoma 42
hydrocephalus 30,60, 173, 208, 236, 370, 373, 378, 402, 406, 412, 524, 530, 604
– obstructive 212
hydrocortisone 184
hydroxyurea 221, 261

hygroma 379
hyperbaric oxygen 137
hypercortisolismus 202
hyperfractionation 410, 477
hyperglycemia 202
hypernatremia 450
hyperplasia, pituitary 62
hyperprolactinemia 191, 192
hyperthyroidism 200
hypertrichosis 614
hypoglobus 282
hypogonadism 182
hypopituitarism 184–196, 195, 514
hypothalamic hamartoma 444
hypothalamic-pituitary axis 548
hypothalamus 355
hypothyroidism 182

I

ifosfamide 526, 535
IGF1 197
immunohistochemistry 5
incidentaloma 186, 500
Indian file 39
infiltrating astrocytoma 104
infiltrative fibrillary astrocytoma 366
inflammatory lesion 626
infraorbital
– fissure 271
– foramen 271
infundibuloneurohypophysitis 520
intensity-modulated radiotherapy 148
interstitial
– brachytherapy 205
– irradiation 125
intrabulbar dissection 266, 267
intracavitary
– brachytherapy 135
– irradiation 511
intracranial
– germ cell tumor 518
– glioma 331
– meningioma 250
intradural spinal cord tumor 600
intramedullary
– hemangioblastoma 624
– lipoma 626
– metastases 625
– spinal tumor 604
intraneural metastases 682
intraoperative electrophysiology 630
intrathecal chemotherapy 297
iodine-125 120, 121
ionizing radiation 250
iridium-192 120
iris hamartoma 329
irradiation
– craniospinal 525, 535
– interstitial 125
– intracavitary 511
– pituitary 199

J

jugular fossa meningioma 260
juvenile
– nasopharyngeal angiofibroma 559
– pilocytic astrocytoma 281, 369, 402
– xanthogranuloma 55

K

Kadish stage 227
Karnofsky performance score 120, 136, 143
karyorrhexis 474
keratin staining 308
Ki-1 lymphoma 53
Klippel-Trenaunay-Weber syndrome 339
kyphoplasty 658, 659
kyphoscoliosis 579
kyphosis 608, 641, 649
– cervical 428

L

labyrinthectomy 259
lacrimal gland
– carcinoma 284
– masse 281
lagophthalmos 275
laminectomy 601, 606, 631, 639, 641, 656
– C1 562
– cervical 425
– osteoplastic 425
laminotomy 606, 631
– osteoplastic 426, 608
Langerhans cell histiocytosis (LCH) 54, 592, 548, 570
Langerhans granules 549
Langerhans-type histiocyte 75
lanreotide 198
lateral orbitotomy 287
Le Fort 1 osteotomy 557, 562
leptomeningeal
– blastomatosis 63
– carcinomatosis 63
– disease 143, 463
– melanocytosis 17
– venous angiomatosis 339
lesion
– histiocytic 54
– melanocytic 51
– of the cerebellopontine angle 219
Letterer-Siwe syndrome 570
Lhermitte-Duclos disease 60, 173
Li-Fraumeni syndrome 59, 128, 346, 466, 530
linear accelerator radiosurgery 224
lipoastrocytoma 66
lipoma 669, 677
– intramedullary 626
lipomatous medulloblastoma 160
liponeurocytoma, cerebellar 35
Lisch nodule 329
LOH on chromosome 22q 163
lomustine 111
low-grade
– astrocytoma 107, 112
– ganglioglioma 397
– glioma 346, 368, 373, 444, 494
– – total resection 110
lung cancer 305, 646
luteinizing hormone (LH) 445
lymphocyte leukemia 526
lymphoma 579

M

macroadenoma
– pituitary 183
macrocephaly 432
macroprolactinemia 192
magnetic
– resonance spectroscopy (MRS) 108
– source imaging (MSI) 108
magnetoencephalography 340
malignant
– astrocytoma 128
– melanoma 51
– neurofibroma 672

