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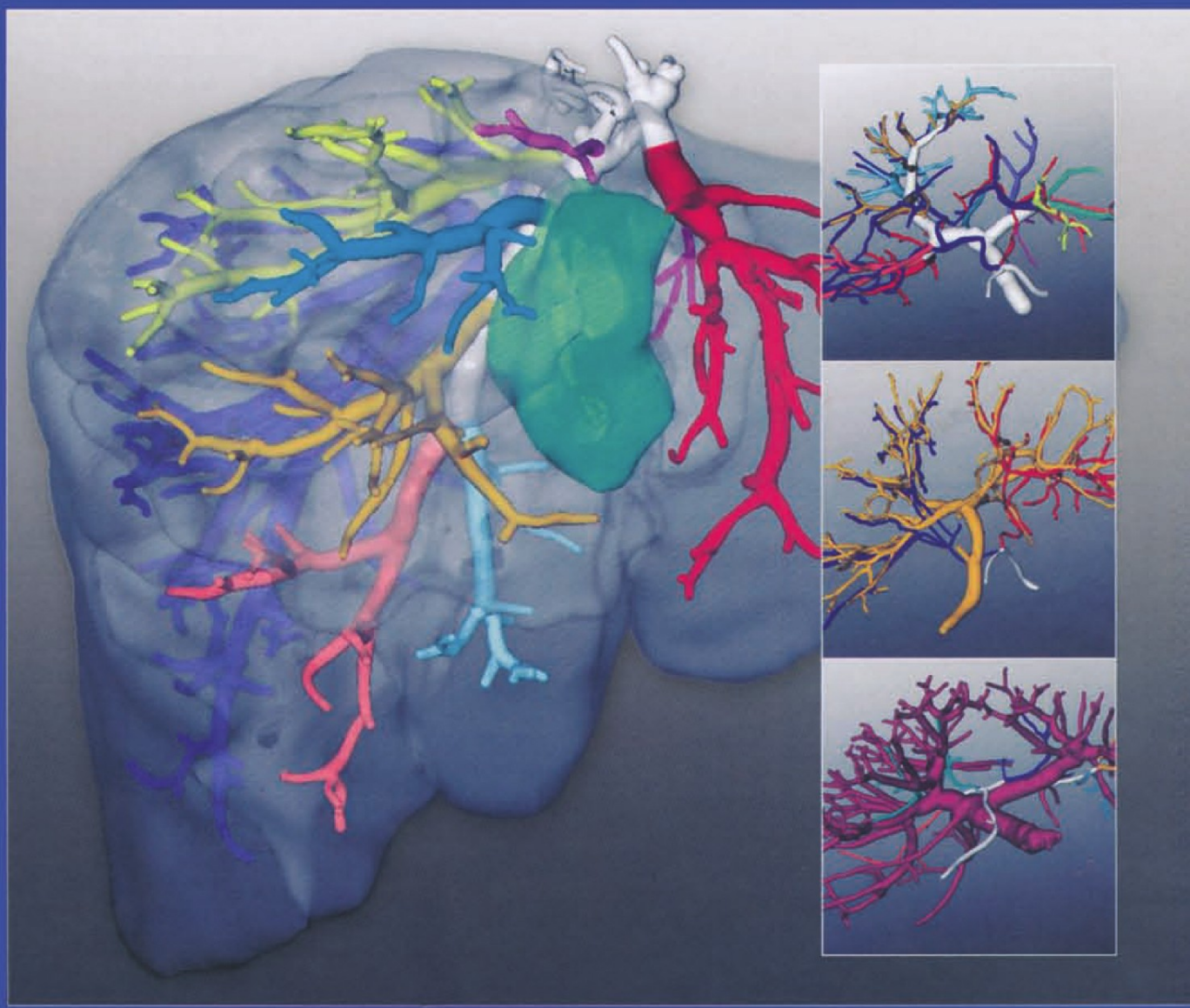
liver and biliary tract surgery

embryological anatomy to 3D-imaging and transplant innovations



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Constantine Ch. Karaliotas
Christoph E. Broelsch
Nagy A. Habib (Eds.)

Liver and Biliary Tract Surgery

Embryological Anatomy to 3D-Imaging and Transplant Innovations

SpringerWienNewYork

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This Book is Dedicated to

Evangelos Papaevangelou

MD, PhD
Professor of Surgery - University of Athens
Former Chairman of Surgery in Red Cross Hospital, Athens - Greece

Former President of the
Hellenic Surgical Society
and 23^{d} Panhellenic Surgical Congress

"In admiration for his scholarship in many fields,
for his zeal as teacher, surgeon, and administrator"

"In the judicious discharge of these interdependent functions
he has unfailingly strengthened the natural alliance
between humanism and surgery"

We are like dwarfs seated on the shoulders of giants.
If we see more and further than they,
it is not due to our own clear eyes or tall bodies,
but because we are raised on high
and upborne by their gigantic bigness.

Bernard of Chartres
Chancellor in 1119

PREFACE

The 25th Panhellenic Surgical Congress is offering the present textbook of surgery to all participants on one of the hot surgical topics: hepatobiliary surgery: "I wonder what the young surgeon learn when they attend a national surgical congress?" It is well known that delegates and young surgeons attend sessions on surgical topics of great interest, such as round table discussions, lectures on specific issues by distinguished Greek and foreign guests, postgraduate courses, follow live operations transmitted from operating rooms, meet experts describing their own techniques, debate scientific problems and ideas with well known pioneers in the field, and go home to review the scientific programme and their notes from the sessions attended.

Pioneers from both the international and Greek Hepatobiliary Club, present their combined experience, describe techniques for hepatic and biliary surgery and explore future trends. It is important for all of us to know what is really "innovative" in hepatobiliary surgery. New thinking is both an initiation and a "nouveaute" that pushes at the frontiers in surgery. This book addresses all the main topics in Hepatobiliary surgery including living related and conventional cadaveric transplantation, new trends in hepatic surgery, new applications for laparoscopic surgery, especially laparoscopic exploration of the biliary tree, the changing face of biliary reoperation and iatrogenic biliary stenoses and strictures, etc.

The book also covers cutting-edge research and technological advances that will shape the surgery of tomorrow. There is little doubt that technological advances in preoperative imaging, such as 3-D reconstruction, preoperative preparation with portal vein embolisation and operative techniques using bloodless RF resection methods, are already changing the nature of liver surgery.

It will be interesting to see how surgery will benefit from advances in stem cell research, gene therapy, genomics, proteomics and miRNA. I hope that this book will inspire young surgeons to invent, to dream and believe in their imagination.

As a surgeon who has participated in the evolutionary steps of biliary and hepatic surgery over the last decades, I want to express my enthusiasm for this book, and my deep appreciation to the Organising Committee and especially the President of the Congress, my friend Constantine Karaliotas, and the hope that this book will be appreciated by all members of the 2006 Congress.

Evangelos J. Papaevangelou
Professor of Surgery
Former President of Hellenic Surgical Society

PREFACE

With the coming of 2007, we are celebrating seventy nine years since the institution of the Hellenic Surgical Society.

These years have proven very productive for surgery in Greece, mainly because the founders of our Society, as well as all the great scientists of the Executive Committees that followed, offered all their knowledge in an effort to upgrading surgery in Greece, so that it is now considered as worthy as surgery worldwide.

Wishing to honour the 79th anniversary of our Society and at the same time holding the 25th Panhellenic Congress of Surgery, the present Executive Committee decided, among other, to publish a book titled "Liver and Biliary Tract Surgery".

The aforementioned book, written in English so as to be read by doctors beyond Greek frontiers, is the result of a very successful team work of some of the most significant scientists of our days. The President of the congress and elect President of the Hellenic Surgical Society, Dr C. Karaliotas, Chairman of the Surgery and Surgical Oncology Department of Red Cross Hospital in Greece, Professor Chistoph Broelsch, Chairman of the Transplantation Center of Essen University in Germany and Professor Nagy Habib Chairman of the Hepatobiliary Department of the Hammersmith Hospital in United Kingdom, are the editors of the present book.

The catalogue of authors includes 68 scientists very well known for their work, knowledge and literature contribution, worldwide, from Greece, Germany, United Kingdom, United States and France.

SpringerWienNewYork, the Publisher is one of the highest reputed publishing Houses, and an additional guarantee of the book's high quality.

Being the representative of the Hellenic Surgical Society, I wish to thank the editors, Doctors Karaliotas, Broelsch and Habib for their hard work, all the authors for their valuable contribution and Springer publishers who gave us the opportunity for that great edition. We look forward to a future cooperation.

It is our wish, this very special work of so many remarkable authors to receive the welcome it deserves.

Theophilos Polymeropoulos
President of the Hellenic Surgical Society

FOREWORD

Since in 2006 the art and practice of HPB surgery can be learnt from a variety of sources, which circumstances did determine and touched the genesis of this book? In spite of the internet and e-learning and the many scientific and medical meetings, a textbook still has a place in today's world as it provides junior and senior surgeons with a definite and fundamental source of information to enhance clinical skill and management strategy.

This textbook has three Editors-authors and four sections, each reflective of their own particular perspective. As each author has chosen different co-authors and topics, the textbook has been enriched with different philosophies and ways of thinking about clinical approaches from which the reader will benefit.

The first and second sections are dedicated to embryology, anatomy and physiology, current diagnostic techniques in hepatobiliary surgery and management of benign and malignant diseases of the biliary tract. Is one of the most classical but basic and difficult knowledge for the HPB surgeon. The topics are mainly written by authors from university centers of Greece and Red Cross Hospital of Athens and Hannover. Invaluable is the offer of the two famous writers, professors A. Dalley and K.L. Moore from USA and Canada who have written the chapter I.

The third section, is written from the Hammersmith Hospital doctors. They contributed to chapters covering three different areas.

The first area reflects the unique activities where HPB department excels. Chapters are dedicated to new techniques developed at the Hammersmith Hospital, such as radiofrequency assisted liver resection. This concept was born and developed at the Hammersmith. It is with great pride that on the first anniversary of the launch of Hammersmith device that one in four of all liver resections in the USA is performed with this technique. The new technique allows HPB surgeons to perform liver resection with excellent results. In the vast majority of cases liver resection can be performed without blood transfusion, and without the need to admit patients to intensive care unit or high dependency unit. The development of the laparoscopic RF resection device is even more significant as it will finally give the liver surgeon the opportunity to undertake laparoscopic liver resection safely. It will also significantly reduce the length of hospitalisation and overall cost, rendering liver resection more competitive than percutaneous tumour ablation and other non-surgical approaches.

The second area describes techniques that were developed by other teams, but adopted recently in Hammersmith HPB service. This includes the use of 3D imaging in the pre-operative planning of surgery and the adjuvant use of SIRTEX for locally delivered radiotherapy.

The third area gives an insight into some of the research undertaken in the department of surgery, such as stem cell and gene therapy. Several clinical trials have been performed and results, so far, are promising. We believe that academic research goes hand in hand with modern surgery. Research holds the key for improvements in HPB surgical outcomes. The up-to-date modern HPB surgeon will have to rely more and more on stem cell biology, gene therapy, molecular engineering, microarray technology, chemotherapy signatures, genomics, proteomics, metabonomics, nanotechnology, tissue engineering, medical device engineering and above all his or her creative surgical handicraft to optimise the management of HPB patients.

The fourth section is dedicated to Liver Transplantations and is written from doctors of Liver Transplantation Unit of Essen University from Germany. In the past two decades liver transplantation has become the standard treatment in patients with chronic liver failure. Currently, it also represents the most effective therapy in acute liver failure and in carefully selected patients with hepatocellular carcinoma. Technical innovations as well as an

explosion of basic and clinical knowledge in organ transplantation contributed to the success of liver transplantation. This includes a standardization of operative preservation techniques and in particular new developments in the field of immunosuppression. As a consequence, short term survival has improved tremendously.

Concerning the factors which gained increasing interest are those determining long-term survival, in particular, recurrence of primary disease. It is one of the major challenges for the future to develop successful strategies for the prevention and therapy of recurrent disease to reduce the risk for recurrence and to increase survival. With increasing success the indication for liver transplantation is more and more broadened, although organ availability will become the limiting factor. To reduce organ shortage, an optimal use of available organs and an extension of the donor pool is inevitable. Split liver transplantation and living-related liver transplantation are the most effective innovations to increase organ availability and to relieve organ shortage.

This textbook comes at a critical time for liver surgery. During the last 3 decades there have been major advances in liver surgery, such as complex liver surgery and liver transplantation. However, no major breakthrough has happened in the last few years, even laparoscopic liver surgery did not gain its expected popularity because of the technology gap. Unfortunately, liver surgery has been on the defensive. Instead of progressing, the contrary has happened, and liver surgery is receding from the high ground. Facing the onslaught of major breakthroughs in interventional radiology and oncology conventional orthodox liver surgery indications, such as resection of small solitary tumour, were being questioned. Furthermore, major HPB meetings were uninspiring, rich in style, but poor in substance. The major chiefs of liver surgery were repeating old positions with loud voices, but with no convincing arguments.

In all our sections of this textbook we have concentrated on new developments, which Professor Papaevangelos alluded to in his preface as "nouveautés", in the hope of firing the imagination of HPB surgeons and of attracting young talent to this speciality.

HPB surgery and medicine are in dynamic motion propelled by knowledge, discovery and innovation. Currently, the HPB surgeon has to face the challenge of how to integrate and to work closely with the oncologist, gastroenterologist, radiologist and pathologist in a multi-disciplinary approach. In the future the challenge will be even greater. In this new era, the HPB surgeon will have to interact with new officers who will make discoveries lead by science and technology. It is in this spirit that this textbook has been designed and prepared.

Finally, we would like to thank our co-authors and all contributors for giving us the privilege to contribute to this textbook and to all our colleagues who assisted with the manuscripts. Lastly, we hope that readers of this book will be inspired by the science, technical surgical handicraft, and spirit of this book which will equip them with new skills to offer optimal management to their patients.

Constantine Karaliotas
Christoph Broelsch
Nagy Habib
Editors

SPECIAL ACKNOWLEDGMENTS

I take special pleasure and satisfaction in acknowledging the assistance of the special and daily contribution of Doctors G. Sgourakis, Th. Christofides, G. Sotiropoulos, Mike Hatzikalis and Ch. Karaliotas during the course of preparation the last 18 months.

I also take matching special pleasure in acknowledging the contribution of Georgina St John in language editing and the contribution of Tania Gaggou in the phototypesetting, giving an excellent result.

Finally I would also like to express my indebtedness for their help to J. Sideris Publishing House, Athens-Greece and to SpringerWienNewYork Publishing House, especially to Raimund Petri-Wieder, Editor-Medicine of Springer in Wien.

My special thanks to Professors Chr. Broelsch and N. Habib, to the President Th. Polymeropoulos and to the members of the Executive Committee of Hellenic Surgical Society. Without the support of all these people I could not have succeeded in this venture.

Constantine Ch. Karaliotas
Editor

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SECTION 1

Chapter 1: Embryological and Surgical Anatomy of the Intrahepatic and Extrahepatic Biliary Tree

Chapter 2: Surgical Anatomy of the Liver

Chapter 3: Anatomical Variations and Anomalies of the Biliary Tree, Veins and Arteries

Chapter 4: Ultrasonographical Anatomy for the Surgeon. The Value of Intra-operative Ultrasonography

Chapter 5: Elements of the Biliary Tract and Liver Physiology

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Chapter 8: Endoscopic Ultrasonography on Gallbladder and Biliary Tract

CHAPTER 1

EMBRYOLOGICAL AND SURGICAL ANATOMY OF THE INTRAHEPATIC AND EXTRAHEPATIC BILIARY TREE

A.F. Dalley, K.L. Moore

1.1. Embryology

The hepatobiliary system develops during the second half of the eight week embryonic stage of development, known as the *organogenetic period* [1]. Many of the anatomic variations of the system are the consequences of occurrences during this period [2]. At the beginning of gestational week 4, early development of only the nervous and cardiovascular systems has occurred. The full length of the flat, three-layered embryonic disc lies in contact with the yolk sac, and the developing heart lies at the rostral end (fig. $1.1A_2$). Rapid growth of the dorsally-placed central nervous system in the long axis of the embryo results in simultaneous folding at the cranial and caudal ends and sides of the embryo. Concurrently, there is relative constriction at the junction of the embryo and yolk sac, so that the full length contact is diminished to a connecting yolk stalk (fig. $1.1C_2$). In this process, the neural folds have thickened disproportionately to the rest of the neural place, forming the primordium of the brain. The thickest, most rostral part, destined to become the forebrain, overhangs the developing heart, contained within a transverse mesodermal fold, the *transverse septum* (fig. $1.1B_2$). As this mass moves ventrally and caudally with the cranial folding, part of the yolk sac on the embryonic side of the constricting stalk becomes incorporated into the cranial end of the embryo between the brain/notochord dorsally and the heart/transverse septum ventrally, becoming the *foregut* (fig. $1.1C_2$). Similarly, part of the yolk sac becomes incorporated into the caudal end of the embryo as the *hindgut.* By the middle of the 4th week, the *midgut* is distinguished from the foregut and hindgut by being widely open to the yolk sac ventrally. After cranial folding, the bulk of the transverse septum lies caudal to the heart. Within the septal mesoderm, three sets of veins [yolk sac (vitelline), umbilical, and common cardinal veins] drain bilaterally into the bicornate caudal end (sinus venosus) of the primitive heart. On approximately the 22nd day, a small endodermal thickening, the *hepatic plate,* appears in the endodermal lining of the caudal part of the foregut, adjacent to the transverse septum [3]. On the 25th-26th day, the plate begins to proliferate and invaginates into the caudal region of the septum between the right and left venous returns, forming the *hepatic diverticulum (liver bud)* (fig. 1.2A).

As the hepatic diverticulum begins to grow into the mesoderm, the septum becomes segregated into cranial pericardial and caudal hepatic regions, the latter sometimes referred to as the *hepatic mesoderm.* The diverticulum itself enlarges rapidly, dividing into cranial and caudal parts.

The initially bulbous "head" of the larger cranial part of the diverticulum bears the cells that constitute the *primordium of the liver parenchyma,* while its "neck" will elongate to become the *extrahepatic portion of the hepatic duct* (fig. 1.2B & C). During the fifth week, the invading and invaded cells interact through mutual induction: the hepatic mesoderm stimulates the invading endodermal cells of the diverticulum to differentiate into *hepatocytes* or the *epithelial lining of the intrahepatic biliary ducts,* and the developing endodermal hepatocytes stimulate the hepatic mesoderm to differentiate into the *endothelial cells of the hepatic sinusoids* (fig. 1.3) [4, 5, 6]. The primordium of the liver

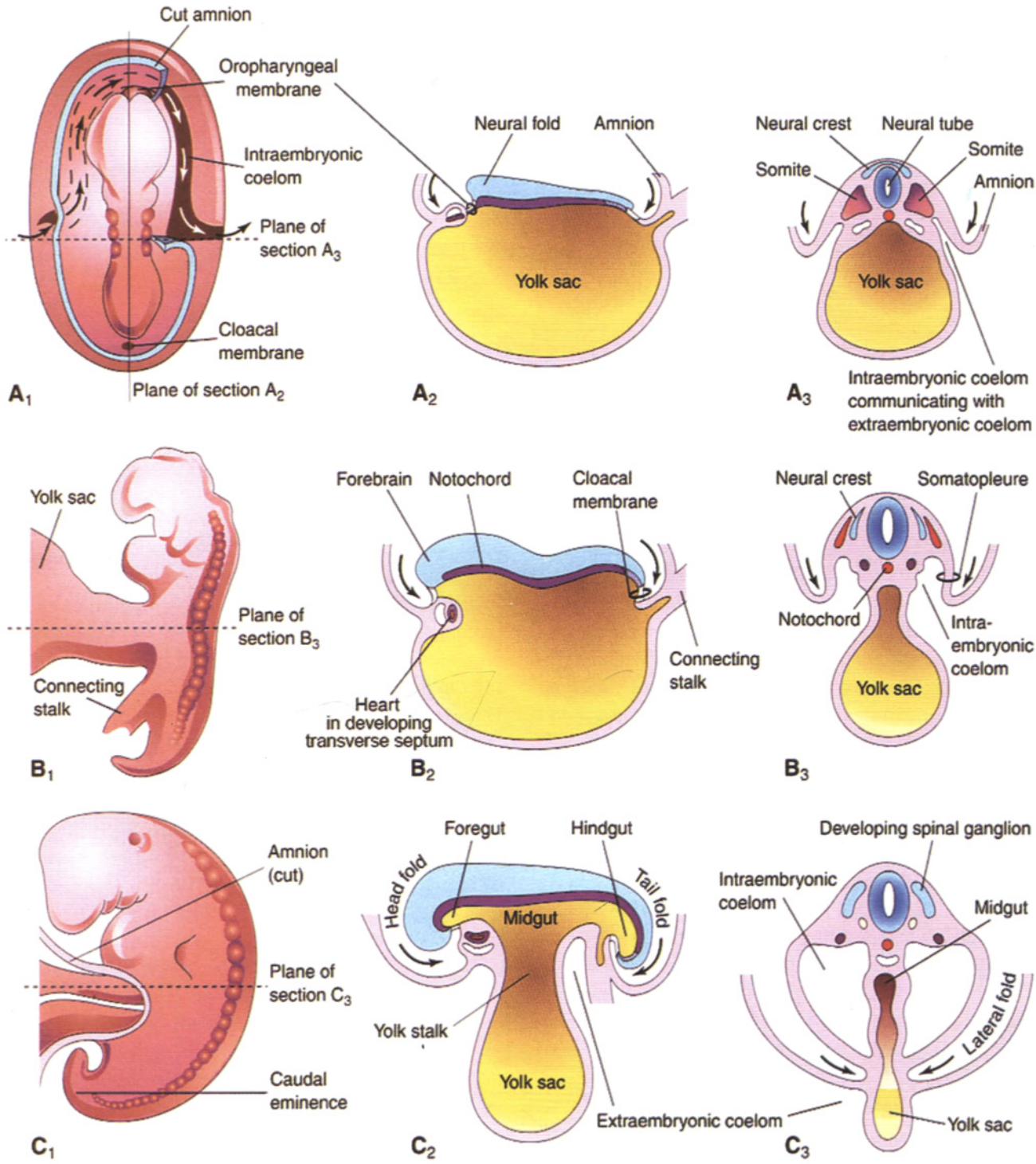


Fig. 1.1. Folding of embryo during 4th week. A figs. Early in 4th week (3 somite stage), B figs. 22 days. C figs. 26 days. A_1, Dorsal view. The conti-nuity of the intraembryonic coelom and extraembryonic coelom is illustrated on the right side by removal of a part of the embryonic ecto-derm and mesoderm. B1 and C1, Lateral views. A_2 - C_2, Sagittal sections at the plane indicated in A_1. A_3 - C_3, Transverse sections at the levels indicated in A_1 - C_1. [From Moore & Persaud (2003), Fig. 5-1, p. 79, with permission of the author].

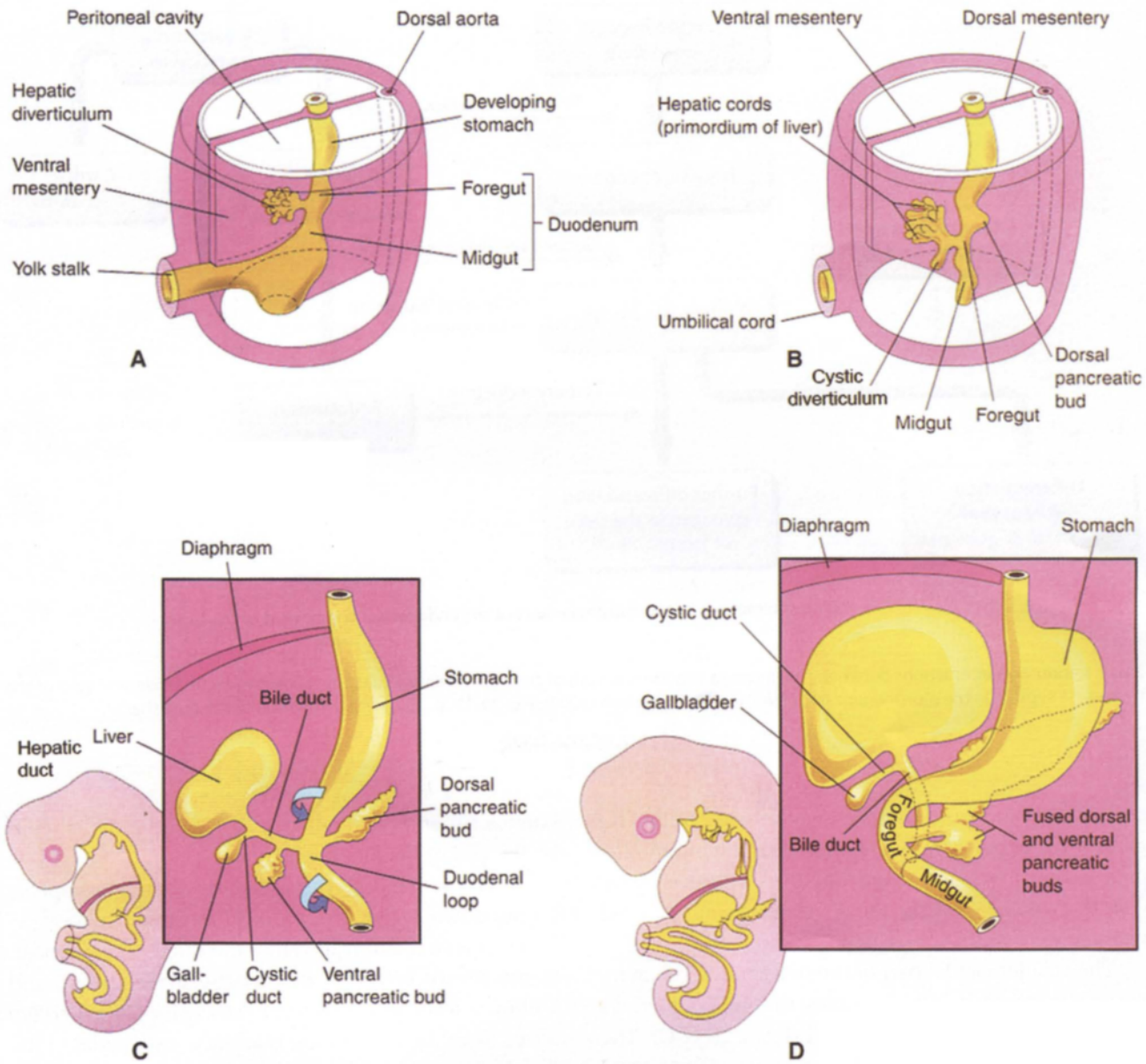


Fig. 1.2. Progressive stages in the development of the duodenum, liver, extrahepatic biliary system, and pancreas. A, 4 weeks; B and C, 5 weeks; D, 6 weeks. Note that the entrance of the bile duct into the duodenum gradually rotates from its initial ventral position (A - C) to a dorsal one (D). This explains why the bile duct passes posterior to the 1st part of the duodenum and head of the pancreas, and how the ventral pancreatic bud joins to the dorsal pancreatic bud. [From Moore & Persaud (2003), Fig. 12-5, p. 262, with permission of the author].

parenchyma branches into many *hepatic cords* (fig. 1.2B), which are closely associated with splanchopleuric mesoderm originating near the cranial (cardiac) end of the developing stomach that will form the mesoblastic *supporting stroma of the liver*. By day 32, the most medially-placed veins in the septum, the vitelline veins, break up into plexuses with their interstices occupied by the proliferating matrix of differentiating endodermal and mesodermal cells. As they are forming, the hepatic sinusoids become connected to the vitelline plexus, so that vitelline blood flows through the developing liver. As early as the fourth week, foci of hemato-

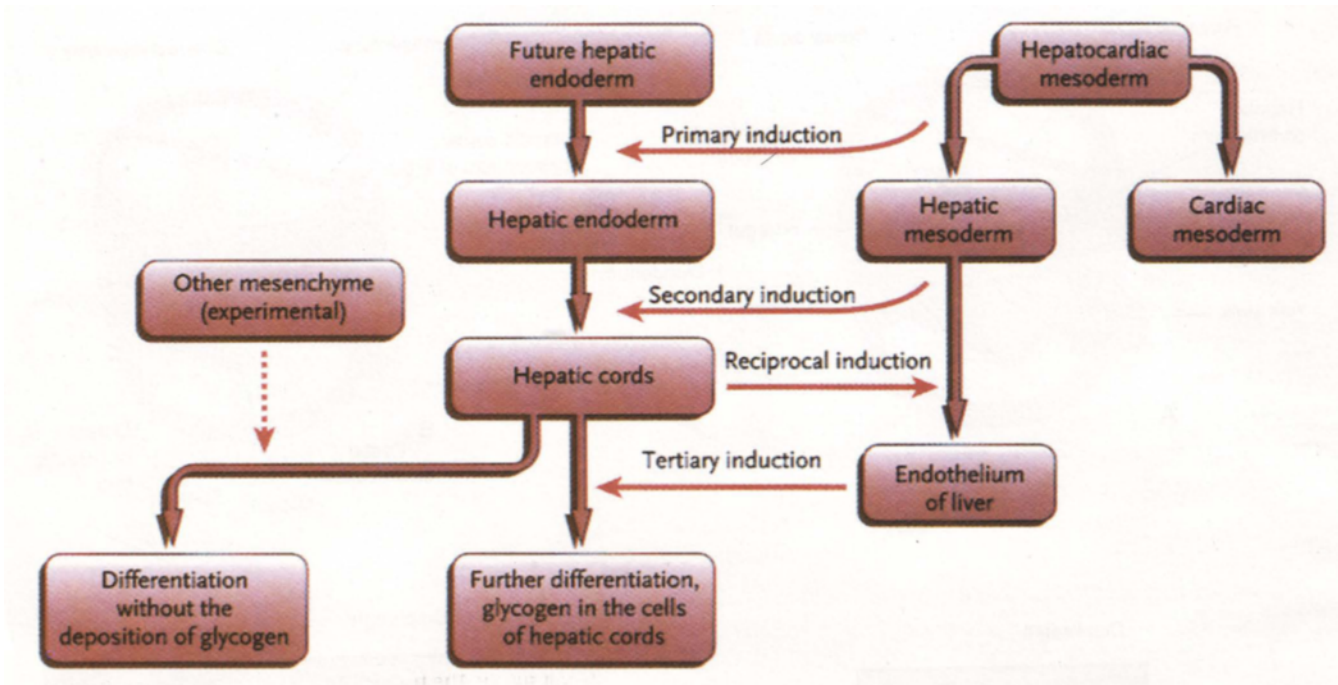


Fig. 1.3. Inductive interactions between the invading endodermal cells of the hepatic diverticulum and the invaded mesodermal cells of the transverse septum in the morphogenesis of the liver. [From Carlson (2004), Fig. 14-17, p. 337, with permission of the publisher].

poietic cells derived from the mesenchyme of this region of the septum transversum appear among the hepatic parenchymal cells and begin to produce blood cells that will egress from the developing sinusoids and vitelline plexus.

The smaller caudal part of the hepatic diverticulum, the cystic diverticulum, becomes the *gallbladder,* its "neck" forming the *cystic duct* [7] (fig. 1.2B & C). The cells forming the gallbladder and cystic duct are from a histologically distinct populations of endodermal cells [8]. The stalk of the hepatic diverticulum, between gut (now differentiating into duodenum) and the cystic diverticulum elongates into the *(common) bile duct.* Variations in the gallbladder and extrahepatic duct arise from developmental anomalies that occur during the 4th week.

During the 5th week, there is an exuberant proliferation of liver cells, and a coincidental elongation of the extrahepatic ductal structures. The gut tube begins to close, forming the duodenum. The lumina of the duodenum and the ducts of the extrahepatic biliary apparatus fill and become occluded with epithelial cells by the end of the 5th week.

At the same time the cystic diverticulum appears (approximately day 26), a *dorsal pancreatic diverticulum* forms in the dorsal wall of the duodenum, opposite the site of origin of the hepatic diverticulum, and within a few days a *ventral pancreatic diverticulum* arises from the developing bile duct, just caudal to the developing gallbladder. Although the hepatic diverticulum arose initially from the ventral aspect of the foregut, growth and rotation of the duodenum causes the entrance of the bile duct and the developing ventral pancreas both to become dorsally-placed, entering the posterior wall of the duodenum and lying within the dorsal mesentery (fig. 1.2D).

At the beginning of the sixth week, the enlarging hepatic mass bulges out of and separates from an intermediate stratum (diaphragmatic part) of the septum transversum, becoming a true abdominal structure lying between the layers of the ventral mesentery formed during closure of the gut and body wall (fig. 1.4 &

1.5). The hepatic mass remains attached to this thin remnant of the septum that becomes part of the diaphragm by *coronary ligaments.* The *bare areas* of the liver and diaphragm remain as vestiges of the liver's septal origin. Other parts of the ventral mesentery, extending between liver and body wall, become the *falciform ligament,* while that extending between stomach and liver becomes the *lesser omentum* (*hepatogastric ligament*). The ventral mesentery provides passage for the ducts and vessels serving the liver, but degenerates caudal to them. The caudal, free edge of the falciform ligament –the *round ligament* (*ligamentum teres*)– conducts the umbilical vein; that of the lesser omentum (*hepatoduodenal ligament*) conducts the portal vein, hepatic artery, and common bile duct – the *portal triad.* About a fifth of the time, a branch of the left gastric artery courses through the cephalic part of the gastrohepatic ligament to become an *accessory* or *replaced left hepatic artery.* Similarly, a branch of the superior mesenteric artery often continues into the gastroduodenal ligament to become an *accessory* or *replaced right hepatic artery.*

During week 6, the extrahepatic ducts recanalize through a process of vacuolation resulting from the de-

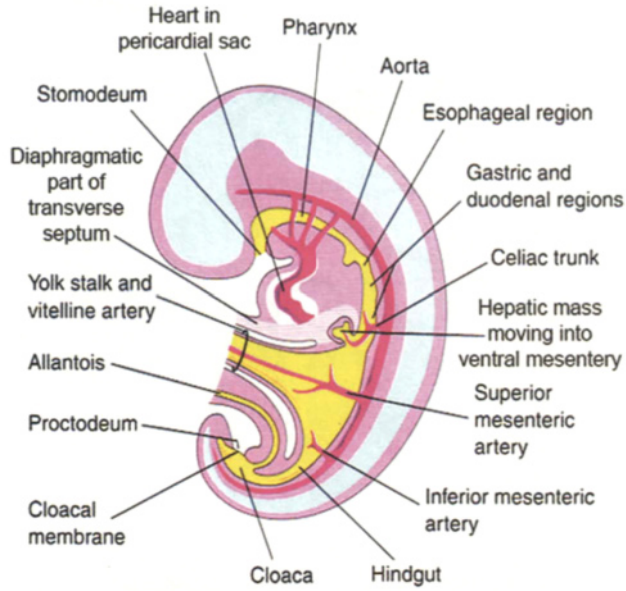


Fig. 1.4. Median section of an embryo showing early digestive system and its blood supply. The transverse septum, once a discrete body, has separated into 3 components: (1) a pericardial part, which will contribute to the caudalmost pericardial sac; (2) a diaphragmatic part, which will form most of the sternocostal diaphragm, including the central tendon, and (3) a hepatic part, which forms the mesodermal part of the liver within the ventral mesentery. [From Moore & Persaud (2003), Fig. 12-1B, p. 256, with permission of the author].

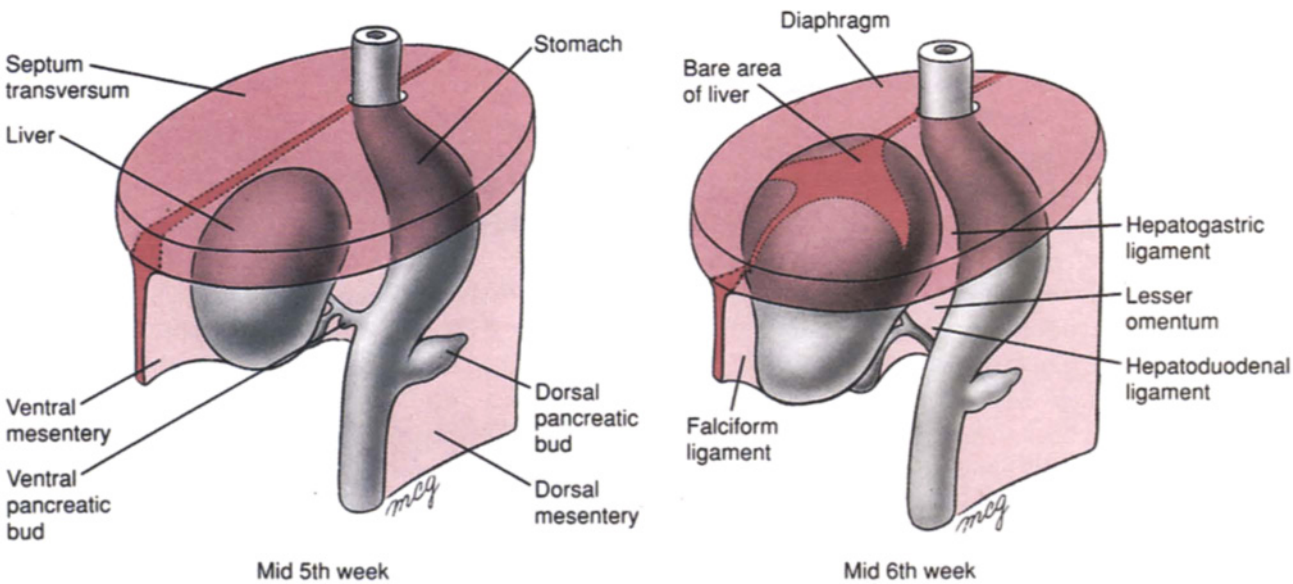


Fig. 1.5. The liver and extrahepatic biliary system developing in relation to the diaphragm and mesenteries. As the developing hepatic mass separates from the diaphragmatic part of the septum transversum, the ventral mesentery forms around it as a consequence of lateral folding of the embyo (see Figure 1A3 - C3). The ventral mesentery differentiates into the visceral peritoneum of the liver, reflected onto the diaphragm at the coronary ligaments, the hepatogastric and hepatoduodenal ligaments, which together constitute the lesser omentum (between stomach and liver), and the falciform ligament, between liver and ventral body wall. The coronary ligaments surround bare areas of the liver and diaphragm, where the two structures remain in direct contact. [From Larson (2001), Fig. 9-8, p. 216, with permission of the publisher].

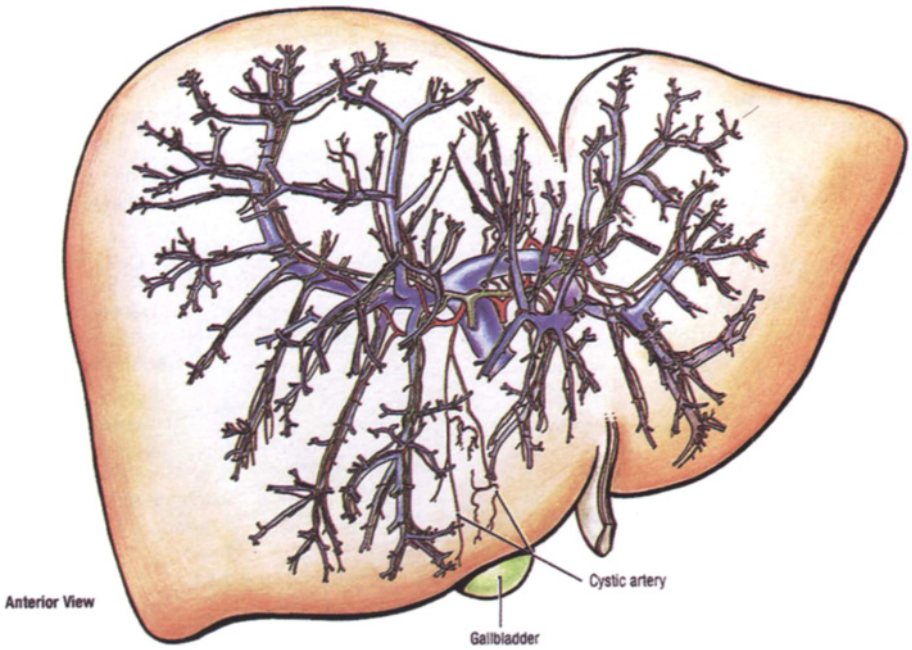


Fig. 1.6. As components of the portal triad, the courses of the intrahepatic bile ducts (green) matches those of the afferent vessels of the liver (hepatic artery, red; portal vein, blue). At all levels of branching, the intrahepatic afferent vessels interdigitate at relatively uniform distances between the corresponding branches of the efferent vessels (central and hepatic veins, not shown in this figure). (From Agur & Dalley (2005), Fig. 2.54A, p. 148, with permission of the authors).

generation of the occluding cells, starting from the duodenal end. Incomplete recanalization results in a *septated common duct. Ductal atresia,* the most serious affliction of the neonatal biliary system occurring in 1 of every 10-15,000 births, was formerly considered to be a malformation due to a failure to recanalize. However, it is now thought to be a secondary phenomenon, resulting from an inflammatory process that leads to sclerosis of recanalized ducts – most likely a viral infection during late fetal development [9]. By the early 6th week, the developing ventral and dorsal pancreatic masses lie adjacent within the dorsal mesentery, and by the end of the week the two have fused to form the definitive pancreas (fig. 1.3D).

By the 6 mm stage, nearly the entire flow from the umbilical veins has been diverted from the caudal end of the heart to the expanding liver, flowing into the venous channels that will become the sinusoids within the investing cellular matrix. The investing parenchyma is at first three to five cells thick between blood channels. With growth of the vascular tree and sinusoids, this is reduced to a single layer.

Definitive liver structure is determined by two guiding principles: (1) achieving maximum interdigitation of afferent and efferent vessels at relatively uniform distances throughout the substance of the liver, and (2) surrounding sinusoids with a single layer of hepatocytes, so that each hepatocyte has at least two sinusoidal surfaces. The first of these applies at both the gross and microscopic levels. At the gross level, it results in (A) the division of the liver into true right and left parts, based on the secondary (right and left) branching of the vessels, and (B) the formation of 8 hepatic segments, based on the tertiary and 4th level branching [10] (fig. 1.6 & 1.7). The hepatic segments center on intrasegmental afferent vessels separated by the extrapolated "planes" (scissura) defined by the intersegmental efferent vessels. Since the macroscopic biliary drainage (intrahepatic ducts) is affiliated with the afferent vessels in the form of triads, the development of the intrahepatic biliary ducts follows the branching pattern of the portal vein radicles [11], the principle of vascular interdigitation effects the biliary drainage as well as the hepatic blood flow.

The second guiding principle of liver structure is at the microscopic (cellular) level. It, too, is significant regarding the biliary system. As the generally single-cell thick muralium of hepatic parenchyma develops, *bile canaliculi* –the intercellular spaces that initially carry bile– form between the attached, non-sinusoidal

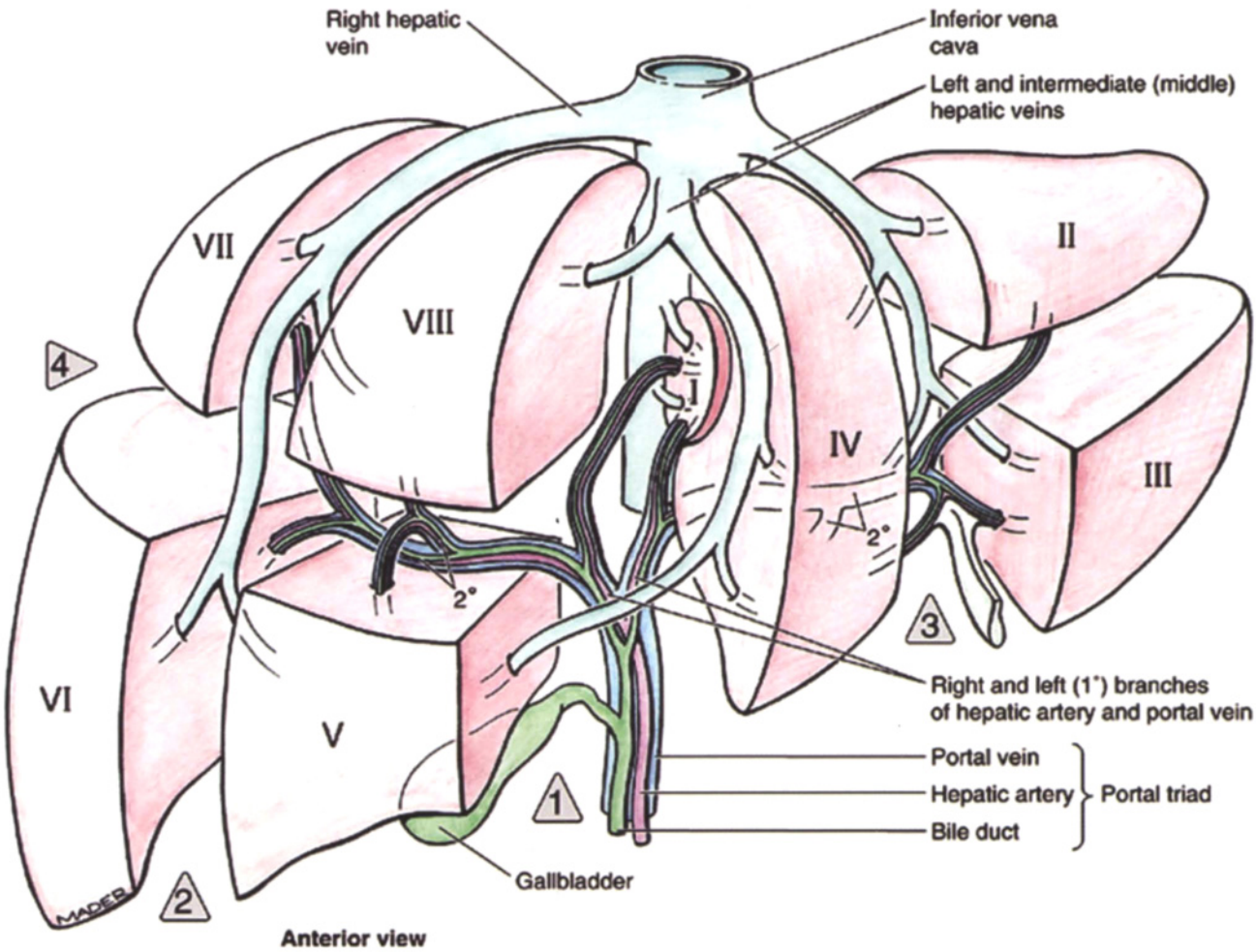


Fig. 1.7. Hepatic segmentation. Except for the caudate lobe (segment I), the liver is divided into right and left livers based on the primary (1) division of the portal triad into right and left branches, the plane between the right and left livers being the main portal fissure (1) in which the middle hepatic vein lies. On the visceral surface, this plane is demarcated by the right sagittal fissure. The plane is demarcated on the diaphragmatic surface by an imaginary line (Cantlie line – Cantlie, 1898) running from the notch for the fundus of the gallbladder to the IVC. The right and left livers are subdivided vertically into medial and lateral sectors by the right portal (2) and left portal (umbilical) (3) fissures, in which the right and left hepatic veins lie. The left portal fissure is demarcated externally by the falciform ligament and the left sagittal fissure. The right portal fissure has no external demarcation. Each division receives a secondary (2) branch of the portal triad (a portal pedicle). [Note: the medial sector of the left liver is part of the right anatomical lobe; the lateral division of the left liver is the same as the left anatomical lobe.] A transverse plane at the level of the horizontal parts of the right and left branches of the portal triad (4) subdivides three of the four sectors (all but the left medial sector), creating six hepatic segments receiving tertiary branches. The left medial sector is also counted as a hepatic segment, so that the main part of the liver has seven segments (segments II through VIII, numbered clockwise). The caudate lobe (segment I, bringing the total number of segments to eight) is supplied by branches of both right and left divisions and drained by its own minor hepatic veins. Each segment thus has its own intrasegmental blood supply and biliary drainage. The hepatic veins are intersegmental, draining the portions of the multiple segments adjacent to them. [From Moore & Dalley (2006), Fig. 2.52, p. 294, with permission of the authors].

surfaces of the hepatocytes (fig. 1.8). The prevailing direction of the bile canaliculi thus parallels the hepatic sinusoids, although the intrahepatic flow is countercurrent to that of the blood at all levels.

Approaching the end of the embryonic period, during weeks 6-8, the left side of the liver undergoes peripheral regression while the right side increases markedly in size. The liver accounts for 10% of body mass

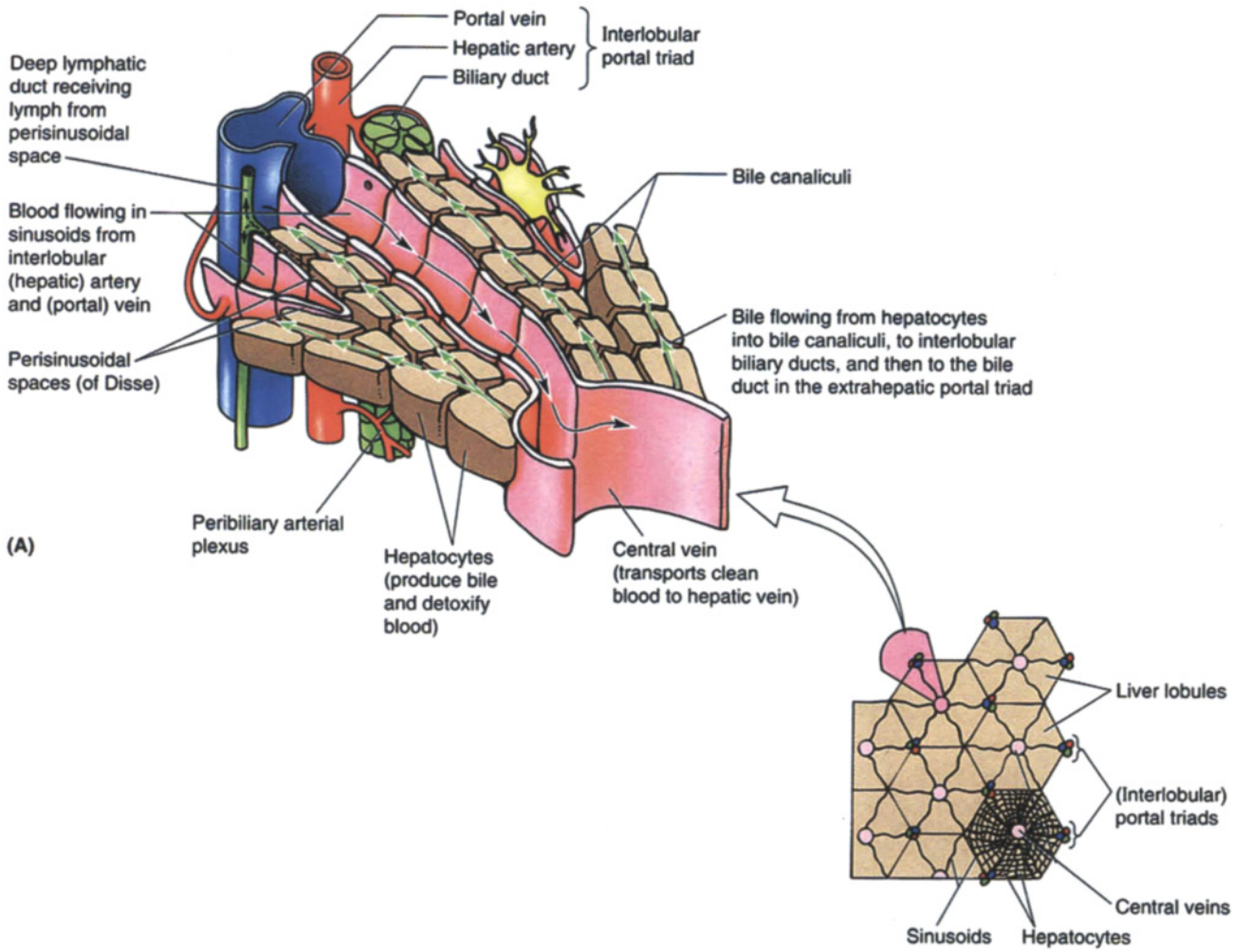


Fig. 1.8. This view of a small section of a classic hepatic liver "lobule" illustrates the components of the interlobular portal triad and the positioning of the sinusoids and bile canaliculi. The enlarged view of the surface of a block of parenchyma removed from the liver demonstrates the hexagonal pattern of "lobules", and the place of the detailed figure within that pattern. [From Moore & Dalley (2006), Fig. 2.53A, p. 296, with permission of the authors].

at the beginning of the fetal period, although this decreases to 5% by the time of birth. The pancreatic ducts fuse, the dorsal duct (Santorini's) forming the distal portion of the definitive duct within the pancreatic tail and body, and the ventral duct (Wirsung's) comprising the proximal duct within the head of the pancreas (fig. 1.9).

At approximately the 12th week, the hepatocytes begin to produce bile, primarily through the breakdown of hemoglobin. The bile drains through the newly formed biliary system and the gallbladder begin its task of storing the secretion. Release bile stains the intestinal contents (meconium) a dark green [12].

1.2. Surgical Anatomy

The *biliary tree* is the system of conduits of increasing diameter that bile flows through as it travels from hepatocytes to the gallbladder (in those mammals that have them) and ultimately into the duodenal lumen.

Normal human hepatic tissue, when sectioned, is traditionally described as demonstrating a pattern of hexagonal-shaped *liver lobules* (fig. 1.8). Each lobule has a central vein running through its center from which sinusoids (large capillaries) and plates of hepatocytes (liver cells) radiate toward an imaginary perimeter

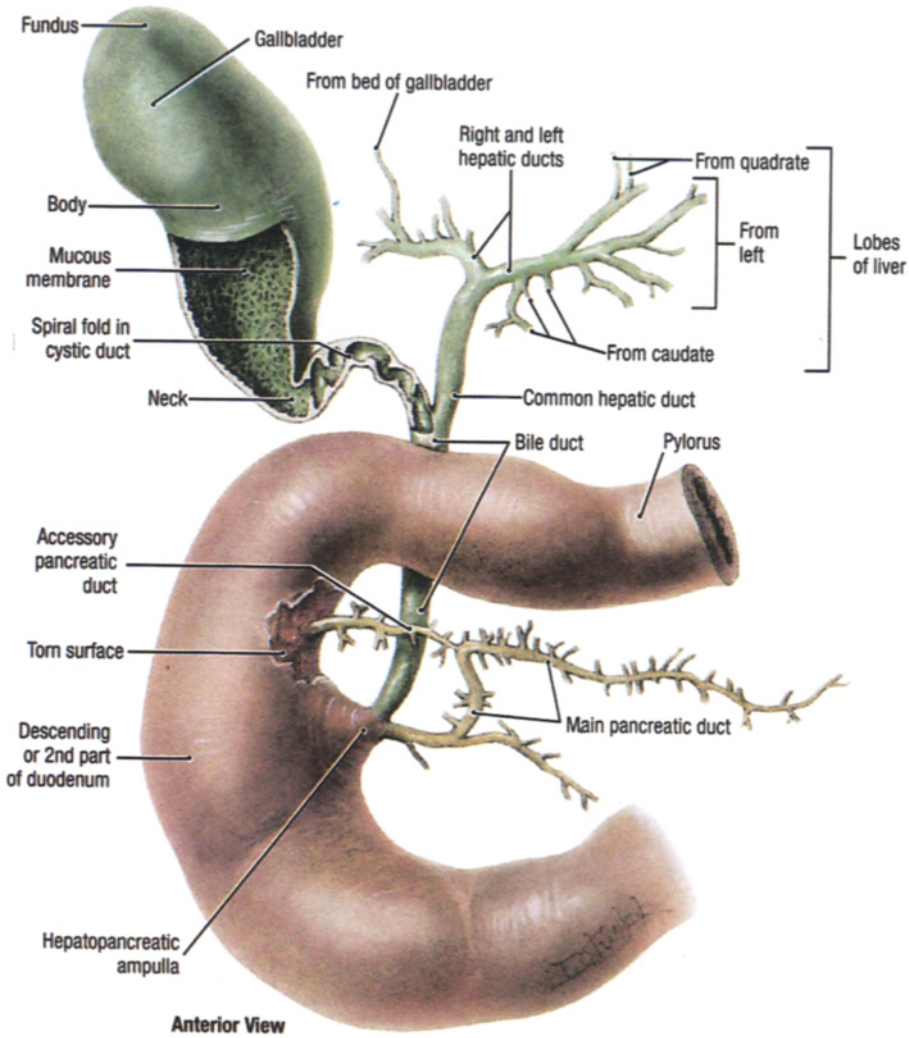
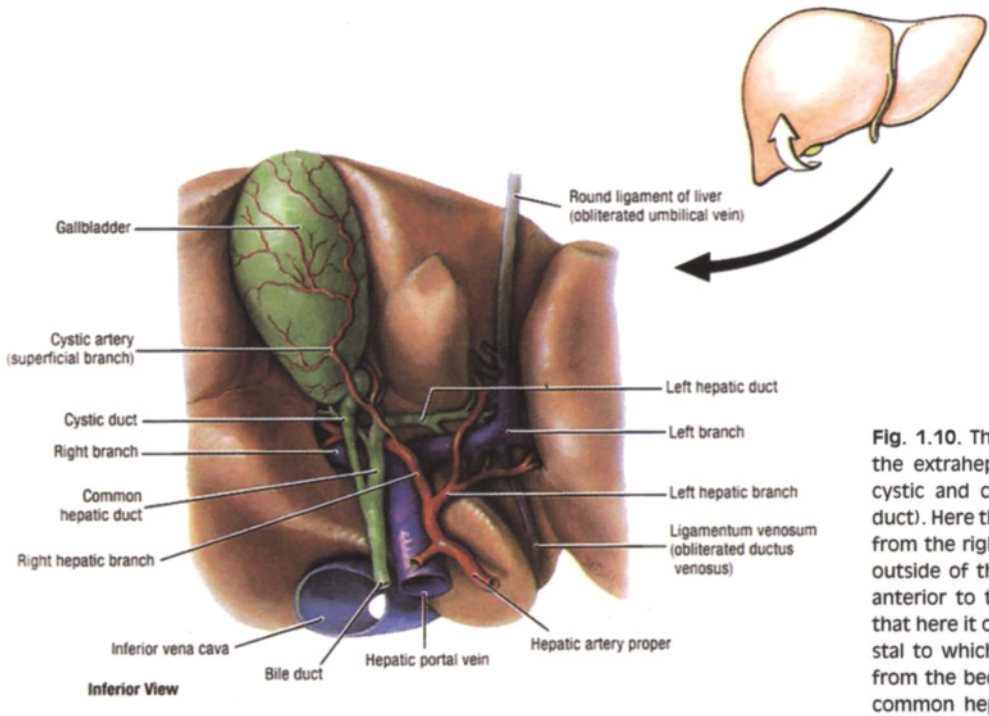


Fig. 1.9. Extrahepatic bile passages and pancreatic ducts. The gallbladder and part of the cystic duct have been opened to demonstrate that the mucous membrane of the gallbladder has a low, honeycombed surface, whereas the cystic duct has a sinuous lumen, with its mucous membrane forming a spiral fold (spiral valve). The right and left hepatic ducts are most commonly formed within the liver by a merging of the segmental/sectorial ducts from the right and left livers. In 95% of people, the hepatic ducts merge outside the porta hepatis to form the common hepatic duct. After passing posterior over the superior aspect of the 1st part of the duodenum, the cystic duct typically unites with the common hepatic duct to form the (common) bile duct. The bile duct descends posterior to the 1st part of the duodenum and head of the pancreas to enter the 2nd part of the duodenum from the left, merging with the main pancreatic duct to form the hepatopancreatic ampulla. [From Agur & Dalley (2005), Fig. 2.37, p. 130, with permission of the authors].

extrapolated from surrounding interlobular portal triads (terminal branches of the portal vein and hepatic artery, and initial branches of the biliary ducts). Although commonly said to be the anatomical units of the liver, classic hepatic "lobules" are not structural entities; instead, the lobular pattern is a physiological consequence of the interdigitation at the finest level of the afferent and efferent vessels and the pressure gradients between them, and is altered by disease affecting the gradients. Because the bile ducts are not central, the hepatic lobule does not represent a functional unit like acini of other glands. However, the hepatic lobule is a firmly established concept and is useful for descriptive purposes [13].

Hepatocytes secrete bile into the bile canaliculi formed between them. The canaliculi are well-defined intercellular spaces formed by apposed grooves in the adjacent non-sinusoidal surfaces of hepatocytes. The canaliculi are approximately 0.5 μm in diameter and drain centrifugally relative to the classic lobule. As they approach the portal areas (but still within the extrapolated boundaries of the lobule), bile canaliculi merge to form short *intrahepatic ductules* (*canals of Hering*), which may be said to be the finest branches (tributaries) of the biliary tree formed of non-hepatocytic cells. Relatively recent studies of ductular response to liver necrosis suggest, however, that the epithelial cells of the ductules may consist of or harbor *hepatic stem cells* [14].

With a caliber of about 1.0 to1.5 μm, the ductules



Porta hepatis and gallbladder

Fig. 1.10. The cystic artery supplies much of the extrahepatic biliary system (gallbladder, cystic and common hepatic and upper bile duct). Here the cystic artery is typical in arising from the right hepatic artery, but is doing so outside of the cystohepatic triangle, passing anterior to the common hepatic duct. Note that here it overlies the right hepatic duct, distal to which a right sectorial duct emerges from the bed of the gallbladder to enter the common hepatic duct. [From Agur & Dalley (2005), Fig. 2.54B, p. 148, with permission of the authors].

convey the bile to the portal areas where they drain to the smaller *interlobular biliary ducts* and then into large *collecting bile ducts* of the intrahepatic portal triad. These ducts range from 15 to 40 μm in diameter, with an epithelium that is cuboidal in the smaller ducts but thickens to columnar in the larger ones. As the ducts increase in size, the gain an increasingly dense investment of connective tissue, with an increasing number of elastic and then smooth muscle fibers as they approach the hilum of the liver.

Collecting ducts merge to form *segmental* and/or *sectorial bile ducts*. The sectorial ducts and their tributaries from the divisions or numbered segments of the liver join in a remarkably predictable pattern on the left, but have a much more unpredictable arrangement on the right. The right posterior (or lateral) sectorial duct usually drains segments VI and VII; the right anterior (or medial) sectorial duct usually drains segments V and VIII (fig. 1.7) [15]. The sectorial ducts formed within the right and left livers, respectively, merge to form a very short *right* and a much longer *left hepatic ducts* that most commonly emerge from the liver at the right end of the hilum (*porta hepatis*) (fig. 1.9 & 1.10). The right and left hepatic ducts thus typically drain the right and left (parts of the) liver, respectively. Right and left hepatic ducts unite near the hilum of the liver (within the substance of the liver in approximately 5% of individuals [17]) to drain into the *common hepatic duct*. Variations are frequently encountered, however. While most commonly the right segmental ducts unite to form a right hepatic duct, which in turn joins the left hepatic duct, in 20-30% of individuals the right posterior sectorial duct drains into the left hepatic duct (fig. 1.11A), and less commonly (3%) the right anterior sectorial duct drains into the left [18] (fig. 1.11B), or the two right sectorial ducts may join the left in a trifurcation [19] (6-12% – fig. 1.11C). In about a third of individuals, the right anterior segmental duct lies directly in the bed of the gallbladder, and may account for a postoperative bile leak. Intrahepatic bile ducts, along with the accompanying branches of the hepatic artery, usually course on the anterior aspect of the branches of the portal vein that they accompany, with the ducts superior [20].

The common hepatic duct usually carries all bile from the liver. Anomalous extrahepatic bile ducts are

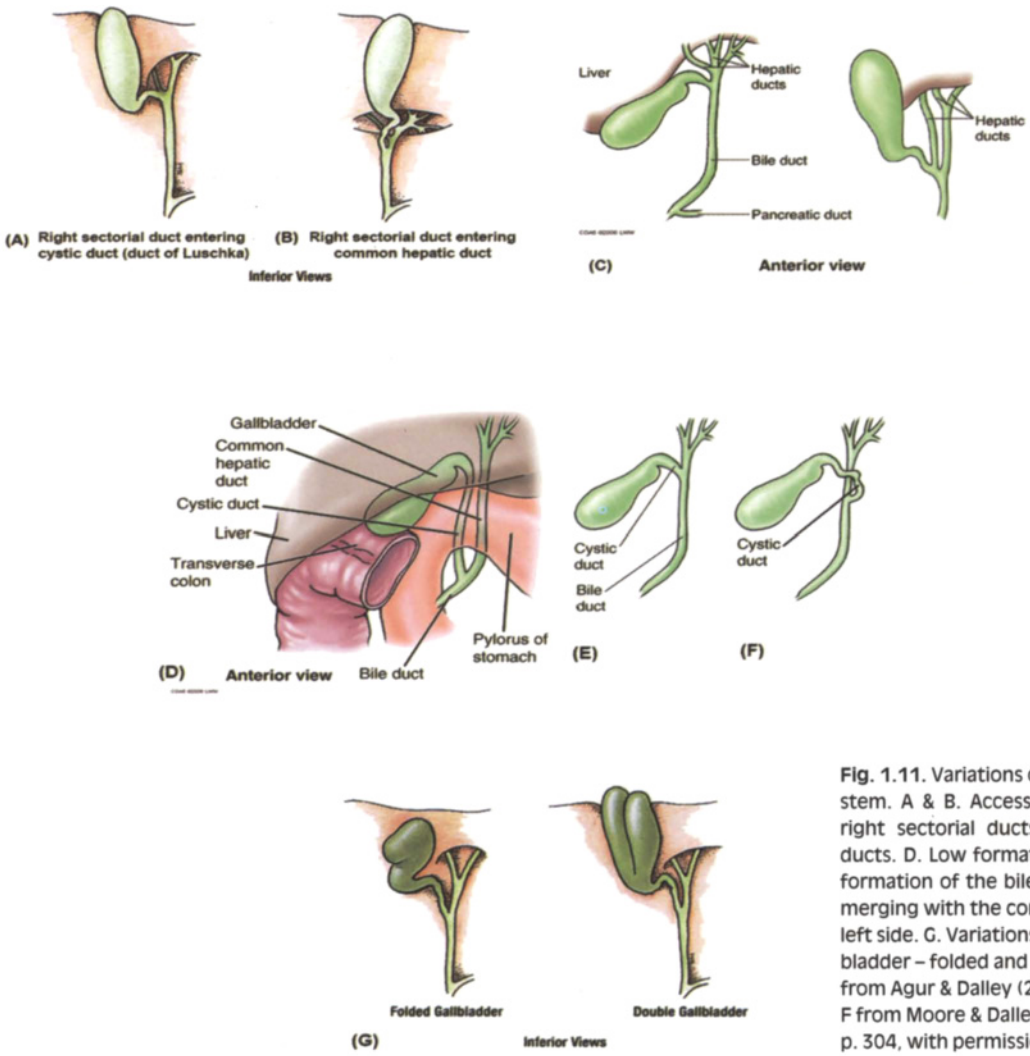


Fig. 1.11. Variations of the extrahepatic biliary system. A & B. Accessory hepatic ducts (aberrant right sectorial ducts). C. Variations of hepatic ducts. D. Low formation of the bile duct. E. High formation of the bile duct. F Sinuous cystic duct merging with the common hepatic duct from the left side. G. Variations in the formation of the gallbladder – folded and partially duplicated. [A, B & G from Agur & Dalley (2005), Fig. 2.59D-G, p. 151; C-F from Moore & Dalley (2006), Figs. B2.21 & B2.22, p. 304, with permission of the authors].

found in about one-tenth of the population, however. They may attach anywhere along the extrahepatic duct system. These anomalies are also most common on the right side, including the occasional *duct of Luschka,* also located within the bed of the gallbladder, that drains directly into the cystic duct [21] (fig. 1.11A). If such a duct is mistaken for the cystic duct and ligated, an area of the liver may be obstructed.

The common hepatic duct is typically about 3 cm long, with a wall that includes all the layers of the alimentary canal except the muscularis mucosae. It merges with the cystic duct to form the bile duct (formerly, *common bile duct*) that conveys the bile to the duodenum (fig. 1.9).

When the *sphincter of the bile duct* (*ductus choledochus* – fig. 1.12) is closed, bile backs up in the bile and cystic ducts, filling the gallbladder where bile is stored and concentrated between meals. Although parasympathetic innervation can open the sphincter of the bile duct [and the weaker *sphincter of the hepatopancreatic ampulla* (Oddi)] and contract the gallbladder, typically these are hormonally-regulated responses to fat entering the duodenum, dumping the accumulated bile into the duodenum. The cystic duct, then, is a two-way connection between the common hepatic duct and the gallbladder. The mucosa of the neck spirals into a fold, the spiral fold (*spiral valve*) [22] (fig. 1.9). The spiral folds help to keep the cystic duct open; thus bile can easily be diverted into the gallbladder when the distal end of the bile duct is closed or pass to the duo-

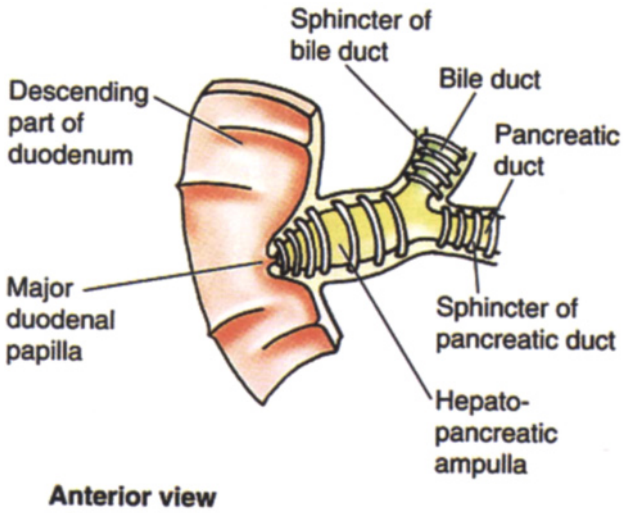


Fig. 1.12. The bile duct and pancreatic duct merge to form the hepatopancreatic ampulla, which opens into the descending (2nd) part of the duodenum. The sphincter of the bile duct (choledochal sphincter) controls the flow of bile while the weaker sphincter of the hepatopancreatic ampulla prevents reflux from the duodenum. [From Moore & Dalley (2006), Fig. 2.53C, p. 296, with permission of the authors].

denum as the gallbladder contracts. The fold also offers additional resistance to sudden dumping of bile when the sphincters are closed, and intraabdominal pressure is suddenly increased, as during a sneeze or cough. The cystic duct passes between the layers of the lesser omentum, often parallel to the common hepatic duct [23].

Cystic duct(s) can vary in shape, length, and number. The junction of the cystic duct and gallbladder, the observation of which is critical during laparoscopic cholecystectomy, may be abrupt and distinct, or tapered and indefinite. The cystic duct's length is variable (most commonly 3-4 cm), and it may be convoluted and folded on itself. In cholecystectomy, it may be beneficial to divide the cystic artery first to enabling straightening to gain more length from a folded duct. Accessory communications between gallbladder and duct may occur, either anomalous or consequent to stone erosion (*Mirizzi syndrome* [24]). Duplication of the cystic duct is rare, and must be distinguished from a Luschka duct.

The typically pear-shaped gallbladder is usually attached to the visceral surface of the liver by a fusion fascia (continuous with the fibrous *Glisson capsule of the liver*), with its fundus projecting from the liver's inferior border against the anterior abdominal wall at the intersection of the transpyloric plane and right midclavicular line (fig. 1.13) [25]. Its body and infundibulum and the cystic duct commonly surround the 1st part of the duodenum of three sides (anterior, superior, posterior), and in cadavers bile commonly stains these aspects of the duodenum bearing testimony to the relationship. In this position, its fossa provides an estimate of the divide between right and left livers on the visceral surface of the liver. *Cantlie's line* [26] (from IVC to notch for gallbladder fundus) demarcates the division on the diaphragmatic surface of the liver (fig. 1.7). When so attached to the liver, veins from the fundus and body pass directly into the visceral surface of the liver and drain into the hepatic sinusoids [27] (fig. 1.14). Since this is drainage from one capillary (sinusoidal) bed to another, it constitutes an addition (parallel) portal system. Cautery of these veins is often necessary following retraction of the gallbladder from the fossa. In the typical position, the unattached surfaces of the gallbladder are completely invested with peritoneum that is continued from the hepatic surface. Occasionally it is complete invested by peritoneum or suspended from the liver by a short mesentery ("mobile gallbladder", found approximately 4% of the time) [28]. Less commonly the gallbladder may be completely intrahepatic, on the visceral surface of the left lobe, or directed posteriorly into the hepatorenal recess of the subhepatic space (Morison pouch). The gallbladder itself may exhibit constrictions or be folded on itself forming a *phrygian cap* [29] (fig. 1.11G). Constrictions may be mistaken for the cystic duct, resulting in incomplete removal of a gallbladder. Partial internal septations and diverticula may be encountered and, less commonly, partial or complete duplications of the gallbladder. In the latter case, independent cystic ducts may enter any of the extrahepatic biliary ducts.

The bile duct forms in the free edge of the lesser omentum, most often by the union of the cystic duct and the common hepatic duct, superior to the duodenum (fig. 1.9). The length of the bile duct varies from 5 to 15 cm (most commonly, 7 cm), depending on where the cystic duct joins the common hepatic duct. The bile duct descends posterior to the superior (first) part of the duodenum (fig. 1.11D & 1.13) and lies in a groove on the posterior surface of the head of the pancreas. On the left side of the descending (second)

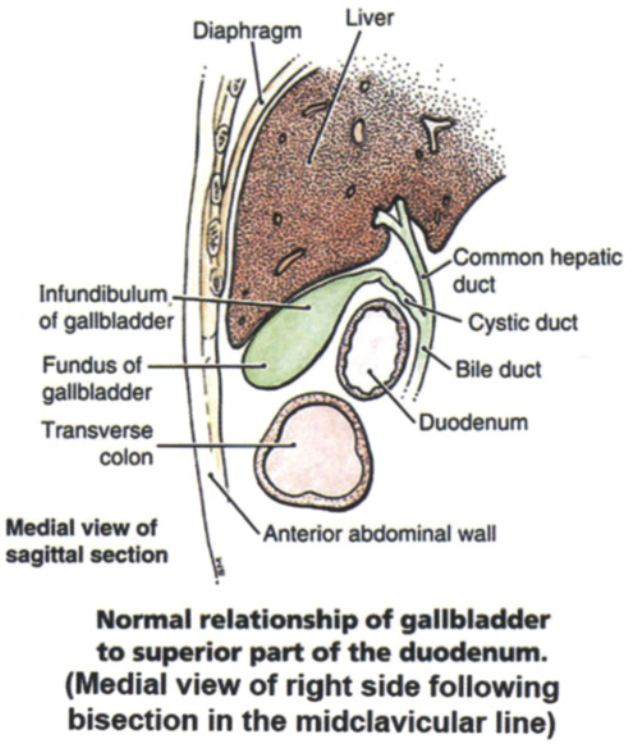


Fig. 1.13. Medial view of right side following sagittal section in the plane of the right midclavicular line demonstrating the normal relationship of gallbladder and extrahepatic biliary ducts to the superior (1st) part of the duodenum. [From Moore & Dalley (2006), Fig. 2.57, p. 302, with permission of the authors].

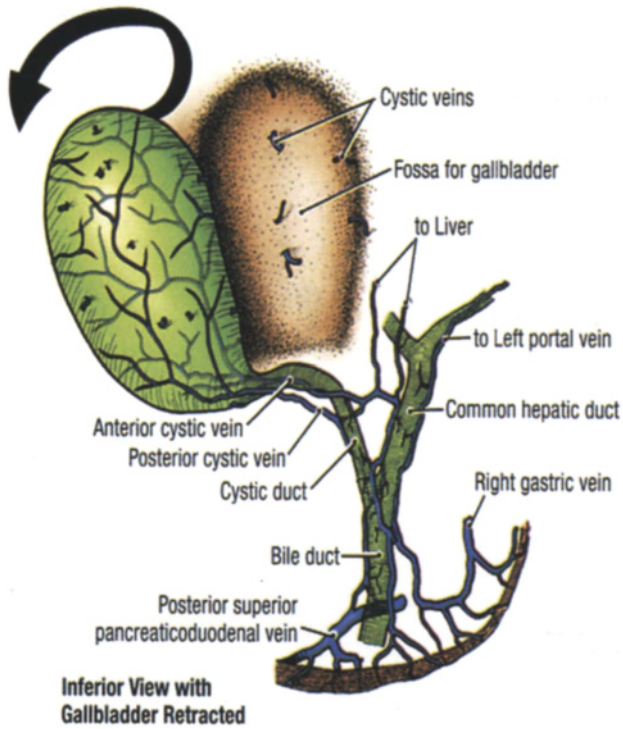


Fig. 1.14. Venous drainage of the gallbladder and extrahepatic biliary ducts. [From Agur & Dalley (2005), Fig. 2.54C, p. 148, with permission of the authors].

part of the duodenum, the bile duct comes into contact with the *main pancreatic duct*. These ducts run obliquely through the wall of this part of the duodenum, where they unite to form the *hepatopancreatic ampulla* (*Vater*), the dilation within the major duodenal papilla (fig. 1.12). The distal end of the ampulla opens into the duodenum through the *major duodenal papilla*.

Although the cystic duct usually joins the supraduodenal bile duct, it may join the biliary ducts at any location, including the junction of the hepatic ducts, or an aberrant hepatic duct (most commonly on the right) (fig. 1.11A, B, D-F). In about a third of individuals, a variable length of the cystic and common hepatic ducts run adjacent and parallel before merging, often bound together by a connective tissue sheath of varying density. Cholangiography may be required to determine the actual junction. Occasionally, the cystic duct enters the bile duct posteriorly or on the left side, passing posterior to the common hepatic duct to do so.

