P. Imbach · Th. Kühne · R. Arceci
Editors

Pediatric Oncology

A Comprehensive Guide

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In Collaberation with
A. Di Gallo, F. Oeschger-Schürch and C. Verdan

Springer

Professor Dr. Paul Imbach
University Children's Hospital Basel
Department of Pediatric Oncology/Hematology
Römergasse 8, CH-4005 Basel
Switzerland

Dr. Thomas Kühne
University Children's Hospital Basel
Department of Pediatric Oncology/Hematology
Römergasse 8, CH-4005 Basel
Switzerland

Robert J. Arceci
Sidney Kimmel Comprehensive Cancer Center
at John Hopkins
1650 Orleans Street
Baltimore, MD 21231, USA

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Foreword

Hardly any field of pediatrics reflects the medical advances of the past three decades as dramatically as pediatric oncology. Thirty years ago, when I began my pediatric training, three quarters of all children with malignancies died of their disease. Today the same proportion are healed. Three reasons for this can be delineated. First, therapy optimization studies have led to constant improvement through adaptation of treatment to individual cases. Second, new drugs, new combinations and new dosages have been developed and tolerance to therapy has been improved by supportive measures. Finally, molecular biological research has increased our fundamental understanding. We now broadly know what molecular mechanisms cause malignant growth and use this knowledge in therapeutic decision-making. We cannot yet – with certain exceptions – intervene specifically in the aberrant regulation of malignant growth, but the foundations have been laid.

Pediatric oncology is rightly viewed as a clinical and scientific subspecialty of pediatrics. This does not mean it need not interest the general pediatrician or specialists in other areas of pediatrics. On the contrary: in the early stages of a malignant disease the symptoms are often nonspecific. Although one may primarily suspect a tumor or leukemia, other diseases cannot be excluded. Conversely the vague general symptoms that can be caused by a malignancy may lead to misinterpretation. Furthermore, a whole team is required to care for the patients: pediatricians, pediatric or specialist surgeons, specialized nurses, psychologists, social workers and pastoral advisors. Pediatric oncology is holistic, integrated medicine in the true sense of the word. And with regard to medical training, nowhere in pediatrics can one gain a closer experience with treatment of infections and other particular topics than in pediatric oncology. Oncology has an undisputed place in the training of every pediatrician. Equally, comprehensive general pediatric training is important for every future specialist.

There are a number of excellent, exhaustive textbooks on oncology that are indispensable in training. However, there is also a need for a compact guide offering rapid orientation in the situations encountered by all who work in pediatric oncology. Precisely that is provided by this book by Paul Imbach, Thomas Kühne and Robert Arceci. I wish them the success they deserve.

Berlin, June 2005

Gerhard Gaedicke
Charité Campus Virchow-Klinikum
Berlin

Preface

The healing process in children and adolescents with oncological diseases depends greatly on the knowledge and experience of all those involved in the patients' care: physicians, specialist nurses, psychooncologists and others. This last group embraces parents, siblings and teachers as well as laboratory staff, physiotherapists, pastoral advisors, social workers and other hospital personnel. Increasingly, the patients' general practitioners and pediatricians and external nurses are also becoming involved. Knowledge and experience on the part of the carers are necessary for full information of the patient, who is thus enabled to play a full part in his or her own healthcare: the power of the informed patient. Whether a young patient is waiting for the diagnosis, undergoing intensive therapy, or suffering a complication or setback, whether he/she knows that the disease has almost certainly been healed or that it is progressing with early death as the probable consequence – in every situation, full information is the basis of optimal care.

This book was written to improve the fundamental dissemination of knowledge. It has no pretensions to replace the standard textbooks and the learned journals on pediatric oncology.

In this new edition contributions by specialist nurses and a child psychiatrist and psychooncologist considerably improve the all-round coverage. The remaining chapters systematically describe the various disease groups. Some of these chapters, together with a new chapter on emergencies in pediatric oncology, were written by Thomas Kühne, for many years my trusted colleague. Robert Arceci of Johns Hopkins, Baltimore, editor-in-chief of "*Pediatric Blood and Cancer*," brought his vast experience to bear on the English translation.

My heartfelt thanks go to all of the contributing authors, to Erika Scheibli for dedicated secretarial and organizational assistance and to the responsible staff at Springer Heidelberg for their commitment to this project.

May this book help to create an atmosphere of trust, hope and joy in the face of potentially life-threatening disease.

Basel, June 2005 **Paul Imbach**

Contents

Contributing Authors

Paul Imbach
(e-mail: paul.imbach@unibas.ch)
Department of Pediatric Oncology/Hematology
University Children's Hospital (UKBB)
CH-4005 Basel, Switzerland

Thomas Kühne
(e-mail: thomas.kuehne@ukbb.ch)
Department of Pediatric Oncology/Hematology
University Children's Hospital (UKBB)
CH-4005 Basel, Switzerland

Robert J. Arceci
(e-mail: arceci@jhmi.edu)
Sidney Kimmel Comprehensive Cancer Center
John Hopkins
1650 Orleans Street
Baltimore, MD 21231, USA

Alain Di Gallo
(e-mail: alain.digallo@upkbs.ch)
Department of Psycho-oncology
University Children's Hospital (UKBB)
CH-4005 Basel, Switzerland

Franziska Oeschger-Schürch
(e-mail: franziska.oeschger@ksa.ch)
STL 910
Children's Hospital KSA
CH-5001 Aarau, Switzerland

Christine Verdan
(e-mail: christine.verdan@ksa.ch)
STL 910
Children's Hospital KSA
CH-5001 Aarau, Switzerland

Abbreviations

aCML	atypical chronic myeloid leukemia
ADH	antidiuretic hormone
AFP	α-fetoprotein
ALCL	anaplastic large cell lymphoma
ALL	acute lymphoblastic leukemia
ALPS	autoimmune lymphoproliferative syndrome
AMCL	acute monocytic leukemia
AMKL	acute megakaryocytic leukemia
AML	acute myelogenous leukemia
AMML	acute myelomonocytic leukemia
ANAE	a-naphthyl acetate esterase
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
β-HCG	β-choriogonadotropin
BL	Burkitt lymphoma
BLL	Burkitt-like lymphoma
BWS	Beckwith–Wiedemann syndrome
CD	cluster determination
CEL	chronic eosinophilic leukemia
CML	chronic myelogenous leukemia
CMML	chronic myelomonocytic leukemia
CNL	chronic neutrophilic leukemia
CNS	central nervous system
CT	computed tomography
CVID	common variable immune deficiency
DI	DNA index
DIC	disseminated intravascular coagulation
DNA	deoxynuclein acid
EBV	Epstein–Barr virus
EFS	event-free survival
EFT	Ewing family of tumors
EM	electron microscopy
ES	Ewing sarcoma
ET	essential thrombocythemia
FAB	French-American-British
FACS	fluorescence-activated cell sorting
FEL	familial erythrophagocytic lymphohistiocytosis
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
GVL	graft vs leukemia
Gy	Gray, dose unit of irridiation
HD	Hodgkin disease
HGA	high-grade astrocytoma
HIV	human immunodeficiency virus
HVA	homovanillic acid
IAHS	infection-associated hemophagocytic syndrome
ITP	idiopathic thrombocytopenic purpura
JMML	juvenile myelomonoytic leukemia
LBCL	large B-cell lymphoma
LCH	Langerhans cell histiocytosis
LDH	lactate dehydrogenase
LGA	low-grade astrocytoma
LI	label index
LL	lymphoblastic lymphoma
LOH	loss of heterozygosity
MDS	myelodysplastic syndrome
MH	malignant histiocytoma
MHPG	3-methoxy-4-hydroxyphenylglycol
MIBG	methylisobenzyl guanidinium
MLL	mixed-lineage leukemia
MPS	myeloproliferative syndrome
MRD	minimal residual disease
MRI	magnet resonance imaging
NDD	neurodegenerative disease
NHL	non-Hodgkin lymphoma
NSA	neuron-specific enolase

PAC	Port-a-Cath
PAS	periodic acid Schiff
PCR	polymerase chain reaction
PET	positron-emission tomography
PNET	primitive neuroectodermal tumor
PV	polycythemia vera
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RAEB-T	refractory anemia with excess blasts in transition
RARS	refractory anemia with ringed sideroblasts
RS	Reed–Sternberg cell
SCID	severe combined immune deficiency
SCT	hematopoietic stem-cell transplantation
TdT	terminal deoxynucleotidyl transferase
TMS	transient myeloproliferative syndrome
VIP	vasoactive intestinal polypeptide
VMA	vanillylmandelic acid
VOD	veno-occlusive disease
WBC	white blood cell
WHO	World Health Organization
WT	Wilms tumor

Introduction

Incidence and Management of Childhood Cancer

Every year 130–140 children per million under the age of 16 years, or around 1 out of 500 children, are diagnosed with childhood cancer. The incidence within the first 5 years of life is twice as high as from 6 to 15 years of age.

Survival probability has considerably changed within the past 30 years. Clinical research by cooperating groups of pediatric oncology centers has progressively increased the long-term survival rate from <20% before 1975 to >70% in the new millennium.

International cooperation contributes to quality assurance, because the majority of children with an oncologic disease are treated according to standard protocols. Reference centers therefore fulfill the important function of controlling, providing a second opinion and assessing the data of each child periodically.

Table 1 shows the average frequency of the different forms of pediatric neoplasia, based on international data.

Overview of the frequency distribution of tumors in children and the incidence per year for children between 0 and 16 years of age

	Proportion of total (%)	Incidence per year and per 1 million children	Cumulative incidence per million children <16 years
Acute lymphoblastic leukemia	28	38	604
Acute myeloblastic leukemia	5	7	108
Myelodysplastic/ myeloproliferative syndrome	2	3	44
Non-Hodgkin's lymphoma	5	7	108
Hodgkin's lymphoma	5	7	108
Langerhans' cell histiocytosis	3	4	65
Brain tumors	19	26	410
Retinoblastoma	2	3	44
Neuroblastoma	8	11	172
Kidney tumor (Wilms' tumor)	6	8	129
Soft tissue tumors	6	8	129
Osteogenic sarcoma	3	4	65
Ewing's sarcoma	2.5	3.5	54
Germ cell tumors	2.5	3.5	54
Liver tumors	1	1.4	22
Rare tumors	2	3	44

While in adults about 80% of cancerous diseases pertain to the respiratory, gastrointestinal and reproductive organs, only <5% of cancerous diseases of children are manifested in these organs. Furthermore, the histopathology of pediatric neoplasia differs markedly from that of adults: in children embryonal and immature cells can be found at very different stages of development which perpetually proliferate and rarely mature.

The variability within a particular childhood neoplasia and in the prognosis is high. Diagnosis and therapy must be adjusted to the individual child according to the clinical manifestation and the extent of the tumor.

Treatment normally requires 1–3 years, followed by check-ups for the following 3–7 years. The child newly diagnosed with cancer is critically ill during the first 2–6 months; after that his or her life continues similar to that of a healthy child, except that periodical treatment adjustment and check-ups are necessary. The initial treatment is carried out alternating between hospital care and care at home, the latter including the general practitioner and pediatrician as well as external nursing under the guidance of a pediatric cancer center.

Children with relapse need special attention and care. Particularly intensive treatments, such as stem cell transplantation or experimental therapies, yield hope. Last but not least, a child with a short life expectancy deserves high-quality palliative care by experienced professionals of the pediatric cancer team.

Management may be divided as follows:
- Guidance/information of child and parents
- Therapy of complications and side effects (Chaps. 18 and 19)
- Specific therapy of the underlying disease, divided into induction of remission, consolidation and maintenance

After confirmation of the diagnosis, an open discussion of all aspects between the parents and the responsible physician should assure the following points:
- Close cooperation of child and family with the oncology team
- Explanation of diagnosis, prognosis, disease course, and treatment plan
- Stepwise orientation of therapy, including effect, side effects, and complications
- Emphasis of the aim to enable the child to lead as normal a life as possible
- To show critical openness in favor of the sick child if paramedical attendance or a second opinion is desired
- To determine how the information should be communicated to the young patient: in age-appropriate fashion, honestly, openly, in simple terms, and without frightening words; the child will want to hear the plan for the next days and weeks, look forward to the next festivity (birthday, Christmas, vacation); long-term prognosis are mainly of interest to the parents and other family members

For more guidance on how to deal with the patient, parents and siblings: see Chap. 20.

General Aspects of Childhood Leukemia

Paul Imbach

Definition and General Characteristics

- Uncontrolled proliferation of immature white blood cells with a different immunological subtype which is lethal within 1–6 months without treatment
- The disorder starts in the bone marrow, where normal blood cells are replaced by leukemic cells
- Morphological, immunological, cytogenetic, biochemical, and molecular genetic factors characterize the subtypes with various responses to treatment

Abbreviations

- ALL: acute lymphoblastic leukemia (Chap 2)
- AML: acute myelogenous leukemia (Chap 3)
- CML: chronic myelogenous leukemia (Chap 4)

Incidence

- Thirty-three percent of all cancers in children are leukemias
- Annually 45 of each million children less than 16 years of age are newly diagnosed as having leukemia
- Incidence peak at 2–5 years
- Occurrence in all age groups during childhood, grouped by type of leukemia:
  - 75% acute lymphoblastic leukemia
  - 20% acute myelogenous leukemia
  - 5% undifferentiated acute leukemia and chronic myelogenous leukemia

Etiology and Predisposing Factors

- The cause of human leukemia is unknown
- Predisposing factors in the pathogenesis of leukemia and other malignant disorders in childhood are described in the section Pathogenesis
- There is a 2–4 times higher incidence of leukemia in siblings than in children in the general population aged 0–15 years (1:720–1,000)
- In a monocytic twin there is an increased risk of leukemia within months after the co-twin develops leukemia

Genetics

- Higher risk in the following congenital disorders:
  - Trisomy 21 (14 times higher)
  - Other trisomies

- Turner syndrome
- Klinefelter syndrome
- Monosomy 7
- Neurofibromatosis type 1 (von Recklinghausen disease)
- Fanconi anemia (high fragility of chromosomes)
- Bloom syndrome
- Kostmann syndrome
- Shwachman–Diamond syndrome (dysfunction of bone marrow and exocrine pancreatic insufficiency)
- Poland syndrome (absence of pectoralis major muscle and variable ipsilateral upper-extremity defects)
- Rubinstein–Taybi syndrome
- Congenital agammaglobulinemia
- Ataxia-telangiectasia (highly fragile chromosomes)
- Wiskott–Aldrich syndrome

Ionizing Radiation

Atomic bomb survivors (from Hiroshima and Nagasaki) developed leukemia with an incidence of 1:60 within a radius of 1,000 m of the epicenter occurring after 1–2 years (peak incidence after 4–8 years). There was a predominance of ALL in children and of AML in adults, which may reflect the different pathogenesis in the various age groups.

Chemicals and Drugs

- Benzene (related to AML)
- Chloramphenicol (usually related to ALL)
- Chemical warfare agent, i.e. nitrogen-Lost (related to AML)
- Cytotoxic agents; e.g. correlation between alkylating agents and Hodgkin disease and other malignancies – especially after irradiation there is a higher incidence of leukemia, ovarian carcinoma, and other solid tumors

Infection

- Correlation between viruses and development of leukemia has been observed, especially after RNA virus infection in mice, cats, chicken, and cows
- Human T-cell leukemia virus (HTLV) has been demonstrated in adults to be linked to T-cell lymphoma in some geographical areas
- Association between Epstein–Barr virus (EBV) and occurrence of Burkitt lymphoma
- Human immunodeficiency virus (HIV): HIV infection and/or immunodeficiency causes a higher incidence of malignancy
- In humans vertical or horizontal transmission of human leukemia has not been demonstrated except in rare cases of a mother with leukemia to her newborn or in identical twins with prenatal leukemia

Immunodeficiency

There is correlation between immunodeficiency and development of leukemias (i.e. congenital hypogammaglobulinemia, Wiskott-Aldrich syndrome, HIV infection)

Socioeconomic Situation

- Higher incidence of neoplasia in higher socioeconomic groups
- Similar frequencies in urban and nonurban areas: no correlation between different nutritional conditions

Pathogenesis

The etiology and/or predisposition (see above) indicates a correlation between leukemogenesis and different risk factors:

- Higher instability/fragility of chromosomes
- Deficiency of the immune response cascade
- Certain exposures (ionizing radiation, chemicals, viruses)

The leukemic cell is pathophysiologically characterized by a certain degree of differentiation during hematopoiesis (see Fig. 1.1.)

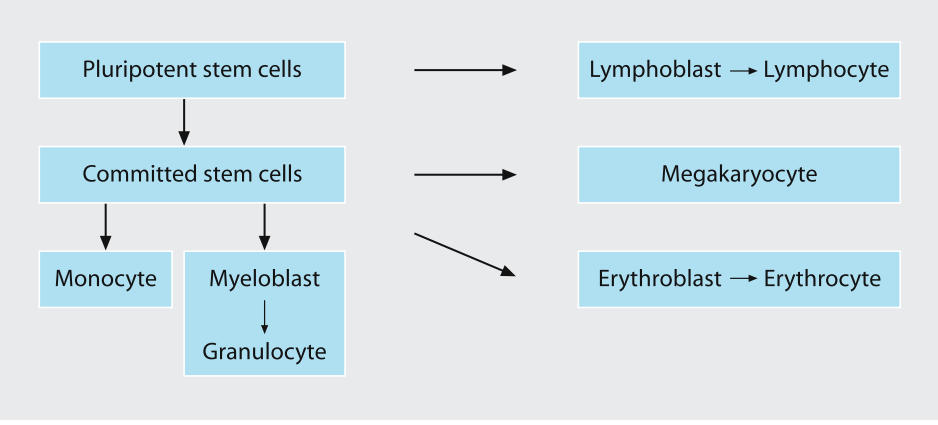

Fig. 1.1 Differentiation during hematopoiesis

Molecular Pathogenesis

- Cytogenetic alterations of genes coding for immunoglobulin and T-lymphocyte receptors, or various transcription factors:
  - Chromosomal deletions, mutations or chemical alterations (i.e. methylation) of DNA may lead to inactivation of the tumor suppressor gene (i.e. p53) or activation of the oncogene
  - Molecular products may disturb normal apoptosis (programmed cell death) mechanisms, such as the Bcl-2 pathway

Minimal Residual Disease

Molecular detection techniques (polymerase chain reaction PCR; fluorescence-activated cell sorting FACS) detect leukemic cells with chromosomal alterations, clonal antigen receptors, or immunoglobulin rearrangements at the level of 1 leukemic cell to 10^4–10^5 normal cells. An early disappearance of minimal residual disease during treatment seems to be correlated with a good prognosis

Acute Lymphoblastic Leukemia

Paul Imbach

Incidence

- Eighty percent of children with leukemia have acute lymphoblastic leukemia (ALL)
- Thirty-eight children in 1 million are newly diagnosed with ALL annually
- Girl-to-boy ratio is 1:1.2
- Peak incidence 2–5 years
- Incidence in white children is twice as high as in nonwhite children

Clinical Manifestation

General Aspects

- The history and symptoms reflect the degree of bone marrow infiltration by leukemic cells and the extramedullary involvement of the disease
- The duration of symptoms is days to several weeks, occasionally several months
- Sometimes diagnosis in an asymptomatic child results from an incidental finding in a blood cell count
- Often low-grade fever, signs of infection, fatigue, bleeding (i.e. epistaxes, petechiae), pallor

Summary of characteristics and symptoms of 724 children with ALL by CCSG Children's Cancer Study Group

Age (years)	**%**
<1	6
1–3	18
3–10	54
>10	22
Gender, ethnic distribution	**%**
Boys	57
Girls	43
White children	59
Nonwhite children	41

Reference

Children's Cancer Study Group (1982) Acute lymphoblastic leukemia. In: Teppi CK (ed) Major topics in pediatric and adolescent oncology. Hall, Boston, pp 3–42

General symptoms	%
Fever	61
Bleeding	48
Bone Pain	23
Lymphadenopathy	**%**
None	50
Moderate	43
Extended	7
Splenomegaly	**%**
None	37
Moderate	49
Extended	14
Hepatosplenomegaly	**%**
None	32
Moderate	55
Extended	13
Mediastinal enlargement	**%**
	7

- The symptoms depend on the degree of cytopenia:
  - Anemia: pallor, fatigue, tachycardia, dyspnea and occasionally cardiovascular decompensation
  - Leukopenia (normal functional cells): low to marked temperature elevation, infections
  - Thrombocytopenia: petechiae, mucosal bleeding, epistaxes, prolonged menstrual bleeding

Specific Signs and Symptoms

Skin

Besides signs of bleeding in neonatal leukemia maculopapular skin infiltration often of a deep red color (leukemia cutis) can be observed; more common in acute myeloblastic leukemia.

Central nervous system

- At time of diagnosis less than 5% of patients have CNS leukemia with meningeal signs and symptoms: morning headache, vomiting, papilla edema, or focal neurological signs such as cranial nerve palsies, hemiparesis, convulsion

- Diagnosis by analysis of cerebrospinal fluid: CNS I: no lymphoblasts; CNS II: less than 5 cells/cm^3, but with leukemic blasts on centrifugation; CNS III: at least 5 cells/cm^3, with leukemic blasts on centrifugation or cranial nerve palsy

Eye
- Bleeding due to high white blood cell count (WBC) and/or thrombocytopenia
- Retinal: infiltration of local vessels, bleeding

Ear, nose, and throat
- Lymph node infiltration, isolated or multiple
- Mikulicz syndrome: infiltration of salivary glands and/or tear glands

Cardiac involvement
- Leukemic infiltration or hemorrhage. In anemic patients there may be cardiac enlargement
- Occasionally cardiac tamponade due to pericardial infiltration
- Tachycardia, low blood pressure and other signs of cardiac insufficiency

Mediastinum
- Enlargement due to leukemic infiltration by lymph nodes and/or thymus
- May cause life-threatening superior vena cava syndrome (especially in T-cell ALL)

Pleura/and pericardium
- Pleural and/or pericardial effusion

Gastrointestinal involvement
- Often moderate to marked hepato- and/or splenomegaly
- Often kidney enlargement of one or both sides
- Gastrointestinal leukemic infiltration is frequent, but mostly asymptomatic
- Perirectal infection with ulceration, pain, and febrile episodes

Testicular involvement
- Seldom apparent at diagnosis; during treatment period and follow-up less than 5%
- Before 1980 frequency between 10 and 23%
- Enlargement of one or both testes without pain; hard consistency

Penis
- Occasionally priapism in association with elevated WBC causing leukemic involvement of sacral nerve roots and/or mechanical obstruction

Bone and joint involvement
- Bone pain initially present in 25% of patients
- Bone or joint pain, sometimes with swelling and tenderness due to leukemic infiltration of the periosteum. Differential diagnosis: rheumatic fever or rheumatoid arthritis
- Radiological changes: diffuse demineralization, osteolysis, transverse metaphyseal lucency, increased subperiosteal markings, hemorrhage or new bone formation

Laboratory Findings and Classification

Hematology

Red cells

- The level of hemoglobin may be normal, but more often moderate and sometimes markedly low
- Low number of reticulocytes

White blood cell count

- Number of white blood cells can be normal, low or high
- In children with leukopenia, few or no atypical lymphoblasts are detected
- In children with a high WBC leukemic blast cells are present
- In children with a high WBC (more than 100×10^9 white blood cells/l) the lymphoblasts are predominant (together with marked visceromegaly)

Platelets

- The platelet count is usually low: in 50% of children less than 50×10^9/l
- Spontaneous hemorrhage appears in children with less than $20–30\times10^9$ platelets/l, especially during febrile episodes

Overview of blood cell counts

		%
Hemoglobin (g/dl)	<7	43
	7–11	45
	>11	12
White blood cell count ($x10^9$/l)	<10	53
	10–49	30
	>50	17
Platelets ($x10^9$/l)	<20	28
	20–99	47
	>100	25

Coagulopathy

- In children with hyperleukocytosis
- More common in children with acute myelogenous leukemia (AML)
- Low levels of prothrombin, fibrinogen, factors V, IX, and X may be present

Serum Chemistry

- The serum uric acid level is often high initially and during the first period of treatment (hyperuricemia)
- The serum potassium level may be high in patients with massive cell lysis (often together with hyperuricemia)
- The serum potassium level may be low in patients with malnutrition or renal tubular loss
- Serum hypocalcemia may occur in patients with renal insufficiency or due to calcium binding to phosphate released by leukemic cells. Symptoms: hyperventilation, nausea, confusion, carpopedal spasms, convulsions, nausea, vomiting
- Serum hypercalcemia in patients with marked leukemic bone infiltration
- Abnormal liver function may be due to liver infiltration by leukemic cells or as a side effect of treatment. Increased level of transaminases with/without hyperbilirubinemia in patients with hepatomegaly. Differential diagnosis: viral hepatitis
- Serum immunoglobulin levels: in 20% of children with ALL low serum IgG and IgM levels

Bone Marrow Analysis

- Bone marrow analysis serves to characterize the blast cells and to determine the degree of reduction of normal erythro-, myelo-, and thrombopoiesis, as well as of hyper- or hypocellularity
- Morphological, immunological, biochemical, and cytogenetic analyses are required
- Differential diagnosis: aplastic anemia and myelodysplastic syndrome
- Usually the marrow is hypercellular with uniform morphology; megakaryocytes are usually absent

Leukemic Cell Characterization and Classification

Morphology

- Leukemic cells are characterized by a lack of differentiation, by a nucleus with diffuse chromatin structure, with one or more nucleoli, and by basophilic cytoplasm
- Differentiation between myeloid and lymphoid cells may be difficult. Criteria include:
  - Cell size: larger in myeloblasts
  - Chromatin structure of nucleus: heterogeneous in myeloblasts, homogeneous/and/or fine in lymphoblasts
  - Nucleoli: at least two in myeloblasts
  - Ratio between nucleus and cytoplasm: markedly higher in lymphoblasts
  - Cytoplasm: in lymphoblasts blue and usually homogeneous (sometimes with vacuoles); in myeloblasts granular and sometimes with Auer rods, particularly in acute promyelocytic leukemia

French-American-British (FAB) classification of lymphoblasts

L1 85% of children with ALL

- Cell size: small cells predominate
- Nuclear chromatin: usually homogeneous
- Nuclear shape: oval, almost fills cell
- Nucleoli: Normal; occasionally clefted or indented
- Cytoplasm: Scanty
- Basophilia of cytoplasm: very few
- Cytoplasmic vacuolation: variable

L2 14% of children with ALL

- Variable in size
- Nuclear chromatin: variable, heterogeneous
- Nuclear shape: irregular clefting, indentation common
- Nucleoli: one or more present, often large
- Cytoplasm: variable, often moderately abundant
- Basophilia of cytoplasm: variable, sometimes deep
- Cytoplasmic vacuolation: variable

L3 1% of children with ALL

- Large homogeneous cells
- Nuclear chromatin: finely stippled and homogeneous
- Nuclear shape: normal, i.e. oval to round
- Nucleoli: prominent, one or more
- Cytoplasm: moderately abundant
- Basophilia of cytoplasm: very deep
- Cytoplasmic vacuolation: often prominent

Cytochemistry

- Peroxidase: positive results in myeloblasts with cytoplasmic granules
- Esterase (a-naphthyl acetate esterase, ANAE): used in identification of mono- or histiocytic elements

- Leukocyte alkaline phosphatase: low or no activity in granulocytes of CML
- Periodic acid Schiff (PAS): most circulating leukocytes are PAS-positive. PAS is strongly positive in lymphoblasts, especially in T-cell lymphoblasts
- Sudan black is usually positive in myeloid cells/especially immature cells

Cytochemical reactions

	Lymphoblasts	Myeloblasts
Peroxidase	—	+
Sudan black	—	+
Periodic acid-Schiff	++	±
Esterase	—	± [b]
Terminal deoxynucleotidyl transferase	+ [a]	—

[a] Often negative in L3 morphology; [b] Also may be positive in acute monocytic leukemia

Immunological Characterization

- Monoclonal antibodies to leukemia-associated antigens differentiate between types of leukemic cells
- Subtypes of clonal cell populations with malignant transformation in different maturational stages can be identified by fluorescence-activated cell-sorting (FACS) analysis

Immunological characteristics

Lymphoid stem cells [a]	Early pre-B cells	Pre-B cells	B-precursor cells in ALL
CD19	CD19	CD19	CD19
HLA-DR	HLA-DR	HLA-DR	HLA-DR
CD24±	CD24	CD24	CD24
		CD10	CD10
		CD20±	CD20

[a] Also called "pro-B ALL"

T-precursor cells			
Lymphoid stem cells [a]	**Early pre-T cells**	**Thymic T-cells/ pre-T cells**	**Mature T cells**
CD7	CD7	CD7	CD7
	CD2±	CD2	CD2
		CD1	CD3
		CD4±	CD4 or CD8
		CD8±	

[a] Also called "pro-T ALL"

Clinical importance of immunological characterization:

- Eighty-five percent of children with common ALL (usually pre-B-cell ALL) are HLA-DR- and CD10-positive, which indicates a good prognosis
- Children with T-cell ALL are characterized by: older age (peak at 8 years of age), with a ratio of boys to girls of 4:1; high initial leukocyte count, mediastinal enlargement, high proliferation rate and/or frequent extramedullary manifestation (initially and at relapse)
- In ALL relapse the immunological phenotype is usually the same as at initial diagnosis

Biochemical Characterization

Some cellular enzymes provide further diagnostic differentiation between ALL and AML.

Terminal deoxynucleotidyl transferase

- TdT DNA synthesis enzyme
- Activity in all circulating ALL cells with the exception of mature B-cell ALL
- Terminal deoxynucleotidyl transferase (TdT) is absent in normal lymphocytes

5-Nucleotidase

- Decreased level of 5-nucleotidase in T lymphoblasts in comparison with pre-B-cell ALL lymphoblasts

Glucocorticoid receptors

- Lower levels of glucocorticoid receptors of T-cell ALL compared with B-precursor ALL

Overview of biochemical and clinical characteristics

	Pre-B-cell ALL	T-Cell ALL	B-cell ALL
TdT	+	+++	+
5-Nucleotidase	++		++
Glucocorticoid receptor	++	+	+
Initial white blood cell count	Low	High	Low or high
Extramedullary leukemia	+	+++	
Ratio of males to females	Equal	4:1	
Peak age (years)	4	9–12	Not known
Organomegaly	++	++++	
Percentage of cases	80	15	1–3

Cytogenetic Characterization

- In 85% of children with leukemia an abnormal karyotype in the malignant clone is detectable
- The analysis combines chromosome banding with fluorescence in situ hybridization (FISH) with spectral karyotyping (SKY) and with comparative genomic hybridization (CGH)
- The cytogenetic abnormalities reflect the number of chromosomes (ploidy) and the structure of chromosomes (rearrangements)
- The DNA index (DI) defines the cellular DNA content determined by flow cytometry

	DI (DNA Index)	
Normo- or pseudodiploid cells	1.0	Normal DNA content
Hyperdiploid	>1.0	>1.1: 53 chromosomes/cell
Hypodiploid	<1.0	

Percentage of DNA index in ALL

	Number of chromosomes	Rate (percentage)	Prognosis
Hypodiploid	41–45	6	Unfavorable
Pseudodiploid	46	41.5	Various
Hyperdiploid	47–50	15.5	Favorable
	>50	27.0	
Normal	46	8.0	

Structural chromosomal abnormalities

Immunophenotype and translocation	Oncogene/hybrid gene	ALL
Pre-B/early pre-B/T-cell ALL t(9;22) Philadelphia chromosome	BCR-ABL	Unfavorable prognosis
Pre-B/early pre-B ALL	TCF3 (alias E2A)-PBX1	Often high WBC
t(1;19)	AF4-MLL	Predominantly infants with poor prognosis
t(4;11)(11q23) t(12;21)	ETV6 (alias TEL)-RUNX1 (previously AMLI)	Good prognosis
T ALL t(11;14)	LMO1 (alias TTG1)/LMO2 (alias TTG2)	Predominantly boys, extramedullary ALL
B ALL t(8;14) t(8;22) t(2;8)	MYC	Predominantly boys, L3 morphology

Some examples of cytogenetic alterations are:

- Translocation t(9;22) (BCR-ABL fusion protein) is present in 5% of children with ALL and is characteristic of a protein with tyrosine kinase activity with the ability to immortalize progenitors and is correlated with an unfavorable prognosis
- The structural abnormality of chromosomal band 11q23 is detected in 5–10% of childhood leukemias, 60–70% of leukemias in infants (ALL and AML) and in 85% of secondary leukemias. The 11q23 abnormality [also called "mixed-lineage leukemia" (MLL) protein] is an important regulator of pluripotent cells. Fusion partners with MLL are also observed on chromosomes 4, 6, 9, and 19 of precursor ALL [i.e. t(4;11)(q21;q23)]. 11q23/MLL abnormalities are correlated with a poor prognosis
- Chromosomal abnormalities disappear during remission (see Minimal Residual Disease, Chap 1) and often reappear during relapse of ALL

Cytometry

Flow cytometry can measure the DNA and RNA content of individual cells.
It provides:

- The incidence of cells in different phases of the cell cycle
- The determination of the DNA content of leukemic cells for prognostication (ploidy)

Cell Kinetics

See Chap 1.

- Leukemic blast cells are characterized by an arrest of maturation at a certain stage of proliferation and by increased cell-survival mechanisms. Physiologically this results in a progressive accumulation of leukemic cells and replacement of normal cells in the bone marrow, lymph nodes and infiltration of other organs
- With the label index (LI) the rate of cells in DNA synthesis is measured 1 h after injection of tritium-thymidine:
  - LI of leukemic lymphoblasts is 15–35%
  - LI of leukemic myeloblasts is approx. 4–15%, which is low in comparison with normal myeloblasts (LI=40–70%). This means that the cell cycle duration for leukemic myeloblasts is 45–48 h in comparison with 15 h of normal myeloblasts
- The cell generation time (doubling time for leukemic blast cells) is in the range of 4–60 days
- Cell kinetic studies were important in the design of timed sequential use of cytotoxic drugs

Prognostic Factors

Prognostic factors (a)	Favorable	Unfavorable
WBC	<10x10^9/l	>50x10^9/l (ca. 20%)
Age (years)	2–7	<2 and >10 (especially in infants)
Gender	Female	Male
Response to steroid treatment	+	—
Response to treatment	<4 week	>4 weeks
Time of relapse after treatment ends	>6 months	<6 months
Surface markers	Pre-B-ALL	T-/B-ALL
Cytogenetic characterization (DI) Structure	Hyperdiploid	Hypodiploid 11q23/MLL-ALL gene rearrangement Ph+
FAB	L1	L2/L3
Mediastinal enlargement	—	(+)
Visceromegaly	+ to ++	+++
LDH	Moderate	High
Ethnic groups	White	Black (b)

(a) In order of importance; (b) Small difference in some studies

Characteristics and Prognosis of ALL in Infants

- Initially often high WBC, massive visceromegalies, severe thrombocytopenia, high rate of CNS involvement, poor response to treatment and high rate of relapse in comparison with childhood ALL, particularly extramedullary relapse
- The leukemic cells of infants mainly display an early stage of differentiation (often HLA-DR antigen-positive, CD10-negative). Frequently involvement of chromosome 11 [11q23, *MLL/ALL-1* gene rearrangement, t(4;11)], simultaneous occurrence of lymphoid and myeloid markers; immunoglobulin genes often in germ line configurations

Differential Diagnosis

- Leukemoid reaction:
  - Bacterial infection, acute hemolysis, tuberculosis, sarcoidosis, histoplasmosis or metastatic tumors
  - Increased WBC (up to 50×10^9/l) and/or peripheral immature granulocyte precursors
  - Occurs especially frequent in neonates and children with trisomy 21
- Lymphocytosis:
  - Pertussis and other viral infections
  - Infants and small children often have physiological lymphocytosis with an incidence of approx. 85%
- Infectious mononucleosis
- Aplastic anemia:
  - Pancytopenia and hypoplastic bone marrow
- Idiopathic thrombocytopenic purpura (ITP):
  - Without anemia (with exception of children with severe bleeding), normal morphology of white blood cell differentiation
- Bone marrow infiltration by a solid tumor (metastatic disorder):
  - Neuroblastoma (increased level of urine catecholamines)
  - Non-Hodgkin lymphoma (when >25% of blasts in the bone marrow are defined as leukemia)
  - Rhabdomyosarcoma and retinoblastoma may have a similar infiltration of the bone marrow as leukemia, but usually with clusters of malignant cells
- Rheumatoid fever and rheumatoid arthritis with similar initial symptomatology, but without alteration of peripheral blood cell count and bone marrow abnormalities

Therapy

- The treatment of ALL is risk-adapted depending on the different individual biological factors of ALL (clinical manifestation, laboratory analysis of morphology, cytochemistry, immunology, molecular cytogenetics, etc.)
- A good cooperation between the experienced center and the referring physician have to be established
- The treatment of ALL is subdivided into remission induction, consolidation with CNS prophylaxis and maintenance phase
- Parents and patients should reach a clear understanding of each stage of therapy and the side effects

Induction of Remission

- Remission means disappearance of all signs of leukemia in clinical examination and peripheral blood analysis; bone marrow analysis with less than 5% atypical cells and normal hematopoiesis established

- Elimination of leukemic cells by a combination of vincristine, prednisone and additional cytotoxic agents such as daunorubicin, doxorubicin, and L-asparaginase
- In parallel to induction treatment decrease in hemoglobin, white blood cells and platelets
- Duration of induction treatment: 4–5 weeks
- Regression of visceromegalies can be observed within the first 2 weeks
- Rate of first remission in ALL: more than 90%
- For prophylaxis of CNS leukemic disease intrathecal application of methotrexate before, during, and after remission has to be performed. The addition of preventive irradiation is probably necessary in children at high risk of ALL as determined in most studies

Consolidation Treatment

- Without continuation of treatment leukemia will reappear within weeks or months
- When remission with normal hematopoiesis is achieved further intensive chemotherapy is necessary to reach a complete eradication of leukemic cells
- Combinations of different cytotoxic drugs reduce the number of remaining leukemic cells and the development of resistance against particular chemotherapies
- Special laboratory analysis (molecular cytogenetic methodology, flow cytometry, cell culture) may detect minimal residual disease (MRD)

Maintenance Treatment

- Risk-adapted maintenance treatment of different duration prevents recurrence of ALL
- Duration of treatment is 1.5–2.5 years with daily 6-mercaptopurine and once weekly methotrexate, with or without reinduction treatment are commonly used
- The dosage of cytotoxic agents must continuously be adapted to the child's condition and blood cell counts at weekly to biweekly intervals
- A lifestyle as normal as possible as before the diagnosis has to be followed during maintenance treatment

Prognosis

- Approximately 80% of children with ALL survive without relapse with 7- to 10-year follow-up after diagnosis (long-term remission)
- In about one of five children a relapse of ALL occurs during maintenance treatment, within the first 6 months after treatment end or later. The risk of leukemia (recurrence) 5–7 years after diagnosis is as low as in children without leukemia
- A relapse within the first 6 months after treatment stop indicates a poor prognosis
- A late relapse (more than 6 months after termination of maintenance treatment) usually has a better prognosis depending on the characteristics of the leukemic cells

Management of Complications and Side Effects

- Prophylactic treatment of tumor lysis syndrome, hyperleukocytosis and uric acid nephropathy (see Chap 18)
- Dehydration, infection, anemia, bleeding and alteration of liver and kidney functions has to be continuously observed and corrected during the different treatment phases
- Anemia:
  - Support with transfusion of erythrocytes is indicated when the hemoglobin level is less than 6 g/l and/or when clinical symptoms of anemia occur: 10–15 ml erythrocytes/kg body weight per transfusion
- Bleeding:
  - Due to thrombocytopenia (decreased production, suppression by cytotoxic drugs), functional defect of platelets, i.e. salicylates, and/or coagulopathy
  - Treatment: platelet transfusion, substitution of coagulation factors, antileukemic treatment
- Infection:
  - Due to reduced humoral and cellular immune response
  - High risk of infection during induction treatment and during episodes of severe neutropenia with absolute neutrophil count (ANC) less than 0.5×10^9/l
  - Symptoms of infection may be atypical during phases of neutropenia
  - Procedure during fever and neutropenia (ANC less than 0.5×10^9/l): blood culture analysis and immediate start of broad-spectrum antibiotics
  - In infection with *Pseudomonas*, *E. coli*, opportunistic organisms (i.e., *Pneumocystis carinii*), virus or fungal infection treatment should be according to resistance analysis of the causative microbe
  - In viral infections antiviral agents, often in combination with addition of intravenous application of immunoglobulins in cases of low serum IgG level
  - When signs of interstitial pneumonia occur: high-dose trimethoprim-sulfamethoxazole: 20 mg trimethoprim/kg body weight

Relapse

- Usually the same pheno- and genotype of ALL as at initial diagnosis
- Rarely another cell line of leukemia (a lineage switch), especially in patients with initial biclonal leukemia. Differential diagnosis: secondary leukemia, which occurs years after initial diagnosis
- Intensive treatment necessary including hematological stem cell transplantation
- Incidence of second remission after intensive reinduction treatment: 90%
- CNS leukemia prophylaxis with chemotherapy and/or CNS irradiation needed in relapse
- Poor prognosis: early relapse during first treatment phase or within the first 6 months after cessation of treatment
- Favorable or unfavorable diagnosis in cases of late relapse more than 6 months after cessation of first treatment depending on type of leukemia
- Event-free survival: after early relapse, 10–30%; after late relapse, 40–50%

- In children at high risk of relapse stem cell transplantation probably provides a higher rate of event-free survival (EFS) than chemotherapy alone

Special Forms

CNS Leukemia

- CNS leukemia occurs in less than 10% of children, mostly diagnosed subclinically in the initial analysis of cerebrospinal fluid or during maintenance treatment or as late relapse
- Definition of CNS leukemia: more than 5 leukemic cells/cm^3
- The CNS relapse occurs isolated or in combination with bone marrow and/or testicular relapse
- Treatment: initially intrathecal chemotherapy until CNS remission in parallel to systemic induction chemotherapy followed by CNS and spinal irradiation and systematic chemotherapy continuation
- Dose-dependent side effects of irradiation: intellectual deficiency (especially deficiency in concentration), growth deficits
- Prognosis: 90% achieve initial remission; if relapse less than 18 months from diagnosis, EFS is approx. 45% compared with those relapsing more than 18 months from diagnosis who have an approx. 80% EFS at 4 years with aggressive therapy

Testicular Leukemia

- Initially rare; during intensive chemotherapy frequency less than 2%
- Preventive biopsy of testes for occult testicular infiltration is not indicated because of side effects of biopsy; systemic treatment eradicates occult testicular leukemia
- Isolated testicular relapse is often followed by systemic relapse; therefore intensive systemic chemotherapy necessary in parallel with local irradiation of both testes
- Side effects: sterility and sometimes reduced testicular function; in the latter case hormonal substitution may be necessary
- Patients with early relapse have an approx. 40% EFS and patients with late relapse have an approx. 85% EFS at approx. 3 years

Acute Myelogenous Leukemia

Paul Imbach

Acute myelogenous leukemia (AML) represents a heterogeneous group of malignant hematological precursor cells of the myeloid, monocytic, erythroid or megakaryocytic cell lineage (see Chap 1).