– peripheral nerve sheath tumor (MPNST) 218, 227, 614, 666
– – histologic variants 45
– – with rhabdomyoblastic dedifferentiation 680–
– schwannoma 672
– Triton tumor 45
mannitol 293
mastoidectomy 259, 561
maxillotomy 557, 654
maximum-tolerated dose 691
McCune-Albright syndrome 76
Meckel's cave meningioma 252, 258
medulloblastoma 14, 37, 160, 462, 472, 526,
– desmoplastic 160, 468
– large-cell (anaplastic) 39, 468
medulloepithelioma 40, 160
megalencephaly 173
Meibomian gland 285
melanocytic lesion 51
melanocytoma 51
melanocytosis, diffuse 51
melanoma 304
– malignant 51
– metastases 17
melanomatosis, meningeal 51
melanosis, neurocutaneous 51
melphalan 298
meningeal
– carcinomatosis 155
– melanomatosis 51
meningioma 15, 183, 221, 246, 250, 332, 486, 496, 559, 641
– anaplastic 85, 95
– atypical 85
– benign 46
– chemotherapy 93
– cranial nerves 218
– en plaque 46
– meningothelial 47
– of the middle cranial base 257
– of the posterior cranial base 258
– spinal 636, 637
– surgery 255
– variant 48
– WHO classification 47
meningiomatosis 642
meningitis 248
merlin 332
MERLIN/schwannomin expression 673
mesenchymal tissue tumor 248
metastases
– intramedullary 625
– intraneural 682
metastatic tumor 63, 594
methionine 480
methotrexate 295
methyl-prednisolone 299, 639
MIB1 positivity 9
microdialysis catheter 691
microgemistocyt 22
microgliomatosis 31
microlumina 457
micromultileaf collimator 240
microprolactinoma 192
microtubule-associated protein-2 432
microvilli 457
midbrain
– hemangioblastoma 380
– tumor 379
middle cranial base lesion in children 558
mifepristone 205, 261–
minigemistocyte 22, 106, 107
mixed neuronal-glial tumor 31
moesin-ezrin-radixin-like protein 673
molecular marker 11
monosomy 22 49
motexafin gadolinium 311
motor-evoked potential (MEP) 607, 640
moya moya syndrome 352, 357, 467
MR spectroscopy 130
mucin staining 308
mucosa-associated lymphoid tissue-type (MALT) lymphoma 53
multiple brain metastases 314
mutism 152
mydriasis 287
myelopathy, radiation-induced 627
myeloradiculopathy 329
myelotomy 426, 606
myxopapillary ependymoma 26, 162

N

N-acetyl aspartate 532
necropsy 445
Nelson's syndrome 203
neoplasm
– cerebral 128
– supratentorial 386
neoplastic neuroepithelium 41
nerve sheath tumor 600, 613, 637
– malignant peripheral 614
nestin 41
neuraxis 356
neurilemmoma 42, 283
neurinoma 42
neuroblastoma 284, 570, 579
– cerebral 472
– olfactory 557
neuroblastomatous ganglioglioma 398
neurocutaneous melanosis 51
neurocytoma 146
– atypical 35
– central 34
neuroendoscopy 153
neuroepithelial tumor 27
– of uncertain origin 29
neuroepithelium, neoplastic 41
neurofibroma 44, 283, 601, 603, 613, 666, 671, 675
– fusiform 613
– malignant 672
– plexiform 614
neurofibromatosis 227, 274, 278, 329, 486, 489, 600, 620, 643, 668
– type 1 58, 219, 329, 346, 454, 480, 612, 638, 673
– type 2 147, 226, 250, 332, 672, 673
– – tumor suppressor gene 83
neurofibromin 329, 354, 388, 672
neurogenic sarcoma 666, 670
neuroglial progenitor tumor 147
neuroma
– palisading encapsulated 676
– traumatic 677
neuronal neuronal-glial tumor 31
neuronavigation 372, 440, 481
neuron-specific B-tubulin 432
neurosurgery 340, 410
nevoid basal cell carcinoma syndrome (NBCCS) 465
nitrosourea 136, 142, 373
nongerminomatous germ cell tumor 495, 525
non-Hodgkin's B-cell lymphoma 294
Non-Langerhans cell histiocytosis 55
non-vestibular schwannoma 227
notochord 244
nucleo-cytoplasmic ratio 464, 473
nutritional status 653
nystagmus 419, 455