The gallbladder, cystic duct and uppermost bile duct are supplied by the cystic artery, a branch usually arising from the right hepatic artery, to the right of the common hepatic duct within the *cystohepatic triangle* (base of liver, cystic duct, and common hepatic duct, as opposed to the *Calot triangle*, in which the cystic artery replaces the base of the liver) [30] (fig. 1.10). In the 25% of individuals in whom the cystic artery arises outside of the cystohepatic triangle, it may arise from any portion of the hepatic artery and usually passes anterior to the hepatic duct. Venous drainage is of these structures is primarily via cystic veins that accompany the cystic artery and enter the portal vein [31]; however, veins from the portions of the fundus and body contacting the liver comprise a separate mini-portal system, mentioned previously (fig. 1.14).

The biliary tree is particularly rich in both the number and variety of variations, with the "normal" pattern occurring less than 70% of the time [32, 33].

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CHAPTER 2

SURGICAL ANATOMY OF THE LIVER

P. Kekis, B. Kekis

2.1. Introduction

The exterior morphology of the liver and the intrahepatic ramifications of its vasculature has been a subject for study throughout the ages. From historical data, which Stieda refers to, images of the liver come into light during the Babylonian era, i.e., 4-5000 B.C. [1].

One of the first reports concerning the study of the liver and its vessels anatomy is the monograph of Glisson in 1654 [2]. Through his famous Tables, Glisson was able to depict the course and the arrangement of the vessels of the liver (fig. 2.1b, 2.1c). We should not forget that his work constitutes the basic preliminary study on which our further knowledge has been supported on the anatomy of the liver.

Since then, lots of works have been published, mainly referring to the Glissonian system. Hyrtl (1873), Rex (1888), Goldsmith and Woodburn (1957), Hjortsjo (1948-1956), Elias and Petty (1952), Healey and Schroy (1954), Gans (1955) and Couinaud (1953-1957) are some of the people that have advanced our knowledge on the liver anatomy [3, 4, 5, 6, 7, 8, 9, 10, 11].

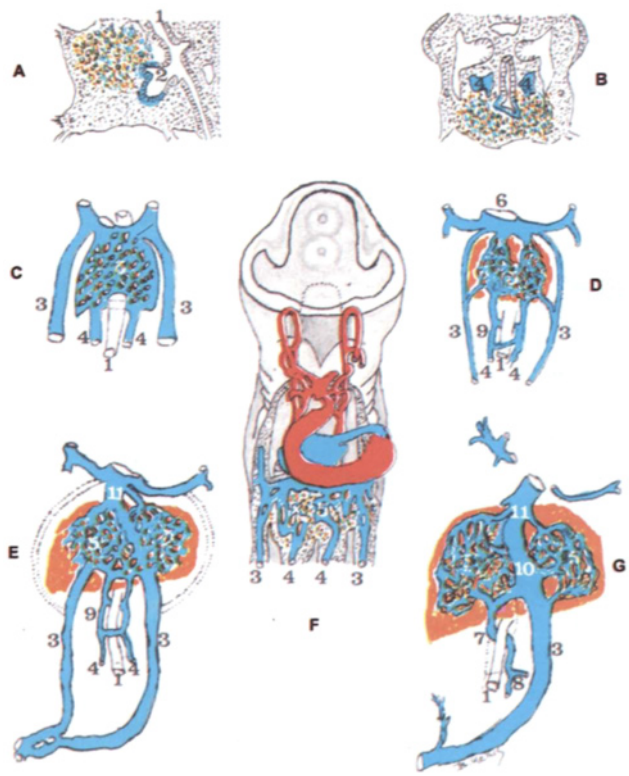

Fig. 2.1. Schematic evolution of the Omphalic and Vitelline or Omphalo-enteric vessels in the region of the liver during embryonic life. (A) Sagittal and (B) Transversal section at the region of the liver. (F) Abdominal aspect in a fetus of 3-5 weeks. (C) Four week fetus (D) Five week fetus (E) Six week fetus & (G) 7 week fetus and older.
1. Primitive enteric tube. 2. Hepatic diverticulum as well as diverticulum of extrahepatic biliary ducts. 3. Umbilical veins. 4. Vitelline or Omphalo-enteric veins. 5. Sinusoids of the liver. 6. Duct of Cuvier. 7. Portal vein. 8. Splenic and upper mesenteric vein junction, for the formation of the portal vein. 9. Anastomoses between Vitelline or Omphalo-enteric vessels. 10. Venous or Arrandius duct. 11. Hepatic veins. 12. Cardinal veins.

2.2. Embryology

Embryologically, the liver originates from a diverticulum of the fetal gastric tube [12, 13]. We distinguish a head, which is going to be differentiated to the hepatic parenchyma and the intrahepatic biliary ducts, as well as an abdominal part, which will form the gallbladder and the extrahepatic biliary vessels. Almost just after its formation, the part of the hepatic diverticulum protrudes cells in the visceral mesoblast. Those rapidly proliferating cells, form a mass that occupies a space between the pericardial cavity and the omphalo-enteric pedicle of the omphalic vesicle. From the beginning, the hepatic diverticulum is next to the pair of omphalo-enteric or vitelline veins, which extend parallel to the enteric tube. The afore mentioned veins give bran-

ches to the mass of the proliferating hepatic cells and, with anastomosis between themselves, form the sinusoids of the liver, which give the spongy aspect to the hepatic parenchyma. Therefore, in an embryo of 5 mm, the liver consists of a semilunar mass, which is found and grows upwards and towards the abdominal cavity from the gut. The two lateral extensions of the initially semilunar liver come in contact with the omphalo-enteric or vitelline veins, which they finally get enclosed within.

At the beginning of the embryonic life of the cyema, there are three vein systems (pairs), [3] i.e.: 1st the pair of Omphalic veins, originating from the chorion; 2nd the pair of Omphalo-enteric or Vitelline veins, originating from the omphalic vesicle and 3rd the pair of Cardinal veins, originating from the body of the foetus. The latter extrude in the sinus venosus of the fetal heart from a common stem, called duct of Cuvier (fig. 2.1). The continuously enlarging liver obviously largely affects the final formation of both the umbilical and the vitelline veins, from which finally the system of the *Portal vein* as well as the *Hepatic veins* originate.

The pair of the Vitelline *veins* follows the umbilical duct and enters the body of the foetus, in a capital course, parallel to its enteric tube and finally extruding in the sinus venosus. During the 4th fetal week, the medium part of the vitelline veins develops –both within the vitelline veins and within the liver– multiple anastomoses, which consist later the sinusoids of the liver. Upon the developmental evolution, the vitelline veins form more anastomoses, especially three bearing particular significance. The first is formed capitally and within the liver. The second-median is formed out of the liver and below the duodenum and the third one is sited caudally to the other two and above the duodenum. The latter two form a kind of ring around the duodenum, the remaining part of which after the evolution, has the shape of an S and forms the *Portal vein,* which meets the *Upper Mesenteric* and the *Splenic vein* (fig. 2.2).

The capital part of the vitelline veins –found between the sinusoids and the sinus venosus– and, especially, the branches –originating from the remaining stem of the right vitelline vein– consist the *Hepatic veins.* The *Umbilical veins,* bringing blood from the placenta through the umbilical cord, extrude in the sinus venosus. As the liver grows laterally, the umbilical

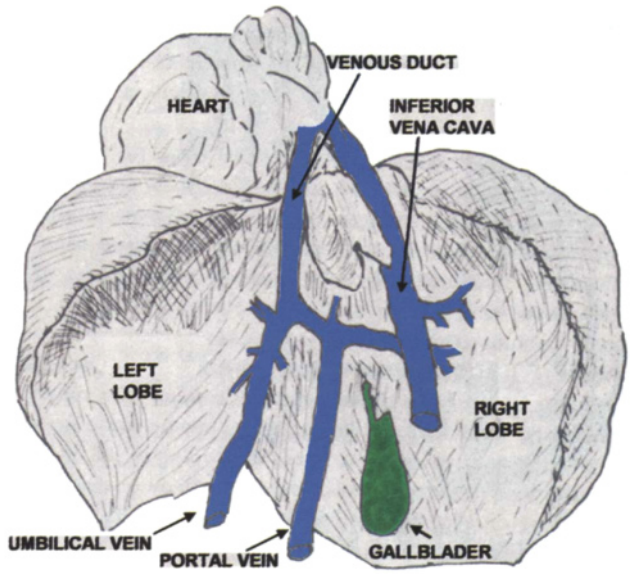

Fig. 2.2. Relations of the veins in human liver upon birth.

veins come rapidly in contact with it and their blood, finding a shorter course, enters directly the heart through the hepatic sinusoid. When all the blood of the umbilical veins enters the liver, and this happens in a foetus of 6 mm, the whole right and the central part of the umbilical veins become atrophic and they soon disappear. In the 7 mm foetus, the remaining distal part of the left umbilical vein is already large enough and remains like that until birth, when it occupies the free end of the falciform ligament and post-foetally forms the round ligament.

Due to the fact that the initial course through the right vitelline vein within the liver is larger than the left one, the blood from the left umbilical vein follows this easier larger course towards the heart. But, as the right lobe of the liver increases, the length of the haematic course increases continuously, thus forming a diagonal haematic flow, independent of the flow of the hepatic sinusoid towards the heart. This diagonal course is the so called duct venosus, which represents the direct haematic course between the placenta and the heart, bypassing at a certain degree the sinusoid of the liver. Thus, the left umbilical vein from one part, sends through the venous duct blood directly to the heart and, from the other, sends and receives an anastomotic branch towards the portal vein (fig. 2.2).

The foetus receives blood from its mother through

the umbilical vein, which continues as a venous duct up to the heart, bypassing the sinusoids of the liver. As the development of the liver lobes continues, the venous duct is shifted abdominally out of the hepatic parenchyma, occupying the left sagittal sulcus. Just after delivery, probably due to the presence of a sphincter mechanism, the venous duct closes and the round ligament is formed. This ligament includes the obstructed umbilical vein and ends at the umbilicus, where the lateral umbilical ligaments begin, including the residues of the umbilical arteries, which are branched at the anterior abdominal wall and communicate with the hypogastric arteries.

2.3. Liver Topography and Gross Anatomy

2.3.1. General Description and Topography

The liver is the biggest of the body's organs, weighs 1400-1600 g in adult men and 1200-1400 g in women, representing about 1/40 of the total body weight. During the neonatal period, when the liver weighs about 150 g, it is relatively bigger (about 1/20 of the total body weight) and occupies 2/5 of the abdomen, a fact that is mostly due to the left lobe, which is bigger [14, 15, 16].

The liver is in the upper abdomen and occupies the right hypochondrium and part of the epigastrium. Its left lobe –varying in size from one person to the other– may extend to the left hypochondrium (fig. 2.3). In a normal person, upon deep inhalation, the lower liver edge can be sometimes palpated below the right costal margin. Alterations of the liver size, position, consistency, as well as the presence of oncotic processes in its parenchyma can modify the palpation site of its lower edge. Upon percussion, it is proper to assume that the lungs cover the upper part of the liver and, respectively, we can assume that the liver covers part of the intestine (right colic loop, part of the small intestine), as well as parts of the stomach.

The liver projections on the body surface differ depending firstly on the position of the person examined and secondly on the person's body shape; especially on the thorax shape itself. The liver is under the diaphragm and the upper edge of the fifth rib, about one centimeter below the breast nipple, in men, by the right lateral line of the body. The upper edge of the left

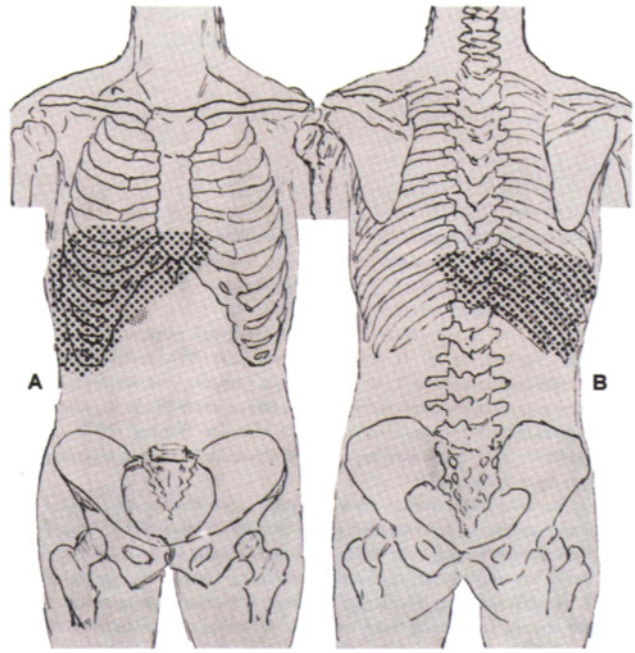

Fig. 2.3. Liver projections on the body' surfaces. (A) Anteroposterior. (B) Posteroanterior.

lobe protrudes at the level of the upper edge of the sixth rib and at this site only the diaphragm separates the liver and the apex of the heart. Part of the left lobe is covered by the sides of the left hypochondrium (fig. 2.3).

In the epigastrium, the liver is not covered by the thoracic wall and extends at about three to four fingers below the level of the xiphoid process at the midline. The anterior edge of the liver is parallel to the right costal margin and at times at the level of the right lateral lime of the body, approximately at the level of the pylorus, crossing it. Villemin et al have studied extensively the morphologic and topographic variations of the normal organ [17].

2.3.2. Liver Ligaments and Surfaces

The liver shape is that of a triangular pyramid, the top of which is formed by a thin flattened part, the left lobe. The base is formed by its right lateral surface, which is located under the right septum and the right thoracic wall. The sides of the pyramid are formed by its anterior, posterior and lower surfaces. The bounder between the anterior and lower surface is the anterior edge of the liver. The liver is covered by peritoneum, ex-

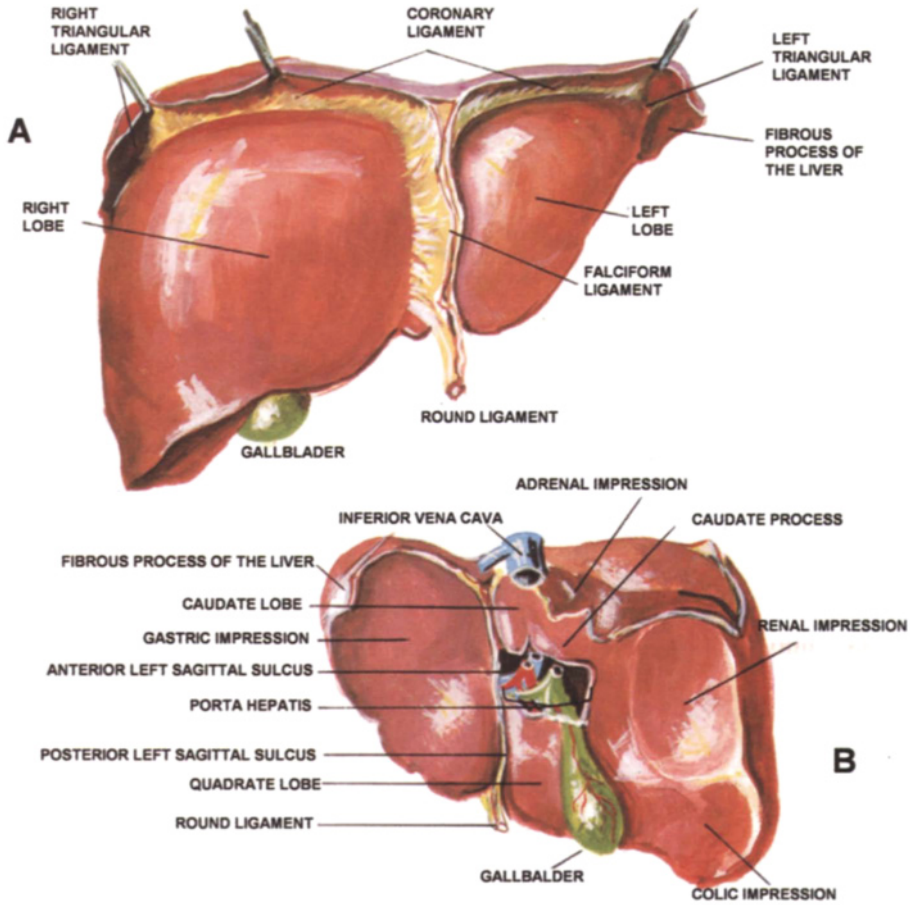

Fig. 2.4. Anterior (A) and inferior (B) surface of the liver (Modified. From "The CIBA collection of Medical illustrations" Frank Netter, 1957 with permission of Novartis).

cept of the gallbladder region, the hilum, the region surrounding the course of the inferior vena cava and a region in contact to the right adrenal gland. The peritoneal reduplications, which extend from the anterior abdominal wall and the diaphragm to the liver, form the ligaments of the organ that maintain the organ at its place [14, 15].

The horizontal reduplication of the peritoneum forms the coronary ligament, which becomes visible if we pull the liver downward, away from the diaphragm (fig. 2.4). The free right edge of the coronary ligament forms the right triangular ligament, while its left end forms the left triangular ligament, which adheres to the apex of the left lobe and reaches the Fibrous Process of the liver, which is steadily adhered to the diaphragm. This process represents a shrunk part of the left lobe, which in the neonate contains hepatic substance and in the adult only residues of biliary ducts (aberrant bile ducts) and blood vessels. At the median part of the coronary ligament, another peritoneal reduplication begins, formed by the Falciform ligament; the said reduplication extends from the liver to the anterior abdominal wall and between the diaphragm and the umbilicus. The lower edge of the ligament forms the round ligament that ends at a groove vertical to the lower liver surface, which as it continues backwards as a sulcus meets the umbilical vein or its residues.

If the anterior edge of the liver is turned upwards, the hepatogastric ligament (lesser omentum) is revealed, (fig. 2.5). This hepatogastric ligament is formed by a reduplication of the peritoneum, which extends from the first part of the duodenum, the minor ventriculi arch and the diaphragm towards the liver, reaching the hilum and the left sagittal sulcus of the posterior surface.

At this point, the two laminae of the peritoneum separate in order to allow the passage of vessels entering the liver and coming out of it. At the right free end of the lesser omentum its laminae that meet again are rein-

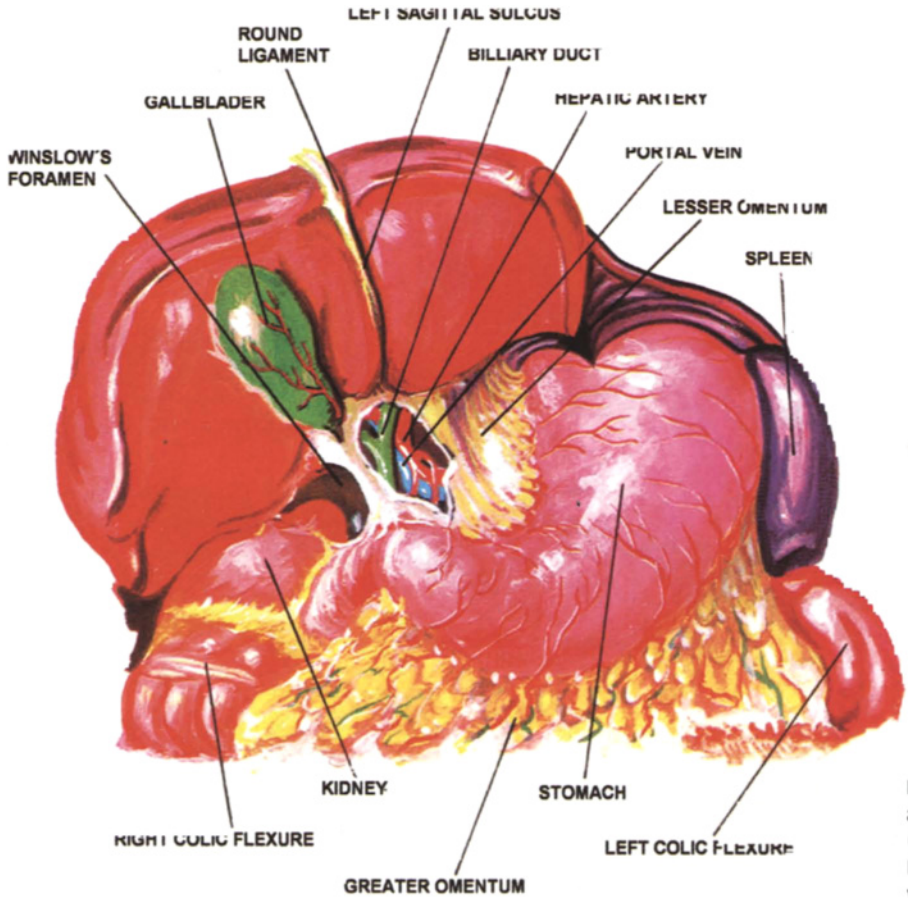

Fig. 2.5. Lifted anterior margin of the liver and anatomic relations to upper GI organs (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

forced in order to form the hepatoduodenal ligament, which constitutes the anterior wall of the epiploic foramen (Winslow's foramen), through which one can enter the lesser sac. The posterior wall of this cavity consists of the inferior vena cava and the caudate lobe of the liver. Adjacently to the right edge of the hepatoduodenal ligament, is the course of the biliary duct, on its right is the hepatic artery and behind of them two is the portal vein (fig. 2.5).

The *lower surface of the liver* is separated from the posterior one by the posterior lamina of the coronary ligament on the right and by the adherence of the lesser omentum on the left. It *presents two sagittal sulci,* the right and the left sulcus and a transversal one: the hilus of the liver (fig. 2.4). The hilus of the liver contains the portal vein, the branches of the hepatic artery and the biliary duct, as well as lymph vessels, lymph nodes and nerves. The *left sagittal sulcus,* which is at times enclosed in a tube, anteriorly contains the round ligament and posteriorly, as it is narrow, receives a fibrous bundle, the venous ligament; at its one end it continuous to the round ligament and at the other to the left hepatic vein. This venous ligament represents the obstructed branch of the umbilical vein (ductus venous or Arandius duct), through which, in the foetus, part of the blood of the umbilical vein is transported through the left hepatic vein directly to the inferior vena cava, bypassing the hepatic circulation. The *right sagittal sulcus,* which is larger, acting like a fossa, receives in front the gallbladder and contains posteriorly the inferior vena cava and the junctions with the hepatic veins. The lower and posterior surface of the liver present colliculi due to the presence of various grooves, as well as various impressions from the adjacent organs. Among the two sagittal sulci and the hilae of the liver, the square part is in front and the caudate or spiegelian lobe is at the back. Its forward extension, separating, as an oblique right crest, the fossa of the inferior vena ca-

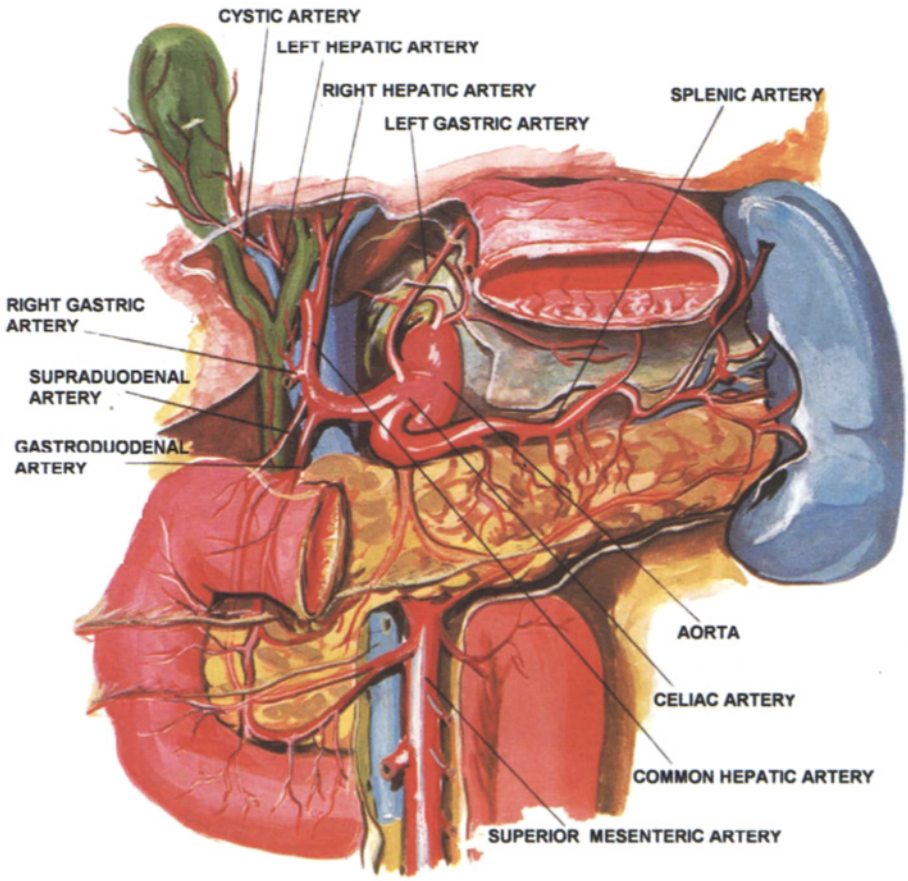

Fig. 2.6. Arterial blood supply of the liver - Anterior view. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

va from the cystic, is called *caudate process* (fig. 2.4). On the lower surface of the liver and, specifically on its right part, three impressions are produced: the colic, from the right colic loop and the transverse colon; the duodenal, from the descending part of the duodenum; and the renal, from the right kidney. On the median part, of the square lobe, the pyloric impression is produced, corresponding to the pyloric part of the stomach. Finally, on the left part, the gastric impression is seen, produced by the anterior surface of the stomach.

On the posterior surface of the liver, on the right part, there is a triangular impression by the inferior vena cava and the adrenal gland, just behind the renal impression; on the left, there is a groove-like impression, the oesophageal impression, which corresponds to the celiac part of the oesophagus.

2.3.3. Vascular Elements

2.3.3.1. *Hepatic Artery*

The exceptionally interesting studies by Michels (1953-1955) showed a certain variety in what concerns the arterial blood supply to the liver and the extrahepatic biliary ducts [18, 19]. According to the conclusions of the afore mentioned researcher, typically, in a 55% of the cases of cadavers examined, the celiac artery or axis, was a very short, thickened arterial stem, originating from the abdominal aorta almost just below the aortic foramen of the diaphragm. It extends horizontally forwards and then it divides almost immediately in three branches: the *left gastric,* the *splenic* and the *hepatic artery* (fig. 2.6) [20].

The hepatic artery, a medium size branch, follows a forward course to the right, in order to enter the right edge of the lesser omentum in the hepatoduodenal ligament, occupying a position on the right of the biliary

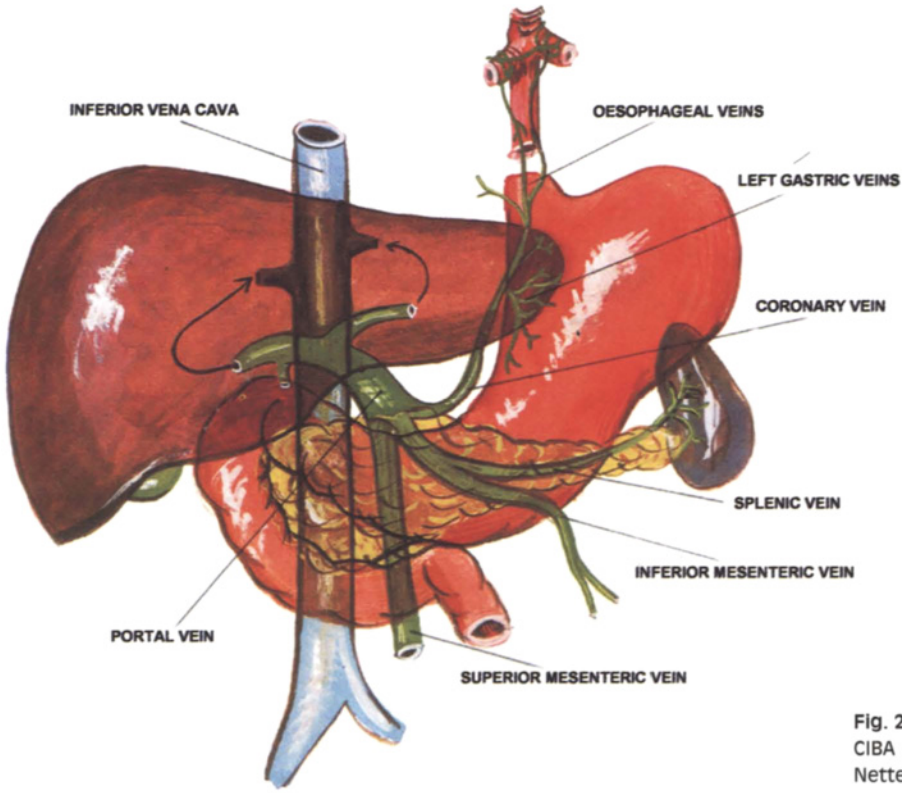

Fig. 2.7. Portal Circulation (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

duct and in front of the portal vein. Along its course to the hilus of the liver, the *duodenogastric,* the *upper duodenal* and the right gastric arteries originate. After the origin of the right gastric artery, its continuation is known as *Common hepatic artery,* which is usually divides in *right, left* and *median artery;* the latter usually originates from the left one. In general, the right hepatic artery passes behind the biliary duct in order to enter the triangle of Calot, which is formed by the biliary duct, the cystic duct and the liver [21].

Healey reports that in 56% of the cases the hepatic artery was solitary [22]. This percentage concords with Michels' conclusions, who, in a study of 200 cadavers found a solitary hepatic artery in a percentage of 58,5%. At times, branches of the hepatic artery can be found very short or totally absent; in case they are absent, a pair of vessels may replace the absent branch. An ectopic origin of a hepatic artery or of one of its branches can be on the left of the gastric or celiac artery or of the upper mesenteric artery.

Healey, in their series observations, found small anastomotic branches among the left and right hepatic artery, at a percentage of 25% [22]. However, these anastomoses, were extraparenchymal, subcapsular and very small, localized as follows:

(a) At the region of the hilae, by the base of the caudate lobe and tiny branches of arteries of the paramedian lobes bilaterally or even between the two arteries of the caudate lobe.
(b) At the left sagittal sulcus among the branches of the left paramedian and the left lateral lobe.
(c) On the right of the portal vein, between the arteries of the caudate lobe and the branch originating at the right hepatic artery.

2.3.3.2. *Portal Vein*

The portal vein, which is formed by the junction of the upper mesenteric and the splenic vein, is usually located behind the head of the pancreas, at the level of the second lumbar vertebra. Its course extends behind the first part of the duodenum and continuous on the right of the lesser omentum through the hepatoduodenal ligament and then, after dividing in two main branches, the *right* and the *left* branch, it enters the liver through its hilus (fig. 2.7) [14, 16, 23].

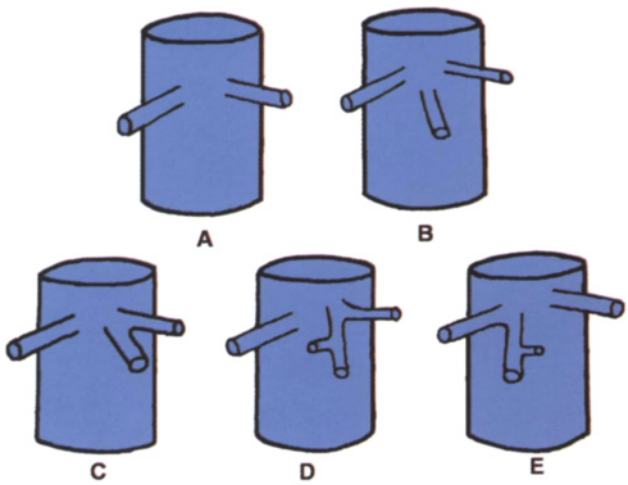

Fig. 2.8. Various ways of extrusion of the three hepatic veins in the inferior vena cava. The commonest variation is type C.

The Coronary vein, which is formed by the left gastric vein and the net of oesophageal veins, extrudes too in the portal vein. In addition, it meets the pyloric vein, which together with the coronary vein, form a loop. The left main branch of the portal vain meets the paraumbilical veins and at times one umbilical vein presents.

The Portal vein, through the coronary, the short gastric veins and the system of the azygos major and azygos minor on one hand and the lower mesenteric and the paraumbilical veins on the other, indirectly communicates with the superior and inferior vena cava, by-passing the hepatic circulation. This is of specific significance in case of liver impairment, when one might say that the afore mentioned bypass consists, at least in the first stages, an ideal solution for the circulation.

2.3.3.3. *Hepatic Veins*

The blood is drained from the liver through the hepatic veins. An anatomic study of the hepatic veins in cadavers showed a large variety in the way they *extrude* in the inferior vena cava. There is always a large right Hepatic vein and a smaller one on the left that abduct the blood from the respective lobes. The varieties concern, typically, the rather peculiar behavior of the third, i.e., the median Hepatic vein. This does not only differ in what concerns the region of its *extrusion,* but also in its relation to the right and left hepatic veins (fig. 2.8) [14, 16].

Practically and, particularly in the case of an hepatectomy, the determination of the relation of the median to the left hepatic vein is of great interest and it is considered favorable if this can be defined before one proceeds to the surgical preparation of the hepatic veins.

In addition to the three main hepatic veins, there are also two other groups of hepatic veins, called short veins. The first group –*Left anterior*– comes out of the caudate lobe, consists of two or three veins and drains the venous blood from the caudate lobe *only* (fig. 2.9).

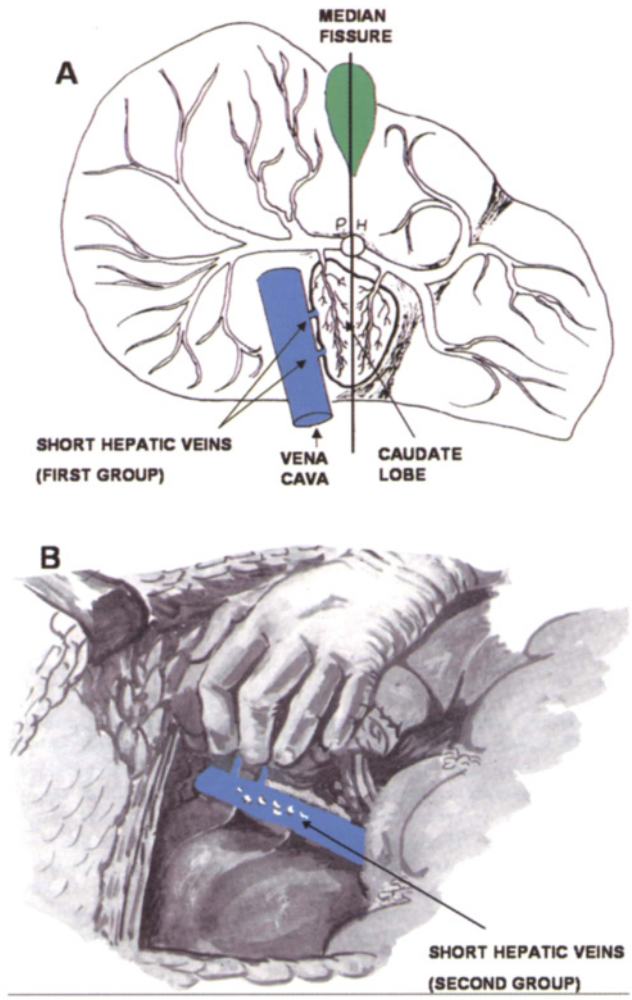

Fig. 2.9.
A) Short hepatic veins – First group.
B) Short hepatic veins – Second group. In the schematic picture, the right lobe of the liver has been pushed back by the hand. We can distinguish the short hepatic veins ligated by their extrusion in the inferior vena cava.

The second group *-Right anterior-* comes out of the celiac part of the right posterior lobe of the liver and extrudes directly in the anterior surface of the inferior vena cava. Their number varies from 4 to 12 branches. In case one of those is quite large, then the size of the right hepatic vein is found relatively smaller than usual.

2.3.4. Lymphatics

Human liver has an abundant network of lymph vessels, found subserously, as well as deeper [13]. The subserous vessels communicate with the lymph vessels of the gallbladder. The deeper lymph vessels follow the course of the branches of the portal vein and the hepatic artery up to their most distal endings. The lymph from the lymph nodes that are found by the hilae of the liver is drained through these vessels. In humans, lymph vessels that follow the branches of the hepatic veins have been noted, draining lymph from the lymph nodes that are found at the end of the inferior vena cava within the thoracic cavity.

2.3.5. Innervation

Sympathetic fibers, issuing bilaterally from the 7th and 10th thoracic ganglion, meet at the semilunar ganglion of the solar plexus with fibers from the right phrenic nerve to form the hepatic nervous plexus [14, 16]. This surrounds the hepatic artery as a thin wrap, sending branches to the biliary duct too. The innervation of the arteries is mostly performed evenly by the sympathetic and parasympathetic nervous system. Several nervous fibers, following the vessels and biliary ducts up to their detailed branches, send branches that innervate the liver lobuli. These intralobular fibers, which are thin and cirsoid, complicate the trabeculae, ending among the hepatic cells.

2.4. Liver Lobes and Segments

2.4.1. Anatomic Lobes

The classic descriptions characterize the liver as having four lobes: right, left, quadrate and caudate. The liver is divided into right and left anatomic lobes by the attachment of the falciform ligament on the anterosuperior surface. On the visceral surface of the liver, the fissures for the ligamentum venosum and ligamentum teres provide the demarcation. The quadrate lobe is demarcated in the visceral surface of the liver by the gallbladder fossa, porta hepatis, and the portoumbilical fissure (fig. 2.5). The caudate lobe is demarcated by the groove for the IVC and the fissure of the venous ligament. The right portion of the caudate lobe is continuous with the right lobe by the caudate process, which forms the superior boundary of the epiploic foramen. The quadrate lobe has been considered as a subdivision of the right anatomic lobe. The authors use the term lobes in discussions of quadrate and caudate anatomy as a matter of convenience; these structures are not true lobes [14, 16, 24, 25, 26].

2.4.2. Functional Lobes and Segments

2.4.2.1. *Fissures*

Separating levels of the hepatic lobes and parts based on the vessels of the Glissonian system.

Median Fissure (Cantli's Line)

The division of the liver in two lobes is possible between the endings of the left and right branch of the portal vein [27, 28]. The position of the median fissure, which separates the right and left lobes, can be clearly defined by filling of the left and right portal vein with a Vinyl Acetate solution of different color (fig. 2.13). The median fissure starts at the notch of the gallbladder in the liver, extends forwards and above the liver and ends on the left of the inferior vena cava at the height of the extrusion of the hepatic veins. Topographically, it starts on the left of the bed of the gallbladder at a percentage of 65%, against a mere 8% on its right, whereas in a 27% it passes from the middle of the gallbladder. The position of the median fissure in relation to the bifurcation of the portal vein was found as follows: on the left of the bifurcation in 72% of the preparations, on the right in 18% and by the bifurcation in 10% (fig. 2.10).

In most cases the median fissure is linear, but in some it can also be a curve. In general, the *median fissure passes from the middle of the caudate lobe and divides it into a right and left part. From the figure we can realize that the square lobe mentioned in the classic books belongs to the left lobe.* The median fissure is constant and separates completely the arterial, venous and biliary systems in each lobe.

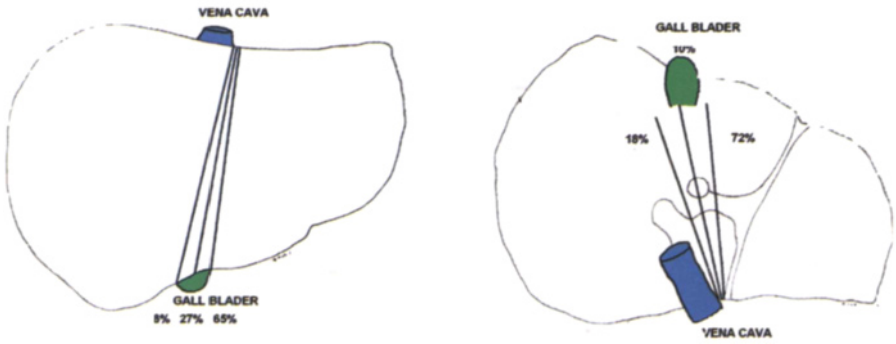

Fig. 2.10. Median fissure (Cantli's Line).

Left Interlobar Fissure

This fissure divides the left lobe in a paramedian and a lateral one. The *latter is the one that the classic books of anatomy describe as left lobe.* This fissure starts by the umbilical notch and extends from the front upwards and slightly inwards, following a course towards the left hepatic vein at the site, it enters the inferior vena cava. The adherence of the falciform ligament can be considered as the guiding point on the upper surface of the liver, although it is often found slightly on its left. On the lower surface of the liver, it is indicated by the left sagittal sulcus.The left interlobar fissure should be considered in most cases linear (fig. 2.11).

Intrasegmental Fissure of the Left Lobe

This fissure starts at the point where the left hepatic vein extrudes to the inferior vena cava, forming an acute angle with the left interlobar fissure. Its course is oblique and slightly horizontal along the left lateral lobe, ending a point found on the edge between the left and median third of the rim of the left lobe. It divides the left lateral lobe in upper and lower lateral parts (fig. 2.11).

Right Interlobar Fissure

The right interlobar fissure divides the right lobe in a paramedian and a right posterior one. This fissure starts approximately at the point where the right hepatic vein extrudes to the inferior vena cava, it follows an oblique, rightward course, ending at a point found on the edge between median and right third of the rim of the right lobe [29]. *The position of the fissure varies significantly,* mostly depending on the size of the right paramedian lobe (fig. 2.11).

Intrasegmental Fissure of the Right Lobe

This fissure starts approximately at the middle of the right interlobar fissure, forming with it an angle of about 80°-85° (with the opening of the angle looking down), and follows an almost transversal course in order to end at a point that divides the posterior right lobe in upper and lower posterior parts (fig. 2.11).

2.4.2.2. *Lobes and Segments of the Liver Based on the Vessels of the Glissonian System*

Based on the dividing levels (fissures) of the Glissonian system, we distinguish in the following lobes and segments (fig. 2.12, 2.13, 2.14):

The liver is divided in two lobes, the *Left* and the *Right,* divided by a fissure extending from the left rim of the impression of the inferior vena cava to the impression of the gallbladder fossa. This fissure is outright and is not crossed by neither the hepatic artery nor the portal or branches of the biliary vessels.

The right lobe is then divided by the right intralobular fissure in two lobes, the *Right paramedian* and the *Right posterior* one; the latter, due to the right intrasegmental fissure can be distinguished in the *Right posterior upper segment* and the *Right posterior lower segment.*

The left lobe is divided by the left intralobular fissure, which is on a plane, passing above and along the adhesion of the falciform ligament on one hand and below and along the left sagittal sulcus on the other, in two lobes, the *Left paramedian* and the *Left lateral* one. The latter is divided by the left intrasegmental fissure in the *Left lateral upper segment* and the *Left lateral lower segment.*

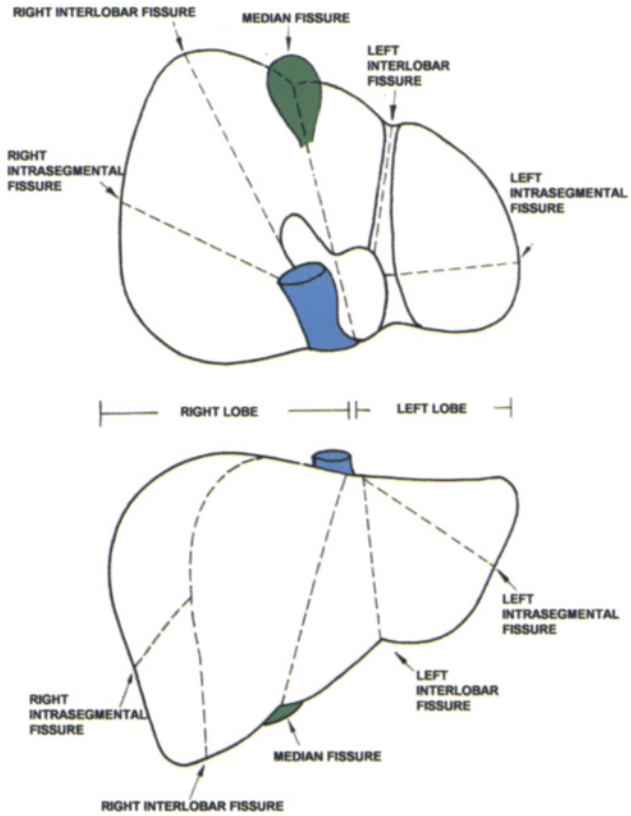

Fig. 2.11. Fissures of the liver based on the Glissonian system.

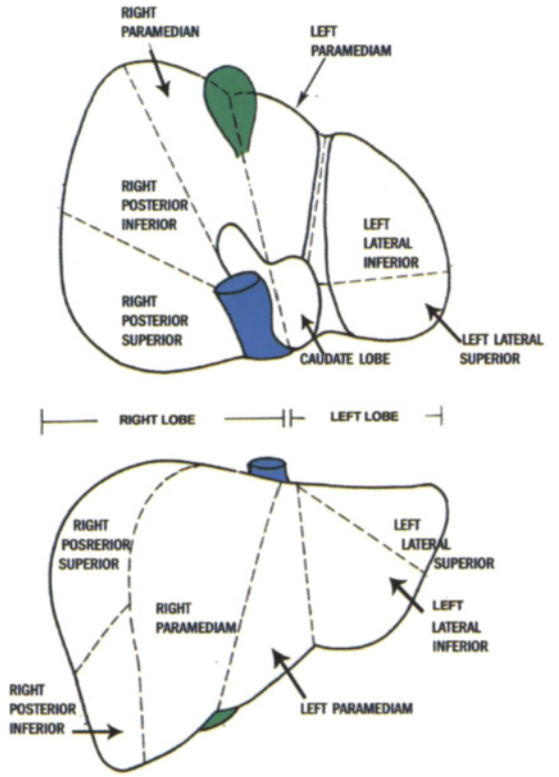

Fig. 2.12. Lobes and segments of the liver based on the vessels of the Glissonian system.

The *Caudate lobe,* which is delineated laterally by the posterior parts of the sagittal sulci and in front by the hilae of the liver, is divided by the median fissure in a *Left* and a *Right segment,* each of which has its own blood supply from the left and right portal veins and the hepatic artery, respectively.

The dorsal liver sector has been recognized as the parenchyma surrounding the vena cava and is quite independent of the remaining liver [30, 31, 32]. It is that part of the organ in which the hepatic portion of the vena cava develops and its venous outflow remains strictly connected with the vena cava by means of multiple, not dissectable effluents as well as with the main hepatic veins. Therefore, this sector is a major shunt between the main hepatic veins and the inferior vena cava, which enlarges and ensures venous drainage for survival, in cases of Budd-Chiari syndrome [33]. The dorsal sector consists of two segments: a left one (segment I) corresponding roughly to the caudate lobe and a right one (segment IX) in front and on the right of the vena cava, including the so-called caudate process. The identification of a dorsal liver sector and its detailed anatomy is of primary importance for surgical practice, since hilar cholangiocarcinoma at the confluence extend to the dorsal sector and makes resection of this sector necessary for efficient therapy and due consideration of the pedicles of segment I and IX is required to perform successful hemihepatectomy as well as liver partition for split liver grafting [34, 35].

At the close of the last century, several investigators, including Couinaud and coworkers, used the term segment IX for an area of the dorsal sector of the liver close to the IVC. In 2002, however, Abdalla, Vauthey and Couinaud wrote, "Because no separate veins, arteries, or ducts can be defined for the right paracaval portion of the posterior liver and because pedicles cross the proposed division between the right and left caudate, the concept of segment IX is abandoned". The genesis

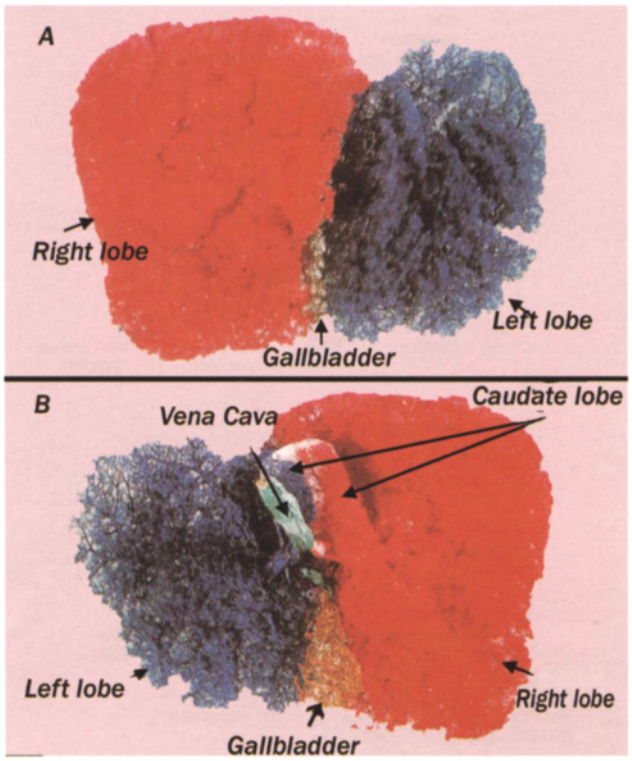

Fig. 2.13. The right (red) and left (blue) lobe of the liver can be clearly defined by filling of the left and right portal vein with a Vinyl Acetate solution of different colour.

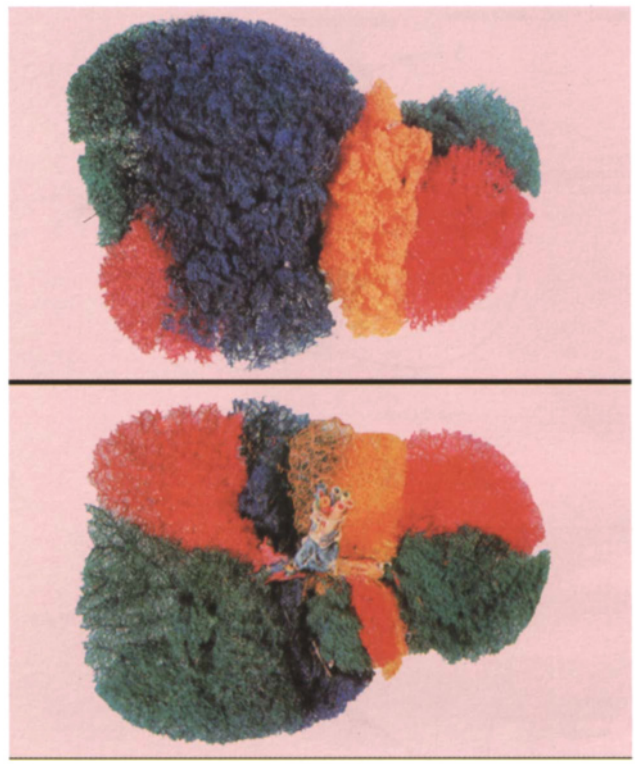

Fig. 2.14. Lobes and segments of the liver. Each segment has been filled with Vinyl Acetate solution of different colour.

and death of segment IX is found in articles by Couinaud and other investigators [36].

2.4.2.3. *Nomenclatures of the Lobes of the Liver*

While all of the researchers agree as far as the intrahepatic division of the liver in lobes and segments is concerned, on the other hand there is much disagreement among them as to the exact borders of the lobes and segments as well as their names.

Mostly, the main disagreement among the various writers is whether the left and right paramedian lobes should be divided into upper and lower segments. Further more, this disagreement extends to the different nomenclatures of the particular lobes and sections of the liver [26, 37, 38, 39].

Rex (1888) divided the liver in two lobes, a right and a left. Each one of them is further divided in to two segments (fig. 2.15). He divided the right lobe, by a sagittal intrahepatic fissure in two segments, an anterior and a posterior one. He completely ignored the transversal fissure of the posterior lobe that divides it in an upper and lower segment. He also spoke of a sagittal fissure originating from the left lateral lobe, whereas the majority of researchers today agree on the presence of a transversal fissure which divides this lobe in an upper and lower segment [4].

Hjortsjio in 1948, he divided the liver into left and right lobes, denying the existence of a transversal fissure proportional to that of Healey and Couinaud [23]. On the contrary, he described a cross-sectional fissure at the right paramedian lobe as well as of another similar one at the left lateral lobe.

Healey and Schroy divided the liver into two lobes and thereafter each of those divided by a transversal fissure and a cross-sectional one, subdividing them into sections and areas (fig. 2.15) [8, 9].

In the division of the liver into lobes and sections by the afore mentioned writers, it is worth noticing the marked permanent existence of the transversal fissure

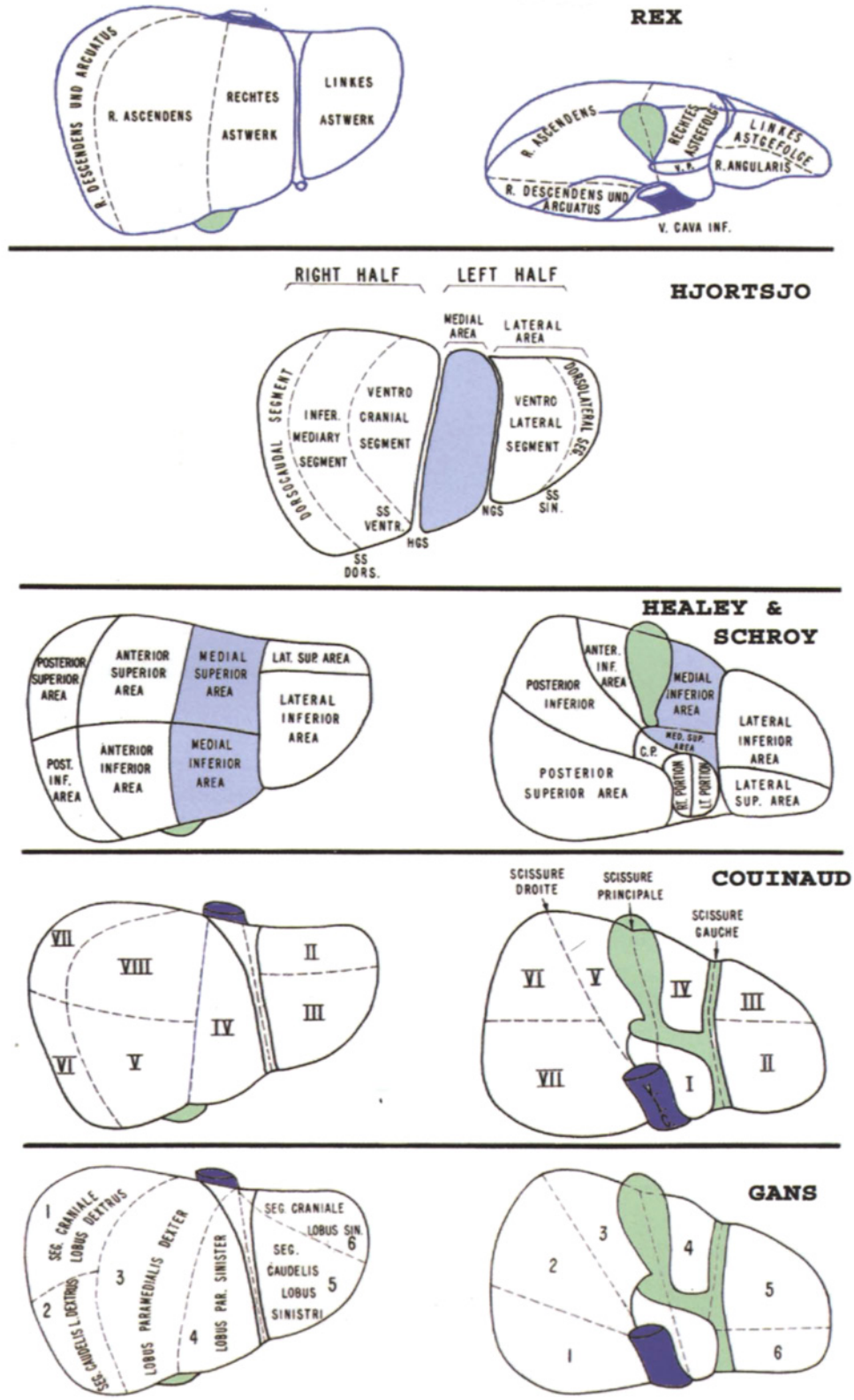

Fig. 2.15. Lobes and segments of the liver according to Rex, Hjortsjo, Healey and Schroy, Couinaud and Gans.

by the left and right paramedian lobes, a fact never mentioned by other investigators, as Couinaud and Gans. Regarding the proposed nomenclature of the sections by Healey and Schroy, we dare to say that this does not respond to their rational topographic positions and this might lead to confusion. Actually, these writers named as median, the left paramedian lobe subdividing it into upper and lower segments. What made them name the left paramedian lobe as median and the right paramedian one as anterior, still remains without explanation.

Couinaud in 1954 divided the liver into eight segments giving them the latin numbers from one to eight [40]. Regardless of the transversal fissure of the right paramedian lobe in dispute, the afore mentioned writer considered the caudal lobe as a single one, not making any mention of its division into two segments. This is a most significant detail, as it will be mentioned later (fig. 2.15).

Gans in 1955 came up with other findings [10]. The afore mentioned investigator, oppositely to the findings of Healey and Couinaud, doesn't accept the transversal fissure as a permanent anatomical finding in none of the paramedian lobes. Also the intrahepatic fissure of the left lateral lobe is not drawn transversally or cross-sectionally but frontally. Finally he divided the liver into two paramedian lobes, and into two lobes left and right subdivided into upper and lower segments. While Gans findings are almost similar to our clinical observation yet we wonder whether someone should accept his denomination of the lobes and sections [41]. And, concretely he gives the name of right lobe to our right posterior and of left lobe to our lateral one, disregarding in some way the fact that on the base of the intrahepatic division after the Glissonian System, one should call right lobe the right paramedian and the right posterior and left lobe the left parametian and left Lateral, separated by the median fissure of the liver. Consequently, the naming of the lobes of the liver after GANS may cause misinterpretation of the way of their blood supply because the correlation of nomenclature in the intrahepatic distribution of the vessels of the Glissonian system is neither correct nor complete.

We would like to point out what made us give different names to the lobes other than those that have been used up to now, by different workers [41]. Since there is a median fissure dividing the right and left lobes, it is fair to name them as paramedian ones. For the nomenclature of the left lobe, one should take into account that indeed this is lying laterally leftwards the liver and towards the left part of the upper abdomen.

Consequently, the right posterior lobe could be named as right lateral. Nevertheless we prefer the term posterior as more precise, since the posterior segment protrudes more posteriorly than the right mammary line of the body and the right median axillary one. For the upper and lower segments of the subdivisions of the posterior and lateral lobes, we suggest these plain divisions to be called as superior and inferior segments.

The North American surgeons today follow the nomenclature proposed by Healey & Schroy (1953), whereas the European surgeons prefer the Couinaud nomenclature (1954) [9, 21].

The scientific committee of the International Liver, Pancreas, Biliary Society, in order to establish a unanimously accepted nomenclature assigned to a special committee for the study of the anatomy and nomenclature of the liver. This committee suggested a nomenclature that is based on anatomic and surgical principles [42, 43].

2.4.2.4. *Lobes and Segments of the Liver Based on the Vessels of the Efferent (Hepatic Veins) System*

The *general distribution* or, rather, the blood drainage from the liver, is *steady concerning the hepatic veins and completely different from the distribution of the elements of the Glissonian system,* i.e., the portal vein, the hepatic artery and the biliary vessels. If one observes a mould with the portal vein, the hepatic artery and the biliary vessels filled, one will note that the separating planes of the lobes of the liver can be clearly distinguished (fig. 2.15). It has already been mentioned above that the hepatic veins drain the blood from certain regions of the liver steadily and with very few variations.

The *Right hepatic vein* receives blood from the *Right posterior lobe,* as well as from a small segment at the lower region of the *Right paramedian lobe.* The *Median hepatic vein* receives blood from the larger part of the Right paramedian and the whole Left paramedian lobe. The *Left hepatic vein* drains the whole Left lateral lobe (fig. 2.16).

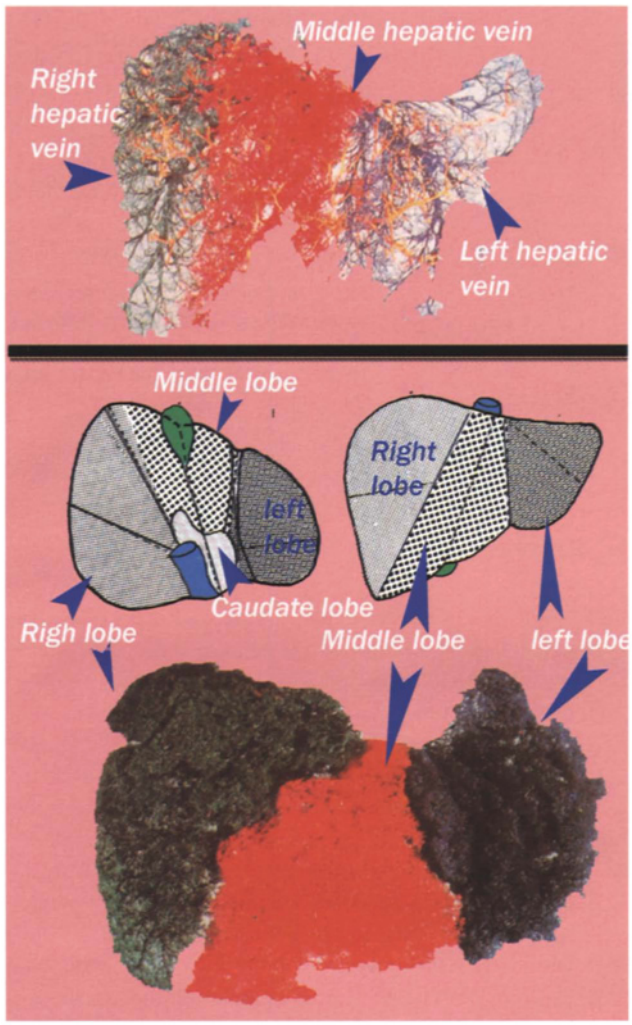

Fig. 2.16. The Lobes and segments of the liver based on the vessels of the efferent (hepatic veins) system. The right lobe (green), the me-dian (red) lobe and the left lobe (blue) of the liver after filling of the three hepatic veins with a Vinyl Acetate solution of different colour.

A fact that deserves special attention is that the hepatic veins not only drain several parts of the liver, but also follow a steady course within the hepatic parenchyma; this course remains always the same. Thus, the right hepatic vein passes always through the right intrahepatic fissure, the course of the median hepatic vein is always along the median fissure and the left hepatic vein is always between the left intrahepatic fissures.

The above become obvious in our preparation (fig. 2.17), in which the portal vein is filled with yellow plastic material and the main stems of the hepatic veins with blue plastic material. It is easy to note the course of the main stems of the hepatic veins in the intrahepatic fissures described.

Taking into account the branching of the efferent venous system of the liver, i.e. the hepatic lobes, we can divide the liver in to the following lobes (fig. 2.16):

The Left lobe, which corresponds to the region drained by the left hepatic vein. This is identical to the left lateral lobe of the Glissonian system, delineated by the same left interlobar fissure.

The Median lobe, which corresponds to the region drained by the median hepatic vein and includes the left paramedian and the right paramedian lobe of the Glissonian system.

The Right lobe, the blood of which is drained by the right hepatic vein and which corresponds to the right posterior lobe of the Glissonian system. At times, a small triangular segment of the distal part of the right para-

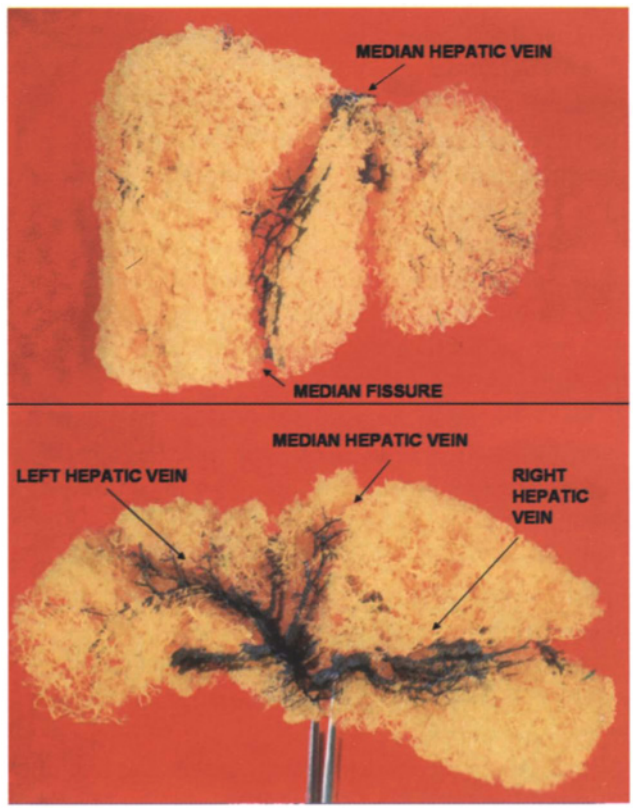

Fig. 2.17. The course of the main stems of the hepatic veins in the intrahepatic fissures are shown in this picture. The portal vein is filled with yellow plastic material and the main stems of the hepatic veins with blue plastic material.

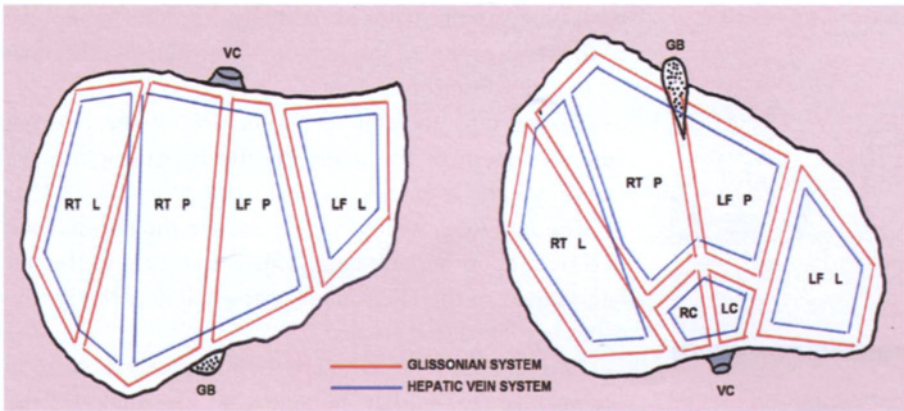

Fig. 2.18. Division of the liver according to the segmental distribution of the Glissonian system (red lines) or according to the ramifications of the hepatic veins (blue lines).

median lobe corresponds to this lobe; its blood is drained by a lateral left branch of the right hepatic vein.

The Caudate lobe, which according to the Glissonian system is divided in two segments, a right and a left one, and drains its blood *directly to the inferior vena cava through two or, sometimes, more venous* vessels (left anterior group of short hepatic veins) (fig. 2.9).

Further more, speaking of relationship between surface landmarks and internal subdivision of the liver, the left interlobar fissure is marked by the falciform ligament superiorly and by the umbilical fissure inferiorly and it is distinct. The median fissure is marked by the line joining the gallbladder fossa with the left wall of the inferior vena cava. The surface landmarks of the right interlobar fissure are not so distinct as the above two fissures. Its location varies greatly with the size of the right lobe.

So, applying in surgery, it is possible to divide the liver according to the segmental distribution of the Glissonian system or according to the ramifications of the hepatic veins (fig. 2.18) [44, 45, 46, 47].

In the same areas both systems co-exist but in others these overlap. As a result, there are only two practical lines of bloodless segmental resection.

1st: Along the left interlobar fissure which is marked by the falciform ligament superiorly and the unbilical fissure inferiorly.

2nd: Along the median fissure. In this case one must be careful to preserve the middle hepatic vein, which are located in this fissure.

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CHAPTER 3

ANATOMICAL VARIATIONS AND ANOMALIES OF THE BILIARY TREE, VEINS AND ARTERIES

Con. Ch. Karaliotas, T. Papaconstantinou, Ch. Con. Karaliotas

3.1. Introduction

A good working knowledge of the incidence and types of anomaly or variation is key to a safe cholecystectomy, as 50% of patients presenting with gallbladder stones or common bile duct stones show a significant variation from what is generally considered as the expected normal pattern. Ignorance of these anomalies may well be responsible for catastrophic injuries of the bile duct during laparoscopy. The onus is therefore on the surgeon to be versed in the possible anatomical variations that he might encounter during surgery and to ensure that this knowledge is passed on to surgical trainees.

Not only must the surgeon be aware of these anomalies, but the radiologist should also possess a thorough knowledge of normal and abnormal anatomy of this anatomical area, if he is to correctly interpret the images provided by the new and older diagnostic imaging techniques, such as endoscopic cholangiography, enhanced CT, MRCP and isotope scanning of the liver.

3.2. Aberrant Ducts

Intrahepatic interductal communication occurs only rarely, if at all [1-5], and is of clinical significance: in the event of a bile duct obstruction, the corresponding segment or subsegment is not shunted through collaterals. Each bile duct drains only the part of the liver that it serves [6], though there are occasional reports of intercommunication between the extrahepatic ducts in the liver hilum [7].

In contrast, accessory bile ducts are commonly described in the literature [8]. The term *aberrant* (which is neither normal nor typical) is preferred over the term accessory (implies a duplication in structure or function) when describing "extra" ducts found in the porta hepatis [9].

Anomalous ducts have been reported in 1.7% to 28% of cases, with an average of 12.1% [10]. These anomalous ducts are encountered most frequently (85%) in the triangle of Calot (space bounded medially by the common hepatic duct, inferiorly by the cystic duct, and superiorly by the cystic altery) [11]. Most surgical injuries to bile ducts occur in this area. The ducts may differ in diameter from just filamentous, serving only tiny lobules of liver, to a considerable duct draining of most or all of a liver segment. These aberrant ducts are also referred to as *segmental* or *sub-segmental ducts* [12]. The right lobe of the liver, mostly the posterior segment, engenders most of these ducts [13]. They commonly unite the common hepatic duct or cystic duct but may also enter the gallbladder or common bile duct.

Intraoperative cholangiography is the best method of identifying these ducts, thus avoiding injury. The visualization of an aberrant duct entering the cystic duct depends on the placement of the cystic duct catheter and its retention clip. If the position is too close to the common bile duct, an aberrant duct joining the cystic duct between the gallbladder and the catheter tip will not be revealed.

A slight bile duct (described by Luschka) rising from the right lobe of the liver in the gallbladder fossa and draining into the right hepatic duct or common hepatic duct [14], measures 1 to 2 mm in diameter and is found in 1% to 50% of the cases. Hepatocholecystic ducts draining directly from the liver into the gallbladder have been confirmed [15] and may also be the source of postoperative bile leaks. In figure 3.1 there

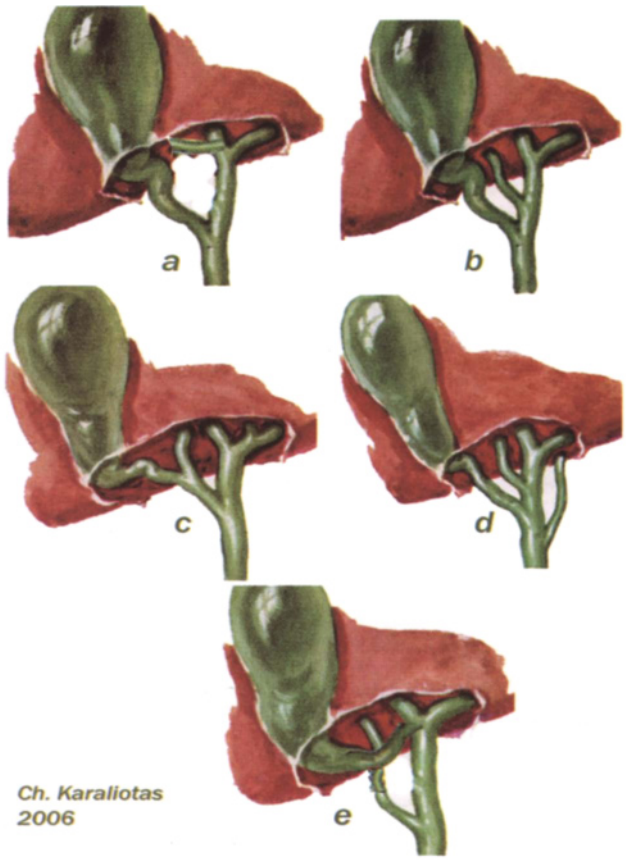

Fig. 3.1.
a) Accessory duct from the liver drains into right hepatic duct, b) accessory duct from the liver drains into the common hepatic duct, c) accessory duct from the liver drains into the cystic duct, d) accessory duct from the liver, drains at a higher level than the cystic duct does – two accessory ducts, e) the accessory duct comes from the liver and drains into the common bile duct at a level lower than the confluence of cystic duct with common hepatic duct. The cystic duct drains into the left hepatic duct. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

are at least six variations of aberrant (accessory) extrahepatic duct near porta hepatic as these structures empty in various positions of common hepatic duct or elsewhere (fig. 3.1). The Luschka bile ducts are schematically illustrated in figure 3.2.

The surgical significance of an aberrant or accessory hepatic duct lies in its vulnerability during an operation. The consequences of its ligation or division will depend upon its size, for instance, if we ligate an accessory duct similar in size to a cystic duct, a significant biliary obstruction could ensue. Dividing a small unrecognized accessory duct will result in bile leakage, biloma, biliary peritonitis, biliary fistula and, possibly, late stenosis of the common bile duct due to the sclerotic action of the leaking bile duct.

3.2.1. Anatomical Variations of the Gallbladder

3.2.1.1. *Agenesis of the Gallbladder*

Agenesis of the gallbladder is extremely rare, with an estimated incidence of 0,02%. In such rare case, polycystic kidneys, absent ascending colon, tracheo-oesophageal fistula, cleft palate and cardiac defects frequently co-exist. The condition can only be diagnosed in the operating theatre table, after a complete inspection of the possible normal and ectopic sites has failed to identify the gallbladder. That said, operative cholangiography is always necessary to confirm the agenesis.

3.2.1.2. *Multiple Gallbladders*

The estimated incidence of multiple gallbladders is 1 in 3800 individuals with many reports in the literature of double gallbladders and very few of triple gallbladders. The variations of this defect may include either an apparently single organ divided by a septum or two or three completely separate gallbladders each with its own cystic duct. Scandalakis J. et al [16] have classified multiple gallbladders according to the supposed embryological defect in the cystic primordium and the primitive hepatic diverticulum from which it arises. There are two groups of multiple gallbladders with different characteristics.

The first group is *the split cystic primordial group* where varying degrees of duplication of the gallbladder are presented but only one cystic duct enters the common bile duct (fig. 3.3a). In the first group, a subgroup represents the mild form that is a longitudinal septum dividing the gallbladder into two separate chambers but the evidence of duplication appears af-

Fig. 3.2.
Schematic illustration of Luschka ducts draining into the gallbladder. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

Fig. 3.3, a to f.
Various types of double gallbladder which illustrate the position of the accessory gallbladder and its relationship with cystic duct.
a) Regular and accessory gallbladders in a normal position with a common cystic duct, the so called "split cystic primordium group".
b) The so-called pattern "multiple cystic primordium group" where two cystic ducts, one for each gallbladder drain into the common hepatic duct.
c) Two cystic ducts, a pattern slightly different from the preceding, where the one cystic duct enters the liver.
d) A second gallbladder with a cystic duct draining at a higher level into the common hepatic duct
e) A second gallbladder (accessory) lain beneath the left lobe of the liver, that drains into the left hepatic duct.
f) A different pattern of doubling gallbladder cysts often smaller and situated in the hepaticoduodenal ligament.

ter the incision of gallbladder's wall (fig. 3.4a). A more severe variation is the division of the gallbladder into two lobes (fig. 3.4b,) each lobe joining at the neck to form a normal common cystic duct.

The second main group is the *multiple cystic primordial group* (*accessory gallbladder*). This group is characterized by the presence of two or three (double or triple) separate gallbladders, each one with its own cystic duct which enters the common bile duct independently (fig. 3.3b, c, d, f). Occasionally, one of the cystic ducts enters either the left or the right hepatic duct (fig. 3.3e).

Multiple gallbladders can cause problems during surgery if the surgeon is unaware of this anomaly. Furthermore, the patient runs the risk of a "retained gallbladder", although a diseased gallbladder has already been removed. The diagnosis of the existence of a double or triple gallbladder by ultrasonography is often difficult and misdiagnosed. Only with preoperative imaging by magnetic or CT cholangiography can multiple gallbladders be 100% diagnosed. Continuation of symptoms after cholecystectomy may be the first indication that a second or a third gallbladder was overlooked during the original operation. However, if during the course of cholecystectomy for gallbladder's calculi a supernumerary gallbladder is discovered, this should be removed even if it appears normal. This recommendation is crucial if a second operation due to new gallstone formation in the remnant gallbladder is be avoided [16].

3.2.1.3. *Ectopic Gallbladder*

Ectopic gallbladders represent cases where a normally formed gallbladder lies in an abnormal site. The inci-

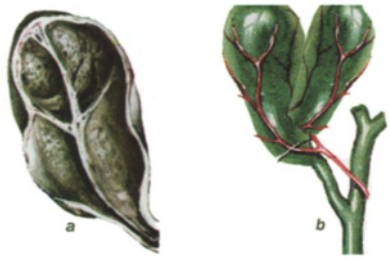

Fig. 3.4. Bilobed gallbladder. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).
a) An internal septum separates the cyst into two departments.
b) Double gallbladder but joined at the common neck with one cystic duct.

Fig. 3.5. Intrahepatic gallbladder. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

Fig. 3.6. Floating gallbladder. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

dence is very rare but, nonetheless, important to the surgeon and radiologist. Although the diagnosis is quite easy, difficulties can arise if the radiologist is unaware of the ectopic sites of the gallbladder, or if the filling defect is wrongly attributed to hepatic metastatic disease. The ectopic gallbladder may be intrahepatic (fig. 3.5), left sided, transverse, retrodisplaced or in rare occasions, be located elsewhere.