Epidemiology

- Incidence: 15–20% of all leukemias in children
- Seven in 1 million children develop AML each year
- Frequency of AML remains stable throughout childhood with a slight increase during adolescence
- There is no difference in incidence of AML between boys and girls
- There is a slightly higher incidence in white children than in other groups

Predisposing Factors

See Chap 1.

Differential Diagnosis

- Infectious mononucleosis
- Juvenile rheumatoid arthritis
- Aplastic anemia
- Acquired neutropenia
- Megaloblastic anemia
- Autoimmune cytopenia
- Leukemoid reaction
- Transient myeloproliferative syndrome in infants with Down syndrome
- Metastatic neuroblastoma, rhabdomyosarcoma, retinoblastoma, non-Hodgkin lymphoma
- Myelodysplastic syndrome
- Myeloproliferative syndrome
- Juvenile myelomonocytic leukemia and chronic myelogenous leukemia

In cases of difficult bone marrow aspiration ("dry" taps), bone marrow biopsy is recommended

Classification

AML is heterogeneous concerning the predisposing condition, pathogenesis, geno- and phenotype and response to therapy. Prognosis depends on age, initial presentation and subtype.

FAB classification of acute myelogenous leukemia	
M0	Immature myeloblastic leukemia
M1	Myeloblastic leukemia – Blasts with few azurophile granules or Auer rods – Positive peroxidase or Sudan black (>5% of blasts) reaction can be helpful
M2	Myeloblastic leukemia with signs of maturation – Myeloblasts and leukemic promyelocytes represent the majority of nucleus-containing bone marrow cells – Auer rods common
M3	Promyelocytic leukemia – Mostly abnormal promyelocytes with lots of granulation; some Auer rods
M4	Myelomonocytic leukemia – Mostly myeloblasts and promyelocytes, promonocytes and monocytoid cells with granulocytic and monocytic differentiation
M5	Monocytic leukemia – Moderately differentiated to well-differentiated monocytic cells – Esterase reaction may be positive
M6	Erythroleukemia – More than 50% of the nucleus-containing cells of bone marrow are erythroblasts – Erythroblasts show a bizarre morphology
M7	Megakaryocytic leukemia

Histochemical Classification and Frequency

Histochemical characteristics							Frequency (%)
M0	-	SB	-	-	-	-	<3
M1	MPO	SB	-	-	-	-	20
M2	MPO	SB	-	-	-	-	25
M3	MPO	SB	-	-	(NSE)	-	5–10
M4	MPO	-	-	NASD	NSE	-	25–36
M5	MPO	-	-	NASD	-	-	15
M6	-	-	PAS	-	-	Glycophorin A	<5
M7	a	-	-	NASD	NSE	-	5–10

Parentheses: variable; underlining: pathognomonic; *MPO* myeloperoxidase, *NASD* naphthol-ASD, *NSE* nonspecific esterase, *PAS* periodic acid-Schiff, *SB* Sudan black; a: Intraplasmatic MPO detectable by electron microscopy only

Myelo-blasts	Cluster determination (CD)												B cell	T cell			
M0	-	13	-	15	33	34	(36)	31/61	42	65	117a	HLA-DR	19	2	(4)	(7)	(56)
M1	-	13	-	15	33	34	-	-	-	65	117	HLA-DR	-	2	-	(7)	(56)
M2	-	13	-	15	33	34	-	-	-	65	117	HLA-DR	-	2	-	7	(56)
M3	11b	13	-	15	33	34	-	-	-	65	117	(HLA-DR)	-	2	-	7	(56)
M4	11b	13	14	15	33	34	36	-	-	65	117	HLA-DR	-	2	4	7	56
M5	11b	13	14	15	33	34	36	-	-	65	(117)	HLA-DR	-	2	4	7	56
M6	-	13	-	-	33	-	-	-	-	65	(117)	-	-	-	-	7	-
M7	-	13	-	-	-	34	36	41/61	42	65	117	HLA-DR	-	2	4	7	56

Parentheses: variable; underlining: pathognomonic

HLA human leukocyte antigen

a: c-kit oncoprotein

French–American–British Classification of AML

The French–American–British (FAB) classification is based on morphological and histochemical characteristics and is supplemented by immunophenotypical and cytogenetic characteristics.

Immunophenotyping

The cluster-determination (CD) classification has a high specificity and sensitivity for distinguishing acute lymphoblastic leukemia (ALL) and AML from normal hemopoietic precursor cells.
Biphenotypic leukemia expresses myeloid and lymphoid markers. Therefore more than one marker of the other cell lineage has to be expressed. Biphenotypic leukemia has to be distinguished from mixed-lineage leukemia, which shows blasts with more than one phenotype. Furthermore there are leukemias that express M6 and M7 markers, and which are described as erythromegakaryocytic.

Cytogenetics

Fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) techniques (Chap 2) detect subtypes of AML according to specific chromosomal abnormalities that correlate to alterations in cell survival, cell differentiation, and cell cycle regulation.

Cytogenetic abnormalities in childhood AML

FAB	Chromosomal abnormalities	Affected gene	Comments
M1/M2	t(8;21)	*ETO-AML 1*	Auer rods
M3	t(15;17)	*PML-RARA*	Promyelocytic leukemia with coagulopathy; ATRA responsiveness
	t(11;17)		Coagulopathy, ATRA unresponsiveness
M4 or M5	t(9:11)	*AF9-MLL*	Infants; high initial WBC
M5	t(11q23)	*MLL*	Infants; high initial WBC
M5	t(1b;11)	*AF10-MLL*	Infants; high initial WBC
M5	t(11;17)	*AF17-MLL*	Infants; high initial WBC
M6			Glycophorin-positive
M7	t(1;22)		Infants with Down syndrome

ATRA all-*trans* retinoic acid, *WBC* white blood cell count

The combination of the characteristics described above helps determine the recommended type of treatment of AML subtypes.

Clinical Presentation

In addition to general symptoms of leukemia (compare Chap 2) patients with AML often present with the following symptoms: bleeding, leukostasis, tumor lysis syndrome and infections.

Bleeding

- Besides thrombocytopenic bleeding there is often coagulopathy with mucosal (epistaxis, oral bleeding), gastrointestinal, or central nervous system (CNS) bleeding
- The coagulopathy results in disseminated intravascular coagulation (DIC) which occurs in parallel with infection and/or release of proteins with anticoagulant activities from the leukemia cells (i.e. thromboplastin). DIC is most frequently observed in acute promyelocytic leukemia (APL, M3)
- Therapy:
  - Platelet transfusion when platelet count is less than 20×10^9/l (substitution of coagulation factors is controversial)
  - In severe anemia, erythrocytes have to be substituted

Leukostasis

- If WBC is higher than 200×10^9/l, leukemic blasts may clump intravascularly. Small vessels may be blocked resulting in hypoxia, infarction and hemorrhage, mostly in the lungs or CNS
- Because of the large size of the monocytes in M5 AML leukostasis may occur with a WBC higher than 100×10^9/l
- Therapy:
  - Rapid cytoreduction if WBC is more than $100–200 \times 10^9$/l by leukapheresis or exchange transfusion
  - Hydroxyurea for prevention of rebound phenomena after leukapheresis
  - Prevention of tumor lysis syndrome

Tumor Lysis Syndrome

See Chap 18.

Infection

- The absolute neutrophil count (ANC) is often below 1×10^9/l and the frequency of fever and bacteremia is high
- For use of antibiotics and cytokines see Chap 18
- The risk of fungal infection is high especially during long periods of neutropenia or aplasia
- Lymphocytopenia may result in opportunistic infections

Therapy

- Before 1970 nearly all children with AML died. Since then cooperative study protocols with different cytotoxic drug combinations have led to long-term remission in 35–38% of children
- The use of autologous and allogenous stem cell transplantation increases the incidence of an event-free survival of more than 50%
- In addition to specific leukemic therapy management of complications and morbidity have to be conducted
- CNS prophylaxis includes either intrathecal cytarabine (ara-C) or cytarabine in combination with methotrexate and prednisone, often in parallel with systematic high-dose cytarabine treatment. This procedure seems equally successful to prophylactic CNS irradiation. The incidence of CNS relapse is dramatically decreased (less than 5%)
- Certain subtypes of AML are still associated with a poor prognosis (for instance AML with monosomy 7 or secondary AML)

Induction Therapy

- Cytarabine (e.g. ara-C) and anthracyclines (e.g. daunorubicin) lead to approximately 70% remission (less than 5% blasts in bone marrow) within 4–6 weeks and no other evidence of leukemias
- Other combinations such as 6-thioguanine, etoposide or the use of other anthracyclines (idarubicin, rubidomycin) and mitoxantrone result in remissions up to 85%
- Supportive therapy and prophylaxis (antibacterial, antiviral, antifungal) and the use of hematopoietic growth factors reduce morbidity and lethality. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) shorten the periods of neutropenia and diminish the frequency of infections and days of hospitalization, but do not influence the rate of remission or overall outcome

Remission and Postremission Therapy

- Consolidation and intensification therapy over the course of approximately 6–12 months results in an overall survival of between 45% and 55%. Some treatment programs use maintenance therapy

Allogeneic Hematopoietic Stem Cell Transplantation

- The possibility of an antileukemic effect of the donor immune system ("graft vs leukemia," GVL) together with supportive therapy and therapy against graft-versus-host disease (GVHD) results in an improved outcome for certain subtypes of AML
- The GVL effect is less effective in transplantation between identical twins or after extensive T-cell depletion of the donor stem cells

- Problems after transplantation include chronic GVHD, growth retardation, sterility and the risk of secondary malignancy
- The frequency of leukemia-free survival after transplantation is 50–70%. Prognostic factors of AML have to be taken into consideration in prognostic estimations

Autologous Hematopoietic Stem Cell Transplantation

- The advantages of this therapy are the absence of GVHD and the availability of donor cells for most patients. The disadvantages in comparison with allogeneic stem cell transplantation are the lack of GVL effect and the potential for leukemic cells in the returned stem cells

Prognostic factors in AML

	Favorable	Unfavorable
WBC	<100,000	>100,000
FAB class	M1 with Auer rods	Infants with 11q23
	M3 (APL)	Secondary AML
	M4 with eosinophils	CNS involvement
Chromosomal abnormalities	t(8;21) and t(15;17)	Mutation of *FLT3* receptor
	inv(16), t(9;11)	(Type-III tyrosine kinase receptor)
	Wild-type *FLT3*	
	Whites	t(9;22)
		del(7) and del(11)
		Expression of MDR P-glycoprotein genes with CD34 antigen (particularly in adults)
		Mutant *FLT3* (particularly internal tandem duplication)
Ethnicity	Whites	Blacks
	MRD-negative	MRD-positive
	Rapid response to therapy in bone marrow within 7–14 days	
Time of remission	>1 year	<1 year

MRD minimal residual disease

- Advantages and disadvantages of the autologous hematopoietic stem cell transplantation and morbidity equalize the prognosis in comparison with intensive postremission chemotherapy

Characteristics of and Therapy for AML Subtypes

- The therapeutic index for AML, the necessary dose of cytotoxic drugs against leukemic cells and the limitation of toxicity for normal precursor cells in the bone marrow are similar

Acute Promyelocytic Leukemia (APL, M3)

- Characterized by malignant cells at the stage of promyelocytes
- Mostly in young adults
- Symptoms: purpura, epistaxis, gingival bleeding
- Hemorrhagic complications are frequent
- Signs of intracranial high pressure as a manifestation of CNS bleeding
- Hepatosplenomegaly and/or lymphadenopathy usually not prominent
- Laboratory findings:
  - Marked thrombocytopenia, WBC variable
  - Bone marrow: mainly promyelocytes with azurophile granules, Auer rods are common; peroxidase-positive, Sudan black-positive, esterase-positive, PAS-negative
  - Prolonged prothrombin time and thrombin time: serum fibrinogen, factor V and factor VII decreased
  - D-Dimers increase in DIC caused by procoagulants from leukemic promyelocytes
  - The t(15;17) chromosomal abnormality is pathognomonic
- Therapy:
  - Standard-risk AML induction treatment plus ATRA (induction of differentiation of promyeloblasts)
  - ATRA maintenance with 6-mercaptopurine and methotrexate in high-risk patients
- Prognosis:
  - In cases of complete, continuous remission there is a high rate of long-term survival

Acute Myelomonocytic and Acute Monocytic Leukemia (M4, M5)

- Five to ten percent of all AML in children
- Symptoms comparable with other acute leukemias
- Hypertrophy of gingiva and ulceration of mucosa in about 50% of children
- Often infiltration of skin and lymphadenopathy
- Laboratory findings:
  - Anemia and thrombocytopenia are common; WBC variable
  - DIC: Release of tissue factors/proteases during lysis of monocytes

Erythroleukemia (Di Guglielmo Syndrome, M6)

- The clinical presentation consists of fatigue, fever, petechiae and often splenomegaly
- Laboratory findings:
  - Initial phase: macrocytic anemia, erythroblasts with two or three nuclei and showing a maturation disturbance, anisocytosis and poikilocytosis, elliptocytes
  - Variable numbers of reticulocytes; oxyphilic normoblasts and often elliptocytes and macrocytes in the peripheral blood; thrombocytopenia variable; megaloblastic hyperplasia of erythropoiesis in the bone marrow; result of glycophorin analysis: low to highly positive
  - Intermediate phase: mixed erythromyeloblastic proliferation
  - Late phase: similar to AML

Acute Megakaryocytic Leukemia (AMKL)

Clinical presentation and laboratory findings are comparable with other AML subtypes, although this type of AML can be associated with low percentages of bone marrow blasts and hepatic and skeletal involvement. This leukemia is most common in children with Down syndrome. In immune phenotyping CD41/61- and CD42 are present.

Myelodysplastic Syndrome (MDS)

In about 3% of children with acute leukemia the disease begins as pre-leukemia characterized by:

- Anemia, cytopenia, blasts in peripheral blood and morphological nuclear abnormalities of blood cells
- Bone marrow: mostly hypercellular, megaloblastic, dyserythropoietic; less than 5% blasts with nuclear anomalies, large or small megakaryocytes; chromosomal abnormalities in hematopoietic cells (monosomy 7); growth irregular in cultures in vitro
- Clinical course: often develops into AML within 6–24 months
- Prognosis: often therapy-resistant subtypes of AML; bone marrow transplantation is curative

Eosinophilic Leukemia

- Rare subtype of AML
- Symptoms: nausea, fever, sweating, cough, dyspnea, thoracic pain, weight loss and pruritus
- Clinical findings: cardiac arrhythmia, cardiomegaly and hepatomegaly are common; in 50% of cases lymphadenopathy; neurological disturbances (without leukemic CNS disease) are common
- Laboratory findings: often anemia and thrombocytopenia; WBC often high, occasionally more than 100×10^9/l with predominantly eosinophilic cells with large granules; chromosomal abnormalities sometimes present
- Clinical course: during progression of disease no difference to AML

- Differential diagnosis: Hypereosinophilia parasitosis (larva migrans, *Toxocara canis*), tropical eosinophilia
- Therapy: transient response to corticosteroids and hydroxyurea; AML therapy may induce remission

Relapse of AML

- Response to reinduction is less successful; resistance against drugs is high
- Continuous, long-term remission without transplantation less than 20% (exception: after first remission of more than 1 year 5-year survival rate is 30–40%)
- Patients who have a relapse affecting the CNS frequently have a simultaneous systemic relapse
- Induction therapy with high-dose ara-C in combination with mitoxantrone, etoposide, fludarabine or 2-chlorodeoxyadenosine and G-CSF
- Prognosis is unfavorable without stem cell transplantation (allogeneic, matched or partially matched), cord blood stem cell transplantation, haploidentical transplantation
- Infusion of donor lymphocytes for increase of GVL-effect may be considered after transplantation if relapse occurs
- After allogeneic or haploidentical transplantation the risk of primary rejection and GVHD is significant – despite T-cell depletion and immunosuppressive treatment (i.e. cyclosporin A)
- In APL (M3) the rate of second remission is greater than 80%

Myelodysplastic Syndrome

Thomas Kühne

Abbreviations

- FAB French–American–British working group
- MDS Myelodysplastic syndrome
- MPS Myeloproliferative syndrome
- WHO World Health Organization
- SCT Hematopoietic stem-cell transplantation

Introduction

- The broad definition of myelodysplastic syndrome (MDS) is generally accepted; however, harmony among experts disappears as soon as details of this heterogeneous group of diseases are discussed. The traditional classification systems of MDS, the FAB system, and the more recently introduced WHO classification are less well accepted in children than in adults
- Childhood MDS differs from that of adults in pathogenetic and biological characteristics
- The FAB classification (see below) was developed and accepted in the late 1970s for adult patients; however, its use in pediatrics is impractical
- The lack of an adequate pediatric classification deters from appropriate disease interpretation and systematic clinical research into MDS

Definition

- MDS is a heterogeneous group of clonal bone marrow disorders characterized by ineffective hematopoiesis with normo- or hypercellular bone marrow resulting in different degrees of peripheral cytopenia and a variable risk of transformation to acute leukemia, frequently – but not always – acute myelogenous leukemia (AML)
- The disease duration varies from months to years, but there is also a more rapid form with transformation into leukemia, the latter being more common among children
- Myeloproliferative syndrome (MPS or chronic myeloproliferative disorders) have predominantly proliferative features with minor or absent dysplastic characteristics. They are comprised of a disease entity described in the 1950s with a clonal proliferative pattern of hematopoietic precursor cells that have a tendency to transform to acute leukemia

Classification

- Concepts and definitions of the FAB classification include morphological aspects of bone marrow cells and the percentage of blasts in peripheral blood and bone marrow with five diagnostic categories (see table below). This system is based on data from adult patients
- Not all children with MDS fit into this classification
- Although generally accepted the FAB classification and its modifications, which differentiates MDS from acute leukemia and defines risk groups among MDS patients, exhibits weaknesses also for adult patients
- A new classification system that is currently used is the WHO classification which has resolved many problems encountered with the FAB classification. However, pediatric MDS remains a problem and is not adequately defined by the WHO classification
- The WHO classification differentiates MDS from MPS, and a new category, "myelodysplastic/myeloproliferative diseases" is proposed
- Problems associated with the WHO classification include the omission of constitutional disorders and bone marrow failure syndromes; unclear definition of hypocellular MDS in children; the significance of secondary MDS; and the prognostic relevance of the system for children
- Freedman proposes a classification system for pediatric MDS that has prognostic potential (Mandel et al. 2002)

Pediatric MDS based on FAB criteria

Disease	Children (%)	Adults (%)	Median age at diagnosis	Blasts in peripheral blood	Blasts in bone marrow
Refractory anemia (RA)	20	28	6 years	<1%	<5%
Refractory anemia with ringed sideroblasts (RARS)	<1	24	-	<1%	<5%, ringed sideroblasts ≥15%
Refractory anemia with excess blasts (RAEB)	26	23	7 years	<5%	5–19%
Refractory anemia with excess blasts in transition (RAEB-T)	28	9	26 months	≥5% or Auer rods	20–29% or Auer rods
Chronic myelomonocytic leukemia (CMML)	20	16	9 months	Monocytes $1x10^9$/l	<20%

Bennett et al. 1976, 1994; Hasle 1994

WHO classification and criteria for the myelodysplastic syndromes

Disease	Peripheral blood	Bone marrow
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only, ≥15% ringed sideroblasts <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1x10^9/l monocytes	Dysplasia in ≥10% of cells in two or more myeloid cell lines No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenia (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1x10^9/l monocytes	Dysplasia in ≥10% of cells in two or more myeloid cell lines ≥15% ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia <5% blasts No Auer rods <1x10^9/l monocytes	Unilineage or multilineage dysplasia 5–9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia 5% to 19% Auer rods ± <1x10^9/l monocytes	Unilineage or multilineage dysplasia 10–19% blasts Auer rods ±
MDS, unclassified (MDS-U)	Cytopenia No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobate nuclei <5% blasts No Auer rods Isolated del(5q)

Jaffe 2001

WHO classification of the myelodysplastic/myeloproliferative diseases

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML)
- Juvenile myelomonocytic leukemia (JMML)
- Myelodysplastic/myeloproliferative disease, unclassifiable

Jaffe 2001

CCC (category, cytology, cytogenetics) system

Category	Idiopathic Syndrome Secondary
Cytology	Refractory cytopenia with ringed sideroblasts Refractory cytopenia Refractory cytopenia with dysplasia All cytopenias described above, with excess blasts (5–30%)
Cytogenetics	Monosomy 7 Trisomy 8 Complex Normal Other

Mandel et al. 2002

Epidemiology

- The incidence is not known because of the rarity of the disease and because oligo- and asymptomatic forms may remain unidentified for a long time. Thus, the incidence of MDS may be underestimated
- Three percent of hematologic malignancies of childhood are suspected to be MDS. If MDS is considered as an initial stage of AML the incidence increases to 12–20%. JMML is estimated to account for 2.5–3% of leukemia in childhood
- Incidence should be interpreted cautiously according to the various classification systems

Predisposing Factors

- Familial MDS is more frequently seen than familial leukemia
- Patterns of inheritance are not identifiable
- Both children and adults are affected; however, MDS is largely a disease of the elderly: incidence rises with increasing age
- Risk of first-degree relatives of adults with MDS is approximately 15 times higher than in the general population
- Although children with familial MDS do not exhibit specific morphological forms of MDS monosomy 7 is frequently observed

Predisposing factors for pediatric MDS

- Constitutional chromosomal aberrations:
  - Trisomy 8 mosaicism
  - Trisomy 21 mosaicism, Down syndrome
  - Klinefelter syndrome
  - t(2;11), t(7;16), t(13;14), ins(16), fragile X syndrome, Turner syndrome
- Syndromes associated with disturbed DNA repair:
  - Fanconi anemia
  - Ataxia telangiectasia
  - Bloom syndrome
  - Xeroderma pigmentosum
- Neurofibromatosis
- Constitutional p53 mutation (Li-Fraumeni syndrome)
- Aplastic anemia
- Congenital neutropenia (Shwachman syndrome)
- Pearson syndrome
- First-degree relatives of patients with MDS
- Alkylating agents and/or radiotherapy
- Miscellaneous conditions:
  - Werner syndrome
  - Pierre Robin syndrome
  - Adams-Oliver syndrome
  - Congenital vitium
  - Hypospadias
  - Endocrine dysfunctions
  - Platelet storage-pool disorders
  - Miscellaneous physical and psychological disorders

Etiology

- Like other malignant tumors a process with multiple steps is suspected with the accumulation of genetic lesions
- The initial and subsequent mutations have yet to be elucidated
- Several recurrent genetic aberrations known (e.g. mutations of the *RAS* proto-oncogene family and their influence with the tumor suppressor gene *NF1*)

Clinical Manifestations

- There are no specific disorders associated with the described morphological categories
- Occasionally abnormalities in blood counts are observed
- Clinical manifestations explained by degree of bone marrow failure
- Paleness, skin hemorrhages
- Sometimes hepato-/splenomegaly, particularly in refractory anemia with excess blasts (RAEB) and in patients with RAEB in transformation (RAEB-T)
- MDS associated with constitutional genetic aberrations is often seen in infants and young children

Laboratory Findings

- Differentiation between MDS and AML may be difficult
- Morphology is based on peripheral blood analysis, bone marrow aspiration and biopsy, interpreted by experienced reference laboratory staff
- The bone marrow is usually hypercellular; reduced marrow cellularity in 15% of patients only
- Consider MDS if maturation abnormalities are associated with dysplasia or if one or more cell lines are present
- Red cell abnormalities and megaloblastic maturation are common; nuclear-cytoplasmic asynchrony (maturation of cytoplasm reflected by hemoglobin and nuclear development). Development of multiple nuclei and nuclear fragmentation (Howell-Jolly bodies)
- Immature myeloid cells could be increased and exhibit dysplastic signs (e.g. hypogranular granulocytes). Pelger–Huët nuclear anomaly. Percentage of myeloblasts is important for the FAB and WHO classification
- Megakaryocytic abnormalities include micromegakaryocytes, increased ratio of nucleus to cytoplasm, various cell sizes, increased or decreased cytoplasmic granules
- Other laboratory investigations: cytogenetics (abnormal karyotype in more than 70% of patients), molecular biology (single-gene mutations, clonal hematopoietic defects), cell culture analysis (often leukemic pattern of the precursor cells, particularly with many micro- and macroclusters)

Differential Diagnosis

- Diagnosis based on history, physical examination, complete blood count, bone marrow cytology and histology with interpretation by a reference laboratory
- Differentiation from acute leukemia according to FAB or WHO classification
- Vitamin B12 and folate deficiency as well as pyridoxine and riboflavin deficiencies are usually well differentiated from MDS

Treatment

- Remains highly controversial
- Many different multiagent chemotherapies have been tried, particularly AML induction chemotherapy
- Conventional chemotherapy is not curative
- Myeloablative therapy and stem cell transplantation appear to be most effective
- Long-term survival of children with MDS after stem cell transplantation is in the range of 40%

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Myeloproliferative Syndromes (Chronic Myeloproliferative Disorders)

Thomas Kühne

- Myeloproliferative syndromes (MPS) are characterized by clonal proliferation patterns of hematological precursor cells with a tendency to develop acute leukemia. Cytopenias typically seen in myelodysplastic syndrome (MDS) are uncommon as are dysplastic morphological features. Hence a pathogenesis different from MDS is suspected which is an important reason to separate the discussion and classification of MPS from MDS
- The new WHO classification of chronic myeloproliferative disorders is not satisfactory for use in pediatric patients

WHO classification of chronic myeloproliferative disorders

- Chronic myelogenous leukemia (CML) – (Philadelphia chromosome, t(9;22)(q34;q11), *BCR/ABL*-positive
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia (CEL) and hypereosinophilic syndrome (HES)
- Polycythemia vera
- Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
- Essential thrombocythemia (ET)
- Chronic myeloproliferative disease, unclassifiable

Juvenile Myelomonocytic Leukemia

- Was termed "juvenile chronic myelogenous leukemia" (JCML)
- Morphological and cytogenetic relationship with CML is poor; however, there are similarities with chronic myelomonocytic leukemia (CMML)
- Cannot be considered as the pediatric equivalent of CMML which occurs mainly in elderly patients (median age is 79 years)
- Aggressive myeloproliferative disorder of the young child which has almost no characteristics of a MDS, although it is classified as such in the modified French-American-British (FAB) classification
- Growth factors such as tumor necrosis factor-alpha and granulocyte-macrophage colony-stimulating factor are pathogenetically important

Clinical Manifestations

- Paleness (69% of patients)
- Fever (61% of patients)
- Exanthema (39% of patients)
- Hepatosplenomegaly (more than 90% of patients)
- Lymphadenopathy (75% of patients; Niemeyer et al. 1997)

Laboratory Findings

- Blood count: more than 10×10^9 leukocytes/l, more than 1×10^9 monocytes/l, low blast number
- Bone marrow is hypercellular; less than 30% blasts
- Cell cultures: spontaneous growth of granulocyte-macrophage precursors (colony-forming units – granulocyte-macrophage (CFU-GM)
- Hemoglobin F (HbF) increased (according to age)
- Clonal genetic aberrations [monosomy 7, del(7q), trisomy 8, trisomy 21, t(13;14), t(1;3)(p13;p21), der 7 t(7;12)(q21;13), t(3;12)(q21;p13), t(3;15)(q13.1;q26), 5q31–33 abnormalities, t(5;12)(q31;q13), and t(1;5)(q22;q33)]. Philadelphia chromosome: t(9;22) negative

Natural History

Variable. The confusing classification and poor understanding of the disorder are obstacles for a systematic analysis of the data. Individual prognosis and time to disease progression have yet to be elucidated.

Prognosis

Factors with prognostic significance:

- Age: infants (less than 1 year old) have a higher chance of survival
- Low platelet count (less than 100×10^9/l or less), increased HbF (more than 10–15%) and more than 4% of blasts in peripheral blood as well as more than 5% in bone marrow appear to be associated with a poor prognosis

Therapy

Therapy is controversial:

- Scant data because of low patient numbers, i.e. there is no standard therapy. Neither mild or intense chemotherapy, splenectomy nor radiotherapy cure the disease. Cytokines (e.g. interferon) and biological response modifiers do not change survival rates
- Currently allogenous stem-cell transplantation is the only therapeutic option with the potential to increase survival. The number of patients to benefit from stem cell transplantation is not known
- Although different agents with a potential effect have been studied (e.g. Ras peptides as targets of specific immunotherapies, farnesylation inhibitors, inductors of apoptosis) the low number of patients represents a significant obstacle to clinical and laboratory research. International research networks are warranted

Chronic Myelogenous Leukemia (Adult Type)

- Incidence of chronic myelogenous leukemia (CML) in children and adolescents aged 0–20 years is approximately 1:100,000/year
- Male-to-female ratio: 1:8

Clinical Manifestations

Often systemic symptoms such as fever and weight loss. Splenomegaly is often present at initial presentation

Laboratory Findings

- Peripheral blood: hyperleukocytosis (more than 100×10^9 leukocytes/l), frequently with the risk of cerebral leukostasis affecting consciousness. Thrombocytosis frequently observed, thrombocytopenia less common. Anemia infrequently
- Bone marrow: Increase in granulocytes with basophilic and/or eosinophilic granulocytes. Often dysplastic signs. Blasts are uncommon in the chronic phase (less than 5%), but are increased during the accelerated phase and particularly during blast crisis
- Philadelphia chromosome t(9;22)(q34;q11) present as well as the fusion gene *BCR-ABL1* resulting in increased tyrosine kinase activity which plays a central role during the chronic phase. May be inhibited by the "designer drug" imatinib mesylate
- Philadelphia chromosome may also occur in acute lymphoblastic leukemia (ALL) and rarely in AML; however, breakpoints of the fusion gene *BCR-ABL1* are different: CML: fusion protein is p210 in *BCR-ABL1*; ALL: fusion protein is p190 in *BCR-ABL1*

Natural History

- *Chronic phase:* usually oligo- or asymptomatic, sometimes persisting for years
- *Accelerated phase:* characterized by an increase in the size of the spleen and with occurrence of blood count abnormalities (leukocytosis, thrombocytopenia, but also thrombocytosis and anemia). The accelerated phase lasts frequently no longer than 6 months and heralds blast crisis
- *Blast crisis:* in children aged more than 3 years. Usually of myelogenous origin; B- or rarely T-cell ALL may also be seen, particularly in young children

Management

- Treatment strategy: curative treatment, maintenance of chronic phase, palliative
- Drugs: imatinib mesylate (see below), interferon-alpha (see below), cytotoxic agents (busulfan rarely used; hydroxyurea, ara-C). Allogenous stem-cell transplantation: scant pediatric data
  - Interferon-alpha has mostly replaced busulfan and hydroxyurea as monotherapy or in combination with ara-C. Combination with hydroxyurea is being studied
  - Imatinib mesylate is a *BCR-ABL1* tyrosine kinase inhibitor and has revolutionized treatment of CML. Success particularly in patients in the chronic phase.

However, many unanswered questions remain (pediatric aspects, timing, dosage, combination with other drugs, role in stem cell transplantation and in relapse). Since 1998 more than 15,000 patients treated. A complete remission of 68% observed in adults with newly diagnosed CML, i.e. chronic phase in contrast to interferon-alpha and ara-C in 7% of patients. There are still no data of long-term survival compared with interferon-alpha. Appears to be active also in accelerated phase and in blast crisis; this needs further study

- Imatinib mesylate influences treatment strategy of patients with CML. Also results of stem cell transplantation have continuously improved. Pediatric patients may benefit from imatinib mesylate; however, no clear data are currently available. The statement that allogenous stem-cell transplantation is the only curative therapeutic option may still be valid

Polycythemia Vera

Diagnosis

- Increased red cell mass
- Arterial oxygen saturation 92% in association with splenomegaly or two of the following factors:
  - Thrombocytosis (more than 600×10^9 thrombocytes/l)
  - Leukocytosis (more than 12×10^9 leukocytes/l)
  - Increased leukocyte alkaline phosphatase or increased vitamin B12-binding capacity
- Additional criteria: low erythropoietin concentration, spontaneous synthesis of erythroid colonies
- Extremely rare in childhood
- Young age does not protect from complications of polycythemia vera (PV). Complications are often present at the time of diagnosis
- Autosomal recessive and dominant

Clinical Manifestations

- Headache, weakness, loss of weight, pruritus, dizziness
- Splenomegaly, leukocytosis and thrombocytosis frequently observed
- Hypercellular bone marrow
- Cell cultures: increased sensitivity to erythropoietin

Management

- Treatment according to symptoms, red cell mass and arterial oxygen saturation (O2 saturation, O2-saturation curve)
- No standard therapy for pediatric patients
- Hematocrit should be less than 45% to prevent thrombohemorrhagic complications
- Red cells may be eliminated by apheresis

- Cytotoxic agents with risk of leukemogenesis; hydroxyurea may have its place in the treatment of PV if there are more than 1,000×10^9 platelets/l

Essential Thrombocythemia

Secondary (reactive) thrombocytosis (more than 450 × 10^9/l): acute and chronic infectious diseases, hemolytic anemia, iron deficiency, trauma, surgery, renal disorders, blood loss, postsplenectomy, drugs (e.g. corticosteroids)

Differential Diagnosis

- Differential diagnosis: preanalytical and analytical problems, reactive thrombocytosis, myeloproliferative disorders
- Essential thrombocythemia (ET) with autosomal dominant inheritance

Diagnosis

- Platelets: more than 600 × 10^9/l
- Hemoglobin: up to 130 g/l
- Normal iron levels
- No Philadelphia chromosome, t(9;22)
- No bone marrow fibrosis
- No signs of secondary thrombocytosis
- Approximately one-third of patients with an asymptomatic or oligosymptomatic course

Management

- Antithrombotic prophylaxis (e.g. acetic salicylic acid) is not established and is controversial
- Cytotoxic agents are not standardized. Symptoms of the disease must be weighed against adverse effects of drugs
- Anagrelide, a quinazoline derivate, decreases platelet count efficiently and has few adverse effects which do not influence myelogenous cells. Its effect is based on its activity in reducing megakaryopoiesis
- Hydroxyurea is active in myeloproliferative disorders; however, it has been replaced by anagrelide
- Interferon-alpha and -gamma inhibit megakaryopoiesis in vitro and inhibit stem cell proliferation and differentiation in the bone marrow

Idiopathic Myelofibrosis

- Bone marrow fibrosis is well known in clonal hematological disorders: often seen in children in AML-FAB M7 and in the preceding MDS phase of this disorder

- In adults often associated with myeloproliferative disorders (CML, PV) and with MDS, particularly in secondary therapy associated with MDS, CMML and unclassified MDS
- In childhood also in nonclonal disorders, e.g. systemic infectious diseases, hematological disorders such as sickle cell anemia or hypereosinophilic syndrome
- Idiopathic myelofibrosis (IM) may precede malignant disorders for weeks and months
- IM should be regarded as a separate entity, but is a myeloproliferative disorder
- Although rare IM is seen in children, most commonly in girls

Clinical Manifestations

- Hepatosplenomegaly often seen
- Bone marrow may be hypocellular, but also hypercellular with multiple reticulin fibers. Dysplastic signs may be present in erythroid cells and less commonly in myelogenous cells
- Extramedullary hematopoiesis may be observed

Natural History

Variable; frequently there is transition in acute leukemia, particularly to megakaryoblastic leukemia but also to lymphoblastic leukemia

Management

- No standard therapy; stem cell transplantation appears to be the treatment with the best curative potential

Hypereosinophilic Syndrome

- Differentiation between clonal and etiologically unclear eosinophilia is difficult. The latter is induced by abnormal cytokine production. Differentiation between chronic eosinophilic leukemia (CEL) and hypereosinophilic syndrome (HES) may be difficult also (see WHO classification)
- CEL or HES is a diagnosis of exclusion; infectious, inflammatory and neoplastic disorders must be ruled out
- After exclusion of the abovementioned disorders HES or CEL may be differentiated based on presence of clonality

Transient Myeloproliferative Syndrome Associated with Down Syndrome

- In approximately 10% of newborns with Down syndrome
- Spontaneous remission in the majority of children

- Approximately 20% of children with spontaneous remission, acute megakaryoblastic leukemia (AMKL) occurs within the first 4 months, i.e. 1 in 50 of children with Down syndrome
- Incidence of AMKL associated with Down syndrome is approximately 500 times higher than in children without Down syndrome
- AMKL exhibits differences between the two forms of AMKL in childhood
  - AMKL of infancy with t(1;22), with an aggressive evolving course associated with a poor response to chemotherapy
  - AMKL in childhood without a long myelodysplastic phase similar to AMKL associated with Down syndrome and also a poor response to chemotherapy
- Transient myeloproliferative syndrome (TMS) appears not to predispose children with Down syndrome to ALL, although incidence of ALL in children with Down syndrome is increased
- Leukemic cells in AMKL and TMS exhibit many similarities: morphology, cytochemistry and antigen expression pattern. TMS cells typically have somewhat more megakaryocytic differentiation
- There are clear reasons to consider TMS as a leukemia:
  - Pathological cells have megakaryoblastic characteristics similar to AMKL cells
  - The disease may be fatal
  - Skin and placenta infiltrations have been detected
  - Clonal proliferation and chromosomal changes have been identified

Mast Cell Disease (Mastocytosis)

- Mast cells have their origin in hematopoietic stem cells with characteristics typical of myelogenous cells
- Heterogeneous group of disorders
- Abnormal growth and accumulation of mast cells in one or multiple organs
- Often clonal proliferation
- Systemic forms are extremely rare in childhood
- Malignant forms are not observed in childhood
- Frequently a mutation of the proto-oncogene *KIT* may be detected (codes for tyrosine kinase receptor for stem cell factor)
- Classification is difficult and controversial; the most accurate is the WHO classification
- Particularly in children younger than 2 years as solitary cutaneous mastocytosis or more frequently as urticaria pigmentosa
- Often a self-limiting disorder in childhood
- Skin and bones may be affected, but not bone marrow
- Often pruritus caused by histamines; thus treatment is symptomatic (antihistaminic agents)

WHO classification of mast cell disease (mastocytosis)

- Cutaneous mastocytosis
- Indolent systemic mastocytosis
- Systemic mastocytosis with associated clonal, hematological non-mast cell lineage disease
- Aggressive systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma

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Non-Hodgkin Lymphoma (NHL)

Paul Imbach

Definition

- Neoplasia of the lymphatic system and its precursor cells with genetically disturbed regulation of proliferation, differentiation and apoptosis.
- Morphologically and cytogenetically heterogeneous disorders with difficult, variable classification.
- If marked bone marrow involvement is present the clinical condition is equal to that of leukemia.