O

oat cell 656
obstructive hydrocephalus 212
occipital ganglioglioma 395
octreotide 198
– scintigraphy 253, 254
olfactory
– groove meningioma 90
– neuroblastoma 557
oligoastrocytoma 14, 19, 23, 105, 140, 347, 481
– anaplastic 24
oligodendrocyte 9
oligodendroglial tumor 140
oligodendroglioma 17, 19, 21, 105, 107, 347, 367, 620, 630
– anaplastic 22
– with neurocytic differentiation 65
oncocytoma 62
ophthalmology 496
optic
– chiasm 354, 512
– glioma 20, 354
– nerve
– – glioma 154, 218, 222
– – meningioma 281
– nerve sheath meningioma 92, 218
– pathway glioma 330
orbital
– cavity schwannoma 222
– cellulitis 277
– cyst 280
– exenteration 288
– fibrosarcoma 286
– hemorrhage 277
– lymphoma 278, 284
– metastases in adults 286
– myositis 274
– tumor 271
– wall 271
orbito-zygomatic craniotomy 447, 450
ossifying fibroma 569
osteoblastoma 75, 584, 587, 647, 651
osteogenic sarcoma 75, 570, 593
osteoid osteoma 75, 584, 586, 647,
osteoma 74, 283, 569
– calvarial 569
– osteoid 584, 586
osteoplastic
– laminoplasty 425
– laminotomy 426, 608
osteosarcoma 570, 580, 588, 648
– of the spine 593
osteotomy 560
– of the zygoma 258
oxygen, hyperbaric 137

P

p53 gene 388
Paget's disease 76, 77, 593
pale island 39
palisading encapsulated neuroma 676
Pallister-Hall syndrome 445
pancoast tumor 680, 681
panhypopituitarism 507, 511
papillary
– craniopharyngioma 61
– glioneural tumor 64, 170
– tumor of the pineal region 65
papilledema 307, 386, 416, 455
papilloma of the choroid plexus 28
paraganglioma 261
– jugulotympanic 35
– of the cauda equina 177
paranasal sinus mucocoele 280
paraplegia 177
paresthesia 129
Parinaud's syndrome 208, 211, 381, 492, 518
pediatric skull base tumor 556
pegvisomant 199
pericranium 256, 405, 426
perifocal edema 176
perineurioma 45, 614, 676
periorbita 272
peripheral nerve tumor (PNT) 612, 666
petroclival meningioma 92, 252, 253
petrosectomy 259, 560
phakomatose 329
phenobarbital 693
phenolization 589
phenytoin 693
pheochromocytoma 237
photon beam therapy 249
physaliferous cell 244, 247
pilocytic astrocytoma 20, 123, 124, 219,347, 349, 366, 403, 416, 422, 622
– juvenile 369, 420
– of the pulvinar 365
pilomyxoid astrocytoma 66, 347
pineal
– area 212
– cyst 492, 494
– germinoma 213
– gland 492
– parenchymal tumor 37
– – of intermediate differentiation (PPTID) 210
– region tumor 208
pineoblastoma 36, 208, 494
pineocyte 492
pineocytoma 209, 213, 494
pituicyte 63, 65
pituicytoma 65
pituitary
– adenoma 61, 171, 182, 184, 191, 197, 198, 203, 503,
– apoplexy 186
– carcinoma 62
– dysfunction 182
– hyperplasia 62
– irradiation 199
– macroadenoma 183
– tumor in children 500
placental alkaline phosphatase (PLAP) 56, 209
plain skull radiography 508
plasmacytoma 76, 647, 656
platinum 525
pleomorphic
– adenoma 281
– – of the left lacrimal gland 285
– xanthoastrocytoma 21, 348, 349, 387, 438
plexiform neurofibroma 283, 330, 331
plexus papilloma 146, 147
polymer wafer 133
polymethylmethacrylate 655, 658
polysomy 13
polyuro-polydipsic syndrome 507
pontomedullary tumor 620
pools of mucin 247
posterior fossa syndrome 316, 427, 454, 456, 467, 540
posterior inferior cerebellar artery (PICA) 464
postlaminectomy kyphosis 608
precocious puberty 450
preoperative embolization 88, 91
primary central nervous system lymphoma (PCNSL) 53, 292
primary lymphoma of peripheral nerve 680
primitive neuroectodermal tumor (PNET) 464, 472, 494, 579

procarbazine 111, 112, 136, 142, 358
progesterone 251
prolactin 62, 500
prolactinoma 191, 502, 503
– pregnancy 195
proptosis 273, 275, 277, 286, 356
prostate cancer 646
protein
– S-100 13
– truncation test 331
proton
– beam irradiation 225, 248
– radiation therapy (PRT) 427
– therapy 222
pseudoinclusion 47
pseudomonas exotoxin 390
pseudo-onion bulbs 45
pseudo-psammoma body 47
pseudorosette 25, 26
– astroblastic 29
pseudotumor 678
pterygopalatine fossa 285
Purkinje cell loss 550