The *intrahepatic gallbladder* is totally embedded in the liver parenchyma. In such cases, and in inexperienced hands, a cholecystectomy can become an exhemely dangerous and hemorrhagic one (fig. 3.5).

Finally, the so called "floating gallbladder", yet another, though not uncommon, anatomic variation is a gallbladder suspended from the liver via a mesenteriole (fig. 3.6). Such cases facilitate the procedure of cholecystectomy.

3.2.2. Extrahepatic Bile Ducts Anatomical Variations

3.2.2.1. *Cystic Duct (See Also Chapter 1)*

Only 33% of patients have a classic anatomic position and course of cystic duct, as well as a classic anatomic relationship with the other adjacent structures. The most important anatomic point of the cystic duct is the angular junction which is formed between the cystic duct and the common bile duct, as well as the point at which the cystic duct drains into the common hepatic duct. The length of the cystic duct also varies. It is reported by Toouli [17], that 20% of ducts are less than 2 cm in length, with the majority being between 2 cm and 4 cm. We strongly believe that one of the main causes of iatrogenic injury of the common hepatic duct is the close proximity, especially of the course, between the cystic duct and common bile duct.

The only safe way to minimize accidental injury to the bile ducts and hepatic artery is the limitation of manoeuver during dissection in the region of the Calot triangle. In general, the wide dissection of structures, especially of the cystic duct, should be limited. We insist that manoeuvers not be avoided but limited until all structures are recognized.

Figure 3.7 illustrates the different types of union of the cystic duct and common hepatic duct and their parallel or non parallel course.

3.2.3. Variations of the Common Bile Duct and Extrahepatic Confluence - Sectoral Ducts

The common bile duct, unlike the cystic duct, is more constant in its length and course, but variations exist mainly in the area of porta hepatis, and at the lower third of the common bile duct (intrapancreatic part). Also, the length of the common bile duct varies from person to person [18-19].

The first most common variation in the anatomy of the common bile duct occurs at the different levels of convergence (confluence) of two hepatic ducts (fig. 3.11). The convergence of hepatic duct varies greatly. Rarely non-confluence of the right and left hepatic ducts occurs, with the independent for each duct into the duodenum ending up at different sites. These variations are very often referred to as sectoral ducts. Sectoral ducts drain the sectors specific parts of the liver [20]. For example, a right sectoral duct drains segments VI and VII or segments V and VIII. Almost in all cases the cystic duct converges with the right sectoral duct.

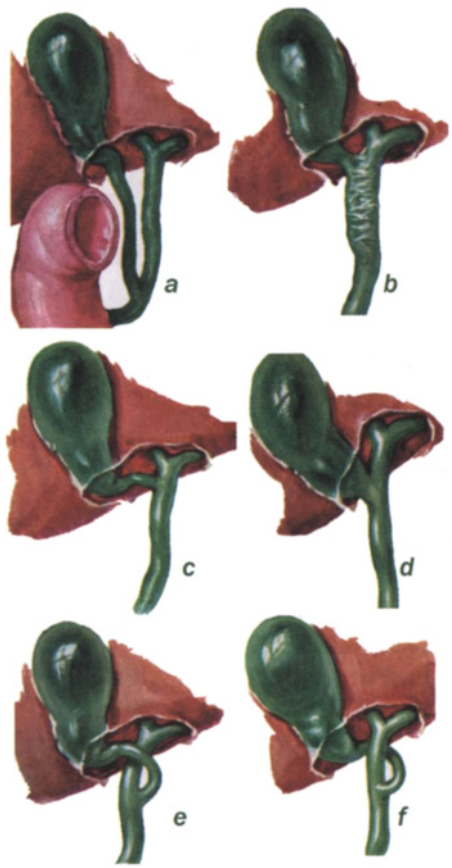

Fig. 3.7. Various types of confluence of the cystic duct and common hepatic duct (Personal series). (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).
a) Low parallel course and union with common hepatic duct (15%).
b) Adherent to common hepatic duct (% unknown).
c) Normal course of the cystic duct (59,9%).
d) Short of absent cystic duct – 3,5% and 0,5% respectively.
e) Ant spiral course to the left side of common hepatic duct (2%).
f) Post spiral course to the left side of common hepatic duct (13%).

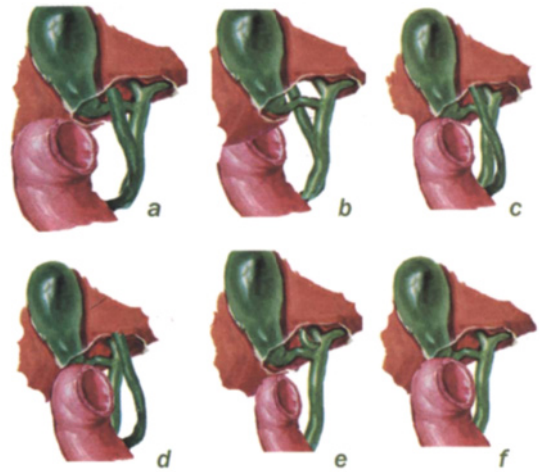

Fig. 3.8. Variations of the hepatic duct (Analysis of personal series from 1230 operations where the variations were recognized).
a) Low convergence of hepatic ducts. Right hepatic duct descents in front of the cystic duct, which is draining into the left hepatic duct (18 cases 1,46%).
b) Low convergence of hepatic ducts. Right hepatic duct descents behind the cystic duct, which is draining into the left hepatic duct (32 cases, 2,6%).
c) Right sectoral duct, where the convergence occurs at a very low level, at the ampoule. Cystic duct drains into the right sectoral duct (2 cases, 0,16%).
d) Right sectoral duct. No convergence occurs with separate drainage of two hepatic ducts into the duodenum (1 case, 0,08%).
e) Trifurcation of hepatic ducts at the porta hepatis (131 cases, 10.7%).
f) Bifurcation of hepatic ducts, the most common anatomic pattern, (1046 cases, 85%).

Figure 3.8 illustrates the afore-mentioned anatomical variations.

3.2.4. Cystic Dilatations of the Biliary Tree (Hepatocholedochal Cysts)

Hepatocholedochal cysts usually present in childhood but their symptoms are so insignificant as to evade early diagnosis, resulting in many cases –at least 20% of patients– being detected in adulthood. Other chapters describe details and radiological imaging relating to their anatomic configuration as well as the clinical findings and treatment. Figure 3.9 illustrates the Todani classification of hepatocholedochal cysts as redrawn by ourselves. Many authors have tried to modify the illustrated classification, as Hohenberger in 1996, but the original classification of Alonso-Lej and Todani is more prevalent [21, 22, 23, 24] (see more details in chapters 11 and 19).

3.2.5. Variations of Intrahepatic Bile Duct Ramifications (After Skandalakis 1989)

Agood knowledge of normal intrahepatic bile duct ramifications and their variations, as well as the variations in the confluence of the hepatic ducts and their first order ramie is of crucial importance to the liver and biliary tract surgeon. Sometimes, the negligence and ignorance of the anatomy of this surgical area lead to definitive and often lethal injuries in both conventional hepatectomies, hepatectomies for living donor liver transplantation, where both recipient and donor must

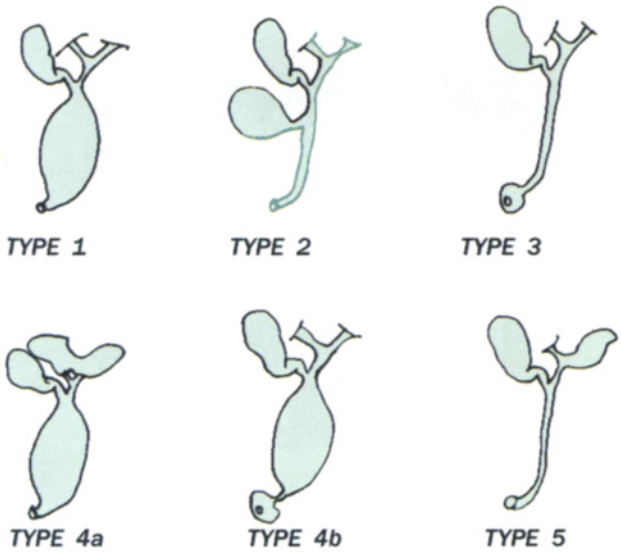

Fig. 3.9. Todani's classification of choledochal cysts.
Type 1: Solitary fusiform extrahepatic cyst.
Type 2: Extrahepatic supraduodenal diverticulum.
Type 3: Choledochocele (intraduodenal diverticulum).
Type 4a: Fusiform extra- and intrahepatic cysts.
Type 4b: Multiple extrahepatic cysts.
Type 5: Caroli's disease (Multiple intrahepatic cysts).

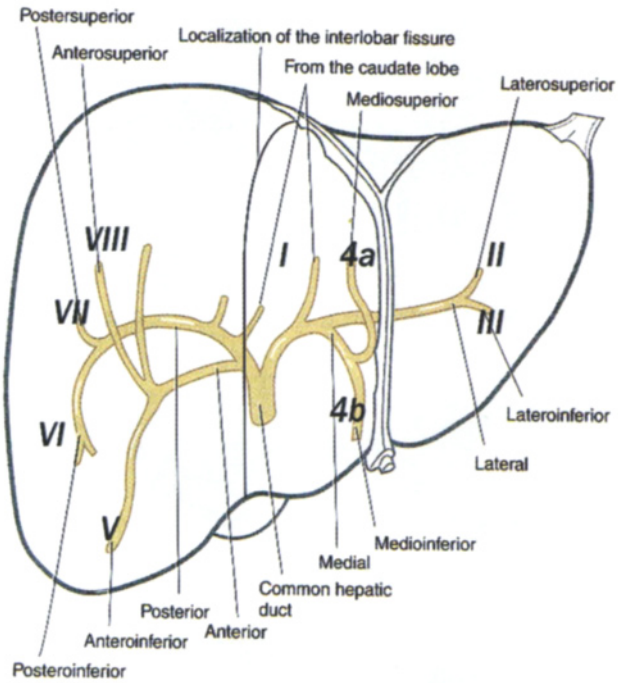

Fig. 3.10. Intrahepatic bile tree nonmeclature and the equivalent of segment terminology according to Couinaud.

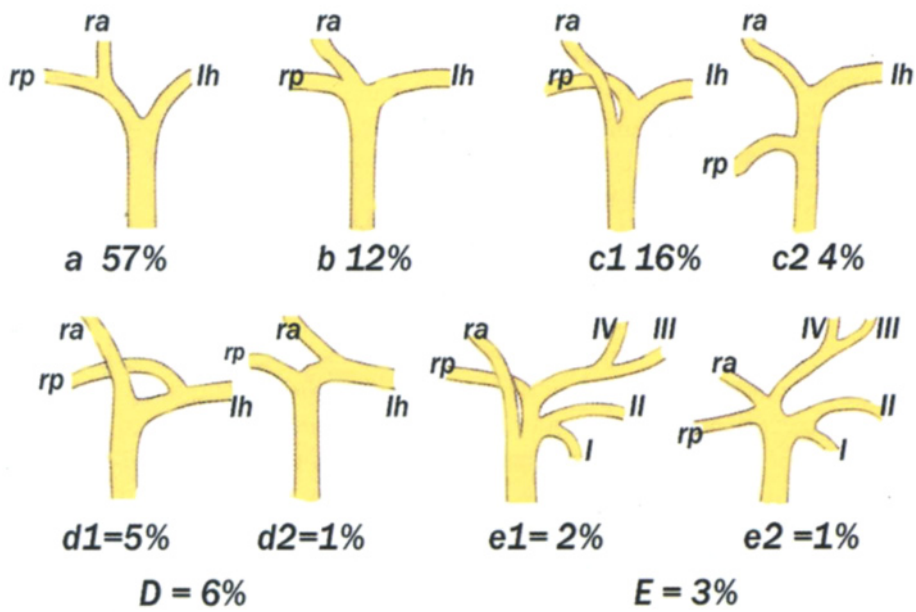

Fig. 3.11. Variations of convergence (confluence) of hepatic ducts at the porta hepatic –extrahepatic– (after Smadja and Blumgart, after Couinaud, 1957, redrawn by us in 2006).
ra = right anterior and rp = right posterior branches typically drain into right hepatic duct, lh = left hepatic duct.
a) the most common typical configuration of hepatic ducts confluence.
b) trifurcation or triple confluence.
c) the *Right anterior duct* drains into the common hepatic duct (c1) and *right posterior duct* also drains into the common hepatic duct (c2).
d) the *Right posterior duct* drains into the left hepatic duct (d1) and the *right anterior duct* also drains into the left hepatic duct.
e) in types e1 and e2 there is an entirely different drainage of hepatic branches. There is also a type f, in which the right hepatic duct drains into the cystic duct.

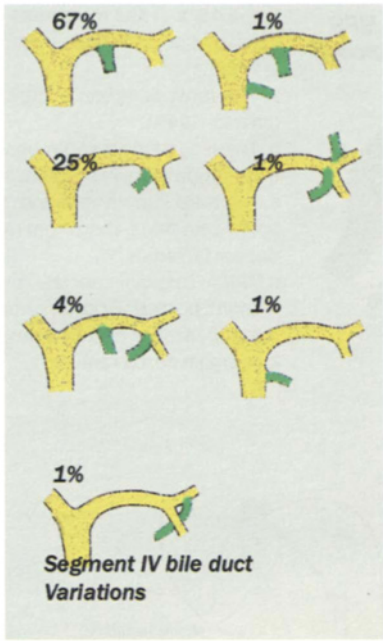

Fig. 3.12. Ramifications of the intrahepatic bile ductal system. Types and incidence rate of the known variations of bile duct IV –the green ramus– (redrawn by us in 2006, after Smadja and Blumgart, 1988, and after Healey and Schroy 1953).

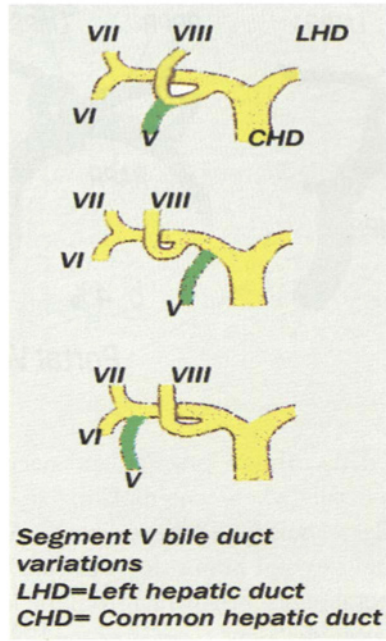

Fig. 3.13. Types and incidence rate of the known variations of bile duct V –the green ramus– (redrawn by us, after Smadja and Blumgart, 1988, and after Healey and Schroy 1953).

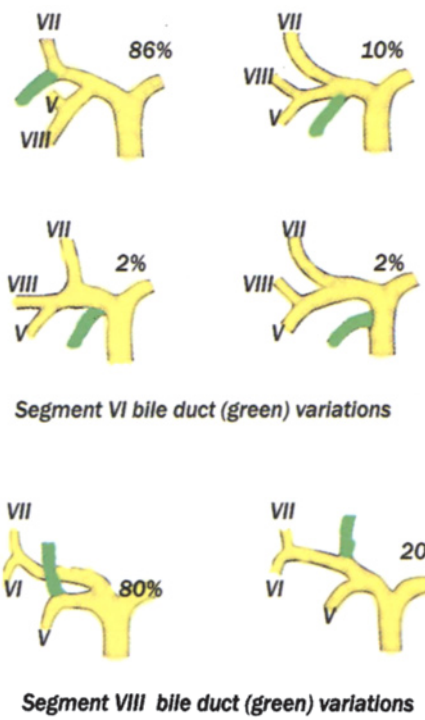

Fig. 3.14. Types and incidence rate of the known variations of bile duct VI and VIII –the green rami– (redrawn by us, after Smadja and Blumgart, 1988, and after Healey and Schroy 1953).

conserve a good functional liver. Figure 3.10 demonstrates a schematic representation of the intrahepatic biliary tree with normal anatomy. The most common and known variations of intrahepatic bile ducts IV, V, VI and VIII are illustrated in figures 3.12, 3.13, 3.14, 3.16 [20, 25, 26].

3.3. Anatomical Variations of Vessels

3.3.1. Portal Vein Variations

Intrahepatic portal anatomy has been well established on liver sonography, CT scans, CT portography during the vein phase of arteriography, MR imaging and, recently, on computer assisted 3D imaging. The most important variation of the portal vein, present in 4%-19% of patients, is the immediate trifurcation of the portal vein into a left main ramus, a right anterior ramus and a right posterior ramus [27, 28, 29] (fig. 3.15b). Two other infrequent variations include the origin of the anterior right (sectoral) ramus from the left main portal vein and the posterior right (sectoral) ramus that originate from the portal trunk (fig. 3.15a, c).

The aforementioned variations are of significant

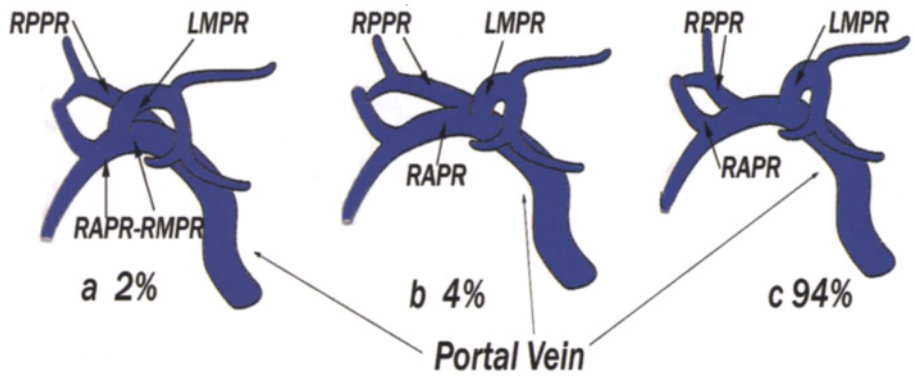

Fig. 3.15. a-c: The main most common variations of portal vein (After Soyer et al 1996).
a. The most common anatomic configuration (94%).
b. The second most common variation: trifurcation of main portal nein.
c. The third known variation: left main portal vein originating from right anterior portal ramus.
[LMPR = Left main portal ramus, RPPR = Right posterior portal ramus, RAPR = Right anterior portal ramus, RMPR = Right main portal ramus].

importance in daily surgical practice and need to be recognized, especially when contemplating an early ligation of the hilar vessels for left hepatectomy. A wrong ligation of portal sectoral ramus, for example the anterior right sectoral ramus originating from the left portal vein, will lead to devascularization of the right liver.

3.3.2. Hepatic Veins Anatomic Variations - Accessory Hepatic Veins

In general, the anatomy of hepatic veins is of significant interest in the initial hepatectomy phase of suprahepatic vascular control with partial or complete occlusion. The normal distribution of intrahepatic rami and the main variations of hepatic vein insertion into the vena cava are illustrated in figures 3.16 and 3.17 respectively. The right hepatic vein is usually controlled independently in over 50% of cases, depending on the anatomic configuration of hepatocaval junction in relation to the diaphragm. The control of median and left hepatic veins with their own common trunk for drain into the vena cava is difficult, dangerous or even impossible. During total vascular occlusion the clamping of the suprahepatic vena cava is straight forward in over 80% of cases [30, 31, 32].

The accessory hepatic veins (fig. 3.16, 3.17) may be on the right or on the left side and are also called retrohepatic veins. On the right side they independently drain parts of the posterior sector of the liver, namely, segments VI and VII. These veins are usually two, superior and inferior accessory, with the latter more constant.

On the left side, the accessory veins are formed by the venules of the caudate lobe. In 50% of cases, a solitary thin vein drains directly to the vena cava, inferior-

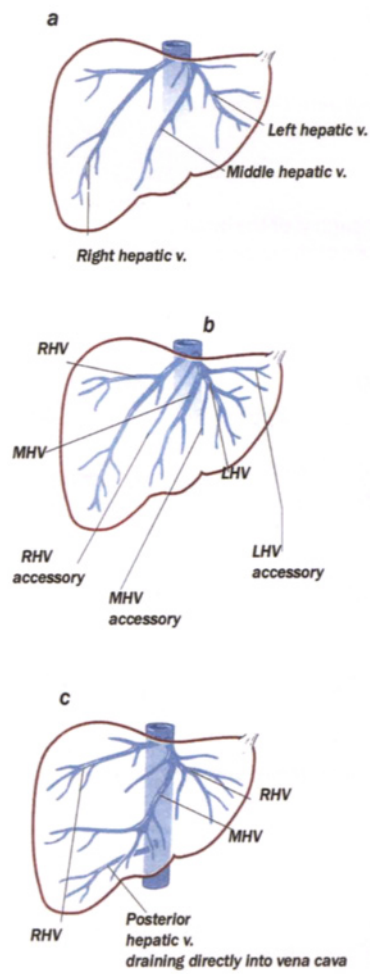

Fig. 3.16. a-c.
a. Normal configuration of hepatic veins.
b. Posterior hepatic vein.
c. Configuration of accessory hepatic veins (from Broelsch et al. 1993).
[RHV = Right hepatic vein, LHV = Left hepatic vein, MHV = Middle hepatic vein].

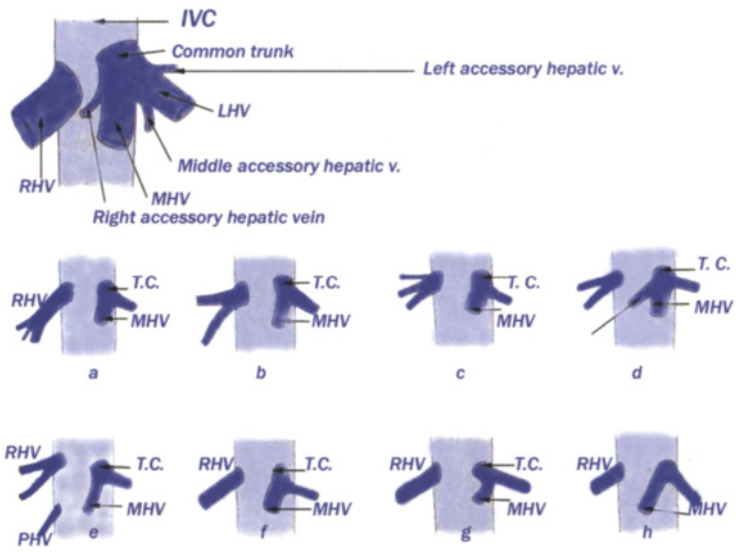

Fig. 3.17. a-f: Schema for hepatic veins variations from Broelch et al 1993.
a. Long branchless trunk of RHV (common).
b. Short trunk of RHV (rare).
c. Thin RHV, "compensated" by well developed MHV.
d. Thin RHV and middle accessory hepatic v (rare).
e. Thin RHV and posterior hepatic vein.
f-h: Variations of the middle and hepatic veins.

ly of the common trunk of the left and median hepatic veins. We must note that there are eight to 20 small venules, which drain into the vena cava originating from the caudate lobe, rendering the resection of segment I (caudate lobe) both difficult and awkward.

3.3.3. Hepatic Artery Anatomic Variations – Cystic Artery Variations

3.3.3.1. *Hepatic Artery Variations*

As we know from previous chapters, the common hepatic artery is mainly a branch of coeliac axis (the so called Haller's tripod). The anatomic variations of the hepatic artery are well recognized by careful dissection during operations of hepatectomies and pancreatectomies as well as in surgical oncology during lymph node dissection.

According to Michels [33, 34, 35], since 1953, over 40% of 200 autopsy dissections have revealed variations in the origin and course of the hepatic artery.

A replaced hepatic artery is an artery which originates from a source different to that in the standard description and substitutes the typical vessel (see below fig. 3.19). An accessory artery is a vessel additional to those originating according to standard description.

Nowadays, advanced technology in radiology imagination (3D imaging, digital angiography, MRA) can be helpful in the preoperative detection of detailed anatomic variations. Many author –radiologists– Marchal et al in 1981 [36], Ralls et al [37] and Rubin et al in 1993 [38] – have presented their experience in the recognition of hepatic artery anatomy, describing that the hepatic artery is normal in anatomic appearance in 75%-80% of cases in sonographic examination as well as in axial CT scans. According to the authors, the preoperative determination of hepatic artery variation using sonography or CT is valuable.

The two most commonly observed variations are the following: a) accessory left hepatic artery with its origin from the left gastric artery (in 10% of cases) and b) right hepatic artery with its origin from superior mesenteric artery (in 10% of cases).

However, in the relatively recent investigation of 1000 patients from Hiatt, Gabbay and Busuttil [39], up to 75% of variations of hepatic artery anatomy was found. They classified 6 types of variations of hepatic artery as follow:

Type I (75.7%)
Common hepatic artery (CHA) arising from coeliac axis, normally, forming the gastroduodenal artery (GDA) and proper hepatic artery (PHA).

Type II (9, 7%)
Replaced or accessory LHA from left gastric artery.

Type III (10.6%)
Replaced or accessory RHA from superior mesenteric artery (SMA)

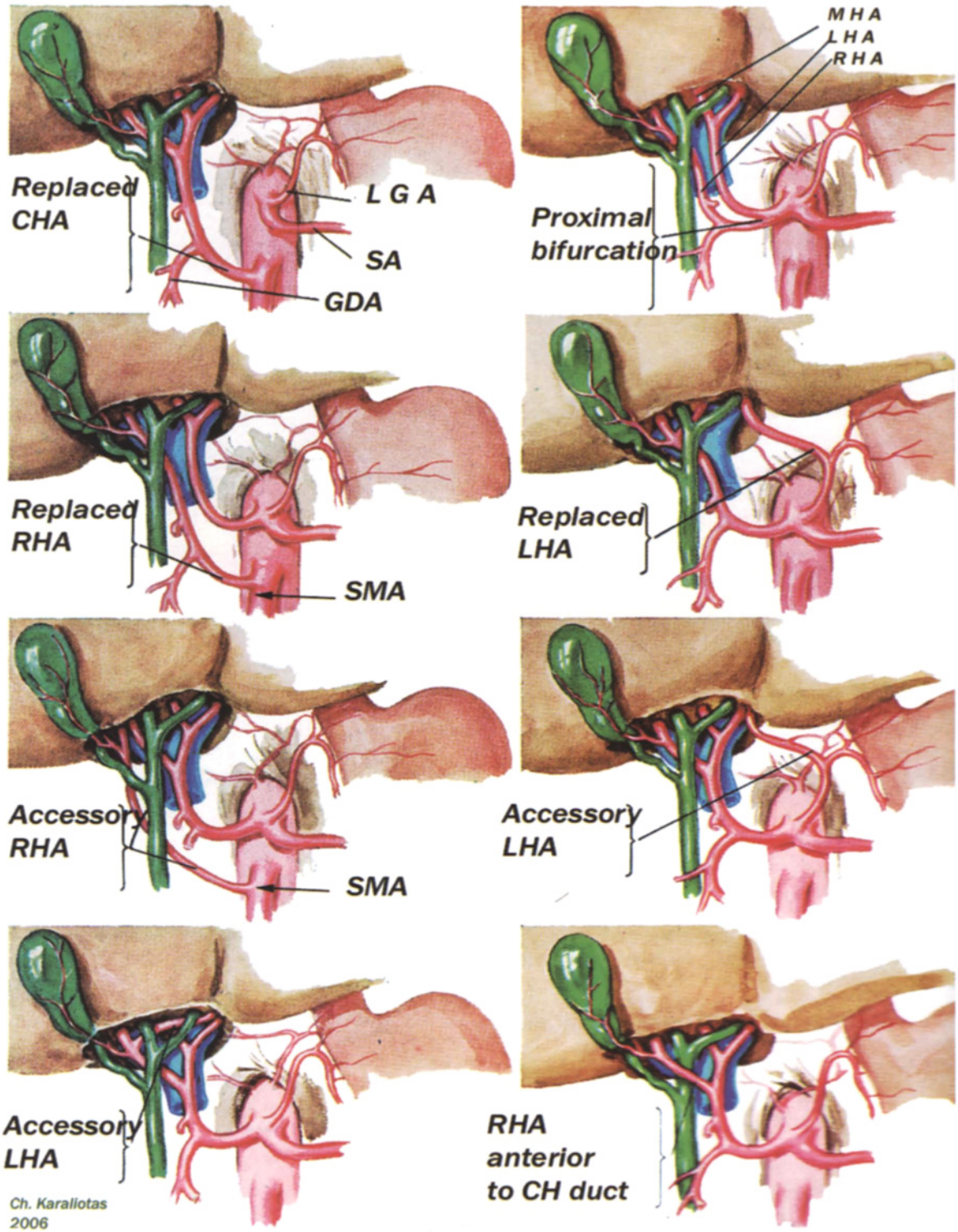

Fig. 3.18. Hepatic artery variations (Modified by us. – The CIBA collection of medical illustrations Volume 3, 1957 with permission of Novartis). (CHA = Common hepatic artery, LGA = Left gastric artery, SA = Splenic artery, GA = gastroduodenal artery, LHA = Left hepatic artery, RHA = Right hepatic artery, MHA = Middle hepatic artery, SMA = Superior mesenteric artery).

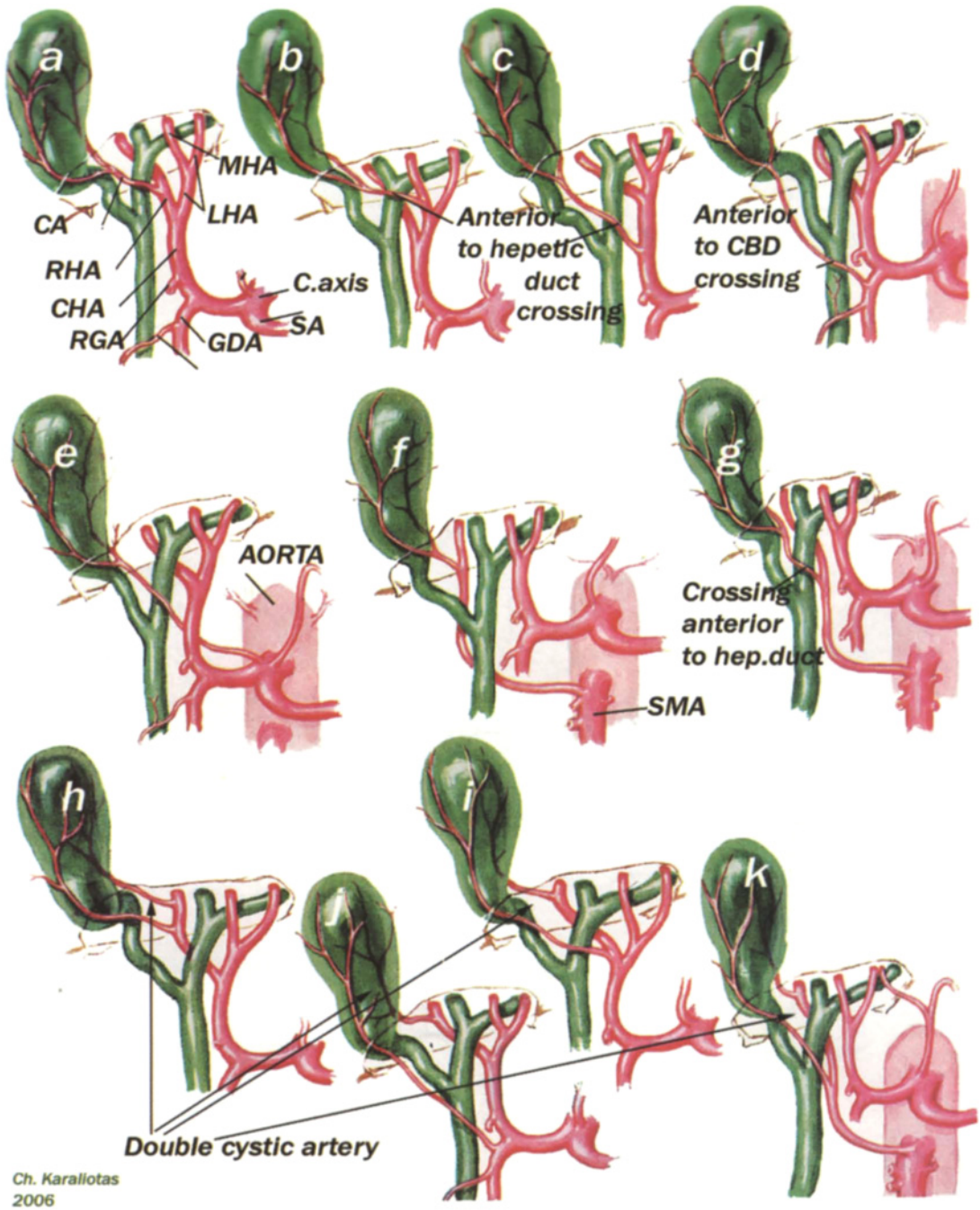

Fig. 3.19. Cystic artery variations (Modified by us. The CIBA collection of medical illustrations Volume 3, 1957, with permission of Novartis).
a. Cystic artery (CA) originating from normal right hepatic artery (RHA) outside cystic triangle.
b. CA originating from middle hepatic artery (MHA) – may also come from left hepatic artery (LHA).
c. CA originating from common hepatic artery (CHA).
d. CA originating from gastroduodenal artery (GDA).
e. CA originating from celiac axis or directly from aorta.
f. CA originating from aberrant right hepatic, the last coming from SMA.
g. CA originating outside Calot triangle from aberrant RHA.
h-k. Variations of double cystic artery.

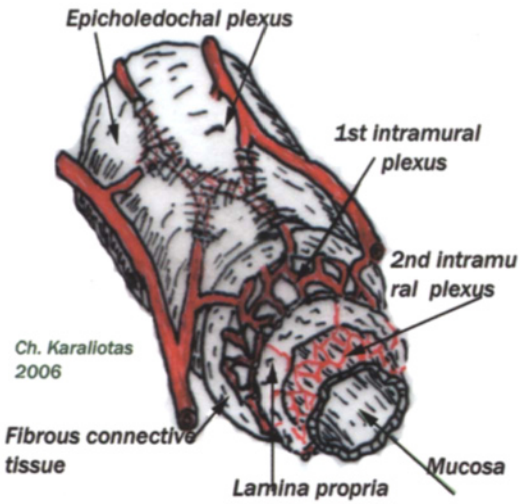

Fig. 3.20. Supraduodenal portion of common bile duct and its blood supply from an epicholedochal artery plexus and two intramural.

Type IV (2,3%)
Double replacement (coexisting variation of Type II and Type III)

Type V (1,5%)
The CHA arises from SMA.

Type VI (0,2%)
The CHA arising directly from the aorta.

3.3.3.2. *Cystic Artery Variations*

The cystic artery originates from the right hepatic artery within the cystic triangle of Calot. Typically divides into an anterior branch for the free surface of the gallbladder and a posterior branch for its bed surface. In about 20 percent of cases, this artery arises from the left or middle hepatic artery, outside the triangle of calot, or, even less frequently, from the common hepa-

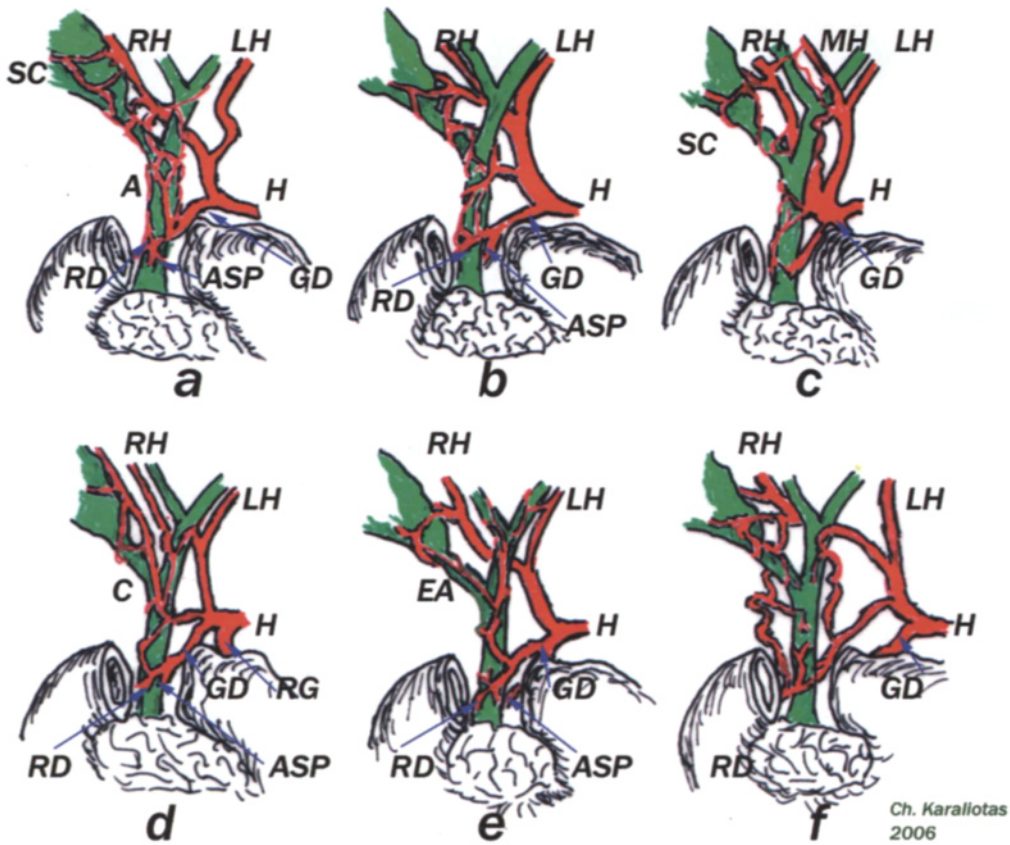

Fig. 3.21. Variations of blood supply of the common bile duct. The primary supply originates from retroduodenal or posterior superior pancreaticoduodenal artery which is a branch of the gastroduodenal artery.
(GD = gastroduodenal artery. SC = superficial cystic artery. ASP = anterior superior pancreaticoduodenal artery. RD = retroduodenal artery. A = marginal artery from retroduodenal. EA = epicholedochal artery. H = proper hepatic artery. RH = right hepatic artery. LH = left hepatic artery. MH = middle hepatic artery.

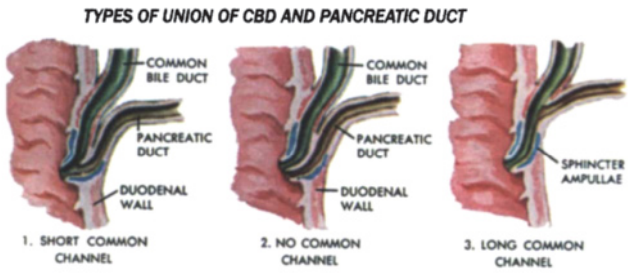

Fig. 3.22. The three different types of CBD union and the main pancreatic duct. From the CIBA collection of medical illustrations Volume 3, 1957, with permission of Novartis).

tic artery. Replacements of the cystic artery, including origins from gastroduodenal, celiac axis or independently from aorta, are rarely found (fig. 3.19).

An aberrant right hepatic artery coming from the superior mesenteric artery may also give origin to the cystic artery. Though encountered in almost 25% of cases, a double cystic artery does not represent an unusual variation. Though the origin of both cystic arteries varies, their great significance in cholecystectomy is obvious.

3.3.3.3. Variations of Blood Supply of Common Bile Duct

The common bile duct in its total course is a very vascular structure, especially in the lower third. There is a rich epicholedochal arterial plexus (fig. 3.20) which may derive from different sources explaning the many variations in the origin of common bile ductal blood supply (fig. 3.21). The classic article of Park, Michels and Ghash in 1963 remains contemporary. The enormous clinical and surgical significance of the rich blood supply of the common bile duct becomes clear when taking into account that, even if the dissection on this duct is a little more than 2 cm in length, it may result in an avascular stricture of common bile duct.

3.4. Anatomical Varations of CBD Union and the Main Pancreatic Duct

This union varies individually. Most frequently, both ducts converge within the wall of the duodenum and form a short common channel. In other cases, each duct drains into the duodenum with a separate opening. The third posibility is that both ducts (CBD and main pancreatic) form a long common channel (fig. 3.22).

3.5. Conclusion

The large number of variations in the anatomic structure of biliary tree imposes an imperative need for surgeons to have an adequate knowledge and understanding of those variations, in order to control the safety of the surgical procedure in this field. A large number of postoperative complications seen in this surgical area results from iatrogenic injuries incurred by a variation of anatomic elements.

Nowadays, given the rich and modern diagnostic armamentarium, the surgeon must be conversant with any potential problem. The significant improvements in the outcome from the procedures ranging from a simple cholecystectomy to the liver transplantation are due to the increased awareness of surgeon.

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CHAPTER 4

ULTRASONOGRAPHICAL ANATOMY FOR THE SURGEON. THE VALUE OF INTRA-OPERATIVE ULTRASONOGRAPHY

S. Mylona, A. Papaevangelou, G. Sgourakis, Con. Ch. Karaliotas

4.1. Introduction

This chapter drew and wrote by the authors intended to evoke the interest of surgeons about ultrasonography on liver and biliary tree. The value of this indispensable tool is that it can be also applied with high sensitivity and specificity intraoperatively and in endoscopic and laparoscopic diagnostic and interventional procedures.

4.2. Transabdominal Ultrasound

Ultrasonography will likely remain the initial mode of evaluation of liver in most clinical practices as it provides safety, ease of performance, portability, availability and speed as well as bearing a relatively low cost. Real-time scanning does not provide global view of the liver and is operator dependent. Modern machines provide images of high quality, enabling 3D reconstruction [1].

Understanding the vascular anatomy of the liver is essential to an appreciation of the relative position of the hepatic segments (interlobar and intersegmental). The major hepatic veins course between the lobes and segments (intrasegmental), with the exception of the ascending portion of the left portal vein, which runs in the left intersegmental fissure [2] (fig. 4.1).

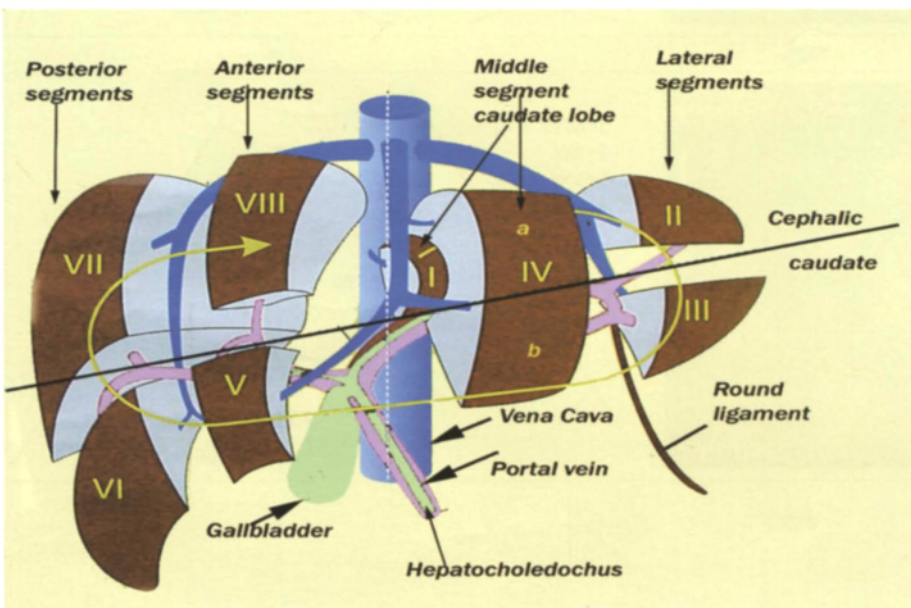
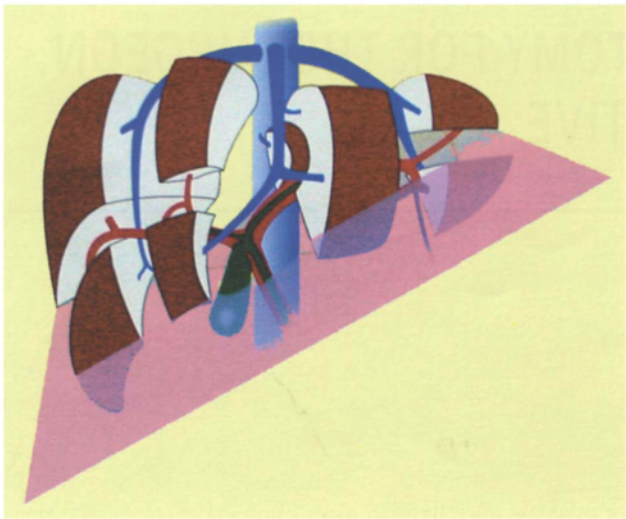
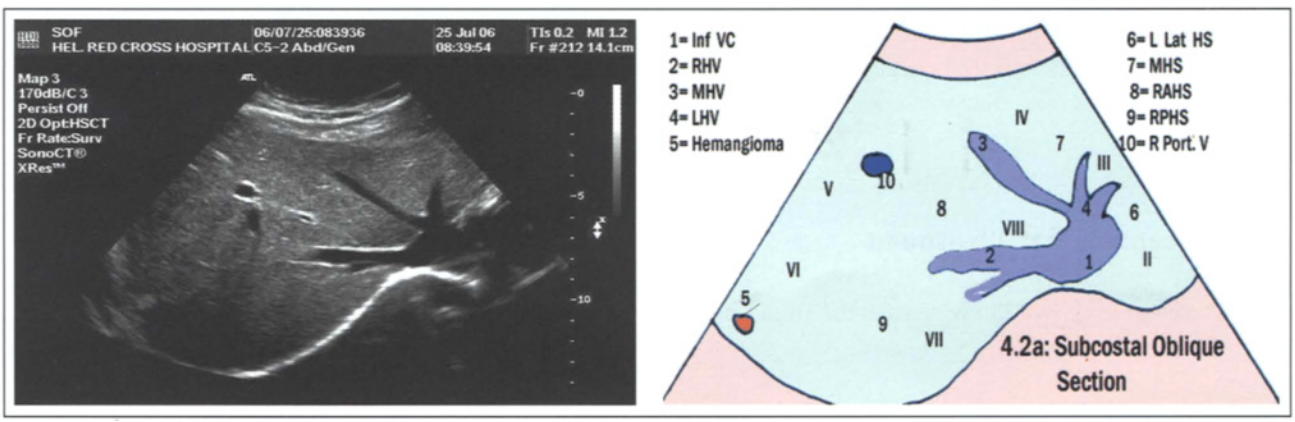


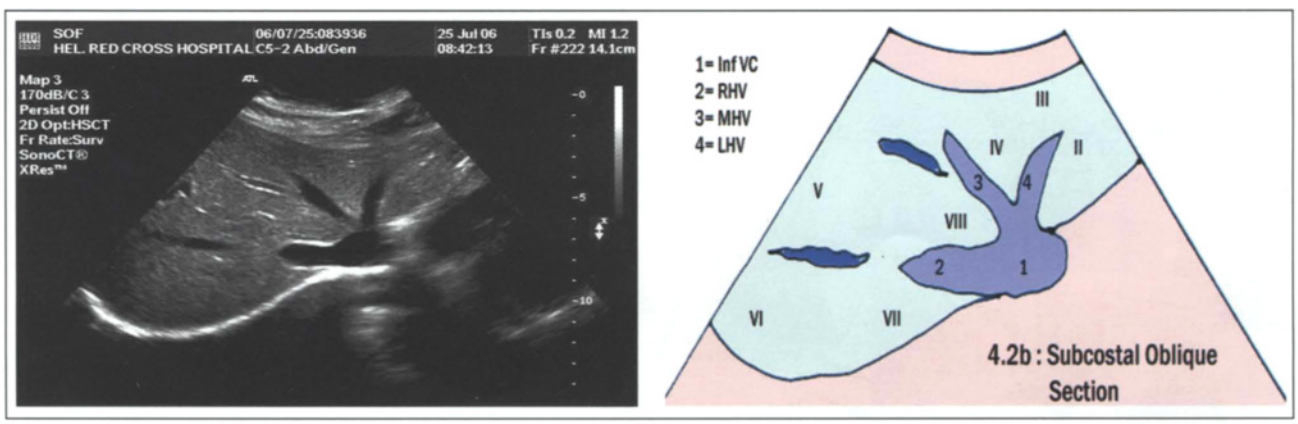
Fig. 4.1. Understanding the vascular anatomy of the liver is essential to an appreciation of the relative position of the hepatic segments.

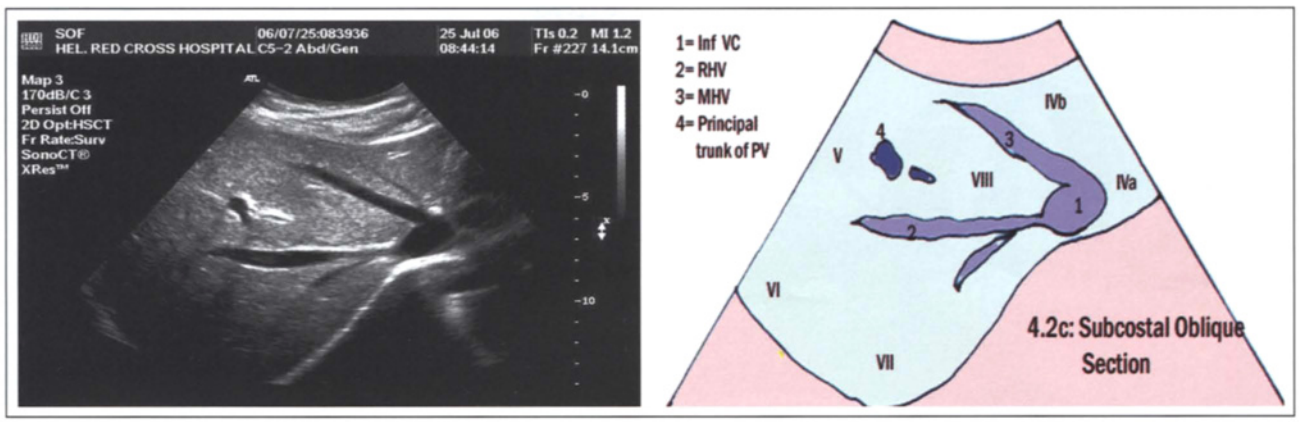


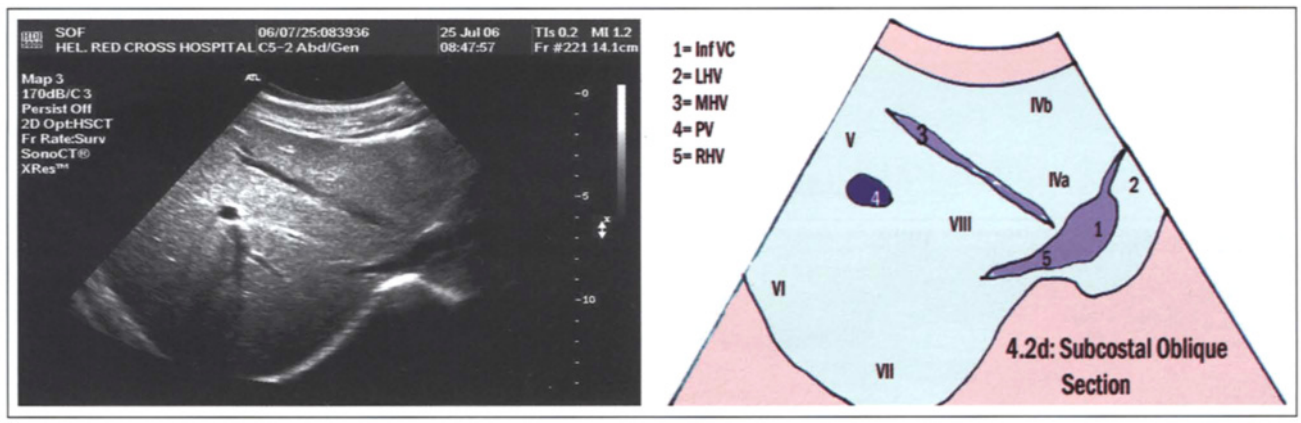
Inf.VC = Inferior Vena Cava.
RHV = Right Hepatic Vein.
MHV = Middle Hepatic Vein.
LHV = Left Hepatic Vein.
L.Lat. HS = Left Lateral Hepatic Sector.
MHS = Middle Hepatic Sector.
RAHS = Right Anterior Hepatic Sector.
RPHS = Right Posterior Hepatic Sector.

Fig. 4.2. The section of the liver seen on the left column of the page is a Subcostal Oblique Section. The sections in ultrasonography which follow are as the afore-mentioned section but parallel in different levels. Firstly study the ultrasonography on the left of the page. Secondly study the schematic illustration to understand the anatomy in IUS. Study again and again the two illustrations.









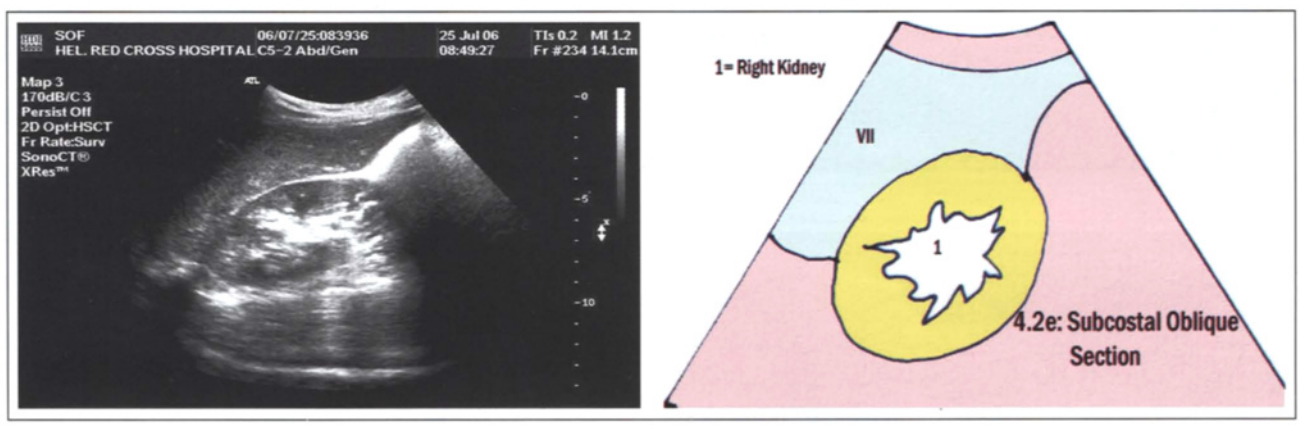
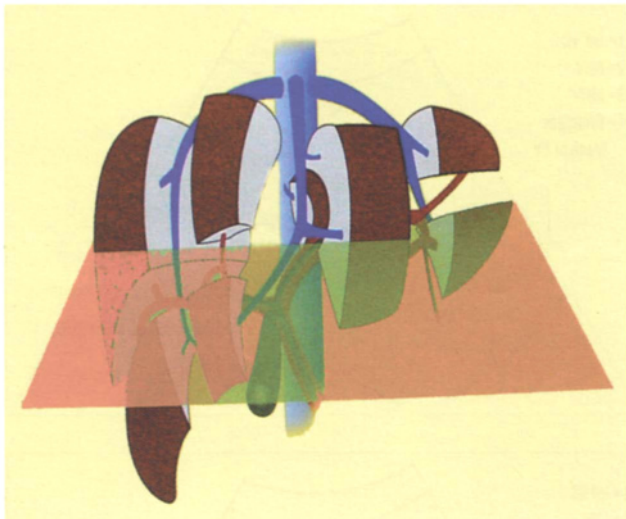
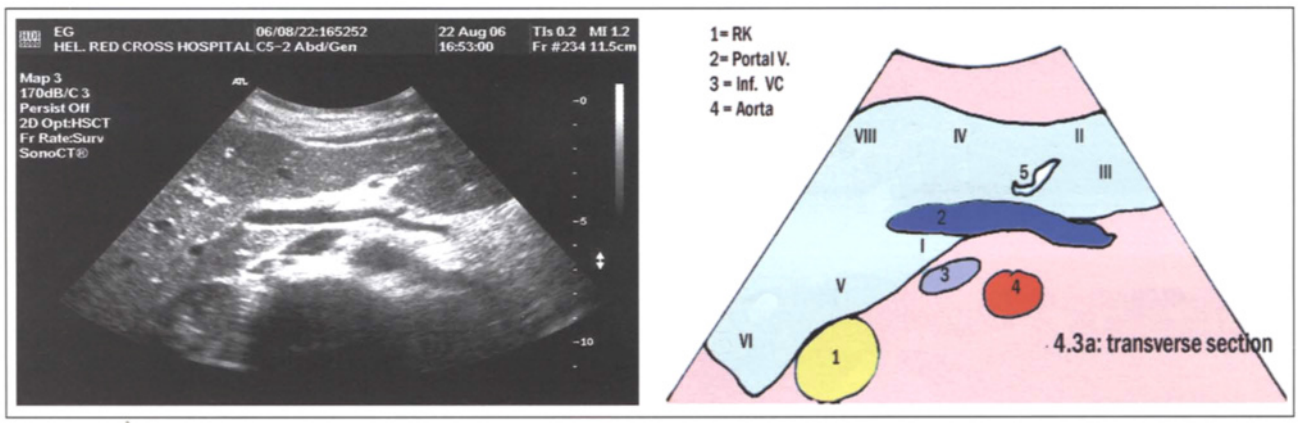


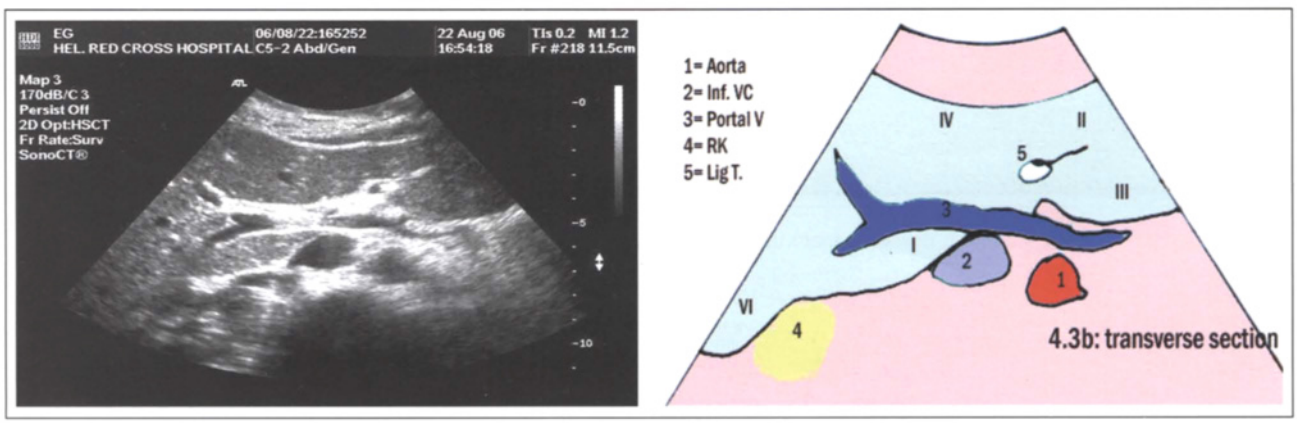
Fig. 4.2. a, b, c, d, e: Liver anatomy in different subcostal oblique sections of physiologic liver.

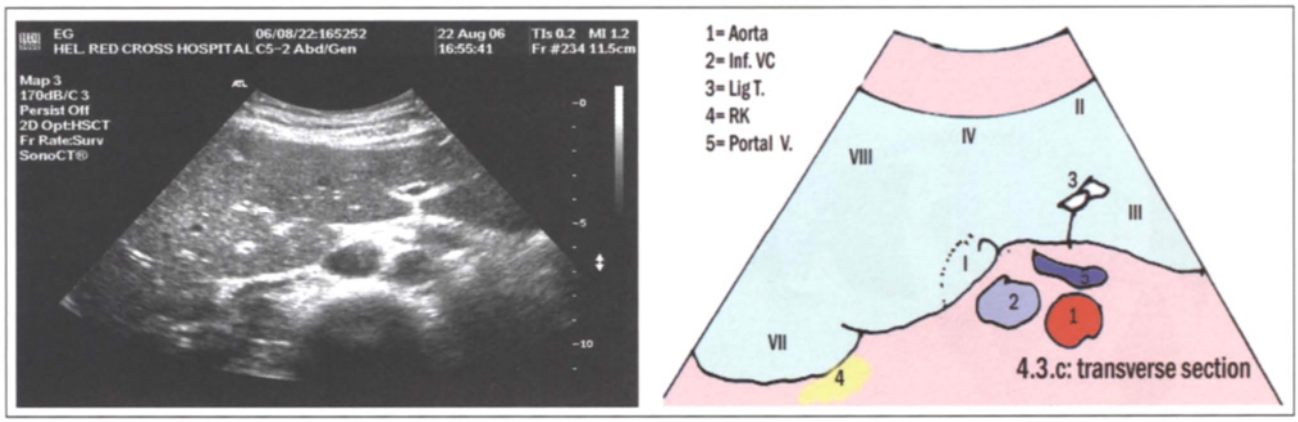


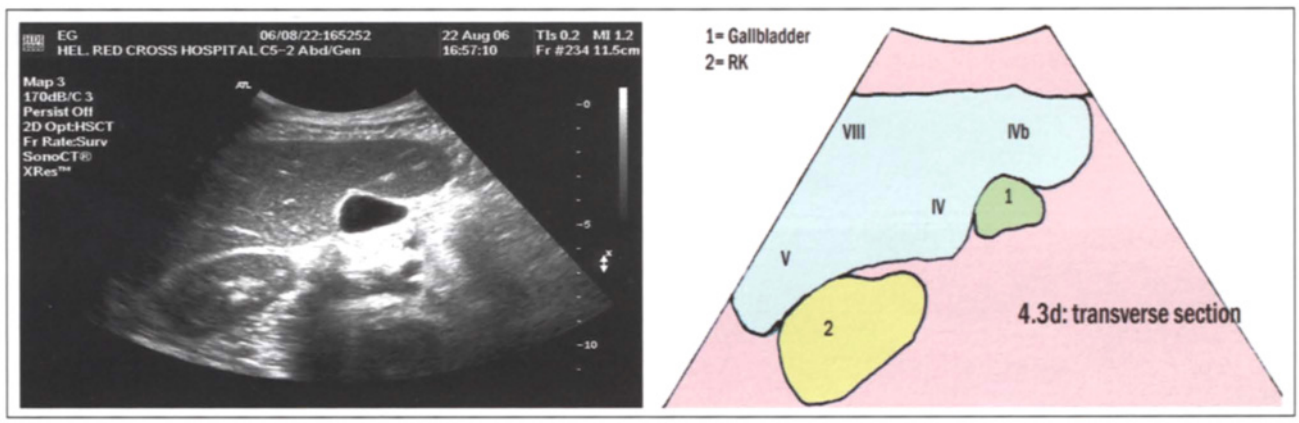
RK = Right Kidney.
Portal V = Portal Vein.
Lig. T. = Ligamentun Terres.

Fig. 4.3. The section of the liver seen on the left column of the page is a Transverse Section. The sections in ultrasonography which follow are as the afore-mentioned section but parallel in different levels. Firstly study the ultrasonography on the left of the page. Secondly study the schematic illustration to understand the anatomy in IUS. Study again and again the two illustrations.









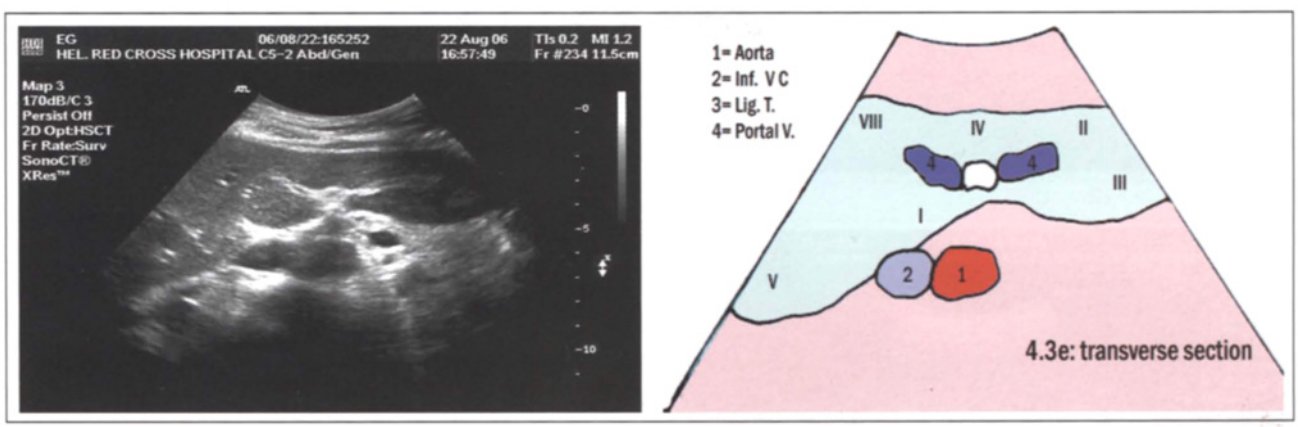


Fig. 4.3. a, b, c, d, e: Liver anatomy in different transverse sections of physiologic liver.

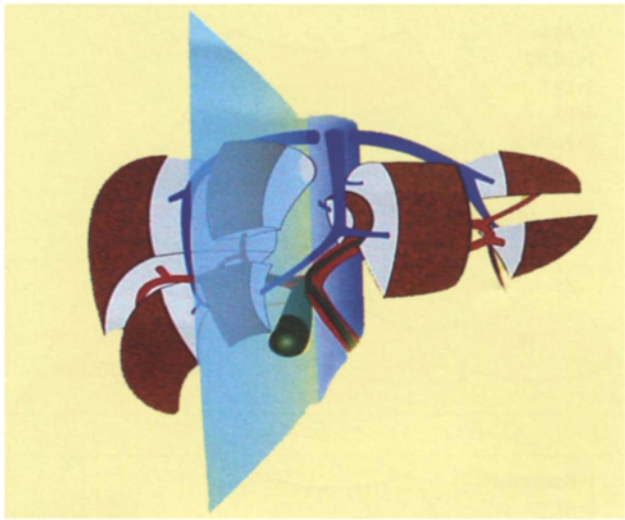
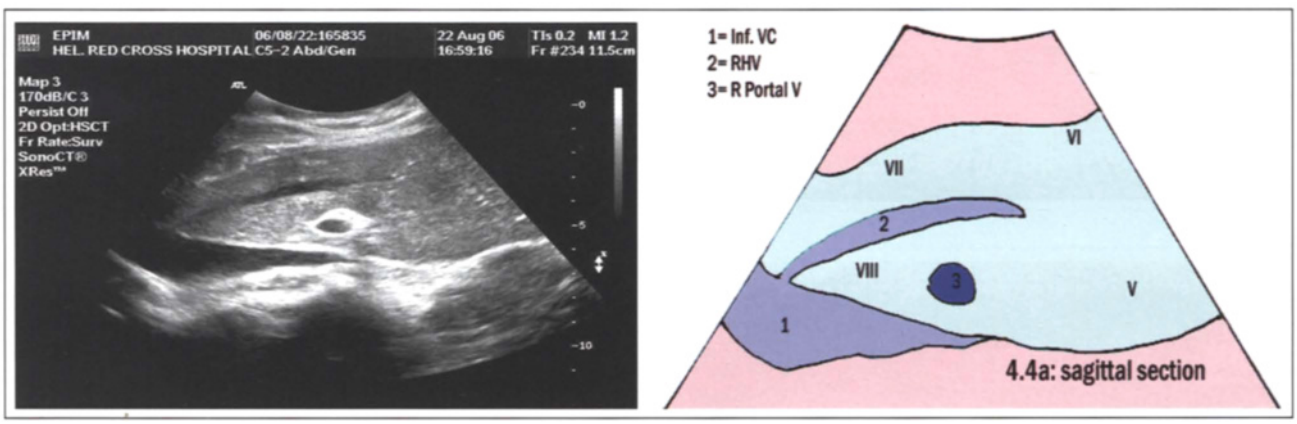
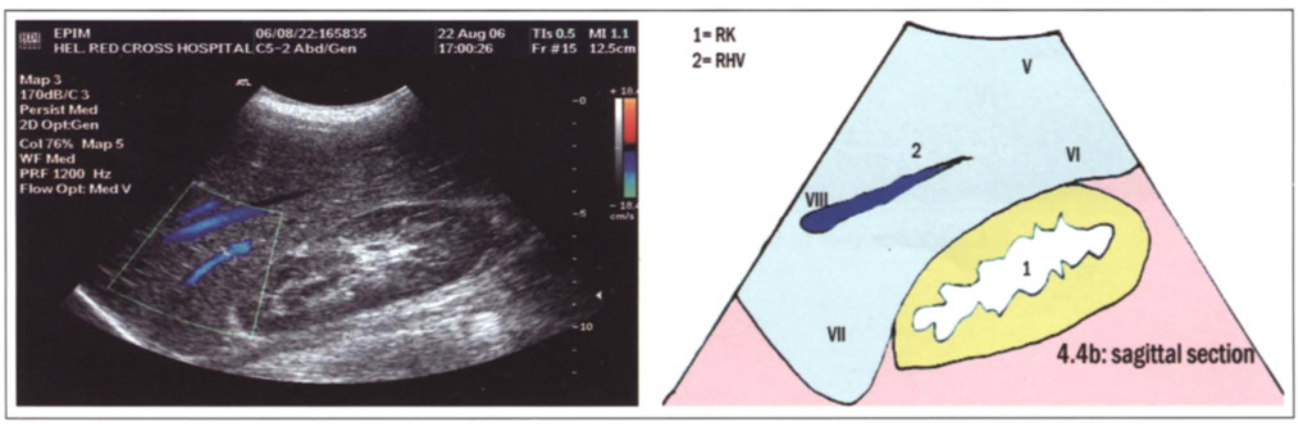
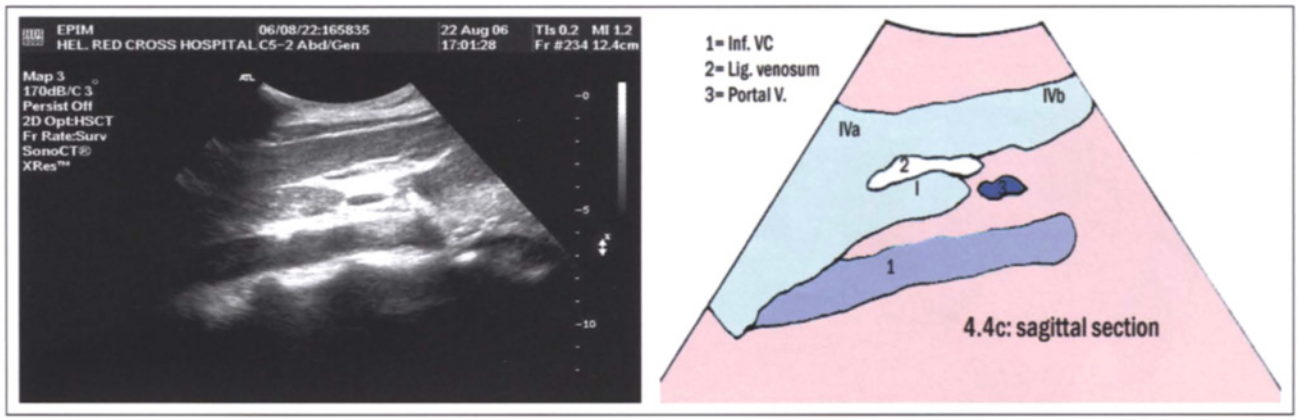
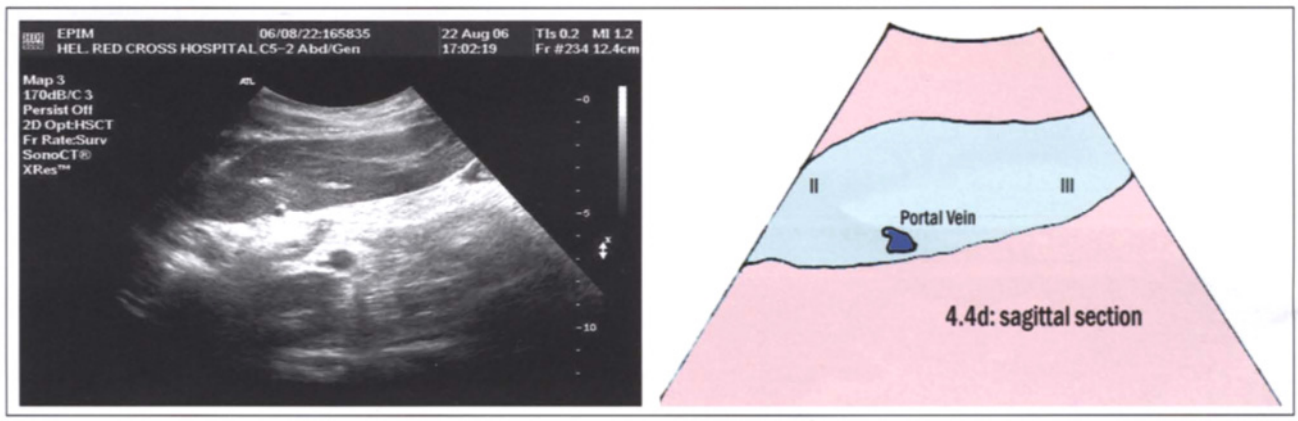


Fig. 4.4. The section of the liver seen on the left column of the page is a Sagittal Section. The sections in ultrasonography which follow are as the afore-mentioned section but parallel in different levels. Firstly study the ultrasonography on the left of the page. Secondly study the schematic illustration to understand the anatomy in IUS. Study again and again the two illustrations.









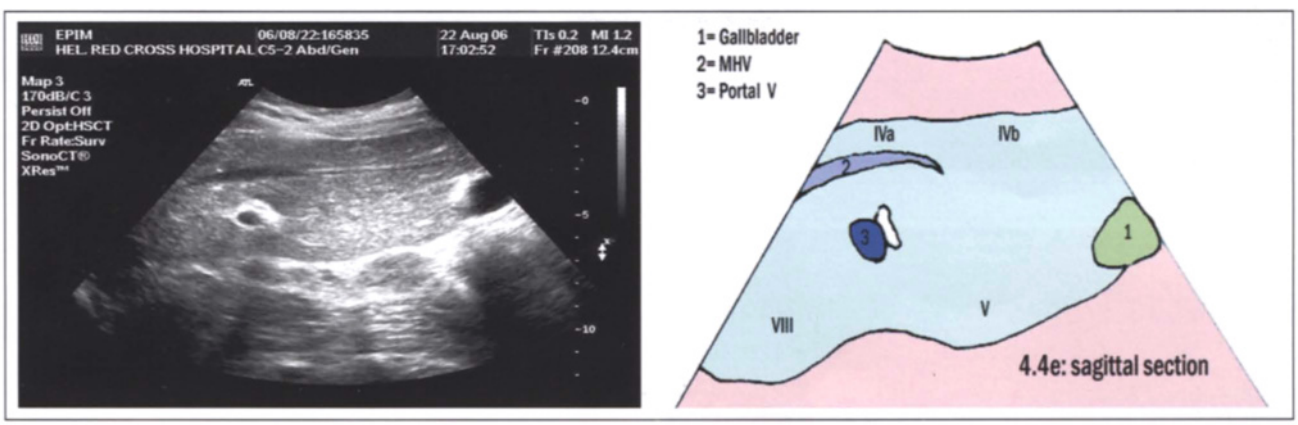


Fig. 4.4. a, b, c, d, e: Liver anatomy in different sagittal sections of physiologic liver.