Incidence

- Five percent of all neoplasias in childhood
- A ratio of 7:1 million children less than the age of 16 years who are newly diagnosed annually
- Peak incidence between 5 and 15 years, rarely before the age of 2 years; in adulthood higher frequency with progressive age
- Ratio of boys to girls is 2:1
- Occasional familial occurrence
- Worldwide variable regional incidence, e.g. in Burkitt lymphoma (BL):
  - Africa: endemic form 10 in 100,000 children; sporadic form 0.2 in 100,000 children
  - Europe and USA: sporadic form only

Etiology, Pathogenesis and Molecular Genetics

- Unknown etiology in humans
- Genetics: often chromosomal alterations are detectable
  - In BL translocation of chromosome 14 t(18:14), the gene location for immunoglobulin production; in addition dysregulation via translocation of c-*MYC* oncogene
- Predisposing factors for Non-Hodgkin lymphoma (NHL) in the following disorders:
  - Acquired immunodeficiency: autoimmune disorders, HIV infection
  - Epstein-Barr virus infection: endemic BL, lymphoproliferative syndrome
  - Congenital B-cell defect: X-chromosomal agammaglobulinemia, selective IgA/M deficiency
  - Congenital T-cell defect with thymus hyperplasia
  - Bloom syndrome, Chédiak-Higashi syndrome, congenital B- and T-cell defects: severe combined immune deficiency (SCID), ataxia telangiectasia, Wiskott-Aldrich syndrome, common variable immune deficiency (CVID)
  - Exposure to irradiation: after atomic bomb explosion; after irradiation of thymus
  - Drug-induced: after immunosuppressive treatment; after hydantoin treatment

Pathology and Classification

- Heterogeneous group of disorders with variable morphological, cytochemical, immunological, biochemical and cytogenetic characteristics of lymphoid or monocytic histiocytic cell elements
- In children mainly the diffuse histological form (i.e. lymphoblastic)
- Nodular form less than 1%
- The earlier different classification and nomenclature systems are now unified in the WHO classification

WHO classification

Histology	Rate	Immunophenotype	Main occurrence
Burkitt lymphoma, Burkitt-like lymphoma	50%	B-cell	Abdomen
Large B-cell lymphoma	7—8%	B-cell	
Lymphoblastic lymphoma	30%	Pre-T-cell or pre-B-cell	Thorax, lymph nodes, bone
Anaplastic, large cell lymphoma	7—8%	T-cell	Lymph nodes, skin, soft tissue, bone
Unclassifiable lymphoma	<5%	Non-T-cell	Variable

Histological, Immunological and Cytogenetic Characteristics of the Different Forms of NHL

Burkitt Lymphoma BL and Burkitt-like LymphomaBLL

- About 50% of NHL
- Localization: abdomen, lymphatic tissue of the adenoids and tonsils (Waldeyer's tonsillar ring)
- Morphology: large vacuolated cells with fine nuclear chromatin, two to five nucleoli, basophilic cytoplasm, L3 morphology (see Chap 2; resembles a starry sky)
- Mainly B-cell NHL with immunoglobulin surface expression (mostly IgM, either of light kappa- or light lambda-chain)
- High Ki-67 value, Mid-1 positivity
- CD19, -20, -22, -77, -79a-positive; sometimes also CD10 and -38-positive; TdT mainly negative
- Eighty percent with translocation t(8;14) or t(8;2) and t(22;8) with c-*MYC* on chromosome 8q24 which stimulates proliferation
- Forty percent with a p53 mutation
- Burkitt-like lymphoma (BLL): mainly with translocation t(14;18) on *BCL6*

Large B-Cell Lymphoma LCBL

- Seven to eight percent of NHL
- Localization: abdomen, peripheral lymph nodes, skin, bone
- Morphology: large cells, frequently with lobulated nucleus and prominent nucleoli (differential diagnosis: Reed-Sternberg cell); sometimes mixture of cells (lymphocytes, macrophages) which makes the exact diagnosis difficult
- Heterogeneous group of B lymphocytes
- CD19, -20, -22, -38, and 79a-positive, occasionally CD10-positive; TdT-negative, surface immunoglobulins negative
- Translocation with *BCL2* and *BCL6* genes, 5–10% with translocation t(8;14)

Lymphoblastic Lymphoma LL

- Thirty percent of NHL
- Morphologically indistinguishable from lymphoid leukemic cells of acute lymphoblastic leukemia (ALL)
- Morphology: mostly uniform cell population, high nuclear to cytoplasmic ratio; mostly lobulated nucleus with fine chromatin structure, nucleoli difficult to discern; morphology is similar to L1/L2 cells (see Chap 2)
- Majority of cells have T-precursor characteristics: CD1, -2, -3, -5, -7, and -8-positive, sometimes also CD4- or CD8-positive which indicates a more mature variant; TdT-positive (as precursor cell)
- Occasionally CD10-positive (CALLA) and HLA-DR-positive
- Mediastinal enlargement (thymus) usually present
- T-cell receptors: Tδ in immature form, Tγ or Tβ detectable in more mature forms
- Ten to fifteen percent with pre-B phenotype: CD10 and -19 as well as HLA-DR positivity; surface immunoglobulins negative
- Various translocations: t(11;14), t(1;14), t(8;14), t(10;14) and others
- Similar to ALL

Anaplastic Large Cell Lymphoma ALCL

- Seven to eight percent of NHL
- Morphology: predominantly anaplastic cells
- CD30-positive, CD15- and -45-positive or -negative; positive for epithelial membrane antigen (EMA)
- Partly T-cell receptor expression (Tβ, Tδ)
- Frequently translocation t(2;5)

Unclassifiable NHL

- Approximately 5% of NHL
- Localization: abdomen, less frequently other locations
- Histology: polymorphic, histiocytic, or follicular forms
- Immunophenotype: predominantly T-cell characteristics

Clinical Manifestations

General Symptoms

- Duration of symptoms: usually a few days to weeks
- Nonspecific symptoms such as fatigue, uneasiness, nausea, anorexia, loss of weight and/or fever

Symptoms in Relation to Location of NHL

Abdomen

- Especially the ileocecal region, mesentery, retroperitoneum, ovaries:
  - Painful spasms, vomiting
  - Obstipation, intussusception: in children more than 6 years of age is suggestive of NHL
  - Appendicitis-like
  - Ileus
  - Ascites
  - Disturbed micturation

Mediastinum

- Mostly in the anterior or middle part of the mediastinum (thymus area):
  - Cough
  - Stridor
  - Dyspnea
  - Wheezing
- Edema of the neck and face with marked dyspnea may indicate superior vena cava syndrome
- Pain of the back or abdomen
- Pleural effusion
- Involvement of adenoid and tonsils, nasopharyngeal lymph nodes, parotid gland swelling, laryngeal compromise with respiratory disturbance

Peripheral Lymph Nodes

- Mostly cervical, supraclavicular and inguinal
- Lymph nodes are firm, not usually tender, but involving multiple lymph nodes that usually occur unilaterally

Other Locations

- Central nervous system (CNS), cranial and peripheral nerves, skin, muscles, bone, thorax, gonads, orbit, parotid gland, epidural region
- Symptoms depend on location

Differential Diagnosis among the Different Forms of NHL

- Burkitt lymphoma BL, sporadic form:
  - Abdomen (25%) with ascites and pleural effusion
  - Pharyngeal and retropharyngeal area including sinuses
  - Bone and bone marrow involvement 20–40%
  - Involvement of CNS is rare
- Burkitt lymphoma BL, endemic form:
  - Mostly in Equatorial Africa
  - Jaw area in about 70% of children less than 5 years of age and in 25% of children more than 14 years of age
  - Abdomen
  - Bone marrow frequency of involvement, 8%
  - CNS and cranial and peripheral nerves including epidural involvement: more frequent in the sporadic than the endemic form
- Burkitt-like lymphoma BLL:
  - Children older than those with endemic BL
  - In contrast to endemic BL more frequent involvement of liver, spleen and mediastinum
- Lymphoblastic lymphoma LL:
  - Intrathoracic and mediastinal in 50–70% of patients
  - Lymphadenopathy in 50–80% of patients, especially supradiaphragmatic
  - Differential diagnosis: ALL has more than 25% of blasts in the bone marrow analyses at diagnosis
- Anaplastic large-cell lymphoma ALCL:
  - Slow progression
  - Involvement of lymph nodes, skin, bone, mediastinum, liver and spleen

Differential Diagnosis of Other Disorders

- Lymph node enlargement in infectious diseases
- Autoimmune lymphoproliferative syndrome (ALPS)
- Hodgkin disease
- Metastatic disease of sarcomas or neuroblastomas
- ALL:
  - By definition: bone marrow analysis with more than 25% of blasts is ALL; with less than 25% of blasts in bone marrow is NHL stage IV
  - Overlap between T-cell ALL and T-cell NHL is possible

Diagnosis

Risk-Adapted Diagnostic Procedure

- Histological diagnosis from lymph nodes, peripheral blood, bone marrow and fluid resulting from pleural effusion or ascites

- In advanced abdominal stage: whenever possible laparotomy should be avoided in order not to delay chemotherapy
- Compression of airways and/or of superior vena cava: emergency situation, noninvasive biopsy and pretreatment with chemotherapy and radiotherapy
- Morphological, immunophenotypical and molecular-cytogenetic analyses are required
- For rapid diagnosis and treatment morphological diagnosis can be adequate
- Serum lactate dehydrogenase (LDH) allows assessment of tumor progression and response to treatment
- Increased serum uric acid levels indicate risk of nephropathy
- Bone marrow aspiration has to be done in at least two different locations
- CSF analysis reveals NHL involvement in about 10% of cases

Radiological Diagnosis

- Ultrasound of peripheral, intra-abdominal and retroperitoneal lymph nodes
- Conventional X-ray or computed tomography (CT) of the thoracic and skeletal disease
- Magnet resonance imaging (MRI) for abdominal and CNS disease; if possible: positron-emission tomography (PET)
- Bone scan

Staging (Murphy/St. Jude)

I	A single tumor (extranodal) or single anatomical area (nodal), excluding mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement
	On same side of diaphragm:
	(a) Two or more nodal areas
	(b) Two single (extranodal) tumors with or without regional node involvement
	A primary gastrointestinal tract tumor (usually ileocecal) with or without associated mesenteric node involvement; gross complete resection
III	On both sides of the diaphragm:
	(a) Two single tumors (extranodal)
	(b) Two or more nodal areas
	All primary intrathoracic tumors (mediastinal, pleural, thymic)
	All extensive primary intra-abdominal disease; unresectable
	All primary paraspinal or epidural tumors regardless of other sites
IV	Any of the above with initial CNS or bone marrow involvement (less than 25%)

Frequency

- Stages I + II: 10–20% of all NHL
- Stages III + IV: 80–90% of all NHL

Therapy

- Due to the rapid growth fraction with tumor doubling time of less than 28 hours and life-threatening complications the diagnostic procedure (staging) and the induction therapy should be begun as soon as possible
- Frequent complications:
  - Tumor lysis syndrome
  - Intussusception of the bowel
  - Ureteric obstruction
  - Cardiac tamponade, obstruction of the airway
  - Paraplegia, meningeal involvement
- Start treatment as early as possible
- Induction of therapy:
  - Careful surveillance of diuresis with monitoring of creatinine, electrolytes, uric acid and liver enzymes
  - Hydration with 3,000 ml/m2 per 24 h i.v.
  - Alkalinization of urine by adding bicarbonate to i.v. fluids
  - Allopurinol (10 mg/kg body weight per day) during the first days of treatment (until normalization of serum level of uric acid); rasburicase, an enzyme that degrades uric acid, may be necessary in severe cases of hyperuricemia
- In high-risk cases, for complications: initial phase with intensive-care monitoring
- Surgical procedure:
  - Total resection in stage I or II with localized tumor masses only
  - Laparotomy for staging and reduction of tumor burden does not influence the prognosis

Therapy and Prognosis of BL, BLL and Large B-Cell Lymphoma LCBL

- Intensive chemotherapy for 3–6 months:
  - Combination with vincristine, corticosteroids, cyclophosphamide or ifosfamide, doxorubicin, etoposide and high-dose methotrexate (5 g/m^2) or high-dose ara-C, respectively
  - Prevention of CNS disease with high-dose methotrexate and ara-C without irradiation in addition to intrathecal chemotherapy
  - Short treatment intervals between chemotherapy courses due to rapid doubling time of NHL cells
  - As soon as ANC (absolute neutrophil count) is more than 500, the next cycle of chemotherapy can be started
  - Prognosis depends on the response rate to chemotherapy and to initial tumor stage

- Decrease in serum lactate dehydrogenate (LDH) level indicates the type of response to chemotherapy
- Overall long-term survival between 70 and 90%

Therapy and Prognosis of Lymphoblastic Lymphoma LL

- Therapy as in ALL: induction, consolidation with CNS-prophylaxis by intrathecal and/or high-dose chemotherapy or irradiation followed by maintenance treatment
- Duration of chemotherapy: 1–3 years as in ALL depending on cell type and stage
- Prognosis: 80–90% long-term survival
  - 30 months after diagnosis relapse is unusual

Therapy and Prognosis of Anaplastic Large-Cell Lymphoma ALCL

- Therapy according to BL/LCBL or LL (see above)
- Results are similar to other NHL with 80% long-term survival

Patients with Partial Response or with Relapse of NHL

- Diagnosis and staging with biopsy as well as positron-emission tomography (PET) concerning vital tumor cells
- Therapy:
  - BL, BLL, LCBL: after reinduction [e.g. ifosfamide, cisplatin, etoposide (ICE)] high-dose chemotherapy with autologous or allogeneic stem-cell transplantation
  - Alternative or adjuvant treatment: CD20 monoclonal antibody (Rituximab)
  - In isolated relapse of CNS conventional therapy and intrathecal chemotherapy (see above)
  - In relapsing LL, after reinduction (see above) allogeneic stem cell transplantation (as in ALL relapse)

Hodgkin Disease

Paul Imbach

Definition

- Hodgkin disease is characterized by progressive, painless enlargement of lymph nodes with continuous extension between lymph node regions
- Diagnostic confirmation by histology of suspect lymph nodes which are infiltrated by different cells (histiocytes, plasmocytes, lymphocytes, eosinophils, and neutrophils)
- The Reed–Sternberg cell is histologically pathognomonic (see below)

Incidence

- Five percent of all neoplasia in childhood
- There are 7 in 1 million children below the age of 16 years with newly diagnosed Hodgkin disease
- Boys more than girls, but during adolescence the incidence is the same in girls as in boys
- Equal frequency between different ethnic groups
- Rare before the age of 5 years; increasing frequency until the age of 11 years; high rate during adolescence and until the age of 30 years
- Peak incidence between 15 and 35 years of age and after 50 years old

Etiology and Pathogenesis

- Correlation with infection (e.g. Epstein–Barr virus), genetic predisposition, disturbed humoral and cellular immune response (see below)
- High incidence in patients with lupus erythematosus, rheumatoid disorders, ataxia telangiectasia, agammaglobulinemia
- Correlation with socioeconomic status: the higher the socioeconomic status the more frequently Hodgkin disease occurs
- Genetics:
  - Familial occurrence known
  - Occurrence in siblings 7 times higher than expected

Pathology

Macroscopic features

- Continuous involvement of directly connected lymph node regions or organs with lymphatic tissue (lung, liver, bone marrow). The spleen is often involved being an important organ of the lymphatic system
- Staging system according to grade of involvement: I–IV, A, or B (see below)

Microscopic features

- Infiltration of the normal tissue structure of lymph nodes by lymphocytes, eosinophilic leukocytes, histiocytes, reticular cells, fibrocytes and collagen tissue

- Pathognomonic: bi- to multinucleated giant cells, i.e. Reed-Sternberg cells: high cytoplasmic content, nuclei multilobulated, diameter of cells 15–45 µm

Molecular Biology

- Cytokines (interleukins, IL). There are associations between:
  - IL-2, -3, -5 and eosinophils
  - Transforming growth factor-a (TGF-a), tumor necrosis factor (TNF) and fibrosis
  - IL-1, -6, TNF and B symptoms (see below)
  - TGF-a, IL-10 and immunosuppression
  - IL-1, -6, -9 and expression of Reed-Sternberg cells

Histological Classification

Classic Hodgkin disease: predominance of T-cell lines

- Nodular-sclerosing: common in adolescents together with mediastinal enlargement; lymphoid tissue separated by collagen bands
- Lymphocyte-depleted: usually advanced stage of disease
- Mixed cellular: pleomorphic with high cellularity
  Diffuse fibrotic type with few Reed-Sternberg cells
  Reticular type with pleomorphic anaplastic Reed-Sternberg cells, also called "Hodgkin sarcoma" with often more rapid progression and unfavorable prognosis

Lymphocyte-predominant Hodgkin disease: predominance of B-cell line

- Favorable prognosis
- Subgroups of lymphocyte-rich and nodular lymphocyte-predominant Hodgkin disease
- Lymphoma with nodular structure, also called "nodular paragranuloma"

Immunophenotype

Phenotype	Cluster determination CD				
Classic Hodgkin disease (nodular-sclerosing, mixed cellular, lymphocyte-depleted)	15+	20±	30+	45–	RS+
Lymphocyte-predominant Hodgkin disease	15–	20+	30–	45+	RS±

RS Reed-Sternberg cell

Approximate Frequency of Histological Subtype and Stage

	Rate (%)	Stage (%)	
		I + II	III + IV
Lymphocyte-predominant	11.5	76	24
Nodular-sclerosing	54.5	60	40
Mixed cellular	32	44	56
Lymphocyte-depleted	2	19	81

- Correlation between histological subtype and age of patients:
  - *Small children:* often lymphocyte-predominant Hodgkin disease, rarely lymphocyte-depleted Hodgkin disease
  - *Children and adolescents:* mostly nodular sclerosing or mixed cellular Hodgkin disease

Staging Classification

Ann Arbor Staging Classification

- I: involvement of a single lymph node region (I) or of a single extralymphatic organ site (I_E)
- II: involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E)
- III: involvement of lymph node regions on both sides of the diaphragm (III) which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ (III_E) or site, or both (III_{ES})
- IV: diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement

A/B Staging

- A: absence of B symptoms (see below)
- B: presence of the following symptoms:
  - Loss of 10% or more body weight in the 6 months preceding diagnosis
  - Presence of unexplained fever higher than 38°C for three consecutive days
  - Drenching night-sweat

Clinical Presentation

- Painless enlargement of lymph nodes mostly in the cervical and supraclavicular regions (see below)
- Swollen lymph nodes are firm, not inflammatory and painful to palpation
- Extension occurs most commonly from one lymph node group to another:
  - Cervical 75%
  - Supraclavicular 25%
  - Axillary 9%
  - Infradiaphragmatic 6%
- Extranodal involvement:
  - Lung 6%
  - Bone 5%
  - Liver 2%
- In mediastinal involvement: a cough is common, sometimes with dyspnea, dysphagia and enlargement of the vessels of the neck
- Infection: predisposition to bacterial or viral infection:
  - Herpes zoster virus
  - *Cryptococcus*
  - *Listeria monocytogenes*
  - *Diplococcus pneumoniae*
  - *Toxoplasma gondii*

B symptoms occurring in 20–30% of patients

- Fever higher than 38°C
- Night sweats
- Loss of more than 10% body weight
- Sometimes pruritus and/or nausea

Involvement of Organs and Organ Systems

Spleen

- Commonly enlarged; enlargement not correlated with extension of Hodgkin disease

Lungs

- Pulmonary involvement in patients with mediastinal enlargement; in about 20% also pulmonary involvement as solitary peribronchial or subpleural lesion
- Intraparenchymal:
  - Nodular form: similar to lung abscess, tuberculosis or fungal infection
  - Alveolar form: similar to pneumonia
- Pleural manifestation when obstruction of lymphatic channels is present (rarely)

Bone marrow
- Bone marrow involvement in patients with B symptoms and with anemia; low WBC and/or thrombocytopenia
- Multiple bone marrow biopsies necessary because involvement is mostly focal
- Bone scintigraphy may indicate biopsy location

Bone
- Involvement via hematogenous spread
- Vertebral involvement with spinal compression or with vertebral body collapse as well as involvement of epidural area is known
- Bone involvement indicates poor prognosis

Liver
- Involvement mostly together with concomitant splenic disease
- Histologically diffuse or nodular pattern
- Hodgkin involvement of the liver is prognostically unfavorable
- Nonspecific hepatomegaly with or without abnormal liver-function tests is often described in Hodgkin disease
- Differential diagnosis: hemolysis, hepatitis due to virus, toxoplasmosis, cytomegalovirus infection, cholestasis, periportal infiltration of lymph nodes

Laboratory Analyses

Blood
- Anemia indicates an advanced stage of disease or an autoimmune phenomena of hemolysis with or without thrombocytopenia and neutropenia
- Neutrophilia and eosinophilia occur in 15–20% of patients
- Occasionally thrombocytosis
- Lymphocytopenia indicates an advanced stage of the disease
- High erythrocyte sedimentation rate in active Hodgkin disease; normal during remission
- Bone marrow involvement (see above)

Chemistry
- Serum copper and ferritin level often high
- Differential diagnosis: high serum copper estrogen induced by contraceptive medication

Immunological analyses
- Immune response decreased
- Decreased mitogen-induced T-cell function
- Hypersensitivity to T-suppressor cells
- Increased risk of bacterial, fungal or viral infections, especially after splenectomy
- Herpes zoster virus infection in 35% of patients during or after irradiation therapy
- In children with complete remission disappearance of immunological deficits after treatment (in contrast to adults)

Radiological Evaluation

Chest

- Evaluation by X-ray, computed tomography (CT), or positron emission tomography (PET)
- Enlargement of mediastinal nodes in the anterior and middle mediastinum mostly
- Posterior mediastinal enlargement usually together with retroperitoneal lymph node involvement
- Lung tissue involvement (see above)
- Manifestation of thoracic Hodgkin disease is often correlated with nodular sclerosing histology

Abdomen

- Ultrasound, magnetic resonance imaging (MRI), and PET for documentation of abdominal involvement
- Lymphangiography is rarely indicated and is contraindicated in patients with mediastinal involvement
- Combination of venocavography and intravenous urography only indicated in unclear retroperitoneal involvement

Bone

- Bone involvement occurs in advanced disease with radiologically sclerotic and lytic appearance, mostly seen in vertebral bone and/or pelvic bone
- Technetium scintigraphy is indicated in patients with bone pain, B symptoms or a high level of serum alkaline phosphatase

Differential Diagnosis

- Toxoplasmosis, tuberculosis, atypical infection by mycobacteria
- Non-Hodgkin lymphoma characterized by rapid progression; high serum level of lactate dehydrogenase (LDH)
- Infectious mononucleosis
- Metastatic disease
- Thymus hyperplasia
- Rheumatoid arthritis, systemic lupus erythematosus, other autoimmune disorders
- Sarcoidosis, chronic granulomatous disorder

Treatment

- Procedure depends on stage and histopathology
- Multidisciplinary management results in a high cure rate
- Mostly a combination of chemo- and radiotherapy is necessary
- Chemotherapy induces marked diminution of tumor burden or remission in stages I, II and IIIA
- In cases of unsatisfactory response to chemotherapy or in stages III and IV radiotherapy and occasionally additional chemotherapy is recommended

Chemotherapy

Combinations of cytotoxic agents at monthly intervals (usually 2–6 courses)		
		Toxicity
(C)OPPA	Cyclophosphamide (Cytoxan), vincristine (Oncovin), procarbazine, prednisone, doxorubicin (Adriamycin)	Hypospermia, cardiomyopathy
OEPA	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin)	Cardiomyopathy
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine	Lung fibrosis

Radiotherapy

- Curative dose between 35 and 40 Gy without adjuvant chemotherapy, between 15 and 25 Gy combined with chemotherapy
- In patients with unfavorable prognostic factors: instead of involved-field irradiation extended-field irradiation used above the diaphragm as total nodal irradiation, i.e. mantle-field irradiation, below the diaphragm as "inverse Y" (para-aortic, iliac and sometimes spleen irradiation)

Favorable prognostic factors in Hodgkin disease

- Low number of involved lymph nodes
- No large tumor burden
- No B-staging
- No extranodal manifestation
- Stages I, II, and IIIA

Relapse

- In the majority of patients relapse occurs within the first 3 years after diagnosis; late relapses in children are rare
- The rate of second remission after combined chemo- and radiotherapy is about 80%
- In patients who do not respond satisfactorily to treatment high-dose therapy with stem cell transplantation is indicated
- The risk of a second malignancy is high after Hodgkin disease

Side Effects and Sequelae

- Initially high susceptibility to infection
- Herpes and varicella infections after irradiation in 30–40% of patients

"Biochemical" or clinical hypothyroidism

- After irradiation in the cervical region often elevation of the serum TSH level with or without T_3 and T_4 elevation within the first 6 years after irradiation, i.e. biochemical hypothyroidism
- Thyroxine substitution is necessary when biochemical manifestations of hypothyroidism occurs (for prevention of hypophysial hyperplasia)

Gonadal dysfunction

- In adolescent girls after irradiation of the retroperitoneal region there is secondary amenorrhea and decreased fertility. Preventive ovariopexy before irradiation is sometimes practiced
- In adolescent boys undergoing procarbazine therapy azoospermia is often persistent; serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are increased and serum testosterone level is decreased. Avoid procarbazine; cryopreserve sperm before treatment

Decrease in bone growth of irradiated area

- Irradiation in children during periods of rapid growth results in diminution of bone growth: seated height is less than 1–3 standard deviations from the norm
- With partial irradiation of vertebral bone scoliosis occurs

Pneumonitis and pericarditis

- After mediastinal involvement pneumonitis and/or pericarditis
- After bleomycin therapy fibrosis of the lung

Infection After Splenectomy

- Without prophylactic measures (see below) life-threatening infections with a lethality of about 4%
- Main pathogens: *Diplococcus pneumoniae*, *Haemophilus influenzae*, *Streptococci*, *Neisseria meningitis*
- Prevention: polyvalent vaccination, continuous prophylaxis with penicillin, emergency card for the patient

Secondary Tumors

- Secondary tumors are common after Hodgkin disease owing to the concomitant immunodeficiency and the effects of radiation and chemotherapy
- The frequency is 8–16% within 20–30 years after diagnosis of Hodgkin disease
- Main secondary tumors: Non-Hodgkin lymphoma, leukemia (mostly acute nonlymphatic leukemia); solid tumors include sarcomas, breast cancer and thyroid cancer

Prognosis

- *Stage I—III*: 80–90% event-free survival
- *Stage IV*: 60–70% event-free survival
- Unfavorable prognostic factors:
  - Mediastinal enlargement
  - B-stage: fever, sweating, loss of weight
  - Histology: lymphocyte depletion
  - Age: a less favorable prognosis for adolescents than for children

Follow-up Observation

- Observation by clinical and radiological examination including ultrasounds during the first 4–5 years after diagnosis
- Observation concerning sequelae: thyroid function tests (after irradiation), electrocardiography and echocardiography (after anthracycline treatment), pulmonary function tests (after mantle-field irradiation and/or bleomycin treatment)
- Diagnosis of sexual function and fertility
- Follow-up of psychosocial integration and support

Histiocytoses

Paul Imbach

Definition and Overview

Histiocytoses are characterized by histiocytic infiltration of tissue and organ systems in localized or disseminated forms.

Conditions

Langerhans cell histiocytosis (LCH)

- Localized form mainly as eosinophilic granuloma of the bone
- Disseminated form with bone lesions, diabetes insipidus, exophthalmos and retro-orbital granulomas (formerly Hand–Schüller–Christian syndrome)
- Disseminated form with involvement of various organs (formerly Abt–Letterer–Siwe syndrome of infants and small children)

Infection-associated hemophagocytic syndrome (IAHS)

Familial erythrophagocytic lymphohistiocytosis (FEL)

Malignant histiocytosis

- Acute monocytic leukemia
- Malignant histiocytoma (MH) mostly as anaplastic large-cell lymphoma of the child (ALCL; see Chap 6)
- Histiocytic sarcoma

Langerhans Cell Histiocytosis LCH

- Disorder with clonal and cytokine-induced proliferation of qualitatively abnormal Langerhans cells
- Extension variable: ranging from a solid lesion of the bone to the disseminated form with or without organ dysfunction
- Spontaneous regression is possible

Incidence

- Three percent of neoplasias in children
- Four to eight in one million children less than 16 years of age are diagnosed each year
- Ratio of boys to girls: 1:1
- Peak age 1–4 years old
- In children below the age of 2 years acute, life-threatening form with multiorgan involvement and organ dysfunction in about 20% of children

Etiology and Pathogenesis

- Unknown cause
- Langerhans cell histiocytosis (LCH) is characterized by infiltration and accumulation of Langerhans cells in addition to an immune mixed-cellular infiltrate of monocyte-macrophage cells with disturbed immunoregulatory function
- Signs and symptoms such as fever, lytic bone lesions, lymphadenopathy and skin rash are due to local expansion of lesions and the release of tissue-damaging cytokines

Histopathology

- The Langerhans cell is characterized by:
  - Birbeck granules (X-bodies) visible on electromicrographs which are cytoplasmic lamellar plates with terminal vesicular dilatation; they have a so-called racket-shaped appearance
  - Positive surface antigens for S100 and CD1a, Fc and C3 receptors, CD11 and CD14 expression
- The lesion consists of mixed cellular infiltrates with macrophages, eosinophils, neutrophils, lymphocytes, multinucleated giant cells and pathological Langerhans cells. The lesion may have zones of necrosis, fibrosis, hemorrhage and hemosiderosis. Macrophages with vacuoles and cytoplasmic debris may be present
- Cytochemically the Langerhans cells may contain adenosine triphosphatase (ATPase), aminopeptidase, cholinesterase, acid phosphatase, sulfatase and/or a-naphthyl acetate esterase

Clinical Presentation

General symptoms

- Often chronic otitis media
- Diabetes insipidus
- Fever
- Weight loss
- Lethargy and irritability

The following organ systems may be involved:

Bone

- Painful swelling of the involved bone
- Localization: mostly in the skull and pelvic bones; in small children often in several different locations
- In patients presenting with a single lesion often additional lesions occur within the next 6 months unless treatment is given

- Radiologically bones show lytic lesions with a punched-out appearance with or without marginal sclerosis and periosteal reactions
- Infiltration of the orbit leads to proptosis, exophthalmos and asymmetry of the eyes
- Infiltration of the jaw with loose, painful teeth, tender swelling of the mandible and/or maxilla
- Infiltration of the mastoid leads to chronic otitis or mastoiditis
- Vertebral lesions may cause collapse of vertebral bone (vertebra plana) followed by scoliosis
- Under treatment bone lesions recover slowly and may remain sclerotic for many years

Skin
- Seborrhoic maculopapular exanthema, sometimes with crusting; usually reddish-brown or purple
- Petechial lesions occur mainly in advanced forms of the disease in infants and small children
- Xanthomatous skin lesions occasionally present
- Ulcerative changes of the oral cavity and in the genital and perianal region are common
- Appearance of the skin and mucosal changes resemble extensive seborrheoic dermatitis (differential diagnosis)
- Skin biopsy confirms the diagnosis

Lungs
- Often asymptomatic
- Occasionally cough, dyspnea, cyanosis, pneumothorax and/or pleural effusion
- Pulmonary dysfunction occurs mainly in children below the age of 2 years, but may also be the first manifestation in adolescents
- Interstitial fibrosis with hypoxemia and cor pulmonale in progressive disease
- Radiologically: reticulonodular pattern of interstitial infiltration expanding from central to peripheral lung tissue; upper lobes most commonly involved
- Pulmonary function tests are useful in following up patients and lung biopsy is necessary for exclusion of concomitant, opportunistic lung infection

Lymph nodes
- Often generalized adenopathy, especially in patients with cervical, axillary and inguinal involvement
- Occasionally localized enlargement of a lymph node or cluster of nodes

Liver
- Hepatomegaly with or without increased serum liver enzymes
- Abnormal coagulation parameters (serum fibrinogen decreased, prothrombin time prolonged) indicate liver dysfunction
- Jaundice in patients with infiltration of intra- and extrahepatic bile system

Spleen
- In one-third of children with LCH spleen involvement
- In marked splenomegaly high sequestration of erythrocytes, leukocytes, and platelets results in pancytopenia and indicates an unfavorable prognosis

Endocrine organs
- *Diabetes insipidus*:
  - In about 10–30% of patients
  - Polydipsia and polyuria
  - May occur before a definitive diagnosis, at the time of diagnosis, whether in treatment or post-treatment
  - Serum antidiuretic hormone (ADH) level is low
  - Diagnostic tests using serum or urine osmolarity; perform water-deprivation test in unclear situations
- *Growth retardation*: often in combination with diabetes insipidus (see also long-term sequelae)
- Thyroid involvement in LCH can occur, but thyroid dysfunction is usually associated with hypothalamic disease

Central nervous system
- Intracranial hypertension or pseudotumor cerebri can be a sign of isolated or multifocal LCH
- There may also be parenchymal and/or leptomeningeal involvement
- Neurodegenerative disease (NDD) occurs in a subset of patients with particular risk factors such as orbital or sphenoid bone involvement. NDD commonly includes signs of cerebellar ataxia

Blood
- Often mild anemia and increased number of granulocytes
- Pancytopenia as expression of hypersplenism or marked infiltration of bone marrow

Immune system
- Multiple dysfunction of the immune cascade from antigen presentation to antibody production
- Occasionally autoimmune phenomena
- Production of anti-erythrocytic antibodies
- Diminution of suppressor T-lymphocytes
- In massive infiltration of lymphatic organs such as the thymus resemblance of immune deficiency with low levels of serum immunoglobulins, altered cellular immune response and increased susceptibility to infections may be apparent

Gastrointestinal tract
- Malabsorption syndrome
- Protein-losing enteropathy (protein-loss syndrome)

Clinical manifestations of LCH (in order of frequency)	
Bone lesions (mainly skull)	65–75%
Solitary bone lesion	40%
Skin and mucosal manifestations	30–40%
Otitis media	15–25%
Exophthalmos	15–25%
Oral cavity changes	15–25%
Diabetes insipidus	20%
Pulmonary involvement	15%
Hepatosplenomegaly	30%
Lymphadenopathy	30%
Hematological changes	30%
Growth retardation	<10%
Sexual retardation	<10%
Protein-losing enteropathy	<10%

Differential Diagnosis

Beside the other forms of histiocytosis (see below):
- Reactive histiocytosis with dysfunction of various organs: in chronic infections (e.g. tuberculosis, atypical mycobacterial infection, toxoplasmosis, cytomegalovirus infection), rheumatoid disorders, sarcoidosis, autoimmune disorders, storage diseases (e.g. silicosis, asbestosis, hemosiderosis), chronic granulomatous disease
- Severe combined immune deficiency (SCID)

Prognosis

- Initial response to therapy in the first 6–12 weeks is the most important prognostic factor.

Unfavorable prognostic factors are:
- Age at diagnosis less than 2 years, especially less than 6 months of age
- Number of involved organs: the higher the number of organ systems involved the less favorable the prognosis (see Lahey score below)
- Presence of organ dysfunction especially of lung, liver or bone marrow infiltration
- Extensive skin involvement (with exception of infants with isolated skin involvement)

Lahey score

Involved	Prognosis					
	Good		Moderate		Poor	
	Infiltration	Dysfunction	Infiltration	Dysfunction	Infiltration	Dysfunction
Bone	+	—	+	—	+	—
Bone marrow	—	—	+	+	+	+
Lymph nodes	+	—	+	—	+	—
Skin	+	—	+	—	+	—
Liver	—	—	+	—	+	+
Spleen	—	—	+	—	+	—
Hypophysis	+	+	+	+	+	+
Lungs	—	—	—	—	+	+

Prognostic rules

- Favorable in children more than 2 years old without organ dysfunction
- Variable in children less than 2 years old without organ dysfunction
- Poor in children less than 2 years old with organ dysfunction

General Therapeutic Approach

Surgery
- Biopsy for diagnostic evaluation
- In patients with isolated bone involvement curettage without risk of sequelae (e.g. collapse of vertebra)

Radiotherapy
- Where there is unifocal involvement and risk of sequelae (e.g. risk of vertebral bone collapse with neurological sequelae)
- Dose of 7–10 Gy is usually sufficient
- Irradiation is indicated in the following locations and/or with high risk of sequelae:
  - Orbit
  - Mastoid
  - Vertebral bone
  - Base of skull
  - Ulceration of skin
  - Untreatable pain
  - Pathological fracture with prolonged recovery

Chemotherapy
- Indicated in disseminated multifocal manifestation
- Active substances: vincristine, vinblastine, prednisone, etoposide, cyclophosphamide, doxorubicin, procarbazine, 2-chlorodeoxyadenosine
- Maintenance treatment with 6-mercaptopurine and methotrexate
- Duration of treatment: 6–12 months; some patients with multiple relapses need long-term treatment

Stem cell transplantation
- In high-risk patients, e.g. disseminated form or in patients who do not respond to conventional treatment
- In patients with life-threatening relapse

Long-term Sequelae

- Occasionally long-term chronic active disorder in patients with generalized LCH including bone involvement
- Sequelae occur in endocrine, pulmonary, skeletal, hepatic, neurological, neuropsychiatric systems or as secondary malignant disorders

Endocrine sequelae
- Diabetes insipidus
- Growth retardation and short stature: often concomitant with diabetes insipidus and together with delay or absence of puberty
- Hyperprolactinemia with or without galactorrhea
- Hypogonadism: in approx. 4% of patients
- Panhypopituitarism
- Hypothyroidism

- Hyperosmolar syndrome with hypernatremia and defective osmolar regulation can be life-threatening in patients with concomitant diabetes insipidus (severe dehydration and hyperosmolar coma)

Pulmonary sequelae
- Opportunistic infection due to *Pneumocystis carinii*, *Aspergillus*, *Pseudomonas* or other infectious agents
- Lung fibrosis in two-thirds of patients with LCH lung involvement or with chronic relapsing lung

Hepatic sequelae
- Liver fibrosis and liver cirrhosis

Psychosocial problems
- Neurocognitive abnormalities
- Psychomotor retardation

Secondary Tumor

Occurring mainly in irradiated locations of LCH patients in the form of:
- Astrocytoma, medulloblastoma, meningioma
- Hepatoma
- Osteogenic sarcoma of the skull
- Carcinoma of the thyroid

Special Forms of LCH

Acute disseminated LCH (formerly Abt–Letterer–Siwe syndrome)
- Severely ill child with involvement of two or more organs
- Mostly acute disease with dysfunction of organs (lung, liver, bone marrow, central nervous system CNS)
- Mostly in infants or children less than 2 years of age
- Unfavorable prognosis

Chronic-disseminated or multifocal LCH (formerly Hand–Schüller–Christian syndrome)
- Often chronic disease
- The majority are children more than 2 years of age
- Rarely organ dysfunction
- Mostly characterized by bone lesions in skull, pelvis and extremities
- Exophthalmos in children with orbital lesions of one or both sides
- Diabetes insipidus: frequently severe form, sometimes partial or transient form: ADH-deficit; in magnetic resonance imaging (MRI) hypodense lesions in the hypothalamic and pituitary region
- Occasionally growth retardation or retardation of sexual maturation caused by hormonal deficiency

Eosinophilic granuloma
- Unifocal or multifocal lesions of bones, lymph nodes or lungs

- In children with eosinophilic granuloma of the bone, usually a favorable outcome
- Peak incidence between 5 and 10 years; occurs also in adolescents and adults
- Often asymptomatic disease with coincidental diagnosis on radiological examination
- Systemic spread occurs rarely and within the first 6 months after first manifestation
- On X-rays the lesions are characterized by a punched-out appearance without sclerosis or periosteal reactions of the bone.
- Occasionally pathological fracture of lesions in the long bones may occur (differential diagnosis: chronic osteomyelitis)
- Lesions in the vertebral bones may collapse with adverse neurological or orthopedic consequences

Percentage of bone lesions of eosinophilic granuloma	
Skull	50%
Femur	17%
Orbit	11%
Ribs	8%
Humerus, mandible, tibia, vertebrae	7%
Clavicle	5%
Fibula, sternum, radius	<5%

Infection-associated hemophagocytic syndrome IAHS

- Similar pathology, clinical manifestation, and laboratory diagnosis to familial erythrophagocytic lymphohistiocytosis (FEL); or primary or inherited hemophagocytic lymphohistiocytosis (HLH) (see below)
- More favorable course when good response to treatment and to associated infection by antibiotics, antiviral agents etc.