Q

quinagolide 194, 198

R

radiation 111, 153
– ionizing 250
– necrosis 313
– neuritis 682
– retinopathy 221
– sensitizer 311
– toxicity 225
radiation-induced
– meningioma 250
– myelopathy 627
– PNT 682
– vasculopathy 359
radiculopathy 592
radioiodine thyroid ablation 201
radionecrosis 449, 511
radionuclide bone scanning 475
radiosurgery 92, 153, 163, 338
– stereotactic 419, 488, 512
– with gamma-knife 267
– with LINAC system 267
Rathke cleft 162
Rathke's pouch 61, 506
reactive
– astrocytosis 308
– lymphoid hyperplasia 284
recurrent tumor 299
relative afferent pupillary defect 276
renal cell carcinoma 241, 646
residual epilepsy 171
reticulin 51
retinal phakoma 335
retinoblastoma 37, 494
retinopathy radiation 221
retrobulbar dermoid cyst 280
retrochiasmatic
– craniopharyngioma 510
– tumor 507
retromastoid craniotomy 562
rhabdoid
– cell 49
– meningioma 255
– tumor 465, 496, 540
– – atypical 41
rhabdomyosarcoma 283, 523, 579
rhinorrhea 510
rhinotomy 557
rituximab 298
Rosai-Dorfmann disease 55
Rosenthal fibers 20, 403
rosette-forming glioneuronal tumor of the fourth ventricle 65

S

S-100 533
sarcoma
– neurogenic 666, 670
– osteogenic 570, 593
scalp flap 255, 256
Schiller-Duval body 55, 521, 522
schwann cell 42
schwannoma 218, 263, 333, 612, 613, 637, 639, 666, 671, 675
– Antoni A/B 42
– malignant 672
– of the cranial base 559
– of the Gasserian ganglion 558
– vestibular 489
schwannomatosis 42, 639, 643, 668, 673
– predisposition syndromes 666
schwannomin 332
sclerosis 586, 588
scoliosis 577, 586, 587, 590, 608, 649
scotoma 276
seizure 692
sella turcica 509
sex hormone 251
single brain metastases 314
single photon emission computed tomography (SPECT) 446
sino-orbital fistula 288
skeletal system 646
skull
– osteoma 74
– tumor 74
– – treatment 77
skull base 244
– meningioma 249
– surgery 266
– tumor in children 556
small cell tumor 578
Smith-Lemli syndrome 446
solitary fibrous tumor 50
somatosensory evoked potential (SEP) 266, 425, 640
somatostatin 502
– analogue 185, 198
– receptor 253
somnolence syndrome 313
sonic hedgehog signaling pathway 162
sphenoid
– sinus 502
– wing meningioma 283
sphenopetroclival meningioma 258
spinal
– column 646
– – tumor 584
– cord 636
– – compression 576, 577
– – dysfunction 422
– – tumor 396
– dural AV fistula 626, 629
– ganglioglioma 396
– hemangioblastoma 238
– intradural tumor 636
– meningioma 636, 637
– metastases 646
– neoplasm 646
spine configuration 424
squamous carcinoma 285
St. Jude's protocol 543
stalk effect 182, 500, 501
stem-cell
– rescue 476
– transplantation 298
stereotactic
– biopsy 109, 121, 134, 142, 292, 293, 371, 409
– fractionated radiation therapy 222, 225
– radiofrequency 448

– radiosurgery/radiotherapy 184, 195, 199, 205, 220, 240, 261, 312, 334, 335, 357, 380, 419, 488, 512
sternotomy 681
steroid 137, 551, 552
– hormone receptor 83
– synthesis inhibitor 205
stimulation mapping 109
stroke 447
Sturge-Weber syndrome (SWS) 339
subependymal
– giant cell 348
– – astrocytoma 57, 146
– nodule 336
subependymoma 25, 26, 162
suboccipital craniotomy 223, 260
subperiosteal space 272
sub-tenon's space 273
superficial cerebral astrocytoma (SCA) 432
superior orbital fissure 272
supraclavicular exposure 681
supratentorial
– craniotomy 475
– neoplasm 386
sustentacular cell 35
Sylvian fissure 510
synaptophysin 33, 34, 36, 39, 62, 433
syncytiotrophoblast 521
syndrome of inappropriate secretion of thyrotropin (SIST) 201
syringomyelia 173, 560, 626