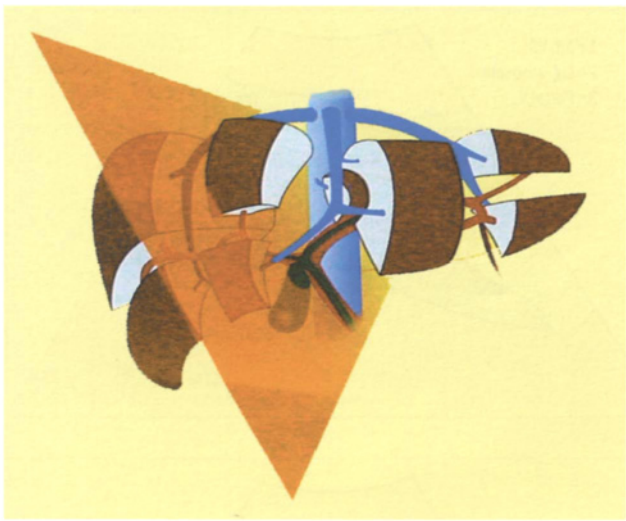
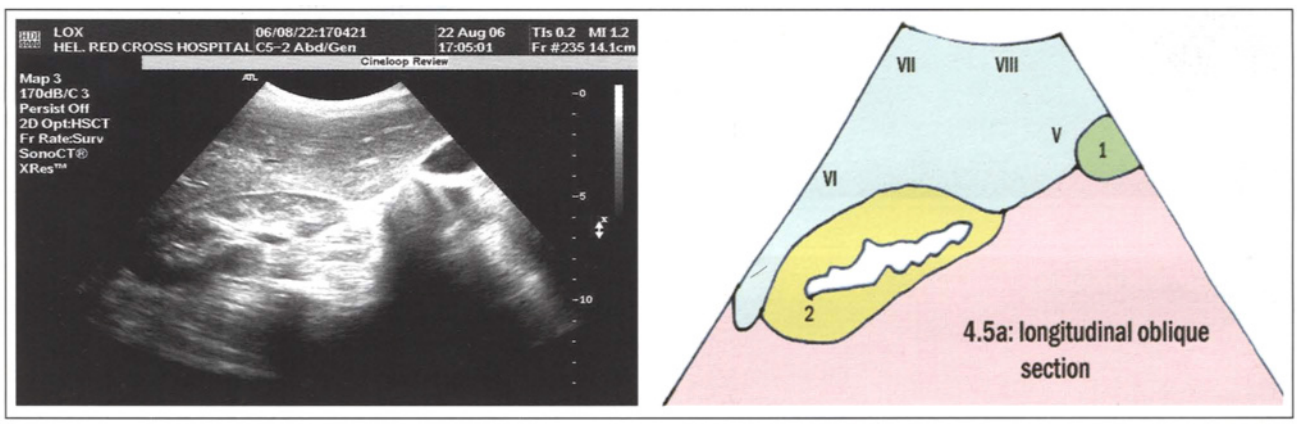
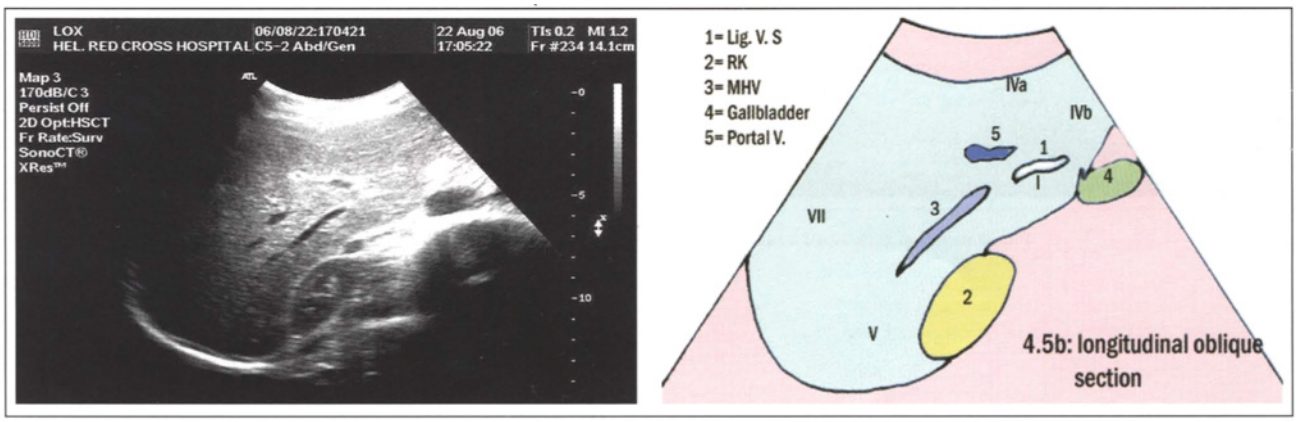
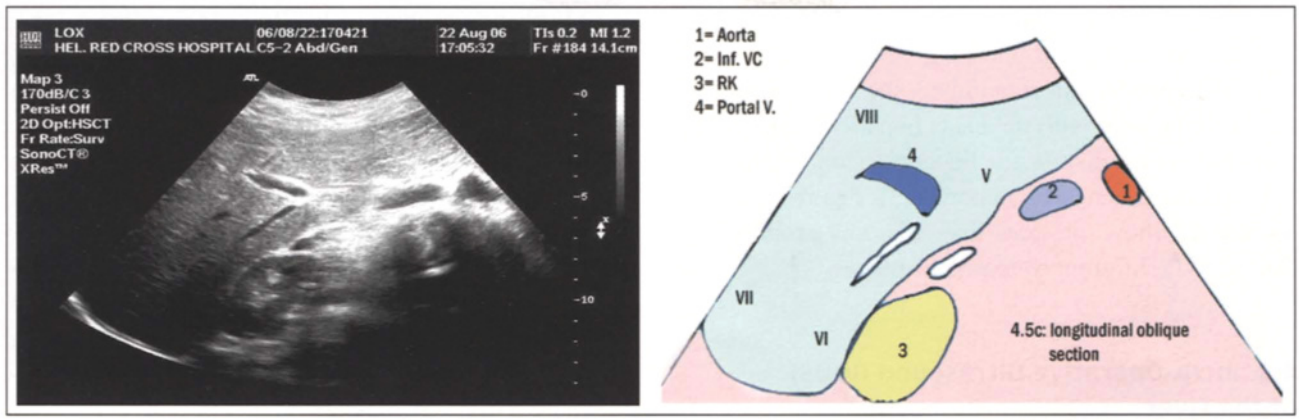
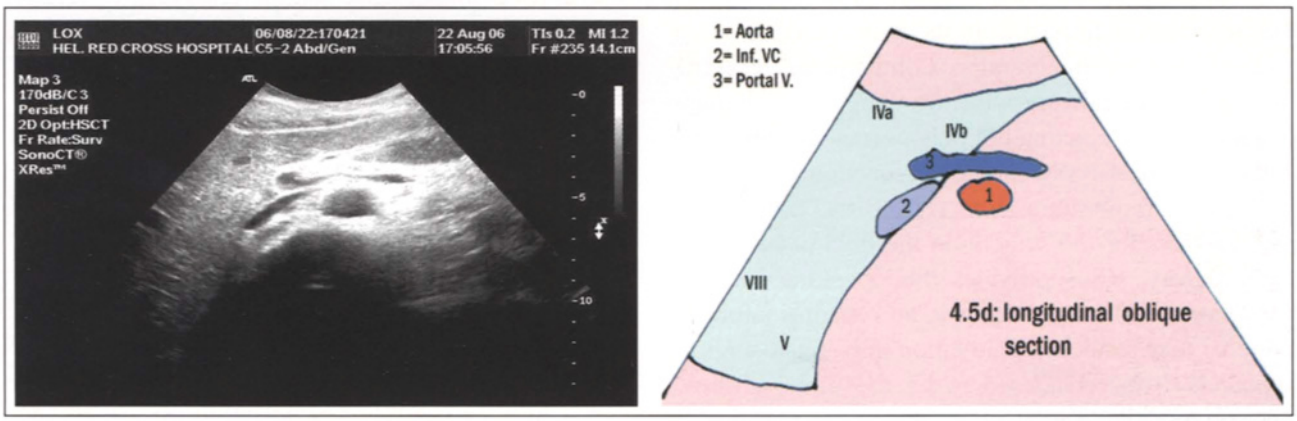


Fig. 4.5. The section of the liver seen on the left column of the page is a Longitudinal Oblique Section. The sections in ultrasonography which follow are as the afore-mentioned section but parallel in different levels. Firstly study the ultrasonography on the left of the page. Secondly study the schematic illustration to understand the anatomy in IUS. Study again and again the two illustrations.









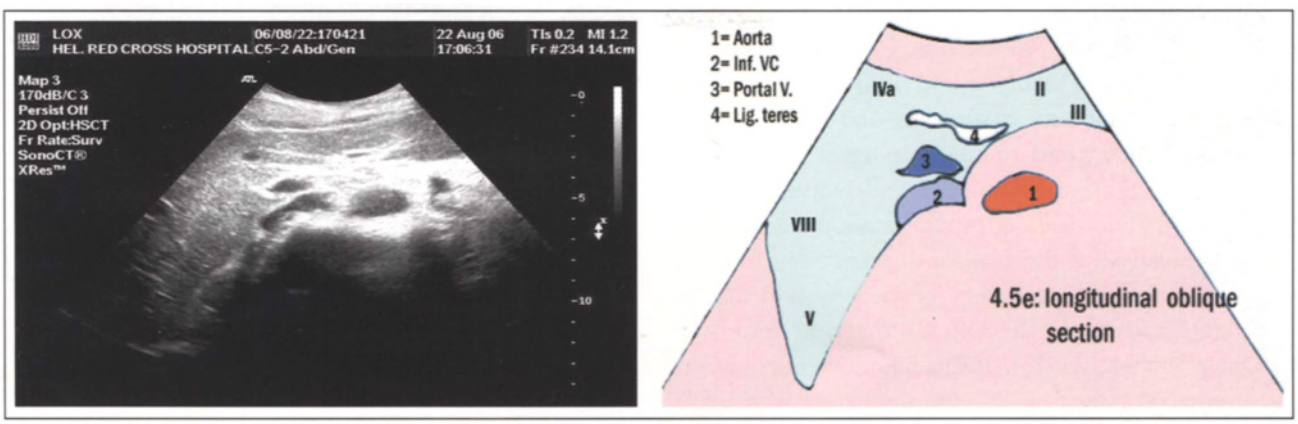


Fig. 4.5. a, b, c, d, e: Liver anatomy in different longitundinal oblique sections of physiologic liver.

A complete survey of the liver with subcostal *oblique, transverse, sagittal,* and *longitudinal oblique* views can give specific information to the radiologist and surgeons, familiar with the exact hepatic anatomy. The universal nomenclature for hepatic lesion localization is based on Couinaud's anatomy [3]. Figures 4.2, 4.3, 4.4 and 4.5 show the exact liver anatomy proposed by Couinaud in different sonographic planes.

4.3. Intra-Operative Ultrasound (IOUS) of the Liver

The resection of tumors from the liver is a demanding and risky surgical intervention. Contemporary imaging modalities can now provide the surgeon with high quality images depicting not only normal anatomy and pathology, but also vascularity and function.

Intra-operative ultrasound (IOUS) has become an essential tool for the surgeon in the field of hepatobiliary surgery. IOUS provides the operating surgeon with useful real-time diagnostic and staging information that may result in an alteration in planned surgical approach. It is considered to be the most sensitive imaging modality for detection of focal liver lesions. It has been shown to affect the clinical management of patients with hepatic metastases (usually colorectal) measuring <2 cm in diameter and primary liver tumors undergoing exploratory laparotomy and segmental resection. It is now used routinely to assist in planning for liver resection, mainly to enable detection of additional tumors –not seen at preoperative imaging– and in the evaluation of the relationship between tumor's major vascular structures. It is inexpensive and can be easily integrated into the OR. With recent improvements in technology [3], IOUS has now become an indispensable means of defining the extent of disease and respectability, providing a guide to anatomic and nonanatomic hepatic resections as well as minimally invasive and percutaneous ablative techniques.

There are several advantages that emanate from the combination of B-mobe ultrasound with color Doppler imaging and/or power flow. These include:

1. Rapid and more precise identification of the anatomical structures, i.e., vessels, ducts and tissue spaces.
2. Detection of small lesions that are difficult or impossible to be recognized by B-mode scanning alone. Small lesions can easily be missed if they have acoustic characteristics similar to those of the adjacent hepatic parenchyma. Also small simple cysts are confidently diagnosed with IOUS.
3. More accurate assessment of vascular encasement/involvement by tumor and precise display of major vessels anatomically related to the tumor. IOUS is useful in depicting venous thrombus showing the relationship between tumor and vessels, and enabling differentiation between extrinsic venous compression and tumor extension into veins.
4. Real-time guidance for safe parenchymal dissection of solid organs with identification and preservation of blood supply.
5. Precise guided needle biopsy or puncture.
6. Visualization of bile flow in the common bile duct by power flow.

To obtain the most useful information with intraoperative US, the sonographer should use a dedicated transducer and a scanning method appropriate for the purpose of the examination. In addition, the radiologist must be familiar with the relevant intraoperative and vascular anatomy and the spectrum of normal and abnormal findings as well as being alert to the pitfalls that frequently occur in the interpretation of intraoperative US images of the liver. The IOUS combined with bimanual palpation of the liver is significantly more accurate than other computed tomography (CT) or percutaneous ultrasonography employed pre-operatively. The ultrasound must be obtained after complete hepatic mobilization [1].

Many studies [4, 6], have shown the superiority of IOUS, compared with helical computed tomography or MR imaging, in the depiction of liver lesions. The liver was evaluated, with knowledge of the CT and MR imaging findings, for the number of lesions, hepatic segmental localization, and the relation of the lesions to the hepatic veins, inferior vena cava, portal vein branches and hepatic hilum. The IOUS proved useful in depicting venous thrombus, showing the relationship between tumor and vessels and enabling differentiation between extrinsic venous compression and tumor extension into veins.

The intra-operative ultrasound is further useful for delineation of hepatobiliary anatomy during laparosco-

pic cholecystectomy [7] (fig. 4.6, 4.7, 4.8, 4.9). Additionally, it can detect useful anatomic information prior to dissection of the cystic duct and is accurate in detecting common bile duct (CBD) stones. In cases of hepatolithiasis, IOUS offers accurate localization of stones, lithotomy (with its guidance), reduction in the rate of residual stones, and a follow up of the outcome of lithotomy. Laparoscopic cholecystectomy (LC) with IOUS is associated with fewer bile duct complications (CBD injuries, bile leaks, and retained CBD stones) than LC without adjunctive imaging. In cases of acute cholecystitis the IOUS is used as an aid to dissection.

IOUS may also be useful in the staging of pancreatic malignancy and pathology of the periampullary region. A complete surgical resection is dependent on accurate preoperative and intraoperative imaging of tumor and its relationship to vital structures. IOUS is a very sensitive method for assessing tumor resectability during surgery. It greatly facilitates intra-operative decision-making [8], whilst adding little time and no morbitity to the operation.

One of the limitations of intraoperative ultrasound is image quality insofar as tumor and vessels are sometimes difficult to delineate. Also small and especially iso-echoic lesions can still be missed and characterization of subcentimetre lesions is difficult. The use of gas-containing contrast agents improves the detection and characterization of focal liver lesions and more particularly the detection of small metastases [2, 5].

However, in cirrhotic patients with hepatocellular carcinoma, contrast-enhanced ultrasound provides such information about tumor vascularity that is useful for nodule differentiation, improving the surgical radicality. Contrast enhanced intraoperative ultrasound also provides information on primary or metastatic tumors of the liver that cannot be otherwise obtained with conventional IOUS (defines the tumor margins).

In oncological liver surgery the aim is to completely resect one or several lesions with a security margin and to resect as little healthy parenchyma as possible. In most cases, however, healthy parenchyma has to be resected if its blood supply and drainage risk being disrupted by surgery. Recently, the involvement of the IO 3D US has increased the orientation ability of the surgeon.

The IOUS is non-invasive, fast, repeatable, and can corroborate real-time visualization of the operative

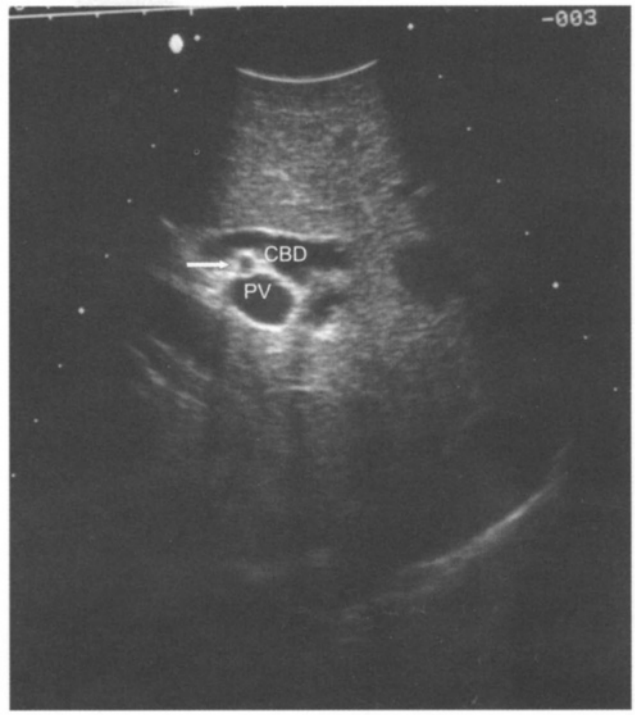


Fig. 4.6. IOUS: CBD, Hepatic artery (arrow) and Portal vein.

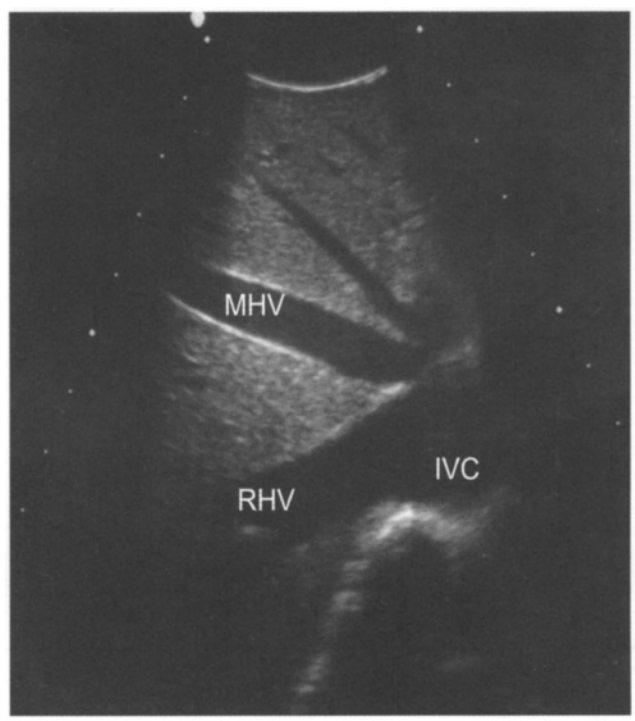


Fig. 4.7. IOUS: IVC and Hepatic veins.

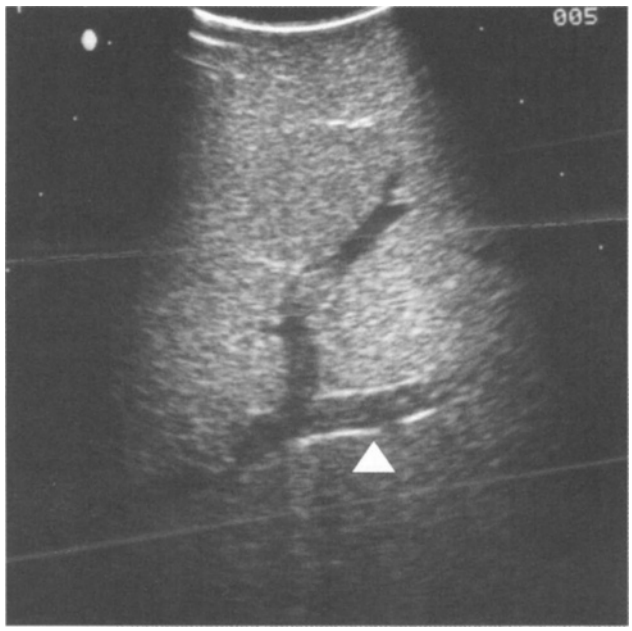


Fig. 4.8. IOUS: Portal vein(arrowhead) and left main portal branch.

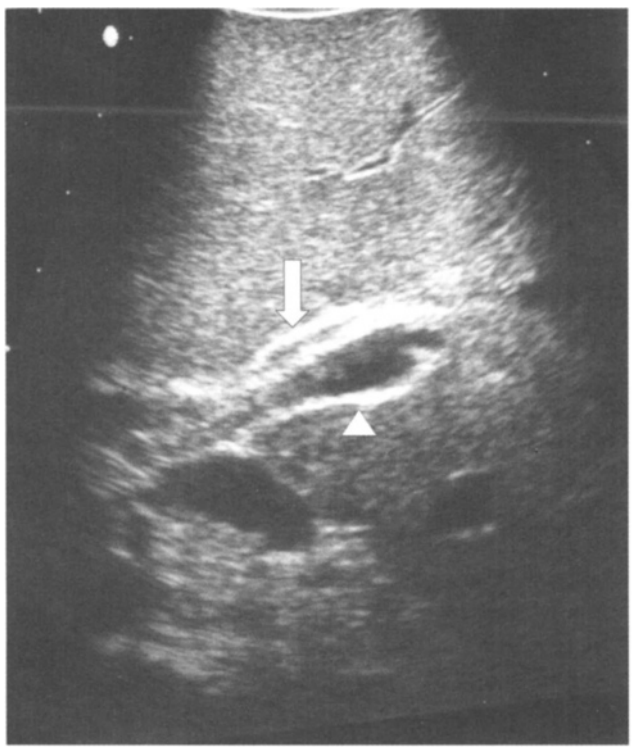


Fig. 4.9. IOUS: CBD (arrow) and portal vein (arrowhead).

field. It pinpoints the exact intraoperative location of the tumor, its relative position to important liver vessels and the boundaries of vascular territories, navigating the way for present day precise and safe liver surgery.

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CHAPTER 5

ELEMENTS OF THE BILIARY TRACT AND LIVER PHYSIOLOGY

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5.1. Bile Composition

One of the most important functions of the liver is the secretion of bile which normally varies between 0,6 and 1,2 lit/day. Composition of bile is given in table 5.1.

Table 5.1. Normal Composition of Bile.

	Liver Bile	Gallbladder bile
• Water	97.5 gm/dl	92 gm/dl
• Bile salts	1.1 gm/dl	6 gm/dl
• Bilirubin	0.04 gm/dl	0.3 gm/dl
• Cholesterol	0.1 gm/dl	Till 0.9 gm/dl
• Fatty acids	0.12 gm/dl	Till 1.2 gm/dl
• Lecithin	0.04 gm/dl	0.3 gm/dl
• Na^+	145 mEq/liter	130 mEq/liter
• Ka^+	5 mEq/liter	12 mEq/liter
• Ca^+	5 mEq/liter	23 mEq/liter
• Cl^-	100 mEq/liter	25 mEq/liter
• HCO_3^-	28 mEq/liter	10 mEq/liter

Table 5.1 shows that, after water, the most abundant component parts secreted in bile are the bile salts [1]. Bilirubin, cholesterol, lecithin and the respective electrolytes of plasma are also secreted or excreted in bile in large concentrations. It should be pointed out that the concentrations of substances in gallbladder bile differ from those in liver bile. Indeed, water and large portions of the electrolytes –with the exception of calcium ions– are reabsorbed by the gallbladder mucosa, after which, the concentrations are lower than those in liver bile. In contrast, all the other components, such as the bile salts and the lipid substances cholesterol and lecithin, are not reabsorbed by gallbladder mucosa as a consequence of which, higher concentrations of these components are observed in gallbladder bile.

The liver cells continually secrete bile which is both stored and concentrated in the "gallbladder sac", or directly flows away into the duodenum. Ultimately two portions of bile empty into the duodenum: the first portion of bile comes directly from the liver via the common bile duct and the second from the gallbladder via the cystic duct.

5.1.1. The Role of Secretin

Secretin, a 27-amino acid neuropeptide, was originally discovered by Bayliss and Starling who demonstrated that this hormone stimulates pancreatic and bile flow in dogs [2]. It is synthesized by specific endocrine cells, S cells, which are mainly localized in the mucosa of the duodenum and proximal jejunum. Secretin is involved in the regulation of the physiology of many organs including the intestine, the liver, the pancreas, and the brain. It has both a stimulatory and an inhibitory effect on gastric mucosa, by enhancing the secretion of pepsin and by blocking the secretion of gastric acid and gastrin from G cells in the gastric antrum. In addition, this hormone decreases the lower esophageal sphincter pressure and relaxes the sphincter of Oddi.

Experimental studies in animal models have shown that secretin increases bicarbonate-rich bile secretion. These studies suggested that secretin-stimulated bicarbonate-rich bile flow derives from the interaction of this hormone with the intrahepatic bile ducts, which is that unit of liver epithilium that is mostly responsible for the secretory/ absorptive activity.

As secretin binds to its receptors (SR), an increase in cAMP levels in extrahepatic bile duct tissue is observed, suggesting that cAMP may be a second messenger system for secretin. This results in activation of the Cl-channel cystic fibrosis transmembrane regulator (CFTR)

with subsequent activation of the Cl^-/ HCO_3^- exchanger leading to bicarbonate secretion in ductal bile [3].

Many factors that influence the secretin-stimulated ductal secretion have been studied. Among these, parasympathetic innervation and the peptides endothelin, VIP, bombesin and substance P are believed to potentiate the effect of secretin. On the contrary alkaline phosphatase, the hormones gastrin and somatostatin and the peptide endothelin decrease its choleretic effect.

What was particularly revealing after the identification and studying of different subpopulations of cholangiocytes, is that secretin receptors are solely expressed by large cholangiocytes in large ducts. The Cl^-/ HCO_3^- exchanger, an important component of secretin-stimulated bicarbonate-rich choleresis, is therefore only expressed by large bile ducts in humans [4].

5.2. Mechanism of Emptying of the Gallbladder

5.2.1. Hormonal and Neuronal Regulation of Gallbladder Emptying

The drainage channel for bile to flow away from the gallbladder into the common bile duct is the cystic duct, but it is the cholecystokinin stimulus that mainly drives the procedure of rhythmical contractions of the gallbladder wall.

The stimulus for the release of cholecystokinin in the blood is a meal abundant in fat. Meal without fat cannot generate excretion with a sufficient quantity of cholecystokinin.

Cholecystokinin is the same substance that causes increased secretion of the pancreatic enzymes, mainly lipase, trypsine, amylase, by acinar pancreatic cells.

It has been known for decades that cholecystokinin (CCK) exerts a stimulatory effect on gallbladder emptying [5]. However the actual mechanisms that lead to hormonal and neural regulation of gallbladder function are not fully understood, given that the nerves that lie within the wall of the organ must be recognized and described.

Results of electrophysiological and immunohistochemical studies showed that ganglia that lie within the wall of the gallbladder are the target for modulatory hormonal, sympathetic and visceral afferent signals that influence its muscle and epithelial activity. The muscular coat and the epithelium of the gallbladder are innervated by neurons that are located in a ganglionated plexus lying between the muscular and serosal layers of the organ. The muscularis and mucosal layers also contain a mixture of intrinsic neurons, sympathetic postganglionic fibers and sensory fibers [6]. The gallbladder ganglia are subjected to two types of excitatory synaptic inputs, the fast excitatory synaptic potentials (EPSP) and slow EPSPs. The fast EPSPs are mediated primarily by vagal inputs, and physiologic signals either act presynaptically on vagal terminals or postsynaptically on gallbladder neurons. No inhibitory synaptic events have been recognized in gallbladder ganglia so far.

The conventional view is that CCK acts directly on smooth muscle cells to cause gallbladder emptying, but recent evidence suggests that a neural mechanism is more important physiologically. Experimental studies indicate that CCK can act presynaptically in gallbladder ganglia to increase synaptic input to gallbladder neurons [7]. Thus, CCK acts on cholinergic nerve terminals to increase the amount of acetylcholine released each time an action potential reaches that terminal. As a consequence the amplitude of the fast EPSP is increased resulting in the release of neurotransmitter onto the muscle.

The ganglionated plexus of the gallbladder contains rich networks of sympathetic postganglionic fibers as well as sensory fibers. Experimental studies throughout 1990 indicate that sympathetic nerves may terminate presynaptically in the ganglionic plexus. An exogenous application of norepinephrine decreases the amplitude of fast EPSPs in gallbladder ganglia by acting on a_2-adrenoreceptors. Therefore, norepinephrine and CCK, which have opposite effects on the contractility of the gallbladder, both act presynaptically, and have opposite effects on the release of acetylcholine from vagus nerve terminals.

5.2.2. Sphincter of Oddi

The effective emptying of the gallbladder is achieved by simultaneous relaxation of the sphincter of Oddi, which guards the distal ends of the common bile duct and the pancreatic duct (either their common or their separate exit into the duodenum).

Consequently for the gallbladder to empty fully, the cooperation of two mechanisms is required: first, the

strong contraction of the wall of the gallbladder (as mediated by the neurohormonal control) and second, the fall of the intraluminal pressure of the common bile duct as a consequence of the reduction in the sphincter of Oddi basal pressure.

Manometric recordings have demonstrated that the human sphincter of Oddi is characterized by prominent phasic contractions superimposed on a basal sphincter pressure 3mmHg above the pressure in the common bile duct and pancreatic duct, as a result of which even the stronger contractile activity of the gallbladder, cannot make emptying possible [8]. Relaxation of the sphincter is a prerequisite for the emptying progress.

Factors affecting the relaxation are as follows: firstly, although cholecystokinin causes contraction of the gallbladder, it acts as relaxant factor on the sphincteric fibers, but this relaxation is not sufficient to allow significant emptying of gallbladder; a second factor is the transmitted peristaltic waves coming from gallbladder contractions, which usually cause a leading wave of relaxation that acts on the sphincter of Oddi, inhibiting the sphincter in advance of the peristaltic wave; the third factor that causes relaxation of the sphincter is the intestinal peristaltic waves. When these waves travel over the wall of the duodenum itself, their relaxation phase exerts a strong relaxing effect of the sphincter [9]. This seems to be by far the most strong and significant factor of all the relaxant factors on the sphincter of Oddi. Subsequently, bile enters the duodenum in a squirt fashion, coinciding with the relaxation phase of the duodenal peristaltic waves.

5.2.3. Bile Acids and their Function

Bile acids are physiologic detergents that facilitate excretion, absorption, and transport of fats and sterols within the intestine and liver. They comprise about 65% of the dry weight of bile. Bile acids have a steroid nucleus and are synthesized in the liver by cholesterol through several intermediary steps. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the major bile acids synthesized by the hepatocytes and are called the primary bile acids.

The 7α -hydroxylation of cholesterol is the rate-limiting step in the pathway for synthesis of the acids. The reaction is catalyzed by 7α -hydroxylase, a typical monooxygenase, that requires oxygen, NADPH and cytochrome P-450 [10]. Another microsomal cytochrome P-450, sterol 12α- hydroxylase is involved in the synthesis of cholic acid and controls the ratio of CA to CDCA. After modifying the steroid ring, sterol 27- hydroxylase catalyzes the steroid side-chain oxidation and cleavage. Cloning of the genes encoding for the regulatory enzymes participating in bile acid biosynthesis has provided molecular tools for understanding the regulatory mechanism. Proving the existence of human mutations in bile acid biosynthetic genes in patients with liver and cardiovascular diseases has provided evidence that bile acid synthesis is linked to cholesterol metabolism and that a deficiency of bile acid synthesis leads to dyslipidemia liver cirrhosis, gallstone disease, and cardiovascular disease in humans [11].

Bacteria in the digestive tract dehydroxylate bile acids to form secondary bile acids such as deoxycholic acid and lithocholic acid. The bile contains both primary and secondary bile acids. Since bile contains significant quantities of sodium and potassium and the pH is alkaline it is thought that the bile acids and their conjugates are made up of a salt form- hence the term "bile salts".

In the intestinal tract the bile acids serve two functions. Firstly they decrease the surface tension of fat particles in the digestive tract, an action known as the detergent or emulsifying function of bile salts. Secondly, bile salts play a significant role in the absorption of the products of fat metabolism. They form complexes called micelles, which are highly soluble because of the electrical charges of bile salts, and lipids are carried to the intestinal mucosa in this form where they are finally absorbed.

5.2.4. Cholesterol Secretion and the Formation of Gallstones

Hepatic cells use cholesterol as a substrate for the formation of bile acids and, as bile acids are secreted into bile, cholesterol is also found there most probably representing a byproduct of bile salt formation and secretion. Depending on the amount of fat an individual consumes, a relevant amount of cholesterol is found in bile since the hepatic cells synthesize cholesterol as one of the products of fat metabolism.

Cholesterol is a hydrophobic molecule, almost

completely insoluble in solution. It is secreted into the bile as cholesterol-phospholipid vesicles. Cholesterol crystals formation seems to occur at the surface of these vesicles. Phospholipids such as lecithin and bile salts combined physiologically, producing an environment where cholesterol is dispersed in the form of micelles which are soluble particles. The vesicles and micelles are the two forms by which cholesterol is held in solution. Any condition that produces an imbalance between the constituents of the micelles predisposes to cholesterol precipitation and gallstone formation. Conditions that can lead to stone formation include increased absorption of either water or bile salts from the bile, increased secretion of cholesterol in the bile and inflammation of the epithelium of the gallbladder. The risk of precipitation is directly related to cholesterol concentration and inversely to the concentration of bile salts and lecithin, giving rise to a triangular coordinate as shown in fig. 5.1 [12].

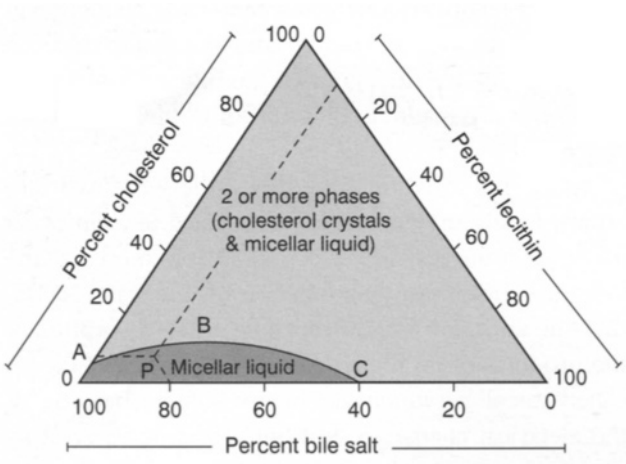

Fig. 5.1. Triangular coordinates relating solubility of cholesterol with concentration of cholesterol, bile salts, and lecithin.

Gallstones are formed when the solubility of bilirubin or cholesterol is exceeded. The cholesterol stone is composed mainly of cholesterol (> 50% of stone composition) and comprises multiple layers of cholesterol and mucin glycoproteins. Pure cholesterol stones are not common; they comprise less than 10% of all stones. Most other cholesterol stones contain variable amounts of bile pigments and calcium. Risk factors for the development of gallstones are well recognized, as is shown in table 5.2.

Table 5.2. Risk factors for the formation of gall stones.

Cholesterol stones
- Obesity.
- High fat diet.
- Estrogens (female, pregnancy, oral contraception).
- Loss of bile salts.
- Impaired gall bladder emptying.

Pigment stones
- Hemolytic disease.
- Biliary stasis.
- Biliary infection.

Obesity, high fat diet, estrogens, heredity, loss of bile salts and impaired gallbladder emptying, can all predispose an individual to a higher risk of developing gallstone disease. A genome wide search was recently published for establishing major susceptibility loci for gallbladder disease in specific minority groups where the prevalence of the disease is particularly high (chromosome 1 of Mexican Americans) [13]. It is also been documented that adiponectin, a protein hormone that modulates a number of metabolic processes including fatty acid catabolism, is associated with gallstone formation. It was found that decreased adiponectin levels is associated with cholesterol gallstone formation and that increased levels of the hormone and increased age is correlated with pigment stone formation [14].

Pigment stones are dark due to the presence of calcium bilirubinate. They contain less than 20% cholesterol and are usually formed secondary both to hemolytic disorders such as sickle cell disease and spherocytosis, and in those with cirrhosis. Two types are recognized, black and brown, both having little in common. Black pigment stones are small and brittle and they almost always formed in the gallbladder. They are the result of supersaturation of calcium bilirubinate, carbonate and phosphate. When the level of deconjucated bilirubin is increased in the bile, precipitation with calcium occurs.

Brown stones may form in the gallbladder or in the bile ducts usually after bacterial infection caused by bile stasis. The bacteria responsible for the infection enzymatically catalyze the conversion of bilirubin glucuronide to insoluble unconjugated bilirubin. The major constituents of these small brownish-yellow soft stones are precipitated calcium bilirubinate and bacterial cell bodies. In western countries, these stones occur as pri-

mary bile duct stones in patients with strictures or in those who develop bile stasis and bacterial infection.

5.3. Physiologic Anatomy of the Liver

The basic structural component of the liver is the hepatocyte, or liver cell. These epithelial cells are grouped together in interconnected plates. The basic functional unit of the liver is the liver lobule of which humans contain many thousands. It is difficult to establish the exact limits of the lobules since they are in close contact in most of their extent. In some regions, the lobules are demarcated by connective tissue containing bile ducts, lymphatics, nerves and blood vessels. These regions, located at the corners of the lobules and occupied by portal triads are called portal spaces. There are three to six portal triads per lobule, each containing a venule (a branch of the portal vein); an arteriole (a branch of the hepatic artery); a duct (part of the bile system); and lymphatic vessels.

According to Rappaport, however, the functional division of the liver is physiologic: each portal triad is perceived as the center, not the periphery, of a functional microvascular unit or acinus. Each acinus is divided into three zones based on the distance from the feeding vessels; the traditional centrizonal region of the lobule is in reality the periphery (zone 3) of two or more acini.

The hepatocytes are arranged radically in the lobule. They form a layer of one or two cells thick similar to bricks of a wall. These cellular plates have a direction from the periphery to the center of the lobule. The spaces between these plates contain capillaries known as liver sinusoids. These sinusoids are irregularly dilated vessels made up mainly of fenestrated endothelial cells. The endothelial cells are separated from the neighboring hepatocytes by a subendothelial space known as the space of Disse, in which projections of the hepatocytes such as reticular fibers and microvilli can be found [15]. As the hepatocyte surface is in close contact with the endothelial wall, it is easy for macromolecules to be exchanged from the sinusoidal lumen to the liver cell and vice versa.

Other types of cells that can be found in the liver lobule, are macrophages and fat-storing cells. The former are called Kupffer cells belonging to the mononuclear phagocyte series, and are found on the luminal surface of the endothelial cells. The fat-storing cells are called Ito cells and are located in the space of Disse.

The blood flow of the liver is derived from two sources, the portal vein and the hepatic artery. It represents 25% of the cardiac output. The portal vein provides about the three fourths of the blood flow and as the portal venous blood has already passed through the gastrointestinal capillary bed, much of the O_2 has been extracted. Blood coming from the hepatic artery is fully saturated and therefore the three-fourths of oxygen used by the liver is derived from the hepatic arterial blood.

As the portal vein and the hepatic artery branch, they give rise to terminal portal venules and hepatic arterioles that enter the hepatic acinus. Blood flows from these terminal vessels to sinusoids which constitute the capillary network of the liver. By directing the blood to the periphery of the acinus, the sinusoids connect to terminal hepatic vessels. Drainage of these terminal venules is made by larger branches of hepatic veins, which are tributaries to the inferior vena cava.

Portal venous pressure is normally about 10 mmHg in humans, and hepatic venous pressure is approximately 5 mmHg. The mean pressure in the hepatic artery branches converging on the sinusoids is about 90 mmHg. The pressure in the sinusoids is lower than the portal venous pressure, so there is a marked pressure drop along the hepatic arterioles. There is an inverse relationship between hepatic arterial and portal venous pressure, and blood flowing in the portal venous and arterial systems varies reciprocally. According to one hypothesis, adenosine is the substance that in part maintains the inverse relation between the arterial and portal venous flow. As it is constantly produced by metabolism, it may accumulate when the portal flow is reduced. The accumulation of adenosine dilates the terminal arterioles. Recently, attention was focused on the role of endothelial cell lining of the sinusoids as well as the stellate cells located in the space of Disse, concerning the regulation of the diameter of the sinusoids and consequently the distribution and velocity of blood flow through these vessels [16].

Changes in the presinusoidal resistance have little effect on the fluid exchange across the sinusoidal wall. On the contrary, changes in the hepatic venous pressure are transmitted to hepatic sinusoids and affect the

exchange of fluids at the level of the sinusoids. The elevation of central venous pressure, as for example in congestive heart failure, causes plasma water to transudate from the liver into the peritoneal cavity leading to ascites.

5.4. Bilirubin Metabolism and the Enterohepatic Circulation

About 250 to 350 mg of bilirubin forms daily; 70 to 80% derives from the breakdown of senescent RBCs, namely the haemoglobin heme group. This takes place in the kuppfer cells of the liver and the reticuloendothelial (RES) system. The remaining amount comes from the catabolism of other haem-containing proteins, such as myoglobin, cytochromes (P-450, c) and catalases [17].

The heam ring is cleaved in the RES to form biliverdin, which in turn is oxidized to bilirubin. Because of internal hydrogen bonding, bilirubin is not water-soluble and, as soon as it is liberated into the plasma, it is transported to the liver bound tightly but reversibly to albumin.

Four phases of hepatic bilirubin metabolism are recognized: (1) uptake, (2) binding (3) conjugation, (4) excretion into the bile [18]. Bilirubin dissociates from albumin and is taken up by the hepatic cell membrane. It is transported to the endoplasmic reticulum by cytoplasmic proteins e.g ligandin, where it is conjugated with an acid, glucuronic acid, and excreted into bile. The reactions for the formation of mono- and diglugu-ronides are catalyzed by the enzyme uridinediphosphate (UDP) - glucuronyl transferase. This conjugated bilirubin is water soluble and is actively secreted into the bile canaliculi and excreted into the intestine with the bile. Because of its large molecular size it is not absorbed by the intestine, but the molecule is hydrolyzed by bacterial enzymes and released free bilirubin. Subsequently is reduced to urobilinogen, a colorless tetrapyrrole. Some of this is excreted in the stools as stercobilinogen. Approximately 20% of the urobilinogen is reabsorbed and undergoes an enterohepatic circulation [19]. Conjugated (direct) bilirubin is both water soluble and less tightly bound to albumin than unconjugated pigment, and is therefore filtered by the glomerulus and appears in the urine when plasma levels are increased.

Knowing the pathways of bilirubin formation, metabolism and excretion allow us to approach the jaundiced patient. An easy way to determine whether conjugated or unconjugated hyperbilirubinemia is present, is to test the urine for bilirubin [17]. If positive, conjugated hyperbilirubinemia is present. An elevation of the direct reacting bilirubin does not provide information in regard to the location of cholestasis. Indeed, bilirubin levels are neither very sensitive nor very specific in detecting liver disease. Furthermore, in cases of localized biliary obstruction as for example in intrahepatic gallstones or tumors, bilirubin can be within normal range for a long time, reflecting the functional reservoir of the normal parenchyma [20].

Mechanisms contributing to predominantly unconjugated hyperbilirubinemia include: (1) increased production, as in hemolytic anemias, (2) decreased hepatic uptake, following administration of certain drugs or due to Gilbert's syndrome, (3) decreased conjucation, as in Crigler Najjar type II syndrome [21]. Crigler-Najjar syndrome type I causes neonatal kernicterus and is almost always fatal. Conjugated hyperbilirubinemia suggests either (1) a defect in intracellular transport of bilirubin or (2) mechanical obstruction to the major extrahepatic bile ducts.

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CHAPTER 6

CONVENTIONAL IMAGING STUDIES OF THE BILIARY TRACT

L. Thanos, S. Mylona

6.1. Introduction - Abdominal Plain X-Ray

The plain abdominal X-ray is the simplest and oldest imaging modality, however it is not very useful in the detection of biliary tract pathology. Findings that relate to biliary tract disease are seen quite by chance in an abdomen X-ray done for other reasons (e.g., detection of free intra or extraperitoneal gas), as the plain X-ray is no longer requested for its detection.

Biliary stones can be shown, if they are calcified. It is estimated that the percentage of gallstones that are radiopaque reaches 20-30%. Gallstones with mixed constituents, namely "mercedes benz" gallstones, have a characteristic stellate faceted appearance with gas containing fissures. Another chance finding is a porcelain gallbladder, caused by calcification of its wall (fig. 6.1), subsequent to chronic inflammatory irritation and predisposed to malignant change.

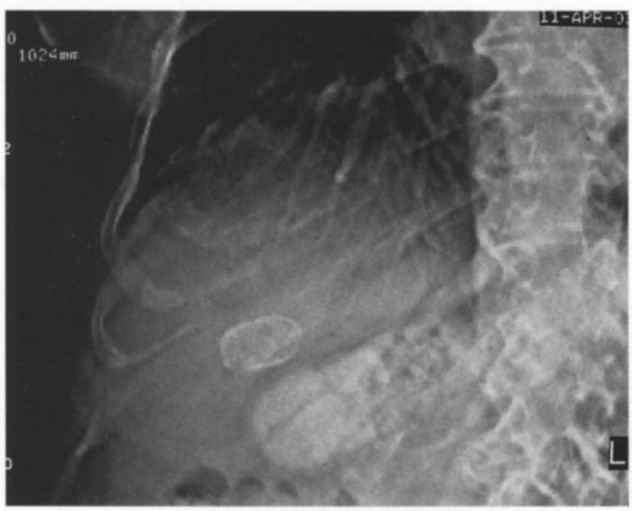

Fig. 6.1. Plain X-ray film: Porcelain gallbladder.

In addition, the presence of gas in the biliary tree, the gallbladder's lumen or gallbladder's wall may be seen in plain film. The gas is seen in the instance of *emphysematous cholecystitis* or as a result of *bilioenteric communication* (former anastomosis due to endoscopic or surgical sphincterotomy or sphincteroplasty, or due to surgical cholecyst-duodenostomy or choledocho-enterostomy). Other rare causes of communication between biliary tract and intestine are abnormal formation of fistulas due to local invasion of malignant tumor, duodenal ulcer penetration into the CBD, or penetration of the gallbladder's wall from a calculus. This late condition may cause obstructive ileus that can also be recognized in a plain abdominal X-ray. Another rare cause of gas in the biliary tree is dysfunction of the sphincter as a result of ampulla malignancy or following recent passage of a stone. In any abnormal bilioenteric communication, when a barium study is performed it may reflux into the biliary tree.

In *chronic liver abscess from Ascariasis,* worms as longitudinal opacities against a gaseous background may detected on plain film.

A hydropic gallbladder is seen upon or below the shadow of the liver as a homogenous slightly hyperdence rounded mass.

In case of the biliocutaneous fistula, a fistulography may be performed by catheterization of the duct and opacification of the abnormal communication with a contrast material injection.

6.2. Transabdominal Ultrasonography of the Biliary Tract

Ultrasound is the most cost effective, most safe stand

method for imaging the biliary tree and the gallbladder with an accuracy rate of 95% [1]. It is the initial examination for investigation of patients with right quadrant abdominal pain and jaundice. It can disclose any abnormality of the gallbladder, and the biliary tree.

6.3. Gallbladder Ultrasonographic Imaging

Cholelithiasis detection is the principal role of gallbladder ultrasonography (fig. 6.2). Gallstones appear as hyperechoic foci with a posterior acoustic shadow and are freely mobile as the patient's position changes. This is the classic triad that characterizes a gallstone. Nonshadowing echo densities correlate with calculi in only 50% of cases [2]. Gallstones as small as 1-2 mm can be detected with modern equipment, resulting in sensitivity and specificity of sonography up to 95% and 97% respectively [1]. Many times these very small calculi may fail to demonstrate an acoustic shadow. Repositioning the patient may give the desired result. Gravity-dependent stone movement it may not be visible if impacted in the gallbladder neck. Occasionally, biliary sludge may appear as a mobile mass in the gallbladder's lumen. Its composition may vary from one subject to another and contains sludge, blood clots, pus, and parasites. This mass has no acoustic shadow [3]. *Mirizzi syndrome* is the result of a gallstone obstructing the cystic duct, causing extrinsic pressure of the common hepatic duct and acute cholecystitis.

Gallbladder *polyps* also appear as echogenic foci, with no acoustic shadow and remain fixed when changing the position of the patient.

The normal gallbladder wall has a thickness of less than 3mm. Many causes predispose to *diffuse thickening of gallbladder wall,* the most common is being acute or chronic cholecystitis. Other significant causes of gallbladder wall thickening include ascites, alcoholic liver disease, hepatitis, artifacts induced by the presence of pericholecystic fluid, hypoalbuminemia, right-sided heart failure, and incomplete gallbladder distention. *Focal gallbladder wall thickening* is associated with primary disease.

Ultasonographic imaging of *Gallbladder carcinoma* may appear as intraluminal mass (10%-28%), asymmetric wall thickening (19%-47%), or a mass replacing the gallbladder (28%-39%). Calcification of the wall is another finding that may coexist [4]. Ultrasound can detect these changes and show possible bile duct dilatation, adenopathy or hepatic metastases [5]. In cases of uncertainty, a percutaneous US-guided biopsy may safely provide a definite diagnosis [6]. *Gallbladder sarcomas* are very rare and have a similar appearance to carcinoma. Other causes of focal wall thickening are metastases (melanoma, gastrointestinal cancer and breast cancer), polyps (adednomatous, cholesterol), or gangrenous cholecystitis, papillary adenomas, adenomyomatosis (fig. 6.3), and tumefactive sludge [7].

Acute cholecystitis imaging is an urgent condition that may differentiate from other pathologic entities that include pancreatitis, appendicitis, peptic disease, hepatitis, renal and intrathoracic conditions. Ultrasound can

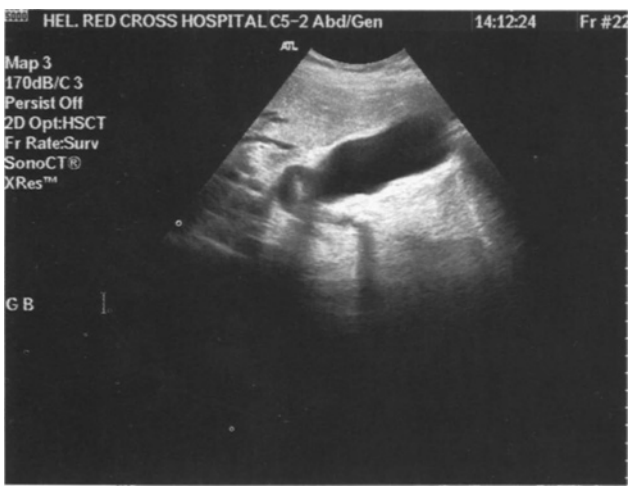

Fig. 6.2. Ultrasonogram of the gallbladder. Stone into the cystic duct.

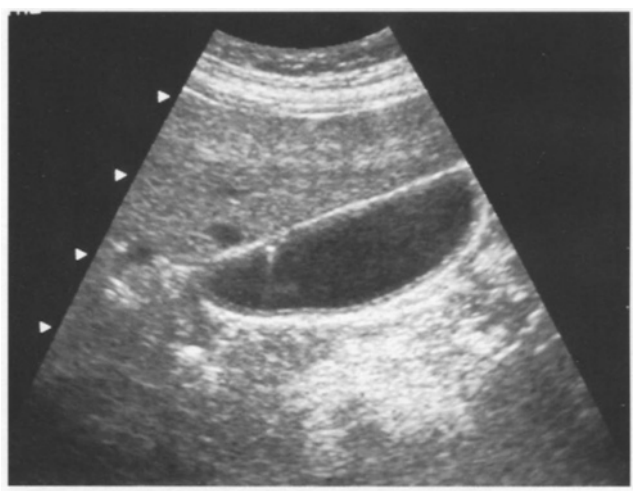

Fig. 6.3. Ultrasonogram. Adenomyomatosis of the gallbladder.

be used to confirm diagnosis and can distinguish acute from chronic cholecystitis in 95% to 99% of cases [8]. Gallstones accompanied by the presence of the sonographic Murphy sign suggest acute cholecystitis. This inflammatory condition is associated with cholelithiasis in 90% to 95%. Other signs of acute cholecystitis include gallbladder dilatation, sludge, and diffuse wall thickening.

Acalculous cholecystitis frequently complicates a critical disease (trauma, burns, surgery, diabetes, arterial chemotherapy, and hyperalimentation) [9]. This condition is hardly ever detected sonographicaly. The sonograpic Murphy sign may indicate the diagnosis. This condition presents complications, such as gangrene and perforation, more frequently than calculous cholecystitis.

Complications of acute cholecystitis include emphysematous and gangrenous cholecystitis potentially leading to perforation. All these conditions display increased morbidity and mortality. Ultrasound can diagnose these complications with great sensitivity and specificity [7].

In *emphysematous cholecystitis* gas-forming organisms invade and devitalize the gallbladder wall and release gas inside its wall and its lumen. Identification of this intramural or intraluminal gas is of great importance since emphysematous cholecystitis may engender gangrene of the gallbladder which is associated with a high mortality rate. Intramural gas is seen as an area of high reflectivity in the gallbladder wall, with distal reverberations. A large amount of gas may mimic calcification; intraluminal gas is seen as a dense band of hyper-reflective echoes, causing reverberation and shadowing that often obscures the posterior wall of the gallbladder. If there is any doubt, the suspected gas collection should be confirmed with plain X-ray film or CT.

Gangrenous cholecystitis may prove fatal for the patient and must be suspected in a symptomatic individual with irregularities, focal thickenings and striations of the gallbladder wall [10]. The presence of wall necrosis and formation of microabscesses predispose to perforation and empyema. Frequently, intraluminal membranes are also seen and are derived from fibrinous strands or exudates, or necrosis and sloughing of the gallbladder mucosa [7].

Hemorrhagic cholecystitis is a further complication of acute cholecystitis. The sonographic findings are similar to gangrenous cholecystitis. Gastrointestinal bleeding may not be obvious.

In such complications (especially in gangrenous cholecystitis) cholecystectomy is usually required to avoid perforation and formation of pericholocystic abscess. If the operation is considered too risky for the patient a *percutaneous clolecystostomy under US guidance* may be performed.

To classify *perforation of the gallbladder* Niemeier has proposed three stages: a) Acute: causes peritonitis, b) Subacute: causes pericholecystic abscess, and c) Chronic: causes internal biliary fistula [11]. Most common of them is type (b). Early identification is essential as it affiliates with 19% to 24% mortality [9]. Sonographically, it may appear as pericholecystic fluid of mixed echogenicity that may envelope the gallbladder, rendering it invisible. Color Doppler may disclose the internal vascularity in the pericholecystic mass. The wall of the gallbladder may not be visible or may be thick or emphysematous. The site of perforation may be seen as a defect of the wall called the "hole sign". If there is a perforation in a bowel loop the fistula may be detected. In many cases CT is considered superior to US for gallbladder perforation detection.

Another urgent condition that may require cholecystectomy or cholecystostomy is *gallbladder torsion.* Sonographically there is little difference from acute cholecystitis, with the exception of two findings - the floating of the gallbladder away from liver surface and a stretching cone-shaped pedicle [12].

In *xanthogranulomatous cholecystitis* the sonographic findings are not specific. Cholelithiasis is presented in 96% and an irregular thickening of the gallbladder wall resembling carcinoma is displayed in 70% [9].

Ultrasound plays an important role in preoperative screening of laparoscopic cholecystectomy. Preoperative ERCP or cholangiography during surgery must be performed to exclude choledocholithiasis if small calculi are presented within the gallbladder. In the event of a bile duct dilatation or cloledoholithiasis, preoperative ERCP or a surgical bile duct exploration is vital. Large gallstones require an extensive umbilical incision. Complications are suspected, open cholecystectomy should be performed. Finally, anatomical variations or other abdominal pathology could cause a change in the surgical approach [13].

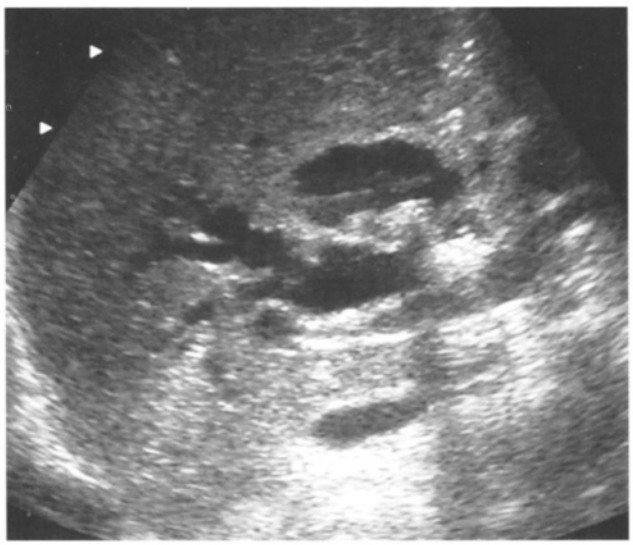

Fig. 6.4. Ultrasound. Dilated intrahepatic bile ducts.

6.4. Common Bile Duct Imaging

Biliary obstruction is easily recognized with sonography indirectly as biliary tract dilatation (fig. 6.4). To determine the cause and the level of this obstruction we must bear in mind that bile ducts dilate centrifugally from the point of obstruction. Dilatation of extrahepatic bile ducts precede intrahepatic bile duct dilatation. Clinically, if a patient has dilated ducts but no accompanying symptoms -elevated bilirubin, pain, sepsis, or elevated liver enzymes, including alkaline phosphatase- the dilated ducts are unlikely to be clinically relevant. However normal duct diameter does not exclude obstruction, as dilatation presupposes a compliant adjacent liver parenchyma. Thus, dilatation of intrahepatic bile ducts may not be apparent in patients with fibrosed or infiltrative liver parenchyma. Moreover, normal duct size cannot exclude incipient or intermittent obstruction. The use of color and power Doppler may be valuable in demonstrating that the dilated structures are ducts and that the normal portal veins and hepatic arteries run adjacent to them. The cause of obstruction may be extraluminal or intraluminal, with stone presence being the most common cause of the latter.

6.5. Choledocholithiasis Ultrasonographic Imaging

Choledoholithiasis is investigated in 70% of patients as bowel loops may impede visualization of the common bile duct [14]. All calculi present an acoustic shadow. An uncommon cause of stone obstruction is Mirizzi syndrome (impacted stone in the cystic duct), which sonographically shows intrahepatic bile duct dilatation with normal CBD and a large stone in the cystic duct or gallbladder neck [15]. *Intrahepatic biliary calculi* are uncommon. They characteristically present in recurrent pyogenic cholangitis, a common disease in Asia, which may occur in prolonged bile stasis. These stones have a varied range of appearance and may not have an acoustic shadow. *Intraparenchymal calcifications* may be difficult to differentiate from intrahepatic biliary calculi. Shadowing from *pneumobilia* may limit the sonographic ability to evaluate the ductal system.

6.6. Cholangiocarcinoma Imaging

Another possible cause of intraluminal obstruction is a focal polypoid mass which is visible in the distal common bile duct and represents *ampullary neoplasm*. An unusual case of dilatation is bile *duct carcinoma* (*cholangiocarcinoma*). This neoplasm is usually located (90%) within the large bile ducts, and the remaining 10% at the periphery. Local Neoplasms located at the convergence of left and right hepatic ducts are called *Klatskin tumors* and represent the 25% of cholangiocarcinomas [16]. Clinically the patient appears with biliary obstruction. The most frequent and possibly the only sonographic finding of this tumor is dilatation of an isolated intrahepatic bile duct. A mass may not be visible, but liver and porta hepatis invasion can be detected. The segmental dilatation and non-union of the right and left hepatic ducts is characteristic. Dilated intrahepatic ducts with normal extrahepatic bile duct are also suggestive of Klatskin tumor. Papillary and nodular types of Klatskin cholangiocarcinoma manifest as polypoid intraluminar masses. The infiltrating type, despite being the most common subtype, is the most difficult to appreciate in ultrasound. It most often appears as an isoechoic infiltration of the peridu-

ctal soft tissue and liver, producing a central mass effect at the liver hilum with altered liver echogenicity, pressure effect on adjacent vessels, especially the portal vein, or focal irregularity of the ducts. Hepatic lobar atrophy indicated by crowding dilated bile ducts, close to the liver surface, is strongly indicative of cholangiocarcinoma [17]. A similar sonographic appearance to common bile duct carcinoma is observed in sclerosing cholangitis, AIDS- cholangitis, oriental cholangitis, invasive hepatoma or gallbladder cancer [7]. Cholangiocarcinoma of the distal bile duct needs to be differentiated from pancreatic head carcinoma, cancer of Vater's ampulla, blood clots, strictures and benign tumors. *Extrahepatic cholangiocarcinoma* usually appears as a polypoid mass or more often as a short stricture. Cholangiocarcinoma is rarely encased in the intrahepatic ducts unless the liver is infected by the Opisthorchis viverrini [18]. *Peripheral cholangiocarcinoma frequently* appears as a nodular or infiltrating lesion. The most common appearance of this tumor at sonography is that of a homogeneous hyperechoic mass, either single or multiple. The larger the tumor, the more hyperechoic it appears. Differential diagnosis from hepatoma is based on the fact that peripheral cholangiocarcinoma does not have a hypoechoic halo, whereas dilatation of bile ducts peripheral to the tumor is quite often observed. When peripheral cholangiocarcinoma cannot be distinguished from metastatic adenocarcinoma, percutaneous guided biopsy serves as a tool to confirm diagnosis.

Intrahepatic biliary neoplasms cause intraluminal obstruction followed by dilatation. Cystadenoma and its malignant counterpart *cystadenocarcinoma* are rare tumors that occur in middle-aged females. The tumors are cystic masses surrounded by a fibrous capsule, with nodularity and internal septation that may be multiple and calcified. They are difficult to differentiate interse. The more prominent the septations and nodularity, the greater the likelihood of malignancy. If hemorrhage occurs, they tend to become more hyperechoic. They must be differentiated from an echinococal cyst, abscess, simple cyst complicated by hemorrhage, and cystic metastasis [19,20]. Adenomas, fibromas, papillomas, hamartomas, granular cell myeloblastoma, neurofibromas and neuromas, rare benign intraluminal neoplasms cannot be differentiated with ultrasonography.

If sonographic evaluation provides evidence of distal bile tract obstruction, yet the cause and site of obstruction cannot be identified, an ERCP should be performed.

Sonography and modern real-time equipment with high spatial resolution and improved techniques can detect the level of dilatation in up to 92% of extraluminal obstruction cases and accurately indicate the cause in up to 71% of cases [21].

When the extrahepatic ducts are normal, the intrahepatic obstruction is usually secondary to cholangitis or liver neoplasia, primary or metastatic. The highest percentage of extraluminal obstructions occur in the distal duct due to pancreatic carcinoma, focal or diffuse pancreatitis, and strictures [7]. Pancreatic carcinoma and focal pancreatitis may be difficult to differentiate. Strictures may not be visible and are attributable to chronic pancreatitis and AIDS cholangitis. Obstruction may also occur at the level of porta hepatis, usually a result of a primary or metastatic tumor or adenopathy. Other causes of obstruction between the pancreas and the porta hepatis include masses of the colon or duodenum and sclerosing cholangitis. In general, intrahepatic biliary duct dilatation can be diagnosed by irregular angular branching, a central stellate configuration, and acoustic enhancement posterior to the ducts. A parallel channel or shotgun sign represents a dilated duct in association with a portal vein branch within a peripheral portal triad. In cases of malignancy, sonography can supply information regarding tumor resectability (hepatic or nodal metastasis, portal vein thrombosis, extensive bile duct obstruction with atrophy of the contralateral hepatic lobe). Vascular patency or portal vein involvement can be detected in 83% to 100% of patients with colour duplex sonography [22].

Choledochal cyst is another cause of obstruction. These are not true cysts but dilatations of the bile ducts. Sonographically, the cysts may resemble an enlarged gallbladder. There are five types according to the part of the biliary tree involved. Type I concerns cystic dilatation of the common bile duct and type V consist of multiple communicating cysts involving the intrahepatic ducts (named *Caroli's disease*). However, they are commonly found close to the head of the pancreas and are frequently (50% of cases) associated with intrahepatic bile duct dilatation. These facts are helpful in the differential diagnosis [23, 24].

Bile duct hamartomas are focal masses that range in

echogenisity from hypoechoic to hyperechoic and they simulate malignancy [25].

Sclerosing and AIDS Cholangitis usually present with smooth or irregular wall thickening of the intrahepatic bile ducts and no or minimal dilatation. It involves the bile ducts of the whole liver, a clue which differentiates these pathologic entities from primary and metastatic neoplasms [7].

In the case of *biliary parasitosis* the patient may present with biliary colic, and acute cholecystitis. The most common parasites to cause this disease include Ascariasis lumbricoides, Clonorchis sinensis, and Fasciola hepatica. Sonography is the first modality which is performed and the diagnosis is given by showing the worm(s) as tubular structure(s) that may be either straight or coiled in the case of *Ascariasis lumbricoides* [26]. In *Clonorchis sinensis* the parasite may not be visible. The involved bile ducts may be thickened with increased echogenicity [27]. Dilatation of small intrahepatic duct is seen. Chronic infections may complicate to cholagiocarcinoma [18,26]. *Fasciola hepatica* may sonographically reveal echogenic foci in the gallbladder and dilated extrahepatic ducts [28].

After laparoscopic or open cholecystectomy complications may occur. The common bile duct or the common hepatic duct could be mistaken for the cystic duct and may be ligated. Injuries from laser or cautery may lead to strictures, or bile duct leak. The effect of these injuries is intrahepatic bile ducts dilatation in the affected segment that can be easily detected with ultrasound. In addition, bilomas due to bile leak is sonographicaly seen as cystic fluid collection. Abscess formation has a mixed sonographic appearance consisting of hyperechoic and anechoic (cystic) components with or without bright lucencies due to air. Other complications involving hematoma, free fluid collection, lymphocele, and peritonitis may be detected as anechoic or hypoechoic nonspecific collections. In the case of mucocele of a cystic duct remnant, a round anechoic lesion is seen in the hepatic hilum.

6.7. Computerized Tomography (CT) Imaging

Ultrasound and MRCP are the primary imaging studies in the investigation of obstructive cholestasis. In the case of obstruction caused by tumor, CT seems to be more sensitive in determining the level of obstruction, characterizing the tumour and staging the disease in the event of malignancy. The intrahepatic duct dilatation is local or generalized depending on the obstruction level (fig. 6.5). The obstruction, as mentioned above, may be caused by stones, strictures, inflammation, intraluminal or extraluminal tumors, and compression. On CT scan they appear as tubular ramified structures of low attenuation running adjacent to the portal venous radicles [29]. After IV contrast material administration they remain hypoattenuated. CT has a reported sensitivity in the detection of stones in the common bile duct distinct (45% to 90%) [29, 30, 31], with a typical target or bull's eye pattern. If there is suspicion of cholangiolithiasis, non-enhanced scans are required with oral contrast material being withheld for better visualization. High attenuation stones can be easily detected in the gallbladder or CBD and CHD with CT. Unfortunately only 20% of duct stones are homogenously hyperattenuated on CT [29], and approximately 15%-25% of biliary calculi are not detectable with CT. Benign distal obstruction causes gradual tapering in the diameter of the bile duct on serial CT sections, whereas malignant obstruction causes abrupt termination of the dilated CBD.

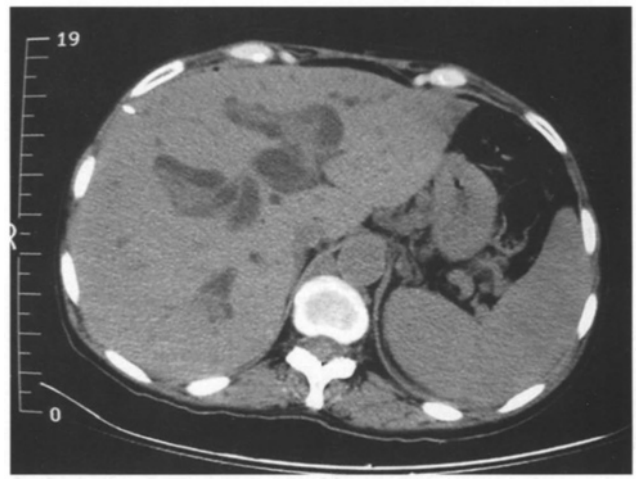

Fig. 6.5. Computed tomography. Dilated intrahepatic bile ducts.

In papillary stenosis, CT plays a limited role as the imaging procedure of choice for its detection is MRCP. CT scanning may reveal a prestenotic dilatation which is often accompanied by pancreatic bile duct dilatation ("double duct sign") [32]. A papillary tumor is difficult

to differentiate from stone or enlarged intaduodenal papilla [30].

Mirizzi syndrome, another cause of obstruction, appears on CT as intrahepatic and extrahepatic ducts dilatation. An impacted stone in the gallbladder neck or cystic duct may be visualised with advanced equipment and thin section collimation [32].

Choledochal cysts are congenital biliary tree abnormalities that may lead to bile duct dilatation. A true choledochal cyst is a localized dilatation of the extrahepatic bile ducts. They appear as cystic lesions up to 15 cm in diameter by the porta hepatis. There is no or minimal intrahepatic dilatation [23]. They may differentiate from simple liver or pancreatic cysts, from encapsulated fluid collections, and from enteric duplication cysts [33]. Type III choledochal cyst is known as *choledochocele.* This is a CBD cyst which protrudes into the wall and lumen of the duodemum. Multislice CT is the best technique to diagnose this lesion [32 ,34]. Type V of this congenital disease, *Caroli's disease,* appears on CT scan as cystic dilatations within the liver parenchyma. This anomaly is usually associated with cysts in kidneys and may differentiate from polycystic liver disease. The differentiation clue in Caroli's disease is the contiguity of the cysts, with dilated intrahepatic bile ducts and the appearance of a central dot inside the cyst [35]. This dot represents the accompanying portal vein that is surrounded by the dilated intrahepatic bile ducts.

Bile duct hamartomas, also called von Meyenburg complexes, are shown in CT as multiple hypoattenuating, cystlike hepatic nodules occurring in both lobes of the liver and typically measuring less than 1.5 cm in diameter. The latter feature is the most essential one in the differential diagnosis from multiple simple cysts. Furthermore, simple cysts bear a typical regular outline, whereas bile duct hamartomas have a more irregular outline. Bile duct hamartomas do not exhibit a characteristic pattern of enhancement after intravenous administration of iodinated contrast material. Although homogeneous enhancement of the lesions has been noted in some cases, most report no enhancement seen on contrast-enhanced CT images [25].

Acute and chronic cholecystitis is an incidental CT finding, as CT is not the modality of choice for their detection. In the *acute* form there is a thick wall that enhances after IV contrast material administration due to hyperemia. Frequently, the gallbladder is hydropic and gallstones are seen. The *chronic* form must be differentiated from gallbladder carcinoma. The gallbladder is increased in size with regular or irregular thickening of its wall, which may appear calcified (*porcelain gallbladder*) (fig. 6.6). In *xanthogranulomatous cholecystitis* the gallbladder wall is thickened and lobulated, and pericholecystic extention is commonly present. *Emphysematous cholecystitis* can be detected on CT with great sensitivity, although sonography and/or plain abdominal radiography establishes the diagnosis. Air is characteristically seen in the lumen and/or gallbladder wall. CT can further assist diagnosis in an irresolute sonographic appearance in the event of a gangrene complication in cholecystitis and absence formation [36].

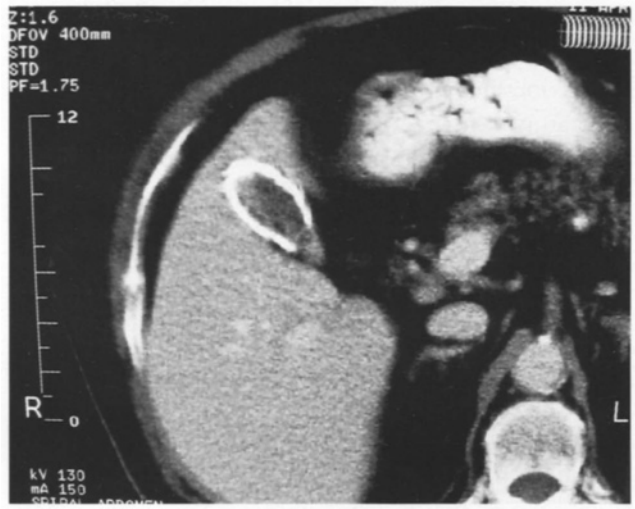

Fig. 6.6. Computed tomography. Porcelain gallbladder.

Acute cholangitis is usually a Gram(-) bacterial inflection secondary to bile duct obstruction, benign or malignant. Charcot's triad (right upper quadrant pain, jaundice, and sepsis) is its clinical manifestation. CT is indicated to detect a possible tumor and complications (e.g., abscess formation). The dilated inrtahepatic ducts may contain gas from gas-forming organisms. Gas may also be seen in the portal vein system [37]. Their dilatation depends on the severity of the disease. In IV contrast material administration, enhancement of the bile duct wall may be seen [38].

Sclerosing cholangitis is a fibrosing inflammatory reaction of the bile ducts. It may be primary or secon-

dary. It causes biliary obstruction, cholestasis, and may lead to biliary cirrhosis and portal hypertention. CT shows intrahepatic ducts with segmental dilatations alternating with stenoses without apparent connection to the central ducts [39]. Involvement of the extrahepatic duct may not be seen. If they are involved mural duct thickening with contrast enhancement and mural nodules are additional CT features [32]. Marked intrahepatic duct dilatation should arouse suspicion of cholangiocarcinoma.

Oriental cholangitis or recurrent pyogenic cholangitis causes biliary strictures, intra- and extrahepatic ductal dilatation and formation of stones, ranging in attenuation from isodense with bile to hyperdense [33]. Stones can be better depicted by CT than sonography, since many of them have a mudlike consistency. Pneumobilia, abscess formation and segmental atrophy are other findings on CT [36].

Biliary cystadenoma is a rare benign tumor which appears on CT as a multilocular hypodense, near water attenuation, intrahepatic lesion. Calcifications may be present in the walls or septa, showing faint enhancement after IV contrast material administration [19, 20]. Differential diagnosis should be made from cystic metastases, large simple or complicated hepatic cysts, complex abscesses, echinococcal cysts, and intrahepatic biloma or hematoma. The aspiration of mucinous or serous material confirms the diagnosis. Thick wall and septations with soft tissue favour the diagnosis of *cystadenocarcinoma* [19].

Extrahepatic cholangiocarcinoma is the most common form of the disease (90%). A characteristic feature is the abrupt loss of visualization of the dilated extrahepatic duct, with intrahepatic bile ducts dilatation, however stone disease may have a similar appearance [33]. The exophytic tumor can be easily detected on CT. The intraductal tumor is better visualized with modern equipment [32] as focal eccentric or concentric mural duct thickening. CT is the modality of choice for staging the disease (metastases, encasement of hepatic artery and portal vein). As mentioned before 10% to 25% of them are *Klatskin's tumors.*

Peripheral cholangiocarcinoma usually appears as a low-attenuation mass with irregular margins with mild peripheral enhancement in both arterial and portal venous phases (fig. 6.7). Mild segmental bile duct dilatation is a common finding. Satellite nodules (65%),

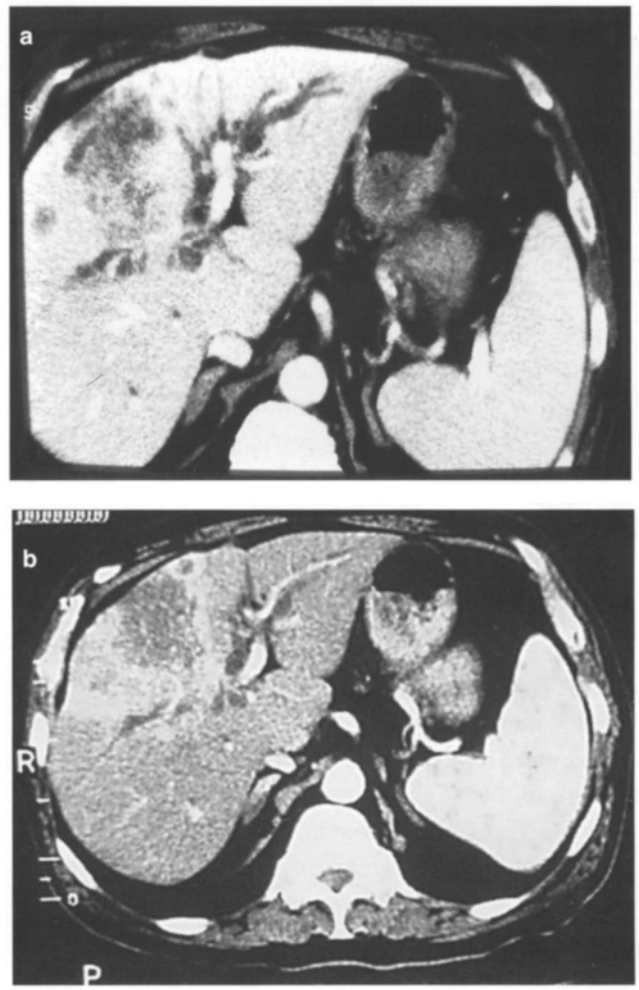

Fig. 6.7. Computed tomography. a) Arterial phase b) portal phase. Peripheral cholangiocarcinoma

regional lymph nodes, irregular or punctuate calcifications (20%) and capsule retraction may be present [32]. In contrast to HCC, these tumors usually do not invade adjacent vessels but encase them [40]. Invasion of the bile ducts, perineural spaces, and lymphatic vessels is seen, however, as resulting in lymph node metastasis and intrahepatic metastasis [41]. Their pathologic differentiation from metastatic disease is difficult and is typically dependent on the identification of another extrahepatic primary carcinoma [42].

Gallbladder carcinoma appears as a soft – tissue mass within or adjacent to the gallbladder, that may expand into the liver parenchyma, or present as mural thickening (fig. 6.8). Intrahepatic duct dilatation is a frequent finding. In the case of mucinous adenocarci-

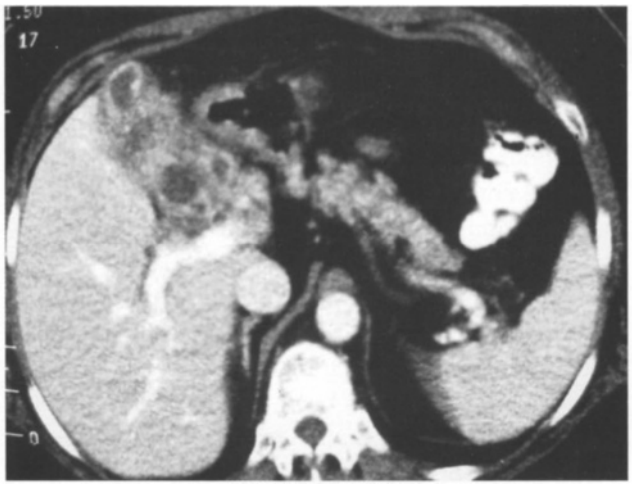

Fig. 6.8. Computed tomography. Gallbladder carcinoma.

noma, punctuate calcifications are seen. Use of contrast-enhanced CT is extremely helpful in tumor staging (spread beyond the gallbladder and lymphatic metastases) [36].

The tumor may differentiate from cholecystitis, polyps, adenomyomatosis, metastases (melanoma, lymphoma, leukaemia), and tumor invasion from adjacent organs.

6.8. Magnetic Resonance Imaging (MRI)

The prime role of MRI in biliary tree disease is the performance of MR cholangiopancreatography (MRCP). MRCP is a virtual non invasive technique that can in most cases replace percutaneous cholangiopancreatography and ERCP to detect the cause and the level of biliary tree obstruction. MRCP – through conventional MR images and administration of intravenous paramagnetic contrast medium if required-permits the visualization of the extra-ductal structures and is a fundamental procedure for the characterization and staging of spreading tumors [43,44], with a specificity and sensitivity comparable to those of CT [45]. Manganese-enhanced MR cholangiography depicts biliary dynamics as they are depicted at cholescintigraphy and provides functional information about the biliary system [46].