Familial Erythrophagocytic Lymphohistiocytosis FEL

Definition

- Familial occurrence with autosomal recessive inheritance
- First occurrence usually in infancy
- Also described as isolated occurrence without familial history

Pathology and Genetics

- Histopathologically characterized by diffuse, mixed lymphohistiocytic infiltration with erythrophagocytosis or hemophagocytosis
- Disturbance of cellular and humoral immunity, particularly of cytotoxic T-lymphocytes and natural killer cells
- Occasional monoclonal gammopathy
- Chromosomal abnormalities of chromosomes 9q21.3–22 and 10q21–22 (10q21–22 is the gene locus of associated perforin deficiency)
- The *UNC13* genes which are involved in cytolytic granule movement are also mutated in some forms of inherited HLH

Clinical Presentation

- Manifestation within the first 3 months of life in the majority of patients; in a minority first occurrence within the first 4 years of life
- Nonspecific symptomatology such as fever, pallor, vomiting, diarrhea, anorexia, irritability
- Often lymphadenopathy and hepatosplenomegaly
- Often multiorgan involvement. *Lung, liver, and CNS*: diffuse perivascular and parenchymal infiltrates with or without involvement of cerebral spinal fluid. *Eyes*: infiltration of vitreous cavity, uvea, iris, retina, choroid and optic nerve

Laboratory Analyses

- Pancytopenia is common
- Bone marrow with erythrophagocytosis and high numbers of histiocytes, lymphocytes, precursor cells of all cell lines with maturation arrest and hyperplasia of erythropoiesis
- Hypofibrinogenemia and hyperlipidemia
- Impaired immunity of the humoral and cellular immune response, hypogammaglobulinemia, anergy to specific antigens although B- and T-lymphocyte subsets may be present in normal distribution
- Natural killer cells are decreased and/or have decreased cytolytic function

Clinical Course

- Intermittent fever
- Progressive pancytopenia
- Liver dysfunction with jaundice
- Hemorrhage
- Meningitis
- Often lethal outcome within weeks or a few months

Differential Diagnosis

- Infection-associated hemophagocytic syndrome (IAHS) and FEL with negative staining for S-100 and CD1 in histiocytes
- Juvenile xanthogranulomatosis of the skin:
  - In newborns and small children
  - Usually a benign course
- Reticulohistiocytosis of the skin during the perinatal period:
  - With multiple, dark red and dark blue skin infiltrations which disappear spontaneously within 3–4 months

Therapy

- Chemotherapy with vinblastine, etoposide, cyclosporine and corticosteroids may result in transient improvement, then can be followed by allogeneic stem-cell transplantation
- Supportive treatment and antibiotics

Malignant Histiocytosis

Incidence

- Disease of adults, occasionally also in children and adolescents
- Predominant in men

Pathology

- Proliferation of atypical histiocytes and precursor cells mostly in the subcapsular part of lymph nodes
- Progressive extension of disease similar to Hodgkin disease (differential diagnosis: Hodgkin disease stage IV, anaplastic lymphoma)

Clinical Presentation

- Fever
- Lymphadenopathy, hepatosplenomegaly
- Maculopapular and nodular skin infiltration of atypical histiocytes
- Pancytopenia due to hypersplenism
- Often rapid onset and progressive disease with multiorgan involvement

Therapy

- Intensive chemotherapy with combinations of vincristine, doxorubicin, cyclophosphamide and prednisone, or M-BACOD (high-dose methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin and dexamethasone)
- Stem cell transplantation is sometimes indicated

Brain Tumors

Paul Imbach

Overview

- Largest group of solid tumors of childhood
- Prognosis depends on location, histology, stage, operability or adjuvant chemo- and radiotherapy
- High rate of morbidity and long-term sequelae

Incidence

- Nineteen percent of all neoplasia in childhood
- Annually 26 in 1 million children below the age of 16 years are newly diagnosed
- Slightly higher frequency in boys (especially for medulloblastoma and germinoma). Ratio of boys to girls 1.25:1

Tumor Types and Frequencies

Tumor type	Mean frequency (%)
Astrocytoma	40
Brain stem tumor	10–25
Optic glioma	4
Medulloblastoma	15
Ependymoma	6–9
Pineal tumor	2
Craniopharyngioma	7
Others[a]	15

[a]Meningioma, oligodendroglioma, primitive neuroectodermal tumor, sarcoma

Etiology and Pathogenesis

- Deletion of chromosome 17 or 20, especially in medulloblastoma
- Relationship to other hereditary disorders (see overview below)

Relationship between Hereditary Disorders and Brain Tumors

Syndromes	Tumor type
Neurofibromatosis 1	Neurofibroma, optic glioma, astrocytoma
Neurofibromatosis 2	Schwannoma, meningioma, ependymoma
Tuberous sclerosis	Astrocytoma (subependymal)
von Hippel–Lindau syndrome	Hemangioma
Li–Fraumeni syndrome	Astrocytoma, medulloblastoma, primitive neuroectodermal tumor (PNET)

- Some familial and sibling occurrence of brain tumors have been described
- High incidence of chromosomal aberrations with development of neoplasia after previous prophylactic or therapeutic radiation in the brain and skull area (i.e. in patients with leukemia)
- Genetic factors

Pathology and Classification

- Classifications are based on histogenesis and predominance of cell type
- Degree of malignancy is defined by grading system, i.e. WHO grade I–IV which is based on the cellular morphology, the rate of mitotic figures, the degree of anaplasia and the frequency of necrosis
- Other classifications include immunohistochemical and molecular biological analysis
- Immunohistochemistry: monoclonal antibodies against cytoskeletal and membrane proteins, hormonal polypeptides and neurotransmitters. Examples: vimentin, neurofilamentous protein (NFP), gliofibrillary protein (GFAP), desmin
- Immunohistochemical and molecular biological markers provide subtypes of tumor according to stage of development and differentiation

Types of brain and spinal cord tumors

1. Neuroepithelial origin of cells glial cells:	**Degree of malignancy**
Astrocytoma	Grade I
Astrocytoma	Grade II and III
Glioblastoma multiforme	Grade IV
Ependymoma	Grade I + II
Ependymoblastoma	Grade III + IV
Choroid plexus carcinoma or poorly differentiated anaplastic ependymoma	—
Oligodendroglioma	Grade I
Oligodendroglioblastoma	Grade II–IV

Neuroepithelial origin of nerve cells:

Medulloblastoma: anaplastic subtype with poor prognosis
Neuroblastoma

2. Pineal tumors
Pinealoma
Pinealoblastoma
Germ cell tumors
Nongerminomatous germ cell tumors (NGGC)

3. Tumor of hypophysis
Craniopharyngioma

4. Mesenchymal origin
Meningioma
Neurofibroma
Angioma
Hemangioblastoma

5. Chordoma

6. Congenital aberrations
Hamartoma
Teratoma
Dermoid cysts
Epidermoid cysts (cholesteatoma)

Clinical Manifestations

Symptoms depending on:

- Location of tumor
  - Infratentorial (posterior fossa) 60%
  - Supratentorial 40%
  - Midline 15%
  - Cerebral hemisphere 25%
- Rate of tumor growth:
  - Slow growth: with displacement of normal nervous structures, slow development of symptoms and large tumors at diagnosis
  - Rapid growth with early symptoms even in small tumor

Hydrocephalus and Manifestations of High Intracranial Pressure

- Blockade of cerebral fluid circulation by tumor causes hydrocephalus, often in the area of the fourth ventricle (posterior fossa) where more than 50% of brain tumors are located
- *Headache:*
  - Initially: bifrontal or diffuse depending on position, early in the morning disappearing after change to the upright position, accompanied by nausea and vomiting
  - As headache develops: paroxysmal occurrence due to high intracranial pressure
- *Nausea and vomiting:*
  - Often in relation to headache
  - Nighttime vomiting
- *Visual disturbances* (mostly abducens palsy):
  - Diplopia
  - Strabismus
  - Visual loss and/or visual field loss
  - Head turns to one side
- *Change of personality*: Lethargy, apathy, irritability, somnolence
- *Head enlargement* in infants and young children (less than 2 years of age)

Focal Neurological Failures

- Dependent on locations
- Epileptic convulsions
- Ataxia
- Visual loss and/or visual field loss
- Cranial nerve palsy
- Peripheral neurological disturbances (see Special Tumor Types)

Tumor Types and Symptoms According to Intracranial Location

Cerebral hemisphere

Most frequent tumor types

- Astrocytoma
- Ependymoma
- Oligodendroglioma
- Meningioma

- Main symptoms: focal cerebral dysfunction and/or epilepsy in cortical tumors; hemiplegia and visual field defects in subcortical tumors
- Frontal: anterior frontal globe:
  - Few clinical signs until a large tumor evokes pressure; personality and emotional changes: blandness and indifference to surroundings
  - Gyrus precentralis to capsula interna: contralateral weakness of the face; of the extremities, change in handedness as early sign; disturbance of fluent speech but intact comprehension (Broca aphasia). Seizure type: adverse turning of the eyes and head toward the opposite side, focal tonic or clonic convulsion of the contralateral extremity
- Temporoparietal
  - Focal seizure with secondary generalization of seizure
  - Postictal, transient neurological deficit
  - Seizure associated with contralateral hemisensory phenomena and with visual field defects (contralateral homonymous hemianopia)
  - Loss of stereognosis
  - Contralateral homonymous hemianopia
- Occipital
  - Visual field defects
  - Uni- or bilateral abducens weakness with diplopia and signs of increased intracranial pressure
- Deep subcortical cerebral tumors
  - With contralateral extrapyramidal symptoms: tremor, athetosis, rigidity, hemiballismus
- Thalamic involvement:
  - Contralateral hemiplegia
  - Increased intracranial pressure
  - Visual field defects

Parasellar-optic chiasma area

- Tumors arise from pituitary gland and hypothalamus

Common Tumor Types

- Craniopharyngioma
- Optic glioma, astrocytoma, hypothalamic glioma, hypothalamic hamartoma
- Hypophyseal adenoma
- Chordoma, germinoma

- Diencephalic syndrome:
  - In infants: anorexia, cachexia and euphoria; nystagmus in about 50% of children
  - In children: hyperphagia and obesity; growth retardation, diabetes insipidus, hypogonadism
  - In adolescents: anorexia nervosa; in hypothalamic hamartoma: precocious puberty
- Bitemporal hemianopia
  - Unilateral blindness with contralateral temporal hemianopia
  - Frequently optic atrophy
- Internal hydrocephalus
  - In tumor progression: occlusion of foramen of Monroi or aqueduct of Sylvius
- Amenorrhea and galactorrhea (high prolactin secretion)
  - In adolescent girls with hypothalamic tumor
- Gigantism
  - In adolescents with growth hormone producing eosinophilic adenoma

Pineal area

- Tumor in the third ventricle, the roof of the midbrain and the aqueduct

Common tumor types

- Pineal blastoma
- Teratoma
- Germinoma
- Astrocytoma of the corpus callosum or thalamus
- Nongerminomatous germ cell tumor

- Early symptoms: brain pressure caused by obstruction of cerebral fluid
- Parinaud syndrome

  - Paralysis of conjugate upward gaze
  - Disturbed pupillary light reflex
- Extension of tumor to midbrain
  - Disturbed ocular motor nerve function and extension with nystagmus, anisocoria and paralysis of convergence ability
  - Caudal extension: tinnitus and bilateral deafness
  - In forward extension: eyelid retraction
- Association with hypogonadism and precocious puberty

Posterior fossa tumors

Common tumor types

- Cystic astrocytoma
- Solid astrocytoma
- Hemangioblastoma (with erythrocytosis and high serum level of erythropoietin in 50% of patients)

- Symptoms
  - Ipsilateral cerebral dysfunction of the extremities: with tremor, dysmetria, rebound phenomenon, dysdiadochokinesia
  - Extension in the direction of fourth ventricle: signs of hydrocephalus (central nervous system (CNS)-mediated hypertension)
  - With extension to foramen magnum (herniation): neck pain, opisthotonus, paresthesiae of the upper extremities, high blood pressure with bradycardia, changes in vision, fever, bulbar signs (dysphagia, dysarthria)

Vermis cerebelli

Tumor type

- Often medulloblastoma with infiltration of the fourth ventricle

- Symptoms
  - Symmetrical ataxia of the trunk
  - Signs of high intracranial pressure and cerebellar tonsillar herniation

Fourth ventricle

Tumor types

- Choroid plexus carcinoma
- Dermoid tumor or teratoma in infants

- Symptom: high intracranial pressure

Brain stem

Tumor type

- Astrocytoma, WHO grade I—IV: infiltration into the brain stem

- Symptoms:
  - Unilateral paralysis of cranial nerves VI and VII
  - Contralateral hemiparesis of the extremities with hyperreflexia, spasticity, positive Babinski sign, vertical nystagmus
  - Occasionally high intracranial pressure
  - Invasion of area of vital functions: high fatality rate
- Differential diagnosis
  - Tumors arising from external structures such as rhabdomyosarcoma, non-Hodgkin lymphoma, neuroblastoma or from primary brain tumors such as medulloblastoma

Cerebellopontine angle tumors

Tumor type

- Acoustic neurinoma

- Symptoms and signs
  - Dysfunction of the auditory and vestibular nerves
  - Ipsilateral corneal reflex palsy or absence

Spinal Cord

Tumor types

- Intramedullary
  - Astrocytoma
  - Oligodendroglioma
  - Ependymoma, often with cysts (differential diagnosis: syringomyelia)
- Extramedullary and intradural tumors
  - Neurofibroma
  - Meningioma
  - Dermoid tumor
  - Teratoma
- Extradural tumors
  - Neuroblastoma
  - Non-Hodgkin lymphoma
  - Tumor of the vertebrae: eosinophilic granuloma, Ewing sarcoma (differential diagnosis: hematoma, inflammatory abscess etc.)

- Symptoms:
  - Compression symptoms: back pain, paraspinal muscle spasm, resistance to trunk flexion, scoliosis, changes of reflexes, disturbances of walking, sensory deficiencies at dermatome level, decreased perspiration below tumor level, muscle weakness, positive Babinski sign, urinary or anal sphincter impairment (incontinence, urinary retention, obstipation), priapism
  - The following list summarizes neurological signs corresponding to different levels of spinal cord tumors

Neurological signs corresponding to different level of spinal cord tumors

C1—C3	Phrenic paralysis (apnea)
C3—C4	Weakness or inability to raise shoulders
C5—C6	Weakness of arm abduction
C7—C8	Weakness of elbow extension, of fingers
T2—T12	Scoliosis, trunk weakness
L1	Weakness of hip flexion
L2	Weakness of hip abduction
L3—L4	Weakness of knee extension
L4—L5	Weakness of abduction and extension as well as dorsal flexion of ankle
L5—S1	Weak hamstrings
S1—S2	Ankle plantar flexion weakness

- Tumor in foramen magnum area: stiffness of the neck, torticollis, cervical pain
- Tumor in cervical spinal channel: nystagmus
- Tumor in cauda equina area: negative reflexes of the lower extremities, muscle atrophy of the legs, urinary and defecation problems

Radiological Diagnosis

Magnetic Resonance Imaging and Computed Tomography

- Magnetic resonance imaging (MRI) and computed tomography (CT) are the basic imaging techniques for brain tumors with demonstration of intracranial structures, lesions and solid and liquid components
- Intravenous application of contrast liquids provides detailed information
- With MRI: tissue structure and anatomical topographic localization of a tumor in three dimensions define the tumor precisely and allow stereotactic biopsy
- The long duration of the procedure is a disadvantage
- MR spectroscopy can be useful in differentiating between high-grade and low-grade tumors

Positron Emission Tomography

- In addition to MRI positron emission tomography (PET) provides detection of metabolites and metabolic alterations within the tissue, thus helping to distinguish tumors or lesions with a volume of greater than 1 cm^3

Conventional Radiography of the Skull

- Conventional radiography shows the bony structure of the skull, separating off sutures due to high intracranial pressure in small children and calcification within the brain

Special Methods for Special Indications

Brain scintigraphy
- Used where tumors are close to bone structures, e.g. cerebral hemisphere tumors

Angiography
- Angiography provides vascular supply and degree of vascularization of the tumor

Ultrasonography
- Can demonstrate the displacement of the midline structure of the brain by tumors

Myelography
- In tumors of the spinal canal
- Determination of focal widening, erosion of the spinal canal and of intervertebral foramen and of changes within the cerebral fluid

Additional Diagnosis

Cerebral fluid analysis

- Chemistry and cytology of the cerebral fluid are used to determine spread of the tumor to the spinal fluid and to indicate the different options of management
- Before lumbar puncture the risk of herniation through the foramen magnum, especially in the posterior fossa tumors, has to be considered
- Xanthochromic cerebral fluid, high protein level and a high tendency to coagulate indicates tumor spread

Electroencephalography

- For examination of unclear focal neurological abnormalities

Stereotactic biopsy

- In inoperable tumors this type of biopsy can provide a pathological diagnosis and help determine the optimal therapeutic approach (radio- and/or chemotherapy)

Differential Diagnosis

- Brain abscess (fever, cardiac murmur in congenital cyanotic heart disease)
- Subdural hematoma: anemia, retinal hemorrhage
- Hydrocephalus: headache, vomiting, subarachnoid hemorrhage, Guillain-Barré syndrome
- Tuberculoma: exposure to tuberculosis
- Pseudotumor cerebri: after otitis media, hormonal abnormalities
- Encephalitis: meningism, fever, seizure, stupor

Metastatic Spread

- Observed in medulloblastoma, pinealoma, germinoma, ependymoma
- Bone metastases occasionally in medulloblastoma
- Metastatic spread via ventriculoperitoneal shunt, via cerebral spinal fluid: mostly in ependymoma with subarachnoid metastases, in medulloblastoma with drop metastases causing paraplegia
- In germinoma metastases also outside CNS
- Secondary brain metastases:
  - Leukemia with intracerebral pressure, hydrocephalus
  - Non-Hodgkin lymphoma with focal neurological symptomatology
  - Langerhans cell histiocytosis, rhabdomyosarcoma, nephroblastoma, Ewing sarcoma, neuroblastoma, melanoma

Therapy

Neurosurgical Procedure

- Neurosurgery including microscopic techniques, ultrasonic aspiration and laser techniques to achieve maximum tumor removal and low morbidity depending on the location and extent of the tumor
- Often preoperative relief of intracranial pressure by ventriculoperitoneal or ventriculoarterial shunt
- Preoperative reduction of tumor edema by corticosteroids (dexamethasone 0.5–1 mg/kg body weight every 6 h) which also reduces the clinical symptomatology. In tumors of the hypothalamic region hormonal replacement presurgery, during surgery and postsurgery is common
- In patients with seizures anticonvulsive therapy is necessary
- In patients with high-risk sequelae from surgery stereotactic biopsy can be carried out using CT-guided techniques
- Histological documentation is necessary with the exception of diffuse, infiltrative chiasmatic or brain stem tumors

Radiotherapy

- Whether radiotherapy is indicated and extension and volume of irradiation depend on the biology and histology of the tumor, the age of the child and combination with chemotherapy or neurosurgery
- Irradiation during the first 3 years of life in special cases only because of rapid growth of the brain and adverse long-term sequelae
- The planning and application of radiotherapy is time-consuming and demands experienced teamwork between radiation oncologists and pediatric oncologists
  - In small children daily sedation is indicated
  - Hyperfractionated irradiation: subdivision of daily radiation volume in two applications with an interval of 6–8 hours
- Reactions to and complications of irradiation:
  - Depends on volume, fractionation and radioactive source
  - Acute reaction: brain edema
  - Subacute reaction: postradiation syndrome with fever, lethargy; often 4–6 weeks after radiotherapy. Duration: usually 1–2 weeks, but can last for several weeks
  - Long-term sequelae: deficiency of cognitive and neuropsychological development, memory deficits, deterioration of intelligence quotient after whole brain irradiation, rarely myelopathy after spinal axis irradiation exceeding 40 Gy
- Methods of irradiation:
  - Conventional external irradiation
  - Three-dimensional irradiation with precise boundary between the irradiated field and the adjacent tissue
  - Stereotactic irradiation (gamma knife) used for small tumors
  - Brachytherapy or interstitial irradiation by transient implantation of radioisotopes
  - Radiotherapy in combination with hyperthermia

Chemotherapy

- Chemotherapy depends on tumor type, age and location
- Efficacy and penetration depend on vascularization of the tumor
- High-dose chemotherapy with or without support by autologous stem cell transplantation especially in children below the age of 3 years
- Palliative chemotherapy:
  - May induce transient remission
  - Increases the quality of life
  - The reduction of symptoms must counteract the side effects of chemotherapy.
- Intrathecal chemotherapy via Rickham or Ommaya reservoir or by drug delivery by lumbar puncture; limitations due to low penetration of drug from cerebral fluid to brain tissue
- Future directions:
  - Adoptive immunotherapy with interleukin-2 or lymphokine-activated T-cell, vaccination or by monoclonal antibodies
  - Gene transfer therapy via virus-mediated delivery systems

Special Tumor Types

For general aspects of brain tumors, see above

Astrocytic Tumors

Incidence

- Most frequent tumor of childhood
- Infratentorial area (cerebellar tumor) or supratentorial (cerebral hemisphere or midline tumors) occurrence
- Mean age of patients: 6–9 years
- In boys more frequently than in girls

Radiological diagnosis

CT and MRI

- Hypodense zone with weak enhancement
- Often calcification present

Classification and prognosis	
Low-grade (LG) WHO I/II: characterized by slow, continuous growth; dissemination into cerebral fluid is rare	
WHO I:	Pilocytic astrocytoma
WHO I/II:	Mixed astrocytoma
WHO II:	Fibrillar astrocytoma
High-grade (HG) WHO III/IV: rapid infiltrative growth, with anaplasia/glioblastoma multiforme; rate of dissemination into cerebral fluid 25—55%	

Characteristics of low-grade astrocytoma (LGA I and II)

- Variable nomenclature:
  - Supratentorial: fibrillary, mixed xanthochromic, pilocytic astrocytoma, oligodendroglioma or ganglioglioma
  - Infratentorial (cerebellar): pilocytic (80%) and fibrillary diffuse astrocytoma (15–20%)
- Therapy: surgical procedure:
  - Degree of tumor removal is dependent on location, tumor size and infiltration which defines the prognosis; in relapsing low-grade astrocytoma again tumor removal should be considered
  - The goal of surgery is to remove as much tumor as is safe
- Radiotherapy:
  - In children with subtotal resection involved-field radiotherapy is used
  - In inoperable, delineated tumors stereotactic radiotherapy might be an option
- Chemotherapy:
  - In children with inoperable low-grade astrocytoma and in those below the age of 3 years
  - Effective drugs alone or in combination: vincristine, carboplatin, nitrosourea, cyclophosphamide
  - Response rate 65–75%

Characteristics of high-grade astrocytoma (HGA III/IV)

- Synonyms: anaplastic astrocytoma, glioblastoma multiforme, mixed oligodendroglioma
- Therapy and prognosis
  - Depending on degree of resectability, infiltration in adjacent brain tissue is frequent
  - Radiotherapy results in short-term, mostly partial remission
  - Multiagent chemotherapy prolongs the survival time with variable long-term remission
  - Effective drugs alone or in combination: cisplatin, carboplatin, cyclophosphamide, ifosfamide, etoposide, topotecan, procarbazine, temozolomide, lomustine (CCNU), carmustine (BCNU)

Optic glioma

Incidence

- Three to five percent of intracranial tumors, two-thirds manifesting within the first 5 years of life
- About 35% of children with neurofibromatosis

Extension of optic glioma

- Optic nerve only
- Frontal part of chiasma
- Posterior parts of chiasma and hypothalamus with involvement of frontal lobes, thalamus and other midline structures

Pathology
- Mostly astrocytoma I–II; pilocytic, occasionally fibrillary histology

Clinical presentation
- Progressive loss of vision
- Bilateral loss of vision by involvement of chiasma
- Exophthalmus in frontal involvement of the optic nerve
- Visual field deficiency variable depending on tumor location and extension
- Fundoscopy: papillary weakness or optic nerve atrophy

Radiological diagnosis
- MRI or CT: weak enhancement in peripheral chiasmatic tumor, moderate enhancement in chiasmatic tumor (i.e. higher degree of malignancy)

Histology
- Biopsy if diagnosis unclear (in children with neurofibromatosis, usually unnecessary)

Therapy and prognosis
- Radical resection rarely possible
- Chemotherapy: in small children and/or in children with extensive tumor of the chiasmatic hypothalamus region
- Neuroendocrine sequelae are infrequent after chemotherapy in contrast to those after radiotherapy
- Effective drugs: see above under Characteristics of low-grade astrocytoma (LGA I and II)
- In tumor progression after chemotherapy irradiation is indicated
- Radiotherapy: reduction of tumor mass and arrest of visual loss in patient with low-grade classification (see Astrocytic Tumors)
- Prognosis: a slow, progressive tumor with high morbidity (loss of vision, panhypopituitarism, diabetes insipidus, involvement of brain nerves)

Brain Stem Tumors

Incidence
- Fifteen to twenty-five percent of all brain tumors in children including those with neurofibromatosis
- Mostly in children between 3 and 9 years of age

Pathology
- Often a large infiltrating tumor at time of first symptoms
- Rarely blockade of circulation of the cerebral fluid, usually inoperable; biopsy with high risk of complications depending on tumor location
- Histologically astrocytomas (two-thirds grades I and II; one-third grades III and IV)
- Rarely embryonic histology: primitive neuroectodermal tumor (PNET) or hemangioblastoma

Location
- Mainly in the pons, occasionally in the medulla oblongata or the midbrain

Clinical manifestations
- Diplopia
- Deficiency of abducens nerve (inability to abduct one or both eyes)
- Ataxia (sign of involvement of cerebellum)
- Involvement of medulla oblongata: dysarthria, dysphagia, deficit of the lower cranial nerves
- Sensory deficit mostly limited to the face (involvement of trigeminal nerve)
- Disturbances of walking

Radiological diagnosis
- Enlarged, hypodense brain stem with or without cysts
- Fourth ventricle in caudal position
- Often mild hydrocephalus

Therapy
- Depending on tumor type:
  - In diffuse infiltrating growth despite therapy poor prognosis
  - In focal tumor long-term survival of 50–90%
- Surgical procedure:
  - Tumor resection with low risk of neuroendocrine sequelae especially in tumors with cystic parts
  - Morbidity during or after surgery is high
  - In high-risk surgery tumor resection as safely as possible, combined with irradiation and chemotherapy
- Chemotherapy:
  - Depending on tumor type, indicated in diffuse infiltrating type
  - Palliative therapy (see above)
  - Effective drugs and combinations (see above under Astrocytic Tumors)
- Radiotherapy:
  - Dose: 40–50 Gy; sometimes higher dosage with hyperfractionation
  - Endocrinological observation and substitution therapy

Medulloblastoma and PNET

Incidence
- Second most frequent brain tumor
- Usually arising from the roof of the fourth ventricle or from the midline structures of the brain
- Dissemination via ventricles and cerebral fluid
- Mean age 4–8 years
- Higher frequency in boys than in girls
- Nomenclature relating to medulloblastoma and PNET is controversial: "sPNET" used for supratentorial cerebral medulloblastoma, pinealoblastoma and central neuroblastoma; occasionally also for ependymoma

Pathology

- Highly malignant, small, round blue cell tumor
- Histologically small cells with high rate of mitosis, some in rosette forms; various degree of fibrils
- Degree of differentiation of cells variable and not correlated with prognosis
- Histological variants:
  - Medulloblastoma with marked stromal components: desmoplastic medulloblastoma in adolescents and adults
  - Large cell and/or anaplastic medulloblastoma: about 4% of all medulloblastomas
- High rate of subarachnoid spread: 11–43% initially, in autopsy series 93% with spread via cerebral fluid
- Extraneural metastatic spread in 4% of patients especially to bones, lymph nodes, liver and lung

Clinical manifestation

- Duration of history shorter than in patients with astrocytoma (due to the rapid tumor growth)
- High intracranial pressure is an early sign of midline tumors

Radiological diagnosis

- MRI and CT: midline tumors with marked enhancement. Radiological examination must include spinal canal (dissemination)

Therapy

- Surgical procedure:
  - Usually preoperative shunt implantation for relief of intracranial pressure and reduction of intra- and postoperative complications
  - Radical resection often not possible due to infiltrative tumor growth
  - Goal of surgery is optimal debulking
  - Microsurgery improves results
  - About 10% of children develop posterior fossa syndromes with transient insomnia and mutism postoperatively
  - Analysis of cerebral fluid intraoperatively via lumbar puncture provides important information of tumor dissemination
- Radiotherapy:
  - Medulloblastoma is radiosensitive
  - Craniospinal irradiation with age-dependent dosing
  - Cranial dose 40 Gy with an additional 10- to 15-Gy involved-field radiotherapy
  - Spinal irradiation dose 30–35 Gy
  - Sequelae after irradiation: growth retardation, neuroendocrine deficits, psychosocial disturbances, neurocognitive deficiencies
- Chemotherapy:
  - Highly chemosensitive tumor especially in small children (below the age of 3 years), in patients with brain stem infiltration or in those with subtotal tumor resection
  - Chemotherapy prior to irradiation might be more effective
  - Combination chemotherapy with cisplatin or carboplatin, vincristine, cyclophos-

phamide, etoposide, high-dose methotrexate with leucovorin antidote according to schemas in cooperative group protocols

Prognosis
- Five-year survival rate: 70–85%
- Unfavorable prognostic factors: large tumor, metastases (cerebral fluid with tumor cells), age less than 4 years, less than 90% tumor resection, chromosome deletion 17p, *MYC* (c-*Myc*) amplification
- Favorable prognosis: small tumor mass, age over 4 years, total or subtotal tumor resection (more than 90% or less than 1.5 cm^3 of residual tumor mass)

Pineal Tumors (Behind the Third Ventricle)

Frequency
- Two percent of brain tumors

Pathology
- Germ cell tumors (germinoma, embryonal carcinoma, choriocarcinoma, teratoma)
- Pinealoblastoma (primitive neuroectodermal tumor, PNET)
- Astrocytoma I–IV with cystic parts, mainly well differentiated; occasionally infiltrating in adjacent tissue

Clinical manifestation
- Parinaud syndrome

Laboratory diagnosis
- Serum and cerebral fluid level of α-fetoprotein (AFP) and/or β-choriogonadotropin (β-HCG) in mixed germ cell tumors often high (also called "non-germinoma germ cell tumors" NGGCT)
- In choriocarcinoma high level of β-HCG alone
- Cerebral fluid analysis with positive results for AFP and β-HCG) which exclude the necessity of biopsy

Radiological diagnosis
- MRI or CT in teratoma or pinealoblastoma: hyperdense tumor with marked contrast enhancement, often with calcifications especially in children below the age of 6 years

Therapy
- Special surgical techniques (microscopic, stereotactic procedure) facilitate biopsy and partial resection
- Radiotherapy: indicated especially in germinoma (highly radiosensitive) with involved field irradiation in combination with chemotherapy with reduced irradiation dosage (35-50 Gy); pinealoblastoma: procedure as in medulloblastoma (see above)
- Chemotherapy: in germ cell tumor treatment as in peripheral germ cell tumor

Prognosis
- Variable, depending on tumor type
- Germ cell tumors: more than 90% event-free survival
- Germinoma, choriocarcinoma and yolk sac tumors: prognosis depending on tumor extension, in general 5-year survival rates of 70–80% with chemotherapy and craniospinal radiation
- Pinealoblastoma as for medulloblastoma

Ependymoma

Incidence
- 9% of brain tumors
- Ratio of boys to girls is 1:1
- Peak at 2–6 years of age
- Supra- and infratentorial appearance:
  - Mainly in the area of the fourth ventricle with hydrocephaly
  - One-third in the area of the lateral ventricle
  - Eight to ten percent in the spinal cord area (cauda equina)

Pathology
- Often solid tumors, occasionally with calcification; invasive growth into the adjacent tissue
- Drop metastases 7–12%
- Microscopically three forms observed
  - Highly cellular ependymoma with tubular structures, rosettes and pseudorosette formation
  - Highly malignant variant: disorganized histology, pleomorphic, high rate of mitosis and necrosis and highly vascular, e.g. anaplastic ependymoma
  - Myxopapillary ependymoma: rare; well-differentiated cells which contain mucus
- Special form: choroid plexus papilloma arising in the lateral ventricle causing overproduction of cerebral fluid and development of hydrocephaly

Clinical manifestations
- Similar to medulloblastoma (especially in the area of the fourth ventricle): headache, vomiting, ataxia

Therapy
- Surgical procedure:
  - Rarely radical tumor resection is possible
  - If residual tumor of more than 1.5 cm^3 after chemotherapy more surgery necessary
  - Surgical morbidity and lethality high
- Radiotherapy:
  - Supratentorial ependymoma without dissemination: cranial irradiation
  - All other stages and locations as for medulloblastoma
- Chemotherapy:
  - As for medulloblastoma (see above)

Prognosis
- Depending on degree of neurosurgical tumor resection as for medulloblastoma
  - Residual tumor more than 1.5 cm^3: long-term survival less than 20%
  - After radical resection without cerebral fluid dissemination: 66–75% long-term survival

Craniopharyngioma

Incidence, pathogenesis and pathology
- Seven percent of all brain tumors
- Solid and cystic parts of epithelial tissue containing keratin, often with calcification (radiologically visible)
- Histologically well differentiated tissue with malignant clinical course by infiltrating the surrounding normal structures and tissue
- Slowly extends into intra- or suprasellar area
- With destruction of adjacent structures

Differential diagnosis
- Residual tissue of the embryonic Rathke pouch
- Extensive optic glioma or suprasellar germ cell tumor

Clinical manifestations
- Headache, vomiting (hydrocephalus), visual field deficiencies, loss of vision
- Growth retardation in about 50% of children
- Variable endocrine deficiencies with delayed puberty
- Neurobehavioral abnormalities
- Growth hormone deficiency in over 70% of children

Therapy
- Surgical procedure:
  - Tumor excision of focal tumor with small risk of neurological or endocrinological sequelae, especially of cystic parts of tumor
  - Preoperative endocrine substitution therapy
  - Where there is a significant risk of endocrine dysfunction, neurological morbidity and neurobehavioral disturbances: partial tumor resection followed by irradiation is recommended
- Radiotherapy:
  - In radical resection of tumor: 40–50 Gy, probably higher doses with hyperfractionation
  - High rate of morbidity
- Chemotherapy:
  - Only in exceptional situations depending on tumor type (diffuse infiltrating character)
  - Effective drugs and combinations: see above under Astrocytic Tumors

Prognosis
- Depending on tumor type; diffuse infiltrating tumor growth with poor prognosis
- Morbidity, long-term sequelae and quality of life have to be considered

- Radical excision or radiotherapy alone: 50–90% long-term survival
- Subtotal tumor excision with radiotherapy: 60–85% long-term survival

Meningioma

Incidence and pathology
- Rare tumor in childhood
- Ratio of boys to girls is 1:1
- Arising in dural, arachnoidal or leptomeningeal area
- Tumor mostly with thin capsule; invasive growth
- Dense tumor with calcification
- Histologically various subtypes without clinical relevance except: angioplastic type (rapid growth, infiltration, sarcomatous degeneration; high rate of relapse and metastatic spread)

Location
- Various locations: intracranial, spinal (mainly thoracic or cervical, seldom lumbar)

Clinical manifestation
- Intracranial pressure
- Seizures
- Hemianopia
- Hemiparesis

Therapy
- Usually radical surgical resection is possible

Intramedullary Spinal Cord Tumors

Incidence
- Five to ten percent of CNS tumors including children with neurofibromatosis
- Mean age 10 years

Pathology
- Astrocytoma 70%
- Ependymoma 10%
- Oligodendroglioma or ganglioglioma 10%
- High-grade glioma 10%
- Differential diagnosis: non-Hodgkin lymphoma
- Often large cysts are present
- Mostly slowly growth and extension within several segments of vertebrae and with compression of normal tissue
- Leptomeningeal dissemination in more than 50% of children

Prognosis
- Depending on tumor type, often slow progression; symptoms may be interrupted by surgical resection and/or laminectomy (enlargement of space for the residual tumor)

Therapy

- Surgical procedure:
  - Occasionally complete resection with osteoplastic laminectomy is possible
  - Ependymoma requires radical resection
  - Postoperatively close orthopedic observation and intervention: deformations of vertebrae develop within 3 years after surgery in 35–45% of children
- Radiotherapy depends on histology, tumor growth and extension and symptoms
- Chemotherapy depends on tumor type

Sequelae in Brain Tumors

- In contrast to other childhood tumors and despite successful therapies the morbidity and the rate of long-term sequelae are high for CNS tumors
- Often the initial symptoms and deficits are persistent
- Both tumor- and intervention-related physical, neurological, endocrinological and/or cognitive deficits and sequelae may be responsible for influence on quality of life
- The risk of a second tumor is high
- Multidisciplinary coordination of sequelae including:
  - Support for patients with neurocognitive disturbances
  - Neuroendocrine substitutive treatment for normal growth, puberty, and sexual development and normal functioning of the thyroid gland, hypothalamic-pituitary axis etc.
  - Audiological and visual aids and support
  - Integration on educational, social, psychological and cultural levels

Neuroblastoma

Paul Imbach

Definition

- Malignant embryonal tumor of precursor cells of sympathetic ganglia and adrenal medulla
- Entity characterized by:
  - Occasional spontaneous regression and differentiation to benign tumor especially in infants less than 12 months of age
  - Usually extremely malignant course in children in the advanced stage

Incidence

- Eight percent of all neoplasia in childhood
- Annually new diagnosis in 11 in 1 million children less than 16 years of age
- Most frequent malignant neoplasia in infants
- Mean age at diagnosis 2.5 years

Cumulative age distribution

<1 year of age	35%
<2 years of age	50%
<4 years of age	75%
<10 years of age	90%

- Rarely observed in adolescents and adults
- Boy-girl ratio of 1.1:1.0

Etiology and Pathogenesis

- Etiology unknown
- Incidence of neuroblastic precursor cells in autopsies of infants less than 3 months old who have died from other causes is 40 times higher than expected
- When discussing etiology factors such as alcohol and other drugs during pregnancy, parental occupation and viral infection should be considered
- Familial occurrence as well as sibling and twin disease with different stages of neuroblastoma within the same family are rarely described
- Association with neurofibromatosis, Hirschsprung disease, heterochromia iridis
- Tumor cell chromosomal changes and various karyotypic abnormalities in the majority of patients are detectable (see below)

Molecular Cytogenetics

- *MYCN* amplification and expression of neurotropic receptors (*TRK1*, *-2*, *-3*), neuropeptides (vasoactive intestinal polypeptide, VIP, somatostatin, SS), DNA index, and chromosomal changes (deletion 1p suppressor gene on chromosome 11, deletion 14, etc.) are prognostic factors which are summarized in the following:

Cytogenetic prognostic criteria

Age at diagnosis	*MYCN*	DNA	*TRK1*	Stage	Prognosis (survival rate)
<12 months	Usually normal	Hyper-diploid	High	1, 2, 4S	95%
>12 months	Usually normal	Diploid	Low	3, 4	50%
1—5 years	Commonly amplified	Diploid	Low	3, 4	25%