T

tamoxifen 261, 689
tanycytic ependymoma 457
T-cell lymphoma 53
technetium-99 649
tectal glioma 378, 423
temozolomide 112, 113, 135, 136, 142, 317, 358, 373, 389, 440
temporal lobe lesion 128
teratoid tumor 465, 496
– atypical 41
teratoma 208, 214, 495, 518, 519, 522, 63,
– immature 56
– with malignant transformation 56
testosterone 185, 559
tetracycline 586
tetraplegia 589
thalamic
– germinoma 369
– tumor 364
thalamo-peduncular tumor 366, 367
thalamus 364
thallium 480
thioguanine 358
thoracotomy 654, 681
three-dimensional conformal radiotherapy technology 248
thromboembolic disease 693
thyroid function 501
thyroidectomy 201
thyrotroph adenoma 200
thyrotropin-releasing hormone (TRH) 200
thyroxine 501
tinea capitis 682
Tinel's sign 612, 666
torticollis 586, 604
TP53 tumor suppressor 13
tracheostomy 412
transcranial
– stimulation 425
– surgery 204
transependymal edema 463
transsphenoidal
– adenomectomy 502
– surgery 184, 198, 203, 501
transthyretin 533
traumatic neuroma 677
trigeminal
– neuropathy 224
– schwannoma 218, 220
trisomy 13
tuber cinereum 509
tuberculum sellae meningioma 256
tuberous sclerosis 146, 346
– complex 58, 334
tumor
– aggressiveness 649
– anaplasia 459
– astrocytic 11, 208
– bilateral thalamic 367
– calvarial 568
– cervicomedullary 620
– choroid plexus 26
– cysts 396
– dermoid 568
– dorsally exophytic 423
– dysembryoplastic neuroectodermal/ neuroepithelial 480
– embryonal 37, 66
– ependymal 25
– epidermoid 568
– germ cell 55, 518, 578
– – intracranial 518
– GH-secreting 500, 503
– giant cell 589
– glial 494
– glioneuronal 620, 623
– in the basiocciput 245
– intramedullary spinal 604
– location 314
– meningeal 46
– mesenchymal 50
– metastatic 63, 594
– neuroepithelial 27
– non-meningothelial 50
– of neural origin 615
– of the brainstem 378, 408
– of the central nervous system 386
– of the choroid plexus 530
– of the cranial nerve 218
– of the hematopoietic system 53
– of the lymphoid system 53
– of the midbrain 379
– of the nervous system 6, 10
– of the neuraxis 332
– of the posterior cranial base in children 560
– of the sellar region 61
– of the skull base in children 556
– of the spinal column 584
– of the spinal cord 396
– – intradural 600
– of the spine 576
– oligodendroglial 13, 21
– or the syrinx 236
– pineal parenchymal 37
– pituitary, in children 500
– pontomedullary 620
– primitive neuroectodermal (PNET) 464, 472, 494
– recurrence 299, 513
– response 690
– retrochiasmatic 507
– rhabdoid 465, 496, 540
– small cell 578
– solitary fibrous 50
– spinal intradural 636
– suppressor gene HIC-1 164
– teratoid 465, 496
– thalamic 364
– thalamo-peduncular 366, 367
– volumetry 224
– within the jugular fossa 264

– yolk sac 523
Turcot's syndrome 40, 59, 128, 466
tyrosine hydroxylase 186, 503

U

uveal malignant melanoma 286

V

vaccine 692
valsalva manoeuvre 275
vanillylmandelic acid 580
vascular endothelial growth factor (VEGF) 236
vascular lesion 496
vasomotor amine syndrome 177
vasopressin 550
VEGF 236
ventricular
– drain 524, 542
– meningioma 146, 150
ventriculocisternostomy 149
ventriculoperitoneal shunt 458, 524, 534
ventriculostomy 152, 403, 404, 425, 466, 542
Verocay body 42, 639
vertebral collapse 549
vertebrectomy 654, 655
vertebroplasty 658
vestibular schwannoma 218, 222, 334, 489
vigabatrin 337
villous hypertrophy 532
vimentin 28, 30, 41, 49, 541
vinblastine 359, 552
vinca-alkaloid 297
vincristine 111–113, 142, 296, 351, 358, 373, 405, 419, 427, 440
Virchow, Rudolph 5
visual loss 507
von Hippel-Lindau disease (VHL) 36, 58, 60, 236, 337, 620, 625
– gene mutation 239
– protein 236
von Recklinghausen's disease 638

W

Weinstein-Boriani-Biagini staging system 585, 652
Wernicke's area 109
WHO
– classification 5, 6
– grading 10
whole-brain radiation therapy (WBRT) 295, 309
winking owl sign 649

X

xanthoastrocytoma 19
– pleomorphic 21, 387, 438
xanthogranuloma
– juvenile 55
– of the choroid plexus 54
xanthoma disseminatum 55

Y

yolk sac tumor 55, 523

Z

Zellballen 35
zona occludens 457