MRI features suggestive of *cholecystitis* are similar to CT findings, namely mural thickening, pericholecystic fluid and cholelithiasis. The bile tends to be hypointense on T1 weighted images, probably due to the decreased concentrating ability of the gallbladder [47]. *Gallstones* appear dark on all sequences; some stones may demonstrate a high intensity nidus [48]. Conventional heavily T2-weighted MR cholangiography is able to depict stones smaller than 3 mm and to show both the proximal and distal parts of the obstruction site despite a complete obstruction. In Mirrizzi Syndrome it can detect an impacted cystic duct or gallbladder neck stones with high sensitivity [47].

Acalculous cholecystitis is a challenging problem. Magnetic resonance cholangiography and endosonography are the best methods for its detection if no diagnosis is reached with sonography and computed tomography [49].

In the detection of complicated acute cholecystitis (*emphysematous cholecystitis, gangrenous cholecystitis, abscess formation, gallbladder perforation, and cholecystoenteric fistula*) CT is the modality of choice with MR providing limited indications [50]. In acute gangrenous cholecystitis MR may demonstrate patchy enhancement of the gallbladder mucosa on gadolinium-enhanced fat-saturated T1-weighted gradient echo images. This interrupted rim of mucosal enhancement correlates with patchy areas of necrosis and inflammation of the gallbladder mucosa on the histopathological examination [51].

Gallbladder torsion is an urgent condition. MR imaging may help confirm the diagnosis [50] and may show tapering and twisting of the cystic duct.

Hemobilia seen in less than 50% of patients is characterized by melena, jaundice and abdominal pain. Two-thirds of cases are iatrogenic, whereas trauma accounts for 5%. It may manifest many weeks after the initial injury [52]. The diagnosis can be reached with US, unenhanced CT, or MR imaging and confirmed with endoscopy (blood from the ampulla of Vater) or angiography. In one review, 43% of cases were managed conservatively and 36% were managed with transarterial embolization [52]. The remainders were managed surgically either because of failed transarterial embolization or at the time of laparotomy for other reasons.

Xanthogranulomatous cholecystitis in MR imaging appears with areas of iso- to slightly high signal intensity on T2-weighted images, showing slight enhancement at early phase and strong enhancement at last phase on dynamic study, expressing areas of abundant

xanthogranulomas. Areas with very high signal intensity on T2-weighted images without enhancement corresponded with necrosis and/or abscesses. The early-enhanced areas of the liver bed on dynamic MR images corresponded with accumulation of inflammatory cells and abundant fibrosis [53].

Suspected parasitosis of the gallbladder is not well documented with sonography but MR is a modality that takes this disease into consideration. In ascariasis, multiple linear/tubular hypointence filling defects in the gallbladder and the CBD are show [54]. *Clonorchis sinensis* causes recurrent pyogenic cholangiohepatitis. MR cholangiography has become the standard of reference for documenting the extent of this disease and developing a road map for planning surgical and/or interventional treatment [55].

Although magnetic resonance (MR) imaging is not typically employed as a primary imaging modality for the gallbladder, it may be useful in cases of focal or diffuse mural thickening in distinguishing gallbladder carcinoma from adenomyomatosis and chronic cholecystitis and also in staging the tumor. MR imaging has a great sensitivity in the evaluation of the layered pattern of gallbladder wall thickening. The layered pattern of thickened wall was classified into four patterns. Type 1 has two layers, a thin hypointense inner layer and thick hyperintense outer layer. Type 2 also has two layers of ill-defined margin. Type 3 shows multiple hyperintense cystic spaces in the wall. Type 4 shows diffuse nodular thickening without layering. MR findings of a layered pattern of thickened gallbladder were well correlated with histopathology. Chronic cholecystitis matches to type 1, acute cholecystitis corresponds with type 2, adenomyomatosis concurs with type 3, and gallbladder carcinomas represent type 4 [56].

Adenomyomatosis is seen in heavy T2WI as markedly hyperintence spots because Rokitansky-Aschoff sinuses filled with bile within the thickening wall of the gallbladder. MRCP is more reliable for this purpose because it can reveal the pearl necklace sign [57].

Gallblabber carcinoma appears as an irregular mass with relatively increased T2 signal lesion compared to liver. When the gallbladder wall is not clearly discriminated from adjacent hepatic parenchyma, it indicates hepatic invasion. MR imaging demonstrates prolongation of the T1 and T2 relaxation times in gallbladder carcinoma. Ill-defined early enhancement is a typical appearance of these tumors at dynamic gadolinium-enhanced MR imaging [58]. MR, with different techniques, helps in the assessment of tumor resectability. Radiologists need to be aware that well-differentiated gallbladder carcinoma with mucin production can have cystic components, which may mimic adenomyomatosis. Careful interpretation of MR images may provide useful information in the differentiation of these two entities [59].

MRCP has emerged as an accurate non-invasive diagnostic modality for investigating the biliary and pancreatic ducts and has been recommended in some institutes as the preoperative procedure of choice for the detection of CBD stones [60]. MRCP provides an excellent anatomic detail of the biliary tract and has a reported sensitivity of 81%-100%, and a reported specificity of 92%-100% in detecting *choledocholethiasis* [61]. The accuracy of MRCP is therefore comparable with that of ERCP and intraoperative cholangiopancraetography (IOC) [61, 62]. These results have led some practitioners to consider MRCP the new gold standard for biliary imaging [61, 63]. MRCP is useful in detecting intraluminal polyps and carcinomas in the biliary tract, pancreatic duct, and ampulla of Vater [45, 58]. MRCP should be used as a diagnostic approach in all cases with suspected bile duct disease (fig. 6.9). This fast

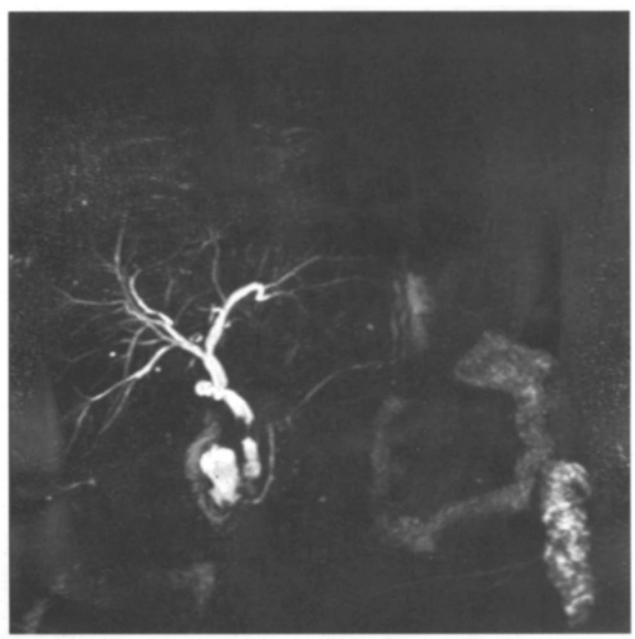

Fig. 6.9. MRCP. Concentric stricture of the common bile duct due to carcinoma.

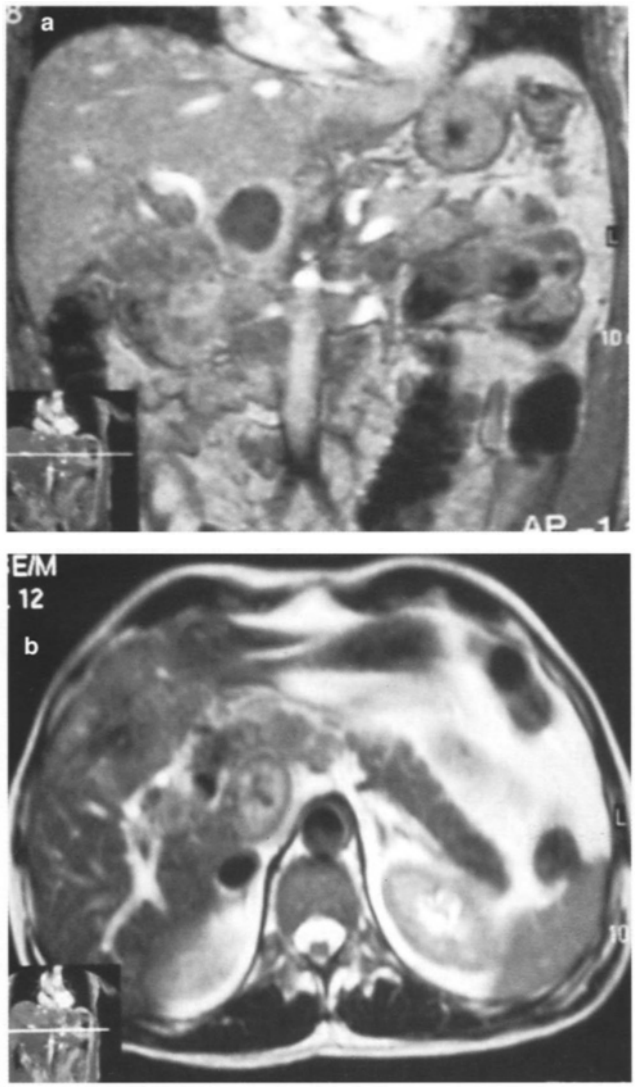

Fig. 6.10. MRI. a) Coronal plane T1WI b) axial plane T2WI: central cholangiocarcinoma.

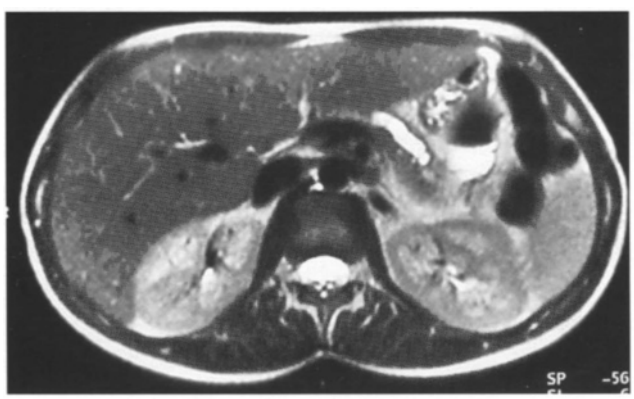

Fig. 6.11. MRI T2WI dilated pancreatic duct.

noninvasive examination will provide the endoscopist and/or the surgeon with useful information on the anatomy of the papilla, presence of aberrant bile and cystic ducts, and choledochocele that might hinder incanulation [64, 65].

Cholangiocarcinoma does not have specific MRI appearance. It can appear isointense or hypointense on T1WI images (fig. 6.10). Well differentiated tumors appear with a high T2WI signal, whereas the infiltrating types with a low T2WI signal.

Cholangiocarcinoma shows little or moderate enhancement at the liver periphery in the early images with progressive central contrast enhancement on later images. MRI, in the same way as CT, can classify the tumor according to TNM criteria and predict its unresectability showing: 1) Major abdominal vascular involvement, including encasement (fig. 6.11), occlusion and tumor thrombosis; 2) Tumor adjacent organs or tissues infiltrations excluding the simple extension into the duodenum; 3) The presence of distal metastases or peritoneal carcinomatosis; 4) regional and distal lymph node involvement [58].

The MR imaging characteristics of an uncomplicated biliary *cystadenoma* are typical of a fluid-containing multilocular mass, with homogeneous low signal intensity on T1-weighted images and homogeneous high signal intensity on T2-weighted images [20]. Variable signal intensities on both T1- and T2-weighted images depend on the presence of solid components, hemorrhage, and protein content [20].

Biliary cystadenocarcinoma appears with a low TI signal, unless the locules contain proteinaceous or hemorrhagic fluid. In the latter case they appear hyperintense on T1 images. The lesion is also hyperintense on T2 images and abscesses and echinococcal cysts must be differentiated.

Choledochal cysts appear as periportal or intraparencymal lesions, hypointense on T1 images and strongly hyperintense on T2 images. This hyperintensity differentiates them from cystic metastases [23].

MR imaging of Caroli's disease shows the dilated and cystic biliary system as hypointense on T1-weighted images and markedly hyperintense on T2-weighted images. After intravenous administration of gadolinium contrast material, the intraluminal portal vein radicals are strongly enhanced. MR imaging usually demonstrates bridges across dilated intrahepatic ducts, which re-

semble internal septa. This appearance is consistent with the wall of an insufficiently resorbed, malformed ductal plate that surrounds the portal vein radicals [66]. In the absence of the central dot sign, MR cholangiography can be extremely valuable in the diagnosis of Caroli's disease by demonstrating the pathognomonic feature of saccular dilated and nonobstructed intrahepatic bile ducts that communicate with the biliary tree [67] (fig. 6.12).

Bile duct hamartomas are hypointense relative to liver parenchyma on T1-weighted images and strongly hyperintense on T2-weighted images. On heavily T2-weighted images, the signal intensity increases further, almost reaching the signal intensity of fluid. At MR cholangiography, bile duct hamartomas appear as multiple tiny cystic lesions that do not communicate with the biliary tree. After intravenous administration of gadolinium contrast material, some authors observed homogeneous enhancement of these lesions, whereas others did not find any enhancement [25]. Recently, thin rim enhancement on gadolinium-enhanced images was reported in four cases. This rim enhancement was considered to correlate with the compressed liver parenchyma that surrounds the lesions at histopathologic analysis [68].

In cases of primary sclerosing cholangitis magnetic MRCP is not always sufficient for imaging the minor pathology of the ducts. Slightly dilated peripheral ducts and central ducts are not in continuity, and this is a characteristic MRCP finding. Formation of mural nodes and thickening in the duct wall, diverticula and webs, can be observed. MRCP plays an important role in following-up the progression of the disease and possible complications in a non- invasive manner [69].

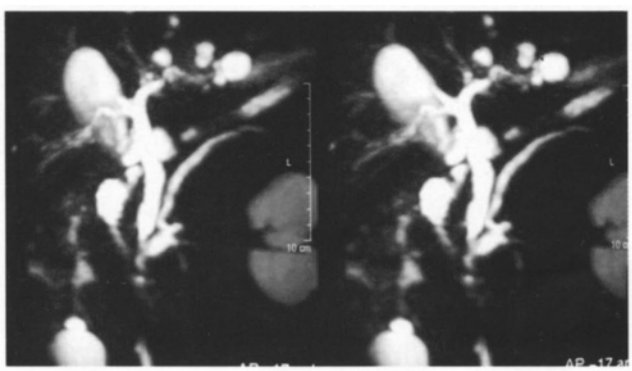

Fig. 6.12. MRCP. Cystic dilatations of the left liver lobe bile ducts. Caroli's disease.

6.9. Biliary Scintigraphy

Biliary scintigraphy, using derivatives of 99m Tc- labeled N substituded iminodiacetic acid as HIDA, PIPIDA, DISIDA, can provide functional and morphological information.

Findings that suggest *biliary obstruction* include an inappropriate slow decrease in parenchymal radioactivity, delayed appearance of radioactive bile outside the liver (>15 min), delay of the time of peak intrahepatic bile duct radioactivity (>45 min.), and appearance of a change in the caliber or intensity of a bile duct at the point of obstruction. The effect of *extrahepatic biliary* obstruction on the parenchymal time-activity curve is the same as that in *intahepatic cholestasis* [70].

Although biliary obstruction is better estimated by other methods, biliary scintigraphy can play a secondary role. Dilatation of the intrahepatic ducts and proximal common bile duct can be demonstrated which along with a delayed discharge of the tracer into the intestine, appears to be reliable evidence of partial extrahepatic obstruction. However, biliary scintigraphy may be more useful in the diagnosis of functional obstruction of the bile duct or so-called biliary dyskinisia uptake, a frequently observed postcholecystectomy syndrome. These patients are believed to have either sphincter of Oddi spasm or stenosis. In the latter case, a biliary scan shows good uptake and excretion and normal transit of bile to the gut but with marked prominence of the biliary system, which fails to drain for 2 hours [71].

Biliary scintigraphy can be used for investigating neonatal jaundice and distinguishing *extrahepatic biliary atresia* (fig. 6.13) from *neonatal hepatitis.* This is of great importance because biliary atresia is amenable to surgery. Tc-99m DISIDA imaging in such patients shows normal hepatocyte intensity and no appearance of radioactive bile outside the liver for 24 hours [72]. Tracer within the small intestine excludes biliary atresia. In contrast, in neonatal hepatitis the hepatocytes are significantly damaged and there is a decreased parenchymal activity in Tc-99m DISIDA. The dinstinction between these two conditions is less clear if imaging is performed relatively late i.e. beyond 2 months of age [73].

Tc-99m DISIDA is very effective in the detection of *bile leaks.* Leaks appear as collections of radioactivity

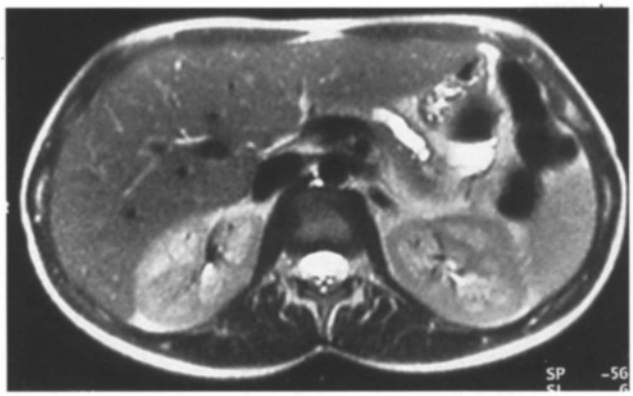

Fig. 6.13. Scintigram. Bile duct atresia. No trace into the intestine 24 hours after the injection of radiopharmaceutical.

that enlarge and increase in intensity with time but do not conform to the expected location and shape of the biliary tree, small intestine, or colon [74].

This test is extremely accurate for the diagnosis of *acute cholecystitis* which is its primary indication. Non-visualization of the gallbladder is suggestive of acute cholecystitis secondary to cystic duct obstruction. A rim of increased radiotracer accumulation within the adjacent parenchyma, along the wall of gallbladder fossa, namely "rim sign" also suggests acute cholecystitis and it is present in 30% of the patients [75]. The accuracy of scintigraphy in the diagnosis of acute cholecystitis depends on normal liver function and bile excretion.

Diagnosis of acalculous chronic cholecystitis can be made by measuring the gallbladder ejection fraction with Tc-99m-DISIDA scintigraphy. An ejection fraction below 35% is abnormal and suggestive of chronic cholecystitis [76].

Hepatobiliary scintigraphy is extremely effective in the assessment of surgical bilioenteric anastomoses. Roux loop obstruction or obstruction of the more distal small bowel resulting in acute cholangitis can be demonstrated as bile stasis within a proximal segment of bowel and delayed transit through the small bowel. Thus, in patients presenting with cholangitis after having undergone biliary- enteric anastomosis, biliary scintigrahy can differentiate progressive intrahepatic disease from Roux loop obstruction.

6.10. Percutaneous Transhepatic Cholangiography (PTHC)

Although new imaging modalities can help in the assessment and characterization of biliary disease, they sometimes fail to confirm the exact site and cause of the obstructing lesion. PTHC or ERCP is the next step in studying the biliary system and revealing the level or cause of jaundice. PTHC is simple and less costly (fig. 6.13). Moreover the length of the occluded or strictured segments can be estimated and the biliary ducts proximal to the lesion can be shown [77]. Hence, PTHC may be advocated as a primary invasive method, although it can neither demonstrate duodenum, Vater's ampulla or pancreatic ducts, nor allow histopathologic samples to be taken.

PTHC can demonstrate if jaundice is due to a surgically treatable obstruction or to intrahepatic parenchymal pathology [78]. In the case of a mechanical obstruction there will be intrahepatic biliary dilatation, providing the liver parenchyma is compliant. *Malignant obstruction* usually causes a funnel-like stricture of the offended biliary duct, whereas a biliary stone causes an abrupt rounded termination of the bile duct [79]. *Intrabiliary calculi* or *extrahepatic choledocholithiasis* are seen as filling effects within the lumen (fig. 6.14) [80]. Cholangiographic features of *Primary sclerosing cholangitis* include multifocal structuring of the bile ducts, usually both intrahepatic and extrahepatic, which may not be dilated due to the sclerotic nature of the disease as mentioned above [80]. *AIDS-cholangiopathy* reveals a similar picture.

Other entities can also be demonstrated. *Cholesterosis* results from diffuse multiple deposits of 1-2 mm pigments of cholesterol on the gallbladder mucosa. Percutaneous transhepatic cholangiography shows fixed mural defects. Differential diagnosis is made from *polyps* [80].

Adenomyomatosis of the gallbladder is caused by the protrusion of the hypertrophic mucosa into the hypertrophic muscle tunica, forming epithelial mucosal sinuses (Rokitansky-Aschoff sinuses). There are three types and in PTC they appear as a fundal nodular filling defect, as strictures at any site of the gallbladder accentuated after gallbladder contraction, and as small mural diverticula (epithelial sinuses) [80].

Percutaneous transhepatic cholangiography can al-

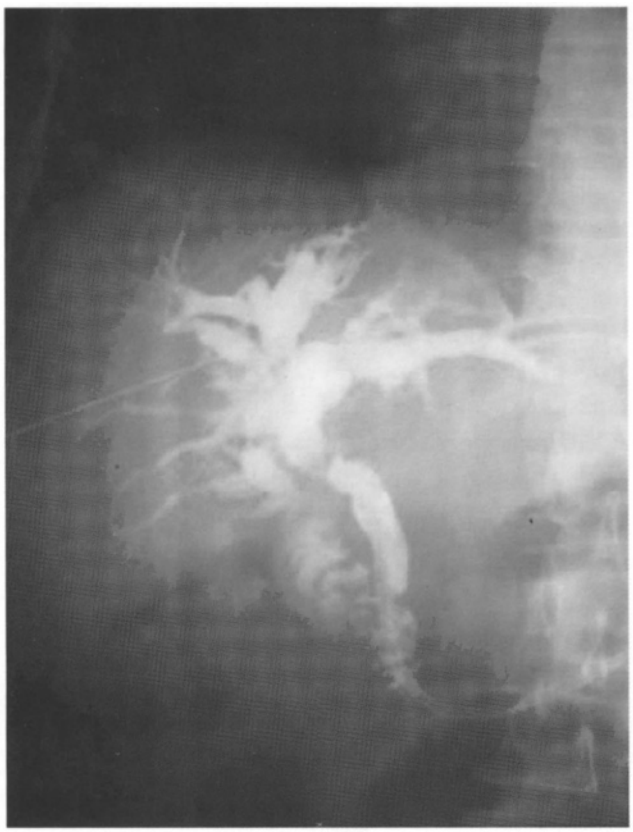

Fig. 6.14. Percutaneou transhepatic cholangiography. Dilated inrtahepatic bile ducts.

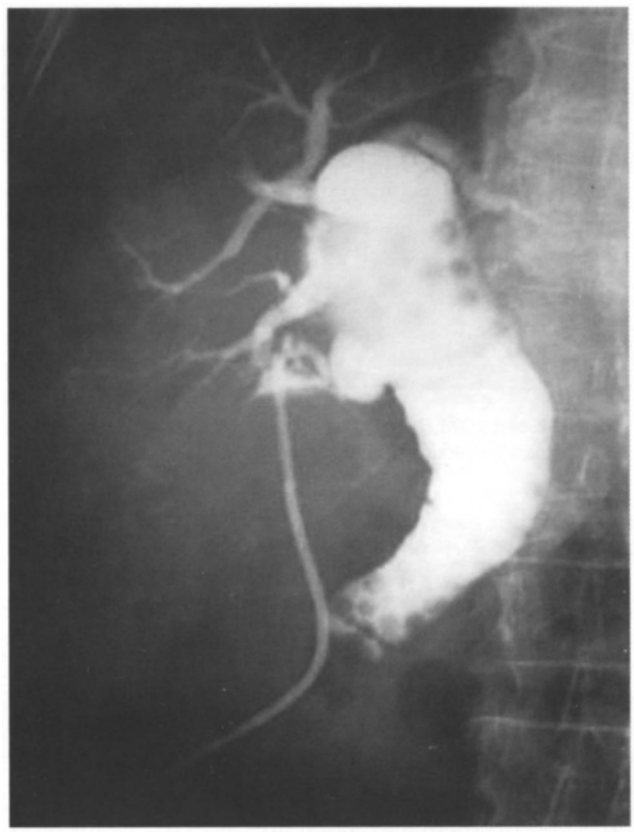

Fig. 6.15. Percutaneou transhepatic cholangiography. Common bile duct and gallbladder full of stones appeared dilated.

so reveal congenital disease such as *choledochal cysts* and *Caroli's disease,* which after contrast media display periportal and intrahepatic rounded formations in the common bile duct and the intrahepatic biliary ducts respectively [81].

Bilioenteric, biliocutaneous or *biliovascular* abnormal *communications* can be revealed and the level of a bile leak can be defined.

Finally, percutaneous transhepatic cholangiography is used in order to top map the biliary tree prior to biliary drainage with or without biliary stenting and which is in fact its prime role today [82].

Percutaneous biliary drainage (PBD) offers the possibility of palliative decompression of bile ducts in either benign or malignant disease with low morbidity and mortality rates [83]. This procedure is indicated in cases of unresectable primary or metastatic malignancy as a palliation treatment in patients who are not candidates for surgical resection, as well as in cases of high or multiple branch obstructions, cardiac cases, pulmonary or renal malfunction or in patients with a short life expectancy. Surgical resection compared to PBD, in similar groups of patients, exhibit similar morbidity and mortality rates. Percutaneous biliary drainage is also indicated for treating benign strictures, particularly stenotic biliary-enteric anastomoses, as well as cases of sepsis secondary to biliary obstruction and for preoperative decompression of the biliary tree. The procedure is contraindicated in cases of bleeding disorders and non-biliary sepsis.

Percutaneous biliary drainage can be performed under fluoroscopic or CT-guidance or a combination of both. Sometimes ultrasonography may help catheterization [80]. Drainage is performed through an external drainage catheter, through internal-external drainage, where the catheter has multiple side holes proximal and distal to the site of obstruction, or through insertion of an endoprosthesis (stenting).

External biliary drainage is indicated for short term diversion of bile, for patients undergoing preoperative decompression, since long term external diversion can cause infections at the entry site, catheter dislocation or accidental removal and bile salt loss. External drainage is also performed as a first step 3-5 day procedure prior to internal drainage catheter insertion, especially if the stenosis is transversed with difficulty. Thus the biliary tree is decompressed and the lesion can be transversed more easily. Internal- external biliary drainage is performed in the majority of patients, since it is more convenient for the patient and avoids the problems of bile salt loss. Biliary stenting has the advantages of an external-internal drainage catheter, without the patient having the catheter in the flank [84]. Moreover there is a significantly lower risk of cholangitis compared to an internal drainage catheter. However there is a higher rate of dysfunction.

Finally, percutaneous cholangioplasty may serve as a minimally invasive means in the management of biliary strictures [85].

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CHAPTER 7

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Kon. Goumas, A. Poulou

7.1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has proven to be a very useful method in the diagnosis of most diseases of the biliary tract. In particular it displays a great accuracy in diagnosing extrahepatic biliary disease, making it the gold standard compares to other diagnostic studies in this field. It further plays a major and most important role in the differentiation between benign and malignant extrahepatic biliary disorders. Despite its preponderance in extrahepatic biliary tract conditions, endoscopic selective biliary cannulation has also offered important improvements in the diagnosis of gallbladder and intrahepatic duct system diseases. It is however worth noting that the diagnostic accuracy of ERCP very much relies on the endoscopist's experience.

Since the introduction and development of magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), the role of diagnostic ERCP has been limited to a handful of indications owing to the high rate of complications associated with the procedure. However, extensive research involving ERCP continues as diagnostic procedures including tissue or fluid sampling during ERCP are usually crucial in the diagnostic field. Furthermore, at the present time, the therapeutic role of ERCP in biliary diseases can not be substituted by any other modality.

Table 7.1. Equipment for Endoscopic Retrograde Cholangiopancreatography.

A. Endoscopic equipment
- Side-viewing duodenoscope with large working channel (≥3.7 mm).
- Cannulation catheter.
- Sphincterotome catheter (double or triple lumen).
- Balloon catheters for stone extraction.
- Basket catheters for stone extraction.
- Balloon-dilation catheters for stricture dilation.
- Biopsy forceps.
- Cytology brush catheter.
- Guidewires.

B. Radiologic equipment
- X-ray apparatus with tiltable, movable table.
- Standard fluoroscopy capability.
- Imaging System.
- Contrast material.

7.2. Technical Features

7.2.1. Equipment

In order to perform an ERCP, a series of endoscopic and radiologic equipment is required (table 7.1). A side-viewing duodenoscope (fig. 7.1) with a wide working channel (≥3.7 mm), allows the use of a wide range of catheters according to the diagnostic or therapeutic objective. Biopsy forceps and sheathed brushes are used to obtain tissue or cytologic specimens (fig. 7.2). Several types of cannulating catheters (fig. 7.3) facilitate the cannulation of the main duodenal papilla and the selective deep cannulation of the common bile or pancreatic ducts. A standard sphincterotome as well as several types of precut sphincterotomes (fig. 7.4) are necessary for an endoscopic sphincterotomy. Balloon and basket-type catheters (fig. 7.5) may be used for stone removal while Gruntzig-type balloon catheters (fig. 7.6) are indicated for dilation of biliary or pancreatic strictures. Per os cholangioscopy and pancreatoscopy during ERCP are now possible using the mother-baby endoscope system. The radiologic equipment for ERCP includes an X-ray apparatus with an adjustable table, standard fluo-

Fig. 7.1. Side-viewing duodenoscope (Olympus-EXERA TJF-145) with a working channel of 4.2 mm.

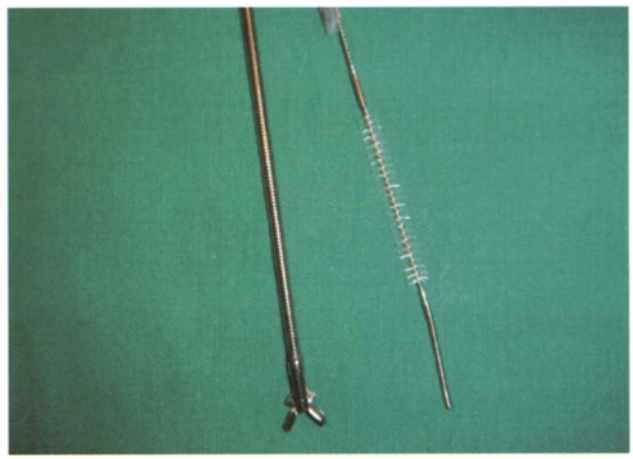


Fig. 7.2. a. Special biopsy forceps for intraductal tissue sampling. b. Sheathed brushes used for cytological specimen acquisition from bile duct strictures.

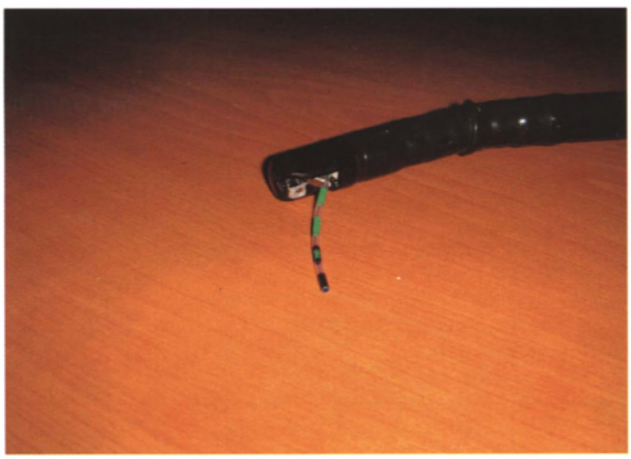


Fig. 7.3. Duodenoscope with a standard cannulating catheter in the working channel.

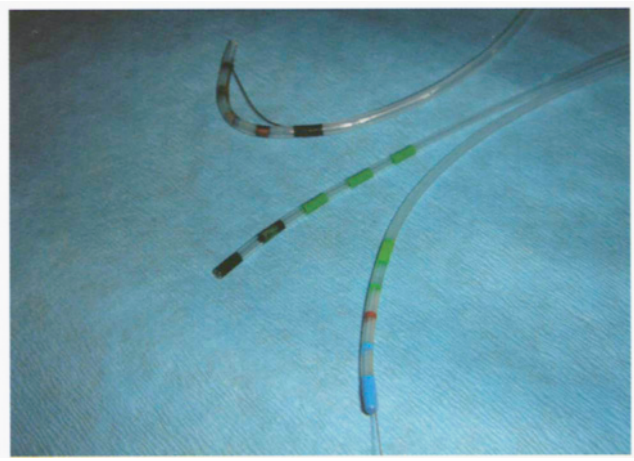


Fig. 7.4. Standard sphincterotome, cannulation catheter, needle knife sphincterotome. These devices are used for cannulation and sphincerotomy.

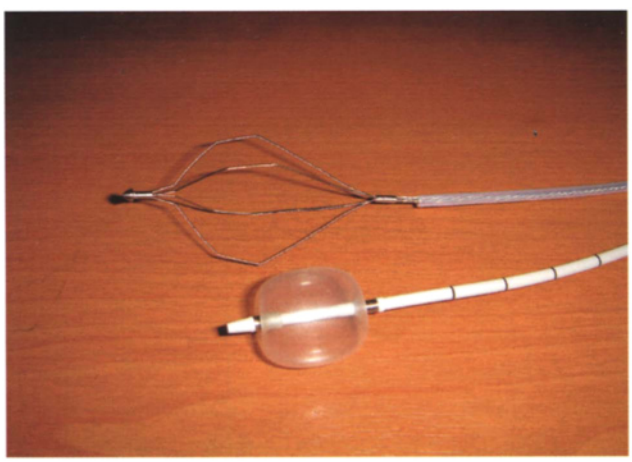


Fig. 7.5. Balloon and dormia basket catheters for extraction of bile duct stones.

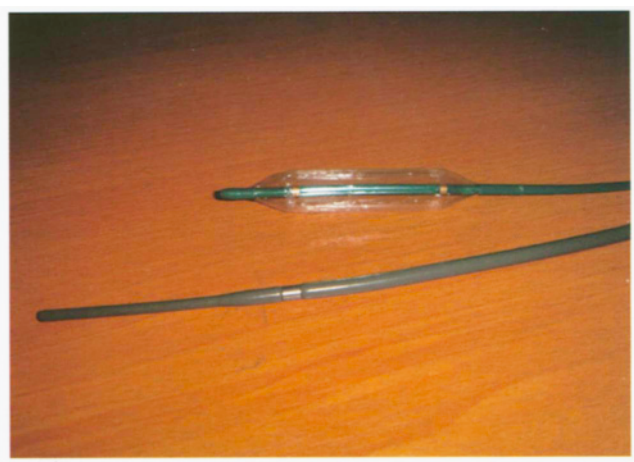


Fig. 7.6. Dilating catheters: Gruntzig-type balloon dilating catheter and «bougie»-type dilating catheter (8.5-French).

roscopy capability, imaging system and use of standard contrast material.

7.2.2. ERCP Diagnostic Technique

The ERCP diagnostic technique is well established [1] although many anecdotal recommendations and tips are exchanged among endoscopists. Usually, both the common bile duct and the pancreatic duct empty via the same orifice. Selective cannulation of the desired duct, requires familiarity with the anatomy of the papillary structures as well as experience in approaching the desired duct. Following cannulation of the main papilla orifice, the common bile duct tends to run in a cephaloid direction whereas the pancreatic duct courses more medially [1]. The selected ducts are successfully cannulated in about 50% ERCP procedures, whereas 25% the procedure though completed requires additional time and repeated attempts. In 15% to 25%, successful cannulation requires a systematic algorithm of procedural skills and techniques (see endoscopic management of choledocholithiasis later in this book).

Selective bile duct cannulation can be achieved more successfully, rapidly and with fewer incidental pancreatic injections using a sphincterotome rather than a standard catheter, due to it's capacity for upward angulation. The use of disposable sphincterotomes incurs a cost increase of 1.4 to 1.8 times [2]. Precut sphincterotomy may be helpful when standard techniques fail. Nevertheless, most experienced endoscopists only rely on precut methods in just 10% to 15% of cases [3] due to higher risks of complications compared to standard cannulation techniques. The combined "rendezvous" technique is also an alternative when the CBD cannulation proves difficult [1]. Successful diagnostic and therapeutic ERC is based on cannulation of the duct in question. Deep cannulation is achieved when the tip of the catheter is passed beyond the papilla into the desired duct. This allows effective injection of contrast medium and the introduction of instruments for therapeutic procedures. Successful cannulation rates of at least 95%, are consistently achieved by the experienced endoscopist [4].

A deep bile duct catheterization is necessary when the examination is focused on the intrahepatic ducts. In such cases, better optimal filling of the intrahepatic ducts may be achieved when the standard catheter is positioned at the bifurcation or selectively in either of the main hepatic ducts. This is especially true when the gallbladder is present. In some cases, better imaging of the intrahepatic ducts can be accomplished by isolating them from the distal biliary tract using a balloon catheter, during the contrast medium injection. Injecting the opaque medium with the catheter tip at the papilla may cause overdistension of the gallbladder and subsequent nausea or even vomiting [1]. Insufficient filling of intrahepatic ducts, usually of the right duct system, could lead to an erroneous diagnosis. For the same reason, over-opacification of ducts with contrast medium or a great amount of contrast medium in the gut, should be avoided. Successful cannulation is not synonymous with a successful ERCP. Once cannulation is achieved, the endoscopist should be able to at least complete the most commonly performed procedures, including stone extraction, relief of biliary obstruction and stent placement. A technically unsuccesful ERCP may result in a substantial cost increase [5].

7.3. Indications

ERCP is indicated to evaluate jaundice, confirm the presence of biliary obstruction and define the location and nature of an obstructive lesion. Nowadays, ERCP has evolved from a purely diagnostic to a predominately therapeutic procedure [6]. The development of novel and often less invasive diagnostic techniques such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography has limited the role of ERCP as an initial diagnostic procedure. The indications for ERCP are summarized in table 7.2 [7]. ERCP should be performed only for an appropriate indication and it is generally not indicated for abdominal pain without objective evidence of pancreatic disease [8, 9] as well as a routine before cholecystectomy [10]. Moreover, ERCP is not indicated as a routine for relief of biliary obstruction in surgically curable patients. Preoperative biliary decompression has not been shown to improve postoperative outcomes, yet it may result in both preoperative and postoperative complications [11]. However, preoperative relief of obstructive jaundice is indicated in cases of acute cholangitis or intense puritus, especially in patients in whom surgery may be delayed [12].

Table 7.2. Indications to ERCP [7].

1. Obstructive jaundice.
2. Clinical and biochemical or imaging suspicion of pancreatic or biliary tract disease.
3. Clinical suspicion of pancreatic malignancy not detectable by other imaging modalities.
4. Pancreatitis of unknown etiology.
5. Preoperative evaluation of chronic pancreatitis or pancreatic pseudocyst.
6. Sphincter of Oddi manometry in suspected sphincter of Oddi dysfunction.
7. Endoscópic sphincterotomy for:
   a. Choledocholithiasis.
   b. Papillary stenosis or sphincter of Oddi dysfunction.
   c. Facilitating biliary stent placement or balloon dilatation.
   d. Sump syndrome.
   e. Choledochocele.
   f. Ampullary carcinoma palliation.
   g. Access to pancreatic duct.
8. Stent placement across benign or malignant strictures, fistulae, postoperative bile leak, or unremovable common bile duct stones.
9. Balloon dilatation of ductal strictures.
10. Nasobiliary drain placement.
11. Pseudocyst drainage in appropriate cases.
12. Tissue sampling from pancreatic or bile ducts.
13. Pancreatic endoscopic therapy.

7.4. Contraindications

The only true absolute contraindications for ERCP procedure are both refusal of the patient to undergo endoscopy or an acute unstable cardiovascular or cardiopulmonary episode [1] (table 7.3). Structural abnormalities of the esophagus, stomach or duodenum may be relative contraindications to ERCP. A large esophageal diverituclum, an unrecognized esophageal stricture, a large paraesophageal hiatus hernia, a gastric valvulus, a gastric outlet obstruction owing to a variety of reasons, a previous partial gastrectomy with Billroth type II anastomosis or a Roux-en-Y jejunojejunostomy may as well be relative contraindications to performing ERCP. The level of experience of the endoscopist is of outmost importance in the decision as to whether the procedure should be undertaken under these circumstances. Finally, a communicating pancreatic pseudocyst is also not an absolute contraindication to ERCP if drainage of the pseudocyst is to be endoscopically or surgically performed.

Table 7.3. Contraindications to ERCP.

a. **Absolute**
- Refusal of patient.
- Cardiovascular or pulmonary instability.

b. **Relative**
- Structural upper gastrointestinal tract abnormalities.
- Gastric surgery (Billroth II, Roux-en-Y anastomoses).
- Communicating pancreatic pseudocyst.

7.5. ERCP and Diseases of the Biliary Tract

7.5.1. Diseases of the Gallbladder

Ultrasonography has proven to be a very effective, non invasive instrument in the diagnosis of cholecystolithiasis [13]. Although endoscopic retrograde cholangiography (ERC) is a very sensitive method for detecting even tiny stones in the gallbladder [14] (fig. 7.7). It is not indicated for the diagnosis of pure cholecystolithiasis.

Imaging of the entire biliary duct system during ERCP may reveal a polypoid mass or filling defect in a stiff, rigid and immobile gallbladder, representing an invasive carcinoma [1]. Advanced carcinoma of the gallbladder may cause stenosis of the common bile duct (fig. 7.8), the common hepatic duct, the intrahepatic ducts and even the duodenum, due to infiltration. ERCP cannot, however, differentiate benign tumour of the gallbladder from a carcinoma.

Other diseases such as a fistula between the gallbladder and the neighboring hollow organs as well as several congenital abnormalities of the gallbladder could be detected during ERCP.

7.5.2. Diseases of the Bile Ducts

7.5.2.1. *Choledocholithiasis*

The most common cause of biliary obstruction is choledocholithiasis. The sensitivity and the specificity of ERCP for detecting common bile duct (CBD) stones is over 95%, although, occasionally, small stones are not detected. Injection with extreme caution of contrast material, may help in detecting stones while overfilling of the ducts may push stones further into the intrahepatic ducts. The accidental instillation of air bubbles into the duct by the injection catheter may be misdiag-

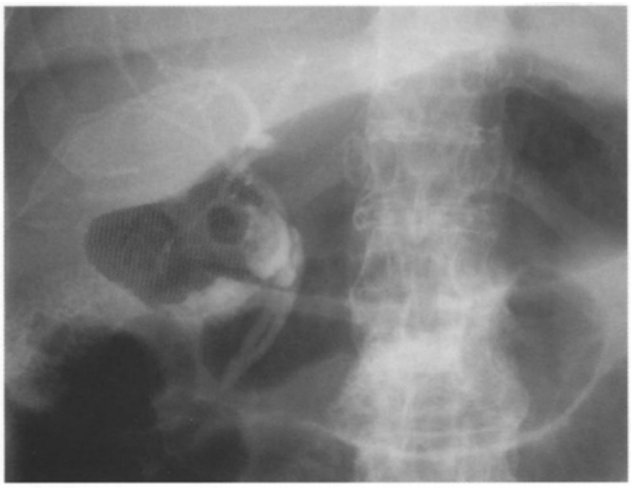
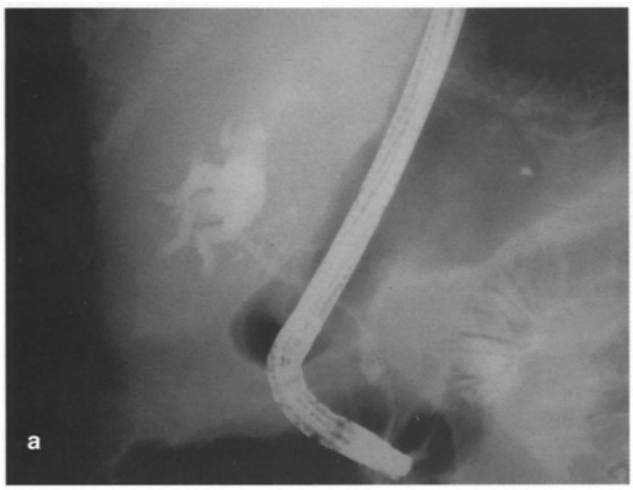


Fig. 7.7. Multiple stones of several size into the gallbladder.



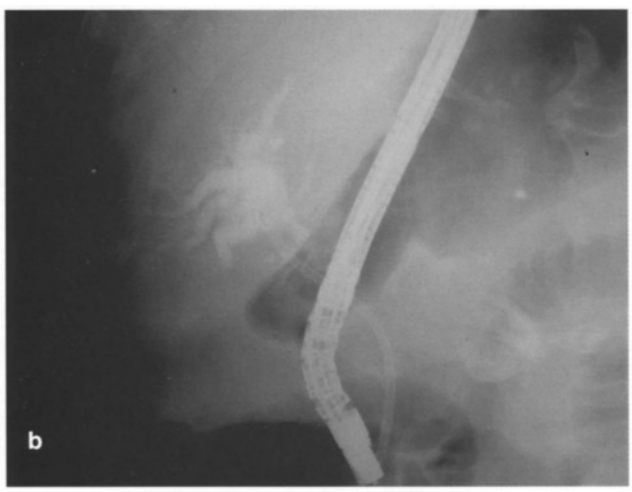


Fig. 7.8. Long malignant stricture of the common bile duct due to a locally advanced gallbladder carcinoma, before (a) and after (b) stenting.

nosed as stones. Choledocholithiasis is one of the most common indications for ERCP (fig. 7.9, 7.10, 7.11).

ERCP still remains the gold standard for diagnosing and treating bile duct stones [12]. Endoscopic biliary decompression is the procedure of choice for the treatment of acute cholangitis. Urgent ERCP is also indicated in selected patients with severe gallstone pancreatitis and suspected biliary obstruction. It is anticipated that a competent ERCP endoscopist can relieve the duct of CBD stones in >85% of cases using sphincterotomy combined with balloon or basket catheters for stone extraction. When standard used techniques fail, mechanical lithotripsy will increase the success rate to reach over 90%, leaving only a small number of patients requiring more advanced procedures such as electrohydraulic, laser, or extracorporeal shockwave lithotripsy, which will increase the success rate further to almost 100% [12]. Indeed, some endoscopy centers with maximum expertise can achieve >99% bile duct clearance rate for any kind of bile duct stones [15].

More information concerning the role of ERCP in the diagnosis and treatment of choledocholithiasis are presented in the chapter "Endoscopic management of common bile duct stones".

7.5.2.2. *Biliary Strictures*

The overall success rate for ERCP as a method of defining the site and nature of a biliary obstruction is equal to 90% [16]. Moreover, ERCP is useful in the assessment and treatment of biliary obstructions, especially those of a malignant nature. Narrowing of the intra- or extrahepatic bile duct can be caused by a wide range of benign or malignant disorders.

ERCP is the gold standard method for biliary tree imaging. The cholangiographic presence of a smooth taper to the stricture can suggest a benign etiology (fig. 7.12). On the contrary, an irregular in contour, eccentric stricture is suggestive of malignancy (fig. 7.13). A prestenotic dilatation of bile ducts is almost always present. Bile duct stones are quite often found in the dilated, proximal to a stenosis, part of the biliary tree (fig. 7.14). Sometimes the cholangiographic appearance of a bile duct carcinoma may be that of a filling defect (fig. 7.15). Rarely, a diffuse infiltrating biliary carcinoma may mimick the appearance of primary sclerosing cholangitis.

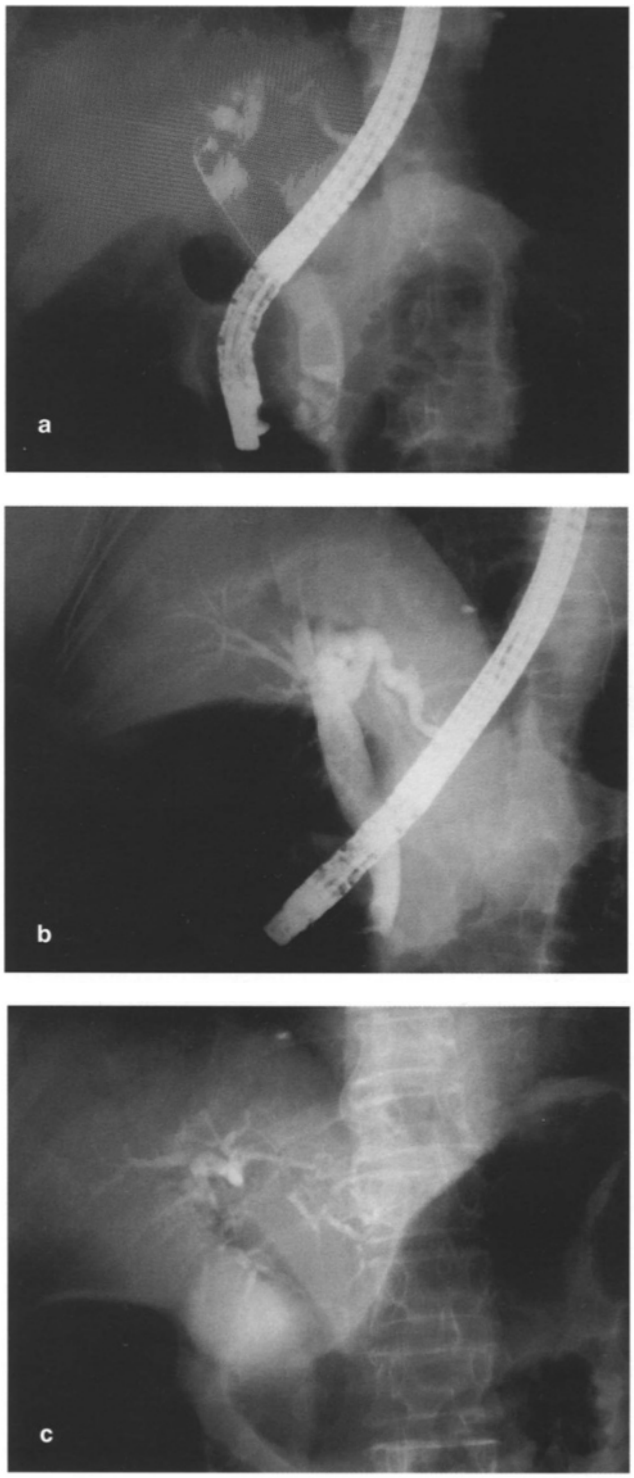


Fig. 7.9.
a. Multiple stones of several size in the common bile duct.
b. After sphincterotomy and mechanical lithotripsy, the common bile duct was cleared using basket and balloon catheters for stones and fragments extraction.
c. Air in the biliary tree after sphincterotomy and complete clearance of the common bile duct from stones.

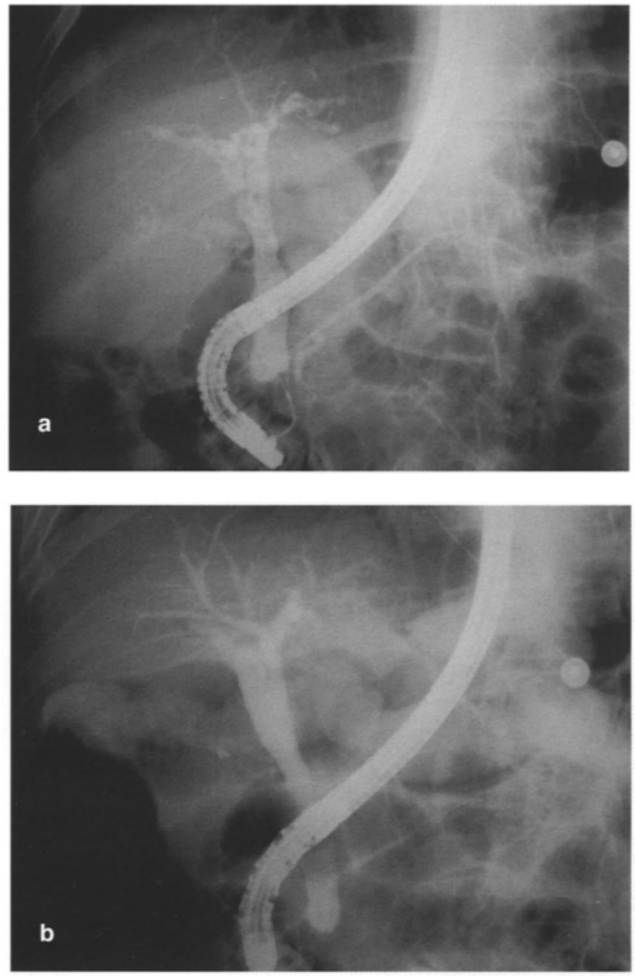
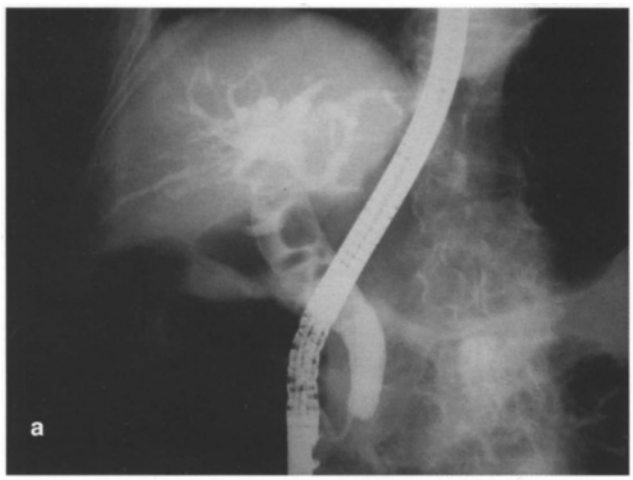


Fig. 7.10. Multiple small bile duct stones in the biliary tree, before (a) and after (b) stones removal from the bile ducts.

After biliary stenosis is diagnosed, the initial challenge for the endoscopist is to distinguish an underlying malignancy from a benign obstructive process. Compared to other imaging techniques, ERCP may yield a definite diagnosis by obtaining tissue specimens for histological or cytological analysis. Brush cytology performed at ERCP has now become the preferred initial method of pursuing tissue diagnosis in patients with biliary strictures. The technique has a low complication rate and allows sampling from most sites within the biliary duct system. The diagnostic specificity of biliary brush cytology is very high (>95%) but its mean sensitivity is no higher than 59% (range 42-85%) [17, 18]. Using endoluminal biopsy forceps, tissue specimens from the stricture could be histological-



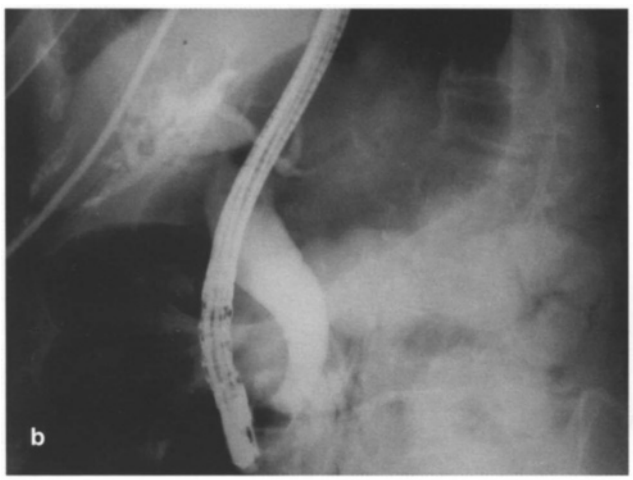
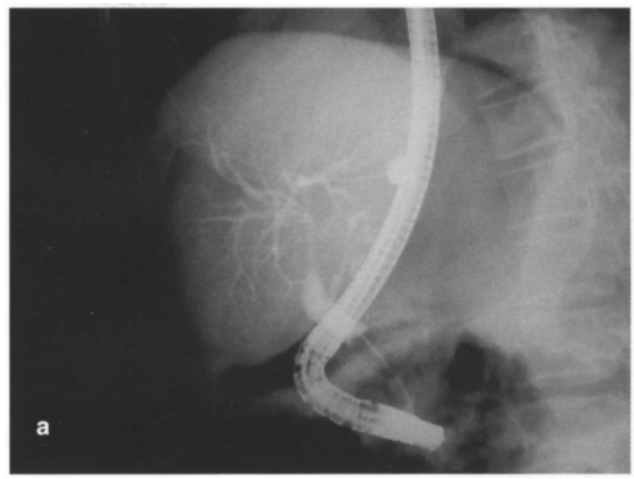


Fig. 7.11.
a. Multiple bile duct stones in a 75-year-old patient with severe acute suppurative cholangitis. Due to patient's unstable clinical status, a plastic pig-tail type stent has been inserted to decompress the biliary tree and prevent stone impaction.
b. After patient's clinical improvement, the stent was removed, a sphincterotomy was performed and the bile duct has been completely cleared from stones. Note the inflated balloon at the distal part of the common bile duct.



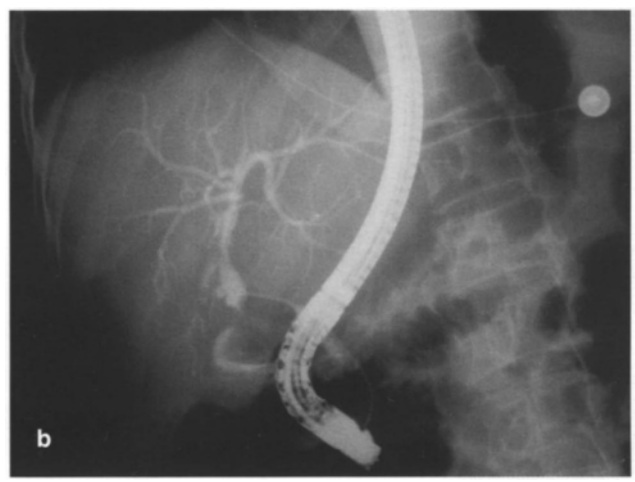
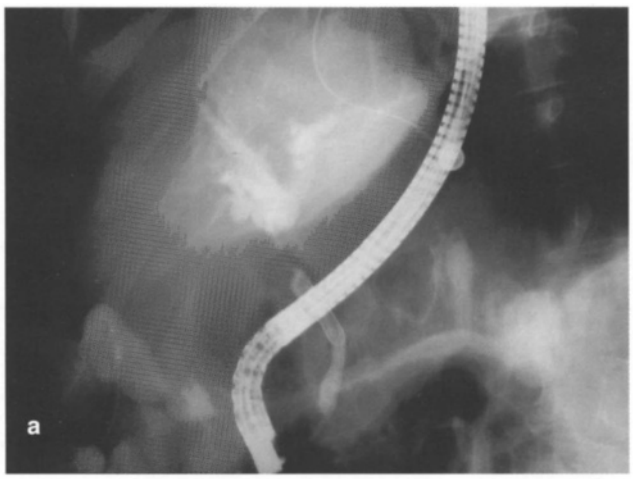


Fig. 7.12.
a. A quite long benign biliary stenosis affecting the common hepatic and common bile ducts. Note the regular in contour appearance of the stenosis, which clinically was manifested with jaundice in the early postoperative period, after an open cholecystectomy for suppurative cholangitis.
b. The same stenosis after endoscopic balloon dilatation. Note the inflated dilation balloon into the common bile duct.

ly analysed. However, biopsies and brushing yield a combined diagnostic sensitivity that is no higher than 62% [19].

Besides its diagnostic value, ERCP is also effective in the treatment of both malignant and benign biliary strictures (fig. 7.12, 7.13). Endoscopic stent placement provides effective palliation in patients with malignant disease and significant biliary obstruction, either as a temporary measure before surgical treatment or for long-term palliation. The role of preoperative biliary decompression for malignant obstruction should be limited to those patients with acute cholangitis or those who have severe pruritus and the waiting list for a surgical resection is long [20] (detailed presentation of the endoscopic palliative management of malignant biliary strictures in the chapter 21).

Benign biliary strictures may be successfully dilated with hydrostatic balloons (fig. 7.12) or a graduated catheter passed over a guidewire. To prevent recurrent stenosis the placement of one or multiple stents through



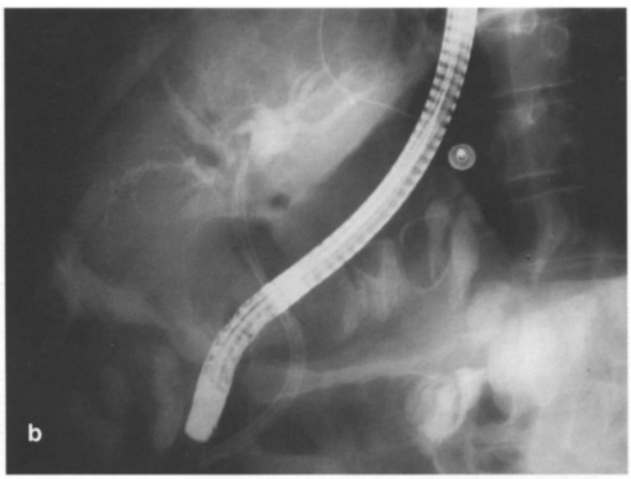
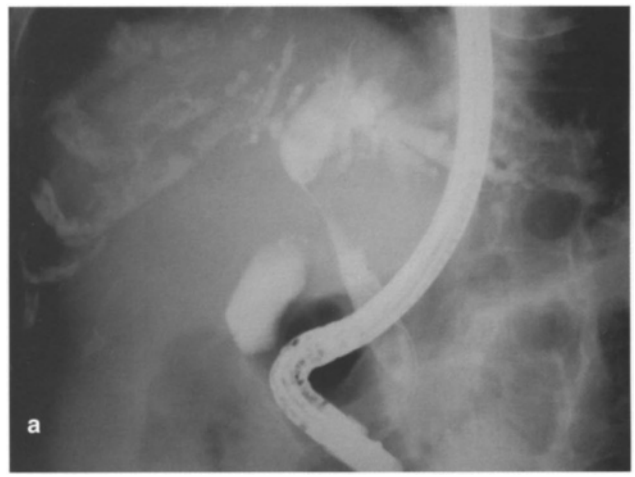


Fig. 7.13. a. A malignant stenosis at the proximal common bile duct due to cholangiocarcinoma. Note the irregularity of the stenosis and the prestenotic dilatation of the intrahepatic biliary tree.
b. A plastic 10-French stent has been inserted through the stenosis for temporary palliation of patient's symptoms.



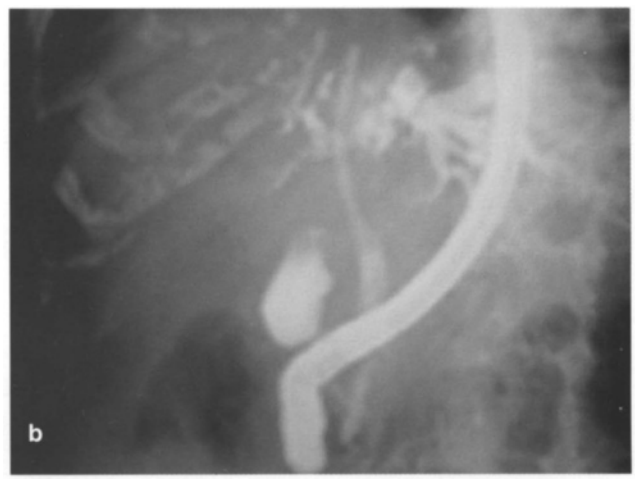


Fig. 7.14. a. A malignant common bile duct stenosis due to cholangiocarcinoma. A prestenotic dilatation of the intrahepatic bile ducts as well as contemporary choledocholithiasis are seen.
b. A plastic stent has been inserted through the stenosis to temporarily reduce deep jaundice.

the dilated stricture may prove helpful [21]. Indications for endoscopic dilation of benign strictures include postoperative strictures, dominant strictures in sclerosing cholangitis, chronic pancreatitis and stomal narrowing after choledochoenterostomy [22].

7.5.2.3. *Iatrogenic Bile Duct Injury*

Post-operative Bile Duct Strictures

Benign postoperative bile duct strictures can occur following cholecystectomy, common bile duct exploration, gastrectomy, pancreaticoduodenal resection or hepatic surgery (fig. 7.16). Direct injury with partial or complete resection of the bile duct, clipping of the bile duct (fig. 7.17) as well as ischemia due to disruption in its blood supply are the most common causes of postoperative bile duct strictures. Most postoperative strictures are short (<10 mm) and they are classified as type I strictures, according to the Bismuth classification [23].

The role of ERCP in the diagnosis and management of patients with benign postoperative bile duct strictures is well established [24]. Strictures may be dilated with hydrostatic balloons and one or multiple stent can be placed. At the first endoscopic session one or two

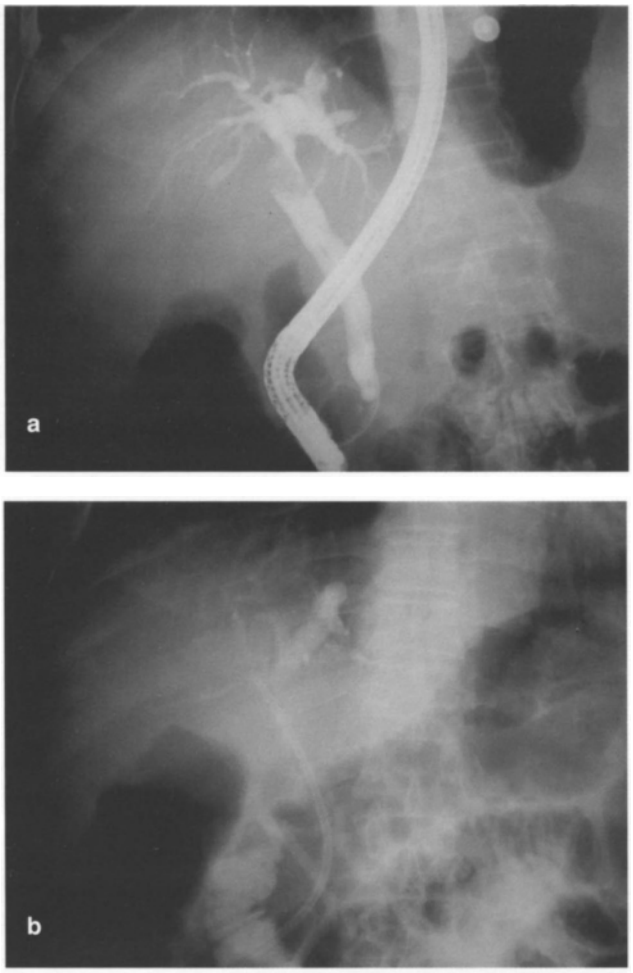


Fig. 7.15.
a. A filling defect into the common hepatic duct of a male patient with cholangitis and hemobilia. Examination of the tissue specimens, obtained at ERCP with biopsy forceps from the mass lesion, revealed a hepatocellular carcinoma infiltrating the bile ducts.
b. A plastic 10-French stent has been inserted into the intrahepatic ducts to improve patient's clinical condition.

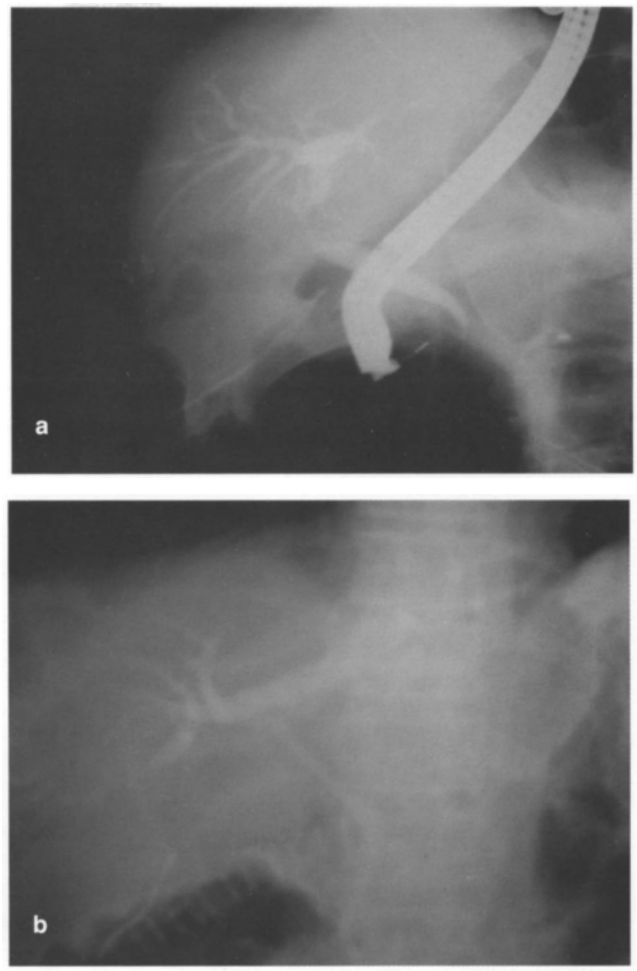


Fig. 7.16.
a. Benign stenosis at the level of the common hepatic duct. This 60-year-old male patient manifested a progressively deteriorating obstructive jaundice, immediately after a troublesome open cholecystectomy for suppurative cholecystitis.
b. A plastic 10-French stent, inserted into the intrahepatic ducts, led to a rapid clinical improvement of the patient.

10-French plastic stents are inserted through the dilated stricture over an atraumatic guide wire. At 6 to 8 weeks, the initial stents are replaced by two or more 10-French plastic stents. Thereafter these are replaced with new stents at 3 months intervals over a period of 12 months. Should the endoscopic management fail or a complete ductal obstruction is noticed the patient should be referred to a surgeon [22, 25]. With regard to benign bile-duct strictures created after cholecystectomy, the outcome of balloon dilation and stent treatment is encouraging but still far from optimal and clinical success rates with these modalities can range from 55% to 88% [21, 25].

Orthotopic liver transplantation (OLT) has seen a rapid developed. However, a variety of complications involving the biliary tract, including anastomotic biliary strictures, may arise in patients who undergo OLT. Though many of these strictures are successfully diagnosed and treated endoscopically, [26] extensive intrahepatic strictures are not suitable for endoscopic therapy. The outcomes of endoscopic therapy of bile duct strictures occurring after liver transplantation tends to

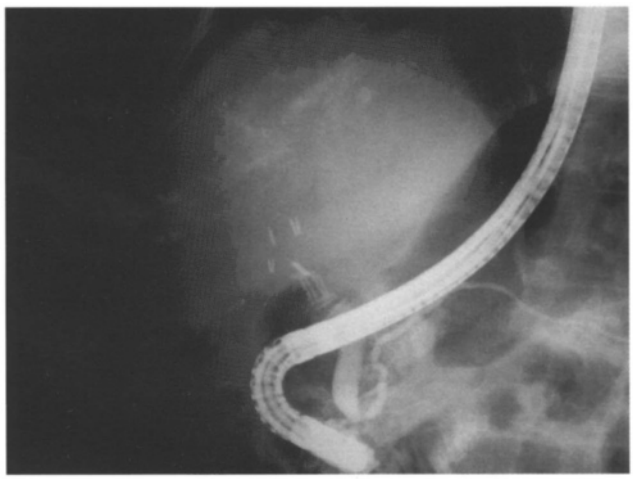
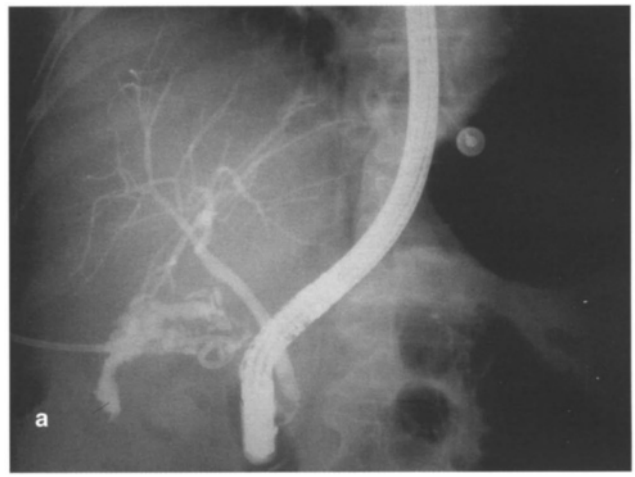


Fig. 7.17. Complete occlusion of the common bile duct due to erroneous clipping at laparoscopic cholecystectomy. This 55-year-old female patient underwent surgery with choledochojejunal anastomosis.



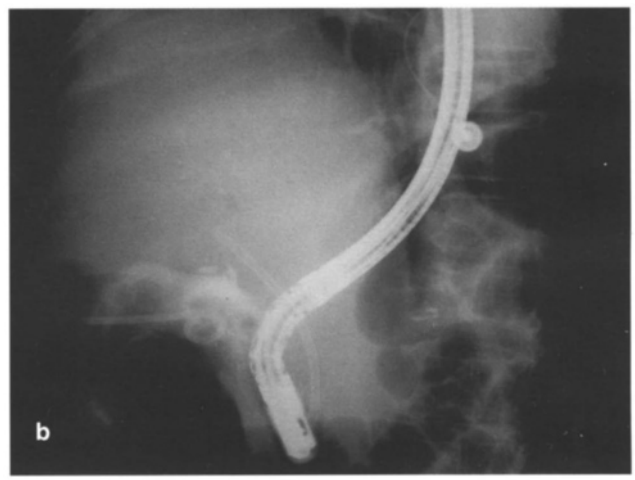


Fig. 7.18.
a. Cystic stump leakage after laparoscopic cholecystectomy.
b. A short 10-French endoprosthesis has been placed in the common bile duct to reduce intrabiliary pressure. Cholorrhea stopped 2 days after the common bile duct stenting. The endoprosthesis was removed 6 weeks later.

be highly variable, with reported success rates as high as 91% to 100%, while other investigators have shown a mere 42% success rate for early postoperative strictures and 8% for late postoperative strictures [26-28].

Postoperative Bile Duct Leak

Direct injury of the bile duct, usually during cholecystectomy, may lead to its complete or partial rupture followed by bile leakage. Although accurate data do not exist, biliary leakage is more common after laparoscopy than after an open procedure. ERCP is the procedure of choice for the accurate diagnosis and successful management of a suspected biliary leakage [29] (fig. 7.18, 7.19, 7.20). Biliary leaks from the cystic duct, which account for the majority of cases, the bile duct and the ducts of Luschka, respond well to decompression of the bile duct by endoscopic stent placement or nasobiliary drainage with or without sphincterotomy [29-31]. Stents are usually placed for 4 to 6 weeks but longer intervals of stent placement may be necessary for larger duct injuries [32]. These principles also apply to bile leaks that occur after liver resection [33, 34]. Success rates for endoscopic closure of bile leaks depend on size and location of the area of leaking and ranges from 80% to 100% [22]. Most amenable to successful endoscopic treatment are the cystic duct stump leaks.

Postoperative Complications of Choledochoduodenostomy

"Sump" syndrome represents a complication of choledochoduodenostomy. Endoscopic retrograde cholangiography via the main duodenal papilla demonstrates stones or debris in the distal blind end of the common bile duct (fig. 7.21). Endoscopic sphincterotomy with bile duct clearance is usually beneficial [35].

Stenosis of a choledochoduodenostomy could possibly result in cholangitis, biliary obstruction and the "sump" syndrome. Endoscopic dilation of a strictured

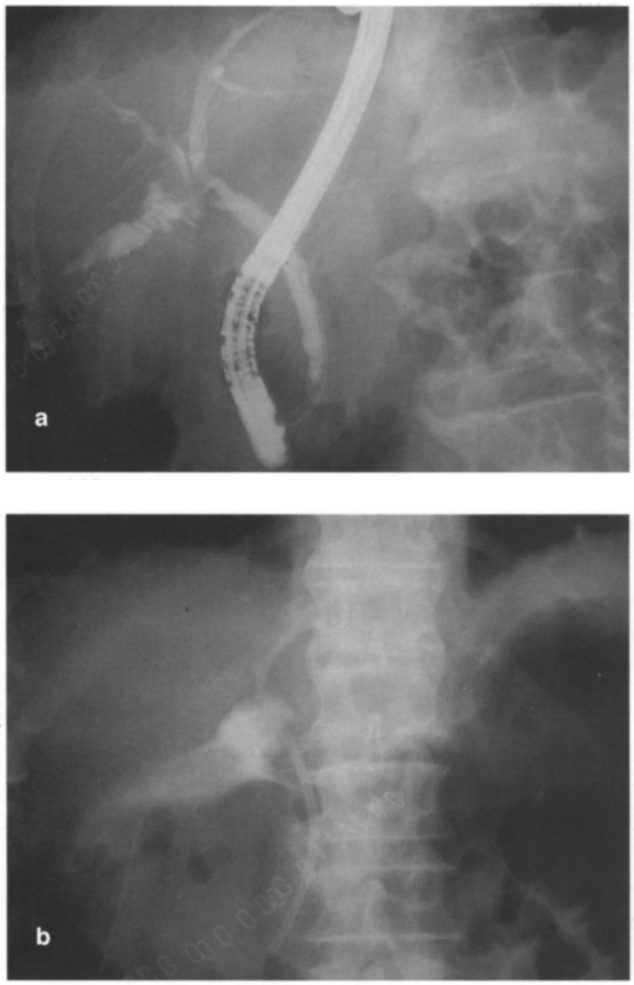


Fig. 7.19.
a. Right hepatic duct leakage consequent to damage at open cholecystectomy.
b. A 10-French plastic endoprosthesis has been inserted in the common bile duct. Cholorrhea stopped 3 days after the common bile duct stenting.