Pathology

Macroscopic Features

Pale gray, soft tumors with necrosis and calcification; in large tumors the demarcations are unclear; and the tumors are highly invasive into surrounding structures

Microscopic Features

- High variability with various differentiation stages of sympathetic nervous tissue ranging from undifferentiated neuroblastoma to ganglioneuroblastoma, to differentiated ganglioneuroma
- Differentiation with:
  - Electron microscopy: for cytoplasmic structures as neurofilaments, neural tubules, neurosecretory granules
  - Immunohistochemistry: immunoperoxidase, neuron-specific enolase (NSE)
  - Fluorescence testing for intracellular catecholamines
- Histologically small round-cell sarcoma which has to be differentiated from:
  - Primitive neuroectodermal tumor (PNET)
  - Embryonal undifferentiated rhabdomyosarcoma
  - Retinoblastoma
  - Ewing sarcoma
  - Lymphoma

- Well-differentiated form: islets with polymorphic nucleus separated by fibrillar material; sometimes cells are characteristically arranged as rosettes

Clinical Manifestations

- Occurrence in any area with sympathetic nervous tissue

Primary locations in order of frequency

Abdomen	65%
Adrenal medulla or sympathetic ganglia	46%
Posterior mediastinum	15%
Pelvic	4%
Head and neck	3%
Others	8%

- Rarely: primary tumor undetectable

Common Symptoms

- Weight loss
- Fever
- Abdominal disturbances
- Irritability
- Pain of bones and joints
- Child will not stand up, will not walk
- Pallor
- Lassitude

Symptoms Associated with Catecholamine Production

- Paroxysmal attacks of sweating, flushing, pallor
- Headache
- Hypertension
- Palpitations

Paraneoplastic Syndromes

- VIP syndrome: untreatable diarrhea and low level of potassium caused by VIP in 5–10% of children
- Opsoclonus: occurring mostly in well-differentiated neuroblastoma
- Occasionally anemia in children with bone marrow infiltration (associated with thrombocytopenia and leukocytopenia) or in children with massive intratumoral hemorrhage

Local Symptoms and Classic Signs

Eyes
- Periorbital edema, swelling and yellow-brown ecchymoses
- Proptosis and exophthalmos, strabismus, opsoclonus
- Papillary edema, bleeding of the retina, atrophy of the optic nerve

Neck
- Cervical lymphadenopathy
- Supraclavicular tumor
- Horner syndrome: enophthalmos, miosis, ptosis, anhydrosis

Chest, Posterior Mediastinum and Vertebrae
- Compression of trachea: coughing, dyspnea
- Infiltration in intervertebral foramina: dumbbell tumor
- Compression of nerves: disturbances of gait, muscle weakness, paresthesia, bladder dysfunction, constipation (the latter symptoms indicate that emergency decompression is necessary)

Abdomen
- Retroperitoneal: intra-abdominal tumor, often firm on palpation; irregular mass often crossing the midline
- Paravertebral and presacral: tendency to grow into the intravertebral foramina causing neurological dysfunction
- Occasionally abdominal distension

Liver
In infants marked hepatomegaly histologically known as "pepper type"

Skin
- Subcutaneous nodules of blue color which become reddish and then white owing to vasoconstriction from release of catecholamines after palpation
- Nodules are mainly observed in neonates or infants with disseminated neuroblastoma

Bone
- Bone pain, sometimes as one of the first signs
- Involvement mainly in the skull and long bones
- On X-rays seen as lytic defects with irregular margins and periosteal reactions

Bone marrow
- Infiltration in more than 50% of patients
- Peripheral thrombocytosis may indicate early stage of bone marrow infiltration
- Peripheral thrombocytopenia and/or anemia indicate advanced stage of bone marrow infiltration

Metastatic Spread

- Lymphatic and/or hematogenous spread
- Often initially present in:
  - 40–50% of children less than 1 year of age
  - 70% of children more than 1 year of age
- In children with local neuroblastoma 35% have involvement of lymph nodes
- Metastatic spread mostly in bone marrow, bone, liver and/or skin, rarely in brain, spinal cord, heart, lung

Laboratory Findings

Urinary catecholamine metabolites (tyrosine metabolism)

- High levels of vanillylmandelic acid (VMA) in 95%, homovanillic acid (HVA) in 90% and 3-methoxy-4-hydroxyphenylglycol (MHPG) in 97% of patients
- Other metabolites of catecholamine metabolism for differentiation of pheochromocytoma, olfactory neuroblastoma, and melanoma
- Spot tests with some false-positive and false-negative results
- Urinary catecholamine metabolite analyses useful: follow-up tumor marker

Bone marrow

- Aspiration and biopsy at two or more locations for detection of bone marrow involvement

Diagnostic Imaging

Conventional X-ray

- Thoracic X-ray for mediastinal tumor
- Abdominal X-ray: often calcifications visible in the tumor
- Skeletal survey for cortical bone metastases (differential diagnosis: bone tumor, Langerhans histiocytosis, infectious disease of bone, battered-child syndrome, metastatic spread of other neoplasia

Methylisobenzyl guanidinium (MIBG) scintigraphy

- Radiolabeled specific and sensitive method for evaluation of the primary tumor and focal metastatic disease

Ultrasound, computed tomography and/or magnetic resonance imaging

- Provision of detailed information on tumor size, extension, metastases of abdominal, hepatic, skeletal, pulmonary, mediastinal and central nervous system involvement

Myelography

- In patients presenting with symptoms of neural compression (paraparesis)

Differential Diagnosis

Besides other tumors (see above Pathology):
- Osteomyelitis
- Rheumatoid arthritis
- Signs of VIP syndrome: infectious or autoimmune intestinal disorders
- In opsoclonus or ataxia: neurological disorders
- In infants with hepatomegaly: storage diseases

Staging

International neuroblastoma staging system

Stage	Description
I	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)
IIA	Localized tumor with incomplete gross excision; representative, ipsilateral nonadherent lymph nodes negative for tumor microscopically
IIB	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
III	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
IV	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin or other organs (except as defined for stage 4S)
IVS	Localized primary tumor (as defined for stages I, IIA, or IIB) with dissemination limited to skin, liver or bone marrow (limited to infants aged less than 1 year)

Therapy

Therapy depends on age, stage, localization of neuroblastoma and molecular features at diagnosis

Surgical procedure

- Initial surgery for staging and eventually tumor excision without injury to vital structures; and for biopsy
- Often radical resection becomes possible after chemotherapy and/or radiotherapy
- Up to 25% of children with neuroblastoma initially have local lymph node involvement
- Complications of surgery:
  - Hemorrhage
  - In adherent tumors to the kidney, nephrectomy
  - Horner syndrome

Chemotherapy

- Combinations of chemotherapy: cyclophosphamide/ifosfamide, cisplatin, doxorubicin and epipodophyllotoxin according to international protocols
- The course of therapy is divided into an induction phase and a consolidation phase

Radiotherapy

- Neuroblastoma is radiosensitive
- Irradiation is limited by:
  - Age of the patient
  - Long-term sequelae
  - Combination with chemotherapy
- Irradiation is indicated:
  - For shrinking of large tumor masses
  - For decompression of intraspinal tumor masses
  - For palliative treatment

Risk-Adapted Management

Low risk

- Stages I, IIA, IIB, IVS (DNA index more than 1)
- No *MYCN* amplification
- Favorable histology
- Radical tumor resection eventually after chemotherapy and/or radiotherapy
- Stage IVS (infants less than 12 months of age): high cure rate of 85–92% after staging and eventually tumor resection without chemotherapy and/or radiotherapy; infants with *MYCN* amplification are high-risk patients (see below)
- In rapid progressive hepatomegaly with dyspnea initial chemotherapy and eventually low-dose irradiation of the liver (1.5–6 Gy) may be helpful
- In children with intraspinal compression chemotherapy alone and/or neurosurgical intervention with laminectomy

Intermediate- and high-risk group

- Stage II: 1–21 years of age, MYCN amplification; unfavorable histology
- Stages III, IV, IVS: 0–21 years of age, *MYCN* amplification; or: 1–21 years of age, unfavorable histology (without *MYCN* amplification)
- Mostly good response to induction chemotherapy (see above)
- Persistent bone and/or bone marrow involvement is prognostically unfavorable

- Induction phase: chemotherapy followed by eventual residual tumor resection, followed by maintenance chemotherapy and/or radiotherapy
- Persistent neuroblastoma:
  - High-dose chemotherapy with autologous stem cell support
  - Allogeneic stem cell transplantation with the objective of graft-versus-tumor effect is still experimental
  - Treatment of minimal residual disease (MRD) provided by MIBG imaging [see Methylisobenzyl guanidinium (MIBG) scintigraphy above]; retinoids for induction of neuroblast differentiation; specific monoclonal antibody against neuroblastoma cell antigen (3F8, GD2a)

Therapy in Relapse

- For curative or palliative goals: topotecan, paclitaxel (Taxol), irinotecan or etoposide
- Radiolabeled MIBG therapy as experimental option

Prognosis

- Dependent on age (favorable if less than 18 months of age at diagnosis), stage (see Staging above) and localization:
  - Favorable prognosis in primary neuroblastoma of thorax, presacral and cervical location
  - Involvement of lymph nodes correlates with poor prognosis
- Low-risk groups (see Risk-Adapted Management above) more than 90% long-term survival
- Intermediate and high-risk groups:
  - Response to initial treatment: 60–78% of children with complete or partial remission
  - After consolidation therapy including double high-dose chemotherapy with autologous stem cell support event-free survival after 3 years is 40–60%

Special Forms

Ganglioneuroblastoma

- Mostly in older children and adolescents
- Location: adrenal medulla and posterior mediastinum
- Often large tumor
- Histologically typical neuroblastoma tissue and areas of differentiation between extensive fibrillar tissue may be seen
- Management as for neuroblastoma

Ganglioneuroma

- Benign tumor
- Mainly in adolescents and young adults
- Often incidental diagnosis from a thoracic X-ray
- Urinary catecholamine levels mainly within normal range
- Macroscopically encapsulated tumor
- Histologically ganglia cells and presence of Nissl granules, bundles of neurofibrils and myxomatous stroma
- Therapy: resection
- Postoperative sequelae after surgery of mediastinal ganglioneuroma: Horner syndrome may occur

Olfactory Neuroblastoma

- Older children and adults
- First peak at 11–20 years
- Second peak at 50–60 years
- Symptoms: unilateral nasal obstruction, epistaxis, anosmia, rhinorrhea, pain
- Metastatic spread in lymph nodes, lung, pleura and/or bone (vertebrae) in about 25% of patients; brain involvement in 14% of patients
- Therapy: radical tumor resection if possible as well as radiotherapy
- Prognosis: about two-thirds of patients are cured

Neuroblastoma Arising from Organs of Zuckerkandl

- Tumor of the midline: behavior and procedure as described for other neuroblastomas

Pheochromocytoma

- Origin is chromaffin cells of the neural crest
- Occurrence:
  - Mostly in adrenal gland
  - 20% bilateral
  - Occasionally multiple tumor locations
  - In children more than 10 years old and in adults
- Symptoms: paroxysmal attacks of flushing, pallor, sweating, headache, palpitations, hypertension
- Weight loss
- Polydipsia
- Urinary catecholamine levels markedly increased
- Diagnostics: ultrasound, magnetic resonance imaging, scintigraphy
- Therapy: before and during any diagnostic or therapeutic intervention prophylaxis of hypertensive crises with alpha- and beta-blockers and intensive care surveillance; surgical resection of pheochromocytoma; multiple surgery might be necessary in multifocal disease

Nephroblastoma (Wilms Tumor)

Paul Imbach

Definition

- Malignant embryonal tumor of renal tissue
- First described in 1899 by Max Wilms as "Mischgeschwülste der Niere" (mixed tumors of the kidney)

Incidence

- Six percent of all neoplasias in children
- Annually new diagnosis in 8 in 1 million children less than 16 years old
- Seventy-eight percent of children with nephroblastoma are less than 5 years old
- Peak incidence between 2nd and 3rd year of age
- Congenital form at delivery or during neonatal period
- Rarely in adolescents and adults
- Different frequency between the different ethnic groups of origin
- Incidence in boys slightly higher than in girls

Chromosomal Association

- Association with chromosomal parts responsible for growth functions and development of nephroblastoma or other anomalies of the germ cell line
- Chromosomal association:
  - Chromosome 11p13 with Wilms tumor suppressor gene *WT1* in 10–30% of nephroblastomas
  - Chromosome 11p15 with Wilms tumor suppressor gene *WT2*
  - Chromosome 17q with familial FWT-1 (chromosomal association in familial Wilms tumor)
  - Chromosome 19q with familial FWT-2
  - Chromosomes 16q, 1p, 7p und 17q with *TP53* mutations
- Association with congenital anomalies
- WAGR syndrome (Wilms tumor, aniridia, genital malformations, mental retardation):
  - Genital malformations: cryptorchidism, hypospadias, pseudohermaphroditism, gonadal dysgenesis
  - Deletion of chromosome 11p13
- Denys-Drash syndrome:
  - Pseudohermaphroditism
  - Glomerulopathy
  - Mutation of chromosome 11p (only one allele of *WT1* with mutation; see below)
- Beckwith-Wiedemann syndrome (BWS)
  - Hemihypertrophy
  - Macroglossia
  - Omphalocele
  - Visceromegaly
  - Associated with *WT2* (see below) on chromosome 11p15 at a rate of 15%

- Isolated hemihypertrophy
- In neurofibromatosis, Perlman syndrome, Simpson-Golabi-Behmel syndrome
- Familial occurrence:
  - 1–2 % of nephroblastomas with chromosomal anomalies and familial gene loci (familial WT-1, familial WT-2; see below)
  - Sometimes bilateral nephroblastoma
  - Increased risk in homozygous twins

Pathology

Macroscopic features

- High variation in tumor size and tissue morphology
- Tumor often with lobular structure of gray to pink color and with a capsule
- Occasionally with cysts and hemorrhages
- Tumor growth in the renal vein
- Bilateral 5–7.5%, multifocal 12% spread in one kidney

Microscopic features

- Mostly mixed form of epithelial blastemic and stromal cellular components as well as with various degrees of cell differentiation
- In well-differentiated forms glandular acini or glomerular structures separated by stroma elements which arrange cells in cords or nests
- Stroma with fibroblastic or myxomatous components containing smooth muscle, skeletal muscle, cartilage and fatty tissue
- Nephrogenic residual tissue:
  - In 1% of all autopsies of small children: in 35% of children with unilateral nephroblastoma and in the majority of children with bilateral nephroblastoma
  - Hyperplastic nephrogenic tissue with differentiation and disappearance under chemotherapy
- Minority with undifferentiated histology:
  - Anaplastic nephroblastoma at a rate of 5%: focal or diffuse anaplasia with large and atypical nuclei, hyperchromatism and abnormal mitosis
  - Clear-cell sarcoma (3%): polygonal cells with crystal-clear cytoplasm separated into nests by thin spindle-cell septa containing blood vessels; high incidence of bone or lung metastases; high rate of relapse; age less than 2 years in 85% of children; occasionally deletion 22q11–12
  - Rhabdoid nephroblastoma (2%): acidophilic cytoplasm, metastatic spread also in fossa posterior of the neurocranium
  - Mesoblastic nephroma: congenital form, mean age at diagnosis 2 months; occasionally translocation t(12;15) (p13;q25); similar to infantile fibrosarcoma

Clinical Manifestations

- Visible and palpable abdominal mass
- Palpation must be done with care – risk of tumor rupture or dissemination
- Unclear febrile episodes, anorexia, vomiting

- Micro- or macrohematuria in 20–25% of patients
- Hypertension in children with renin-producing tumor cells
- Rarely association with secondary polycythemia due to high production of erythropoietin by tumor cells
- Occasionally varicocele, inguinal hernia, acute renal failure, coughing, pleural pain, and/or pleural effusion in children with pulmonary metastases
- Special symptoms in association with congenital anomalies (see above)

Laboratory Diagnosis

- Chemistry: exclusion of renal failure, high level of serum calcium in children with rhabdoid nephroblastoma
- Urine: microhematuria; after concentrating urine malignant cells may be detected
- Acquired von Willebrand coagulopathy in about 8% of patients
- Differential diagnosis of neuroblastoma: 24-h urine catecholamine analysis

Radiological Diagnosis

- Conventional abdominal radiography: intestinal displacement by tumor mass with punctuated calcifications (in 2–3%)
- Ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI; with contrast urography) of the abdomen including the hepatic area (metastases) and chest CT
- Angiography may be indicated in bilateral nephroblastoma
- Radioisotope scans and/or skeletal survey in patients with suspected skeletal metastases
- Central nervous system (CNS) MRI in patients with clear-cell sarcoma or rhabdoid kidney sarcoma and in patients with possible brain metastases

Differential Diagnosis

- Multicystic kidney, hydronephrosis, cystic nephroma
- Renal abscess
- Cyst of ductus choledochus or mesenteric cyst
- Neuroblastoma, rhabdomyosarcoma, hepatoblastoma
- Other solid tumors in retroperitoneal area
- In neonates: congenital mesoblastic nephroma (fetal hamartoma)
- Lymphoma of the kidney (rare)
- Renal cell carcinoma

Staging

National Wilms Tumor Study Group staging system	
Stage	**Description**
I	Tumor confined to the kidney and completely resected. No penetration of the renal capsule or involvement of renal sinus vessels
II	Tumor extends beyond the kidney but is completely resected (none at margins; no lymph nodes). At least one of the following has occurred: (a) penetration of the renal capsule, (b) invasion of the renal sinus vessels, (c) biopsy of tumor before removal, (d) spillage of tumor locally during removal
III	Gross or microscopic residual tumor remains postoperatively including inoperable tumor, tumor at surgical margins, tumor spillage involving peritoneal surfaces, regional lymph node metastases, or transected tumor thrombus
IV	Hematogenous metastases or lymph node metastases outside the abdomen (e.g., lung, liver, bone, brain)
V	Bilateral renal Wilms tumors at onset

Therapy

- Due to Wilms tumor study groups the prognosis has changed from a 90% lethality rate to a 90% cure rate
- Treatment according to staging (see above) aims to eliminate the nephroblastoma while avoiding short-term or long-term side effects/complications
- Primary surgical resection or preoperative chemotherapy (mostly with marked tumor regression and reduction of intraoperative tumor rupture) has to be considered according to staging
- Biopsy: only in children with unclear presentation or diagnosis
- After biopsy stage I is excluded
- Primary surgery in infants less than 6 months old and in adolescents more than 16 years of age

Surgical procedures

- Transabdominal tumor resection with abdominal exploration including liver and contralateral kidney
- Biopsy of suspected tissue especially lymph nodes
- Where there is large tumor mass: preoperative chemotherapy, probably radiotherapy (see below)

Chemotherapy

- Preoperative chemotherapy: vincristine and actinomycin D; in children with primary metastases addition of anthracycline
- Postoperative chemotherapy: duration and drug combination according to stage and histology
- Toxicity: veno-occlusive disease (VOD) of the liver especially in infants and small children

Radiotherapy

- Nephroblastoma is radiosensitive
- Due to combined chemotherapy irradiation is indicated only in high-risk patients: i.e. Stage II with lymph node involvement, high malignancy and metastatic spread
- Start of radiotherapy within the first 10 postoperative days
- Dose: 15–30 Gy with higher doses to the tumor bed and remaining tumors

Therapy in Relapse

- Favorable prognosis in children with relapse 6 months after tumor resection, in nonirradiated areas with one organ system involvement only, without lymph node metastases excluding highly malignant variants; chemotherapy with combination of vincristine, actinomycin D, doxorubicin, ifosfamide, carboplatin, and etoposide
- Relapse with poor prognosis: high-dose chemotherapy with autologous stem cell transplantation

Prognosis

- Before era of radiotherapy and chemotherapy, surgery only: survival rate 20–40%
- After multidisciplinary approaches according to tumor stage and standard therapy 85–90% cure rate
- Prognosis depends on stage and histology

Prognosis according to stage	
Favorable histology	Survival 94–100%
Standard histology	Survival 90%
Unfavorable histology	Survival 70%

- Unfavorable factors:
  - Diffuse anaplasia
  - Viable malignant cells after preoperative chemotherapy
  - Infiltration of tumor capsule
  - Invasion of tumor cells into vessels
  - Nonradical surgical resection of tumor

- Lymph node involvement
- Tumor rupture (also after biopsy)
- Metastatic spread
- Large tumor volume
- Histology: rhabdoid tumor
- Molecular genetics: alteration of loss of heterozygosity on 1p, 11q, 16q, and 22q; *p53* mutations

Subtypes

Bilateral Wilms Tumor

- Often initially bilateral tumor characterized by:
  - Mean age: 15 months (unilateral Wilms tumor: 42 months)
  - Age of mother: mean age 34 years (unilateral: 28 years of age)
  - Association with other malformations: 45% (unilateral: 4%)

Therapy
- Individual procedure
- Unilateral nephrectomy, partial resection of the contralateral kidney or bilateral partial resection
- Preoperative chemotherapy, possibly in combination with radiotherapy
- Bilateral resection of both kidneys followed by renal transplantation after chemotherapy
- Radiotherapy with low-dose irradiation: 10–20 Gy

Prognosis
- Usually favorable

Congenital Mesoblastic Nephroblastoma (Fetal Renal Hamartoma)

- Frequency: more than 80% of neonatal nephroblastomas and 50% of nephroblastoma in infancy (fibromatous variant)
- Potential malignant cellular variants in infants and small children

Pathology
- Mostly marked kidney enlargement, with bundles of spindle cells and frequent mitoses

Clinical manifestations
- Mostly large abdominal tumor masses in children after birth until 1 year of age
- Staging according to Wilms tumor (see above)
- Rarely hyperreninemia with hypertension, secondary aldosteronism and high serum level of renin

Therapy
- Nephrectomy
- After incomplete resection occasionally tumor relapses
- Where there is suspicion of malignant histology or after subtotal resection therapy as in nephroblastoma

Renal Cell Carcinoma

- Frequent renal tumor in adulthood
- 1–2% in patients over the age of 21 years, mostly in children over the age of 5 years
- Possible abnormality of chromosome 3

Pathology
- Tumor origin of epithelial tissue of the proximal tubule

Clinical manifestations
- Pain, intra-abdominal tumor, hematuria
- Diagnostic procedure as in nephroblastoma (see above); often tumor calcifications
- Metastatic spread often in lung, liver, regional lymph nodes and bone

Therapy
- Complete resection
- In high-risk patients after surgery combination treatment with interferon-a, interleukin-2 or high-dose radio- and chemotherapy since renal cell carcinoma is only moderately sensitive to radio- and chemotherapy

Soft Tissue Sarcoma

Paul Imbach

Overview

Definition

Soft tissue sarcomas are a heterogeneous group of malignant tumors which stem from muscles, vessels, lymphatic tissue, connective tissue, synovial tissue or primitive mesenchymal cells.

Subtypes

Tissue of origin	Tumor
Mesenchyma	Myxoma, mesenchymoma
Striated muscle	Rhabdomyosarcoma
Smooth muscle	Leiomyosarcoma
Fatty tissue	Liposarcoma
Connective tissue	Fibrosarcoma
Synovial tissue	Synovial sarcoma
Blood vessels	Angiosarcoma, hemangiopericytoma
Lymphatic vessels	Lymphangiosarcoma
Nerve sheath	Neurofibrosarcoma (malignant schwannoma)

Differential diagnoses

- Accidental or traumatic tumor or hemorrhagic tumor
- Benign lipoma, myoma, neurofibroma
- Myositis (ossificans, inflammatory)
- Inflammatory myofibrohistiocytosis (pseudosarcoma, pseudotumor of the bladder)
- Other neoplasias:
  - Non-Hodgkin lymphoma (NHL)
  - Neuroblastoma
  - Ewing sarcoma
  - Langerhans cell histiocytosis (LCH)

Incidence

- In childhood 7.5% of all neoplasias
- Annually new diagnosis in 8 in 1 million children less than 16 years old
- Seventy percent of children are less than 10 years old at diagnosis
- Ratio of boys to girls 1.4:1

Rhabdomyosarcoma

Incidence and Localization

- About 50% of all soft tissue malignomas
- Annually new diagnosis in 4.3 in 1 million children less than 16 years old
- Sixty-seven percent of children are less than 10 years old at diagnosis
- Ratio of boys to girls 1.15:1

Age distribution

Age (years)	Frequency (%)
<1 year	7
l–4 years	35
5–9 years	25
10–14 years	20
>15 years	13

Location	Frequency (%)
Head and neck (without orbit)	26
Orbital	9
Genitourinary	22
Extremities	18
Trunk	7
Retroperitoneal	7
Perineal and anal	2
Others	9

Etiology and Pathogenesis

- Mostly sporadic forms
- Some with genetic predisposition as in Li-Fraumeni syndrome with mutation of the p53 suppressor gene (*TP53*): high incidence of brain and breast tumors and adrenocortical carcinoma in families with a child with rhabdomyosarcoma
- Increased risk in fetal alcohol syndrome; also in mothers using marijuana or cocaine during pregnancy
- Cytogenetics: *NRAS* oncogene abnormalities in 35% of patients
- Mouse models with inactivated p53 or pRB demonstrate disturbance of muscle differentiation and neoplastic development

Histopathology

- Muscle-specific proteins are histologically detectable, such as actin, myosin, desmin, and myoglobulin

Four subtypes of rhabdomyosarcoma

- Embryonal:
  - Frequency: 53–64% of all rhabdomyosarcomas in childhood
  - Location: orbit, head and neck, abdomen, genitourinary tract
  - Microscopically resemblance to embryonic muscle tissue; mainly primitive round cells, some spindle cells with central nucleus and eosinophilic cytoplasm; cross striations characteristic of skeletal muscle in about 30% of cases
  - Subtype: Sarcoma botryoides (6% of all rhabdomyosarcomas in children); in vagina, bladder, uterus; microscopically as embryonal type with polypoid mass and presence of a dense subepithelial cell layer
- Alveolar:
  - Frequency: 21% of all rhabdomyosarcomas in children
  - Location: mainly extremities
  - Histology: round cells with eosinophilic cytoplasm, occasionally with vacuoles; multinucleated giant cells; rarely cross-striations; groups of tumor cells separated by fibrotic septation (alveolar structure)
- Pleomorphic:
  - Frequency: 1% of all rhabdomyosarcoma in children
  - Occurrence: mainly in adulthood
  - Histology: undifferentiated muscle tissue; spindle cells with variable eosinophilic cytoplasm and pleomorphic nuclei, frequently mitotic cells, often cross-striations, structured in rows and bundles
- Undifferentiated subtype:
  - Frequency: 8% without muscle-specific gene proteins

Cytogenetics

- t(2;13q35;q14 with 1p36) which changes the transcription pattern of the tumor cells.
- *PAX3* and *PAX7* are characteristic genetic alterations, detectable at the abovementioned chromosomal loci

- LOH (loss of heterozygosity) at 11p15 locus in connection with the gene of growth factor IGF-2
- Hyperdiploidy (more than 53 chromosomes) indicates a more favorable prognosis than the diploid form with 46 chromosomes

Clinical Manifestations

Symptoms depend on tumor location.

Head and neck area

- Frequency: 35%, including diseases of the orbit
- Location: orbit and parameningeal, such as middle ear, mastoid, nasal and paranasal area, pharynx, fossa pterygopalatina and fossa infratemporalis; tumors of the neck
- Symptoms:
  - Orbit: proptosis (an early sign)
  - Middle ear: pain, chronic otitis media, polypoid mass obstructing the ear canal
  - Paranasal: sinusitis, obstruction of one side of nasal airway, pain, epistaxis, swelling
  - Nasopharyngeal tract: obstruction of airways, sinusitis, local pain, epistaxis, difficulty in swallowing; eventually polypoid tumor visible in the pharynx or the nasal area
  - Neck: hoarseness, difficulty in swallowing, visible tumor
- Complications: extension to central nervous system (CNS) by direct extension: meningeal symptoms, cranial nerve palsies, respiratory disturbance due to infiltration into the brain stem

Genitourinary tract

- Frequency 22%
- Location: urethra, vagina, uterus, prostate, bladder, testes, paratesticular area, spermatic cord
- Symptoms:
  - Problems of urination
  - Hematuria, vaginal bleeding
  - Sarcoma botryoides
  - 40% with involvement of lymph nodes (especially in paratesticular rhabdomyosarcoma)

Extremities and trunk

- Frequency: 18% in extremities; 7% in the trunk
- Location: trunk, chest, abdomen, paraspinal area
- Symptoms:
  - Indolent mass; often large tumor at diagnosis
  - Symptoms of spinal compression
  - Dyspnea (differential diagnosis: pulmonary metastases)

Retroperitoneal area

- Frequency 7%
- Symptoms:

- Mostly a large tumor mass prior to first symptoms
- Abdominal pain resembling appendicitis
- Tumor mass with or without ascites

Rare locations

- Biliary tract (frequency 3%)
  - Symptoms as in cholecystitis
  - Hyperbilirubinemia
- Intrathoracic (frequency 2%)
- Perineal area (frequency 2%)

Laboratory Diagnosis

- Besides biopsy of the tumor (including material for electron microscopic analysis) specific laboratory analyses depend on location of the tumor:
  - General blood and serum analyses, urine analysis
  - Bone marrow aspiration and biopsy
  - Lumbar puncture for cerebrospinal fluid analysis

Radiological Diagnosis

- Conventional X-ray imaging
- Ultrasonography
- Magnetic resonance imaging (MRI) preferable to computed tomography (CT)
- Bone scan

Staging

- The Intergroup Rhabdomyosarcoma Study (IRS) group distinguishes between:
  - Local extension
  - Postsurgical residual tumor mass
  - Local and distant metastases

Clinical staging according to Intergroup Rhabdomyosarcoma Study (IRS)

I	A	Localized tumor confined to site of origin, completely resected
	B	Localized tumor infiltrating beyond site of origin, completely resected
II	A	Localized tumor, gross total resection, but with microscopic residual disease
	B	Locally extensive tumor (spread to regional lymph nodes) completely resected
	C	Extensive tumor (spread to regional lymph nodes, gross total resection, but with microscopic residual disease)

III	A	Localized or locally extensive tumor, gross residual disease after biopsy only
	B	Localized or locally extensive tumor, gross residual disease after major resection (50% debulking)
IV		Any size of primary tumor with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor

Stage	Frequency (%)
I	16
II	20
III	48
IV	16

- In addition, TNM staging:
  - Tumor extension
  - Lymph node involvement
  - Metastases

TNM staging correlated with Intergroup Rhabdomyosarcoma Study (IRS)

Stages	Prognosis	Sites	Tumor invasiveness	Tumor size	N	M
I	>90%	Orbit, head and neck, genitourinary (nonbladder/nonprostate)	T1 or T2	All	N0, N1, Nx	M0
II	80–90%	Bladder/prostate, extremities, cranial parameningeal, other	T1 or T2	≤5 cm	N0, Nx	M0
III	70%	Bladder/prostate, extremities, cranial, parameningeal, other	T1 or T2, T1 or T2	≤5 cm, >5 cm	N1, N0, N1, Nx	M0, M0
IV	30–40%	All	T1 or T2	All	N0, N1	M1

T1 limited to organ of origin, T2 expansive tumor size
N (regional lymph nodes): N0 negative, N1 positive, Nx unknown
M metastases): M0 none, M1 present

Metastatic Spread

- Metastases via lymphatic and/or hematogenous spread
- Variable frequency of metastases in relation to localization of the primary tumor (see below under Special Locations)

Therapy

Overview

- Multidisciplinary approach according to location, primary presentation (resectability, staging) and histology
- Examples:
  - Orbital, parameningeal, female genitals, biliary tract or prostate: primary biopsy followed by chemotherapy, radiotherapy, rarely surgery necessary or possible; second-look biopsy due to false-negative results
  - Local tumor of the trunk, extremities or paratesticular area: surgical total excision, chemotherapy, eventually irradiation
  - In other locations without metastases: initial chemotherapy followed by surgery (debulking only) of the remaining tumor; depending on the result: radiotherapy, additional chemotherapy

Surgical procedure

- Total resection:
  - If surgery is possible without major functional deficits
  - If irradiation can be avoided or reduced
  - If the field of irradiation can be reduced
  - If group III stage is likely to become group I or II stage
- Lymph node involvement: biopsy of tumors involving the extremities, the genitourinary tract and in metastatic lymph node involvement; total regional lymph node resection is not necessary in combined chemo- and radiotherapy and surgery

Radiotherapy

- Group I: no irradiation
- Groups II–IV: radiotherapy after initial chemotherapy eventually after surgery with micro- or macroscopic residual disease indicated
- Therapy using less than 40 Gy results in a higher rate of local relapses
- Pulmonary metastases: 14–18 Gy total pulmonary irradiation and an additional 30 Gy of residual metastases
- In solitary bone metastases, 50–60 Gy
- In multiple metastases individualized irradiation
- In hepatic involvement 25–30 Gy

Chemotherapy

- Highly chemotherapy-sensitive tumor especially in combined procedure (surgery and irradiation and chemotherapy)
- Improved results after combined chemotherapeutic drugs with minimal overlapping resistance patterns and toxicities

- All patients with rhabdomyosarcoma need chemotherapy due to high frequency of occult (micro-) metastases
- The initial surgery or biopsy is followed by the first phase of chemotherapy (for reduction of tumor burden and elimination of micrometastases) followed by combination with radiotherapy
- Effective cytotoxic agents: vincristine, actinomycin D, doxorubicin, ifosfamide, etoposide and cisplatin

Special Locations

Head and neck area

The majority of patients belong to group III: first biopsy, then chemotherapy and radiotherapy followed by resection of remaining tumor and additional chemotherapy according to the histological findings

Parameningeal site

- Location: ear including middle ear, mastoid, nasal cavity, paranasal sinuses, pharyngeal area, fossa pterygopalatina and fossa infratemporalis
- Surgical procedure:
  - Radical excision without cosmetic and/or functional deficits
  - Surgery after initial chemotherapy
  - Excision of suspicious lymph nodes
- Radiotherapy (see above):
  - In tumor extension and involvement of CNS: involved-field or extended-field irradiation
  - In CNS extension with cerebrospinal fluid involvement: craniospinal irradiation combined with intrathecal chemotherapy
- Chemotherapy (see above): always combined with surgery and/or irradiation

Orbit

- Often localized tumor with favorable prognosis (more than 90% event-free survival)
- Surgical procedure: initially biopsy only; total excision in children with local relapse or nonresponders; chemo- and radiotherapy
- Combination treatment with chemo- and radiotherapy because the majority of patients are in group IIIB

Pelvic area

- Mainly genitourinary area, bladder, vagina, uterus
- Surgical procedure: initial biopsy including lymph nodes if indicated followed by chemotherapy, then second-look surgery often with radical resection
- Chemotherapy:
  - Primary chemotherapy before second-look surgery during 8–16 weeks – if resection is subtotal combined radio- and chemotherapy
  - When macroscopic and microscopic complete resection is possible:
  - Postoperative chemotherapy alone
  - In progressive disease after primary chemotherapy: debulking followed by radio- and chemotherapy; in cases of persistently active tumor treatment with radioactive seeds, eventual exenteration

- Radiotherapy:
  - In combination with surgery and chemotherapy
  - Reduced dosage in small children

Paratesticular rhabdomyosarcoma

- Surgical procedure:
  - Testicular and/or spermatic cord involvement: orchiectomy is necessary
  - Scrotal involvement: scrotectomy and biopsy of inguinal lymph nodes
  - In groups II and III irradiation with transient implantation of the contralateral testicle outside the irradiation field
  - In retroperitoneal involvement of lymph nodes (positive rate in 30–40%) intensive chemo- and radiotherapy with eventual unilateral retroperitoneal lymph node dissection
- Irradiation: in patients with microscopic residual disease
- Chemotherapy: see above

Retroperitoneal rhabdomyosarcoma

- Surgical procedure: Often large tumors without the possibility of total resection
- Radiotherapy: see above
- Chemotherapy: see above

Extremities

- Surgical procedure:
  - Radical tumor excision without amputation
  - Parallel regional lymph node biopsy (involvement up to 50%)
- Radiotherapy: local irradiation to include regions of positive lymph node and adhesive negative lymph node region
- Chemotherapy: see above

Metastatic spread (in relation to primary location)

Primary site	Site of metastatic spread with ranking of frequency
Head and neck	CNS, lung, lymph node
Trunk	Lung, CNS
Genitourinary	Lymph nodes, lung, liver, bone, bone marrow, soft tissue, CNS

Prognosis

- General event-free survival is 20–80% depending on stage – in comparison with 24% before the chemotherapy and radiotherapy
- Before multidisciplinary treatment approaches the disease spread in the majority of affected children within the 1st year after diagnosis
- Prognosis according to stage (see above)
- Prognostic factors include: tumor size and extension after surgery

- Favorable prognosis in tumors of orbit or genitourinary tract (exception is the prostate): early stage
- Moderate to poor prognosis:
  - Extremities: early metastases frequently, histologicaly of alveolar type
  - Retroperitoneal site – often late diagnosis and large tumor
- Variable prognosis in rhabdomyosarcoma of the head and neck area
- Poor prognosis with involvement of CNS
- Unfavorable prognosis in children with alveolar and pleomorphic histology – high rate of local relapse and metastases
- Age:
  - More favorable prognosis in children less than 7 years old
  - More than 7 years old more frequently advanced stage and alveolar rhabdomyosarcoma

Therapy and Prognosis in Nonresponding or Relapsing Rhabdomyosarcoma

- In nonresponding rhabdomyosarcoma combination therapy with topotecan, vinorelbine, taxol, and irinotecan has been used

Survival after relapse	
Group I	48±12%
Group II	12±9%
Group III	11±5%
Group IV	8±4%

- The majority of relapse occurs within 2–3 years after diagnosis
- In patients with local relapse standard chemotherapy plus ifosfamide, doxorubicin, etoposide or other cytotoxic agents (see above)
- In children with disseminated relapse poor prognosis
- Experimental procedure:
  - Double high-dose therapy with autologous stem-cell transplantation
  - Allogeneic stem-cell transplantation with the possibility of antitumor effects caused by the donor's immune response (graft-versus-tumor effect)
  - Blockade of tumor growth by tyrosine kinase-receptor antagonists and endothelial cell growth antagonists (e.g. endostatin and angiostatin)
- Palliative therapy: irradiation, surgery, chemotherapy

Secondary Tumors

Of 1,770 children in the Intergroup Rhabdomyosarcoma Study I and II 22 had secondary cancers mainly osteosarcoma and leukemia (acute myelogenous leukemia, AML, or myelodysplastic syndrome, MDS)

Fibrosarcoma

Incidence

- Eleven percent of all soft tissue sarcomas in childhood
- Seventy-five percent in children less than 10 years old including 36% in newborns (congenital fibrosarcoma)
- Ratio of boys to girls 1.2:1

Location

Ranked by frequency:
- Lower extremities
- Upper extremities
- Head and neck
- Trunk
- Pelvic area
- Rarely retroperitoneal and visceral area, chest

Pathology and Cytogenetics

- Fibrosarcoma mainly in muscles of the extremities
- Tumor infiltration into normal tissue
- Histology:
  - Congenital form: uniform fibroblasts or myofibroblasts; low rate of mitosis; cytogenetics: translocation t(12;15)
  - Fibrosarcoma: anaplastic spindle cells in herring-bone pattern with parallel arrangements of tumor cells, collagen detectable; cytogenetics: translocation t(x;18), t(2;5), t(7;22); mutation of tumor suppressor gene *TP53* associated with poor prognosis

Grading	
Grade 1	Well differentiated, less cellular
Grade 2	Moderately differentiated
Grade 3	Moderately undifferentiated with higher rate of mitosis
Grade 4	Undifferentiated, highly cellular, high rate of mitosis

Differential Diagnosis

- Nodular fascitis
- Myositis ossificans
- Inflammatory pseudotumor
- Neurofibrosarcoma
- Malignant peripheral nerve sheath tumor/schwannoma
- Poorly differentiated embryonal rhabdomyosarcoma
- Monophasic (spindle cell) synovial sarcoma

Clinical Manifestations

- Painless swelling of soft tissue and muscle

Therapy

Surgical procedures
- Primary total resection; amputation rarely necessary
- Regional lymph node biopsy indicated (involvement about 4–10%)

Radiotherapy
- Residual tumor after surgery or relapsing fibrosarcoma: 60–65 Gy necessary

Chemotherapy
- In metastatic fibrosarcoma: management as in rhabdomyosarcoma (see above)
- In patients with grade 3–4 fibrosarcoma: following resection procedure as in rhabdomyosarcoma (see above)

Follow-up

- Thirty percent to seventy-five percent of patients show relapse within 18–20 months after first diagnosis; late relapse within the first 20 years after initial disease is possible
- More than 50% of patients with grade 3–4 staging develop metastatic disease after localized tumor treatment (without systemic chemotherapy)
- Metastatic spread: mainly lung, CNS and bladder

Prognosis

- Grades 1 and 2: 10-year survival rate in 70% of patients
- Grades 2 and 4: 10-year survival rate in 30–40% of patients
- Age:
  - Below the age of 5 years of age: 80% survival rate, metastatic spread in 4–8% of patients
  - In children older than 10 years, 60% survival rate, metastatic spread in 50% of patients

Synovial Sarcoma

Incidence

- Five percent of soft tissue sarcoma in childhood
- Mainly in adolescents and young adults
- Ratio of boys to girls 1.2:1

Location

- In the extremities 80–90%, mostly in the lower extremities
- Frequency (ranked): thigh, foot, knee, forearm, lower leg and hand; rarely head and neck, chest, spine and skull

Pathology and Cytogenetics

- Tumor rarely connected with the joints
- Histology: two cellular types: spindle cells, structured in whirls or sheets surrounded by epithelial cells with periodic acid-Schiff (PAS)-positive polysaccharide and glandular-like structures
- Immunohistochemistry: keratin antibodies detectable
- Cytogenetics: translocation t(x;19) (q11;Xp11)

Clinical Manifestations

- Painless swelling in about 60%, pain-sensitive swelling in 22% and painful tumor in 18% of patients
- Metastatic spread: lung, lymph node, bone, rarely brain

Radiological Diagnosis

- MRI and/or CT: frequently calcifications within the tumor

Therapy

- Due to high frequency of metastatic spread combined therapy with surgery, chemotherapy and radiotherapy

Surgical Procedure

- Total resection and regional lymph node biopsy (involvement in 25% of cases)

Radiotherapy

- Local irradiation of 50–60 Gy including positive regional lymph nodes

Chemotherapy

- As in rhabdomyosarcoma (see above); without chemotherapy 75% of patients develop pulmonary metastases within 3 years of diagnosis

Prognosis

- Groups I + II: 80% 5-year survival
- Groups III + IV: 17% 5-year survival
- Relapse possible still after 10 years after diagnosis
- Groups III + IV: preoperative high-dose therapy with cisplatin, ifosfamide plus doxorubicin, eventually etoposide with higher rate of long-term survival

Liposarcoma

Incidence

- Four percent of all soft tissue sarcomas in childhood
- Peak incidence during infancy and during adolescence
- Ratio of boys to girls 2:1
- Often tumor during adulthood

Pathology and Cytogenetics

- Origin from precursor cells of lipoblasts with five histological types:
  - Well-differentiated type: most frequent form; similar to lipoma; however with atypical cells together with fibroblasts, spindle cells and sclerosis
  - Myxoid type: monomorphic, fusiform or starry cells within a mucoid matrix
  - Round-cell type: round and oval cells with central nucleus and foamy cytoplasm
  - Pleomorphic type: pleomorphic cells with vacuoles, uni- or multinucleated, eosinophilic cytoplasm
  - Mixed type
- Cytogenetics: translocation t(12;16)(q13;p11)

Clinical Manifestations

- Tumor mass in any lipomatous tissue mainly in the thigh and the retroperitoneal area, but also in the area of head and neck, shoulder, chest, foot and omentum, rarely in the kidney
- Metastatic spread: lung, liver; rarely brain, pleura, pancreas or bone

Therapy

- Depending on the histological subtype: 70% of patients have the well-differentiated type with rare metastatic spread, but sometimes with local relapse

Surgical procedure
- Radical resection if possible

Radiotherapy
- In patients with subtotal surgery and histologically unfavorable type: 50–60 Gy irradiation necessary

Chemotherapy
- Chemotherapy in undifferentiated forms only, similar procedure to rhabdomyosarcoma (see above)

Prognosis

- Depends on the degree of tumor excision and histological type:
  - Well-differentiated type: favorable, more than 80% 5-year survival
  - Myxoid type: variable, up to 80% 5-year survival
  - Round-cell and pleomorphic type: poor prognosis; 15–30% 5-year survival
  - Retroperitoneal liposarcoma: poor prognosis

Malignant Peripheral Nerve Sheath Tumor

- Benign variant: schwannoma

Incidence

- In childhood 3–4% of soft tissue sarcomas
- More than 5% in children with neurofibromatosis type 1

Location

- Extremities: 42%
- Retroperitoneal area: 25%
- Sacral area: 21%
- Other locations: rarely

Pathology and Cytogenetics

- Originates from peripheral nerve (plexus, spinal nerve roots), histologically similar to spindle cells; difficult to differentiate from fibrosarcoma; rate of mitosis correlated with grade of malignancy
- Morphological differences between malignant nerve sheath tumor and schwannoma by electron microscopy
- Immunohistochemistry: S-100 antibody positive
- Genetic: high association between neurofibromatosis with 17q11.2 chromosomal alterations and chromosomal abnormities of chromosomes 1, 11, 12, 14, 17, 22 which may be associated with loss of tumor suppressor genes on 17p and 22q

- Other histological subtypes: epithelial, glandular or cartilaginous forms
- Due to neuroectodermal origin there are mesodermal and ectodermal variants:
  - Melanoma-rhabdomyoblastoma variant
  - Epithelial, mucin-producing variant

Clinical Manifestations

- Swelling
- Rarely pain

Therapy

- Approach similar to that used in grade III and IV fibrosarcoma and rhabdomyosarcoma (see above)

Leiomyosarcoma

Incidence

- Less than 2% of all solid tumors in childhood
- Fifty percent in children less than 5 years old
- Second peak during adolescence
- Ratio of boys to girls 1:1
- Association with HIV infection and other immune deficiencies

Location

- Visceral, mainly gastrointestinal (stomach), genitourinary , retroperitoneal or rarely in peripheral soft tissue

Pathology

- Histologically spindle cells with cigar-shaped nuclei and prominent nucleoli; sometimes longitudinal myofibrils detectable in the cytoplasm
- Degree of malignancy depends on:
  - Number of mitoses (more than 10 mitoses per microscopic field is prognostically unfavorable)
  - Degree of anaplasia
  - Number of bizarre forms

Clinical Manifestations

- Depending on the localization of the sarcoma
- Gastrointestinal: melena, hematemesis, anemia; rarely vomiting, abdominal pain, nausea and weight loss
- Genitourinary :

  - Location: uterus, bladder, prostate
  - Symptoms: vaginal bleeding, dysuria, retention of urine; visible or palpable tumor
- Peripheral leiomyosarcoma: visible tumor

Therapy

- Favorable histology: usually radical surgical resection is sufficient
- Unfavorable histology:
  - Often metastatic spread to lung, liver or regional lymph nodes; genitourinary sarcoma with intra-abdominal spread of lymph nodes
  - Combined treatment as in rhabdomyosarcoma (see above); radical surgical excision since the leiomyosarcomas are not very sensitive to radiotherapy

Prognosis

- In general 20–25% 5-year survival
- Unfavorable prognosis in tumor involving visceral areas (high rate of metastatic spread), favorable prognosis in other primary locations with total resection

Hemangiopericytoma

Incidence

- Three percent of all soft tissue sarcomas in childhood

Location

- Predominantly in (lower) extremities, in the retroperitoneal area and in head and neck; also paraspinal area
- Infants: tongue and sublingual area

Pathology and Cytogenetics

- Originates from vascular pericytes
- Histologically difficult differentiation between benign, intermediate or malignant forms
- Metastatic spread: mainly in lung and bone
- Cytogenetics: translocation t(12;19)(q13;q13.3), t(13;22)(q22;q11)

Therapy

- Radical resection
- Chemo- and radiotherapy according to rhabdomyosarcoma (see above)

Prognosis

- In general 30–70% 5-year survival
- Prognosis depends on extent of disease
- In children predominance of favorable prognosis with hemangiopericytoma

Congenital Hemangiopericytoma Variant

- Location in subcutis
- Therapeutically surgical excision is sufficient
- Prognosis: more favorable than hemangiopericytoma in childhood

Malignant Fibrohistiocytoma MFH

- Rarely in childhood compared with adulthood
- In children 5–8% of all soft tissue sarcomas
- Karyotypic abnormalities of chromosome 19p+
- Location: extremities, skull, kidney
- Differential diagnosis: fibrosarcoma, angiomatoid malignant fibrohistiocytic sarcoma
- Rarely metastatic
- Therapy:
  - Resection
  - Chemotherapy in the advanced stage and where histological findings show a high rate of mitosis: treatment according to rhabdomyosarcoma

Osteosarcoma

Thomas Kühne

Definition

- Primary malignant tumor of bone
- Origin: primitive mesenchymal stem cell capable of differentiating toward bone (but also fibrous tissue and cartilage)
- Osteoid tissue or immature bone production of malignant proliferating mesenchymal tumor cells
- Represents a heterogeneous group of tumors (Table 13.1.)

Epidemiology

- The sixth most common group of malignant tumors in children
- Adolescents and young adults: the third most common malignant tumor
- The most common bone tumor in children and adolescents (approximately 35% of primary sarcomas of bone)
- Rare in the first decade of life (less than 5%)
- Approximately 60% of patients are between 10 and 20 years old
- Occurs most frequently during the adolescent growth spurt
- Bimodal age distribution: the first peak during second decade of life and a small peak (controversial) in patients older than 50 years
- Male-to-female ratio is 1.3–1.6:1
- Peak incidence in second decade of life is somewhat higher in white males than in males of other races

Location

- Skeletal regions affected by greatest growth rate, i.e. distal femoral and proximal tibial metaphyses
- Approximately 50% of osteosarcoma in knee region
- Humerus is third most frequently involved bone, usually proximal humeral metaphysis and diaphysis
- Pelvis, i.e. ilium in approximately 10%

Etiology and Tumor Genetics

- Etiology is unknown
- Relation between rapid bone growth as in adolescence and development of osteosarcoma
- Ionizing radiation
- Viral cause not proven
- Alkylating agents and anthracyclines may be etiologically involved in secondary osteosarcoma
- Association with Paget's disease
- Familial osteosarcoma has been reported

- Osteosarcoma following hereditary retinoblastoma or associated with mutations in the retinoblastoma (*RB*) gene without manifestation of a retinoblastoma are well described. However normal *RB* alleles are found in most investigated osteosarcomas
- Further evidence of genetic background of osteosarcoma is reflected by *TP53* mutations (*TP53* is a tumor suppressor gene)
- Li-Fraumeni syndrome, a familial cancer syndrome, associated with a germline *TP53* mutation is strongly associated with osteosarcoma

Pathology

- Morphological classification (e.g. osteoblastic, chondroblastic, fibroblastic)
- Classification according to growth pattern (e.g. intramedullary osteosarcoma (origin and growth primarily within bone tissue) and surface osteosarcoma (growth at surface of bone with periosteal or parosteal tissue)
- There are various classification systems without standardization
- Classification is mainly descriptive; there is often a variability of several tissue types, i.e. production of osteoid, anaplastic stroma cells, different amount of bone tissue, small and large round cells, giant cells, normal osteoclasts. There is no clear phenotypic association with the morphological subtypes
- Approximately 50% of bone tumors are malignant
- Telangiectatic osteosarcoma
  - Rare type osteosarcoma that appears to be a separate entity although similar to conventional osteosarcoma in clinical aspects

Table 13.1. Morphological classification of osteosarcoma

Conventional osteosarcoma	**Secondary osteosarcoma** (retinoblastoma, Paget's disease, irradiation induced, fibrous dysplasia and others)
- Osteoblastic	
- Chondroblastic	
- Fibroblastic	**Surface osteosarcoma**
- Small cell	- parosteal (juxtacortical)
- Giant cell	- periosteal
- Epithelioid	
Telangiectatic osteosarcoma	
Well differentiated ostiosarcoma	**Multifocal osteosarcoma**

  - The previously reported poor prognosis being much worse than conventional osteosarcoma has improved and now is no different from conventional
  - Management as conventional osteosarcoma
- Small-cell osteosarcoma
  - May be confused with Ewing sarcoma, but distinguishable by osteoid production
  - Biopsy: adequate tumor sample is required for diagnosis
  - Management as for conventional osteosarcoma

Clinical Manifestations

- The most frequent symptom is pain originating from the involved region often for weeks or even months
- Sometimes swelling with local signs of inflammation
- Loss of function
- Weight loss is unusual and points to metastatic disease if present

Metastasis

- At time of diagnosis macrometastases are present in approximately 15–20% of patients, but micrometastases (mainly lungs) much more frequently present
- Lung metastases predominate
- Rarely skeletal metastases with or without simultaneous lung metastases
- Multiple bone metastases may also reflect multifocal osteosarcoma with a poor prognosis

Evaluation

- Clinical work-up: history, physical examination (pain, location, swelling, signs of inflammation, function)
- Radiology: plain radiographs in two planes, magnetic resonance imaging (MRI) of primary site of at least complete involved bone plus adjacent joints (tumor extent in bone and soft tissues); MRI is more appropriate than computed tomography (CT) scan
- Metastases: chest X-ray, CT scan of thorax, skeletal radionuclide scan with MRI of hot spots
- Assessment of organ functions
- Open biopsy of tumor before chemotherapy (preferably performed by the same orthopedic team involved in future surgery of the patient; close collaboration with pathology and pediatric oncology is the basis for successful management)

Radiology

- High variability
- Radiological classification of lytic and sclerotic tumors; both components often present
- Tumor matrix may be mineralized resulting in variable dense opacities of different sizes and shapes
- Tumor margins may be poorly defined. Destructive growth pattern with lytic and sclerotic areas and normal bone tissue commonly observed
- Cortex exhibits frequently destructive growth; the tumor is rarely limited to medullary space
- Extension into soft tissue common
- Periosteal reaction often present with various features, occasionally as radiating striations called "sunburst signs," or as open triangles overlying the diaphyseal side of the lesion (Codman's triangle) or in the form of multiple layers ("onion skin")

Differential diagnosis

- May be confused with benign and malignant bone lesions
- Callus formation following fracture
- Osteogenesis imperfecta (type I)
- Acute and chronic osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Benign and aggressive osteoblastoma
- Chondrosarcoma
- Malignant fibrous histiocytoma
- Giant-cell tumor
- Metastatic carcinoma (extremely rare in childhood)

Treatment

- Management ideally done using national or international clinical trials
- Combined modality treatment essential
- Neoadjuvant chemotherapy with standardized evaluation of chemotherapy response of the tumor at the time of definitive surgery followed by risk stratification and postsurgical risk-adapted therapy
- Surgery: goal is a wide resection. Limb-saving surgery with allograft or prosthesis. In situations of unclear surgical resection (questionable wide resection) and in poor chemotherapy responders consideration of amputation
- Adjuvant postsurgical chemotherapy according to tumor response to chemotherapy and according to a standardized risk stratification
- High-dose chemotherapy with autologous stem-cell transplantation has not been proven to be of value
- Osteosarcoma is relatively radioresistant

Treatment of relapsed disease

- Prognosis is poor; 5-year post-relapse survival seems to be less than 30%; patients are often heavily pretreated
- Complete surgery seems to be the most important prognostic factor
- Therapy is not standardized

Prognosis

- Results from the German Cooperative Osteosarcoma Study Group (COSS)
  - Five-year overall survival is approximately 65%
  - Five-year overall survival in patients without metastasis at the diagnosis of osteosarcoma is approximately 70%
  - Five-year overall survival in patients with metastasis at the diagnosis of osteosarcoma is approximately 30%. Favorable prognostic factors: single metastasis, complete surgical resection of tumor
  - Patients who respond well to neoadjuvant chemotherapy have a significantly better prognosis than poor responders
  - Other important prognostic factors:
    Location of primary tumor (osteosarcoma of extremities has a better prognosis than other locations), tumor size, surgical result (patients with incomplete resection have a worse prognosis)

Complications

- According to location of the lesion
- Secondary malignancy
- Psychological complications (related to diagnosis, location, therapy, body image and functional limitations)
- Social problems (costs, school, professional guidance, social contacts, insurability)

Ewing Sarcoma Family of Tumors

Thomas Kühne

- EFT Ewing family of tumors
- ES Ewing sarcoma
- PNET Peripheral primitive neuroectodermal tumor
- EM Electron microscopy

Definition

- Defined by the presence of t(11;22) resulting in the fusion gene *EWS/FLI*.
- Several different cytogenetic abnormalities, e.g. t(21;22), t(7;22)
- Histological subclassification based on neuroectodermal differentiation:
  - Classic Ewing sarcoma (ES) of the bone
  - Extraskeletal or soft tissue ES
  - Askin tumor (chest wall)
  - Peripheral primitive neuroectodermal tumor (PNET) of the bone and/or soft tissue
- Common aspects of Ewing family of tumors (EFT):
  - Neuroectodermal histogenesis
  - Genetics (see below)

Epidemiology

- Second most common malignant bone tumor in childhood and sixth most frequent malignant bone tumor
- Annual incidence is 2.7 patients per million children younger than 15 years old (USA)
- Male-to-female ratio is 1.5:1
- Eighty percent of tumors occur in patients younger than 20 years of age
- Fifty percent of the tumors occur in the second decade of life
- The mean age at diagnosis is 15 years
- More common in the white than in the black population

Localization

- Mainly lower extremities involved and less frequently in the upper extremities
- Pelvis
- Chest wall
- Less common in the spine or paravertebral region
- Less common in head and neck

Pathogenesis

- Not associated with preceding irradiation therapy (in contrast to osteosarcoma)
- Not associated with familiar tumor syndromes

- Originating from a precursor cell with the potential for neuroectodermal differentiation based on ultrastructure, immunohistochemistry and genetics

Genetics

- In approximately 95% of patients there is a reciprocal translocation of the *EWS* gene on chromosome 22q12 with one of the genes of the *FLI* oncogene family. The *FLII* gene on chromosome 11q24 or the *ERG* gene on chromosome 21q22 belong to the latter family

Pathology

Classification in ES and PNET is controversial and based on subjective and semiquantitative analysis of the grade of neural differentiation

Macroscopic aspects

- Gray-white tumor with various necrotic, hemorrhagic or cystic parts
- Glistening moist appearance on sectioning
- Tumors are capable of extensive growth in the medullary cavity of bones with or without cortical invasion. However, typically the cortex diffusely involves small tumors which may penetrate the cortex and invade the adjacent soft tissue
- Early invasion of periosteal soft tissue is frequently seen
- Often the extraskeletal part is more prominent than the bone tumor

Microscopic aspects

- Typical small, blue round-cell tumor
- Proliferation of undifferentiated mesenchymal cells, usually in solid, cellular broad sheets
- Monomorphous appearance of tumor cells
- Round cells with scant cytoplasm, high ratio of nuclear to cytoplasmic material, basophilic nucleus which is central
- Chromatin is homogeneous with fine granularity and one to three nucleoli
- Often a biphasic pattern with light and dark cells; the latter represent tumor cells undergoing apoptosis
- Sometimes rosette-like structures may be formed by tumor cells (less than 20% in ES, more than 20% in PNET and termed as Homer-Wright rosettes)
- Ultrastructure may be particularly helpful in identifying neuroectodermal differentiation

Immunohistochemistry

- Periodic acid-Schiff (PAS) reaction staining for glycogen is positive
- Expression of *CD99* (*MIC2*) in approximately 90% of ES and PNET:
  - Important for differential diagnosis
  - Codes for a membrane protein (p30/32)
  - Not specific for tumors of the EFT
- Vimentin-staining test results in 80–90% of cases are positive

- Neuron-specific enolase test results are positive
- S-100, Leu-7, HNK-1 and other proteins

Clinical Manifestations

- Related to the sites of the disease
- Painful, palpable mass
- Fever (in approximately 20%)
- Anemia, leukocytosis, increased sedimentation rate
- Pathological fracture in approximately 10% of cases
- Often trauma preceding diagnosis of tumor
- Symptoms caused by metastases (e.g. decreased muscular strength in legs. Dysuria with intraspinal tumor growth)

Metastases

- Based on the identification of the typical genetic translocation found in EFT early metastatic spread of tumor cells causing micrometastases is often observed
- Macroscopically visible metastases are present in 20–30% of children with EFT
- Hematogenous route is most frequent pattern of spread: lungs, then bone and bone marrow
- Rarely seen in lymph nodes, liver or central nervous system
- Askin tumors, i.e. tumors of the chest wall may invade the adjacent pleural space with subsequent pleural effusion (cytology of the material may be diagnostic)
- Patterns of metastasis seem to be associated with the primary tumor location

Evaluation

- Optimal management of the patient requires a multidisciplinary team (pediatric oncologists, orthopedic surgeons, pathologists and radiologists)
- Laboratory findings:
  - Complete blood count
  - Tumor lysis parameters, electrolytes, kidney and liver parameters, lactate dehydrogenase
  - Consider vanillylmandelic acid and homovanillic acid to rule out neuroblastoma; blood sedimentation rate, and C-reactive protein
- Radiology:
  - Primary site: conventional X-rays (periosteal reaction,"onion-skin phenomenon", represents layers of periosteum due to de novo bone formation). MRI preferred over CT scan for measurement of tumor volume
  - Metastases: radionuclide scan of skeleton with X-rays or MRI scans of affected areas, chest X-ray, chest CT, bone marrow aspiration (cytology and molecular biology)
- Open biopsy

Differential Diagnosis

- Osteomyelitis (20% of patients with EFT have fever)
- EFT rarely represents a diagnostic problem because of immunohistochemistry and molecular biology characteristics
- Small, blue round-cell tumors
  - Metastatic neuroblastoma (mainly infants and young children)
  - Non-Hodgkin lymphoma
  - Rhabdomyosarcoma
  - Small-cell osteosarcoma
  - Undifferentiated sarcoma
  - Desmoplastic round-cell tumor
- Acute leukemia

Treatment

- Therapeutic success reflected by multimodal therapy based on prospective randomized studies
- Risk-adapted individual therapy is the ultimate goal
- Close collaboration of the involved disciplines necessary
- The impressive improvement of clinical results is based on collaborative study groups with the introduction of neoadjuvant and adjuvant chemotherapy in addition to surgery and careful use of radiotherapy
- High-dose chemotherapy followed by autologous hematopoietic stem-cell therapy has not proved helpful; however, there are still many unanswered questions (e.g. timing and intensity of high-dose chemotherapy); thus clinical trials investigating this therapeutic option are needed
- Local therapy: intensive neoadjuvant chemotherapy followed by surgery with the aim of resecting the tumor completely. The tumor tissue is then analyzed for chemotherapy response and surgical success (tumor margins). The standardized results of pathology (complete, partial or no response) serve as stratification procedure according to study protocols
- Complete surgical resection is associated with a survival advantage. Patients treated with irradiation therapy alone are less likely to be cured than patients treated with surgery or surgery and radiotherapy
- EFT are radiosensitive. Irradiation therapy should be carefully evaluated and applied according to study protocols. Poor chemotherapy responders may benefit from radiotherapy

Prognosis

- Dependent on surgical resection, tumor localization, tumor volume, presence of macroscopic metastases, molecular biological aspects
- Overall 5-year survival in 1970, 5–10%; currently (2004) approximately 70%

Complications

- Relapse
- The increased survival rate is associated with the occurrence of late effects
- Musculoskeletal abnormalities (surgery, radiotherapy)
- Secondary tumors
- Psychological and social problems

Retinoblastoma

Paul Imbach

Definition

- Malignant, congenital tumor of the retina of the eye
- Hereditary and acquired forms
- High rate of cure
- High rate of secondary tumors in hereditary forms of retinoblastoma

Incidence

- Two percent of all neoplasias in childhood
- Annually 3 in 1 million children less than 16 years old are newly diagnosed
- Annually 11 in 1 million children less than 5 years old are newly diagnosed; after the 5th year of life occurrence is rare
- Median age at diagnosis: 2 years
- Boy-to-girl ratio of 1:1
- Bilateral involvement in 20–30% of cases
- Clinical manifestations not usually all at the same time; mostly within the 1st year of life
- Bilateral involvement more frequent in girls
- Unilateral involvement in two-thirds of the children affected by the disease, mainly during the 2nd and 3rd years of life

Etiology, Genetics and Pathogenesis

- Sporadic form (60%): members of the family and relatives without retinoblastoma
- Hereditary form (40% overall: 15% unilateral, 25% bilateral): two mutational events are required for tumor occurrence:
  - Step 1: mutation of the germ cell
  - Step 2: mutation of the target cell (retina cell)
  - Hereditary retinoblastoma is an autosomal dominant trait with high penetrance, i.e. nearly 50% of relatives develop a retinoblastoma (mostly bilateral)
- The chromosomal alteration is located on chromosome 13q14 involving the *RB1* retinoblastoma gene which is in the chromosomal region linked to the development of osteosarcoma. Osteogenic sarcoma is the most frequent secondary tumor following retinoblastoma
- *RB1* is also expressed in normal human tissues including brain, kidney, ovary, spleen, liver, placenta and retina; it is involved in cell cycle regulation inducing the transition from G1 to S-phase
- In the hereditary form of retinoblastoma siblings and family members should be tested genetically and screened by an ophthalmologist within the first 4 years of life
- Occasionally occurrence of combined deformities: microencephaly, microphthalmia and skeletal and urogenital anomalies
- Retinoblastoma, neuroblastoma and medulloblastoma have a common neuroectodermal origin and also common characteristics such as similar necrotic nests in the

tumor and radiosensitivity; retinoblastoma and neuroblastoma both undergo spontaneous regression

Pathology

Macroscopic features

- One or more tumor sites mainly arising from the ora serrata retinae
- Two types of spread:
  - Exophytic: from the retina into the subretinal space with detachment of the retina
  - Endophytic: Growing into the vitreous cavity producing floating tumor spheres named vitreous seeds
- Extension of tumor toward the choroid, the lamina cribrosa sclerae, the optic nerve or via the subarachnoid space and central nervous system (CNS)
- Distant metastases in lymph nodes, bone marrow, bone and liver; rarely pulmonary metastases (similar to neuroblastoma)

Microscopic features

- High cellularity with small hyperchromatic cells and high nuclear-to-cytoplasm ratio, often grouped in cell rosettes (similar to neuroblastoma)
- Frequently mitotic cells and necrotic areas, some containing calcium deposits

Reese-Ellsworth Classification

Group			
1a	Solitary tumor	Less than 4 disk diameters in size	At or behind the equator
1b	Multiple tumors	None more than 4 disk diameters in size	All at or behind the equator
2a	Solitary tumor	4–10 disk diameters in size	At or behind the equator
2b	Multiple tumors	4–10 disk diameters in size	At or behind the equator
3a	Tumor anterior to the equator		
3b	Solitary tumor	More than 10 disk diameters	At or behind the equator
4a	Multiple tumors	More than 10 disk diameters	
4b	Tumor anterior to the ora serrata		
5a	Massive tumors involving more than half the retina		
5b	Vitreous seeding		

- Ca. 80% of unilateral retinoblastoma and 90% of bilateral retinoblastoma have group 5 classification at time of diagnosis

Clinical Manifestations

- Leukokoria ("cat's eye" reflex) in the pupil of the eye is the first symptom in the majority of patients
- Strabismus
- Anisocoria
- Loss of vision
- In examination of the fundi following chemical dilatation, often under general anesthesia in young children, tumor mostly present in the area of ora serrata retinae, frequently with vitreous hemorrhages and detachment of the retina
- Ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) for detection of extension within the orbit, the optical nerve and the intracranial area
- Diagnosis of metastases: cerebrospinal fluid analysis by lumbar puncture, bone marrow analysis, bone scintigraphy and chest X-ray
- Occasionally there is a high level of serum a-fetoprotein or carcinoembryonic antigen (CEA)

Differential Diagnosis

- Granuloma caused by *Toxocara* infection (with or without eosinophilia in WBC)
- Retinal astrocytoma is rare
- Leukokoria in hyperplasia of the vitreous body
- Detached retina: retinopathy in the preterm infant, Coats syndrome, congenital retinal detachment, the juvenile form of retinoschisis, von Hippel-Lindau syndrome
- Vitreous hemorrhage: traumatic, neonatal bleeding
- CT and/or MRI allow differentiation and assessment of extension of the pathological process

Therapy

- The objective is to maintain vision without endangering the life of the child
- In advanced stages (groups 3–5) and in unilateral retinoblastoma enucleation of the eye is necessary; in bilateral retinoblastoma the eye with the more extensive tumor/loss of vision may need to be enucleated while the remaining eye can be treated with other therapeutic options
- In extraocular retinoblastoma of the CNS craniospinal irradiation in children above the age of 2–3 years may be necessary

Surgical management

- Enucleation

Chemotherapy

- Reduction of the tumor by combination of vincristine, etoposide and carboplatin, and eventually cyclophosphamide or anthracycline followed by other treatment modalities (see below)
- Chemotherapy is the first therapeutic option in bilateral retinoblastoma reducing the need for radiotherapy and the risk of secondary tumors
- In extraocular retinoblastoma and/or metastatic retinoblastoma: combination chemotherapy followed by autologous stem-cell transplantation
- In palliative care: vincristine, cyclophosphamide or vincristine combined with doxorubicin may be helpful

Chemothermotherapy

- Chemotherapy may be augmented by a combination of ultrasound, microwaves, and/or infrared treatments which increase the temperature of the tissue to 42–60 °C and result in excellent outcomes, especially in multiple, small retinal tumors

Radiotherapy

- Retinoblastoma is highly radiosensitive
- High-voltage irradiation (linear accelerator) is used most commonly
- Dosage: 35–45 Gy
- Sedation of the child and use of a plaster cast may be necessary

Laser photocoagulation

- Indications: Small retinal tumors (diameter less than 4.5 mm and thickness less than 2.5 cm2) in relapse after irradiation
- Complications: hemorrhage of vitreous body, detachment of retina

Cryotherapy

- In small tumors, especially in the area of the equator
- Cryotherapy produces intracellular crystal formation which destroys the tumor by interrupting microcirculation

Brachytherapy

- Implantation of radioactive seeds transiently with 40-Gy activities within 7 days

Management of the Different Manifestations of Retinoblastoma

Unilateral Intraocular Retinoblastoma

- Enucleation including the optic nerve is curative; in tumor involvement of the optic nerve therapy similar to extraocular disease may be required (see below)
- Groups 1–3: above mentioned treatment options (irradiation, laser photocoagulation, cryotherapy, chemotherapy) without enucleation
- Groups 4 and 5 with no family history: enucleation in patients with invasion of the retinal pigment epithelium, choroid, optic nerve and/or lamina cribrosa sclerae often necessary

Unilateral Extraocular Retinoblastoma

- In patients with involvement of sclera, lamina cribrosa sclerae, orbit, cerebrospinal fluid, CNS or extracranial metastases: chemotherapy, eventually radiotherapy or other local control approaches and intrathecal methotrexate therapy

Bilateral Retinoblastoma

- Initial enucleation of one eye in patients with asymmetric tumors, e.g. one eye groups 1 or 2; the other eye groups 3–5. Sometimes both eyes and vision can be preserved with initial use of chemotherapy
- Otherwise first treatment choice is chemotherapy in combination with the other mentioned options (see above); in nonresponders uni- or bilateral enucleation may be necessary

Prognosis

- Survival: 80–90% of all patients with retinoblastoma after risk-adapted therapy

Risk of Secondary Tumors

- In bilateral retinoblastoma risk is 11–13%
- Occurrence of second malignancy is highest several years after first tumor, but risk persists throughout life
- Most frequent tumors:
  - Osteogenic sarcoma – 75% within the irradiated area, with remainder in nonirradiated sites; incidence 500 times higher than the primary osteogenic sarcoma in patients without inherited retinoblastoma
  - Rhabdomyosarcoma, sinus maxillaris sarcoma and others

Germ Cell Tumors

Paul Imbach

Definition

- Tumors develop from embryonal germ cells and may have tumor constituents representing ectodermal, mesodermal and endodermal lineages

Incidence

- One percent of all neoplasia in children
- Annually 2.4 children in 1 million less than 16 years old are newly diagnosed with germ cell tumors

Pathogenesis

- At 4th or 5th week of gestation extraembryonic germ cells migrate to gonadal ridge of the embryo
- At 6th or 7th week of gestation: after sex differentiation in the gonadal ridge:
  - Ovarian differentiation to oocytes
  - Spermatocytes form if Y chromosome is present
- Extragonadal germ cell tumors of children develop after aberrant migration of germ cells. This way germ cell tumors occur in the brain, mediastinal area or sacrococcyx depending on where the aberrantly migrating germ cells settle

Histological classification of gonadal and extragonadal tumors

A	Germ cells and germinoma/dysgerminoma and embryonal yolk sac tumor (pluripotent cells): (a) Extraembryonic structures: - Yolk sac or endodermal sinus tumor - Choriocarcinoma (b) Embryonal ecto-, meso-, endodermal origin tissues represented: - Teratoma (c) Embryonal carcinoma
B	Gonadal germ cells and stroma tumors (Sertoli and Leydig cells)
C	Epithelial cells (ovarian origin) and granulosa cell tumor or mixed form as well as epithelial cell tumors more common in adults

Genetics

- Ovarian germ cell tumor of adolescents:
  - Mature teratoma with normal karyotype
  - Immature teratoma with heterogeneous karyotype: partly isochromosome 12p, either diploid (mostly in grade I or II tumors) or aneuploid (grade III tumors)
  - Malignant ovarian tumor: aneuploidy and isochromosome 12p and/or alteration of chromosomes 21, 1q13 and 8
- Testicular germ cell tumor of adolescents:
  - Aneuploidy and isochromosome 12p
  - Loss of heterogeneity on chromosomes 12q13 and 12q22

Histological Classification

Classification of gonadal/extragonadal tumors

A. Gonadal tumors With germ cell characteristics		**Without germ cell characteristics**	
Girls	**Boys**	**Girls**	**Boys**
Teratoma	Yolk sac tumor	Epithelial carcinoma:	Leydig cell tumor
Dysgerminoma	Embryonal carcinoma	Granulosa, Sertoli, Leydig cell tumors	Sertoli cell tumor
Immature Teratoma and Embryonal carcinoma	Teratoma	Mixed tumor	
Mixed-cell tumor	Teratocarcinoma		
Choriocarcinoma	Gonadoblastoma		
Gonadoblastoma	Seminoma (adult)		
	Choriocarcinoma		
	Mixed-cell carcinoma		

B. Extragonadal tumors
(sacral, mediastinal, retroperitoneal, pineal region, rarely in other areas)

Teratoma ± yolk sac tissue

Teratoma ± embryonal carcinoma

Diagnostics

- Clinical manifestations: see particular germ cell tumors
- Radiological diagnosis: ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI)
- Tumor markers

α-Fetoprotein(AFP): parameters of initial diagnosis and follow-up	
Newborns:	48,000 ± 34,000 IU
Up to 1 month	9,000 ± 12,000 IU
Up to 2 months	320 ± 280 IU
Up to 4 months	74 ± 56 IU
Up to 6 months	12 ± 10 IU
Up to 8 months	8 ± 5 IU
High levels during embryogenesis and fetogenesis as well as until 8 months after birth	

- α-Fetoprotein: (AFP):
  - High level of AFP usually indicates malignant germ cell tumor
  - Half-life of AFP 5–7 days
  - High levels of AFP also possible in hepatoblastoma, pancreatic tumor, Wilms tumor and other disorders of liver
- β-Human chorionic gonadotropin (HCG):
  - Increased levels seen in germinoma/dysgerminoma, choriocarcinoma; during tumor lysis after chemotherapy of β-HCG-positive tumors
  - Half-life 24–36 h
  - Normally high levels of β-HCG during pregnancy produced by cells of the placenta
  - Normal serum β-HCG level in adults less than 5 U/ml
- Serum lactate dehydrogenase (LDH) level: nonspecifically increased when rapid proliferation of cells is present
- Fetal isoenzyme of alkaline phosphatase in the serum: increased levels in 30% of patients with germ cell tumors (in 100% of adult patients with seminoma)

Therapy: Overview

- The heterogeneity of germ cell tumors demands an individual therapeutic procedure depending on the location of the tumor

- Besides surgical excision/biopsy the addition of chemotherapy markedly improves long-term survival:
  - Cisplatin in combination with actinomycin D, etoposide, vinblastine and bleomycin as well as cyclophosphamide/ifosfamide
  - In children receiving treatment for refractory or relapsing germ cell tumor high-dose chemotherapy with autologous stem cell transplantation may be indicated

Testicular Germ Cell Tumors

- Two percent of solid tumors in boys
- In children 0.9–1.1 in 100,000 boys less than 16 years old
- Higher risk in boys with undescended testes
- Symptoms: scrotal enlargement, commonly associated with hydrocele
- Imaging: ultrasound, CT and/or MRI
  - Detection of metastases: bone scintigraphy, CT of lungs

Testicular Yolk Sac Tumor

Synonyms: yolk sac tumor, endodermal sinus tumor
- Frequency 26%
- Mean age 2 years
- AFP level usually high

Macroscopic features
- Solid, homogeneous, fragile tumor with cystic and necrotic areas

Microscopic features
- Network of stromal tissue
- Papillary structures with central vessels
- Intra- and extracellular eosinophilic compartments that are periodic acid-Schiff (PAS)-positive, AFP-positive and α1-antitrypsin-positive

Staging

- Stage I: Tumor limited to testes, no evidence of disease beyond the testes
- Stage II: Involvement of retroperitoneal lymph nodes
- Stage III: Additional solitary or multiple metastases

Therapy
- Radical en bloc excision, chemotherapy in stages II and III or in relapse; long-term survival rate of 80%

Testicular Teratoma

- Frequency of 24%
- Mean age 3 years

Histopathology

Teratomas originate from pluripotent germ cells that can give rise to tissues of all three embryonic germ layers:

- Ectodermal: epithelial and neuronal tissue
- Mesodermal: muscles, teeth, bone and cartilage
- Endodermal: mucinous parts of gastrointestinal and/or respiratory tissue
- Histology can be embryonal, fetal or adult

Histological grading of testicular teratoma

- Grade 0: Mature tissue without mitoses
- Grade 1: Some immaturity of tissue without or with limited neuroepithelium
- Grade 2: Immature tissue with moderate presence of neuroepithelium
- Grade 3: Prominent immature tissue and neuroepithelium

Therapy

- Radical en bloc excision with favorable prognosis in stage I
- In stages II and III as well as in adolescents after puberty: chemotherapy, then irradiation

Testicular Embryonal Carcinoma

- Mostly in boys older than 10 years of age
- Frequency is 20%
- AFP ± β-HCG frequency level usually high
- Therapy: radical surgery and chemotherapy

Testicular Teratocarcinoma

- Frequency 13%
- Mostly in boys older than 10 years of age
- Eighty percent with stage I and with a survival rate of 75% after surgical excision alone
- In advanced stages chemo- and radiotherapy

Testicular Seminoma (in Adults)

- Mixed tumor with germ cells and choriocarcinoma cells
- Rarely in boys and adolescents

Ovarian Tumors

- One percent of girls with neoplasia have an ovarian tumor
- Frequently in girls between 10 and 14 years of age
- In decreasing frequency: mature teratoma, dysgerminoma, yolk sac tumor, immature teratoma, mixed-cellular germ cell tumor, embryonal carcinoma, gonadoblastoma
- Symptoms: abdominal pain; acute abdomen
- Diagnosis: ultrasound, CT, MRI show cystic abdominal/retroperitoneal mass

Ovarian Teratoma

- Mature form: Frequency 31%; surgical total resection followed by observation (relapse risk 18%); if partial resection is performed chemotherapy is necessary
- Immature form: Frequency 10% (for Staging see Testicular Teratoma); one-third of patients with high AF level; unilateral tumor in 50–79%; management depends on stage; chemotherapy in stages II and III

Ovarian Dysgerminoma

- Histologically similar to seminoma in man
- Frequency 20%; bilateral occurrence in 20% of girls
- Therapy: Chemotherapy, commonly radiotherapy
- Ninety percent long-term remission

Macroscopic features
- Involvement of the ovary is diffuse
- Homogeneous, gray-pink mass with occasional necrosis, hemorrhage and cysts
- Sometimes huge tumor more than 15 inches in diameter
- Bilateral involvement in 10%