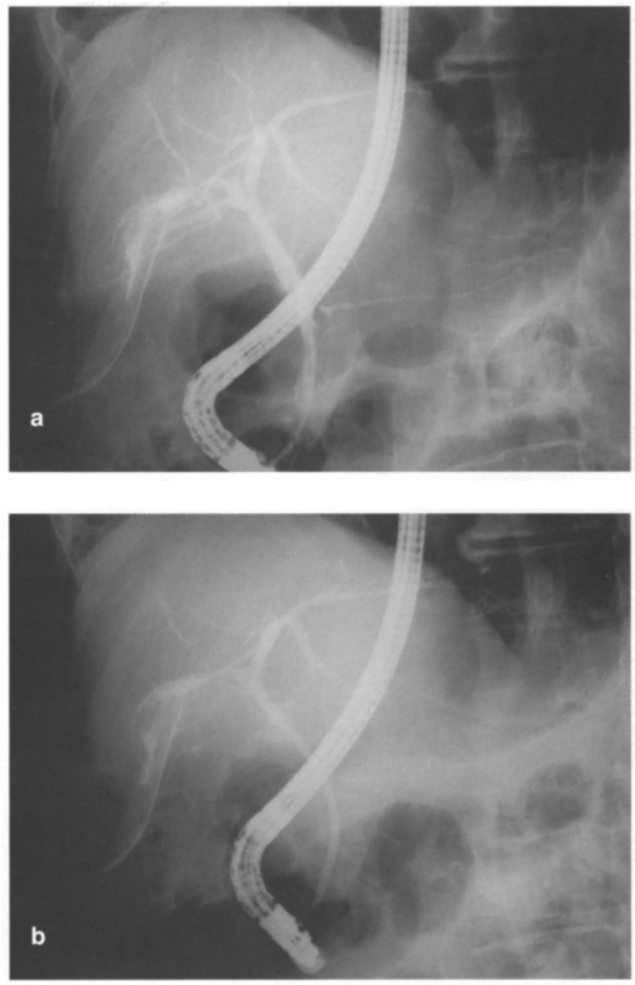


Fig. 7.20.
a. Long-standing cholorrhea from a small intrahepatic bile duct at the site of a hepatic hydatid cyst removal. Note the small residual cyst cavity.
b. A 10-French plastic endoprosthesis has been placed in the common bile duct, which resulted in discontinuation of the bile duct leakage a few days later.

anastomosis with sequential bile duct clearance may be curative [36].

7.5.2.4. *Mirizzi's Syndrome*

The impaction of a large stone either in the neck of the gallbladder or in the junction of the cystic duct with the common bile duct, which is rare, may usually cause compression of the common hepatic duct [37]. The typical finding of endoscopic retrograde cholangiography is that of a smooth stenosis, usually of the common hepatic duct (fig. 7.22). The main differential diagnosis is malignancy of the gallbladder or common bile duct. Sometimes accurate diagnosis is made only during surgical procedure.

7.5.2.5. *Sclerosing Cholangitis*

Primary Sclerosing Cholangitis

ERCP provides high quality imaging of the biliary tree in cases of primary sclerosing cholangitis (PSC) including those with minimal biliary abnormalities (fig. 7.23). The cholangiographic appearance of PSC is characteri-

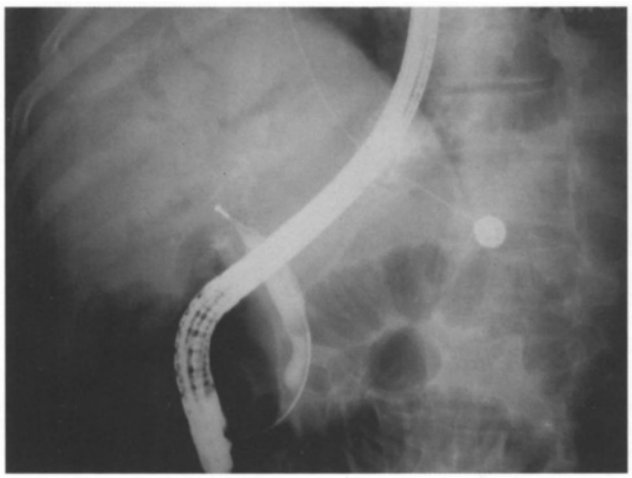
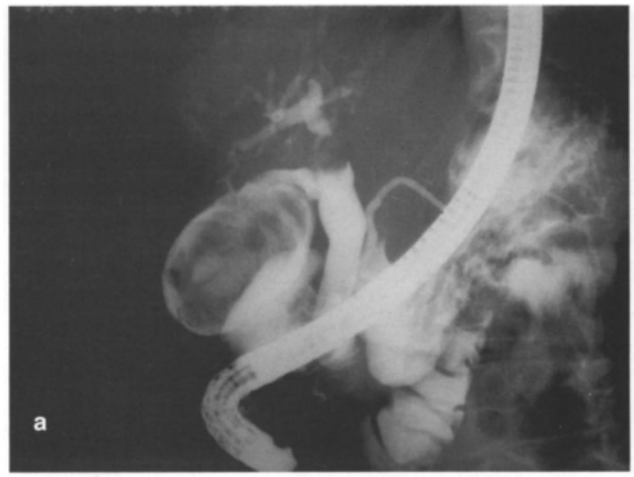


Fig. 7.21. «Sump» syndrome in a patient with choledochoduodenal anastomosis and recurrent episodes of cholangitis. Endoscopic retrograde cholangiogram via the duodenal papilla demonstrates small stones and debris in the distal blind end of the common bile duct.



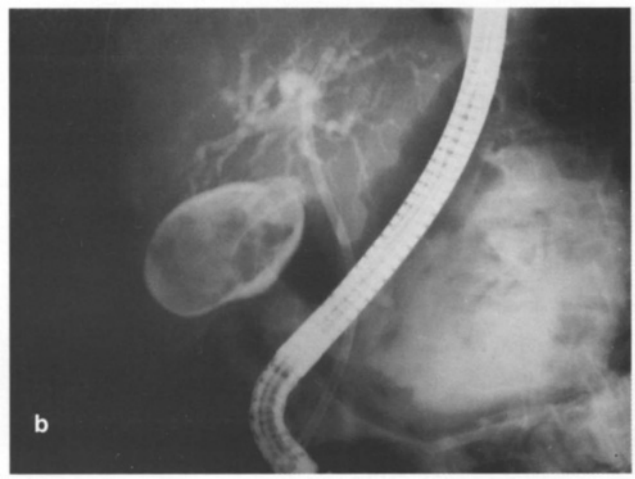


Fig. 7.22.
a. Mirrizi's syndrome. Common hepatic duct obstruction caused by the impaction of a stone in the junction of the cystic duct with the common bile duct. Note another huge stone occupying the whole gallbladder cavity.
b. A long 10-French plastic endoprosthesis has been inserted in the intrahepatic ducts, resulting in rapid decompression of the biliary tree from bile and pus.

zed by multiple short strictures of both the intrahepatic and the extrahepatic biliary tree, with the cystic duct and gallbladder remaining normal [38]. A beaded appearance of the biliary tree is characteristic of PSC. The presence of a polypoid mass, markedly dilated ducts proximal to a stricture or rapidly progressive stricture formation are cholangiographic findings signaling the development of cholangiocarcinoma.

Sometimes PSC may present difficulties for the endoscopist such as, difficult catheterization of the retracted papilla due to biliary fibrosis, an increased risk of bile duct perforation by guidewires and problematic selective cannulation of the individual hepatic duct. In addition, patients with PSC undergoing ERCP carry a greater risk of procedure-related cholangitis [39, 40]. Moreover, the cholangiographic diagnosis of a PSC complicating cholangiocarcinoma is mostly impossible. Fortunately, a significant increase in diagnostic accuracy may be made by obtaining tissue specimens at ERCP for cytological or histological analysis. Several studies have attempted to improve the diagnostic yield of these modalities but without notable success [41, 42]. The sensitivity and specificity rates of the cytologic evaluation of tissue specimens obtained at ERCP from dominant stenoses of patients with PSC are similar to those reported for biliary stenoses of another etiology (42-85%) [17, 18].

The main therapeutic role of ERCP in PSC is to improve bile flow in cases of obstructive jaundice, acute bacterial cholangitis or pruritus due to the presence of severe fibrotic strictures or developed biliary malignancy. Strictures that develop in patients with PSC tend to respond well to endoscopic therapy, with balloon dilation either alone or in combination with endoscopic stents placement. The limited data available on this topic suggest that balloon dilation may suffice and that the use of stents is possibly associated with an increa-

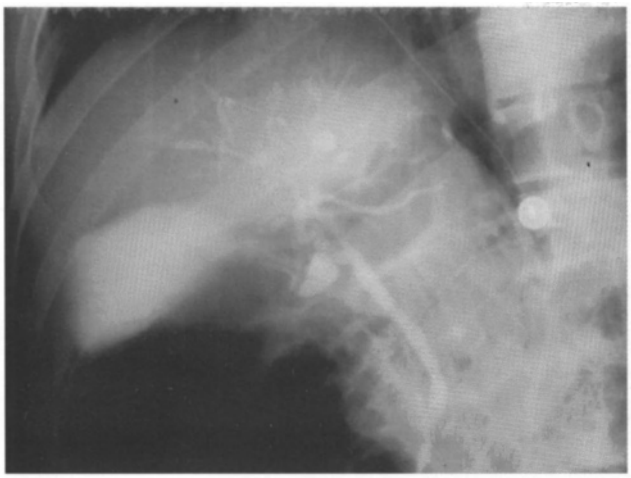


Fig. 7.23. Retrograde cholangiogram of a patient with ulcerative colitis and hepatic biochemical abnormalities demonstrating minimal changes of primary sclerosing cholangitis. Few short segmental intrahepatic stenoses alternate with areas of normal calibre or dilation.

sed risk of complications, including bacterial cholangitis [43, 44].

Endoscopic therapy of strictures has been shown to be overally beneficial in patients with PSC. Van Milligen de Wit et al [39] reported that endoscopic therapy was technically successful in 84% of their patients in all of whom a significant improvement in liver function tests was reported within 6 months of insertion of the prosthesis. Stents were thereafter replaced electively every 2 or 3 months or in an acute basis in patients who developed cholangitis. Complications occurred in 14% of the 105 procedures. During a median follow-up of 29 months, after final stent removal, 57% of their patients remained asymptomatic with stable liver function tests [39]. In 4 (19%) of the patients clinical and biochemical parameters deteriorated, but all responded to additional sessions of endoscopic treatment. Bjornsson and colleagues [43] evaluated 125 patients with PSC to determine the prevalence of dominant strictures and the course of liver function tests over 1 year of follow-up, in patients with or without dominant strictures. The prevalence of dominant strictures was 45% and some of the patients underwent endoscopic therapy. During a follow-up period of 2-21 months after the initial diagnostic cholangiography, the mean values for alkaline phosphatase and total bilirubin did not significantly differ between patients with untreated dominant strictures and those without dominant strictures. The investigators suggested that endoscopic therapy of dominant strictures should not be routinely carried out [43]. Vuddagiri et al [40] reported on their 20-year experience of endoscopic treatment for dominant stricture dilation and stone removal in 110 patients with PSC. Endoscopic sphincterotomy was carried out in 74 patients, brush cytology in 60 patients, temporary stent placement in 42 and biliary balloon dilatation in 51 patients. Complications occurred in 5.6% of 393 ERCPs performed, including exacerbations of cholangitis in 4 patients and sepsis in 2 patients. An overall beneficial response to endoscopic therapy was observed in 63 of 88 evaluated patients (72%). One study suggested that endoscopic treatment in PSC may improve survival [45]. Although endoscopic therapy in PSC has not been shown to delay liver transplantation or to allow early identification of cholangiocarcinoma, cholangiograms obtained at ERCP have been shown to have some prognostic value [46].

Acquired Immunodeficiency Syndrome (AIDS) - Related Sclerosing Cholangitis

ERCP may be very helpful in diagnosing HIV-related cholangitis. Cholangiographic findings are mostly similar to PSC. Diffuse, irregular intrahepatic stenoses with a distal extrahepatic stenosis, and/or intrabiliary filling defects owing to biliary squamous metaplasia, have been described in patients with the HIV virus, infected by cryptosporidia and cytomegalovirus [47]. Diffuse intrahepatic biliary dilation in combination with a smooth distal common bile duct stricture as well as stenosis of the main duodenal papilla have also been reported [47, 48]. Endoscopic treatment in patients with HIV-related biliary disorders should be applied according to the general indications.

7.5.2.6. *Parasitic Infections Involving the Biliary Tract*

Oriental Cholangitis

Several parasites (clonorchis sinensis, Ascaris lumbricoides, Opisthorchis species etc) may predominantly involve the biliary tree causing oriental cholangiohepatitis, a syndrome characterized by recurrent episodes of abdominal pain jaundice and acute cholangitis. Cholangiography may also disclose biliary strictures, main-

ly at the hepatic duct confluence, pigmented bile duct stones, as well as long and thin filling defects due to intrabiliary parasites [49, 50]. Although therapeutic endoscopic intervention has been reported for stones or parasites removal [51] as well as for dilating biliary strictures, the role of ERCP in this disease setting remains controversial as most associated biliary disorders are intrahepatic [50].

Hepatic Hydatidosis

Hepatic hydatidosis, caused by the parasite Echinococcus granulosus, is characterized by the development of hydatid cysts of variable diameter in the liver. Hepatic hydatid cysts can cause obstructive jaundice and cholangitis due to either cyst rupture into the biliary tree (fig. 7.24, 7.25) or compression of intra- or extrahepatic bile ducts by a large cyst [52, 53, 54]. Moreover after surgery, which is the treatment of choice in the management of biliary complications of hydatid cysts, a bile secreting fistula sometimes develops due to a communication between the residual cyst cavity and the biliary tree [55] (fig. 7.20).

ERCP is considered a reliable method in both the detection and the effective management of hepatic hydatidosis-induced biliary involvement [52, 54]. Bile ducts clearance from daughter cysts and residual hydatid material can be successfully accomplished by means of therapeutic ERCP. Endoscopic therapy has further proved to be most effective in the management of postoperative bile leaks [54] and biliocutaneous fistulas [55].

7.5.2.7. *Sphincter of Oddi Disorders*

Anatomic

Diagnosis of a suspected ampullary carcinoma or adenoma is yet another indication for ERCP (fig. 7.26). Tissue biopsies for histological analysis and cytology specimens for cytological evaluation can be obtained at ERCP. Moreover, ERCP provides an opportunity to evaluate the extent of disease within the common bile duct. Although the therapeutic management of papillary tumors is mostly surgical, therapeutic ERCP (sphincterotomy, dilation, stent placement) is a well-confirmed option for biliary decompression in cases of concurrent acute cholangitis or palliation in inoperable malignancy. In the case of an ampullary adenoma, an en-

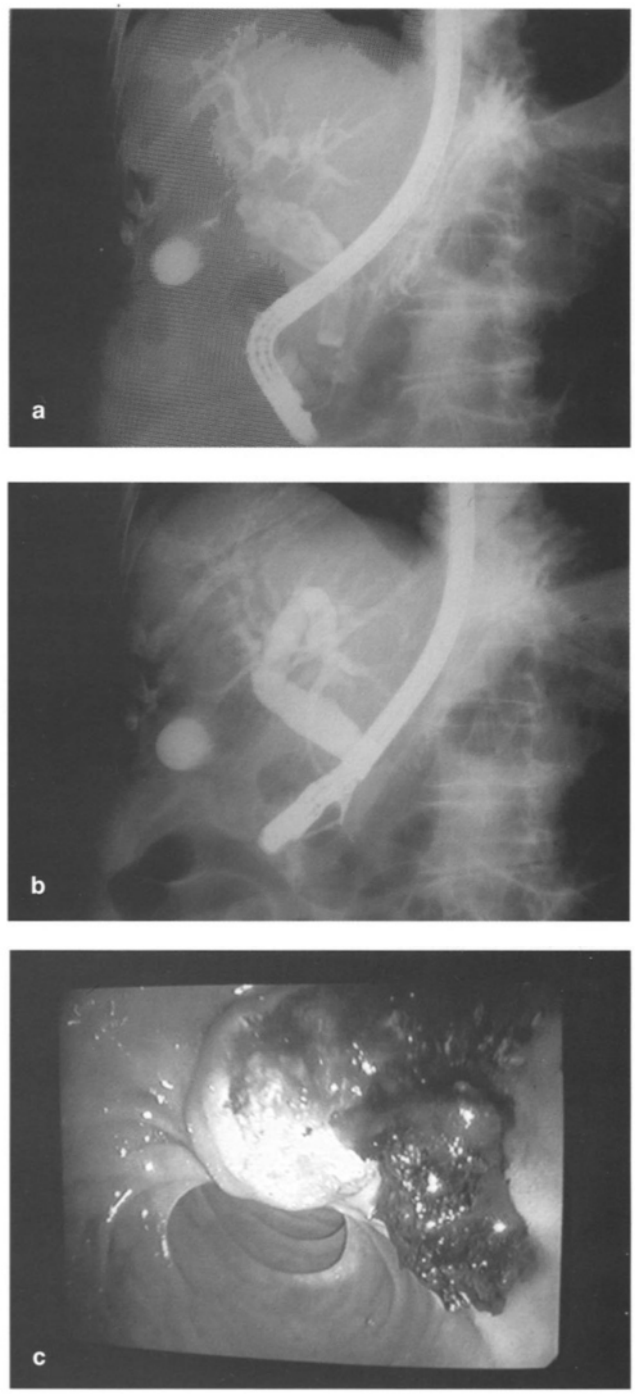


Fig. 7.24.
a. Intrabiliary rupture of a hepatic hydatid cyst. The biliary tree is full of daughter cysts and hydatid material. This 60-year-old female patient presented with symptoms of acute suppurative cholangitis.
b. Retrograde cholangiogram of the same patient showing complete clearance of the biliary tree from hydatid material, using a balloon catheter for stone extraction, after a large sphincterotomy.
c. Endoscopic view of the same patient showing the extracted hydatid material at ERCP.

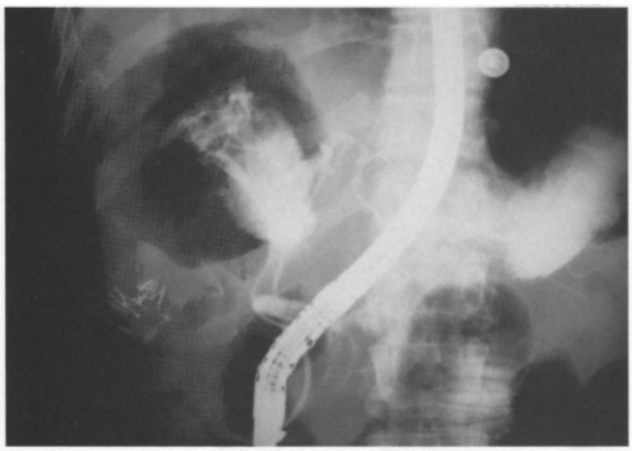


Fig. 7.25. Retrograde cholangiogram of a patient with a large hepatic hydatid cyst and symptoms of acute cholangitis. Opacification of the cyst, by intrabiliary injected contrast medium, demonstrated the cyst rupture into the biliary tree. Note a small amount of hydatid material into the distal bile duct.

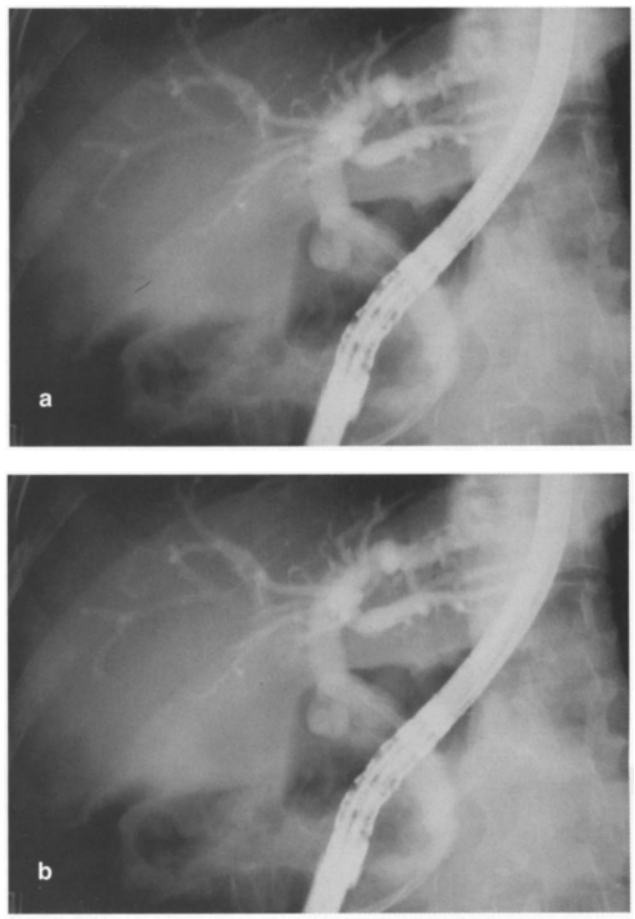


Fig. 7.26.
a. Retrograde cholangiogram of a patient demonstrating an irregular filling defect in the distal common bile duct, which represents infiltration of the common bile duct by a papillary carcinoma. Note the prestenotic dilation of the biliary tree.
b. A short 10-French stent has been placed in the common bile duct for temporary palliation of the patient's deep jaundice and pruritus.

doscopic ampullectomy is considered as safe and effective as the surgical therapeutic approach [56].

Benign stenosis of the main duodenal papilla has been reported in some patients with gallstones due to scarring of the papilla resulting from the passage of stones from the bile duct into the duodenum. Papillary stenosis has also been endoscopically diagnosed and treated in patients with AIDS without concurrent gallstone disease [48].

Functional

Dysfunction of the Sphincter of Oddi may present with signs and symptoms of biliary and/or pancreatic disease. It is usually diagnosed using sphincter of Oddi manometry [57)]. ERCP provides the means for placing a manometry catheter to measure pressures within the sphincter, common duct and pancreatic duct [58]. After diagnostic ERCP, the manometry catheter is inserted through the working channel of the endoscope into the papillary orifice and directed into the common bile duct or the pancreatic duct. The ductal pressure is recorded initially. The catheter is then slowly withdrawn by 2-mm increments into the duodenum. At each station, pressure recordings are obtained for 2 to 3 min.

Moreover, ERCP allows therapeutic intervention in clinically selected or manometrically confirmed cases of biliary or pancreatic sphincter dysfunction. Endoscopic treatment for sphincter of Oddi dysfunction is associated with a successful outcome in more than 90% of patients and is more cost-effective than the surgical approach [57]. Therapeutic biliary or pancreatic sphincterotomy in these cases is associated with a high rate of acute pancreatitis after the procedure [59]. To decrease the incidence of post-ERCP pancreatitis in patients with sphincter of Oddi dysfunction undergoing either manometry or therapeutic sphincterotomy, a temporary pancreatic stent should be placed into the pancreatic duct.

7.5.2.8. *Choledochal Cysts*

Choledochal cysts and anomalous junction of the biliary and pancreatic ducts are uncommon etiologies of bile duct strictures. Choledochal cysts are congenital dilatations of the biliary tree, more common in females [60)] (fig. 7.27, 7.28). Todani et al classified choledochal cysts in 5 types (IA, IB, IC, II, III, IVA, IVB, V) [61]. They may be identified on ultrasound examination or more commonly during cholangiography [60, 62]. Current treatment of choledochal cysts is essentially surgical.

Apart from its effectiveness in precisely diagnosing choledochal cysts, ERCP is also therapeutically indicated in cases of suspected complications such as bacterial cholangitis, biliary lithiasis, rupture and cholangiocarcinoma. Although not conclusive, endoscopic therapeutic approach is effective in managing these cases by performing sphincterotomy, biliary dilation with stent placement and stone extraction [62, 63]. Ciambotti et al successfully treated a patient with monolobar Caroli's disease (type V choledochal cyst) and multiple intrahepatic stones by stent placement for 1 year, together with administration of ursodeoxycholic acid until the stone burden was eliminated [64]. However, endoscopic treatment is the method of choice for uncomplicated choledochocele (type III choledocal cyst) [63, 65] (fig. 7.29). Patients with choledochal cyst require life-long follow-up. Whether this should be performed with ERCP, MRCP or endoscopic ultrasound (EUS), remains to be established.

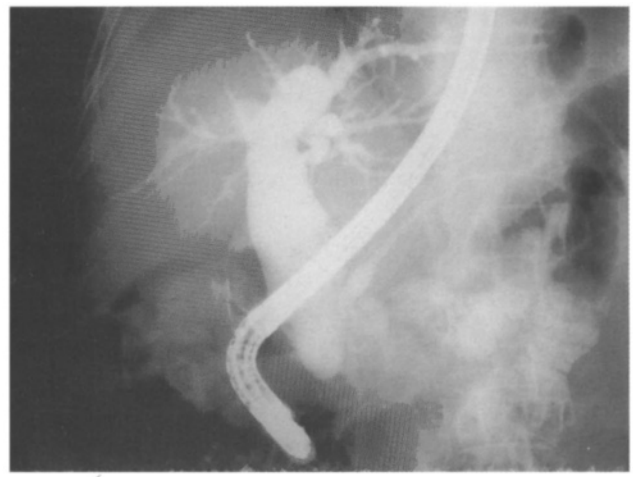


Fig. 7.27. Diffuse dilation of the common bile duct with distal bile duct stenosis, representing a Type I choledochal cyst.

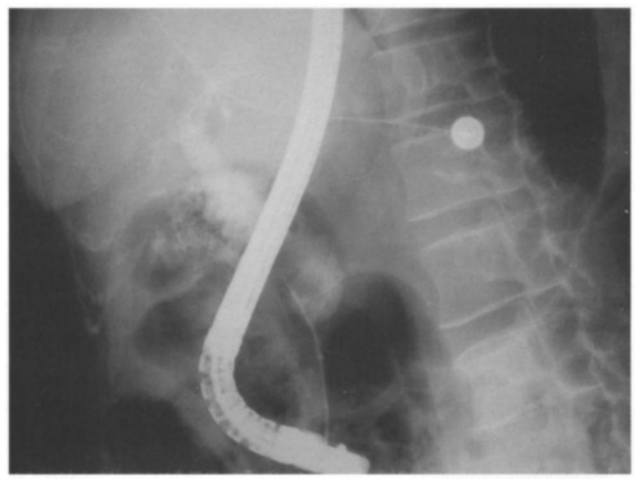


Fig. 7.28. Diffuse dilation of the common bile duct in a female patient with a Type I choledochal cyst. Note the normal common hepatic and intrahepatic ducts as well as a stenosis of the distal common bile duct. The patient was suffering for years from recurrent episodes of acute cholangitis.

7.5.2.9. *Pancreatic Diseases*

Pancreatic diseases, especially those of the head of the pancreas, may usually involve the distal part of the bile duct compromising bile flow.

A variety of pancreatic disorders can be diagnosed and treated with ERCP. However, controlled trials evaluating its therapeutic efficacy are limited. The main indications for ERCP in pancreatic diseases are presented here with special references to pancreatic disorders affecting the biliary tract. The role of ERCP in this context is still under evaluation.

Acute Pancreatitis

Nowadays, the role of ERCP during the crucial phase of an acute pancreatitis is limited. More specifically, in this clinical case, it is restricted to patients with severe acute pancreatitis and concurrent cholestasis, especially when considering a known or highly suspected choledocholithiasis. In this context, ERCP has been found beneficial, reducing disease morbidity and mortality [66, 67]. On the contrary, ERCP is not useful during the acute phase of acute pancreatitis unrelated to cholestasis [68]. Most common cholangiographic findings in acute pancreatitis include biliary lithiasis and distal common bile duct stenosis due to compression from the pan-

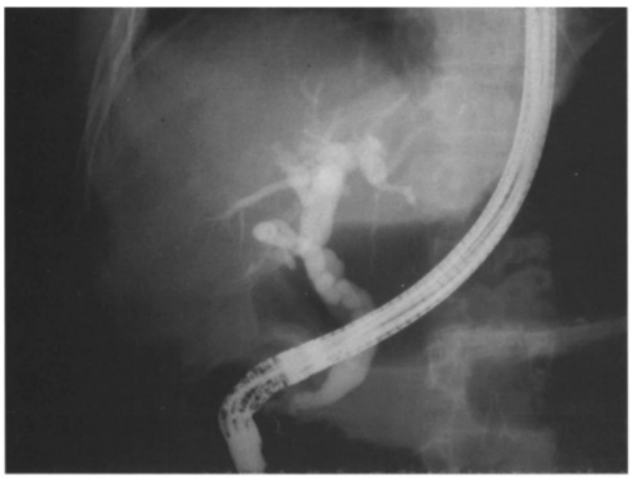


Fig. 7.29. Retrograde cholangiogram showing a Type III choledochal cyst (choledochocele).

creatic oedema or a developed pseudocyst. In rare cases, a parasitic biliary infection, pancreas divisum and a pancreatic or papillary tumor may be diagnosed [69].

The majority of patients with acute pancreatitis recover uneventfully with conservative management of the disease. Choledocholithiasis in these patients should be treated with ERCP after complete recovery from the acute episode of pancreatitis. The need for ERCP following an isolated episode of pancreatitis of unknown origin has not been confirmed.

Acute Recurrent Pancreatitis

In cases of acute recurrent pancreatitis, it would be ideal if ERCP should be reserved for treatment of abnormalities spotted already by means of less invasive imaging techniques such as MRCP and EUS. These modalities may detect microlithiasis, choledocholithiasis, unsuspected chronic pancreatitis and in some cases, pancreas divisum and annular pancreas [70, 71]. In selected patients with microlithiasis confirmed by bile analysis, the endoscopic sphincterotomy may be useful in preventing recurrent pancreatitis [72].

The role of pancreas divisum as a cause of recurrent acute pancreatitis remains controversial. In selected patients, minor papilla sphincterotomy may prevent further attacks of acute recurrent pancreatitis. Furthermore, fewer hospitalizations and better quality of life with substantial pain relief has been reported in these patients, after minor papilla sphincterotomy [73, 74].

Chronic Pancreatitis

Chronic pancreatitis may cause distal bile duct strictures mostly due to fibrosis (fig. 7.30, 7.31). ERCP is effective in diagnosing and typically treating these strictures with dilatation and stent placement [75].

In the past, it was believed that ERCP is essential prior to surgery for chronic pancreatitis. Nowadays, asymptomatic or symptomatic chronic pancreatitis can be successfully diagnosed by less invasive imaging techniques, such as MRCP and EUS [70]. However, ERCP still remains the gold standard diagnostic modality in order to obtain definitive imaging of early ductal abnormalities seen in chronic pancreatitis. Abnormalities include reduced number of branches (focal, multifocal, diffuse), which may be shortened, dilated or narrowed and irregular in contour. Moreover ERCP remains useful in the preoperative assessment of pathologic changes in pancreatic anatomy, demonstration of a communication between pancreatic ducts and a pseudocyst and determining the presence of strictures, of obstruction or pancreatic stones [76].

ERCP also provides direct access to the pancreatic duct for treatment of symptomatic stones, strictures and pseudocysts. Pancreatic strictures can be successfully treated with dilation and stent placement. Pancreatic sphincterotomy and stone removal may be difficult or even impossible and stone fragmentation may require extracorporeal shock wave lithotripsy [77]. Pancreatic endotherapy pain relief varies widely, with reported short-term improvement rates of 77% to 100% and long-term improvement rates of 54% to 86% [76, 78, 79]. However, it appears that pancreatic endotherapy, with strictures dilation and stone removal does not improve pancreatic function [79]. Compared to endotherapy, surgery is superior for long-term pain reduction in patients with obstructive chronic pancreatitis.

Pancreatic Duct Leaks and Pseudocysts

Pancreatic duct leaks may result due to severe acute or chronic pancreatitis and pancreatic trauma. They may be manifested as pancreatic ascites and/or pseudocyst formation. ERCP is sometimes indicated for preoperative assessment of the disorder. However, pancreatic leaks and communicating pseudocysts can often be treated with transpapillary pancreatic stent placement [80, 81] with reported success rates of 80% to 90% [76,

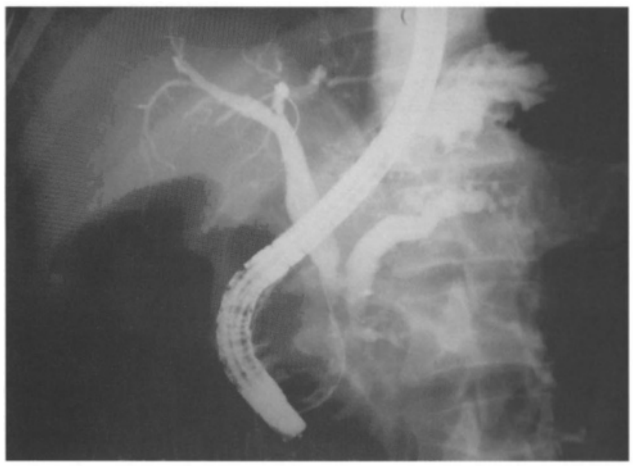


Fig. 7.30. Retrograde cholangiopancreatogram of a patient with chronic pancreatitis and cholestasis. Note the distal bile duct stenosis due to fibrosis. The main pancreatic duct and its side branches are dilated.

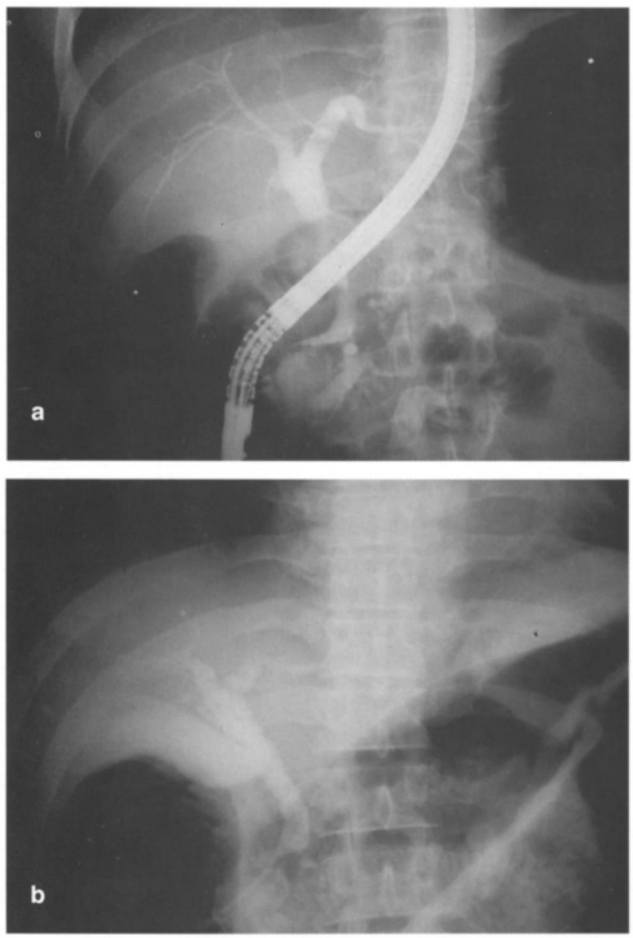


Fig. 7.31. a. Retrograde cholangiopancreatogram of a patient with chronic pancreatitis and cholestasis showing a pseudocyst at the head of the pancreas. The pseudocyst causes distal bile duct stenosis due to compression. b. A plastic stent has been placed to improve patien's clinical condition.

83]. Succesful transmural drainage of pseudocysts through the gastric or duodenal wall by an experienced endoscopist can be successful in more than 80% of cases [83].

Pancreatic Tumors

ERCP is very effective in diagnosing adenomas of the main duodenal papilla, by obtaining biopsies under direct vision for tissue analysis (fig. 7.26). Moreover, snare ampullectomy may offer definitive treatment of ampullary adenomas, without intraductal extension, in approximately 80% to 90% of patients [56]. At the time of resection, pancreatic stent placement reduces the risk of post-ERCP pancreatitis [84].

The role of ERCP in the management of pancreatic malignancies is presented in another chapter of this book. ERCP is mostly indicated for palliation of obstructive jaundice in selected patients with inoperable or unresectable pancreatic cancer.

7.6. Complications of ERCP

Complications of diagnostic ERCP include those that are associated with any upper gastrointestinal tract endoscopic procedure, categorized to those related to the pre-procedural sedation, the use of radiation during the procedure as well as those specific to ERCP.

Early studies have reported that perforation of the upper gastrointestinal tract wall with the side-viewing endoscope rarely occurs [85]. Such a complication is greatly related to endoscopist experirence as well as the presence of structural abnormalities (e.g., Zenker's diverticulum, eosophageal stenosis, gastrectomy with Billroth type II anastomosis). Whenever such a structural abnormality is suspected, it is prudent to perform first an endoscopy, with a forward-viewing endoscope. Perforation of the duodenal wall from the use of guide wires or other accessories is also very rare.

Complications of conscious sedation during ERCP are usually related to oversedation due to repeated doses of sedative and analgesic agents. Elderly patients as well as those with a history of significant cardiopulmonary disease are more prone to hypoxia under these circumstances. The risk of adverse events due to sedation should be systematically identified before ERCP. Careful monitoring of the patient's vital functions by an independent assistant is mandatory during the proce-

dure [86]. Benzodiazepines and opioids are most commonly used during ERCP. Propofol has been given safely by endoscopists [87] but its wider use depends on local rules and laws.

Both patient and endoscopists are exposed to radiation during ERCP. Radiation dosages in patients undergoing ERCP are comparable with other radiographic procedures. Radiation to which endoscopists and assistants are exposed during ERCP can be decreased to negligible amounts by reducing the duration of fluoroscopy and following the general instructions for protection against radiation [88]. Even during pregnancy ERCP can be safely performed using extra protection measures [89].

Particular procedure-related complications of ERCP most commonly include acute pancreatitis, perforation of the duodenal wall during sphincterotomy (fig. 7.32), sepsis and bleeding. These complications are presented in the chapter of "Endoscopic management of bile duct stones". In our days, ERCP is a mostly a therapeutic procedure and endoscopic sphincterotomy of the main duodenal papilla is quite often. As a result, it is difficult to differentiate the complications which are related to the diagnostic part of the procedure, from those associated to the therapeutic intervention. Nonetheless, the risk of major bleeding as well as perforation of the duodenal wall from a diagnostic ERCP is very low and should be near zero in experienced hands. Finally, according to current guidelines for upper gastrointestinal tract endoscopy, prophylactic administration of antimicrobial agents prior to procedure in order to prevent cholangitis, should be administered in patients with suspected biliary obstruction [90].

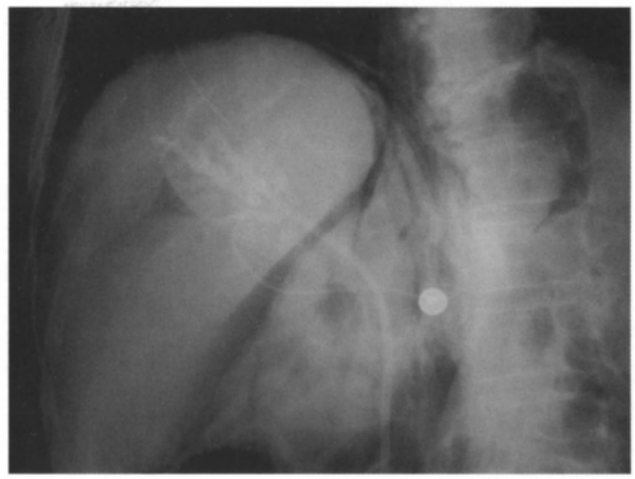


Fig. 7.32. Post-sphincterotomy perforation. Note the presence of air below the diaphragms and around the liver and right kidney. This female patient was successfully managed conservatively.

7.7. The Role of ERCP in Biliary Disorders in the Era of MRCP and EUS

ERCP has been widely used for the evaluation of biliary diseases and represents not only an accurate diagnostic modality but also an effective therapeutic technique. However, diagnostic ERCP is associated with morbidity and mortality rates of 1-6% and 0.1-0.6%, respectively [91]. When compared to surgery, such complication rates may be acceptable in therapeutic ERCP, but these complication rates are not acceptable when ERCP is used as a diagnostic method. Moreover, ERCP is highly operator-dependent with incomplete examination and unsuccessful cannulation rates of 6% and 3-9% respectively [92]. Nonetheless, ERCP with sphincterotomy is still considered the gold standard method in evaluating biliary duct diseases, also providing the opportunity for tissue or cytological analysis.

MRCP, since its introduction in 1991, has shown many technical advances and it is now widely available. Most recent studies have shown MRCP to be comparable to ERCP in identifying choledocholithiasis and biliary strictures, with sensitivity of 81-100% and specificity of 85-100% [93-95]. Drawbacks of MRCP include its absolute contraindications in patients with a permanent pacemaker or cerebral aneurysm clips, the unwillingness of some claustrophobic patients (≃ 4%) to undergo the examination and the nonspecificity of the signal voids which, apart from calculi, could be due to air, mucus or blood. On the contrary, MRCP is a non invasive and minimally operator-dependent diagnostic method, with negligible morbidity and mortality related to the procedure [96].

EUS has been suggested as an excellent means of evaluating biliary tree diseases, such as choledocholithiasis, gallbladder disorders as well as bile duct malignancies. The accuracy of EUS in the diagnosis of common bile duct stones is very high (sensitivity of 93-97% and specificity of 97-100%) [97, 98]. Compared with ERCP in a prospective study, EUS seemed to be

the best choice for diagnosing extrahepatic cholestasis of indefinite origin [96]. EUS is a more invasive procedure than MRCP, with morbidity of 0.05% and mortality of 0.01% [96]. The method is highly operator-dependent and is not yet widely available. EUS provides greater accuracy than MRCP in the detection of bile duct calculi [99]. However, as a procedure in the detection of microlithiasis, Burtin estimated that MRCP was most cost effective ($361) than EUS ($438) [96].

The accuracy of MRCP and EUS in the diagnosis of biliary disorders has resulted in a dramatic decrease of diagnostic ERCP cases. Nevertheless, diagnostic ERCP is still favoured for some indications. In a recent series in a center where EUS is currently available, out of 1159 ERCPs performed, 9.5% were diagnostic procedures [100].

Conclusively, diagnostic ERCP should be performed following absolute indications. MRCP generally appears to be more advantageous than EUS in detecting choledocholithiasis. In other biliary disorders the selection of the most appropriate method remains controversial.

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CHAPTER 8

ENDOSCOPIC ULTRASONOGRAPHY ON GALLBLADDER AND BILIARY TRACT

Kon. Goumas, A. Poulou

Endoscopic ultrasound (EUS) has recently emerged as a very reliable imaging modality for the pancreaticobiliary system. Apart from other applications, EUS is a minimally invasive imaging technique which is widely used all over the world for identifying biliary abnormalities. Lesions as small as 2 to 3 mm in diameter, can be visualized by EUS. In France, 48.039 EUS procedures were performed during 1999, 58% of which related to pancreaticobiliary diseases [1]. In a recent series in a center where EUS is currently available, the rate of diagnostic endoscopic retrograde cholangiopancreatographies ($ERCP_s$) was only 9.5% in a total of 1,159 ERCP procedures [2]. Recent years have seen new technical developments recorded in the field of EUS.

Despite, however, EUS being more than 20 years old, it remains a highly inaccessible and very operator-dependent procedure as well as an expensive technology with some definite and many debatable indications in diagnosing biliary diseases.

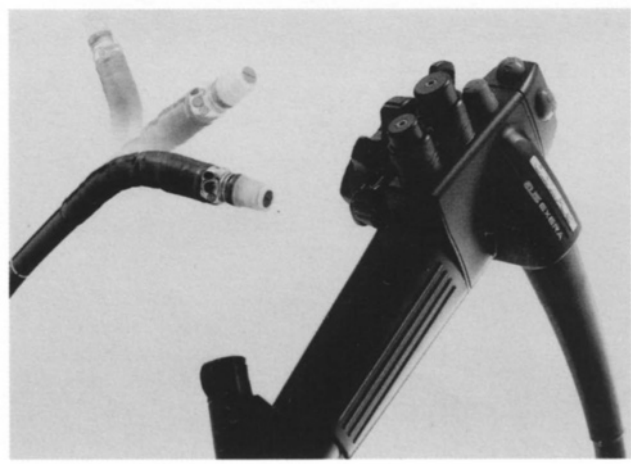

Fig. 8.1. Radial EUS EVIS - EXERA (OLYMPUS).

8.1. Equipment and Technique

Endoscopic ultrasonography (EUS) is a combination of endoscopy and high-frequency ultrasound. The incorporation of a small ultrasonic transducer into the tip of endoscopes, allows precise diagnostic application of ultrasounds very close to a target lesion or organ. "Echo-endoscopes" used for the examination of pancreas and biliary tract are usually oblique-viewing endoscopes. Depending on the type of instrument used, generation of ultrasound could be mechanical or electronic, the later being suitable for Doppler ultrasound [3].

There are two main types of echoendoscopes. The first type (fig. 8.1), which is the most frequently used, generates a radial image of 360° oriented perpendicular to the long axis of the instrument. The second type (fig. 8.2) generates a linear-type image (110-250°) directed parallel to the shaft axis of the endoscope, being appropriate for EUS -guided fine- needle aspiration punctures. Both types are equally suitable for valuable pancreaticobiliary imaging [4]. Acoustic coupling of the ultrasonic transducer to the mucosal surface of the gut is achieved either by the application of a water-filled balloon around the tip of the echoendoscope, acting as a fluid interface between the transducer and the gut wall or by infusing a volume of water directly into the lumen [4]. A very small and narrow ultrasonic transducer mounted on the tip of a catheter has also been developed. Apart from other applications, this mini ultrasound probe can be inserted through the main duodenal papilla into the bile duct for intraductal ultrasound (IDUS) during an ERCP procedure [5]. IDUS mini probes due to their high ultrasound frequency

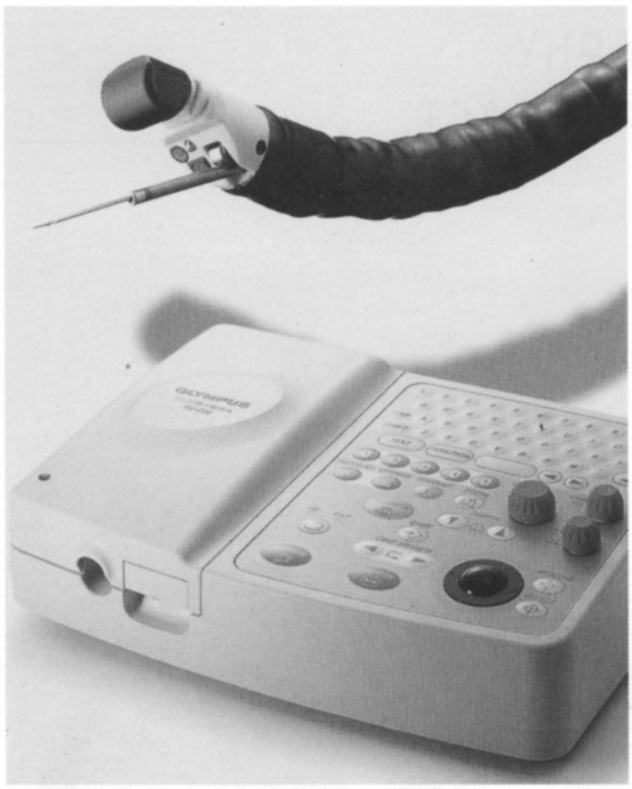

Fig. 8.2. Linear EUS EVIS - EXERA (OLYMPUS).

and limited penetration depth are suitable for evaluating intraductal biliary stenoses.

The range of ultrasound frequencies used varies from 5.5 MHz to 30 MHz [6], with 7.5 MHz being the most frequently applied frequency. High frequencies produce the highest resolution images, but at the expense of a limited depth of penetration. In contrast, lower frequencies provide imaging of lower resolution, but of greater depth of penetration from the transducer (up to approximately 5 cm). Mini ultrasound probes generate very high frequency ultrasound (20-30 MHz) providing fine detail of mucosal lesions.

For pancreaticobiliary EUS, the patient is usually placed on his left lateral position. The procedures are performed under titrated "conscious" sedation (e.g. benzodiazepine, opioid analgesics). Patients usually leave the hospital within 2 hours of the procedure. The echoendoscope must be inserted into the descending duodenum. The positions of the radical scanning echoendoscope, within the duodenum and stomach, for visualizing the pancreaticobiliary system are not substantially different from those of linear EUS scanning [7]. With the ultrasound transducer being within the descending duodenum, the head of the pancreas, the main duodenal papilla as well as the distal part of both the common bile duct and pancreatic duct can be endosonographically scanned. After withdrawal of the echoendocsope, with the transducer being at the level of the superior duodenal curve, the common bile duct can be scanned to the hepatic bifurcation and into both hepatic ducts. The gallbladder can be visualized from either the descending duodenum, the duodenal bulb or the gastric antrum, depending on its relative position [8], usually exhibiting a three-layer wall structure. The pancreatic body is better visualized from the distal or middle portion of the gastric body and the pancreatic tail from the gastric fundus. During withdrawal of the echoendocscope from the descending duodenum to the gastric fundus, several landmarks (mainly vessels) are used by the endosonographer to identify the region of diagnostic interest [8].

8.2 The Role of EUS in Biliary Diseases

EUS has been proven to be a valuable tool in evaluating the biliary system. It has been suggested as a valuable imaging method for the detection of common bile duct stones, with a sensitivity of 93-97% and specificity of 97-100% [9, 10]. The sensitivity of EUS for the detection of dilated bile ducts and biliary obstruction ranges from 55% to 91% [11, 12]. Furthermore, EUS has been found to be highly accurate in the local staging of tumors of the main duodenal papilla [13]. Moreover, several diagnostic and therapeutic biliary applications of EUS are under development and/or clinical evaluation [14]. At present, the main diagnostic indications of endosonography in the biliary tree are choledocholithiasis, biliary neoplasms, tumors of the papilla and pancreatic disorders affecting the common bile duct (e.g., exocrine and endocrine tumors, chronic pancreatitis etc.) [15].

8.2.1. Choledocholithiasis

The results of several early as well as more recent studies of EUS in patients with suspected bile duct stones have shown that the accuracy of EUS is comparable to

that of ERCP for the diagnosis and exclusion of choledocholithiasis [10, 15-25] (fig. 8.3). Although in most studies the radial scanning principle was applied, a similar accuracy was achieved when linear scanning echoendoscopes were used [26].

In 62 patients with suspected bile duct stones, Amouyal et al [15], using ERCP or intraoperative cholangiography as the reference standard for the presence or absence of duct stones, reported a sensitivity for EUS 97% versus 25% for transabdominal ultrasound (US) and 75% for computerized tomography (CT). Although specificity and positive predictive values were similar for EUS, US and CT, endosonography showed a significantly higher negative predictive value (97%) compared with those of US (56%) and CT (78%) [15]. In the same study, EUS was also more sensitive than US and CT in detecting bile duct stones less than 1 cm in diameter. In another study, Prat et al, found the sensitivities, specificities and positive and negative predictive values of ERCP and EUS to be similar in detecting choledocholithiasis in patients highly suspected to have duct stones [10]. Canto et al [18] also reported a similar overall accuracy of ERCP and EUS for bile duct lithiasis. However, the negative predictive value of EUS was high (91% to 100%) for patients with moderate and low risk for bile duct stones. Similar results were obtained in subsequent, more recent trials [18-24]. In a prospective study by Napoleon et al [22], 238 patients with a normal EUS were evaluated over one year. The negative predictive value of EUS for common bile duct stone diagnosis was 95%. The authors concluded that patients with normal EUS findings have a low risk for an ERCP in a one year period [22]. In a study by Buscarini et al [24], 239 patients had EUS and ERCP, where the probability of bile duct stones was considered to be high. EUS diagnosis was confirmed in 237 patients out of 239 with ERCP. This yielded a sensitivity of 98%, specificity of 99%, positive predictive value of 98%, negative predictive value of 98% and accuracy of 97%. EUS has also been proven highly reliable for diagnosing bile duct stones in patients with acute pancreatitis [17, 18, 25], being superior to US [17, 18] and CT and equivalent to ERCP [25] in evaluating these patients.

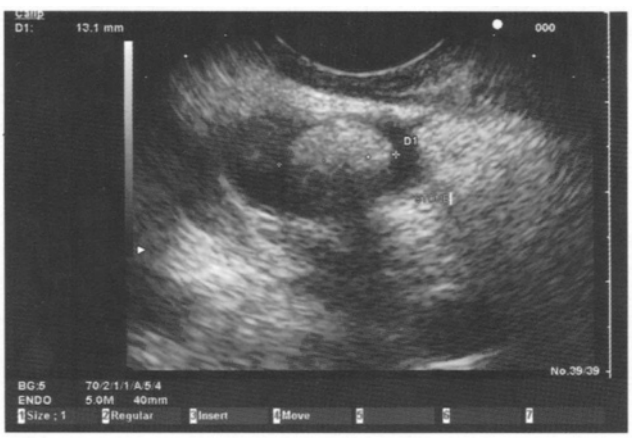

Fig. 8.3. Endosonographic image of a common bile duct stone.

Two limitations of these studies should be mentioned. Firstly, most of them included patients with a moderate to high probability of having a bile duct stone [15, 17-21] and endosonographers might have been influenced from the known inclusion criteria. Secondly, the used reference standards in most studies (intraoperative cholangiography or ERCP) cannot provide a 100% confirmation of the presence or absence of duct stones. If the reference standards used were totally reliable (e.g., ERCP with sphincterotomy or surgery), the EUS sensitivity and negative predictive value in diagnosing choledocholithiasis might be somewhat lower.

Although data are limited, intraductal ultrasound (IDUS) with high-frequency catheter probes inserted into the bile duct, during ERCP, increases the accuracy of ERCP in identifying bile duct stones. Das et al [5] compared ERCP in solo with ERCP combined with IDUS and found that the overall accuracy for diagnosis of stones was higher with IDUS (97% vs 87%, $p < 0.05$).

According to the existing limited data EUS and MRCP have comparable sensitivity in the detection of bile duct stones. De Ledinghen et al [21] compared MRCP with EUS in 43 patients with suspected choledocholithiasis. ERCP with sphincterotomy or surgery were used as the reference standard. They reported that the sensitivity, specificity and the positive and negative predictive values for EUS were 100%, 95.4%, 90.9% and 100%, respectively. Corresponding values for MRCP were respectively 100%, 72.7%, 62.5% and 100% [21]. Scheiman et al found EUS to be superior to MRCP for bile duct lithiasis [27]. However, Burtin [28] estimated EUS to be more costly than MRCP ($438 vs $361, per procedure) and he noted increased morbidity and mortality rate with EUS compared to MRCP (0.05% vs 0% and 0.01% vs 0%, respectively).

Ainsworth et al [29] studied 163 patients who had

been referred for ERCP with MRCP and EUS. ERCP was the reference standard. They reported no difference in the diagnostic accuracy and clinical impact between EUS and MRCP in the majority of patients (93% vs 91% respectively). They also concluded that the impact of EUS or MRCP on the ERCP workload was highly dependent on the presumed probability of needing endoscopic therapy [29].

In conclusion, EUS is a valuable diagnostic method in detecting choledocholithiasis, comparable to MRCP and ERCP. However, taking into account its higher cost and relative inaccessibility, EUS may be considered for evaluation of bile duct lithiasis as a prelude to ERCP, when there is low to intermediate suspicion for common bile duct stones or when there is an increased risk for performing an ERCP [30].

8.2.2. Biliary Strictures

It is important to distinguish between benign and malignant biliary strictures as their management differs. The appropriate diagnostic modality should precisely demonstrate and effectively provide histological diagnosis of the stricture. The results of several studies suggested that EUS can be helpful in identifying biliary strictures [13, 31-34]. EUS demonstrates biliary tumors as a localized mass lesion around the bile duct or as a thickening of the bile duct wall, frequently similar to that caused by inflammatory stenoses. Lee et al found that a bile duct wall thickness equal to or more than 3 mm had a sensitivity for predicting malignancy of 79%, specificity of 79%, positive predictive value of 73% and negative predictive value of 80% [13]. Endosonographic assessment of biliary tumors and their local invasion has been shown to be accurate, especially for those sited distally or proximally (fig. 8.4). EUS evaluation of lymph node metastasis as well as infiltration of right hepatic duct by a tumor is sometimes difficult to be demonstrated. EUS is also useful for accurate assessment of local invasion of gallbladder carcinoma [8].

Rosch et al [35] compared ERCP with CT, MRCP and EUS in a series of 50 patients with suspected biliary stricture. The sensitivity and specificity for diagnosis of malignancy were 85% and 75% for ERCP and percutaneous transhepatic cholangiography (PTC), 85% and 71% for MRCP, 77% and 63% for CT and finally 79% and 62%, respectively, for EUS. The combination of MRCP and EUS improved specificity [35]. In another

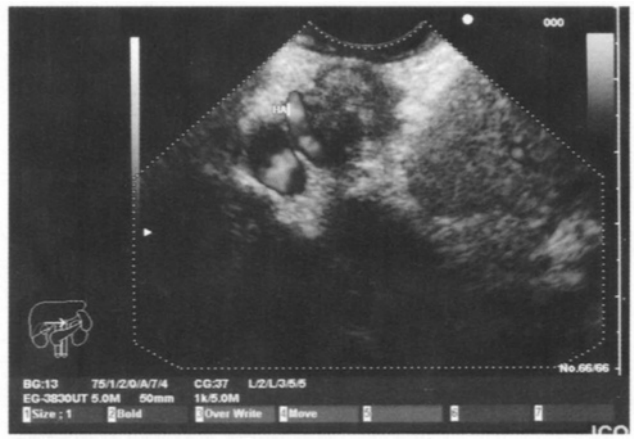

Fig. 8.4. Endosonographic image of a cholangiocarcinoma.

study, Scheiman et al [27] compared EUS with MRCP using ERCP as reference standard, in patients with a low suspicion of biliary disease. In this study EUS had a higher specificity and positive predictive value for the diagnosis of biliary stricture (100% and 100%) compared to MRCP (76% and 25%).

ERCP is the conventional test for the accurate diagnosis of biliary strictures. IDUS is considered as a promising adjunct to ERCP, as it accurately distinguishes malignant from benign strictures [36-38]. Tamada et al [36] reported that IDUS within the bile duct stricture can significantly enhance diagnostic accuracy compared to classical endosonography (89.1% vs 75.6%, $p < 0.002$). Domagk et al [37] found that ERCP and MRCP allowed correct differentiation of malignant from benign bile duct strictures in 76% and 58% ($p = 0.057$), respectively. However, ERCP with IDUS increased the accuracy of correct differentiation of malignant from benign biliary lesions significantly to 88% ($p < 0.005$) [37].

Endoscopic ultrasonography provides the opportunity of establishing a cytological diagnosis based on biopsy specimens obtained by fine-needle aspiration (FNA) [31, 32, 39]. FNA is done safely only with linear-type echoendoscopes which provide visualization of the entire needle course during the puncture process [4]. Immediate assessment of the specimen (in-room cytopathology) may increase the accuracy of this procedure [40].

In a study of 50 patients with obstructive jaundice in whom a tissue diagnosis was required, EUS was compared with ERCP for accurate diagnosis of bile duct strictures. ERCP-based techniques were more sen-

sitive in the biliary tumors subgroup (ERCP 75% vs EUS 25%), whereas EUS-guided biopsy was superior for pancreatic mass (EUS 60% vs ERCP 38%) [36]. Lee et al used EUS to examine 40 patients who had unexplained common bile duct strictures after ERCP and intraductal tissue sampling. They reported a low sensitivity of EUS-FNA for malignancy of 47% with specificity of 100%, positive predictive value of 100% and low negative predictive value of 50% [13].

However, EUS-FNA may be more sensitive in hilar cholangiocarcinoma. Fritscher-Ravens et al used EUS-FNA to characterize potentially operable hilar cholangiocarcinoma [31]. They cytologically identified hilar cholangiocarcinoma in 26 patients, metastases in 5 and benign disease in 12 patients. The overall diagnostic accuracy, sensitivity and specificity were 91, 89 and 100%, respectively. EUS-FNA resulted in a major change of management in 20% of the patients in whom surgery was avoided. In the prospective study of Eloubeidi et al [33], 28 patients with suspected cholangiocarcinoma were evaluated with EUS-FNA. Final diagnosis (by imaging, surgery or autopsy) was used as reference standard. The authors reported a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of EUS-FNA of 86%, 100%, 100%, 57% and 88%, respectively [33].

A therapeutic role is emerging for endosonography. In a report of 5 cases,Kahaleli et al scribed how bile duct drainage and decompression had been effectively performed in all five patients with obstructive jaundice and unsuccessful attempts with ERCP [38]. This was accomplished with formation of an enterocholedochal fistula. Moreover, Giovannini et al [41] successfully performed hepaticogastrostomy entirely under EUS guidance to decompress intrahepatic ducts of a patient with hilar cholangiocarcinoma.

8.2.3. Papillary Tumors-Periampullary Malignant Tumors

Tumors of the main duodenal papilla can be visualized and evaluated by EUS. In general EUS is valuable in the local staging of these tumors [42-45], precisely determining their local extent, namely the neoplastic involvement of the common bile duct, pancreas and local lymph nodes. However, Rosch et al suggested that EUS is not reliable in distinguishing papillary adenoma from

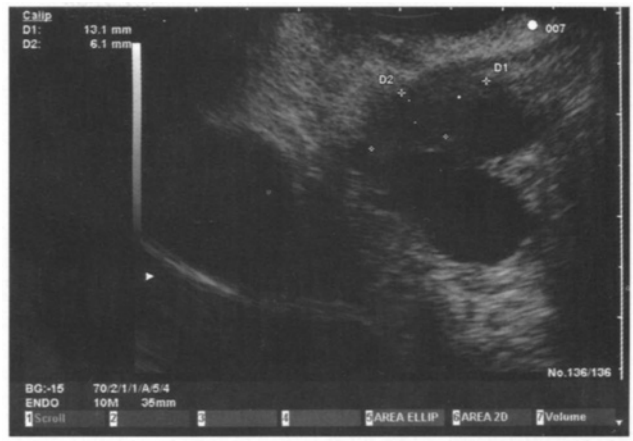

Fig. 8.5. Endosonographic image of a periampullary malignant tumor.

focal or localized carcinoma, in cases of inconclusive histology [46].

Apart from ampullary tumors, the periampullary region can be involved by a heterogeneous group of malignancies including those from pancreas, distal common bile duct and duodenum. These tumors are however, homogenous in their highly malignant nature, delayed clinical manifestation and usually dismal prognosis. Radical surgical resection provides the only curative treatment in patients with these tumors. Preoperative detection and staging of periampullary malignancies are currently based on CT scan evaluation. However, several studies have demonstrated that patients with periampullary malignancies are more accurately staged by EUS [42, 47-54] (fig. 8.5). Sensitivities for EUS in most studies range from 71% to 100% and for CT from 24% to 92%.

EUS is not useful for differentiating local chronic pancreatitis from cancer [55] and its accuracy in locoregional staging of malignancy is seen both enthusiastically [42, 55, 56] as well as more skeptically [57]. For pancreatic and biliary cancer staging helical CT is probably at present the method of choice, but due to its widespread existence alone, EUS might be used as a second line test when CT is uncertain or for additional information (FNA) or treatment (plexus neurolysis) [58].

8.3. Complications of EUS

Complications are very rare in EUS and relate to either

the endoscopic portion of the procedure or those parts of the procedure associated with FNA biopsy.

Complications related to the endoscopic portion of the procedure include oxygen desaturation due to sedation, cardiovascular complications, such as cardiac rhythm abnormalities and hypertension, respiratory depression and minor bleeding [59]. Perforations have been reported [60, 61], often in combination with FNA, but sometimes were caused by echoendoscope introduction [61] or after dilatation of a stricture to facilitate the introduction of the echoendoscope [4]. In a national survey in the United States, cervical perforations by EUS occurred in 16 of 42,852 EUS procedures (0.03%). EUS-FNA complications have been reported in a large multicenter series in a rate of 0.5% [62]. These include rare cases of acute pancreatitis, perforation, extraluminal hemorrhage and aspiration pneumonia. Pneumoperitoneum has also been reported when endoscopy closely follows EUS-FNA, due to intestinal insuflation [6]. It is worth emphasizing that when performed by an experienced endosonographer, EUS is a safe procedure.

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SECTION 2

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CHAPTER 9

HEPATOBILIARY DISEASE AND ANAESTHESIA

P. Georgakis, L. Rizzotti, I. Katsouli-Liapis

9.1. Introduction

The term hepatobiliary disease refers to acute or chronic disorders of the hepatic cells and/or the biliary tract. In this chapter are firstly described the clinical forms of the hepatobiliary disease and, secondly, the pathophysiologic mechanisms that are responsible for hepatic cell damage. Since surgery in patients with pre-existing severe hepatobilary disease is associated with significant morbidity and mortality rates, the anaesthesiologist should be able to diagnose and evaluate hepatic dysfunction during the perioperative period. Even with careful attention to history and symptoms, some cases of liver disease can be misdiagnosed. However, in most cases the cause of misdiagnosis results from failure to ask simple questions or to look for obvious findings on physical examination. Laboratory investigation of the hepatobiliary disease lacks in specificity in defining a certain liver disease. Instead of this, laboratory testing of liver function helps to differentiate the diagnosis among hepatocellular injury, impaired hepatocellular synthetic function and cholestasis. To this aim, clinical and laboratory investigation of the hepatobiliary disease is crucial for the anaesthesiologist. Anaesthesia for hepatobiliary surgery requires special considerations, concerning the assessment of risk factors that predispose to post-operative liver dysfunction, the effects of anaesthetic drugs and techniques on hepatic blood flow and liver function, the effects of hepatic dysfunction on metabolism and pharmacokinetics of drugs used in anaesthesia and the perioperative management of patients with distinct forms of hepatobiliary disease. Emphasis is placed on the prevention and treatment of serious complications that accompany the advanced hepatobiliary disease. Finally, anaesthetic considerations for hepatic resection procedures are presented. However, anaesthesia for liver transplantation is also omitted because it is beyond the scope of this chapter.

9.2. Clinical Forms of Hepatobiliary Disease

Clinical forms of hepatobiliary disease are acute or chronic hepatitis, which affects the hepatic parenchyma and cholestatic disease (cholestasis). The final result of these two different forms of hepatobiliary disease is just the same: both of them can cause hepatocellular injury.

Any disease of the hepatic parenchyma [1, 2, 3] acute or chronic, regardless of its exact cause, is responsible for progressive changes in histologic structure and function of liver anatomic units, which lead to hepatic cells injury or destruction and, consequently, to clinically detectable deterioration of liver's functions. Advanced disease of the hepatic parenchyma usually includes some elements of cholestatic disease. Fulminant hepatic failure, a process that results from massive necrosis of hepatic cells, is presented in a number of patients with acute injury of the hepatic parenchyma [4].

Common causes of acute hepatocellular injury are viral and bacterial infections, toxicity from drugs and toxins, alcoholism and drug induced immune reactions.

Chronic viral hepatitis B or C and alcoholism are the most common causes of chronic hepatocellular injury. Cirrhosis and portal hypertension are the end-stage of chronic liver disease [4, 5, 6, 7]. Other possible causes of cirrhosis, except for chronic hepatitis and alcoholism, are hemochromatosis, Wilson's disease, primary and idiopathic biliary cirrhosis. Cirrhosis is characterized by the distortion of normal anatomy of the

liver. As hepatic cells die, connective and fibrous tissue formation occurs, while areas of regenerating normal liver tissue (nodules) are produced. Hepatic cells are encircled by fibrous tissue, and, as cirrhosis evolves, blood flow resistance through the portal system increases and portal hypertension becomes clinically apparent. The clinical signs of cirrhosis and portal hypertension are anorexia, nausea and vomiting, weakness, jaundice, ascites, splenomegaly, esophageal varices, renal dysfunction due to hepatorenal syndrome [8], compromised pulmonary function (hepatopulmonary syndrome) [9] and hepatic encephalopathy [10]. Consequently, cirrhosis and portal hypertension derange the physiologic function of many vital organs and systems, since they are accompanied by cardiovascular, respiratory and renal dysfunction, encephalopathy or even coma, anemia, coagulation disorders, activation of secondary fibrinolysis and endocrine abnormalities. Portal hypertension is often complicated by rupture of esophageal varices and severe gastrointestinal bleeding.

Cholestatic disease is initially presented as a progressive disturbance of biliary drainage [11, 12]. Cholestasis can be either intra-hepatic (acquired or inherited) or extra-hepatic, due to mechanical obstruction to bile drainage. As cholestatic disease progresses, both, conjugated and non-conjugated, bilirubin levels are increased. Hepatic cells are injured, since the non-conjugated bilirubin disrupts their energy production pathways and causes membrane dysfunction. Cholestasis affects not only the pharmacokinetics of certain drugs that are excreted by the liver, but it is also responsible for cardiovascular and renal dysfunction and coagulation disorders.

9.3. Pathophysiologic Mechanisms of Hepatocellular Injury

Hepatic cells are extremely sensitive to hypoxia. Therefore, in all forms of hepatobiliary disease the main underlying pathophysiologic mechanism of hepatocellular injury [13] is the disturbance of the balance between oxygen delivery to hepatic cells and oxygen consumption by them.

There are four different ways that lead to hepatocellular injury in patients with hepatobiliary disease. Two of them cause death of the hepatic cells directly, through the processes of necrosis and apoptosis. Ischemia-reperfusion injury [14] and disturbance of hepatic defensive systems to oxidative stress are the remaining two ways that can lead to death of hepatic cells indirectly, through a generalized inflammatory process.

Each distinct clinical form of hepatobiliary disease can lead to hepatocellular injury or death by one or more of the ways mentioned above. This topic is to be discussed later in this section.

Prolonged and excessive splachnic hypoxia or anoxia is usually the result of circulatory shock or arrest. In this circulatory derangement, oxygen delivery to all tissues and, of course, to the liver is severely compromised. Deprivation of hepatic cells from oxygen causes abrupt failure of energy dependent ion pumps, loss of cellular membranes integrity and, finally, swelling and rupture of hepatic cells. Breakdown pro-inflammatory products, such as leukotrienes, platelet activating factor, eicosanoids, lipid peroxides and aldehydes, as well as intracellular enzymes, are released into the surrounding tissues and into the circulation. Some of these substances activate circulating neutrophils, triggering a generalized inflammatory response that further deteriorates hepatic necrosis.

Other factors, such as viruses, toxins and immune reactions [15, 16] trigger apoptosis of hepatic cells. Under normal conditions, this process is normal and secures the death of older cells throughout the body. Apoptosis of hepatic cells [17] is triggered by activation of tumor necrosis factor TNF receptors. As a result, before death, hepatic cells and their nuclei shrink, while several intracellular organelles are encapsulated and broken by lysosomes. Since during apoptosis intracellular organelles remain intact, this process does not trigger a generalized inflammatory reaction.

Following brief periods of hepatic ischemia, reperfusion stimulates hepatic cells, as well as Kuppfer cells and macrophages of the liver, to produce highly reactive oxidants, such as hydroxyl radicals, superoxide and hydrogen peroxide [18]. These oxidants can lead to necrosis or trigger apoptosis and are implicated in the ischemia-reperfusion injury of hepatic cells. During ischemia, transformation of xanthine dehydrogenase to xanthine oxidase is, probably, the special pathophysiologic mechanism that triggers ischemia-reperfusion injury of hepatic cells. Xanthine oxidase generates highly reactive oxidants, which stimulate the production

and release of leukotrienes and a platelet activating factor. These substances activate circulating neutrophils and platelets, causing the destruction of the microcirculation's integrity and a systemic inflammatory reaction is initiated. Both, damaged hepatic microcirculation and systemic inflammatory reaction, further deteriorate hepatic cell injury or necrosis. The role of xanthine oxidase, except for ischemia-reperfusion hepatocellular injury, is also valid in patients with acute hepatitis or cholestatic disease and transplanted liver.

Under normal or hypoxic conditions, at the level of mitochondria of hepatic cells, free, highly reactive radicals of oxygen (hydroxyl radicals, superoxide, hydrogen peroxide) are produced. Moreover, activated cells of the liver (Kuppfer cells, endothelial cells, neutrophils, macrophages) favor the production of oxygen and nitro radicals. Accumulation of these free radicals in the mitochondria poses hepatic cells to severe oxidative stress. The liver has several antioxidant defensive systems (vitamin E, vitamin C, ferritin, glutathione), but the most important antioxidant system is that of glutathione. Glutathione is synthesized by the hepatic cells and is actively taken up by their mitochondria, to inactivate accumulated free radicals. In adverse conditions, such as in ischemia and reperfusion, malnutrition and chronic alcohol intake, levels of glutathione in the hepatic cells are decreased. Low glutathione levels make hepatic cells very susceptible to oxidative stress. Treatment of patients in oxidative stress with N-acetylcysteine, a thiol rich substance, helps to restore glutathione synthesis and protects hepatic cells against oxidant injury.

Viral and bacterial infections can cause acute hepatocellular injury. Hepatotropic viruses and endotoxins released by Gram-negative bacteria, activate Kuppfer cells and macrophages of the liver to produce mediators that induce a generalized inflammatory reaction and hepatic cell damage.

Several drugs and exogenous toxins can induce hepatocellular injury by different mechanisms. For example, metabolism of imidazole antibiotics, nitrofurantoin analogues or cocaine leads to a toxic free radicals formation. Other drugs, such as acetaminophen [19], can cause acute liver damage because they reduce the stores of glutathione, the major antioxidant system of hepatic cells. Reye's syndrome following administration of aspirin, tetracycline or valproic acid can be attributed to increased oxidative stress, which leads to interruption of mitochondrial function, and to triggered apoptosis of hepatic cells.

Hepatic injury caused by alcohol abuse, either subclinical (fatty liver) or with severe clinical manifestations (alcoholic hepatitis or cirrhosis), can be interpreted by several pathophysiologic mechanisms. Even if there is genetic predisposition to the alcoholic liver disease, increased oxygen consumption by the liver, production of free radicals, disturbance of hepatic defensive antioxidant systems and acetaldehyde induced liver damage, play a role in the manifestation of hepatocellular injury. Acetaldehyde is a product of ethanol oxidative metabolism. Acetaldehyde reduces glutathione levels, binds and inactivates intracellular proteins, stimulates the production of pro-inflammatory molecules and favors collagen production and fibrosis generation.

Halothane hepatitis is the main example of drug-induced immune reactions that destroy the liver [20, 21]. The development of this immune reaction revolves genetic predisposition. Hepatitis, after exposure to halothane for the first time, has a delayed onset. After repeated exposures to the same agent, hepatitis onset is hastened. The underlying mechanism is formation of antibodies against the trifluoroacetylated products of the halogenated anaesthetics hepatic metabolism. These antibodies are toxic against vital organelles of hepatic cells.

9.4. Anaesthesia for Hepatobiliary Disease

Anaesthesia and surgery in patients with liver disease may cause mild to severe deterioration of hepatic function post-operatively [22, 23]. Mortality, even following simple surgical procedures, can be high, especially when liver disease is misdiagnosed, either is acute or acutely deteriorated. For these reasons, the goals of perioperative care of patients with hepatobiliary disease must be: firstly, to diagnose pre-existing liver disease to anaesthesia and surgery, by using all the available diagnostic tools (history, physical examination and laboratory tests) secondly, to identify the exact cause and the extent of the underlying liver disease preoperatively, thirdly, to optimize liver function prior to surgery and lastly, to avoid any factor that is known to

deteriorate hepatic function throughout the perioperative period. Acute hepatocellular injury is the most important form of liver disease to be diagnosed preoperatively because it is the most frequently missed diagnosis and the most likely to be accompanied by high rates of post-operative morbidity and mortality.

The liver has eight functionally independent segments. This anatomic structure of the liver facilitates hepatobiliary surgery. However, certain surgical procedures increase the risk of post-operative liver dysfunction. Except for the surgery itself, anaesthetic drugs and techniques have adverse effects on liver blood flow and hepatic function and may predispose to post-operative complications after hepatobiliary surgery, especially in patients with pre-existing liver disease. On the other hand, pre-existing hepatobiliary disease has its own effects on pharmacokinetics of certain drugs used in anaesthesia.

Preoperative functional liver reserve [24] is of great importance for the anaesthesiologist, since it defines the risk factors for post-operative hepatobiliary complications, even after non-hepatic surgery [25]. Moreover, when treating patients with pre-existing liver disease, it should be kept in mind that inadequacy of oxygen supply to the liver is simply the most important threatening condition to hepatic function during the perioperative period.

In this section, apart from the risk factors for post-operative liver dysfunction, the effects of anaesthetic drugs and techniques on hepatic blood flow and liver function, the effects of hepatobiliary disease on metabolism and pharmacokinetics of drugs used in anaesthesia, the perioperative management of patients with asymptomatic, chronic, acute and severe hepatobiliary disease as well as cirrhosis will be presented.

9.4.1. Risk Factors for Post-Operative Liver Dysfunction

Known and proven risk factors for liver dysfunction after hepatic or non hepatic surgery [26] are acute and chronic hepatitis, cirrhosis [27] and certain types of surgical procedures, such as hepatic resection and surgery on the biliary tract, colon and stomach [28]. Cardiac surgery, especially under cardiopulmonary bypass (CPB), and possibly thoracic and vascular surgery are risk factors for post-operative liver dysfunction in patients with severe pre-existing liver disease [29]. Volatile and intravenous anaesthetics, as well as spinal and epidural anaesthesia, influence hepatic blood flow and liver function.

All the existing data from previous retrospective clinical studies point out that there is a great risk (approximately 10%) for the development of acute hepatic failure, even death, after elective surgery in patients with acute hepatitis, regardless of its exact cause (viral, alcoholic, drug, toxin or immune induced). For this reason, any elective surgical procedure in patients with acute hepatitis should be postponed until hepatic function has been restored to normal. When an urgent therapeutic intervention is required in a patient with acute hepatitis, such as liver biopsy or biliary tract obstruction, a minimally invasive interventional technique should be chosen instead of open surgery, if this option is feasible.

In patients with chronic hepatitis the risk of post-operative deterioration of liver function is proportional to the severity and the extent of preoperative hepatic dysfunction. This means that in any patient with chronic hepatitis a full laboratory testing for the precise estimation of hepatic function should proceed before an elective surgery. It is recommended elective surgery to be postponed if the results of these tests indicate severe hepatocellular injury. The most sensitive screening tests for the designation of the severity of hepatic cells dysfunction are PT prolongation, INR [30], albumin and bilirubin levels. When an elective or an urgent surgery cannot be avoided, care should be taken that there is not to a deterioration of the already impaired hepatic function during the perioperative period.

Cirrhosis is a known, major risk factor for increased post-operative morbidity and mortality in patients undergoing major surgery [31]. Patients with cirrhosis are classically classified into three risk categories, A, B and C, according to Child and Pugh criteria. These criteria are currently used in order to predict perioperative risk for liver dysfunction in cirrhotic patients undergoing abdominal surgery [32].