Microscopic features
- Round cells with clear cytoplasm; nuclei with one or more prominent nucleoli
- Mitotic cells are usually detectable
- Structure: cell nests separated by fibrous stroma
- Sometimes polynuclear giant cells which react immunohistochemically for chorionic gonadotropin

Therapy
- In localized, encapsulated tumor: unilateral salpingo-oophorectomy and biopsy of the contralateral ovary, exploration of para-aortic lymph nodes with biopsy, lavage of the pelvic area followed by cytological analysis

- Advanced stage or relapse: chemotherapy, eventually irradiation; ovarian dysgerminoma is highly sensitive to treatment

Yolk Sac Tumor

- Frequency 16%
- AFP level is often high
- Due to high relapse rate chemotherapy is necessary even in stage I
- Long-term survival rate is 80%

Ovarian Mixed-Cell Malignant Germ Cell Tumor

- Frequency 11%
- Occurrence often in precocious puberty
- AFP/β-HCG levels often high
- Therapy: after resection chemotherapy

Embryonal Carcinoma of the Ovary

- Frequency 6%
- Manifestations and management as in mixed-cell malignant germ cell tumors (see above)

Ovarian Gonadoblastoma

- Rare disorder
- Occurrence in dysgenic gonads
- Polyembryoma, choriocarcinoma with early metastases

Extragonadal Germ Cell Tumors

- Midline tumor
- Aberrant migration of embryonal gonads (see Pathogenesis)
- Main sites of involvement: sacrococcygeal, mediastinal, intracranial, retroperitoneal
- Majority of teratomas have favorable prognosis after total resection alone or after combined radio- and chemotherapy

Sacrococcygeal Teratoma

- Sixty-eight percent of all extragonadal tumors
- Newborns: 1:40,000
- Ratio of boys to girls 1:3
- Occasionally detectable by ultrasound during pregnancy
- Sometimes connected with other congenital anomalies

- In about 17% malignant components (high levels of AFP and β-HCG, mostly as embryonal carcinoma) present
- Early complete resection important including removal of coccyx
- Cure rate 95%
- Malignant form: after resection chemotherapy used

Intracranial Teratoma

- In the area of the pineal gland or suprasellar region or combined
- Symptoms: visual disturbances, diabetes insipidus, hypopituitarism, anorexia, precocious puberty
- AFP and β-HCG levels often high
- Histology: predominantly germinoma, otherwise mixed form, choriocarcinoma or teratocarcinoma
- Sometimes intracranial spread drop metastases
- Management: biopsy, chemotherapy, eventually radiotherapy (see above)

Mediastinal Teratoma

- Anterior mediastinum involved
- Mean age 3 years
- Symptoms: dyspnea, wheezing, thoracic pain, superior vena cava syndrome
- Majority are benign dermoid cysts; sometimes with calcium deposits visible on X-ray
- Differential diagnosis: thymoma, lymphoma, bronchogenic cyst, lipoma, intrathoracic thyroid tissue
- Management: surgery
- Prognosis: if a malignant component is present unfavorable prognosis is common despite combined chemo- and radiotherapy (30–50% of patients have initial metastases of lung, bone and/or bone marrow)

Hepatic Tumors

Paul Imbach

Forms

Hepatic tumors and frequency	
Hepatoblastoma	43%
Hepatocellular carcinoma	23%
Sarcoma	6%
Benign vascular tumors (hemangioendothelioma)	13%
Hamartoma	6%
Others	9%

Incidence (Except Benign Hepatic Tumors)

- One percent of all neoplasias in childhood
- Annually 1.4 in 1 million children less than the age of 16 years are newly diagnosed
- Ratio of boys to girls 1.4–2.0:1.0
- Different incidences worldwide, e.g. Far East more than Europe or the USA
- Relationship to hepatitis B in Taiwan: Due to systematic hepatitis B vaccination the number of patients with hepatic carcinoma has been reduced
- Relationship to preterm birth rate: Inverse relationship between birth weight and frequency – 15 times higher risk in infants with birth weight less than 1,000 g
- High incidence in genetically associated syndromes: Beckwith-Wiedemann syndrome, familial adenomatous polyposis, trisomy 18, glycogen storage disease, hereditary tyrosinemia type 1, Alagille syndrome, Li-Fraumeni syndrome, ataxia-telangiectasia, tuberous sclerosis, Fanconi anemia

- Hepatoblastoma: Mostly in infants, rarely after the age of 3 years. Intrauterine development of hepatoblastoma possible

- Hepatocellular Carcinoma: Mostly in children older than 4 years of age; more common in adolescents. Histologically identical with carcinoma in adulthood

Pathology and Genetics

Macroscopic Features

- Large, solid tumor mass; diameter less than 1 inch to more than 3 inches
- Main occurrence in right hepatic lobe
- Minority with multinodular, bilateral spread (15–30%)

Microscopic Features

- Hepatoblastoma: Two patterns of differentiation:
  - Epithelial type with embryonal or fetal features
  - Mixed epithelial-mesenchymal type, partly with osteoid formation
  - Some variants with variable embryonal differentiation
- Hepatocellular carcinoma: Histologically similar to hepatocellular carcinoma of adults
- Karyotype (hepatoblastoma):
  - Commonly trisomy of chromosomes 2 and 20, rarely of chromosome 8 are associated
  - Loss of heterozygosity (LOH) of chromosome 1p15 (as in other embryonal tumors, e.g. nephroblastoma or rhabdomyosarcoma)

Clinical Manifestations

- Expansive palpable mass in the upper abdomen or generalized enlargement of the abdomen
- Weight loss
- Anorexia
- Vomiting
- Abdominal pain
- Pallor
- Jaundice and ascites
- Occasionally precocious puberty in hepatocellular carcinoma
- Metastatic pattern: Commonly in lungs; rarely in bone, brain and bone marrow

Laboratory Diagnosis

- Serum a-fetoprotein levels elevated in 70% of children with hepatoblastoma, in 40% with hepatocellular carcinoma; serum human β-chorionic gonadotropin (β-HCG) levels can be high in both; both parameters are markers of diagnosis, therapeutic response and follow-up
- Level of bilirubin increased in about 15% of children with hepatoblastoma and in about 25% of children with hepatocellular carcinoma
- Often anemia, occasionally thrombocytopenia or more commonly thrombocytosis are observed

Radiological Diagnosis

- Ultrasound and X-ray of abdomen: Enlarged liver with displacement of stomach and colon, elevated diaphragm on the right side; occasionally calcification within the tumor mass is observed
- CT scan and MRI useful for determination of extension and involvement of adherent organs
- Liver scintigraphy: Useful to obtain additional information about localization of tumor, postoperative regeneration of liver or relapse

Differential Diagnosis of Hepatoblastoma and Hepatocellular Carcinoma

- Hemangioendothelioma
- Adenoma
- Cavernous hemangioma
- Malignant mesenchymoma of the liver
- Mesenchymal hematoma of the liver
- Liver metastases of other tumors

Staging

- Stages I–IV similar to other solid tumors

Therapy

Surgical Management

- Initially more than 50% of liver tumors are not totally resectable
- Presurgical chemotherapy often leads to making large tumors resectable, particularly for hepatoblastoma
- Complete resection is required for cure with lobectomy often necessary

Liver Transplantation

- In patients with incomplete surgical resection of tumor or with unsatisfactory response to chemotherapy (see below) liver transplantation may be indicated
- Five-year survival rate is more than 60% by partial liver-lobe donation or liver donation postmortem

Radiotherapy

- Only rarely useful or curative

Chemotherapy

- Initial tumor reduction before surgery
- Active drugs: Vincristine, doxorubicin, 5-fluorouracil, actinomycin D, cisplatin

Prognosis

- After complete tumor resection and chemotherapy survival 65–75% in children with hepatoblastoma and 40–60% in children with hepatocellular carcinoma
- Some patients may be cured with only complete resection
- Prognosis dependent on:
  - Stage of tumor: two-thirds of children with hepatoblastoma initially have high risk of stages III or IV (the key is surgical resectability)
- Rare subgroup with exclusive fetal form of hepatoblastoma and primary total resection is prognostically favorable without chemotherapy

Emergencies in Pediatric Oncology

Thomas Kühne

Tumor Lysis and Hyperleukocytosis

General

- Spontaneous or chemotherapeutic drug-induced cell lysis causes hyperkalemia, uric acid elevation, hyperphosphatemia, and hypokalemia and occurs in tumors with high proliferation rate, e.g. Burkitt lymphoma, T-cell acute lymphoblastic leukemia (ALL) and NHL, less frequently precursor B-cell ALL, acute myelogenous leukemia (AML) and neuroblastoma stage IVS.

Diagnosis

- Symptoms caused by hyperkalemia; probably hypocalcemia (see Therapy)
- Laboratory analysis: blood gas analysis, complete blood count (CBC), blood smear and leukocyte differentiation, sodium, potassium, calcium, magnesium, urea, creatinine, phosphorus and uric acid. Other diagnostic investigations according to suspected diagnosis
- Observations: Vital signs (pulse, blood pressure, respiration rate, temperature), ECG, daily weight
- Measure input and output continuously: output every 4 h; if output is less than 60% of input give furosemide 0.5–1.0 mg/kg i.v.
- Urine pH after each void should be 6.5–7.5
- Laboratory investigations every 2–4 h

Treatment

- Avoid potassium
- Avoid calcium except in the case of hypocalcemic tetanus (clinical investigation: Chvostek sign, Trousseau sign)
- Intravenous line, central line optimal, otherwise peripheral intravenous line
- Hydration (3–5 l/m2 body surface area)
- Alkalinization of urine: goal is for urine pH to be 6.5–7.5 (start with sodium bicarbonate 8.4% (50 mEq)/l fluid
- Allopurinol 400 mg/m2 per day or 10–20 mg/kg per day orally or i.v. in three or four doses per day (dose limit 400 mg/day) or recombinant uratoxidase enzyme (0.20 mg/kg per day, once daily as an infusion over 30 min)
- Discuss necessity for hemodialysis with nephrologist if signs and symptoms show progression

Hyperkalemia

General

- Often caused by tumor lysis (transcellular shift of potassium from the intracellular to extracellular fluids; see above). Other causes include diminished renal excretion,

impaired renal function, high potassium intake (dietary, iatrogenic, transfusion of old packed red cells), hemolysis, drugs (e.g., corticosteroids, digitalis overdose, potassium-sparing diuretics (spironolactone). Collaboration with nephrology and intensive care departments recommended

Diagnosis

- Symptoms: neuromuscular effects: paresthesia, weakness, ascending paralysis. Cardiac effects: alterations in cardiac excitability resulting in dysrhythmias and potentially ventricular fibrillation and cardiac arrest
- ECG: peaked T waves (early manifestation), prolongation of PR interval, loss of P waves, widening of the QRS complex
- Laboratory analysis: CBC (rule out hemolysis), sodium, potassium (normal value 3.5–5.5 mmol/l), urea, creatinine, other investigations according to origins of the hyperkalemia

Treatment

- No potassium
- Treatment indication when potassium is more than 6.5 mmol/l. Often there are "house rules"
- Alkalinization with $NaHCO_3$ 2 mmol/kg per 10–15 min
- Calcium gluconate 10% 0.5–1 ml/kg over 10 min with ECG monitoring and/or 0.5–1.0 g glucose/kg and 0.3 U insulin/g glucose over 30 min i.v. (hypoglycemia is a possible complication)
- Cation exchange resins, e.g. sodium polystyrene sulfonate (Kayexalate or Resonium) 0.5–1g/kg per day by enema and orally if possible or calcium polystyrene sulfonate (1 g/kg per day by enema and orally if possible in a ratio of 1:1)
- Collaboration with nephrology department; consider peritoneal dialysis or hemodialysis if abovementioned treatment is not successful

Hypercalcemia

General

- Rare in children with malignant tumors. Mainly seen in children with acute lymphoblastic leukemia, non-Hodgkin lymphoma, skeletal metastases (e.g., non-Hodgkin lymphoma), Ewing sarcoma, rhabdomyosarcoma, neuroblastoma

Diagnosis

- Symptoms: Anorexia, nausea, vomiting, polyuria, diarrhea followed by dehydration. Other symptoms include polydipsia, obstipation, ileus, bradycardia, arrhythmia, lethargy, depression, fatigue, stupor, coma
- Pathophysiology of oncological hypercalcemia: humoral, osteolytic and vitamin D-mediated hypercalcemia.

- Factors interfering with serum calcium: thiazide diuretics, antacids with calcium carbonate, lithium, hypervitaminosis (A or D), renal disorders, adrenal gland insufficiency, fractures, immobilization, oral contraceptives
- Laboratory analysis: serum calcium and ionized calcium, magnesium, phosphorus, sodium, potassium, protein, albumin, alkaline phosphatase, urea, creatinine
- Urine (spot test): calcium, creatinine, (calculate calcium, creatinine and phosphorus reabsorption)
- Radiology: ultrasonography of kidneys to rule out nephrocalcinosis and lithiasis

Treatment

- Consider treatment when calcium concentration is more than 2.8 mmol/l. Calcium concentration more than 3.5 mmol/l needs immediate treatment
- Hydrate with NaCl 0.9% (10–20 ml/kg per hour for 1–4 h) Furosemide 1–2mg/kg i.v. every 2–6 h
- Monitoring: sodium, potassium, excretion of sodium and potassium, urine volume, substitute losses (because of dehydration)
- Consider glucocorticoids (e.g. oral prednisone 2 mg/kg per day)
- Consider calcitonin 2–4 IU/kg every 6–12 h (effects within hours)
- Consider i.v. mithramycin or pamidronate
- Adults: $NaHCO_3$. There are few data regarding children
- Life-threatening hypercalcemia: hemodialysis in collaboration with nephrology department

Airway Compression

General

- One of the few oncological emergencies which needs immediate diagnosis and involvement of intensive care, anesthetic and oncology departments
- Differential diagnosis of malignancies: non-Hodgkin lymphoma, neuroblastoma, Hodgkin lymphoma, rarely germ cell tumors, Ewing sarcoma, rhabdomyosarcoma, thymoma and others

Diagnosis

- Symptoms: cough, hoarseness, stridor, dyspnea, orthopnea, chest pain, headache, syncope and others
- Laboratory analysis: blood gas analysis, complete blood count with differential count
- Sodium, potassium, calcium, magnesium, urea, creatinine, phosphorus, uric acid, lactate dehydrogenase (LDH)
- Radiology: chest X-ray: mediastinum, tracheal shift, pleural effusion
- CT scan: compression of trachea and bronchi; space-occupying process; location of compressing tumor (anterior or posterior mediastinum); infiltration of lungs
- Compression of superior caval vein

- Diagnostic algorithm in collaboration with oncologist (e.g. biopsy of lymph nodes, bone marrow aspiration, thoracocentesis, pleurocentesis)

Treatment

- Request an anesthesist and/or intensive care immediately
- Intravenous line
- Immediate initiation of specific treatment (e.g. cytotoxic agents, in the case of non-Hodgkin lymphoma or leukemia)
- Possibly dexamethasone after oncology consultation (initially 0.2–0.4 mg/kg, then 0.3 mg/kg per day in three or four doses per day)
- Consider radiotherapy

Spinal Cord Compression

General

- Differential diagnosis of malignancies: neuroblastoma, non-Hodgkin lymphoma, metastatic brain tumor, neuroectodermal tumors, metastases, Langerhans cell histiocytosis

Diagnosis

- Symptoms: local or radicular back pain, local tenderness to percussion, loss of motor strength of the upper and/or lower extremities (according to location of the compression), sensory loss, urinary retention
- Laboratory analysis: Complete blood count with differentiation of leukocytes
- Sodium, potassium, calcium, magnesium, urea, creatinine, phosphorus, uric acid, LDH
- Radiology: Chest X-ray and possibly abdominal X-ray: rule out space-occupying process, control of spinal integrity
- MRI: extra- and/or intraspinal tumor
- Possibly CT scan (multislice technology), interpretation of skeletal structures

Treatment

- Consult neurologist and oncologist
- Dexamethasone, initially 0.2–0.4 mg/kg, then 0.3 mg/kg per day in three or four doses per day. Consider immediate radiotherapy although rarely indicated

Superior Vena Cava Syndrome and Superior Mediastinal Syndrome

General

- Compression of superior caval vein. Rare in pediatrics. Oncological/hematological etiology: mediastinal tumors (non-Hodgkin lymphoma, neuroblastoma, Hodgkin lymphoma, sarcomas, germ cell tumors and others), thrombosis (often in association with central vein catheters), thrombophilia, drugs (e.g. asparaginase)

Diagnosis

- Symptoms: cough, coarseness, dyspnea, orthopnea, possibly anxiety, confusion, fatigue, headache, distorted vision, lethargy. Aggravated symptoms in supine position. Physical examination: Swelling, plethora of face, neck and upper extremities, wheezing and stridor, edema of conjunctiva. Veins on chest wall may be prominent. Possibly pleural effusion and/or pericardial effusion
- Radiology: chest X-ray, further diagnostic steps after consultation with oncology, anesthetic and intensive care departments
- Laboratory analysis: complete blood count with differential count
- Sodium, potassium, calcium, magnesium, urea, creatinine, phosphorus, uric acid, LDH

Treatment

- Possibly intensive care
- Treatment of the primary disease

Pleural and Pericardial Effusion

General

- Transudate (low concentration of proteins, specific gravity less than 1.015, few cells) or exudate (high concentration of protein, often more than 0.25 g/l, specific gravity more than 1.015, high cellularity)
- Small pleural and pericardial effusion often asymptomatic

Diagnosis

- Symptoms: variable, asymptomatic – respiratory insufficiency. Painful respiration and cough mainly if pleura is involved, paradoxical pulse
- Radiology: chest X-ray, ultrasound (pericardial effusion)
- Laboratory analysis: complete blood count with differential count. Thoracentesis or pericardiocentesis after consultation with oncologist (cellularity, cytology, microbiology, concentration of protein, specific weight, LDH)
- ECG

Treatment

- Possibly intensive care
- Treatment of primary disease

Cardiac Tamponade

General

- Left ventricle cannot maintain output because of external pressure or intrinsic tumor mass. Duration of pressure on left ventricle is important. Slow accumulation of fluids in pericardium makes compensation possible

Diagnosis

- Symptoms: cough, chest pain, dyspnea, hiccups, possible abdominal pain, cyanosis and paradoxical pulse. Auscultation: friction rubs, diastolic murmurs and arrhythmia may be present
- Radiology: chest X-ray, echocardiography
- ECG

Treatment

- According to cause of cardiac tamponade, e.g. ultrasonography-guided pericardiocentesis. Possibly hydration, oxygen therapy. Possibly surgical consultation (consult oncologist before punction, diagnostic work-up)

Hemolysis

General

- Not usually an emergency

Diagnosis

- Symptoms of anemia
- Laboratory analysis: complete blood count with reticulocyte count, red cell morphology, nucleated red cells (normoblasts) visible? Coombs test (direct antiglobulin test)
- Signs of hemolysis: LDH, bilirubin (direct and indirect), liver enzymes, haptoglobin
- In case of hypoplastic or aplastic anemia (low reticulocyte count, no signs of hemolysis): bone marrow aspiration and consider differential diagnosis of aplastic anemia (infectious diseases, e..g. parvovirus B19 and many others, drugs, bone marrow in-

filtration, myelodysplastic syndrome, inherited bone marrow failure syndromes, idiopathic aplastic anemia)

Treatment

- Treatment of primary disease, possibly packed red cell transfusion

Abdominal Emergencies: Abdominal Tumor

General

- Differential diagnosis of oncological etiology: nephroblastoma (often abdominal pain as the initial symptom in a child who is otherwise healthy), neuroblastoma (frequently accompanied by additional symptoms such as fever, fatigue, diarrhea and others), non-Hodgkin lymphoma (mainly Burkitt lymphoma with a fast-growing tumor with early signs of spontaneous tumor lysis and its complications (may present as intussusception), rarely sarcomas, germ cell tumors
- Abdominal emergency may occur as a complication in immune-compromised patients: esophagitis, cecitis, hemorrhagic pancreatitis, hepatomegaly, paralytic ileus caused by drugs, e.g. vinca alkaloids, opioid analgesics, acute abdomen

Diagnosis

- History and physical examination are basis of a correct diagnosis. Early consultation with oncology department. Indication for surgery after oncology consultation
- Symptoms: abdominal pain, constipation, ascites, complications: hemorrhage, compression of organs, vessels and nerves
- Laboratory analysis: complete blood count with differential count
- Sodium, potassium, calcium, magnesium, urea, creatinine, phosphorus, uric acid, LDH, liver function tests
- Radiology: ultrasound, X-ray of abdomen with left lateral films. Further radiological examination after consultation with radiology and oncology consultants (clinical condition of patient, age, working hypothesis of etiology): MRI, CT scan

Treatment

- According to primary cause

Hemorrhagic Cystitis, Oliguria, Anuria

General

- Causes of hemorrhagic cystitis: viral infections (e.g. adenoviruses, particularly in the immune-compromised patient), drugs (e.g. ifosfamide and cyclophosphamide).

Early phase of cystitis: edema of mucous membranes, inflammation, ulceration. Late complications: fibrosis of bladder, vesicoureteric reflux, hydronephrosis
- Causes of dysuria: disorders of spinal cord, pelvic space-occupying processes, drugs (opioids, phenothiazines, vinca alkaloids)

Diagnosis

- Symptoms: dysuria, hematuria, clots in urine
- Radiology: ultrasound
- Laboratory analysis: complete blood count with differential count, hemostasis testing (prothrombin time, PT, activated partial thromboplastin time, aPTT, thrombin time, TT), fibrinogen, D-dimers, urinalysis and culture (bacteria, fungi, viruses). Possibly cystoscopy (ice-water irrigation, electrocoagulation)

Treatment

- Consider urethral catheter. Hydration, possibly packed red cell and platelet transfusion as well as support of hemostasis (fresh-frozen plasma, factor VIIa, antifibrinolysis and pain control)

Acute Alteration of Consciousness

General

- Neurological emergencies in oncology may be based on direct or indirect effects of cerebral space-occupying processes and their management. Causes of acute alteration of consciousness: intracranial hemorrhage, brain infarction, infectious diseases (encephalitis, brain abscess), metastases, leukoencephalopathy, increased intracranial pressure

Diagnosis

- Symptoms: multidisciplinary collaboration needed. Time of occurrence of symptoms and their duration affect differential diagnosis: fatigue, somnolence, coma, seizures
- Vital signs, emergency history and emergency physical examination including Glasgow coma scale
- Signs of cerebral herniation (breathing pattern, pupillary size and reactivity, extraocular movements, response of patient to verbal or physical stimuli) and of increased intracranial pressure (often subacute and nonspecific signs, fatigue, personality changes, intermittent headache, nausea, vomiting)
- If signs of increased intracranial pressures are present consider CT scan or MRI before lumbar puncture
- Laboratory analysis: blood gas analysis, complete blood count with differential count. Parameters of hemostasis (PT, aPTT, TT, fibrinogen), D-dimers, electrolytes, glucose, kidney and liver function tests, C-reactive protein (CRP)

- Radiology: CT scan or MRI
- EEG

Treatment

- Life-saving measures. Stabilization of blood pressure, oxygenation, specific therapy in collaboration with oncology and intensive care experts

Seizures

General

- Focal seizures, duration longer than 15 min; recurrent seizures with or without fever differentiate complex from simple seizures

Diagnosis

- Symptoms: focal seizures, generalized seizures according to primary disorder
- Laboratory analysis: complete blood count with differential count, electrolytes, glucose, kidney and liver function tests, CRP
- Radiology: CT scan or MRI of head
- EEG

Treatment

- In collaboration with neurologist: anticonvulsive therapy: diazepam, chlorazepam, phenobarbital, phenytoin and others
- Specific therapy of primary disorder after consultation with oncology, neurosurgery and other departments

Oncological Nursing Care

Franziska Oeschger-Schürch, Christine Verdan

The Role of the Nurse in Pediatric Oncology

Direct Care

- Taking care of children with oncological illnesses presents a major challenge to nurses
- The patient enters the hospital not only for chemotherapy but also for the treatment of complications and side effects such as infections, stomatitis, transfusions, blood count checks
- Nonmechanical intensive care has psychosocial consequences such as pressure on the family, absence from school, limited social contacts and short or long hospitalizations
- Involvement of the entire family from the outset is crucial and represents a focal point in care of the patient

Eight features of holistic care for oncological patients (modified from I. Bachmann-Mettler):

1. Ongoing information and instruction (initial information is given by the physician; the nurse, as the key carer, checks the understanding of conveyed information and refers observations of the patient to the doctor)
2. Establishment of a durable relationship with the patient and their entire family (nursing measures become effective through the quality of the nurse's relationship with the patient, and the patient needs to be convinced by professional nursing skills)
3. Knowledge of the treatment plan (induction, consolidation and maintenance phase; simultaneously the nurse has to be informed about the course of illness as well as the aim of the current treatment with chemotherapy)
4. Knowledge about mode of action (alkylating agents, antimetabolites, mitotic inhibitors, chemotherapeutic agents, antibiotics, etc.)
5. Safe handling of chemotherapeutic agents (we need to be aware of the fact that these drugs, when wrongly administered or given in an incorrect dose, can lead to life-threatening complications)
6. Knowledge of side effects
7. Formulation of goal and planning as part of the nursing process (the first part of nursing care strategy is collection of information about the needs of the patient; the concept of nursing care is designed for everyday use, particularly in oncological nursing care planning; determination of goals and the knowledge about the effects of specific measures for the prevention of side effects is of great importance)
8. Close, respectful cooperation between nursing staff physicians and other personnel

Parents of children with cancer contribute significantly to comprehensive care. Holistic care demands involvement of the sick child and their entire family which includes showing empathy toward them. Family members who are listened to and supported become a valuable resource for the patient as well as the nurse.

Children have inquisitive personalities, they are able to assess themselves well and only do or permit what they can tolerate. The nursing care regime has to take into consideration the ability of the child and the parents to cope with the oncological illness:

- Take time for the patient and their next of kin, convey commitment and care, answer questions comprehensively, respond to wishes and concerns
- Develop an empathetic relationship toward patient and family based on mutual trust. Without trust and understanding good communication cannot take place
- Be informed about the disease and understand its consequences for everyone involved
- Information needs to be adequate in quantity and quality regarding requirements of the child and their entire family, their age, physical and psychological state, their mental resilience and their familial situation
- Accept that parents are the prime persons of reference, as far as a social network is existent; therefore involve the parents in the nursing care and collaborate with them
- Remember to pay a compliment to the parents from time to time
- Take note of needs and wishes as part of the nursing process (collecting information) accordingly formulating the respective goal as well as planning and revising measures taken
- Where there is a poor prognosis accompany the patient giving them support, guidance or advice, since hope can give rise to strength, courage and regeneration
- Information needs to be shared (a nurse should also be present during family-patient conversations with the physician)

Nursing Care Research

- Nursing care activity is scientifically supported by means of nursing care research. Professional handling is encouraged through systematic scientific methods
- Cost effectiveness is shown
- Research in the field of oncology nursing leads to improvements in quality and facilitates working with nursing care standards (e.g. *Nursing Care Standards in Oncology* by Suzan Tucker, 1998)

Side Effects of Treatment

Nausea and Vomiting/Emesis

- Nausea and vomiting are two of the burdensome side effects of chemotherapy; they vary greatly in their individual extent and depend on the type of chemotherapeutic drugs
- Vomiting and nausea can occur separately or in combination
- There are potent drugs capable of preventing, alleviating or almost fully suppressing these side effects

Cause

Nausea and emesis are usually caused by irritation of certain centers of the brain. Chemotherapeutic agents activate the vomiting center of the brain. In addition serotonin is released from intestinal cells which further activates the vomiting center.

Forms of nausea and vomiting

- Acute vomiting: within the first 24 h of chemotherapy
- Delayed vomiting: symptoms occur more than 24 h after cessation of chemotherapy, potentially over the course of several days
- Anticipatory vomiting: occurs before treatment or at the very thought of it, e.g. the sight of the hospital, an i.v. bottle, the color or smell of the hospital, a nurse

Symptoms

- Nausea is a subjective sensation of sickness in the throat and/or stomach with or without vomiting. Nausea may be accompanied by sweating, drooling, pallor and tachycardia
- Emesis is a forceful emission of stomach contents and/or bile fluid out of the mouth. So-called dry vomiting describes a vomiting act without ejection of stomach contents

Prophylactic care

- Immediately before and after treatment the patient ought to eat with restraint, have frequent, small meals and avoid sweets and fat. Better tolerated is food such as mashed potato, apple puree, ice cream, crispbread, toast, curd cheese or bananas
- Plenty of fluids (but no fizzy drinks; apple juice, tea, lemonade and chilled drinks are better tolerated)
- The patient should avoid strong smells (this is difficult in hospital)
- Distract the patient through music, video games, conversations, board games, magazines or TV
- Relaxation, e.g. massage
- Occasionally the patient's mouth should be rinsed with diluted lemon water or their teeth brushed
- Sugar-free sweets alleviate bad tastes in the mouth

- Go for walks with the patient in the fresh air
- Personal motivation and a positive attitude of the patient toward the treatment have a major impact on the course of events

Treatment

- Administer drugs to prevent nausea and emesis according to the doctor's prescription
- Prophylaxis of nausea and emesis: do not give medication once the patient is vomiting
- In case of anticipatory vomiting: aid with anxiolytic drugs or general preventative measures against anxiety
- Create an antiemetic plan adjusting and amending the plan to the individual response and needs of the patient
- Enquire about side effects of antiemetic drugs keeping protocol
- Where treatment lasts several days daily assessment
- The patient should try their best to eat and tolerate food during chemotherapy
- Advise the patient to sleep through the times when there is high risk of nausea and vomiting which varies depending on age
- Should antiemetic drug administration at home be necessary: take antiemetics 2 h before commencement of therapy
- Side effects of antiemetic drugs: headache, fatigue, constipation or diarrhea

Hair Loss/Alopecia

Depending on the treatment scheme, general condition and hair condition before treatment hair may become sparse (partial loss of hair) or fall out all together. The hair of the scalp is particularly affected; however, eyebrows, eyelashes, chest hair, axillary hair, pubic hair and hair on the legs and arms may disappear temporarily

Causes

- Chemotherapeutic drugs also affect normal hair follicles that have high cell-division activity
- Chemotherapeutic drugs can cause a complete atrophy of the hair follicle leading to hair loss. What happens more frequently, caused by partial atrophy of the hair follicle, is that the hair shaft is rendered weak and constricted
- The severity of alopecia is primarily dependent on the type of chemotherapy
- External influences such as washing hair and combing easily lead to fracture of the already weakened hair

The following factors can influence the extent of hair loss:

- Application mode, dose and general treatment scheme
- Age of patient
- General condition of patient
- Condition of hair before beginning of therapy
- Severe concurrent illness

Symptoms

- Loss of hair shows great individual variability and onset is normally 2–4 weeks after start of treatment. Several days before commencement of hair loss the scalp may be specially sensitive or itchy
- Renewed hair growth in individual cases may start during low-dose continuation therapy; although it usually starts 2–4 weeks after completion of treatment
- Newly grown hair may differ from the original type of hair in color and texture. It is commonly softer and more dense than before
- With chemotherapy loss of hair is always only temporary. Hair grows again after the end of therapy
- Chemotherapeutic agents that are closely associated with alopecia: doxorubicin, daunorubicin, cyclophosphamide, ifosfamide, etoposide
- Where the skull has been irradiated, there is partial to total hair loss depending on radiation dose and individual factors. Hair does not always grow back depending on the radiation dose

Treatment

- The patient needs to be informed prior to commencement of therapy about hair loss
- The absence of hair and especially the bare skin of the scalp can psychologically be traumatic for many children and adolescents
- Promise acceptable hair substitution
- Assure the patient that hair loss as a result of chemotherapy is not permanent

Nursing tips concerning hair loss

- Suggest an easy-to-maintain hairstyle prior to treatment
- Wash hair with a mild shampoo (e.g. baby shampoo) and dry carefully with a towel
- Comb hair carefully
- Should hair substitution be required a hairdresser or wig specialist ought to be contacted early on, so that they get to see the original hair growth
- Apart from the wearing of wigs there are other possibilities such as stylish scarves, hats, caps
- The head should be covered outdoors so as not to burn the skin of the scalp in summer and to minimize heat loss in winter
- A cloth roller removes shed hair from clothes

Coverage of costs for hair substitution

Hair substitution is a medically prescribed hair prosthesis which may be partially covered by health insurance

Stomatitis and Mucositis

Sometimes chemotherapy and radiotherapy heavily reduce regeneration of mucosa which can lead to ulceration or inflammation of mucous membranes in mouth, throat, and intestines resulting in a dry and sore mucous membrane of the mouth. This can serve as an entry path for pathogens such as bacteria, viruses or fungi. Before and during treatment daily checks on oral hygiene need to be performed.

Cause

The natural balance of flora and mucous membranes is disturbed by direct damage to cells of mucous membranes through chemotherapy and/or radiation as well as indirect damage due to neutropenia

Risk factors

Dental caries and peridontal disease, inadequate oral hygiene, cigarette and alcohol consumption, disruption of daily activities, e.g. eating, chewing, swallowing and talking; presence of oral cancers; and immunodeficiency are all risk factors

Stages of stomatitis

Stage I	Redness of oral mucous membrane
Stage II	Isolated small ulcerations or white spots no substantial problems with eating and drinking
Stage III	Confluence of ulcerations or white spots, covering more than 25% of oral mucous membrane, patient only able to drink
Stage IV	Bleeding ulcerations covering more than 50% of oral mucous membrane; patient no longer able to eat or drink

WHO grading system

- 0 = no problems
- 1 = painful mouth, no ulcerations
- 2 = painful mouth with ulcerations, normal eating possible
- 3 = only liquid/mashed food possible
- 4 = eating and drinking impossible

Symptoms

- Disruption of taste sensation
- Redness
- Wound or sores in mouth or throat
- Burning tongue
- Pain
- Impeded flow of saliva (dry mouth)
- Trouble with swallowing, even talking
- Swelling
- White, spreading coating (thrush) or small red blisters and ulcerations

Prophylactic care

- Performing good and consistent oral hygiene during the whole course of chemotherapy (in hospital as well as at home)
- Consistent oral and dental care is recorded, documented and performed differently according to guidelines of clinic
- Aims of oral hygiene:
  - No caries, no ulcerations, no fungal infection, early detection of disturbances
  - Keeping mucous membranes moist and clean in order that mucous membrane barrier remains intact and free of infection; this helps prevent the development of an acid environment in the mouth and hence a suitable medium for bacterial growth
  - The frequency, thoroughness, regularity and basics of prophylaxis are to be adhered to
- A dry mouth can be prevented by:
  - Ample drinking (not too many sweet drinks)
  - Chewing gum (sugarless)
  - Keeping the nasal passages open using cream or drops when there is a blocked nose (mainly at night)
  - Sucking on ice cubes

General tips on nursing care

- Nutrition: protein-rich milk products protect mucous membranes
- Abstain as far as possible from very hot or very cold food
- Avoid spicy hot, sour (e.g. citrus fruit), crunchy or roughly cut food
- Eat soft food
- Avoid too much salt (e.g. preserved meat)
- Not only do mucous membranes of the mouth dry out but also the lips. It is particularly important that they not become brittle and cracked. Hence a normal lip seal or greasy cream may be used as long as mucous membrane is intact

Treatment

Treatment of stomatitis is performed according to clinical guidelines

Myelosuppression

- Treatment using chemotherapy and/or radiotherapy reduces the number of white blood cells, platelets and red blood cells. Therefore a blood count is performed before and at different time points following each treatment and, if necessary, the dose of chemotherapeutic agents is modified
- As a result of cancer and/or its treatment deficiencies in the production of blood cells may occur which are summarized by "myelosuppression"
- Leukopenia (increases the risk of infection), thrombocytopenia (increases the risk of bleeding) and anemia (leads to fatigue and pallor)
- These side effects present a major challenge to the nurse. By early detection of infections and bleeding life-threatening complications may be avoided

Causes

- Hematological malignancies or solid tumors that replace normal bone marrow
- Chemo- or radiotherapy

Leukopenia

- Leukopenia predisposes to infection
- Risk of infection increases at a leukocyte count less than 1,000/µl and becomes high at less than 500/µl
- Source of infection: intestines, skin
- Nosocomial sources of infection: patient (intestinal flora), staff, visitors, blood products, infusions, air
- Agents of infection: bacteria, viruses, fungi
- In order to prevent infections special precautionary measures need to be taken regarding hygiene, behavior, occupation and nutrition. Guidelines vary depending on the clinic

Prophylactic care

- Goal: protection of patients from infection by means of creation and maintenance of a clean environment and by good personal hygiene. Maintenance of best possible quality of life
- Reduction of fresh infections (strict disinfection of hands)
- Limitation of invasive procedures (e.g. few injections, avoidance of use of urinary catheter)
- Enhancement of immune defenses (e.g. immunoglobulins)
- Single bedroom, reverse isolation, positive-pressure rooms, HEPA-filtered air in special circumstances

Risk factors

- Fever higher than 38.5°C (101°F) or persistent low-level fever, signs of cold (cough, sore throat, freezing or sweating, fatigue, weakness)
- Frequent or painful urination
- Injuries, wounds that will not heal or that turn red or swell
- Contact with other sick children

Treatment

- Treatment of infection:
  - Antibiotic therapy needs to be initiated promptly at onset of first clinically suspicious signs and before culture and resistance results are available
  - Antimycotics when appropriate
  - Antiviral agents when appropriate
- Growth factors of myelopoiesis (especially after high-dose treatments and bone marrow transplantation), e.g. granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage CSF (GM-CSF)
- Immunoglobulin infusion

  Nursing care including codes of conduct for nursing staff, patients, visitors and the care itself are determined by clinic-specific guidelines

Thrombocytopenia

Symptoms

- Bleedings occur as a consequence of too few platelets or decreased ability to clot blood normally
- The risk of spontaneous bleeding rises with decreasing number of platelets, particularly less than 20,000/ cm^3
- Bleedings occur mainly in nasal and oral mucous membranes, intestines, skin and central nervous system
- Clinical signs: appearance of petechiae (small, red, punctual skin or mucous membrane bleedings which do not blanch with pressure), hematoma (purple hemorrhages under the skin)
- Bleeding of mucous membranes, nose bleeds
- Bloody stools or urine

Prophylactic care

- Avoidance of activities with potential of serious injury for the child
- No intramuscular or subcutaneous injections
- No sports activities with potential for injury
- No drugs with antiplatelet properties, e.g. Aspirin
- Caution when cutting and filing nails
- Avoidance of tight clothes
- Clean nose carefully; if necessary humidify air (but take care: higher risk of fungal infection), nose cream
- No enemas, suppositories or rectal temperature measurements
- No intake of specially hard (e.g. bread crust), hot or spicy food
- In case of constipation use of laxatives
- Keep lips soft
- Use of soft tooth brush; no dental floss

Treatment

- Transfusion of platelets according to medical instructions
- Single-donor platelet transfusion for patients who are sensitized to various HLA antigens
- Platelet concentrates contain few leukocytes which are mostly removed through a leukocyte filter
- Effectiveness of platelet transfusions: determination of platelet count after 1 h and 24 h
- Should platelet count fall rapidly after reaching a high or expected level, this indicates an increased consumption of platelets such as in the case of sepsis or disseminated intravascular coagulation. The initial rise after transfusion may be due to host anti-platelet antibodies
- Transfusion reactions are: chilling, fever, agitation, anxiety, shortness of breath, headache, joint pain, aches, nausea, vomiting, urticaria, redness of skin, rising temperature, fall in blood pressure, signs of shock, oliguria
- Further measures: in case of large hematoma cold packs may be of help, pressure bandage for bleeding wounds; for nose bleeds sit in an upright position, cold packs on the neck or on the bridge of the nose and press wings (alae nasi) of nose against nasal septum

Anemia

Symptoms

- Dependent on extent of anemia and general condition of patient
- General symptoms: performance decline, fatigue, dyspnea, tachycardia, palpitations, dizziness, headache, rapid pulse, difficulty concentrating
- Circulatory overload, infection, symptoms of transfusion reaction: chilling, fever, agitation, anxiety, nausea, vomiting, headache, possibly signs of shock

Prophylactic Care

- Adapting physical activities to the situation
- In the case of dizziness: getting up and walking about only with accompaniment
- Adapting visiting times of relatives to allow patient enough rest and sleep

Treatment

- Depending on symptoms and condition of child a transfusion of red blood cells needs to be performed (generally at a hemoglobin level less than 7 g/dl)
- Indication for transfusion of red blood cells by the physician
- Transfusion reaction comprises hemolytic transfusion reaction, reactions against HLA-antigens, leukocyte or platelet antigens
- Filtering of erythrocyte concentrates: transfusion bags are equipped with special transfusion devices to remove leukocytes (special filters can reduce the leukocyte content of transfused blood by more than 99%)
- Irradiation of blood supplies: for immunosuppressed patients blood donations should be irradiated before administration to avoid graft-versus-host reactions. Donor lymphocytes are thereby prevented from attacking and damaging the cells of the recipient

Loss of Appetite

- Loss of appetite is a common and transient symptom. It may be associated with the primary disease or with the side effects (such as stomatitis, nausea and vomiting, changes in taste)
- During treatment in particular sufficient and balanced nutrition is of special importance: balanced nutrition, high in protein, vitamins and calories protects against weight loss and imparts energy. Correct nutrition strengthens the organism and alleviates side effects of the treatment
- Start nutritional therapy before appearance of first signs of undernourishment

Causes

- Psychological (anxiety, nervousness)
- Drugs such as some chemotherapeutic agents, analgesics
- Stomatitis
- Pain
- Fever
- Nausea
- Constipation
- Malignancy

Prophylactic care

- Despite loss of appetite encouragement to eat

Care tips

- Provide food that the patient likes
- No big portions, but small, more frequent meals
- Some exercise before meals, e.g. going for a walk in fresh air
- Avoid food that is filling or causes flatulence (e.g. cabbage, broccoli, fresh mushrooms, salads, raw fruit, e.g. prunes, plums)
- Complementing and enriching meals: a number of specialized products are available through nutritionists
- Fruit milk shake (high in protein and energy)
- Energy drinks and complementary nutrition can be specifically discussed with the nutritionist
- Eating should not be an imposition
- Drinking between rather than during meals as fluids fill the stomach and easily lead to early satiety

- No sweet drinks; drink at least 30 min before eating
- Where food intake is painful consult the doctor
- Appearance of food has a huge effect on appetite
- Loss of appetite under chemotherapy usually disappears after completion of therapy which is something the patient must know

Eating habits are very individual and quality of nutrition is therefore variable. The nutritionist or nurse should be consulted for advice

Digestive Disorders (Constipation and Diarrhea)

Digestive disorders such as constipation and diarrhea curtail well-being. An optimal treatment is possible only when the underlying cause is identified

Constipation

Constipation is the absence of bowel movements over several days or when action of the bowels is perceived as abnormal (e.g. feeling of illness, loss of appetite, abdominal pain, painful straining to defecate, hard and dry stools)

Causes

- Drugs: e.g. chemotherapeutic agents: vincristine; iron preparations, opiates, spasmolytic agents, antidepressants
- Metabolic disorders such as deficient activity of the thyroid gland (hypothyroidism)
- Pain
- Prolonged bed-ridden state, lack of activity
- Dehydration, roughage-deficient nutrition
- Psychological influences such as depression, anxiety
- Neurological disorders such as spinal and cranial nerve lesions

Prophylactic care

- Fiber-rich nutrition: wholemeal products, cooked vegetables, raw fruit (e.g. berries) and raw vegetables (e.g. carrot or cucumber salad); if patient's condition allows cooked fiber-rich vegetables (e.g. leeks and green beans, dried fruit)
- Avoidance of foodstuffs that can cause constipation: carrot soup, white rice, white bread (white flour products), black tea, chocolate, hard cheese, boiled eggs
- The patient needs to drink plentifully
- As much physical activity as possible
- Psychological measures: no time pressure, paying attention to ensuring privacy
- When signs of constipation are present discuss with physician

Treatment

Constipation can be treated in many ways. Usually laxatives with different modes of action are used:

- Osmotic laxatives: not resorbable, bind water. Saline laxatives are used frequently.
- Enemas: act locally in the gut. If thrombocytopenia and/or leukopenia are present, use only with doctor's consent
- Lubricants: facilitation of bowel movement by way of lubrication. Paraffin and glycerin are commonly used
- Expanding agent: substances containing cellulose which, at intake of water, swell and thereby expand the volume of intestinal content

Diarrhea

- Increased frequency of bowel movements: three or more per day, stools being unformed, mushy or liquid
- Concomitant phenomena can include pain with bowel movements, abdominal cramps
- General health is usually compromised, often also electrolyte shifts occur and, as a consequence, dehydration may ensue

Causes

- Medication: chemotherapeutic agents (impairment of mucous membranes with methotrexate, doxorubicin, daunorubicin), antibiotics (alteration of natural intestinal flora), laxatives
- Radiation of abdomen and pelvis
- Inflammatory bowel diseases
- Tube feeding
- Dietary errors
- Food poisoning

Treatment

Following establishment of cause according to doctor's orders:

- Medication
- For patients not able to take in sufficient fluids orally rehydration via nasogastric tube or i.v.
- Nutrition:
  - White bread, potatoes, pasta, peeled rice, semolina, bananas (rich in potassium), grated apples, cottage cheese, boiled eggs, oatmeal, porridge, maize (corn), dry pastry, black tea
  - Eat easily digestible, salty meals and drink plenty
  - Foodstuffs to be avoided with diarrhea: wholemeal bread and cereals, nuts, chips, fried, greasy food, raw fruit and vegetables, fruit juice, dried fruit, broccoli, onions, cabbage, hot spices
  - Several small meals per day
- Psychological factors:
  - Diarrhea for the patient is often highly unpleasant. Sensitive action with respect for privacy and sense of shame
- Anal hygiene:
  - Due to diarrhea the skin is very tender. Therefore attention should be paid to soft, possibly moistened toilet paper

- Use of cream and baths with chamomile as well as local anesthetic ointments may be helpful
- Where there is pain at around the anus (irritated skin): after every bowel movement clean anus with warm water followed by careful dabbing; warm baths also ease the discomfort. Use soft toilet paper; possibly ointment around anus. Check for ulcerations or blood in stool beforehand

Neuropathy

Some chemotherapeutic agents may cause disruption of nerve and muscle function (especially vincristine, vinblastine and cisplatin).