Data from older retrospective clinical studies indicate that overall mortality rates after biliary tract surgery or other major abdominal procedures in cirrhotic patients of Child and Pugh classes A, B and C were about 10%, 30% and 75-80% respectively [33]. Moreover, perioperative mortality was found to be six fold

greater in urgent, compared to elective surgery. Considering other surgical procedures, besides major abdominal and hepatobiliary surgery, the overall perioperative mortality rate in cirrhotic patients was 11.5%. This mortality rate was not relevant to the anaesthetic technique, which had been used (general, regional or local). Also, in any case, mortality was 10-35 times greater in patients Child and Pugh class C compared to mortality of otherwise normal surgical patients. According to the existing data and despite the lack of well-designed prospective clinical studies, it is advised that elective surgery is contraindicated in Child and Pugh class C patients. Exceptions to this rule are portocaval or other types of portosystemic shunting procedures, which are performed in order to decompress severe portal hypertension and ascites. Minimal invasive techniques are preferred to open surgery in patients with cirrhosis, when this option is possible.

A variety of major abdominal procedures are considered as important risk factors for post-operative liver dysfunction. This complication can be attributed to a common feature of all major abdominal procedures, that are accompanied by a considerable reduction of hepatic blood flow of both hepatic arterial and portal circulation. Reduction of total hepatic blood flow during all major abdominal surgery can be attributed to surgical manipulations in the region of the upper abdomen, intraoperative systemic hypotension or dilation of the capacitance vessels of the splachnic circulation.

Cardiac surgery, especially when performed under cardiopulmonary bypass exposes hepatic cells to risk of hypoxia and predisposes the patients with pre-existing hepatic disease to deterioration of liver function [34, 35]. This can be attributed to a significant decrease of total hepatic blood flow due to systemic hypotension, microembolisms of the hepatic microcirculation or low cardiac output, accompanied by liver hypoperfusion [36].

Thoracic and vascular procedures are considered as independent risk factors for post-operative deterioration of liver function in patients with cirrhosis, but this aspect has still to be proven.

In asymptomatic patients undergoing surgical operations, slight elevations of commonly ordered biochemical tests of liver function (AST, ALT and ALP) is not considered as a risk factor for post-operative hepatic dysfunction. These patients, usually, do not need any further laboratory investigation prior to anaesthesia and surgery. Of course, asymptomatic patients with greater increase of the above mentioned liver tests (double or even greater increase compared to normal values), need more thorough clinical and laboratory evaluation before surgery. This is recommended because these patients may suffer from either subclinical, viral or drug induced acute hepatitis, or from chronic hepatitis. In asymptomatic patients with significant elevation of AST, ALT and ALP levels, the diagnosis of ongoing acute hepatitis or exacerbating chronic hepatitis should be precluded prior to an elective surgical procedure. As it was stated elsewhere, AST, ALT and ALP are not special tests for liver disease, because these enzymes are found in many other tissues and organs, except for the liver. For this reason, more specific tests are indicated in this group of patients, such as gamma glutamyl-transpeptidase γ-GT, prothrombin time PT, INR, serum albumin, bilirubin and, of course, specific serologic tests for the diagnosis of viral infections or hepatic tumors.

9.4.2. Effects of Anaesthetic Drugs and Techniques on Hepatic Blood Flow and Liver Function

Inhaled anaesthetics are metabolized by the liver, each one to a different extent. Their metabolism can lead to the formation of reactive and potentially toxic products for the liver and kidneys. According to the principles of pharmacokinetics, metabolism of any drug is affected by age, concurrent diseases, interaction between drugs, environmental and genetic factors. Inhaled agents undergo oxidation, reduction, hydrolysis and conjugation in the hepatic cells. Oxidative metabolism of the inhaled anaesthetics through the phase I reactions is catalyzed by the cytochrome P450 enzymatic system [37] and is responsible for the formation of their major metabolite, the trifluoroacetic acid (CF_3COOH). Chloride (Cl^-), bromide (Br^-) and fluoride (F^-) anions are produced in lesser quantities by oxidative and reductive metabolism of the inhaled anaesthetics. Trifluoroacetic acid is converted to trifluoroacetyl chloride. This molecule reacts with components of liver cells membrane to produce hepatotoxic trifluoroacetylated protein adducts.

As it was mentioned earlier, each one of the inhaled anaesthetics is metabolized to a different extent. For example, 20% of the absorbed halothane is metabolized, whilst only 2.5%, 0.2% and 0.02% of the absorbed enflurane, isoflurane and desflurane is metabolized, respectively. Sevoflurane metabolism does not lead to the production of trifluoroacetylated protein adducts, so sevoflurane is not considered as a hepatotoxic agent [38]. The possibility for direct or indirect (immune mediated) liver toxicity from inhaled anaesthetic agents to occur is proportional to the extent of hepatic metabolism of these agents.

Halothane induced liver toxicity may be either mild or fulminant and severe. Mild liver dysfunction occurs in about 20% of the adult population to whom halothane was administered and is manifested by a slight increase of AST and ALT levels. This kind of liver dysfunction is shelf terminated and is generally benign.

The fulminant form of halothane induced liver dysfunction is called halothane hepatitis. The incidence of halothane-induced hepatitis is approximately one case out of ten thousand anaesthetics in adults and one case out of 200,000 anaesthetics in children. The diagnosis of halothane hepatitis is definitive only when all the other possible causes of fulminate hepatic injury have been excluded. Halothane hepatitis is mainly immune mediated, is more likely to occur after multiple exposures to this anaesthetic agent, is characterized by a dramatic increase of all hepatic enzymes that are indicative of hepatocellular necrosis and has a mortality rate of over 50%. For this reason, halothane is no longer used in adults' anaesthesia, but it is still used in paediatric anaesthesia.

The end product of enflurane, isoflurane and desflurane metabolism is also trifuoroacetylated protein adducts [39]. For this reason, the use of these agents may cause liver toxicity by (an exactly) the same mechanism to that of halothane. Even though in the literature there are few case reports of hepatitis following enflurane, isoflurane and even desflurane administration [40], the incidence of hepatitis after exposure to these agents is much lower than that of halothane. In fact, the incidence of hepatitis with isoflurane and desflurane is negligible [41]. Isoflurane, desflurane and especially sevoflurane are safe for use during anaesthesia, even in patients with pre-existing liver dysfunction. Enflurane is no longer used in Europe. Since there is a risk of cross sensitization reactions among different halogenated inhaled anaesthetic agents, it is generally advised that enflurane, isoflurane and, probably, desflurane should be avoided in patients with a history of halothane hepatitis or recent previous exposure to halothane.

Moreover, all volatile anaesthetic agents decrease cardiac output and mean arterial pressure. Perhaps this is the main mechanism by which these agents affect total hepatic blood flow across a range of minimum alveolar concentrations. The results of clinical studies on healthy volunteers and of experimental investigations suggest that most of the volatile anaesthetics reduce portal blood flow. Even though hepatic arterial blood flow may be increased at the same time (buffer autoregulative response), this increase is not sufficient to restore total hepatic blood flow to normal levels. Volatile anaesthetics also affect hepatic arterial and portal vein vascular resistance.

In detail, halothane decreases both portal and hepatic arterial blood flow, causes vasoconstriction of hepatic arterial microcirculation and reduces hepatic oxygen supply. Although isoflurane reduces portal blood flow, it preserves hepatic arterial blood flow better than halothane or enflurane. This finding perhaps can explain transient elevation of ALT and ALP values, which is more commonly observed after halothane anaesthesia. Sevoflurane is superior to isoflurane in maintaining total hepatic blood flow and oxygen supply to the liver. The effects of desflurane on portal blood flow and hepatic arterial microcirculation are similar to those of isoflurane.

On the contrary, the effects of volatile anaesthetic agents on hepatic function in patients with pre-existing liver dysfunction have not been studied extensively. In general, it is suggested to avoid the use of halothane in patients with hepatic dysfunction. Alternatively, modern inhaled anaesthetic agents, which lack any undesirable effect on liver function and hepatic blood flow, can be safely used.

Propofol preserves or even increases total hepatic blood flow because it dilates both hepatic, arterial and portal circulation. Among the older intravenous anaesthetics, thiopental and etomidate increase vascular resistance of the hepatic artery and decrease total hepatic blood flow, while ketamine lacks any significant effect on hepatic blood flow. In any case, the effects of intravenous anaesthetics on hepatic blood flow are

transient and have a negligible impact on liver function, even in patients with hepatic dysfunction.

Spinal and epidural anaesthesia have been found to decrease total hepatic blood flow. This effect is attributed to the concomitant drop of mean arterial pressure during high levels of sympathetic blockade.

Fentanyl, when administered during isoflurane anaesthesia, was found to protect hepatic function, provided that mean arterial blood pressure drop is less than 30%, in comparison to its pre-anaesthetic levels. This finding rather reflects the preservative effect of isoflurane on hepatic function and not a protective effect of fentanyl itself. In fact, fentanyl is deprived of any direct effect on hepatic circulation. This is confirmed by the findings of other studies, where the concomitant use of fentanyl during halothane anaesthesia did not improve the undesirable effects of halothane on hepatic blood flow and oxygen supply to the liver.

On the other hand, opioids have been reported to cause spasm of the Oddi's sphincter in patients with biliary tract obstruction. Spasm of the sphincter of Oddi is an undesirable effect of all opioid drugs. Spasm is dose dependent and can be treated with naloxone, nitroglycerine or glucagon.

9.4.3. Effects of Hepatobiliary Disease on Metabolism and Pharmacokinetics of Drugs Used in Anaesthesia

Hepatobiliary disease is responsible for altered metabolism and pharmacokinetics of various drugs that are commonly used in anesthesia. The anaesthesiologist must be familiar with these alterations in order to administer safe anaesthesia to patients with hepatobiliary disease. Principles of pharmacology define the mechanisms by which hepatic disease alters the metabolism and pharmacokinetics of several drugs. These mechanisms cause in general alterations in volume of distribution, protein binding, hepatic enzyme activity and enterohepatic circulation in cholestatic disease, but the main alteration is the reduction of the metabolism and delay in elimination of certain drugs with high extraction ratios by the liver. The presence of shunts between portal and systemic circulation should be kept in mind, in any case of enteric drug absorption. In such a case, large quantities of a drug are absorbed into the systemic circulation, before a fraction of the dose that was administered, had been inactivated by the diseased liver.

The final clinical result of altered metabolism and pharmacokinetics by the hepatobiliary disease is prolongation of half-life and increased potency of morphine, meperidine and alfentanil [42, 43]. Elimination of normeperidine, the active metabolite of meperidine, is also delayed in severe liver disease. Normeperidine is accumulated in plasma and its neurotoxicity may become manifested. Fentanyl and sufentanil, even though are both metabolized by the liver, do not have prolonged effect in patients with advanced liver dysfunction, provided that they are administered in a single dose regimen. The new synthetic opioid, remifentanil, is metabolized by ester hydrolysis in blood and in other tissues. This means that its elimination is independent of liver function. For this reason the use of remifentanil is safe, even in patients with liver insufficiency.

A single dose of any intravenous anaesthetic agent that is used in clinical practice (propofol, thiopental, etomidate and ketamine) is unlikely to cause any prolongation of its hypnotic effect in patients with advanced liver disease. This happens because these agents undergo rapid redistribution, whilst some of them have a large volume of distribution (thiopental). However, continuous infusion of propofol, an agent that is extensively metabolized by the liver and has a high hepatic extraction ratio, may cause prolongation of the anticipated recovery time.

Benzodiazepines have prolonged and intense sedative effects in patients with hepatic dysfunction. These drugs are highly binding to albumin and their metabolism by the liver is slow. Because albumin levels are low in hepatocellular disease, the unbounded-active fraction of benzodiazepines is increased.

Aminosteroid neuromuscular blocking agents (pancuronium, vecuronium and rocuronium) undergo metabolism and elimination by the liver [44]. Prolonged neuromuscular blockade is anticipated when these agents are used in patients with hepatobiliary disease. In contrast to these neuromuscular blocking agents, atracurium and cis-atracurium undergo Hofmann degradation and hydrolysis by non-specific plasma esterases. Termination of their effect is independent of liver function, so the use of atracurium or cis-atracurium is safe in patients with hepatobiliary disease. Plasma cholinesterase synthesis by the liver is decreased in he-

patic dysfunction. Due to reduced plasma cholinesterase levels, prolonged effect of succinylcholine (depolarizing neuromuscular agent) and mivacurium (non depolarizing neuromuscular agent) is anticipated in advanced liver disease.

Amide local anaesthetics have high hepatic extraction ratios and their clearance is mainly dependent on hepatic blood flow. For this reason meticulous dose adjustment is required, especially when large quantities of amide local anaesthetics are administered (peripheral nerve blocks, epidural anaesthesia and analgesia, wound infiltration, intravenous administration).

9.4.4. Perioperative Management of Patients with Distinct Forms of Hepatobiliary Disease

Asymptomatic patients with mild elevation of AST, ALT and ALP levels do not need any further laboratory investigation, so undergo anaesthesia and surgery uneventfully.

Asymptomatic patients with moderate to high elevated AST, ALT and ALP levels, as well as patients with chronic liver disease, must be thoroughly evaluated before an elective surgery, in order to preclude ongoing acute hepatitis or exacerbation of chronic hepatitis. In such a case, an elective surgery is better to be postponed, until hepatic function has fully recovered. Whenever an urgent or a scheduled procedure is absolutely necessary in asymptomatic patients with elevated liver enzymes in patients with pre-existing chronic liver disease or in cirrhotic patients Child and Pugh class A, it is imperative to preserve the remainder of hepatic function and to prevent further hepatic deterioration. Potential hepatotoxic drugs, such as halothane, acetaminophen and non- steroidal anti-inflammatory drugs (NSAIDs), should be avoided throughout the perioperative period. With the exception of halothane, the use of any other inhaled anaesthetic agent is not contraindicated during anaesthesia in this group of patients. At the same time, measures should be undertaken to improve hepatic oxygen balance, such as avoidance of hypoxia, maintenance of normal blood pressure, substitution of circulating blood volume, transfusion of red blood cells for correction of anemia and prophylactic use of antibiotics for prevention of sepsis. Regional anaesthesia, when compared to general anaesthesia, has not proven to offer any favorable effect or postoperative morbidity and mortality of these patients.

The goals of perioperative care in patients with acute and severe liver dysfunction irrespectively of its exact cause (viral, toxic, immune or drug induced hepatitis, sepsis and shock), and also of cirrhotic patients Child and Pugh classes B or C, are prevention and treatment of common complications, such as hepatic encephalopathy, cerebral edema, coagulation disorders, hemorrhage [45], portal hypertension, ascites, hepatorenal and hepatopulmonary syndromes and fulminant acute liver failure. Control of intravascular volume and glucose administration before, during and after surgery, are mandatory. When time permits, some of the modifiable risk factors for post-operative complications should be treated. Modifiable risk factors that can be improved prior to surgery are coagulation disorders and anemia, prerenal azotemia, electrolyte and pH abnormalities, nutritional depletion, encephalopathy and ascites exacerbation. It is imperative to avoid any drug that is hepatotoxic, to improve oxygen balance at the level of liver cell, to administer lower dosage and to increase time intervals between repeated doses of drugs that are extensively metabolized by the liver. These are some general principles for the management of any patient with advanced liver disease.

Hepatic encephalopathy is mainly attributed to ammonia, a non-metabolized neurotoxic substance absorbed from the gut, which is accumulated into systemic and cerebral circulation. Moreover, hepatic encephalopathy is attributed to depression of neuronic metabolism, presence of false neurotransmitters and excess of the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Other possible causes of hepatic encephalopathy are altered neurotransmission of cortical neurons due to the presence of glutamate, an excitatory neurotransmitter, and cerebral edema formation. Cerebral edema formation is the end result of cerebral vascular dilation and of disturbances in osmotic pressure gradients across the neuronic membranes due to the accumulation of glutamine in the brain cells.

Except for the general principles for the management of any patient with advanced liver disease, special interventions should be made to avoid worsening of hepatic encephalopathy. These interventions include control of upper gastrointestinal bleeding, reduction in the quantity of protein in the gut and correction of electrolytic or arterial pH disturbances. Hypokalemia and alkalosis worsen the undesirable effects of

circulating ammonia on brain function and should be managed carefully. Lactulose, a non-absorbable disaccharide, is usually administered to these patients, in order to decrease ammonia production from the gut. Opioids and benzodiazepines may either induce or worsen hepatic encephalopathy and should be avoided or meticulously used.

Coagulation disorders are treated with parenteral administration of vitamin K and transfusions of fresh frozen plasma or of certain coagulation factors synthesized by the liver, whose plasma levels are low. It should be noted, however, that correction of PT by vitamin K occurs only in patients with biliary tract obstruction and that any positive result is anticipated within 24 hours from the beginning of vitamin K administration.

Life threatening hemorrhage can occur as a result of either undertreated or sustained coagulation disorders or ruptured esophageal varices. If a gastrointestinal hemorrhage occurs, transoesophageal sclerotherapy, combined with local and systemic vasopressin and somatostatin administration, are considered as the treatment of choice. Many centers, prefer sclerotherapy to emergency portacaval shunting. Embolism of varices and collateral veins, via a catheter inserted in the portal vein, can be used to achieve temporary control of bleeding. In the presence of esophageal varices, the placement of nasogastric catheters or other relatively rigid oesophageal probes is better to be avoided because of the risk of variceal bleeding.

Retention of sodium and water produced by the kidneys in conjunction with low oncotic pressure due to hypoalbuminemia and portal hypertension lead to ascites formation. The presence of large quantities of ascitic fluid in the peritoneal cavity causes restrictive pulmonary dysfunction and exposes the patients to the risk of gastric aspiration during induction of anaesthesia. Administrations of spironolactone or loop diuretics, combined with sodium and water restriction are the conservative measures for reducing ascites formation, or exacerbation. Paracentesis for the evacuation of the abdominal cavity is indicated prior to surgery, in order to improve pulmonary function. Ascitic fluid is in dynamic equilibrium with intravascular blood volume. For this reason, abrupt evacuation of large quantities of ascitic fluid can cause hypovolemic shock. Intravascular blood volume substitution is better managed with low salt colloid solutions.

Hepatorenal syndrome is a form of acute renal failure that is manifested in the final stage of liver disease. This form of renal failure is characterized by creatinine and blood urea nitrogen elevation and low urine production with high osmolality and low sodium concentration. The primary cause of the hepatorenal syndrome is renal hypoperfusion, due to decreased effective blood volume. This cause is exacerbated by vigorous diuretic therapy for the treatment of ascites. Abdominal com-partment syndrome in the presence of tense ascites further decreases renal perfusion.

Hepatopulmonary syndrome is characterized by hypoxemia, which is moderate to severe. Dyspnea worsens on assuming the sitting or standing position. Among the factors that contribute to hypoxemia are: the presence of arteriovenous shunts, diffusion-perfusion disturbances, due to dilated pulmonary vessels and pre-existing chronic obstructive pulmonary disease. In more advanced hepatic disease or in the presence of tense ascites, restrictive pulmonary dysfunction and/or pleural effusions are additional factors that aggravate hypoxemia.

Fulminant liver failure complicates an acute liver injury and is characterized by intense clinical signs of hepatic encephalopathy, several days after jaundice onset. Fulminant acute liver failure is often accompanied by cerebral edema and elevated intracranial pressure. Treatment is conservative and these patients are candidates for liver transplantation, if they fulfill the currently established criteria for the transplantation procedure.

Patients with extra-hepatic bile duct obstruction due to gallstones [46] or tumors are at great risk of perioperative morbidity and mortality, especially when hyperbilirubinemia is high and coexists with advanced age, coagulation disorders, low albumin levels, malnutrition, malignancy, anemia, sepsis or renal dysfunction. Renal failure is a common complication of common bile duct obstruction combined with high levels of bilirubin. Renal failure is mainly of a pre-renal origin. The underlying mechanism of renal failure is a progressive decrease of renal blood flow. This can be attributed to hypotension, secondary to vasodilation and to hypovolemia, due to forced diuresis caused by the circulating bile salts. Since the circulating bile salts act as diuretics, urine production alone is not a reliable monitor of the effective blood volume. Prevention of

renal failure is based on careful maintenance of sufficient circulating blood volume. Consequently, this goal is better achieved with interventional cardiovascular monitoring (central venous or pulmonary artery pressure monitoring). Administration of mannitol, loop diuretics or low dose dopamine has not proved to offer any additional protection of renal function.

In the same group of patients, opioids cause spasm of Oddi's sphincter. For this reason, dosage of fentanyl, morphine and meperidine should be reasonably restricted during the perioperative period.

9.5. Anaesthetic Considerations for Hepatic Resection Procedures

Indications for same degree of hepatic resection are primary single liver tumors or metastasis, usually from gastrointestinal cancer. In many cases, more lesions that can be resected are found, either from preoperative assessment or from direct thorough examination of the abdominal cavity, during laparotomy. Ultrasonography may be used intraoperatively to localize lesions. Hepatic surgery is also indicated in some patients with abdomen trauma. The preferred surgical incision for hepatic resection procedures is right subcostal. For large or inaccessible right-sided lesions,this initial incision may be extended into the right chest. Major liver resections are considered wedge, lobe, right or left extended lobectomy and left lateral segmentectomy [47]. The goal of any curative hepatic resection is to completely remove the tumor. Wedge resections are usually performed for small lesions located at the periphery of the liver. However, in many cases, the final decision about the kind and the extent of the appropriate resection is made only after the direct examination of the abdominal organs and the liver, during laparotomy.

Even though a single wedge resection is not associated with considerable hemorrhage, all major liver resections, large or multiple wedge resections, as well as surgical procedures at close proximity of the major hepatic vessels, must be expected to have the potential for sudden and significant intraoperative blood loss. Modern surgical equipment, such as the Cavitron Ultrasonic Aspirator CUSA, and techniques, such as the Radio Frequency Ablation, allow liver surgery to proceed with better control of intraoperative bleeding.

9.5.1. Preoperative Considerations

The anaesthesiologist should be aware about the degree of any hepatic dysfunction relied on preoperative clinical, biochemical and imaging evaluation of the patient [48]. Usually, most patients undergoing hepatic resection have near normal liver functional laboratory tests. Severe anemia, coagulation disorders or any other modifiable risk factor for post-operative liver dysfunction, if present, should be corrected preoperatively [49]. The risk assessment is based on the same criteria as for any other major abdominal surgery. For the planning of anaesthesia, the anaesthesiologist must collaborate with the surgeon, in order to know the kind and the extension of the procedure that is scheduled.

9.5.2. Intraoperative Considerations

Since the risk of sudden and significant intraoperative blood loss is great during hepatic resection procedures, one or two large-bore peripheral venous lines must be secured. Placement of an arterial line for continuous measurement of invasive arterial pressure and for arterial blood gases estimations can be established before or shortly after the induction of anaesthesia. A central venous line is placed, usually after the induction of anaesthesia. Many anaesthesiologists prefer to postpone invasive monitoring, until a definitive decision to proceed with a major hepatic resection has been made by the surgeon. Others prefer to establish invasive monitoring from the beginning of the procedure. Blood glucose levels should be monitored during long lasting and extensive surgery, because the risk of hypoglycemia development is present. Measures should be taken to keep the patient normothermic. The choice and dosage of anaesthetic drugs should be based on the extent of pre-existing hepatic dysfunction, if present, as well as on the anticipated impairment of post-operative liver function, resulting from loss of the hepatic parenchyma following an extensive hepatic resection or from surgical manipulations on the liver.

Controversy exists, concerning fluid management during hepatic resection. If blood and fluid administration is towards keeping a normal to elevated central venous pressure, then hemorrhage will be greater during surgery. If blood and fluid administration is restrictive and central venous pressure is kept low, then intraoperative blood loss will be minimized, but there will

be a risk for air embolism to occur [50]. Trendelenburg's position of the patient helps to control excessive bleeding during the procedure, since this position lowers intrahepatic venous pressure. Furthermore, Trendelenburg's position improves venous return to the right atrium, increases cardiac preload and cardiac output and actually reduces the risk of air embolism from open hepatic veins.

9.5.3. Post-Operative Considerations

Post-operatively, patients who have undergone major hepatic resection should be transferred to an intensive care unit. Patients undergoing small wedge resection or other limited hepatic resection can be managed routinely. During major or vigorous hepatic resection, patients usually undergo excessive traction on their upper abdomen and diaphragm. These intraoperative forces predispose to the development of post-operative pulmonary complications, such as atelectasis, pneumonia or pleural effusion up to 90% of the patients. Effective treatment of acute post-operative pain is crucial, as an effort to reduce morbidity from pulmonary complications. In our hospital epidural analgesia or systemic opioids administration are the methods of choice for post-operative pain management, following hepatic resection. Careful titration of the dosage of opioids and local anaesthetics to the desired analgesic effect is mandatory, because they are both highly metabolized by the liver and have decreased clearance in patients with post-operative hepatic dysfunction. Non-steroidal anti-inflammatory drugs, acetaminophen and other possibly hepatotoxic drugs should be avoided in the post-operative period. Other common and serious complications following major hepatic resection are sepsis, biliary leakage, hepatic failure and hemorrhage. Regeneration of the remaining liver tissue following hepatic resection is marked by decreasing levels of bilirubin and by ameliorating values of other liver functional tests. Survival is promoted by hepatic regeneration, while the regeneration process itself is promoted by preserving normal levels of plasma phosphates. In order to avoid hypophosphatemia, phosphates should be added to intravenous fluids during the early post-operative period.

Improvement of outcome following major hepatic resection is based on thorough preoperative evaluation and preparation of patients, on meticulous management of anaesthesia, to achieve optimal conditions for hepatic and total body homeostasis, as well as on intensive and close post-operative monitoring and preservation of liver function.

9.6. Conclusion

In patients with liver disease, anaesthesia and surgery may post-operatively cause deterioration of hepatic function. Mortality, even following simple surgical procedures, can be high, especially when liver disease is misdiagnosed or is acute or acutely deteriorated.

The goals of perioperative care in patients with hepatobiliary disease are to preoperatively diagnose existing liver disease, to identify the exact cause and the extension of the underlying liver disease and to optimize liver function, as well as, throughout preoperative period, to avoid any factor that is known to deteriorate hepatic function. Acute hepatocellular injury is the most frequently missed diagnosis and the most likely to be accompanied by high rates of post-operative morbidity and mortality. Known and proven risk factors for liver dysfunction after hepatic or non hepatic surgery in patients with severe pre-existing liver disease are acute and chronic hepatitis, cirrhosis and certain types of surgical procedures, such as hepatic resection and surgery on the biliary tract, colon, stomach and cardiac surgery.

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CHAPTER 10

CONGENITAL MALFORMATIONS IN THE EXTRAHEPATIC BILIARY TREE IN CHILDREN BILIARY ATRESIA

D.C. Keramidas

10.1. Introduction

Biliary atresia is a disorder in which there is obliteration or discontinuity of the extrahepatic biliary tree. If untreated it leads to cirrhosis, liver failure and death in less than 2 years after birth. The disorder of the biliary tree is the end result of a panductal sclerosing process appearing before birth with gradual loss of patency of the biliary system which is completed around birth. The biliary structures disappear and fibrous tissue remains at 4 months. The histology of the liver is characterized by a non-specific giant cell transformation and portal expansion by fibrous tissue with ductural proliferation followed by ductopenia, fibrosis and cirrhosis [1].

The incidence of biliary atresia varies according to several series from 1 in 9600 to 16.700 live births and occurs in half of all cases of neonatal cholestasis with a preponderance of females [2, 3, 4]. Associated congenital malformations occur in about 3-10% of biliary atresia cases [2]. Such malformations are polysplenia or asplenia, situs inversus, malrotation, absent vena cava, produodenal portal vein, cardiac anomalies, annular pancreas. The association of biliary atresia with splenic malformations has been described as the BASM syndrome suggesting that damage may occur early in embryonic life [5]. The associated malformations, especially cardiovascular, have an increased mortality effect in children with biliary atresia [6].

10.2. Etiology

The combination and interaction of several elements having a role in etiology and pathogenesis of biliary atresia remains unconfirmed despite progress in research in this field.

The typical pathogenetic manifestations are most prominent at the porta hepatis. Comparison of pathomorphological and histological findings of patients with histological findings in human and rat embryos suggests that biliary atresia could be attributed to disturbances or interruption of epithelium/mesoderm interaction during embryogenesis [7, 8].

Patient based studies have identified genetic and environmental factors that may interact. Chief factors are infectious and immunological processes [9]. Patient and animal based experiments indicate interactions between infectious agents and inflammatory circuits [10]. Studies using immunofluorescence suggest an association between reovirus 3 infection and biliary atresia [11]. Group C rotavirus has been detected in infants with biliary atresia [12]. Studies at different phases of the disease point to a pro-inflammatory commitment of lymphocytes at the time of diagnosis and to their potential role in obliteration of bile ducts [9]. Osteopontin, a Th1 cytokine, is involved in several fibro-inflammatory and autoimmune diseases. Its increased expression by interlobular biliary epithelium correlates with biliary proliferation and portal fibrosis suggesting a role in the pathogenesis of the disease [13].

In biliary atresia associated with congenital anomalies, abnormalities in different genes seem to predispose. In this "fetal" group of biliary atresia, which is a minority, the symptoms start shortly after birth. In the majority of patients, in addition to genetic susceptibility, several factors, mainly infectious, have a role in pathogenesis [1].

10.3. Classification

There are three main types of biliary atresia according to the level of obliteration of the extrahepatic biliary system (fig. 10.1).

Type I. The level of obstruction is within the common bile duct. The gallbladder contains bile. This type is rarely encountered.

Type II. The level of obstruction is within the common hepatic duct. The hepatic ducts contain bile. The gallbladder does not contain bile. This type is rarely encountered.

Type III. The level of obstruction is within the porta hepatis. This is the commonest form of biliary atresia (>90%).

While details of subdivisions of these main types or variations based on the structure of the gallbladder and the distal bile ducts exist, they have no influence on the mode of surgical treatment. Rarely, during cholangiography, a cystic form of biliary atresia can be disclosed containing either mucus or bile within some part of the extrahepatic bile ducts with a thickened wall. There may be communication with abnormal intrahepatic ducts [5].

10.4. Clinical Manifestation and Diagnosis

All infants still jaundiced at 2 weeks after birth need investigation to determine whether conjugated hyperbilirubinemia is present. Work-up for diagnosis should be completed the soonest possible. Neonates and infants with prolonged jaundice on a hepatic parenchymal basis due to neonatal hepatitis, a-1 antithrypsin deficiency, giant-cell hepatitis, cytomegalovirus hepatitis, cystic fibrosis, biliary hypoplasia or Alagille's syndrome must be separated from those on an obstructive cholestatic basis.

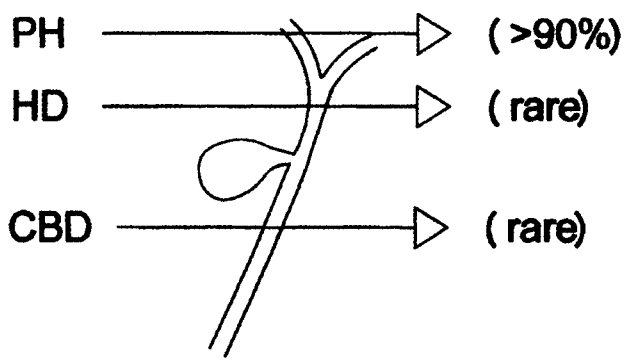

Fig. 10.1. Levels of obliteration of the extrahepatic biliary tree in biliary atresia.

Biliary atresia represents the majority of cases of cholestatic jaundice. The infant will be admitted having pale stools and dark urine due to the inability to excrete conjugated bilirubin into the intestinal tract. In some infants there is vitamin K-related coagulopathy and bleeding.

In the differential diagnosis of biliary atresia, other causes of extrahepatic obstruction must be included: choledochal cyst, spontaneous perforation of the bile duct and the inspissated bile syndrome.

The following diagnostic means have been used for the diagnosis and differential diagnosis of biliary atresia:

1. Ultrasonography is the initial imaging technique of choice for neo-natal jaundice. In biliary atresia the liver parenchyma is disclosed homogeneous, the bile ducts are not identified, and the gall bladder is either not visualized or empty and tiny. Visualization of a triangular or tubular echogenic density just cranial to bifurcation of the portal vein is diagnostic [14]. Rarely a cystic dilatation of the extrahepatic duct is demonstrated corresponding to the bulbous end of a nonobliterated common hepatic duct. The sensitivity of ultrasound scanning for biliary atresia and the specificity of the findings are high. Structural abnormalities of the biliary tree are excluded and a prenatal diagnosis may be made. Moreover, ultrasound scanning can reveal associated malformations of the spleen and vascular malformations.
2. Radioscintigraphy using imino diacetic acid (IDA) derivatives is useful in the study of hepatocyte clearance, hepatobiliary transit and excretion. Early in the course of biliary atresia, clearance of the isotope is adequately maintained. Given that discrimination between nonsurgical and surgical causes of jaundice can be difficult, biliary atresia is excluded when excretion of the isotope is not visualized in the gut.
3. Percutaneous Liver Biopsy (PLB) is useful for the differential diagnosis of biliary atresia from the various forms of intrahepatic cholestasis. Liver biopsies from patients with a-1-antitrypsin deficiency may

be confused with biliary atresia. Histochemical and immunohistochemical staining contribute to differential diagnosis.

4. Magnetic Resonance Cholangiography (MRC) can show the biliary anatomy and periportal thickening which corresponds to the histologic findings of expanded fibrosis of the porta hepatis [15]. The accuracy and sensitivity of MRC are 98% and 100% respectively for diagnosis of biliary atresia [16].
5. Endoscopic Retrograde Cholangiopancreatography (ERCP) was successfully used in 47 of 52 examinations in biliary atresia [17]. The procedure requires endoscopic skill in infants and may not be free of complications such as cholangitis, pancreatitis and duodenal perforation.
6. Laparoscopy and laparoscopic-guided cholangiography was reported successful in the diagnosis of biliary atresia [18].

10.5. Surgery in Biliary Atresia

The initial operation of biliary atresia is hepatic portoenterostomy as proposed by Kasai in the year 1959 [19]. Nevertheless, almost 90% of patients will be subjected sooner or later to a further operation for liver transplantation. During the last twenty years many studies have been published concerning optimal surgical treatment [20-25]. Cirrhotic children who do not drain bile, are malnourished due to fat malabsorption, low caloric intake, increased energy expenditure and insensitivity to the growth hormone [26, 27]. Malnutrition increases the mortality and morbidity of liver transplantation. The advantage of hepatic portoenterostomy is that during the pretransplant period the patients can gain weight and grow [25]. However, the development of adhesions in the upper abdomen following hepatic portoenterostomy increase the risks of the transplant procedure in these cirrhotic patients. Laparoscopic hepatic portoenterostomy has the advantage that no adhesions develop after the operation. Esteves et al described laparoscopic hepatic portoenterostomy for biliary atresia in 2002 [28]. With the improvement of laparoscopic instruments and pertinent surgical skills, Martinez-Ferro, Esteves and Laje successfully performed and standardized the procedure in a larger series of patients in two different centers [29].

10.6. Kasai Hepatic Portoenterostomy

The procedure of conventional hepatic portoenterostomy will be described according to the authoris experience and practice. In parallel, specific modifications for the needs of the laparoscopic procedure will be added as worked out and described by Martinez-Ferro, Esteves and Laje [29].

Preoperatively, vitamin K is administered intramuscularly for 2-3 days and neomycin orally for 24 hours. After induction of anesthesia, antibiotics are given intravenously and continued for 3-4 days after the operation. Attention must be paid to meticulous bowel preparation before the laparoscopic procedure. The bowel must be properly cleaned with polyethylene glycol solution or three to four saline enemas during the last 6 hours terminating 1 hour before surgery.

10.6.1. The Operating Table

Open procedure: The patient is placed in supine position on a thermostatically controlled heated operating table with facilities to perform operative cholangiography should the latter be deemed necessary.

Laparoscopic procedure: Neonates and infants are placed across the table on a 10 cm high platform to facilitate the range of instrument movements.

10.6.2. The Incision

Open procedure: A small right subcostal incision is made and the gall bladder is aspirated. If bile is present, cholangiography through a gallbladder catheter is carried out. Diluted contrast material is injected to demonstrate continuity of the biliary tree and duodenum. Diagnosis of biliary atresia is excluded on the basis of demonstration of a patent common bile duct and communication with intrahepatic ducts. In the majority of cases the gallbladder is fibrotic, the lumen usually occluded rendering cholangiography impossible. The small right subcostal incision is extended laterally dividing the rectus muscles to adequately expose and inspect the liver. The presence or absence of ascites and associated anomalies are noted and a needle biopsy of the right lobe of the liver is taken. Exploration of the extrahepatic biliary tree follows.

Laparoscopic procedure: Four trocars are placed and fixed. The first one to the peritoneal cavity through an

open infraumbilical port. It is used for the telescope insertion and CO2 insuflation. The second trocar is placed in the left flank. It comprises a silicone leaflet valve and is used for the insertion of a curved needle. The third and fourth trocars are placed in the right flank and used respectively for the insertion of grasping and dissection forceps and for the insertion of instrument for aspiration-irrigation.

10.6.3. Main Steps of Hepatic Portoenterostomy are the Following

a) *Mobilization of the liver. Open procedure*: The ligaments of the liver are divided to adequately expose the porta hepatis.

Laparoscopic procedure: The liver is retracted so as to expose the biliary tree and stabilized using two percutaneous transhepatic stitches which enter the abdominal cavity near the left and right costal margins. A third stitch from below the xiphoid process can be used to snare the round ligament.

b) *Dissection of the gallbladder and bile ducts. Open procedure*: The cystic artery which is usually enlarged is divided and the gallbladder dissected from its bed. Thickened peritoneum and lymph nodes are dissected and excised to expose the fibrous remnant of the common bile duct. The latter is ligated and divided at its distal end and dissected with the cystic duct and gallbladder attached. Using the gallbladder as a handle, the proximal hepatic duct is dissected upwards above bifurcation of the porta vein. The branches of the portal vein and hepatic arteries are exposed up to the liver.

Laparoscopic procedure: Dissection starts with the gallbladder and proceeds towards the fibrous remnants of the common bile duct which is divided to its distal end. Dissection continues towards the hepatic duct leading proximally to the porta hepatis.

c) *Excision of bile duct remnants. Open procedure*: The fibrous tissue in the porta hepatis is transected to remove the bile duct and the gallbladder. The plane of transection is parallel to the liver capsule. This plane is bounded by the two branches of the portal vein laterally and extended behind the posterior surface of the portal vein. The material excised from the porta hepatis is examined histologically to identify ductules and their size. Bleeding is controlled by direct pressure. Diathermy is not used as it may cause damage to small biliary ductules (fig. 10.2a).

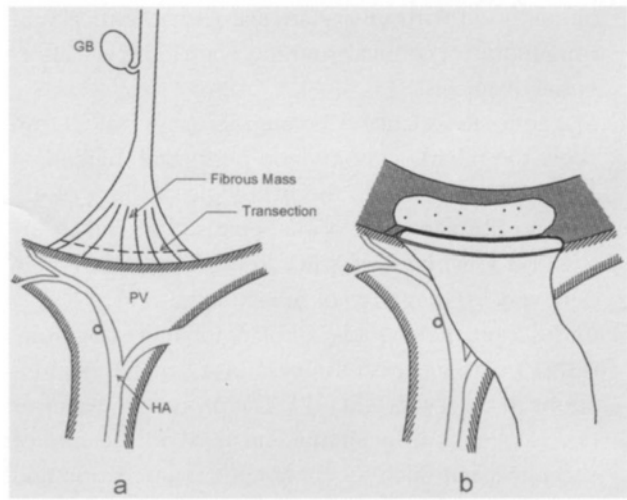

Fig. 10.2. a. Diagrammatic demonstration of transection line of fibrous mass between the branches of the portal vein. The rudimentary extrahepatic biliary tree is dissected free and elevated superiorly to expose the porta hepatis. b. Jejunal loop at the porta hepatis for anastomosis after excision of the fibrous mass.

Laparoscopic procedure: The fibrous tissue of the porta hepatis is gently dissected and sharply excised with 3 mm curved endoscopic scissors. Small vessels are meticulously coagulated with the hook to increase the portal plate. Bile flowing from small bile ducts still patent is expected to be observed under magnification.

d) *Preparation of jejunal loop and Roux-en-Y hepatic portoenterostomy. Open procedure*: The jejunum is transected 20 cm distal to the Treitz ligament and pulled up to the porta hepatis in a retrocolic position. An end-to-side jejunojejunostomy is established at 35 cm from the end of the transected loop to re-establish continuity of the small bowel. It is the author's practice to perform end-to-end portoenterostomy using interrupted sutures with the knots outside the lumen (fig. 10.2b). Two guy sutures of 5/0 absorbable material are placed in the liver capsule at the medial and the lateral sides of transected tissue in the porta hepatis, next to the bifurcation of the portal vein and slightly posterior to it. The guy sutures are full thickness, to the mesenteric and antimesenteric borders of the jejunal conduit without tying them. The posterior row of sutures is inserted in between the guy sutures, the jejunal loop is pulled into position and the sutures are tied in series. The anastomosis is completed by an anterior row of sutures.

Laparoscopic procedure: The Roux-en-Y limb is performed outside the abdominal cavity using the umbilical port which is adequately enlarged to facilitate exteriorization of the intestine. Before exteriorization the proximal and distal ends of the loop are marked with two dots by applying the tip of a monopolar hook to the seromuscular wall. The marked areas are resected after exteriorization. The anastomosis to the porta hepatis is performed using 5/0 PDS-Ethicon with a CI needle. The sutures are placed in and out of the peritoneal cavity through the trocar of the left flank. Two percutaneous sutures are placed at each corner of the posterior wall of the anastomosis to facilitate the precise placement of the posterior row of sutures exiting very close to the portal vein. Extracorporeal Roeder knot tying is used. The anastomosis is completed with the anterior row of sutures.

10.7. Complications After Hepatic Portoenterostomy

10.7.1. Cholangitis

Recurrent ascending cholangitis is the usual complication after hepatic portoenterostomy. This complication is manifested by decreased bile flow and fever accompanied by a rise in serum bilirubin levels and leukocytosis. It may be followed by cessation of bile flow. Intrahepatic bile stasis and enteric bacterial colonization of the conduit are the predisposing factors of cholangitis. Colonization of the conduit usually with Escherichia coli, Proteus spp. and Klebsiella occurs within the first month after the operation. Blood cultures and liver biopsy cultures are necessary for identification of the bacteria. Fever usually resolves in two days following treatment with intravenous antibiotics against Gram-negative microorganisms but resumption of bile flow may take one week. Phenobarbitone and cholestyramine are administered to enable bile flow. Steroids [30], ursodeoxycholic acid [31] and chronic intravenous antibiotics are advocated to improve bile flow after the operation.

Episodes of cholangitis are unusual after the first postoperative year. They may be the result of stasis in the conduit as revealed by percutaneous cholangiography and reoperation is required.

In order to prevent cholangitis, construction of "valves" in the jejunal biliary conduit has been used. This has beem proved ineffective [32]. On the other hand, temporary exteriorization of the conduit by fashioning cutaneous stoma has also been used to observe bile flow and prevent cholangiitis. The double-Y conduit, the double barrelled conduit and total exteriorization of the conduit are mentioned among several configurations of temporary exteriorization. There is no evidence that the incidence of cholangitis is prevented. Moreover, stomal varices causing bleeding may develop and technical difficulties are encountered during the operation of liver transplantation, should the latter become necessary at a later stage.

In some patients cholangitis may be associated with intrahepatic biliary cysts requiring percutaneous aspiration or internal drainage [33, 34]. The possibility of biliary atresia associated with biliary cysts must be considered in infants with prolonged jaundice and cholangitis [35]. An intrahepatic biliary cyst with recurrent cholangitis was described in a patient treated with resection 29 years after Kasai procedure [36].

10.7.2. Portal Hypertension

The degree of fibrosis at the time of hepatic portoenterostomy, the response to surgery and episodes of recurrent cholangitis predispose to cirrhosis and portal hypertension. Complications of portal hypertension are variceal bleeding and less frequently hepatopulmonary syndrome [37]. They occur in more than 60% of long-term survivors [38]. Endoscopic sclerotherapy in infants and endoscopic variceal ligation in older children are employed to control bleeding [39]. Thirty per cent of patients needing early transplantation due to non response to hepatic portoenterostomy have a history of serious bleeding from oesophagel varices [5].

Hepatocellular carcinoma is a long-term complication. It may develop in patients with cirrhosis without clinical evidence of portal hypertension [40].

10.8. Results of Hepatic Portoenterostomy

The rate of decline of serum bilirubin values after the operation corresponds with good prognosis. Biliary drainage after the operation is usually sluggish for 2-3 weeks and in many cases no significant resolve of

jaundice occurs. A classification of long-term results as good, partial and poor was proposed based on total bilirubin levels within three months after the operation [41]. Ten to 15% of patients will be free of complications with long-term excellent results, normal liver function but abnormal histology [5]. The native liver 5-year survival as a turning point to either liver transplantation or death is 29% to 68% according to large series [1, 42-45].

The majority of patients will be submitted to liver transplantation at some later period of life.

10.9. Prognosis

A combination of the following parameters has a role in prognosis:

a) The age of the infant. Although the operation is most effective in patients under 6 weeks of age, good results have been reported beyond that age [46].

b) The histological identification of biliary ductules in the excised tissue from the porta hepatis. Ductules with diameters greater than 150 μm may be a positive prognostic factor for adequate biliary drainage.

c) The degree of cirrhosis. The levels of serum hyaluronic acid, a marker of hepatic fibrogenesis may be of prognostic value preoperatively [47].

d) The frequency of relapsing cholangitis and degree of response of cholangitis to treatment.

e) The existence of associated malformations, especially cardiovascular with development of pulmonary arteriovenous shunting after the operation [6].

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CHAPTER 11

CHOLEDOCHAL CYSTS OF THE BILIARY TREE IN CHILDREN

D.C. Keramidas

11.1. Choledochal Cysts - Introduction

Choledochal cysts are rare congenital dilatations of the extrahepatic bile ducts which may also involve the intrahepatic biliary system. According to the author's material of 21 cases over a ten-year period (1991-2000), choledochal cysts come second to biliary atresia in frequency with a female to male ratio 4:1, and consitute the majority of cholestatic jaundice cases in childhood. The incidence in western countries is estimated between 1 in 100,000-150,000. In eastern countries the incidence of choledochal cysts is higher [1, 2].

11.2. Etiology

Endoscopic retrograde cholangiopancreatography for the evaluation of pancreaticobiliary disorders disclosed choledochal cysts associated with anomalous junction of the pancreaticobiliary duct in 87% of patients [3]. The anomalous junction is the result of early fusion of the common bile duct with Wirsung's duct outside the duodenal wall and arrest of migration of the junction into the duodenal wall before the eighth week of embryonic life [4]. This abnormal arrangement of the pancreaticobiliary ducts leads to formation of a long pancreaticobiliary canal or "common channel".

Although no inheritance pattern has been established, there may be a genetic factor on the basis that anomalous junction of the pancreaticobiliary duct has been reported in families and it occurs more frequently in eastern countries [5]. Anomalous pancreaticobiliary junction has been described in monozygotic twins suggesting a genetic origin [6].

The presence of a long common channel predisposes to a two-way reflux of bile and pancreatic juices and is associated with various pathologic conditions such as pancreatitis, stenosis of the papilla of Vater and choledochal cysts [1, 2, 6, 7]. The reflux of pancreatic enzymes into the common bile duct is followed by degeneration of the elastic fibers and ectasia. This development sometimes extends up to the intrahepatic biliary tree. The chemical effect of pancreatic fluid on the bile duct in the antenatal period is unclear. The diagnosis of choledochal cyst can be made as early as the fifth month of embryonic life but the fetal pancreatic enzymes are not functional at that gestational age [8].

Dilatation, stenosis and partial obstruction of the common channel due to debris, protein plugs and inflammation cause reflux of bile into the pancreatic duct. Acute pancreatitis is reported in 17-68% of patients with a long channel [7, 9]. There are rare types of choledochal cyst in patients without a long common channel. These types are the following: diverticulum on the common bile duct, duodenal choledochocele and intrahepatic bile duct dilatation or Caroli's disease.

11.3. Classification

Classificaiton of choledochal cysts was first proposed by Alonso-Lej et al in the year 1959 [10]. According to Todani et al classification [11], there are the following types: Type I, a) choledochal cyst, b) segmental choledochal dilatation, c) diffuse or cylindrical dilatation; Type II, diverticulum of the whole extrahepatic duct; Type III, intraduodenal common bile duct dilatation; Type IVa, multiple intra- and extrahepatic ducts dilatations; Type IVb, multiple extrahepatic dilatations; Type V, intrahepatic dilatation(s).

A practical classification of choledochal cysts based on the anatomy of the dilatation in association with cholangiographic findings of the pancreaticobiliary junction was proposed by Miyano et al [8]. According to this classification there are two groups of choledochal cysts. In the first group comprising the majority of cases, choledochal cysts are associated with pancreaticobiliary maljunction. There are three types of cysts in this group: cystic, fusiform and forme fruste. In the second group comprising the minority of cases, no anomalous pancreaticobiliary junction exists. There are three types of cysts in this group: cystic diverticulum of the common bile duct, duodenal choledochocele, intrahepatic bile duct dilatation or Caroli's disease (fig. 11.1, 11.2, 11.3).

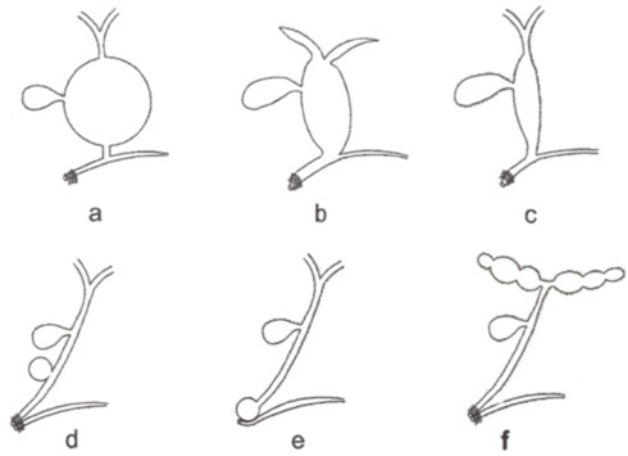

Fig. 11.1. Classification of choledochal cysts in context of association with a common channel (a, b, c: common channel - d, e, f: separate ducts).

11.4. Clinical Presentation

Jaundice is the main presenting symptom in children in contrast to abdominal pain which appears with a significantly higher incidence in adults [1]. Acholic stools, vomiting and a palpable abdominal mass with or without jaundice appear in neonates and young infants according to the degree of obstruction. In older children, fever and pain may also occur and relate to recurring pancreatitis.

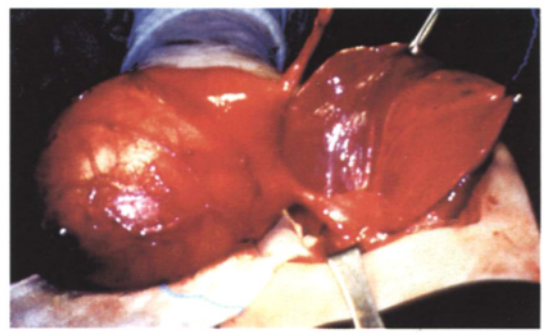

Fig. 11.2. A cystic form choledochal cyst during dissection.

11.5. Diagnosis

Identification of biliary tree anomalies before birth can be done using ultrasound scan. However, differential diagnosis between choledochal cyst and biliary atresia, mainly with obstruction at the level of common hepatic duct is difficult [12].

For prenatal ultrasound scan, the following patterns and sizes have been proposed in differential diagnosis: anechoic small cyst in the hilum and echoic large or small cysts. The former is highly suspicious for biliary atresia. The latter are respectively suggestive of obstructed or unobstructed choledochal cysts [13]. Should it be impossible to distinguish between choledochal cyst and biliary atresia on antenatal ultrasound scan, early exploration is recommended to exclude potential biliary atresia [14].

For symptomatic patients, especially when a differential diagnosis of biliary atresia is doubtful, early exploration is needed before 2 months. Definitive surgery at 6 months of age is proposed for asymptomatic patients with prenatally diagnosed choledochal cyst [15]. In infants and children, visualization of the entire bilio-

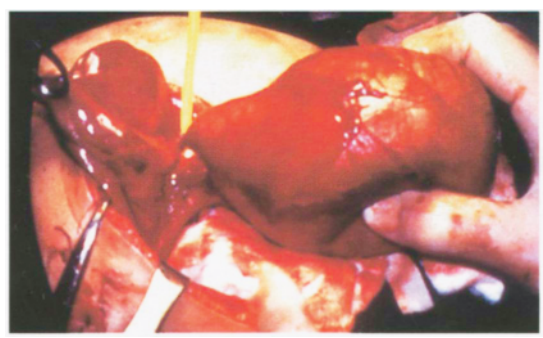

Fig. 11.3. An unusually large diverticulum of the common bile duct.

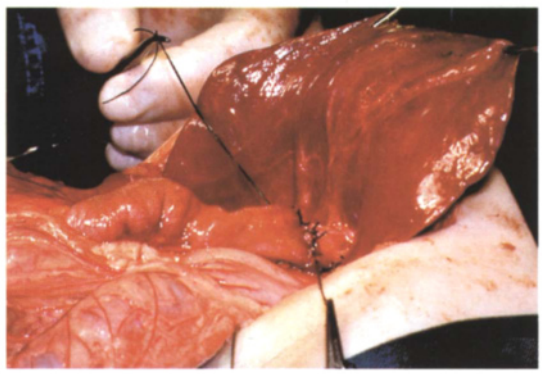

Fig. 11.4. End-to-end hepaticojejunostomy after excision of a cystic form choledochal cyst.

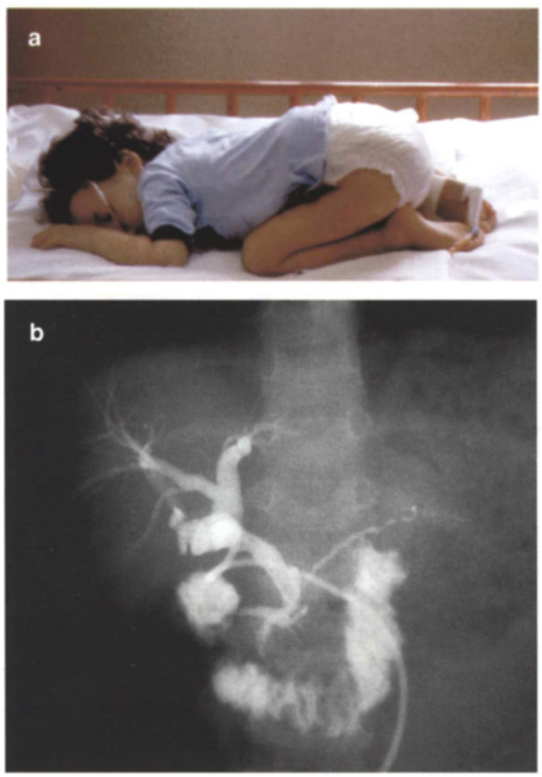

Fig. 11.5. a-b. A six-year-old patient with pancreatitis due to common channel as revealed by cholangiography during surgery.

pancreatic system is the epicenter of procedures for the diagnosis of choledochal cysts. Abdominal ultrasononography, endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) are mainly used [1, 8]. In addition, intraoperative cholangiography is a precise and effective technique in differential diagnosis and in determining the appropriate method of treatment [16].

Ultrasonography is the primary screening method for congenital biliary dilatation. However, the entire duct visualization is limited. The undilated common channel and pancreatic duct cannot be clearly demonstrated.

ERCP can accurately demonstrate the pancreaticobiliary system. However, this procedure requires endoscopic skill in infants and may not be free of complications. Pancreatitis is a contraindication for ERCP.

MRCP has the advantage of being non-invasive and effective in visualizing the pancreatic duct upstream to an obstruction or stenosis. It can accurately demonstrate narrowings, dilatations and filling defects in the pancreatobiliary sytem.

11.6. Surgical Treatment

Choledochal cysts are associated with the development of both cholangiocarcinoma and gallbladder cancer. Therefore surgical treatment should consist of complete excision of the extrahepatic biliary tree with Roux-en-Y hepaticojejunostomy (fig. 11.4). The bile duct should be excised at the intrapancreatic portion if the latter is involved in the choledochal cyst [17].

It is important during the operation to thoroughly investigate the entire biliopancreatic ductal system for anomalies of the common channel or pancreatic duct, dilatations or strictures of the intrahepatic bile duct and possible presence of debris, protein plugs, stones or stenosis of the papilla of Vater (fig. 11.5). For this exploration the following diagnostic means can be effectively used: intraoperative cholangiography and intraoperative endoscopy [8, 18].

Cholangiography should be performed separately for the intrahepatic duct and the distal common bile duct during the procedure of cyst excision.

Endoscopy of the common channel, pancreatic duct and intrahepatic duct is performed using a pediatric cystoscope or a neonatal cystoscope. With irrigation, debris and protein plugs are washed out through the papilla of Vater following duodenotomy if necessary.

The cystic form of choledochal cyst is the usual type of congenital biliary dilatation in newborns and young infants [19]. The content of large cysts is aspirated to facilitate dissection from the surrounding tis-

sues. In this age group complete excision is easier due to thin wall and few adhesions. The gallbladder is dissected. An incision close to the duodenum is carried out to prevent damage of possible anomalous opening or openings of the hepatic duct in the distal part of the cyst. The author has experienced a postoperative complication of bile peritonitis due to an anomalous opening of an accessory bile duct in a baby girl who was subsequently reoperated by redoing the hepaticojejunostomy to include the accessory bile duct. After circumferential dissection from the hepatic artery and vein, traction slings are passed around and the distal portion is dissected and excised at the level of distinct caliber change. If the cyst is of fusiform type, without distinct caliber change, excision should extend just above the pancreaticobiliary junction.

The common channel is irrigated and the stump sutured. When excision up to and above the level of pancreaticobiliary junciton is difficult, mucosectomy of the distal part of the cyst is recommended in order to avoid injury to the hepatic artery, portal vein and pancreatic duct and protect from possible malignancy [20].

In patients with bile peritonitis or in neonates in poor condition, a staged procedure can be undertaken. Excision and hepaticojejunostomy is performed 1 or 2 months after external biliary drainage or percutaneous drainage of the cyst [8].

In rare cases of dilatation of the intrahepatic bile duct and stricture at the hilum, segmentectomy or intrahepatic cystoenterostomy and ductoplasty-cystojejunoplasty are respectively recommended [21, 22]. In the rare anomaly of pancreaticobiliary maljunction without bile duct dilatation, presenting symtoms of pancreatitis, excision of the extrahepatic biliary system and biliary reconstruction by Roux-en-Y hepaticojejunostomy is recommended [23].

11.7. Laparoscopic Surgery

Laparoscopic surgery for the excision of choledochal cyst in a 6-year old girl was reported by Farello et al in 1995 [24]. Since then, a few authors have reported their cases [25, 26] and experience from larger series have been published [19, 27].

The patient positioning and port placement were described in the chapter of biliary atresia. Dissection begins with the gallbladder which is used for traction. The cyst is rotated for dissection from both sides. Upward dissection proceeds up to the proximal narrowing of the cyst. The hepatic duct is temporarily ligated in two points in order to be transected between the two ties to prevent bile leakage. Dissection distally from the duodenum and pancreas is carried out using the hook.

Interrupted stitches or clips are used to seal the distal end [27]. The Roux-en-Y limb is constructed extracorporally using the dilated umbilical port wound. Hepaticojejunostomy either end-to-end or end-to-side is carried out following placement of two cutaneous stay sutures which are placed on each corner of the posterior wall of the anastomosis. This part is closed with running suture and the anterior part with interrupted stitches.

11.8. Postoperative Complications

Postoperative follow-up of patients is essential due to their frequently prolonged elevation of serum alanine aminotransferase and possibility of residual intrahepatic dilatation [28].

Review of 200 children after cyst excision with hepaticojejunostomy showed that 9% developed complications of cholangitis, intrahepatic bile duct stones, pancreatitis, intrapancreatic bile duct stones or pancreatic duct stones [18]. The rate of complications was 4 times lower than in adults. All were related to stone debris in the common channel and intrahepatic ducts, to protein plugs and strictures. Intraoperative endoscopy of the common channel, pancreatic duct and intrahepatic duct to examine the ductal system for debris and stenosis, and irrigation to wash out the pathological material is recommended [22].

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CHAPTER 12

GALLSTONE DISEASE

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12.1. Introduction - Prevalence and Incidence

Most epidemiological studies, aimed at estimating gallstone prevalence and incidence rates, do not represent the general population. Until recently, data were mainly derived from autopsy studies (which were often subject to selection bias) and cholecystectomy rates (which fluctuate as much as fivefold between, different countries and periods of time) [1]. At present, accurate data from sonographic screening studies regarding prevalence of cholelithiasis, are available for Western Europe and US. The median prevalence ranges from 5.9% (Chianciano, Italy) to 21.9% (Bergen, Norway) in European studies [2]. In US, the NHANES III study [3] indicated an age standardised prevalence of gallstones higher among Mexican Americans (8.9% and 26.7% in males and females respectively).

In populations of Native American ancestry, the prevalence of gallstone disease is high (30-70%) and very high incidence of gallstones has also been reported in certain ethnic groups like Pima-Indians in Arizona (more than 70% of Pima women over 25 years of age had gallstones or a history of cholecystectomy) and Mapuche Indians in Chile. In Santiago, Chile, gallstone prevalence was found to be as high as 14.5% for males and 37.4% for females [1]. On the other hand, the lowest cholesterol gallstone prevalence rates (<5%) were recorded among Asian and African populations.

In almost all sonographic surveys, gallstones are more frequent in women than in men and the majority of individuals were unaware of having gallstones. Gallstones may remain silent (asymptomatic) for a certain period of time or they can produce biliary pain by transient obstruction of the cystic duct. Furthermore, complications related to cholelithiasis may develop in some individuals, namely acute cholecystitis (including hydrop and empyema of gallbladder), choledocholithiasis with or without jaundice or cholangitis, gallstone pancreatitis, gallstone ileus, Bouveret's syndrome, and even gallbladder carcinoma.

12.2. Symptomatic Gallstones

12.2.1. Chronic Cholecystitis

In clinical practice, the term chronic cholecystitis is used in a dual mode. From the clinical point of view, chronic cholecystitis refers to ongoing or recurrent episodes of short-term cystic duct obstruction, manifesting with a variety of atypical symptoms with or without biliary colic caused by the spasm of cystic duct obstruction. Over time, these recurrent episodes result in chronic inflammatory changes of the gallbladder wall: subepithelial and subserosal fibrosis, mononuclear cell infiltration and scarring. This chronic inflammatory process, which is not present in all patients with recurrent biliary pain attacks, often leads to a nonfunctioning gallbladder and is also recognized histopathologically as chronic cholecystitis.

As many as one third of patients with gallstones will develop symptoms most of which (70-80%) will develop pain often labeled as biliary colic [4, 5]. Biliary colic is a misnomer, because the pain is not usually as intermmitent and spasmodic as the term suggests. Biliary pain has a sudden onset (often awakens the patient during the night) and increases in intensity over a 15 minutes interval to a plateau that can last from as long as many hours up to a day. The intensity of the pain is often so severe that the patient seeks immediate medical attention.

The pain is usually located primarily in the epigastrium and/or right upper quadrant. It is incorrect to interpret pain located in the epigastrium as non-biliary. Biliary pain frequently radiates to the right upper back,

right scapula, right shoulder or to the interscapular region. Typically, the pain of biliary colic occurs after a fatty meal, although this connection is not reported by all patients. Such an association of pain with meals is present in only 50% of patients in whom the pain usually develops more than an hour after eating. In most patients, the pain is temporally only related to meals and generally begins at night.

The duration of biliary pain is typically 1 to 5 hours. The episode rarely persists for less than one hour or more than 24 hours. Pain lasting beyond 24 hours suggests the presence of acute cholecystitis. The attacks are often so discrete and severe that the patient can accurately recall and enumerate them. They are usually less frequent than one episode per week with nausea and vomiting often accompaning each episode in 60 to 70% of cases. Other dyspeptic symptoms such as bloating, belching, abdominal discomfort and heartburn are also present in 50% of patients, but they are most likely unrelated to the gallstones themselves and frequently persist after surgery [6]. Fever and jaundice occur much less frequently with simple biliary colic.

The findings of a physical examination are usually completely normal in patients with chronic cholecystitis, particularly between pain attacks. During an episode of biliary pain, mild right upper quadrant tenderness may be present. Liver function tests (LFTs) are also usually normal in patients with uncomplicated cholelithiasis.

The diagnosis of symptomatic cholelithiasis is based on the sonographic examination of the gallbladder in selected patients with suggestive symptoms. Among symptoms and signs, a steady upper abdominal pain, radiating to the upper back, occurring at least one hour after fatty meals and lasting at least 30 minutes, is the most sensitive clinical indicator of cholelithiasis. The confirmation or exclusion of gallstone disease in patients with symptoms attributable to gallstones is achieved by Ultrasonography which provides 95-98% sensitivity and specificity for the diagnosis of gallstones greater than 2 mm in diameter [7]. Ultrasonography also provides additional anatomic information on the presence of gallbladder polyps, common bile duct diameter, or any hepatic parenchymal abnormalities.

Patients with symptomatic cholelithiasis are at significant risk of developing recurrent painful episodes and complications. Approximately, 6-8% (but in some series up to 36%) will experience recurrent pain attack(s) each year and 1-2% will present gallstone complications, although there is evidence that these figures may underestimate the real risk [8, 9]. The risk of acute cholecystitis is greater in patients with large solitary stones as is of biliary pancreatitis in those with multiple small stones (microlithiasis) or sludge.

The treatment of choice for patients with symptomatic cholelithiasis is elective laparoscopic cholecystectomy (LC). Large series of patients undergoing elective LC for chronic cholecystitis report a mortality rate of approximately 0.1% (8.6-16 deaths per 10,000 patients) with cardiovascular complications being the most common cause of death [10]. The morbidity of the procedure is less than 10%, with iatrogenic injury to the biliary tract presenting an infrequent but often disastrous complication requiring long hospitalization, multiple reoperations, repeated invasive procedures and long stenting of the common bile duct (CBD). The incidence of CBD injury ranges from 1/160 to 1/320 LCs, in most clinical series [10]. Conversion to laparotomy is necessary in less than 5% of patients with the elderly, obese, male and those with periumbilical scars from previous laparotomies being at greater risk.

The long-term results of laparoscopic cholecystectomy in appropriately selected patients with chronic cholecystitis are excellent. Nearly 90% of patients with typical biliary pain are rendered symptom-free after cholecystectomy. However, persistent dyspeptic symptoms (fatty food intolerance, flatulence, belching or bloating) frequently occur following cholecystectomy, especially in patients with evidence of significant psychological distress and a prolonged history of such symptoms prior to surgery [11].

12.2.2. Acute Cholecystitis

Acute calculous cholecystitis is the distinctive clinicopathological entity characterized by acute inflammation of the gallbladder caused by the obstruction of the Hartmann's pouch or cystic duct comprising impacted gallstones or biliary sludge. The inflammation of the gallbladder wall is chemical, at least during the early phase. The increase of intraluminal pressure and the presence of supersaturated bile along with trauma to the mucosa caused by the gallstone, trigger an acute inflammatory response. Following this early phase, 20-

50% of patients manifest a proliferation of aerobic enteric bacteria, and occasionally anaerobes, resulting in secondary bacterial infection of the organ.

Microscopic features of the disease include necrosis of mucosa, edema and hemorrhages in the gallbladder wall. The gallbladder is distended, tense and vascular. Planes along gastrohepatic omentum can be edematous after 24-48 hours and adhesions of omentum (and probably of duodenum) to the distended gallbladder can be perceived as palpable mass. The course of the inflammatory process depends on the degree and the duration of obstruction, the severity of bacterial attack, the age of the patient and the concurrence of accompanying diseases.

Patients with acute calculous cholecystitis may have a history of episodic biliary pain attacks or they may have hitherto been asymptomatic. Clinical diagnosis is based on the presence of symptoms and signs suggestive of localized peritonitis in the right upper abdominal quadrant. The presence of three features, namely: (1) constant biliary pain lasting for at least 12 hours, (2) tenderness in the right upper quadrant (with or without Murphy's sign and with or without a palpable mass) and (3) inflammatory response (fever, leucocytosis) implicates the diagnosis and requires ultrasound scanning to confirm or exclude acute cholecystitis.

Ultrasonography is the initial imaging modality of choice for the evaluation of acute pain in the right upper quadrant [7]. Typical sonographic findings include a distended gallbladder with edematous wall, pericholecystic fluid (or even abscess), elicitation of Murphy's sign during examination and presence of gallstones often impacted in gallbladder outlet. Ultrasonography also permits an accurate diagnosis of other underlying causes of a patient's symptomatology, including hepatic, renal, pancreatic, adrenal and even pulmonary problems. At the present time, a firm diagnosis of acute calculous cholecystitis can be established in 90% of patients with suggestive symptoms based on the clinical and sonographic findings.

In the remaining uncertain cases, radionuclide cholescintigraphy (hydroxyiminodiacetic acid (HIDA) scan), having sensitivity and specificity rates of (0.97 and 0.90), is the best able to confirm or rule out the presence of acute cholecystitis (within 4 hours or 30 minutes, respectively). However, contrast-enhanced CT is the most often preferred complementary to US imaging modality, being especially valuable in the assessment of acute cholecystitis complications, in particular emphysematous cholecystitis and perforation of gallbladder [12].

Patients with acute cholecystitis (10-15%) may have mild jaundice (serum concentrations of bilirubin up to 4 mg/dl). Although the pathologic basis of this finding is unclear, it is attributed either to edema and inflammation spread along the hepatoduodenal ligament resulting in functional disturbances of bile flow, or to direct compression of bile duct by the distended gallbladder. Concentrations of bilirubin of more than 4 mg/dl suggest a diagnosis of choledocholithiasis or Mirizzi's syndrome (compression of the common hepatic duct by an impacted gallstone in Hartmann's pouch) [13].

All patients with suspected acute cholecystitis should be referred to hospital. Acute cholecystitis in the majority of patients subsides spontaneously or responds to conservative frontline medical treatment. In approximately 10-20 percent of patients, acute cholecystitis progresses to the local complications of empyema formation with or without gangrene, or perforation with the formation of a pericholecystic abcess. Perforation most often occurs at the fundus of the gallbladder, in elderly patients having a history of cardiovascular disease, due to compromise of vascular supply [14]. Acute free perforation of the gallbladder and generalized biliary peritonitis is an uncommon complication. Features suggesting the presence of complications of acute cholecystitis include deterioration of the patient's condition (perpetual pain, persistent pyrexia/hyperpyrexia, leucocytosis exceeding 15,000 leucocytes/ml), signs of generalized peritonitis and imaging findings of emphysematous cholecystitis. Patients with free perforation of the inflamed gallbladder, usually develop peritonitis after a transient relief of their symptoms and seek medical attention after some delay. They need urgent surgical intervention, associated with a mortality of 30% [15]. Patients with localized perforation of gallbladder or empyema with or without gangrene need also emergency surgery, preferably laparoscopic cholecystectomy.

Localized perforation of the gallbladder rarely results in the formation of internal fistulae by adhesion and erosion of the other parts of gastrointestinal tract or extrahepatic bilary tree. Most common sites of cholecystoenteric fistulae are the adjacent duodenum and

less frequently the hepatic flexure of the colon. Perforation and evacuation of gallbladder septic contents into the intestinal lumen usually result to decompression of the gallbladder and resolution of cholecystitis. Diagnosis can be established preoperatively recognizing pneumobilia (air in the biliary tree) on plain abdominal radiographs, but most often, only intraoperative suspicion based on severe inflammatory findings and cholangiography can document the presence of such a pathologic communication.

A large gallstone dislodged to the duodenum may pass through the intestinal tract up to the terminal ileum where it can be impacted causing acute intestinal obstruction (gallstone ileus). The presence of pneumobilia, gallstones in uncommon sites and air-fluid levels on abdominal radiographs of elderly patients with no obvious cause for intestinal obstruction should raise a strong suspicion of gallstone ileus. It is interesting that most patients with gallstone ileus do not report a history of acute cholecystitis. The condition requires emergency surgery . High mortality (20%) is attributed either to delayed medical attention or to accompanying medical diseases.

Mirrizi's syndrome (fig. 12.1a, 12.1b) is a distinct clinical entity, representing the sequel of persistent or recurrent episodes of acute cholecystitis. The syndrome, described by Mirizzi in 1948, characterizes the presence of obstructive jaundice in patients with impacted gallstones in the Hartmann's pouch. Recurrent inflammation of the distended gallbladder results in the compression of the common hepatic duct by the tense Hartmann's pouch. Progressively, this may lead to erosion of the gallbladder and common hepatic duct wall by the impacted stone, resulting in the formation of a fistula. Diagnosis of the syndrome is based on the pre-operative evaluation of biliary tree by Endoscopic Retrograde Cholangiopancreatography (ERCP) in jaundiced patients. Although ERCP cannot often document the presence of a fistula, indirect signs (lateral filling gap of the common hepatic duct and central dilation of the biliary tree) establish a strong suspicion of the syndrome. Operative management of patients with Mirizzi's syndrome, especially if a fistula is present, is a real surgical challenge. Although successful attempts of laparoscopic management have been reported, conversion to laparotomy is most commonly required, with no less technical difficulties and significant mortality

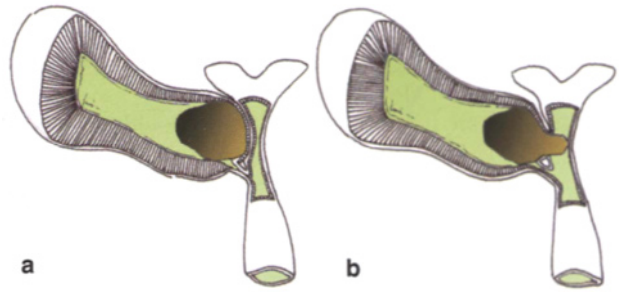

Fig. 12.1. Mirizzi's syndrome type I (a) and type II (b).

(see also about Mirizzi's syndrome in: Other Benign Biliary Diseases and Lesions).

12.2.3. Choledocholithiasis

Choledocholithiasis occurs either as a primary formation of stones in the CBD or migration of gallstones from the gallbladder through the cystic duct. Secondary choledocholithiasis is much more common, although there is an ongoing debate regarding the true incidence of common bile duct stones in patients with concurrent cholelithiasis. Migration to the CBD involves relatively small caliber stones and a dilated cystic duct. However, migratory stones into the CBD may subsequently enlarge as the result of deposition of pigments and debris on their surface. In this case, the stone receives the shape of duct but on section the small, hard, faceted calculus is recognized in its core. The origin of CBD stones is represented in their chemical composition. Migratory stones from the gallbladder are cholesterol stones composed mainly of cholesterol. Primary lithiasis of CBD necessitates the presence of one or more of the following factors predisposing the in situ formation of sludge as lithogenic core. As far back as 1923, Ascoff had recognized biliary stasis as the principal contributing factor resulting in the formation of "brownish yellow, 'earthy', soft, frequently laminated and easily crushed CBD stones". Presence of bacteria in the bile (bactibilia), increases bilirubin excretion (as in congenital hemolytic anaemias), with chemical imbalances also being predisposing factors of primary choledocholithiasis. Increased incidence of CBD stones among Asian populations is attributed to bile stasis and suppurative cholangitis caused by Ascaris lumbricoides and Clonorchis sinensis.

The incidence of choledocholithiasis among patients diagnosed with cholelithiasis ranges from 8-16 per cent, rising to 25-50 % in patients older than 60 years [16]. In autopsy series of individuals over 60 years of age who had died from unrelated causes, the incidence of CBD stones is approximately 1% [17]. The incidence is estimated to be even higher among Asian populations. The majority of individuals with CBD stones remain asymptomatic for unpredictable periods of time. During diagnostic workup and therapeutic management, the presence of silent hitherto CBD stones is revealed in 5-7% of patients with cholelithiasis. It is also well documented that CBD stones may remain silent (asymptomatic and unsuspected through LFTs and Ultrasonography) or may spontaneously pass through Vater's ampulla to the duodenum [16].

In symptomatic patients, CBD stones cause partial or complete obstruction of the biliary tract. Pain is the most common symptom; located in the right pper abdominal quadrant or the epigastrium, it is transient, intermittent, moderately severe and can also be accompanied by nausea and vomiting. The pain caused by CBD obstruction cannot be differentiated from biliary pain caused by stones in the gallbladder. The obstruction of the biliary tract results in the reflux of conjugated bilirubin to the bloodstream in proportion to the degree of obstruction. If the obstruction is significant, the patient becomes jaundiced dark-colored urine with or without clay-colored or light stools being reported in most patients. Pruritus usually accompanies longstanding jaundice and is more intense on the extremities. In the unjaundiced patient, raises levels of LFTs (especially of alkaline phosphatase and γ-glutidyltransferase of serum) and / or the dilation of CBD in Ultrasonography suggest a partial and intermitted obstruction. The increase in serum bilirubin which accompanies the pain caused by the obstruction rarely exceeds 10 mg/dl and returns to normal values when the obstruction is relieved. On the contrary, alkaline phosphatase and γ-GT levels may persist for many weeks after the relief of the obstruction.

In unjaundiced patients with choledocholithiasis, physical examination is usually unrevealing. The presence of right upper quadrant pain, jaundice and fever accompanied by chills (classic Charcot's triad) establishes the diagnosis of acute cholangitis and indicates the obstruction of the biliary tract (due to calculi or other causes) complicated by bacterial inflammation. The complete triad of symptoms is present in only 70% of cases, with fever being the most constant symptom (in 92% of patients) [18]. The severity of the attack ranges from a mild self-limiting illness to septic shock (observed in 5% of patients), and depends on the degree, the duration of the obstruction and the bacterial load. The clinical presentation of the Charcot's triad , along with septic shock and mental symptoms (apathy, confusion) indicates acute suppurative cholangitis and requires urgent decompression of CBD. The diagnosis is often missed despite the distinctive diagnostic pentad (Raynauld's pentad) because the manifestations of sepsis often overshadow those of biliary disease.