Symptoms

- Tingling (especially in fingers), pins and needles, numbness, muscular pain, muscle weakness in hands and feet (difficulty with walking on toes and heels; foot drop), impairment of fine motor control (particularly of hands) and sensation in hands and feet, unsteady gait, muscle cramps
- Changes are usually reversible

Prophylactic care

- None

Treatment

- Dose reduction or interruption of treatment, use of alternative therapeutics
- Promotion of sensation and fine motor activity by means of ergotherapy
- Use of walking aids and devices

Fatigue

Fatigue can manifest itself in many ways, e.g. as weakness, exhaustion, drowsiness or weariness. It is a transient side effect of chemo- or radiotherapy. Fatigue may also be a direct consequence of the disease as such. After cessation of treatment strength gradually returns

When, how long and how badly side effects occur will differ between individuals and depends on the type of treatment

Causes

- Pressure from tumor and metastases
- Unbalanced production of cytokines, pathological collection of metabolites, bone marrow infiltration (anemia)
- Chemotherapy as such via hypoplasia of normal tissue
- Infection, tumor-associated fever
- Inadequate nutrition: deficient in protein and calories or undernourishment

- Lack of sleep
- Physical exhaustion
- Pain
- Other drugs, e.g. analgesics, antidepressants, neuroleptics, sedatives, cough medicine
- Electrolyte deficiency, hypokalemia
- Radiotherapy
- Fear, nervousness, depression, boredom during hospitalization
- Uncertainty, uncertain prognosis, psychological stress caused by workup of disease
- Financial and family problems

Symptoms

- Tiredness, dizziness, headache, weakness, decrease in muscle strength
- Every person experiences these symptoms and their sequelae differently. Fatigue for instance is a subjective sensation and is described by those affected as an insurmountable, persistent feeling of exhaustion
- The consequences of fatigue are multidimensional and impair the quality of life of patients

Prophylactic care

- The child needs to ration activity, not giving up on usual activities but adapting them to preserve energy (e.g. playgroup, kindergarten or school attendance), setting priorities, reducing stress
- Generating strength by sufficient sleep, vitamin and iron supplementation, relaxation exercises, coping with stress
- Drinking sufficient amounts in order to stay well hydrated
- Distraction through visiting friends, playing games, but not strenuous hobbies
- Exercise in fresh air
- Attempting to keep to normal day-and-night rhythm, finding a balance between activity and rest, planning periods of respite, possibly a midday nap, shifting activities to times of less tiredness
- No excessive demands, but neither being negligent

Treatment

- The treatment of fatigue is always guided by its causes. For this reason a detailed history is most important. Discussion with psycho-oncologists
- Appropriate packed red blood cell transfusions

Significance of fatigue nursing care

Nurses cannot as with nausea and vomiting resort to a wealth of established methods of action or reserve medication. Detailed knowledge of the relationship between illness, treatment and fatigue is most important.

Pain

- Pain in children occurs often at establishment of diagnosis or after painful interventions
- To enable pain relief through medication an appropriate assessment is critical

Causes
- Due to malignancy
- Caused by treatment, e.g. with tests such as bone marrow aspiration or biopsy and intrathecal drug delivery; headache as side effect of drugs
- Following surgical procedures
- Enhanced sensation of pain through stress and anxiety

Symptoms
- The way in which a person perceives pain and expresses it is individual
- Pain can be: pulsating, burning, stinging, nagging, excruciating, mild, strong, radiating, spasmodic, etc.
- Pain assessment is achieved through conversation, observation, evaluation, a good relationship between patient and nurse
- Pain can be scaled from 1 to 10: 1 equaling no pain and 10 the strongest imaginable pain
- Assessment of pain: localization, type, intensity, concomitant factors, psychosocial factors, sequelae, mental processing, behavior of patient, risk groups

Prophylactic care
- In cases of chronic pain it is of particular importance that analgesics are applied regularly, not only once pain has set in; and follow staged priority of medication according to the WHO analgesic ladder: nonopioid analgesics, weak opioids, strong opioids according to the following scaled plan:
  - By mouth
  - By the clock: at regular intervals
  - By the ladder: following the WHO analgesic ladder with targeted use of adjuvants
- Horizontal position after intrathecal drug delivery in order to prevent development of headache

Treatment
- Medication: pain-relieving drugs according to doctor's prescription
- Alternatives: there are a number of psychological and physical methods for pain relief: distraction, e.g. listening to music, drawing, reading; for aching, e.g. warm bath, packing, heated cushion, rubbing in cream, massage, minimal mobilization

Central Catheter Care

- When long-term chemotherapy is needed the placement of a central venous catheter (CVC) such as the Port-a-Cath is useful and sometimes essential for treatment
- CVCs comprise all venous catheters introduced into the vena cava for the purpose of administering infusions and/or drugs. A distinction is to be made between CVCs introduced into the superior vena cava by puncture of a major vein such as the internal jugular or subclavian veins, completely implanted CVCs (so-called port systems), catheters leading to the superior vena cava via a tunnel under the skin (e.g. Broviac catheter), and CVCs introduced through a peripheral vein (peripherally introduced central catheter, PICC)

Port-a-Cath (PAC, Entirely Implanted Catheter Systems)

Reasons to use a Port-a-Cath

- Hardly accessible peripheral veins
- Use of chemotherapeutic agents which irritate blood vessels
- Frequent blood sampling
- Repeated injections and infusions of chemotherapeutic agents, antiemetics, antibiotics, possibly hypercaloric nutrition, transfusions, etc.
- During infusion time the child has use of both hands
- When PAC is not in use, there are no restrictions on activities of the child

Complications

- If difficulty in drawing blood movement exercises, change of position, flushing with saline solution and/or heparin solution as well as increased flow of i.v. solve the problem
- Blockage of PAC rarely occurs, but if it does occur, with urokinase or TPA the system can be rendered patent again
- Risk of infection is high(infection of reservoir at tip of catheter)
- The needle can dislocate out of the grommet causing the drug or infusion to flow not into the vein, but into the tissue. Toddlers should preferably receive chemotherapy via a port system in a resting position
- Defects of PAC membrane
- Changed position of PAC
- Discontinuation of tube system (detect leakage with contrast agent)

Considerations for Domestic PAC Management

- Apply anesthetic agent over skin covering PAC approx. 1 h before puncture
- In case of redness, swelling or blue marks appearing at puncture site consult the physician

- When PAC is accessed but not used (with inserted needle and tube) sports activities should not be allowed

Managing PAC

- Duration of needle use, frequency of change of dressing, method used to change dressing, procedure for puncture of PAC, removal of needle, treatment of PAC infection, blood sampling and administration of drugs differ according to guidelines of local clinic
- PAC is to be used only by qualified, experienced nurses and physicians. A strictly aseptic procedure is absolutely essential. PAC must always be flushed with a heparin solution after use in order to prevent the formation of blood clots and hence an obstruction of the catheter

Broviac and Hickman Catheters

- These catheters are usable over the course of several months and are therefore especially suitable for long-term and complex forms of treatment (e.g. stem cell transplantation)
- The catheters have a relatively large lumen. They share the advantage of making possible the numerous necessary blood samplings without having to puncture a peripheral vein
- Both catheters require regular sterile dressings at their point of entry into the skin
- Indicators for catheter infection can be: redness, swelling, pain around area of entry and fever; positive blood cultures
- Advantages: no punctures, two or three separate lumens
- Disadvantages: infections, obstruction, thrombosis, material defects
- Management as with PAC

Chemotherapy

General

- Chemotherapeutic agents are either natural products or chemically synthesized substances that affect tumor cell growth and survival
- Chemotherapy also influences healthy cells, especially those with rapid proliferation such as:
  - Cells of hair follicles (hence hair loss in chemotherapy)
  - Mucous membrane cells in mouth, throat and intestines
  - Blood-producing cells of bone marrow (depletion of leukocytes, platelets and red blood cells) which can lead to unwanted effects
- The impact is dependent on the individual drug, dosage, mode of administration and duration of treatment
- The side effects of chemotherapy are usually reversible

Administration

- Chemotherapeutic agents are prepared under specific conditions of the workplace on the ward or preferably in the pharmacy
- For information on various commercial products, solutions, administration, storage and stability, side effects, information on medication and specialized information check reference literature
- According to the physician's prescription of chemotherapy the preparation is controlled by two qualified nurses concerning type of medication, accurate dilution solution, correct calculation, exact volume, identified patient, expiry date, shelf life, and calculated infusion speed
- Ahead of every injection or infusion of chemotherapeutic agent the correct placement of the cannula must be confirmed by infusing physiological saline solution and aspiration of blood
- Injections of chemotherapy drugs are usually administered slowly. In cases of prolonged infusions (30 min to 24 h) chemotherapeutic agents are regularly monitored. Additional measures such as circulation checks and urine sampling are performed according to the doctor's instructions

Protective Measures when Handling Chemotherapeutic agents

- Chemotherapeutic agents can irritate skin, eyes, mucous membranes and other tissues
- Nursing staff handling chemotherapeutic agents must know the professional guidelines
- Numerous studies and research projects document precautionary measures for the protection of medical staff
- The aim is to reduce to a minimum absorption by way of direct skin contact and inhalation of drugs using standardized procedures
- Each clinic has its own internal guidelines on personal protective measures in preparation and administration of chemotherapeutic agents (e.g. gloves), disposal of excretions (stools, urine, and vomit), laundry, residues of chemotherapeutic agents and procedures in cases of contamination
- Pregnant and nursing women must reduce or avoid direct contact with chemotherapeutic agents

Extravasation

- The leakage of certain chemotherapeutic agents outside of the vein into surrounding tissue is serious and occurs in 0.5–6% of all patients receiving chemotherapy
- After intravenous administration of certain drugs such as vincristine and anthracyclines various local problems may occur:
  - Local hypersensitivity. Symptoms: redness, urticaria, itchiness (without extravasation)
  - Local irritation; chemical phlebitis. Symptoms: burning pain at injection site, redness and swelling, hardening of tissue and/or vein (without extravasation)
- In cases of extravasation measures are taken and documented according to clinic-specific guidelines

Risk of tissue damage in the case of extravasation of various chemotherapeutic agents

Chemotherapeutic agent	High risk	Dubious/ slight risk	No risk
Asparaginase			+
Bleomycin			+
Carboplatin			+
Cisplatin		+	
Cyclophosphamide			+
Cytarabine			+
Dacarbazine (DTIC)	+		
Dactinomycin	+		
Daunorubicin	+		
Doxorubicin	+		
Epirubicin	+		
Etoposide (VP 16)		+	
5-Fluorouracil		+	
Idarubicin	+		
Ifosfamide			+
Melphalan		+	
Methotrexate			+
Mithramycin	+		
Mitomycin C	+		
Mitoxantrone		+	
Thiotepa			+
Vinblastine	+		
Vincristine	+		
Vindesine	+		
Vinorelbine	+		

Giving Information to the Child and Parents

Giving information is the basis for effective nursing care
Giving information must be:

- Need-orientated
- Appropriate to the ability of receptiveness
- Able to be understood
- Appropriate amount
- In language that is understandable
- In verbal and written form
- Repeated

Care at Home

Children and parents are confronted with side effects of chemotherapy at home without being under constant surveillance by the hospital. Therefore tips and advice for facilitating and supporting everyday life at home are very important. Completeness of information is necessary in order that parents, siblings and other relatives are prepared for the many possible side effects

- Side effects occur differently in each individual
- Not all known side effects will occur at once
- Most side effects subside again at end of treatment
- The team of doctors and nurses are available at any time for questions or problems; 24-h telephone service should always be available
- It is advisable to involve nonhospital home care services for toddlers, children and adolescents that can offer assistance. The aim is to facilitate qualified care at home including the social environment in liaison with the treating pediatric oncological team

Long-term Care

- Long-term care is managed by the interdisciplinary team (Fig. 19.1)
- Long-term care poses a major challenge to the nurses as there is no clear line between nurse, patient and family
- Involvement of the family in this long-term care is of great importance from the outset. Holistic support and care for the whole family is appropriate

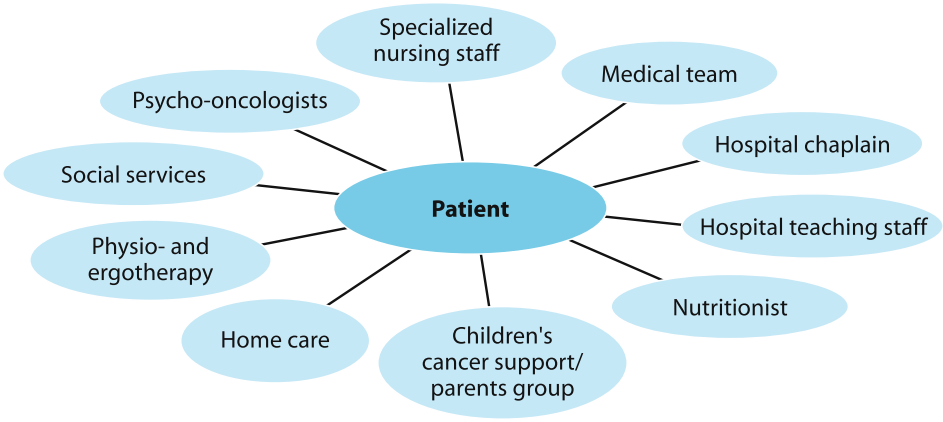

Fig. 19.1. Interdisciplinary team for long-term care of children with oncological diseases

Psychology and Psychosocial Issues in Children with Cancer

Alain Di Gallo

Significance for Contemporary Pediatric Oncology

- Thanks to progress in medical treatment in recent years pediatric cancer has been transformed from a primarily acute and fatal condition to (in more than 70% of cases) a curable disease with long-lasting physical, psychological and social implications
- Demanding and increasingly successful applied therapies such as hematopoietic stem-cell transplantation present additional challenges to sick children and their families
- Pediatric oncology covers a large number of different diseases with different symptoms, therapies and prognoses
- Surgery, chemotherapeutic drugs or radiation can lead to long-term and lasting physical, neuropsychological and psychosocial damage
- For certain diseases there remains a risk of recurrence even after years of remission and following treatment for neoplasia the risk of secondary tumors is increased throughout the rest of the patient's life
- In terms of quality of life and closest personal contacts a young child's requirements are different from those of a school-aged child or adolescent. All members of the family are affected. The burdens of a cancer and its meaning for patients and their families are correspondingly multifaceted

The implications of a child's cancer include:

- for the family as a whole:
  - Profound disruption of emotional and social equilibrium
  - Collective bearing of strong and contradictory emotions such as fear, anger, trust, despair, guilt, hope, hopelessness or mourning
  - The need to redefine values, objectives and expectations of the future

- for the patient:
  - New, unfamiliar and threatening experiences linked to separations that are often frightening
  - An assault on the patient's physical and psychological integrity and thus damage to the self-image and sense of self-worth
  - A real or threatened loss of health, safety, autonomy, the private sphere and intimacy, familiar environment, contact with peers, school and hobbies, hair, body image or years of life

- for the parents:
  - Engagement with the physical and psychological effects of the disease on the child
  - The handing over of responsibility to hospital professionals, often linked to a perceived loss of the parents' own authority
  - A double challenge: mastering their own personal concerns and fears while supporting the sick child and its siblings and helping the children cope with the therapy
  - A threat to communication if the spouses have different coping strategies

- for the siblings:
  - The perception of change in the sick brother or sister
  - Having to play a "supporting role" if attention is primarily directed at the sick brother or sister
  - Ambivalent feelings of guilt and jealousy

To offer the sick child and its family biopsychosocial care of optimum quality and to support them as they cope with the disease and the crisis, pediatric oncology must supplement medical treatment and care with a wide range of psychosocial approaches

Structure

Concepts

Psycho-oncology has two overarching concepts:

- Conciliar psycho-oncology: The psychosocial staff is called on by the oncological treatment team if needed, primarily in situations of crisis
- Liaison psycho-oncology: The psychosocial staff carries out their activities in close cooperation with the oncological treatment team, and their involvement is an established component of therapy and care for all patients and families

Psychosocial liaison has proven its worth and become established in most pediatric oncology centers. It facilitates acceptance of psycho-oncological care by the affected families, guarantees timely interventions and increases the possibility of preventing severe disorders

Staff

Psycho-oncological care is carried out by members of various professional fields. It requires both the clearly defined distribution of tasks and open and continuous interdisciplinary communication

The most important tasks are outlined below

Medical and nursing staff

In addition to providing somatic care medical and nursing staff establish a foundation for emotional and social support through:

- Constancy of treatment and care
- Provision of information
- Continuity of contacts and relationships

Child psychiatry and psychology

- Investigations into child and adolescent psychiatry and psychology including the family and wider social environment (school, peers, workplace, etc.)
- Specific neuropsychological tests

- Brief, problem-centered interventions in crisis situations
- Long-term support
- Psychotherapy after careful investigation and diagnosis
- Collaboration with family physicians and psychotherapists (e.g. for existing or reactive psychological and psychosomatic conditions)

Social work

- Advice and support of parents or adolescent patients in social difficulty
- Organization of the care of siblings
- Provision of aids, care services and financial support
- Contact with employers

Education in hospital

Education in hospital serves to strengthen the patient's motivation and self-confidence forming a bridge to normal life through creativity, games, and learning.

- Hospital school:
  - Lessons at the right age and level for children and adolescents of school age during their stay in hospital or outpatient clinic
  - Regular contact with class teachers and school authorities (discussion of subjects to be covered obtaining appropriate teaching materials, reintegration, implementation of supportive measures, change of class)
  - Talks with patients and parents about school issues
  - School visits
- Education through art and play:
  - Development of a trusting relationship through regular contacts during creation and play
  - Encouraging the working through of difficult hospital experiences in a play situation
  - Involvement of parents and siblings and support in educational matters
  - Helping to create a child- and adolescent-friendly atmosphere in the hospital

In addition to these core professionals pastoral care as well as art and music therapy contribute significantly to psychosocial work. In many clinics parents' associations and foundations also provide supporting activities and self-help groups for affected families.

The Practice of Pediatric Psycho-oncology

Objectives

At the center of psycho-oncological work is the promotion of individual and family resources during the crisis of disease, therapy and – in some cases – dying, death, and mourning. The core is formed by a supportive relationship oriented according to the physical, psychological and social challenges and opportunities of the sick child and his or her social environment and taking into account individual variations in coping and adapting. The objectives of psycho-oncological work include:

- Creation of a trusting and meaningful dialogue
- Provision of information and expert help
- Promotion of adaptive and active disease management and the mobilization of resources to prevent or reduce disease burdens
- Treatment and support in crisis situations

Procedure

Investigative phase

- The investigation that precedes every psycho-oncological treatment serves to identify the coping and adaptation strategies that are available to the sick child and the social environment. It also provides important basic information for the family and an initial evaluation of what they need from psycho-oncology. The objective of the investigation is not to uncover conflicts, but primarily to create the required support
- The first interview – if possible with the whole family – allows the psycho-oncologist a preliminary insight into the way that they are handling the burden of illness and therapy and into family relationships and coping strategies
- The investigation is generally not completed after the first interview. As a result of situations that often change rapidly during the course of the therapy (e.g., clinical complications, relationship crises, relapse) the assessment must be continuously adapted and updated

Areas investigated

- Family:
  - Socioeconomic situation (place of residence and domestic situation, school, profession, finances, etc.)
  - Social network
  - Existing resources and problems
  - Orientation and cohesion
  - Cultural, ethical and religious values
  - Intrafamilial communication
  - Communication with the outside, flexibility of boundaries
  - Mutual distribution of responsibility and expectations

- Patient (and possibly siblings):
  - Emotional, cognitive and physical state of development
  - Most significant individual coping strategies and their state of development
  - Handling of earlier, critical life events
  - Level of information and understanding
  - Principal fears and concerns
  - Feeling of self-worth, body image
  - Compliance (willingness to cooperate)
  - Relationships with parents, other adults, siblings, contemporaries, treatment team
  - Ability to use relationships maintain their own psychological equilibrium

- Parents (or their representatives and other significant figures):
  - Most important coping strategies

- Handling of earlier, critical life events
- Level of information and understanding
- Compliance, trust in the treatment and the treatment team
- Principal anxieties
- Relationship between the partners (communication, emotionality, expectations)
- Relationship to the sick child and their siblings
- How the children are given information
- Ability and willingness to express themselves and to accept support from their environment and from psycho-oncologist

In practice the investigation phase may often be difficult to distinguish clearly from the phase of treatment and support; both merge into each other. To prevent misunderstandings and disappointment, however, it is important to discuss and establish each family's needs and expectations as soon as possible. Responsibilities for the different tasks must be clarified within the treatment team and with the family. In general one person cannot take on all the psycho-oncological functions (e.g. act as confidant to both patient and a heavily burdened young sibling).

Treatment phase

- Psycho-oncological support or treatment is individual. Standardizing the procedure is difficult since the needs of families and the course of diseases and therapies differ widely. The provision of help must be low-threshold and the family must know how, when and where the staff of the psycho-oncological team is available
- For families with whom no firm collaboration can be agreed the regular presence of the psycho-oncological staff on the ward can often provide opportunities for chance contacts that help to build trust

Basic Attitudes

In psycho-oncological work it is not a psychiatric problem that is foremost, but a psychoreactive problem sparked off by the life-threatening illness of a child. The psycho-oncological approach is correspondingly not primarily problem-oriented but resource-oriented and informative. The objective is to support an active and constructive coping model and to prevent severe psychological burdens, developmental disorders or emergencies

Psycho-oncological care requires:

- Benevolent and supportive basic attitudes
- Openness to all subjects
- Respect for any adaptive and defensive mechanisms necessary for survival (e.g. partial repression)
- Honest information that is tailored to the situation and answers to questions that take into account the age and developmental stage of the child and the individual life situation of the family
- No playing down of hard facts, no making of promises that cannot be kept, no premature comfort
- Sensitive handling of cultural differences
- Balance between empathy and distance

Problems and Possible Interventions

The heterogeneity of oncological diseases, the different therapies and courses, the wide developmental spectrum of the patients from infancy to adolescence and the multifaceted structures, resources and existing difficulties of the affected families all require a careful individual assessment of psycho-oncological needs.

The following summary of specific problems and requirements that may confront the patients and their families over the course of the illness can therefore only offer a basic orientation. This also applies to possible reactions and suggested psychosocial interventions.

Before Diagnosis

Problems
- Undiagnosed, possibly painful, and disabling symptoms
- Unfamiliar examinations
- Foreboding
- Waiting for diagnosis

Requirements
- Ability to tolerate the lack of uncertainty
- Cooperation in diagnostic examinations
- Appropriate dialogue within the family

Reactions
- Fear, insecurity, confusion
- Parents' efforts to shield the children from their own concerns

Interventions
- Orientation aids: emotional, organizational, informative

After Diagnosis

Problems
- Existential assault on the family's world
- Certainty of life-threatening disease
- Confrontation with the prognosis and the impending therapy

Requirements
- Emotional control
- Engagement with diagnosis, therapy, side-effects and prognosis
- Ability to absorb and process important information
- Adaptation of family life to the new situation
- Informing friends, school, employer, etc.

Reactions
- Being flooded with feelings of shock, fear of death, impotence, helplessness, loss of control, anger, guilt, blame
- Denial
- Desire to run away

Interventions
- Orientation aids and information
- Empathetic acceptance of emotions without premature comforting or giving of advice
- Support of open communication

Start of Therapy

Problems
- Preparations for therapy (central venous catheter, simulation of radiotherapy, etc.)
- Handing authority and responsibility to the treatment team
- The prospect of hospital stays lasting from days to weeks
- Side-effects of therapy
- Giving written informed consent
- Dealing with the desire for and recommendation of alternative forms of therapy

Requirements
- Engagement with therapy, side-effects and the as yet unfamiliar treatment team
- Adequate care and support of patient by parents
- Involvement and informing of siblings

Reactions
- Fear of therapeutic interventions and their side effects (e.g. pain, nausea, loss of hair)
- Regression
- Parents' overprotectiveness toward the patient

Interventions
- Individual, problem-centered support of patient and family
- Supportive measures: preparation for medical interventions using relaxation techniques to reduce the fear of medical interventions
- Discussion of desire or recommendation for alternative therapy

Course of Therapy

Problems
- Long duration of therapy
- Physical and emotional exhaustion
- Altered appearance (e.g. loss of hair, loss or gain of weight)
- Psychological changes (high-dose corticosteroid therapy)
- Complications and postponement of treatment

- Separation from the family (patient, parents, siblings)
- Missing contact with friends
- Missing time at school
- Parental neglect of siblings
- Parents' own problems at work
- Uncertain prognosis

Requirements
- Adaptation and organization of daily life in the family, at school and work
- Flexibility (e.g. when therapy is postponed at short notice)
- Clear and consistent attitude toward the sick child
- Involvement of siblings
- Time taken by parents for their own relationship and interests

Reactions
- Patient: regression, fears and phobias, social withdrawal, depression, disorders of self-worth and body image, refusal of therapy
- Parents: exhaustion, depression, anxieties, sleep disturbances, psychosomatic problems, conflicts within the relationship, concentration of attention on the sick child, neglect of the siblings
- Siblings: jealousy, guilt, forced independence, social isolation, failure at school, psychosomatic problems, hypochondria

Interventions
- Support for the understanding of therapy and willingness to cooperate
- Encouragement of responsibility
- Support for intrafamilial communication
- Reinforcement of individual and familial resources and promotion of adaptation to the changes in family life caused by the disease and therapy
- Psychotherapeutic support if indicated
- Support of the parents in educational matters with inclusion of sibling children
- Educational encouragement, contact with the patient's school and possibly with siblings' school(s)
- Other supportive measures (relaxation techniques, art and music therapy)

Surgical Intervention

Problems
- Fear of the intervention and the result
- Postoperative pain and complications
- Loss of physical integrity, mutilation

Requirements
- Adapting to fear and uncertainty before the intervention
- Dealing with physical change and impairment or disability
- Motivation in postoperative care (e.g. physiotherapy)
- Parental support of the child in coping with possible disablement

Reactions
- Acute stress reactions
- Longer-term depressive developments, disorders of self-worth and body image
- Inability to tolerate or denial of disability, creation of taboo
- Lack of compliance with postoperative rehabilitation

Interventions
- Preoperative preparatory information (picture books, games, etc.)
- Support in pain management, interdisciplinary pain treatment
- Promotion of emotional processing of the physical change, impairment or disability
- Support for rehabilitation measures
- Help in reintegration and obtaining aids

Radiotherapy

Problems
- Preparations for radiation (fitting and wearing aids, e.g. face masks; simulation)
- Unfamiliar treatment team and strange environment
- Unfamiliar "machines"
- Forms of treatment that are difficult to comprehend (nothing to feel or hear)
- Sedation or narcosis of young children
- Side effects (dependent on dose and site, e.g. nausea and vomiting, dizziness, diarrhea, skin irritation, fatigue)
- Delayed effects (particularly neuropsychological impairments following irradiation of the head)

Requirements
- Cooperation with the treatment team
- Lying immobile, sometimes in an uncomfortable position
- Adapting to being alone during irradiation
- Dealing with possible delayed effects

Reactions
- Fear of isolation, panic
- Helplessness and defenselessness

Interventions
- Information and preparation (visits to the radiotherapy department, handling the apparatus, illustrated material)
- Practicing "lying still" during the radiation procedure through play (swapping roles, "irradiating" cuddly toys)
- Supportive measures (autosuggestion techniques)

Hematopoietic Stem-Cell Transplantation

Problems
- High-risk therapy, sometimes the "last chance"
- Life-threatening complications (toxicity of therapy itself, infections, graft-versus-host disease)
- Isolation, separation from the family
- Identification of a donor among family members
- Waiting to find a donor
- Differential meanings for donor and nondonor siblings, influence on mutual relationships
- Long-term risks (relapse, chronic graft-versus-host disease, immunosuppression)

Requirements
- Dealing with the risks and delayed effects
- Enduring a long stay in hospital, in isolation
- Organization of the family (often "two homes")
- Dealing with what is "self" and "other"

Reactions
- Acute disturbances, often marked by severe regression
- Disorders of body image
- Medium- or long-term difficulties in taking food and medication
- Parental exhaustion if the stay in hospital is long and they have to be present throughout
- Strong sense of responsibility among donor siblings; guilt if the result is poor
- Feelings of neglect on the part of the nondonor siblings

Interventions
- Involvement of the entire family in the preparations
- Organizational measures (childcare, presence of parents at the hospital or at work, etc.)
- Continuous support during isolation
- Discussion of the influence of transplant on the donor and nondonor siblings and on intrafamilial relationships
- Supportive measures (relaxation techniques, art and music therapy)

End of Therapy

Problems
- Therapy has caused loss of security
- Fear of recurrence
- Unrealistically high expectations of the return to normal life

Requirements
- Separation from the treatment team and reestablishment of self-responsibility
- Reintegration into school and social life, sometimes reorientation and engagement with changed educational and/or job prospects

- Dealing with fears of relapse and family expectations and ideas

Reactions
- Fear (of relapse, school phobia, social anxiety, lack of perspective, etc.)
- Exhaustion (often only now "allowed")
- Family conflicts (different expectations or ideas about return to normal life)

Interventions
- Interdisciplinary interview to conclude therapy
- Clarification of fears, hopes and expectations of the future
- Support during reintegration
- Family-oriented rehabilitation measures

Long-Term Remission and Cure

Problems
- Fear of relapse
- Long-term effects (disability, infertility, etc.)
- Problems at school and at work

Requirements
- Integration of the experience of illness and therapy into individual and family biography
- Dealing with long-term effects

Reactions
- Anxiety disorders
- Depressive development
- Psychosomatic problems
- Disorders of self-worth
- Relationship disorders
- Denial as a coping strategy

Interventions
- Measures that promote integration (information, clarification of open questions, dealing with fears, self-doubt and body image disorders)
- Problem-centered psychiatric/psychological investigation and therapies

Relapse

Problems
- Existential threat
- Deep insecurity ("it's all starting again")
- Knowledge that the first treatment has been unsuccessful
- Serious or hopeless prognosis
- Preparation for further burdensome curative therapy and/or engagement with palliative care, dying and death

Requirements
- Ability to take in and process the information
- Emotional control, rebuilding motivation and hope
- Engagement with the new situation and the new therapeutic protocol
- Communication within and outside the family
- Adaptation of family life to the new situation

Reactions
- Irruption of violent feelings: shock, fear, despair, impotence, anger, resignation, blame
- Desire to run away

Interventions
- Orientation aids
- Empathetic acceptance of emotions without premature giving of advice (an existing relationship with the family is often very helpful)
- Support in the rebuilding of trust and motivation
- Encouragement of open and honest communication that includes the siblings

Dying, Death, Mourning

Problems
- Disease symptoms: pain, dyspnea, paralysis, etc.
- Loss of comprehension, feelings of meaninglessness
- Existential loss
- Separation and isolation

Requirements
- Leave-taking, letting go
- Accompanying the dying process at home or in hospital
- Mourning
- Finding new structures

Reactions
- Denial, fear, despair, anger, longing, guilt
- Clinging to the lost relationship, inability to reorientate oneself, pathological mourning

Interventions
- Support of the patient and their family, taking into account family needs and possibilities
- Continuous supportive relationship
- Tolerating resentment and the "unanswerable questions"
- Encouragement of sibling involvement in the dying and mourning process
- Support of open communication and verbal and nonverbal dialogue (e.g. drawing, body contact, silent presence)
- Helping to prepare appropriate palliative treatment
- Follow-up talk(s) with the family of the child who has died

Treatment Team

- Engaging with children and their families in situations of major existential difficulty pediatric oncology requires collaboration with other professional fields, departments and often hospitals
- The work makes heavy demands on all team members and on interdisciplinary communication:
  - Processes of therapy and care are intensive and complex
  - The workload can change drastically within short periods (new illnesses, relapse, complications)
  - The outcome of the disease is unknown; cure and death are often in close proximity
  - Professional groups are perceived differently by affected families because of differential distribution of tasks
  - In addition to the treatment of the patient there is often also an intensive engagement with their family
  - Dying and death, and the confrontation by one's own limits are omnipresent
- The challenges contain the risk of individuals overworking and conflicts within the treatment team, especially at the interfaces between somatic and psychosocial medicine
- To minimize the risk of misunderstandings the apportioning of blame or projections psycho-oncological work must take place within the framework of the whole oncological treatment plan. This integration requires structured and regular exchange of information (e.g. team conferences). In addition and particularly in situations of crisis (e.g. medical complications, relapse, escalation of intrafamilial conflict) rapid and informal interdisciplinary communication must be possible. Otherwise there is the risk of multitrack care with loss of interface between or, in extreme cases, splitting of the team
- The prerequisites for constructive cooperation are knowledge of the individual tasks and respect for the way the other professionals work. Experience shows that collaboration does not happen by itself, but must be actively and continuously fostered by all those involved
- Regular departmental meetings, team supervisions and joint training events are components of the work

Research

- Following therapeutic progress in recent decades the terms "coping," "quality of life" and "psychosocial long-term effects" have gained in significance in pediatric oncology and form the priorities of psycho-oncological research which has developed various models to conceptualize and systematically record these variables
- The results of scientific studies now form valuable bases for the development of psycho-oncological concepts and flow into daily clinical work. For example it is accepted that a workable social network, the willingness to communicate openly and the ability to use partial repression effectively all create favorable conditions for a successful psychosocial adaptation to the pressures of the illness

- Some results of psychosocial research in pediatric oncology are based on uncontrolled studies with small and/or heterogeneous patient groups and methodological procedures that do not fulfill rigorous scientific criteria

Other areas – particularly the usefulness of psycho-oncological interventions – have hardly been researched at all. Subjects that require further intensive research (preferably as part of multicenter studies) include:

Coping with Illness and Therapy

- Based on hypothesis-supported methodologies
- Taking into account significant variables (e.g. age and developmental stage of the patient, type of disease and therapy, cultural background of the family)
- Differentiation of the terms "coping" (process) and "adaptation" (result) which have previously often been used synonymously
- Combination of quantitative and qualitative methodological approaches to do justice to the complexity and individuality of the illness experience

Conceptualization of the Term "Quality of Life"

- Currently a large number of assessment methods based on different concepts are available
- Delimitation from psychopathology and general psychosocial and physical condition

Efficacy of Psycho-oncological Interventions

- Controlled and theory-based prospective investigations
- Establishment of quality standards
- Specific interventions during and after illness and therapies that affect the central nervous system

Further Reading

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