Imaging is difficult as ultrasonography and CT scan are insensitive to the search of stones in CBD [19]. MRCP and ERCP may be indicated depending on the centre's preference and experience regarding management of cholelithiasis with concurrent choledocholithiasis, availability of equipment and expertise, patient's clinical presentation and suspected underlying cause.

Complications of choledocholithiasis include acute gallstone pancreatitis, acute ascending cholangitis, biliary strictures and biliary fistulae. Long-standing ductal infection can produce intrahepatic abscesses, hepatic failure and secondary biliary cirrhosis.

12.2.4. Biliary Pancreatitis

The etiologic role of gallstones in the pathogenesis of acute pancreatitis was initially suggested by Opie, when he documented a gallstone impacted in Vater's ampulla during the autopsy of a patient who had died of pancreatitis. Among patients with gallstones, 4-8% will present acute pancreatitis. In patients with multiple calculi less than 3 mm in diameter (microlithiasis) the risk escalates to 30%.

Gallstones are responsible for 50% of all cases of pancreatitis. Most patients with gallstone pancreatitis have a mild clinical course and laparoscopic cholecystectomy has been proved safe and cost-effective in these patients when performed during their initial admission, after clinical resolution and normalization of liver function tests [20]. This approach has gradually replaced delayed cholecystectomy (up to 8 weeks after the acute episode) in the majority of patients with mild

pancreatitis, eliminating the need for a second hospitalization and the risk (as high as 35-61% during the following three months) of a recurrent attack [21].

12.3. Preoperative Management of Gallstone Disease

Assessment of the patient's general condition and anesthesia risk factors is crucial to the perioperative management of the patient. Equally important for the patient with gallstones is the attribution of atypical symptoms to gallstones or other possible causes, as they tend to persist after cholecystectomy.

Prior to surgery, all candidates for laparoscopic cholecystectomy should be thoroughly informed about the operation and its potential complications. It is important to make clear that while every effort will be made to perform the procedure laparoscopically, it cannot be guaranteed, and the decision to convert to laparotomy must be left to the surgeon, at the time of surgery. The patient should also be informed about the results of preoperative investigations and possible suspicion of concurrent choledocholithiasis. If operative cholangiography is to be performed, alternative options regarding exploration of the common bile duct (CBD) and postoperative ERCP should be discussed in detail. The patient should also be told about the expected speediness of recovery and both the patient and relatives should be reassured that early mobilization is both beneficial and encouraged. Overprotective environments tend to delay the patient's recovery and their return to normal activity.

It is highly recommended that every laparoscopic procedure be recorded on videotape or DVD format. As this valuable documentation contains long periods of irrelevant material, requiring lengthy explanation of no actual value to the patient, we do not encourage patient's access to copies of these video files.

The routine preoperative investigations have been completed, 1-2 days prior to surgery. The patient is admitted to hospital the same morning of surgery. After admission to the ward, the patient is shaved from nipples to well under the umbilicus. The patient is then asked to void urine immediately prior to surgery. Catheterization of the bladder at the beginning of operation is not recommended as duration of the operation rarely exceeds three hours and bladder is at risk only during the initial phase, when the Veress needle is blindly inserted into the peritoneal cavity.

Although the routine injection of low molecular weight heparin (LMWH) is under debate, its selective administration in high risk patients is widely accepted [22]. The use of antithrombotic stockings during surgery and early mobilization are highly recommended to all patients.

During introduction to anesthesia, we administer 2 gr. of a second generation cephalosporine intravenously. We routinely continue chemotherapy (cephalosporine in combination with metronidazole), only when (a) acute cholecystitis is present (b) immunosuppresion is present, or (c) spillage of bile and/or stones occurred during the operation.

12.3.1. Non-Operative Treatment for Gallstones

Admirand and Small documented the relevance of cholesterol saturation to cholesterol gallstone disease, in 1968, implying that supersaturation of bile with bile acids would succeed in dissolving cholesterol stones. Gallstone resolution with chenodeoxycholic acid was first reported in 1972, and since then, many further studies have confirmed the therapeutic effect of the naturally occurring substance of bile. However, results during the 1980's were quite disappointing. As Perissat mentions in an editorial devoted to Minimally Invasive Surgery "... hope was great, and so was the ensuing disappointment" [23]. The National Co-Operative Gallstone Study involving 916 selected patients receiving chenodeoxycholate for up to 2 years, revealed complete gallstone dissolution in only 13.5% of patients [24].

The only other agent with a conclusively documented efficacy in the dissolution of gallstones is ursodeoxycholic acid. The more expensive ursodeoxycholate is given in a lower dose, causes fewer side effects (mainly diarrhea) and does not increase low-density lipoprotein [25]. In a recent study involving 154 selected symptomatic patients, no substantial difference in efficacy was noted between combined chenodeoxycholic acid with ursodeoxycholic acid and ursodeoxycholic acid alone. The mean dissolution rate after one year treatment was 59% [26].

Pre-requisites for the dissolution treatment are: (1)

radiolucent stones, (2) stones no greater than 20 mm in diameter (3) a functioning gallbladder. Among patients with symptomatic cholelithiasis, only a small percentage (3-25%) would benefit from bile acid therapy and up to 50% of those patients with proven dissolution, can expect a recurrence of gallstones, during the next five years. At present, bile acid therapy is indicated only for patients unfit or unwilling to undergo surgery [27].

After the disappointment of dissolution treatment and the successful application of Extracorporeal Shock Wave Lithotripsy (ESWL) in Urology, there was in the mid 1980' saw an interest in the use of lithotripsy in gallstone management. ESWL shatters the stone into small fragments that can either be dissolved more quickly using dissolution treatment with ursodeoxycholate or may pass spontaneously into the intestine. Analysis of stone fragments in the feces of patients who had undergone ESWL showed that 3 mm fragments can pass to the intestine without causing symptoms.

The largest published study (711 patients) of ESWL combined with ursodeoxycholate therapy confirmed that 68% and 84% of patients with radiolucent solitary gallstones less than 20 mm in diameter, were stone free 6 and 12 months respectively after treatment [28]. Another study, demonstrated that following successful therapy of ESWL combined with bile acid, stone recurrence was reported to be 7% after 1 year increasing to 31% at 5 years [29]. The ESWL procedure requires administration of propofol anaesthesia i.v., on an outpatient basis. Complications are minimal (petechiae, transient hematuria, liver hematoma) but almost half of the patients experience one or more episodes of biliary pain. Furthermore, biliary pancreatitis can develop in 1-2% of the patients. Urgent or elective cholecystectomy has to be performed in 3-7% of patients.

Dissolution and ESWL treatment for gallstone disease are less cost-effective than laparoscopic cholecystectomy and should only be recommended in (1) elderly patients with symptomatic cholelithiasis unfit to receive general anesthesia and (2) patients with symptomatic cholelithiasis actively refusing to undergo operative treatment if they have noncalcified, solitary gallstones, no greater than 2 cm in diameter.

12.3.2. Operative Treatment for Gallstones

12.3.2.1. *Laparoscopic Cholecystectomy*

The treatment of symptomatic cholelithiasis has been operative since 1882 when Langenbuch performed the first successful cholecystectomy in Berlin. Today, laparoscopic cholecystectomy is the gold standard of treatment compared to the open procedure offering reduced hospital stay, rapid mobilization, excellent cosmesis, rare wound complications and rapid return to normal lifestyle.

In the early years of laparoscopic surgery, the media focused on this novel, minimally invasive technique with the aura of applied new technology in the operating room and widely promoted (along with companies actively involved in the production of the necessary equipment and instruments) this new concept among candidate patients [30]. However, almost concurrently, a tide of disastrous complications during LC was recorded, namely iatrogenic injuries of the CBD. Although the specific complication was not unknown in the era of open cholecystectomy (0.2-0.3%), its incidence in the early series of LCs was as high as 2.2% [31].

This early unacceptable incidence of CBD injury attributed either to inadequate training or to inherent difficulties relating to the nature of the procedure, motivated surgical societies to establish integrated laparoscopic curricula for the training of junior surgeons. Today, residents in surgery have minimal exposure to open cholecystectomy due to the fact that the majority of cholecystectomies are performed laparoscopically. In 1995, 90% of the cholecystectomies in USA were performed through the laparoscope and this percentage may be even higher in Western Europe.

Indications

During the 1990s, the number of cholecystectomies performed in USA and Europe has increased by 30%, although the indications for the removal of gallbladder had not changed. This paradox may be either the result of the lower threshold of patients (and possibly referring doctors) undergoing laparoscopic treatment or the result of a versatile application according to patient's needs.

Patients with Gallstones and Suggestive Symptoms

The presence of symptoms or complications of gallstones is the absolute indication of laparoscopic cholecystectomy. However, atypical dyspeptic symptoms (bloating, belching, abdominal discomfort and heartburn) are present in 50% of patients with cholelithiasis and should be explored carefully as they are probably unrelated to gallstones themselves and frequently persist after surgery.

Patients with Gallstones Without Symptoms

The majority of individuals (60-80%) with gallstones are asymptomatic at the time of diagnosis and most of them will remain asymptomatic during their lifetime [32]. Given the low relative risk of asymptomatic patients developing symptoms (2-4% per year) and the even lower relative risk of the first clinical manifestation of hitherto silent gallstones presenting complication, no specific treatment is indicated for asymptomatic patients [32]. However, decision analysis models support that prophylactic cholecystectomy in selected patient groups (such as asymptomatic young adults with cholelithiasis) prolongs life expectancy by more than three months. Although, according to the previous decision analysis models, all asymptomatic patients would benefit from prophylactic cholecystectomy as far as biliary pain and gallbladder carcinoma (1/1000 patients with gallstones per year) are concerned, adoption of such a policy would exhaust healthcare resources. Given the current CBD injury incidence, such an "open-to-all" policy is not justifiable.

Conclusively, prophylactic laparoscopic cholecystectomy in asymptomatic patients is not indicated except (a) in children and (b) in young women who are at increased risk of presenting symptoms during a future pregnancy. Elective laparoscopic cholecystectomy is also indicated in asymptomatic patients who are candidates for organ transplantation in order to avoid possible future biliary complications under immunosupression [32].

Patient groups with asymptomatic gallstones, at high risk of gallbladder carcinoma, would also benefit from prophylactic laparoscopic cholecystectomy:

(i) Patients with porcelanoid gallbladder: the estimated incidence of carcinoma is up to 25%.
(ii) Patients with stones greater than 3 cm in diameter, as they present a tenfold risk of malignancy compared with the general population of patients with gallstones.
(iii) Patients with gallstones and gallbladder polyps exceeding 10 mm in diameter. If the diameter of gallbladder polyp transcends 18 mm, open cholecystectomy is indicated because of the significant increase in gallbladder carcinoma incidence.
(iv) Patients with anomalous pancreatobiliary junction.
(v) Carriers of *Salmonella typhosa.*

Finally, candidates for laparoscopic cholecystectomy include asymptomatic patients living in remote areas, without standard access to healthcare services.

Patients Without Gallstones but with Suggestive Symptoms

Chronic acalculous cholecystitis is a heterogeneous clinical syndrome characterized by typical biliary attacks in patients without cholelithiasis. The clinical condition of patients between attacks is excellent. Possible causes of this syndrome include presence of biliary sludge into the gallbladder, presence of cholesterol crystals in the bile, and gallbladder motility disorders. Laparoscopic cholecystectomy improves the clinical course of selected patients with gallbladder dyskinesia but the symptoms persist in more than 50% of the remaining patients [34]. Detailed selection of patients is based on motility studies of gallbladder cholecystokinin cholecystoscintigraphy) and a microscopic study of bile collected during ERCP.

Contraindications

The main absolute contraindication for LC is the poor condition of the patient not permitting administration of general anesthesia. Under these circumstances, open cholecystectomy is also contraindicated. If the anesthetic risk is unacceptably high, in patients with acute cholecystitis resistant to medical therapy, percutaneous cholecystostomy under local anaesthesia can control biliary sepsis.

A diagnosed or highly suspected gallbladder carcinoma in a patient with gallstones is yet another absolute contraindication for LC. However, it should be mentioned that localized gallbladder carcinoma is a rare malignancy most often diagnosed either intraoperatively or postoperatively, in the histopathological examination of the specimen.

Several contraindications to LC, widely accepted when the technique was originally introduced have either remained as such or have become primary indications for the specific procedure. For example, LC in patients with acute cholecystitis, jaundice, and obesity in whom the laparoscopic approach was initially contraindicated, turns out to be surprisingly easy, affording a smooth, uneventful recovery. Uncontrolled coagulopathy, and liver cirrhosis stage Child IV, are two of the few current contraindications for LC.

Technique [35]

The operative ports may be inserted in a variety of orders and positions. In our practice, two 10 mm ports are inserted across linea alba, at subumbilical and subxiphoid locations and two 5mm ports at subcostal area, across anterior axillary amd midclavicular lines. After an initial laparoscopy is carried out, the patient is rotated to the left and in deep anti-Trendelunburg position. The gallbladder is visualized and the fundus is grasped and pushed up to the right shoulder. Other forceps are used to grasp the Hartmann's pouch retracting it outwards to the anterior iliac spine. With the combined maneuver of grasping forceps the hepatocystic triangle is displayed vertically to optical axis (fig. 12.2).

Adhesion to the gallbladder can be detached by blunt dissection if slight or alternatively divided with scissors and diathermy. Once the Hartmann's pouch is separated from the adjacent organs, the peritoneum wall is opened, close to the gallbladder wall and for as long as is possible, on both sides (fig. 12.3). When the neck of the gallbladder is fully mobilized and the peritoneum has been opened, dissection of the cystic pedicle continues superficially, close to the gallbladder wall, through division of strands on and around the possible cystic duct. After the identification of the cystic duct, the dissection is continued with mobilization of its posterior aspect with fine pointed atraumatic graspers, avoiding accidental injury to cystic artery which may run quite closely.

If it is preferable to dissect the cystic artery early in the operation as it permits easier manipulation of cystic duct. If the artery is dissected close to gallbladder wall, the anterior and posterior branches have to be divided separately. The lymph node adjacent to cystic duct is a useful and relatively stable anatomical landmark which provides useful confirmation regarding the level of surgical dissection. The cystic artery is usually located behind the lymph node in close proximity to the posterior aspect of cystic duct.

Once the cystic artery and the cystic duct have been clearly dissected, they are both identified running across the window between the cystic duct and the liver (fig. 12.4). The surgeon confirms the identity of the mobilized structure, once certain that this duct is in direct continuity with the neck of the gallbladder. Should

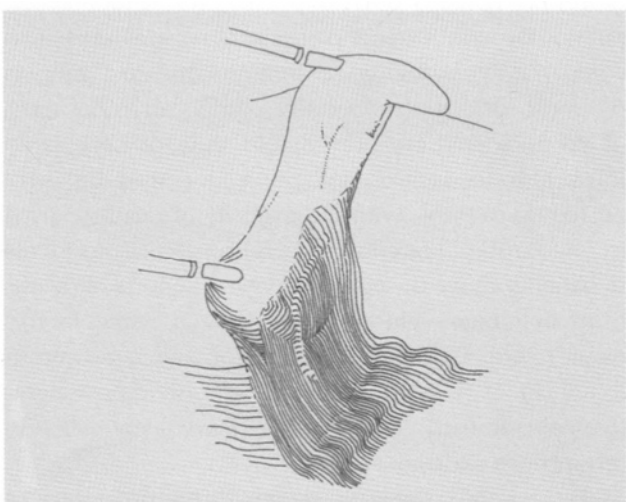

Fig. 12.2. The combined maneuver of grasping forceps expose the hepatocystic triangle to optical axis.

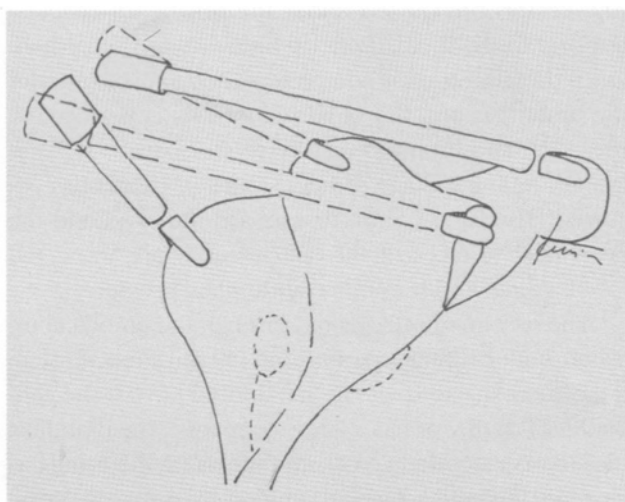

Fig. 12.3. The plane of surgical dissection is kept close to the gallbladder wall in both sides.

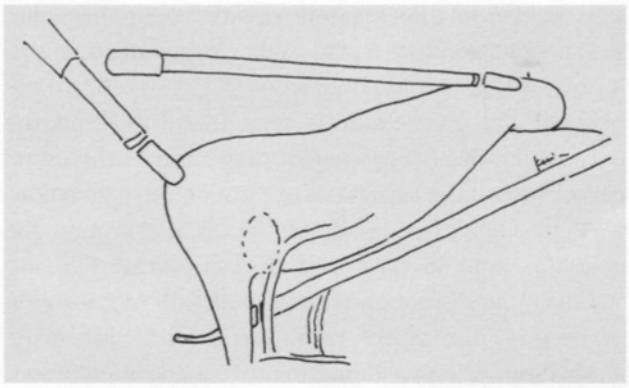

Fig. 12.4. The cystic duct and the cystic artery are safely identified as the only structures running across the window formed by the neck of the gallbladder and the liver.

there be any doubt, dissection continues towards the gallbladder. Only when the identity of cystic duct has been confirmed, are clips applied and the structures divided.

After clipping and division, the gallbladder is held on the stretch by the two grasping forceps, one in the fundus the other on the detached neck. The dissection of the gallbladder from the liver bed starts at the gallbladder neck and proceeds along a definite plane towards the fundus, keeping in the loose fibrous layer and avoiding injuries both to the gallbladder and liver parenchyma. The dissection is usually carried out with scissors applying diathermy and is straightforward in patients with a non-inflamed, functioning gallbladder. Any vessels recognized under the serosa are coagulated or clipped if small biliary branches are suspected. Once the dissection is complete, the organ is left under the umbilicus and thorough hemostasis is performed. Irrigation and drainage of subhepatic space is not necessary unless spillage of bile, stones or debris has occurred. The lateral 5mm trocars are removed and the peritoneal surfaces of the stab wounds are inspected for bleeding, under minimal abdominal pressure.

The specimen is extracted through the umbilical incision under direct laparoscopic visualization through the camera inserted via the subxiphoid port. If the gallbladder is bulky or has a large stone load, the umbilical incision is extended across midline using the canula as a protecting guide. Once the incision seems adequate, the gallbladder and the canula are removed en masse through the abdominal wall. The extension of umbilical incision does not have any adverse effect on the patient's recovery.

After the successful extraction of the specimen, the linea alba is closed and the pneumoperitoneum is restored under minimal abdominal pressure. The laparoscope is reinserted through the subxiphoid port and the liver bed, subhepatic space and peritoneal surfaces of all port sites are vigorously inspected. The camera is removed and the remaining subxiphoid trocar is used for abdominal desufflation and then gradually removed under direct vision to ensure that there is no abdominal wall bleeding. All the wounds are sutured using subcuticular absorbable sutures.

Results

Laparoscopic cholecystectomy was the first surgical procedure to gain wide acceptance among patients and doctors, for reasons quite different from improvement in morbidity and mortality. The dramatic reduction of postoperative pain and hospital stay (one day compared to 4-6 days for Open Cholecystectomy, OC), the rapid return to normal activity (1-2 weeks instead of 4-6 weeks for OC) and the minimal intervention o lifestyle were initially appreciated more by patients than physicians. Surgeons were principally focused on securing these advantages combined with the safety and effectiveness achieved after more than a century of experience with open cholecystectomy.

In published series of patients undergoing LC, morbidity ranges from 1.6 to 10% [10]. Undoubtedly, pulmonary and wound complications are much less compared to open surgery. Common bile duct injury is the most serious postoperative complication but most of the incidents are preventable and not necessarily inherent to the laparoscopic procedure. Mortality is reported up to 0.1%, with the majority of deaths caused by myocardial infarction or cerebrovascular accidents in patients above the age of 65 years. Reports of deaths from pulmonary embolism have been rising in frequency. Although early mobilization and rapid return to full activity is encouraged by diminished postoperative pain, an early discharge may leave silent calf vein thromboses undiagnosed.

Laparoscopic cholecystectomy is the procedure of choice for the vast majority of candidates for cholecystectomy. However, in 2-5% of them, the laparoscopic

procedure is converted to laparotomy [10]. Conversion may be either forced due to intraoperative bleeding or other iatrogenic complication (intestinal, common bile duct injury) or elective when the surgeon encounters an unacceptable risk in proceeding with dissection at the hepatocystic triangle due to inflammatory tissue changes.

Complications

Common Bile Duct Injury (CBDI)

Iatrogenic injury of biliary tree is the least frequent complication but it is often described as a real catastrophe (fig. 12.5a, b, c, d). The incidence of CBDI ranges in most published series from 0.36 to 0.47%, which is considerably higher than its historic incidence in published series of open cholecystectomy (0.19-0.29%) [10]. Moreover, it is widely accepted that the above incidence figure is likely to be underestimated since up to 30% of injuries manifest months or even years after the operation. The prognosis of CBDI, often dramatically compared to that of malignant disease, is shaped by frequent re-operations, long stenting of CBD, long hospitalization, and mortality as high as 10%.

Based on our personal experience [35], of more than 5000 successful LCs without CBDI, we believe that this specific complication does not represent an unavoidable adverse effect.

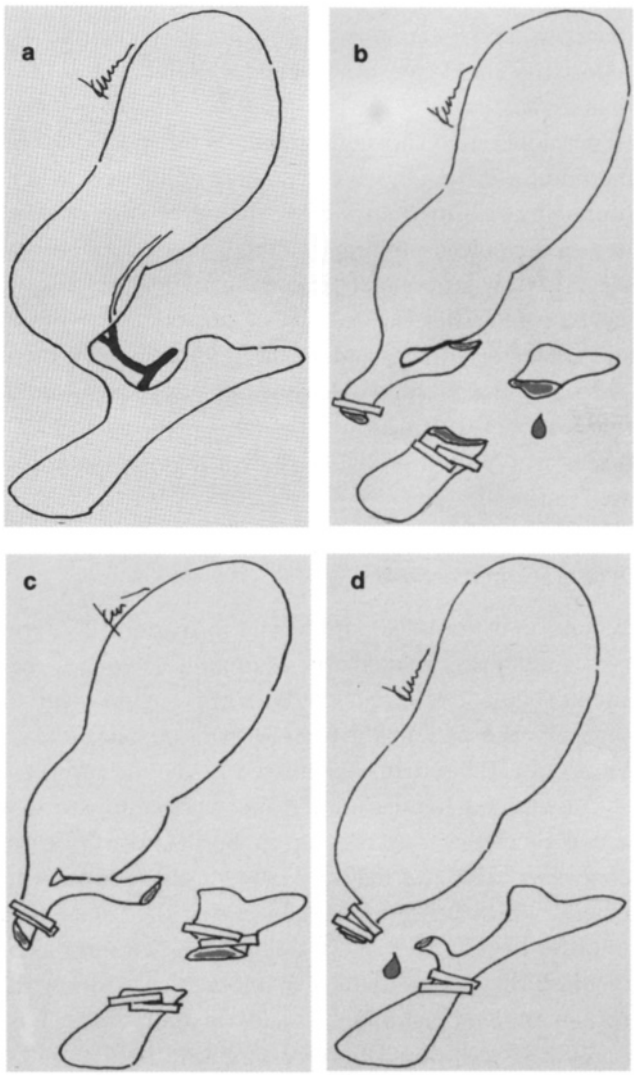

Fig. 12.5. Normal anatomy (a) and common patterns of common bile duct injury (b, c, d) during laparoscopic cholecystectomy.

Bleeding

Intraoperative hemorrhage occurs either during dissection of the cystic pedicle or when the gallbladder is dissected off the liver and is the commonest cause for enforced conversion to laparotomy (1-2%). In most cases, laparoscopic control of the bleeding is achieved if visual access to the operative field is maintained, grasping the spurting vessel or compressing the bleeding liver parenchyma. Blind clamping or aggressive electrocoagulation must be avoided at all costs.

Postoperative hemorrhage is most commonly due to either liver lacerations or the peritoneal surfaces of port sites. If the bleeding requires surgical intervention, re-laparoscopy is often adequate for providing prompt identification and control of the bleeding point.

Bile Leakage

Postoperative bile leakage is the commonest (0.5-2%) complication of LC requiring prolongation of hospital stay. It is presented either early as bile drainage through the tube placed intraoperatively, or later as bile collection in subhepatic space, often several days after patient's discharge. In the latter case, percutaneous guided catheterization of the bile collection is required.

The severity, prognosis and treatment of this complication depends on the extravasation site along the biliary tree. Possible sites and causes include (a) iatrogenic common bile duct injury, (b) the slipping of the cystic duct stump clips, and (c) injury of the intrahepatic biliary duct during dissection of the gallbladder off

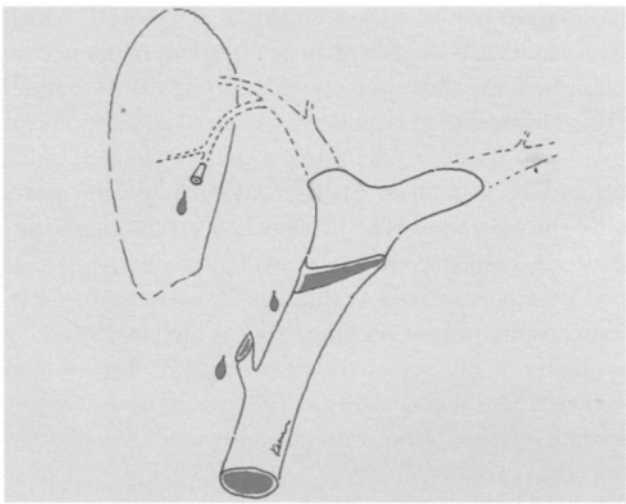

Fig. 12.6. Possible bile extravasation sites in patient with postoperative bile leakage: common bile duct injury (a), cystic duct stump (b), accessory bile duct (c).

the liver bed (fig. 12.6). All postoperative bile leakages require investigation, especially when the leakage persists for more than three days or the daily output is more than 500 ml ("major bile leak") [36]. The principal aims of investigation are (a) the precise identification of bile extravasation site and (b) the exclusion of common bile duct injury. This can only be achieved by ERC. Should a CBD injury be recognized, it warrants further treatment which is discussed in the next Chapter. Having established CBD integrity and recognized precisely the extravasation site, endoscopic stenting of common bile duct injury usually results to in resolution. If the bile extravasates through cystic duct stump, laparoscopic ligation of the stump is an alternate option preferred by some authors.

Retained CBD Stones

Retained stones are gallstones diagnosed during the first two years after cholecystectomy or common bile duct exploration. However, it is not uncommon for undiagnosed silent common bile duct stones to present symptoms several years after cholecystectomy. The incidence of retained stones in patients undergoing LC is less than 0.5%, regadless of the adopted policy for the diagnosis and treatment of concurrent silent CBD stones in patients with cholelithiasis.

Preoperative ERCP or MRCP in patients with cholelithiasis on the basis of suggestive criteria (history of jaundice, history of cholangitis, history of gallstone pancreatitis, abnormal Liver Function Tests – LFTs, CBD more than 8mm in caliber in Ultrasonography) reveals CBD stones in 50-60% of patients with symptomatic cholelithiasis. Endoscopic sphincterotomy achieves stone removal in most of cases (85-90%) and LC can be performed safely 24-48 hours later. However, 2-5% of patients with cholelithiasis have concurrent CBD stones without any clinical, chemical or sonographic evidence, missed during preoperative cholangiography. Subsequently, the expected rate of retained CBD stones is 2-5%. However, most silent CBD stones either remain asymptomatic for a long time or pass through to the duodenum spontaneously. In most published series, authors adopting such a policy for the diagnosis and treatment of concurrent cholelithiasis, report the incidence of retained CBD stones at less than 0.5%.

Intraoperative cholangiography is the most reliable method for the diagnosis of choledocholithaisis. When routinely performed during LC, the percentage of false negative results is minimal. Removal of CBD stones diagnosed by intraoperative cholangiography either by laparoscopic CBD exploration or postoperative ERCP and sphincterotomy could result in virtually zero incidence of retained stones. However, this approach would lead to over-treatment of patients with silent CBD stones who would probably remain asymptomatic for their entire life.

Wound Complications

Wound infection (1%) and hernia formation (2%) are rare and mostly related to the umbilical wound, the site of gallbladder extraction. Both of them are diagnosed after the patient's discharge from hospital and it seems likely that many are missed hence the previously mentioned figures may in fact underestimate the actual incidence rate. As far as hernia formation is concerned, the vast majority present at the umbilical wound which is often enlarged during the procedure in order to remove a bulky gallbladder. We must also mention that a considerable number of patients with cholelithiasis (fat, fertile, females in their forties) is also a high risk population for umbilical hernia development.

Intraoperative Cholangiography

The debate regarding the use of Intraoperative Cholangiography (IOC) during cholecystectomy has first begun in 1936, when Mirizzi introduced IOC. Controversy has grown with the advent of laparoscopic cholecystectomy and opinion remains divided concerning the routine, selective or not at all use of IOC.

The principal arguments for routine IOC, during laparoscopic cholecystectomy, are that it both provides an accurate anatomical map of the biliary tree at the time most needed and reveals silent common bile duct stones [37]. Although routine use of IOC does not necessarily prevent common bile duct injuries, it is widely accepted that it diminishes both the incidence and the severity of these injuries [37]. Furthermore, it is more probable for such an injury to be diagnosed intraoperatively if a routine cholangiography is obtained, thereby improving the overall prognosis of the patient.

The discovery of preoperatively unsuspected common bile duct stones (5-7%) in routine IOC requires ductal clearance either through the cystic duct or common bile duct exploration. Some authors suggest that patients with detected small, silent, CBD calculi, less than 5mm in caliber, and confirmed free flow of bile to duodenum, may be either referred to postoperative ERCP or treated conservatively. This policy has not been widely accepted. Although laparoscopic or endoscopic clearance of common bile duct in all patients with intraoperatively diagnosed silent stones seems an unnecessary treatment for those who will remain asymptomatic, the risk of a subsequent cholangitis or pancreatitis justifies the invasive approach, at least in patients with a significant life expectancy.

Selective use of IOC provides the advantages of the "road map" when most needed in specific circumstances, namely during difficult LCs. However, the majority of common bile duct injuries occur during "easy" procedures, when the surgeon is erroneously confident about the interpretation of the anatomy. On the other hand, selective use of IOC can overlook silent common bile duct stones since there is no preoperative or intraoperative sign of their presence which could indicate IOC performance. Moreover, the advantages of IOC are most obtained when the operative team has acquired significant experience which predisposes its routine use.

Technique

There are two techniques of laparoscopic cholangiography: cystic duct catheterization and cholecystocholangiography, both of which require a modern, mobile, C-arm image intensifier. The cystic duct catheterization is the method of choice as cholecystocholangiography is not feasible in the gallbladder's outlet obstruction and in shrunken, fibrotic gallbladders. Moreover, it carries the risk of flushing small calculi into the common bile duct.

The catheterization of the cystic duct is attempted when sufficient length of the duct has been dissected. A clip is applied at the distal end, close to the neck of the gallbladder, and a small incision is performed at the anterior surface. The gentle dilation of the opening permits the introduction of a cholangiography catheter over a distance of 1 cm. A clip is applied at the cystic duct to affix the catheter, avoiding complete obstruction of its lumen. Ensuring that are no air bubbles in the delivery system, the contrast is infused slowly and the ductal filling is observed. The whole intrahepatic and extrahepatic biliary tree should be outlined. On completion of cholangiography the catheter is withdrawn and the clip is gently removed. The proximal end of the cystic duct is either secured with metal clips or ligated and the duct is divided.

12.3.2.2. *The Difficult Laparoscopic Cholecystectomy*

Difficult Induction of Pneumoperitoneum Due to Adhesions

Periumbilical intraperitoneal adhesions from previous surgical interventions pose a significant risk of visceral injury if blind insertion of the Veress needle is attempted for the establishment of the pneumoperitoneum. When the possibility of significant adhesions is high, we recommend insertion of the initial trocar of subumbilical port under direct vision with the open technique. Preoperative or intraoperative mapping of intraperitoneal adhesions using ultrasonography is another option. We prefer "open" access to the peritoneal cavity through the subumbilical incision, not having ever experienced failure or intestinal injury. When the peritoneum is identified and incised, a minimal space for the initial trocar is created using blunt finger dissection. When the port is inserted, through the in-

cision temporally closed with a purse-string suture, the laparoscope is used as a dissection instrument extending through the available space towards the right subcostal area. In the presence of dense adhesions obstructing safe access, we insert a second trocar, away from the site, for laparoscopic division of adhesions.

In most patients with dense periumbilical adhesions, the subhepatic space is free and an uneventful LC can be performed. Despite the use of an additional port or/and the longer duration of the procedure, the overall safety is unquestionable and the patient gains the advantages of minimally invasive surgery [38].

Exposure Difficulties

The exposure of the hepatocystic triangle to the optical axis may be difficult due either to liver size and gross anatomy or to gallbladder pathology. More often, a floppy left lobe or an enlarged quadrate lobe obstruct both optical access and movement of the instrument inserted through the subxiphoid port. Only rarely is the introduction of a retractor through an additional port required. Rotating the patient in deep anti-Trendelenburg position and mobilization of peritoneum around the gallbladder neck are usually adequate measures.

In patients with liver cirrhosis or chronic hepatitis, manipulation of the gallbladder may prove extremely difficult and risky, since the firm nodular liver resists upward lift and possible tears in the liver parenchyma could result in major bleeding. Under these circumstances, there are no guidelines accommodating the encountered difficulties and the endoscopic surgeon should proceed with a low threshold for conversion to laparotomy.

The tense, distended gallbladder often encountered in patients with acute cholecystitis may be difficult to grasp. Using the Veress needle attached to the suction, the percutaneous decompression of the distended gallbladder improves grasping and manipulation. The paracentesis is performed at the fundus of the gallbladder and the small perforation does not usually leak (fig. 12.7). Otherwise, it is secured using self-holding grasping forceps.

Difficulties Due to Abnormal Anatomy

Congenital variations of extrahepatic biliary tract are quite common and are schematically presented in fig. 12.8. The possible configurations of cystic duct entry to the common hepatic duct include termination of the cystic duct on (a) the posterior wall, (b) the medial aspect or (c) the lower part of the common hepatic duct after running a long parallel course. Entry of a short cystic duct into the right hepatic duct is also reported. Although all these variations can be demonstrated using intraoperative cholangiography,

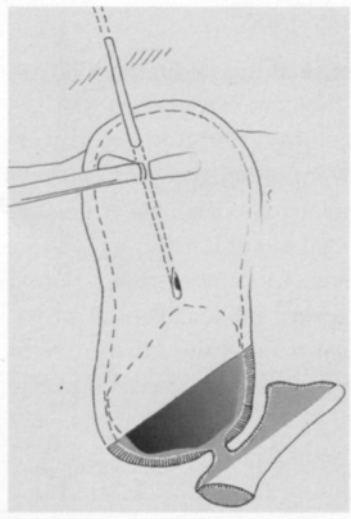

Fig. 12.7. Decompression of the distended gallbladder using the Veress needle.

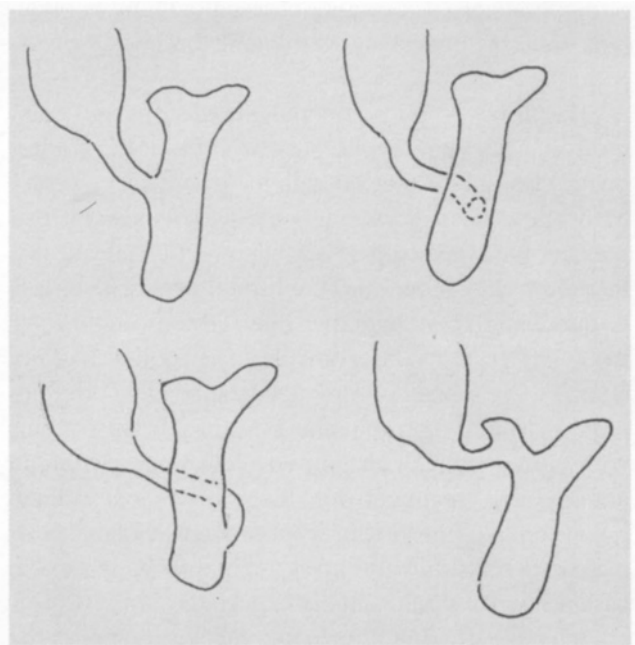

Fig. 12.8. a, b, c, d. Common variations of the cystic duct entry to the extrahepatic biliary tree.

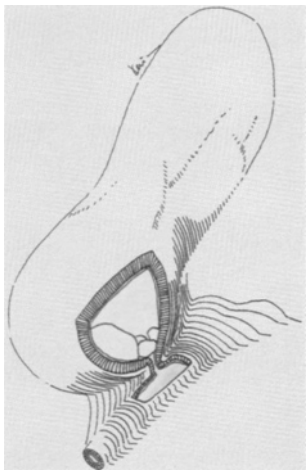

Fig. 12.9. Short cystic duct due to chronic calculous disease.

they do not pose significant difficulties during the dissection of cystic triangle providing the dissection plane is kept close to the gallbladder wall. In point of fact, if intraoperative cholangiography is not performed routinely during LC, most of these variations remain unnoticed and consequently do not burden the surgeon's attempt to recognize cystic duct in its junction with the gallbladder neck.

The presence of a short cystic duct, which is more often secondary to chronic calculous disease (fig. 12.9) rather than congenital abnormality, may pose difficulties in providing sufficient length for clip application. We do not hesitate to divide the short cystic duct at its junction with the gallbladder after securing clips medially; the gallbladder stump remains open and is grasped with forceps. Usually, the presence of a short cystic duct accompanies a large stone impacted in Hartmann's pouch, obstructing bile leakage through the unclipped opening. If the cystic duct is so short that even clips cannot be safely applied medially, the duct is divided at the gallbladder's curve and the stump ligated using endoscopic loop suture. In the presence of a short cystic duct, great care is required during manipulation of the gallbladder in order to avoid bringing the cystic duct in line with the common or right hepatic duct which could result in an erratic perception of the hepatic duct as its continuation, with disastrous consequences.

Variations of the cystic artery are also common. The cystic artery may run anteriorly to the gallbladder requiring early clipping and division in order to provide adequate exposure of the cystic duct. When the cystic artery runs in close proximity to the cystic duct, great care is needed in order to avoid bleeding during dissection. A short cystic artery which usually accompanies the looped right hepatic artery is clipped and divided on the gallbladder wall and the right hepatic artery is teased gently away. As our standard practice is to keep the plane of laparoscopic dissection on the gallbladder wall, we often locate a small cystic artery near the hepatic parenchyma, behind the cystic duct and the neck of the gallbladder. This is actually the medial branch of the cystic artery and careful dissection of the neck laterally permits recognition, clipping and division of another lateral branch. We do not proceed to the detachment of the gallbladder if both branches have not been recognized and secured.

Difficulties Due to Inflammatory Changes in Hepatocystic Triangle

The difficulties often encountered in patients with acute cholecystitis are represented in the increased conversion rate which accompanies non-elective LCs. Adhesions of the omentum and duodenum to the gallbladder may be so extended that even recognition of the gallbladder may be difficult (fig. 12.10). Usually, during the acute phase of inflammation, these adhesions are loose and are easily separated either by blunt dissection or by scissors and gentle electrocoagulation. As the dissection proceeds, the exposure of the hepatocystic triangle may also be difficult. The impacted gallstones may cause extensive distention of the Hart-

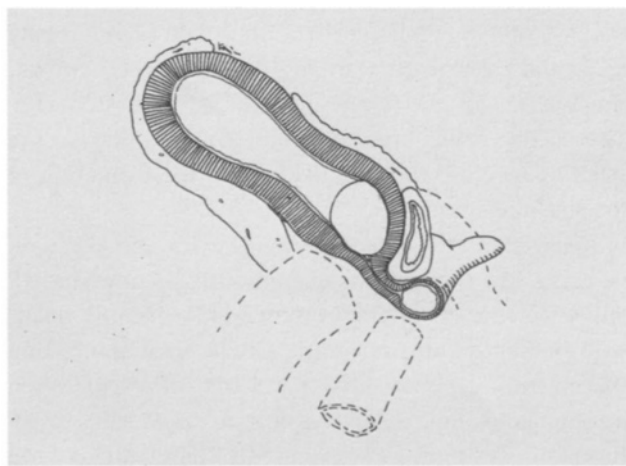

Fig. 12.10. Typical inflammatory changes in patients with acute cholecystitis.

mann's pouch often adhering to the hepatoduodenal ligament. Under such circumstances, grasping of the pouch may be impossible and the open jaws of the forceps are used as a retractor, pushing the gallbladder upwards. As the dissection around the neck of the gallbladder proceeds, manipulation of the pouch becomes less difficult and gradually permits access to the hepatocystic triangle.

Inflammatory adhesions during the early phase of acute cholecystitis are usually loose and the blunt dissection is quite effective in both identification of the cystic duct and removal of the gallbladder from the liver bed. The plane of dissection is always kept close to the gallbladder wall following the curve of the distended Hartmann's pouch. The dissection should be quite easy in patients with hydrop, when the tissue edema signifies the correct plane. On the other hand, when the time interval from the onset of symptoms of acute cholecystitis is more than a week, the adhesions may be dense, thereby obscuring the planes of surgical dissection. We find hydro-dissection quite useful in such cases and we often succeed in recognizing the optimal path despite the obvious risk.

In patients with a strong suspicion of cholecystocholedochal fistula (Mirrizzi syndrome - type II, fig. 12.1b), any attempt either to separate the gallbladder from the CBD or to dissect the fistula is hazardous, irrespective of the surgeon's experience, and conversion to laparotomy is indicated. However, this syndrome is rare and the intraoperative diagnosis quite doubtful in the unjaundiced patient.

Recurrent attacks of cholecystitis may result in contraction of the gallbladder. The shrunken organ usually has a full stone load, partially buried in the liver parenchyma and the cystic pedicle is shortened (fig. 12.11). The difficulties encountered relate both to the inability to grasp the gallbladder and the dissection of the shrunken cystic duct.

Conversion to laparotomy is always a safe alternative and a low threshold is unanimously recommended. However, the specific recommendation seems relatively ineffective in preventing CBDIs. It is interesting that in most series of LCs, high CBDI incidence often accompanies high conversion rate and vice versa. Probably, decision to conversion often creates a false feeling of control over the surgical field and the illusion that it is itself adequate for a successful solution.

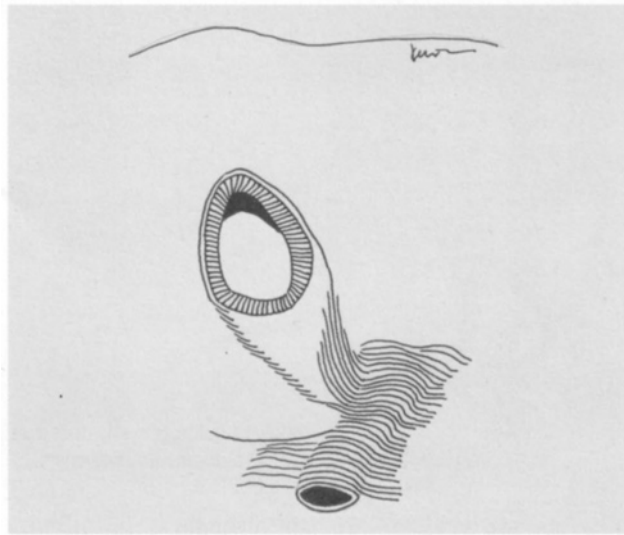

Fig. 12.11. Shrunken gallbladder due to recurrent attacks of cholecystitis.

In this situation, a decrease in vigilance leads to an unsurprisingly high incidence of CBDI during converted LCs. The indication to conversion is clear and time-independent: whenever perceived information mining by the operative field is inadequate and at risk of violating a concrete established theory of the area's anatomy, we convert the laparoscopic procedure to laparotomy. If laparoscopic dissection proceeds in the line with information mining, without violations and despite slowness, we virtually lose no time.

Analyzing operative performance during laparoscopic cholecystectomy on the basis of cognitive psychology, we identified seven critical points for the establishment of safety during LC:

I. *Preoccupation with Failure*

All members of the surgical team must be circumspective in their interpretations and avoid the obvious by reminding themselves of two things: (a) we have not yet experienced all potential failure modes that could occur during LC, and (b) we have not yet deduced all potential failure modes that could occur during LC.

II. *Team Work*

Safety is not inherent to one person, device or department, but results from the interactions of a system and its components.

III. *Error Traps and Reversible Procedures*

Error detection techniques, incorporated in operational flow, are significant tools for error reduction during LC: (i) standard checks after the completion of every surgical task searching for visible consequences of possible errors, (ii) direct-error hypotheses formation and (iii) error suspicion. It is interesting that only negative evaluation is fruitful during error detection, in LC. Positive confirmation is often biased and is not effective for the recognition of possible errors.

IV. *Adherence to the Procedures*

Observing procedures is a difficult to attain principle, especially when observance is not rewarded and violations are not always punished by the adverse effect.

V. *"Stop off" Rules*

There is no absolute rule which if applied would relieve the surgeon from the stress of a laborious identification of the cystic duct. There is no gold standard technique (procedures, skills or rules) that would guarantee safety providing the surgeon strictly adherent to it.

VI. *Conversion to Laparotomy*

The perspective of conversion relieves the surgeon from the stress of a demanding laparoscopic problem but does not solve the surgical problem. Decision to conversion often creates a false feeling of control over the surgical field and the illusion that it is itself adequate for a successful solution. Under these circumstances, decrease of awareness leads to an unsurprisingly high incidence of CBDI during converted LCs.

VII. *Crew Resource Management*

In aviation, Crew Resource Management (CRM) addresses the nature of human error and teaches behavior as error countermeasures, such as leadership, briefings, monitoring and cross-checking, decision making, and review and modification of plans. The application of CRM to surgical training does seem to make sense and researchers have already devoted significant energy to interventions with CRM-type team training programs, primarily in the emergency room setting.

12.3.2.3. *Open Cholecystectomy*

Open Cholecystectomy can be performed through either a right subcostal (Kocher) incision or an upper midline or right paramedian incision. The Hartmann's pouch is pushed laterally, the peritoneum incised and the cystic duct recognized in its junction with the common hepatic duct. If the anatomy is unclear, especially during converted laparoscopic procedures, the gallbladder can be dissected from the fundus downwards toward the gallbladder neck. When the gallbladder has been fully mobilized, identification of the cystic duct and artery is easy in the pedicle remained attached to the hepatoduodenal ligament. If the presence of a short cystic imposes conversion, it can be safely ligated proximally and divided.

Postoperatively, a nasogastric tube remains until signs of bowel movement are present. Usually, the patient can tolerate fluid intake the second postoperative day. Early mobilization is encouraged and requires systemic administration of analgesics (NSAIDs and opioids). Pulmonary physiotherapy is also indicated during the first and second postoperative day especially in patients with chronic obstructive pulmonary disease or in patients who undergo a converted procedure of long duration.

Normally, the patient is discharged from hospital the 4th-5th postoperative day and can return to full activity 2-3 weeks later.

12.3.2.4. *Cholecystostomy*

Percutaneous or open cholecystostomy is a life-saving procedure performed either as an emergency procedure in patients with an unacceptable and extreme anesthetic risk or as a safe bridge to the second-stage elective cholecystectomy when safe resection the of gallbladder presents unusual technical difficulties in the first encounter.

Acute cholecystitis in high risk surgical patients has a mortality rate calculated to range from 18.2% to 77.6% for American Society of Anesthesiologists (ASA) class 3 and 4, respectively [39]. Mortality rates up to 67% have been documented particularly in cases of acute acalculous cholecystitis commonly associated with critical illness and recovery from major surgical procedures, whether percutaneous decompression of the inflamed gallbladder, avoiding the use of general

anesthesia, can effectively manage biliary sepsis in critically ill patients, remains unproven. There is no solid evidence that percutaneous cholecystostomy is a better treatment of acute cholecystitis in high-risk patients, than laparoscopic cholecystectomy. In two recent studies, the 30-day mortality of high risk patients who underwent percutaneous cholecystostomy was 13.8% and 36% respectively [40, 41]. Furthermore, there are two major disadvantages of the drainage procedure: (1) there is no confirmation of the diagnosis in patients with sepsis of uncertain origin, even when a clinical response is recorded and (2) gangrenous changes of the gallbladder wall may result in subsequent bile leakage and generalized peritonitis.

It is currently accepted that in patients with acute cholecystitis from whom general anesthesia is contraindicated due to extreme toxicity or concurrent medical illness, percutaneous cholecystostomy is indicated. This group of patients is a sub-group of ASA 4 class. Diagnostic dilemmas and septic complications could be avoided through a bedside diagnostic laparoscopy and drain insertion with laparoscopic assistance.

An intraoperative decision to convert an initial attempted laparoscopic or an open cholecystectomy to cholecystostomy is indicated when unusually extreme technical difficulties make laparoscopic or open dissection of anatomic structures in hepatocystic triangle impossible or extremely difficult. An adequate incision at the gallbladder fundus permits evacuation of stones and inflammatory debris. Impacted stones in the neck of gallbladder or in cystic duct can be usually milked back to the gallbladder. After all contents have been evacuated, a Foley-catheter is inserted, the incision is closed through one or two purse-string sutures which then anchor the fundus to the parietal peritoneum (fig. 12.12). In patients with gangrenous cholecystitis, excision of the gangrenous distal part of the gallbladder and drainage of the remaining part (subtotal cholecystectomy) is recommended by some authors.

The cholecystostomy tube is brought out through a separate small stab incision. Exploratory cholangiography is performed a few days later, injecting contrast material through the tube, in search of residual stones and imaging of the biliary tree. The tube can be removed not earlier than the fourteenth postoperative day.

If cholangiography reveals residual stones in the gallbladder, a second-stage cholecystectomy is indicated as soon as the patient's condition permits surgery. Elderly patients, in poor general condition without prospects of improvement, with a clear cholangiography, should be left without further intervention. In younger, fit patients, an elective cholecystectomy is indicated as the majority of them will develop recurrent stones, 50% of them within three years of the cholecystostomy. Most patients with residual stones revealed in postoperative cholangiography, will develop symptoms within a few months.

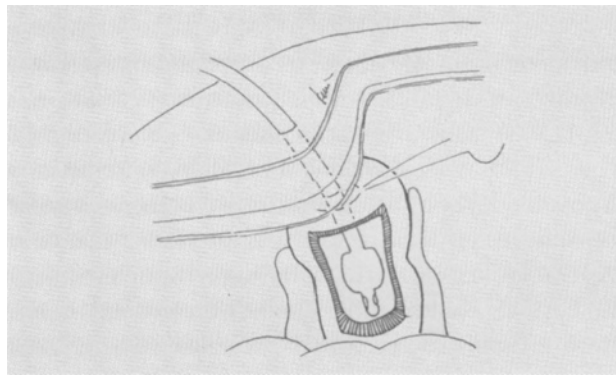

Fig. 12.12. Operative cholecystostomy.

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CHAPTER 13

COMPLICATIONS IN THE PERFORMANCE OF LAPAROSCOPIC CHOLECYSTECTOMY. WHAT CAN GO WRONG? HOW DO COMPLICATIONS HAVE TO BE MANAGED?

G. Quast, A. Kuthe

13.1. Introduction

The operative removal of the gallbladder is a standard and one of the most often performed procedures in general and visceral surgical hospital departments. The operation is indicated in cases of gallbladder stones creating disease symptoms and pain, in cases of acute infection of the gallbladder with or without stones and in cases of adenomatous structures in the gallbladder that may develop malignity [1, 2].

Nowadays more than 90% of the elective cholecystectomies are performed laparoscopically. The total amount of operations for Germany rose from almost 150.000 in 2002 to slightly over 170.000 in 2004 [1].

Without a doubt, operative therapy has to be judged as the method of choice in the treatment of symptomatic gall stone disease as opposed to conservative treatments. But though laparoscopic cholecystectomy has become the gold standard of treatment it does not preclude complications, whether major or minor.

13.2. The Perioperative Setting

As regards the several different ways of patient positioning on the operation table and the positioning of the surgeon performing the operation and his assistants, we recommend a setting where the patient is comfortably stretched out with the left arm extended and the monitor system is on the right patient side. The surgeon and his camera assistant who is basically the "eye" of the surgeon should stand on the left patient side in order to have the same viewing direction. Should there be a second assistant he should stand on the right patient side in order to fulfil his role which is mainly static, by lifting the gallbladder up from underneath the liver to expose the infundibulum.

13.3. The Use of Perioperative Prophylactic Antibiotics

The majority of hospitals adopt a protocol of perioperative antibiotic regimen mainly using cefazolin in order to prevent postoperative infectious complications such as infections of the gallbladder bed, intraabdominal abscesses and particularly surgical site infections. In addition, high-risk patients or patients hospitalized because of an acute cholecystitis are subjected to an aggressive antibiotic treatment prior to the operation [3].

Two studies dating back in 1998 and 2001 respectively came to the conclusion that, probably as a reflection on the perioperative antibiotic treatment, the overall rate of infective complications is negligible and does not correlate with the presence of bacteria in the bile or gallbladder wall [3, 4] and thus routine antibiotic prophylaxis might be questionable [4]. On the other hand it seems obvious that both open surgery and poor control of comorbidity –such as diabetes mellitus– can significantly increase the rate of surgical site infections [5, 6].

A recent prospective randomized study from Taiwan involving 277 patients, published in Jun 2006,

concludes that the use of prophylactic antibiotics in elective laparoscopic cholecystectomy is not recommended because they do not decrease the already-low rate of postoperative infectious complications [7].

In our personal experience where our patients had all received a perioperative antibiotic prophylaxis, we noted a very low infection rate of less than 1%. We believe that high-risk patients with co-morbidities, that tend to increase the risk of wound infections, should unquestionably receive antibiotics whereas patients with an acute cholecystitis should receive not only post-operative but also preoperative treatment with cefazolin and metronidazole. Furthermore we believe that reports related to low infection rates in laparoscopic surgery are, on the one hand, due to small incisions that are less susceptible to major problems but on the other hand also reflect the overall very common use of antibiotics. To cease the perioperative use of antibiotics in elective cholecystectomy totally would in our opinion, warrant a much larger prospective randomized study than those carried out so far.

13.4. The Approach to the Abdomen

In order to establish a pneumoperitoneum, the two main practices adopted include the Veress needle insertion technique as well as an open "mini-laparotomy" with consecutive direct trocar placement known for the positioning of the first trocar before the camera is able to enter the abdomen. In 1999, a study cited the following complications incurred by Veress needle insertion: injury of the omentum with consequential haemorrhage, intestinal and mesenteric injuries as well as injuries of the urinary bladder and the great blood vessels of the retroperitoneum. In addition the initial insufflation of CO2 through an inappropriately placed needle can create subcutaneous emphysema, mediastinal emphysema and pneumothorax [8].

A recent study in 2005, evaluating 274 laparoscopic cholecystectomies showed that the complication risk of performing pneumoperitoneum by direct trocar placement was less than that arising from needle usage and that direct trocar entrance also reduced operation time, thereby concluding that the direct trocar entrance method is a more reliable and less time consuming method than the Veress needle technique [9].

These findings concur with our personal experience of both techniques. A number of years ago we have switched from Veress needle to "mini-laparotomy" with direct trocar placement having also found that the placement of the first trocar "under view" is far safer than the Veress needle and also quicker. Thus, we strongly recommend resigning from Veress needle techniques and switching to the open technique in which layers of the abdominal wall are opened one after the other under view, until the first trocar can be placed and the pneumoperitoneum created.

To avoid further, and sometimes severe trocar placement complications with other trocars necessary for the operation, -such as injuries of the liver, spleen, stomach, intestines or the falciform-, we rigorously stress the significance of placement "under view". Whether operating in a three or four trocar technique the surgeon must predict the route trocars should take and follow their course. Any arising injuries of organs must be immediately addressed.

Trocar channel bleedings may stop during trocar placement which places a certain pressure on the bleeding vessel, but may also reoccur again during the operation due to movement of the trocar or at the end of the procedure due to removal of the trocar. It is important to identify such events which can be effectively dealt with via electrocoagulation or suture, such as the Reverdin's needle.

13.5. Bile Duct Injuries – Anatomy, Prevention Techniques, Treatment

After establishment of the pneumoperitoneum, placement of trocars and exposition of the infundibulum of the gallbladder, the operating surgeon is confronted with the well-known anatomic variability of the bile duct system. It is his duty to clearly identify structures such as cystic duct and ductus hepatocholedochus in order to avoid injuries. It is not rare for a kinking of the ductus hepatocholedochus to cause the duct to get very close to the gallbladder. On the other hand, the length of the cystic duct can vary a lot as can its direction in relation to the arterial system and its junction with the common duct can.

Our experience concludes that a very clear identification of the whole cystic duct and its junction with

common bile duct is necessary. These identifications are, in our opinion only possible, with the use of a 30° optic system that not only affords the surgeon the opportunity of inspecting important structures but also allows a close three-dimensional view of the rather large cavity of this particular type of operation. We most definitely do not recommend a straight optic system due to the lack of view on the sides or behind vascular or ductal structures.

Whilst on the subject of the use of the camera system, we also found that better identification of the cystic duct on the one hand and the common bile duct on the other is easier when the gallbladder is exposed in a slightly lifted camera direction rather than directed towards the liver or barely risen in the direction of the abdominal wall.

Several description and classification systems (such as Strasberg or Sievert) categorise bile duct injuries as mild i.e. injuries of a smaller bile duct, incomplete cystic duct occlusion, partial or lateral injury of greater ducts or severe i.e injuries of choledochus duct or hepatic duct. Bile duct injuries must be viewed as potentially very severe complications bearing high morbidity, probable long-term hospitalization, disease chronification and possibly life threatening [8].

A review of the publications from 1999 to 2006 shows that the percentage of described bile duct injuries varies between 0.2% and 0.7% [10, 11, 12, 13, 14, 15]. In 2001 a Germany study reported a significant increase in common bile duct injuries from 1991 to 1994 of 0.3% to 0.7%, decreasing to 0.2% in 1995 and 1996 in an analysis that included 28,753 operations [13].

In line with the afore mentioned need for clear structure identification, it is widely accepted that not only is correct interpretation of the anatomy and very careful dissection exceptional crucial [16] but working with electrocoagulation or harmonic scalpel close to sensitive and as yet unidentified structures must also be avoided.

Several recent studies stress the importance of intraoperative cholangiography (IOC) [16, 17, 18]. In another 2001 study in Germany, this technique was highlighted as being the most strongly recommended approach for intraoperative diagnostics, yet was routine practice in only 6% of the hospitals that performed laparoscopic cholecystectomy [17].

Two 2006 studies [16, 18] postulated that routine IOC is associated with a lower incidence and early recognition of bile duct injuries as well as being a safe, accurate, quick and cost-effective method for the identification of the bile duct anatomy and also probable bile duct stones.

The same result was presented in a US nationwide study of 93,578 patients based on year 2000 data [19] where cholecystectomies outcomes were evaluated taking into consideration patient and hospital demographics: overall, cholangiogram was clearly identified as safe whilst decreasing morbidity.

We would define a careful dissection at this step of the operation as a dissection that is kept very close to the gallbladder since structures might not be clearly identified. IOC is routinely being performed on all patients in our hospital via a small catheter inserted distally into the cystic duct close to its junction to the gallbladder infundibulum.

IOC enables early detection and repair of a bile duct injury. In the event of a bile duct injury the patient should be immediately referred to a surgeon experienced in bile duct repair. As regards major bile duct injuries, optimum long-term results can apparently be achieved with a proximal tension free, end-to-side mucosa-to-mucosa hepaticojejunostomy Roux-en-Y [16, 20, 21]. Minor lesions such as peripheral leakages or short strictures can be selectively treated laparoscopically or endoscopically.

With regard to the problem of additional bile ducts such as Luschka's duct, it is clear that a non-identification may lead into constant leakage that can become clinically apparent, prompting a revision operation in which the duct has to be ligated and safely closed.

In cases of acute cholecystitis in particular, it is unsurprising that due to the more difficult intraoperative situation the rate of clinical and subclinical bile leaks may be higher than expected. An interesting American study in 2006 evaluated 100 patients with acute cholecystitis after laparoscopic cholecystectomy by performing a cholescintigraphy scan on postoperative day 1. Eight scans disclosed positive bile leaks though no patient had experienced a clinically symptomatic bile leak [22]. This demonstrates that the risk for primary sub-clinical bile duct injuries can become relevant especially when a first sub-clinical leak turns clinical.

The development of a biloma can also be a slow process as demonstrated in a Japanese case report in

2005 that described the development of a biloma out of a Luschka's duct over a period of 6 month postoperatively [23]. Clinical symptoms resulting from either biloma or the development of biliary peritonitis deserve treatment including operative revision, whereas without symptoms a patient can just be kept under regular observation.

Major bile duct injuries, even the most skilfully treated, can often lead to a long-term illness with necessary repeated treatment of the patient due to injury-related long-term complications and their ramifications [16]. These can include recurrent stenosis of the bile ducts or a chronified cholangitis or, in the event of a more severe complication the development of a biliary cirrhosis followed by a propable necessity for liver transplantation.

13.6. Gallbladder Perforation and Loss of Stones

Due to the way the gallbladder is held and manoeuvred during the operative procedure and due to its wall structure of the organ and probable grade of infection, the risk of a rupture of the gallbladder during laparoscopic cholecystectomy is quantitatively high and may lead to an increase of postoperative complications such as wound infections or intraabdominal abscess formations, subhepatically.

A Swiss article in 1997 [24] pointed out that up to then there were already 39 studies had been published involving 53 such that reported the frequency of lost stones due to torn gallbladder as ranging would from 9% to 40%.

A 1999 Mexican study found gallbladder rupture to be associated with increasing wound infections [25]. Several case reports, reviews and analyses [26, 27, 28, 29, 30, 31, 32, 33, 34, 35] from 2002 to 2006 refer to this subject and highlight particular aspects of the problem: clinical symptoms might develop a long time after the initial procedure [26, 27], spilled gallstones can act as foreign bodies and can cause abscess formations, for example sub-hepatical [28, 30] sub-phrenical and pleural [32], or with multiple locations [34] forming the basis of a recurrent bacteraemia [28] and thus can't be considered harmless as originally thought in the beginning of laparoscopic cholecystectomy [29].

A UK multivariant logistic regression analysis in 2006 considered that: laser use during the operation, male patients with a history of acute cholecystitis or an operation during an acute attack of cholecystitis all bear an increased risk of iatrogenic gallbladder perform [33]. On the whole complications from spilled gallstones through gallbladder perforation may necessitate rather prolonged and multiple treatment [34, 35].

From the viewpoint of personal experience we have to ratify the UK results and add the significance of surgical skill in handling the organ itself during the operation. We recommend the organ not be grasped too forcefully, all movements be under view including those of any assistant and the movements of the surgeon allowing careful attention to be given to the prevention of a perforation. It also appears that not only instrument manipulation but also the usage of scissors and electrocoagulation devices or the harmonic scalpel for the preparation close to the organ can potentially tear the gallbladder.

Should a perforation occur, we advise against continuing the operation. The bile liquid has to be promptly retrieved with adequate aspiration devices as it can also form the basis for a later infection. It is imperative that spilled stones be completely identified and extracted from the abdominal cavity. We can't stress enough how important this is.

In addition there is a good reason for thorough and abundant irrigation and aspiration followed by an intensive postoperative control of the patient like as stressed in a Turkish study in 2003 [36]. In our opinion, necessary postoperative checks include: blood sample esp. leukocytes, CRP, liver parameters, and ultrasound and in certain unclear cases immediate CT control for tracing probable lost stones.

We routinely perform a blood sample including blood cell count, CRP and liver (cholestatic) enzymes on the day after the operation and individually repeat this test according to possible pathological findings. In cases of fever attacks or extensive pain, an immediate ultrasound is indicated. If this fails to show an interpretable result, CT should follow. Pain increase or complications may prompt the need for surgical re-intervention may. Otherwise the patient is kept under close observation and possibly entailing a longer hospitalization.

13.7. Blood Vessel Injuries

The surgeon performing the laparoscopic cholecystectomy needs to be aware of the variability in the blood vessel supply of the gallbladder: The cystic artery usually rises out of the right hepatic artery but there is also a chance for it coming from the common hepatic artery, the left hepatic artery, crossing the main bile duct or forming the main branch of the right hepatic artery [37].

Statistically, bleeding complications occur in Germany in about 1,3% of the cases. It is therefore necessary to discuss intraoperative bleedings, postoperative bleedings and complications that further arise from such bleedings. When discussing the risk of intraoperative bleeding, we must point out that the most important element in the prevention of bleeding, which is undoubtedly the best way of avoiding further complications is that of the clear identification of the vessel, and its course.

In order to clearly identify the cystic artery, without injuring larger branches, we need to identify the vessel where it enters the wall of the gallbladder and divides itself. This point better enables us to clip the vessel without anatomic misinterpretation. Just as in the preparation of the cystic duct, so in preparing the cystic artery we need to stay close to the gallbladder. A closer preparation in the structures of the hepatoduodenal ligament bears the risk of injuring more central structures and thus causing severe and massive bleeding which is appreciably to stop. In the event of bleeding a "blind" clipping or the "blind" use of diathermy is not the method of choice though it sometimes appears to be the fastest way to stop bleeding. Such methods should only be performed when confident that we are dealing with a second branch of the cystic artery and not with a more proximal serving vessel. Precarious clip placement or the extensive use of diathermy on such a larger supply vessel may result in a reduction of the liver blood supply especially when dealing with a common hepatic artery.

It is also necessary to understand that iatrogenic hepatic vascular injuries during laparoscopic cholecystectomy mostly occur in combination with bile duct injuries [38] which in itself constitutes a risk factor for the development of biliary complications [39] making it even more understandable why a thorough and professional preparation in this area is so important.

Though it seems that isolated injuries of the right hepatic artery usually remain clinically insignificant in otherwise healthy patients, additional risk factors such as hypoxemia, cholangitis, sepsis, liver cirrhosis or abnormally reduced portal venous blood flow, all create a high risk for the development of ischemic liver necrosis, abscess formations in the liver and further complications such as destructive cholangitis and secondary biliary cirrhosis [38].

When such a major injury leads to a biliary complication it is recommended that those patients with major bile duct injuries should be assessed for additional vascular injury as the outcome of bile duct reconstruction is worse in patients with concomitant arterial injuries [39]. Should such an injury occur during laparoscopic cholecystectomy, the patient should be immediately referred to a surgeon with adequate expertise in bile duct repair and hepatic arterial reconstruction [40].

If biliary complications such as ischemic liver necrosis or abscess occur late after the laparoscopic operation a percutaneous abscess drainage can be attempted but should it fails and the patient not recover, a hemihepatectomy may become necessary.

Postoperative bleeding complications involve cases of cystic artery damage, prolonged haemorrhage from the gallbladder, parenchymal liver injuries [8] and also in our experience trocar channel bleedings. Causes can be attributed to insufficient clipping, slipped clips, inadequate diathermy or to the fact that the decrease of intraabdominal pressure at the end of the procedure when the pneumoperitoneum is being re-established can lead to a re-opening of compressed vessels and to new bleeding as a consequence.

We have experienced cases of clear dryness at the end of the operation followed by postoperative bleedings that quickly resulted in re-intervention. The prevention of postoperative bleedings clearly prompts the surgeon to steadily increase accuracy in the preparative care of the vessels. He should thoroughly set his clips on the right vessel in the right position and the clip should remain in place without being moved or handled too heavily.

Bleeding should be detected and taken care of when it does not stop by itself. The surgeon must bear in mind that lower pressure vessels may reopen and allow himself time during the last minutes of the ope-

ration. When the trocars are being extracted the trocar channels should be inspected for bleeding until the surgeon is finally satisfied. Irrigation and aspiration instruments should be used, in particular to clear the liver bed for small, but constant bleedings. Liver parenchyma injuries or injuries of the omentum major must be inspected for constant bleeding and treated with diathermy or if not possible with ligature or haemostatic tissues.

The use of drainages on patients that had stronger bleedings throughout the operation is not prevention against ongoing bleeding but may contribute to less blood remaining in the abdomen causing pain or infection and it might enforce diagnosis in cases of continous postoperative haemorrhage. Nevertheless as postoperative bleedings can't be fully prevented, patient care dictates that a blood sample, including erythrocytes and haemoglobin, be part of postoperative controls on the first day after the operation. In case of a suspected bleeding ultrasound or in selected cases, CT can confirm diagnosis.

Furthermore it appears that prolonged postoperative haemorrhage is an indication for re-operation [8].

13.8. Specific Points for a Successful End to the Laparoscopic Procedure

The use of diathermy –whether mono- or bipolar– for electrocoagulation or the harmonic scalpel varies from hospital to hospital and follows the main criteria that whatever has proved always successful in the past will continue to be used in the future – a viewpoint with which we mainly agree because our hospital has also historically adopted a certain technique with which we are generally satisfied.

We recommend, in particular, that these devices be used only under clear anatomic circumstances. That means for example we consider it highly dangerous to begin the laparoscopic cholecystectomy mainly with a preparation using diathermy – a common practise in several hospitals.

It can't be overemphasised that diathermy and ultrasound scissors cause the tissue to shrink due to the temperature it is exposed to. This can create damage on tissue that is not yet cleared for safety. We believe that when the cystic duct and the cystic artery are not defined and prepared, the use of these instruments demands extreme caution and should be reserved for fatty and connective tissue or very small and unimportant vessels.

After preparation of the cystic duct and cystic artery the gallbladder is removed from underneath the liver bed. At this point diathermy can be of great assistance in the preparation since small vessels in the liver bed can easily be coagulated together with the separation of the connective tissue between the gallbladder and liver bed. Nevertheless the risk of an iatrogenic gallbladder perforation remains as at this point of the procedure the preparation must remain close to the gallbladder, but not so close that the gallbladder tears.

When the operation reaches the point of extraction the gallbladder from the abdominal cavity, it is recommended that a plastic recovery bag be placed in the abdomen and the gallbladder put inside for removal. The organ should not in our opinion be removed in direct contact with the abdominal wall since it may be contaminated by bacteria and these bacteria may, in turn, come in contact with the abdominal wall of the trocar channel where the removal takes place causing a local wound infection.

Though studies [4, 5] focus on the effect of emergency operations, operations in acute cholecystitis and co-morbidity regarding the risk of wound infections, it is known that positive bile culture exists in about 22% of the laparoscopic gallbladder operations [4]. Hence, we see a quantitatively high risk of bacteria contamination of at least the inside of the organ. If the gallbladder would is removed through the trocar channel without a plastic cover, the pressure of the narrow channel may cause bile to spill out of the gallbladder or might even cause a rupture of the organ in the channel with spillage.

Bacteria can then spread to the trocar channel possibly generating a later infection. In the case of a ruptured organ, inside a plastic recovery bag, the organ and any spilled bile can be removed safely. The industrial plastic bags on the market are quite strong in terms of stretching, however it can rupture when it is dragged too much and stretched over. The rupture can be quite strong and almost explosive with a widespread spillage of bile or maybe also stones into the inside of the abdomen. In short, a rupture of the bag when under traction stress must be avoided at all costs.

Such cases mostly occur when the removal channel is too narrow for the organ and its stones and it is recommended that the channel is widened either bluntly with the fingers or sharply under view with scissors. The bag with the organ should finally be removed without too much stress on the bag. It is known that the removal of the gallbladder is most likely performed through one of the 10 mm trocar places. In our hospital, we perform the removal through the umbilical trocar channel under view. The gallbladder is safely stalled in the plastic recovery bag, the bag grasped with one of the clamps and then under view guided to the umbilical trocar where it is led out while the camera constantly retracts itself.

After the clamp has led the bag out, the bag will be grasped from the outside and softly extracted with particular care so contents do not spill back into the trocar channel. We have chosen the umbilical trocar position for extraction since, in our experience, it provides a more vertical channel where the muscles cannot easily close the channel like stage wings facilitating any necessary stretching more than other positions.

After the safe removal of gallbladder, it is inspected visually and sent off for histopathological examination. We strongly recommend a "last look into the abdomen". Any final bleedings, particular from the liver bed, must be detected and taken care of. Should the liver have already assumed its normal position, it needs to be elevated for control of the liver bed. We need to look for leaking blood vessels and also for leaking additional bile ducts that have to be closed.

Finally at this point of the operation, the need for a drainage system has to be determined. Generally speaking over the years the amount of drainages placed in laparoscopic gallbladder surgery has decidedly decreased due to increased awareness concerning the safety of operations and also the fact that whilst drainage is indicated in specific instances, it should be avoided in others.

Since there is nothing significant in the literature concerning this topic and given that every surgical department has its own rules, we would like to indicate the situations where drainage is appropriate: significant bleeding during the operation in combination with a probable bleeding co-morbidity, significant bile leakage, severe infections or even abscess formations in acute cholecystitis with pus production and/or pus leakage out of the organ or out of abscesses. When drainage is indicated we recommend the passive drainage system.

The trocars must also be removed under view. This lowers the risk of an undetected trocar channel bleeding. As long as trocars are in place, bleedings are very likely under pressure and hence cannot be seen; as soon as the trocars are retracted the injured vessel may reopen and start to bleed. We must stress that whilst bleeding can start from one second to the next, it can also delay till sufficient pressure in the vessel mounts up, flushing coagulating blood away, thereby prompting the vessel to bleed again.

Also the intraabdominal pressure generated by the pneumoperitoneum during the operation may well be sufficient to reduce the trocar channel and even liver bed bleedings. It is therefore wise to observe the trocar channel and the liver bed during the decrease of the pneumoperitoneum and intraabdominal pressure in order to detect potential bleedings.

In general terms, if the end of the operation is to maintain the strategy of bleeding avoidance, the surgical team needs to take a thorough and close final look around the operation area to ensure it is clean.

The closure of the abdomen in laparoscopic surgery is very straightforward since the 5 mm trocar positions simply require a skin suture or use of sterile stripes as necessary. The 10 mm trocar positions and especially the position where the gallbladder has been removed, need closure both, the peritoneum and the anterior sheath of the rectus muscle. This is mandatory practice in order to prevent a trocar hernia. A 10 mm trocar that has been placed non-vertically but more horizontal does not, in our opinion, warrant fascia suture.

13.9. Forensic Aspects and Malpractice in Laparoscopic Cholecystectomy

From 1989 to 1997, 40 legal cases of possible malpractice in laparoscopic cholecystectomy were reported in Germany [42] 16 of which were found guilty of malpractice. The most common cause was bile duct injury (26 cases). Malpractice was decreed in seven of these cases, 2 of which constituted grave errors. The determinant factors of malpractice included delay in converting to open surgery, delayed revisions and la-

paroscopic rather than open revision in unclear situations.

Another 1999 article on malpractice in laparoscopic cholecystectomy from Germany [43] reported established medical malpractice in 25 cases up to August 1998 in the area of the Medical chamber of Nordrhein, Germany. The malpractice cases mainly involved bile duct injuries with biliodigestive reconstruction or end-to-end anastomosis or T-tube. In 4 cases a bile duct injury was not considered the results of malpractice due to intraoperative detection and immediate treatment. In two cases a trocar injury was confirmed as malpractice and in one case it was not. In addition, the following single cases were also seen as malpractice: one lost gall stone, one dislocated Roedersnare, one electric injury, one delayed reintervention and one insufficient patient information. Cases that were considered as non-malpractice concerned 2 cases of a slipped clip, 5 cases of subhepatical haematoma or abscess formation three cases of secondary bleeding, one of a lesion of the splenic capsule and one wound infection with subsequent incisional hernia. One electric injury of the bowel, one bile duct lesion and one information rebuke three cases with fatal consequences are also mistakes implicated in.

We consider bile duct injury as the main high risk in laparoscopic cholecystectomy because despite well-established immediate or later highly optimized treatment techniques, it can seriously compromise the future health of the patient. This in mind, we stress the necessity of a very detailed and informative talk with the patient and (if wished the relatives) in which risks of the operation and consequences have to be truthfully conveyed. In cases of intraoperative injuries we recommend immediate treatment by a surgeon who is well skilled in the management of this specific complication in order to avoid further legal case. This may well involve a patient being sent to another hospital for revision.

13.10. Conclusion

Based on our own experience as well as on the international literature of malpractice, we want to underline the importance of thorough documentation, honesty with the patient, professional training of future laparoscopic surgeons, an appropriate oparative technique that observes anatomic rules and accepts that structures may only be divided when they are clearly identified, a high level of proficiency in the handling of complications, an immediate reaction to complications as soon as they present, without further delay.

We believe that if these points are kept in mind, the gold standard of laparoscopic cholecystectomy for the different gallbladder diseases will further improve –along with a decrease in complications– even though a very high grade of professionalism has already been achieved. With an increase in standardization –which will most certainly include further studies on several aspects that lack a common opinion on treatment strategy– overall patient satisfaction and benefits will increase accordingly, corroborating surgery as the mainstay of treatment for this widespread, universal disease.

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CHAPTER 14

IATROGENIC INJURY OF THE EXTRAHEPATIC BILE DUCTS. SURGICAL RECONSTRUCTION

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14.1. Introduction - History

The majority of biliary tract injuries are iatrogenic. They are usually associated with operations in the upper abdomen. More than 80% occur during cholecystectomy, one of the most common intra-abdominal operations. Langenbuch performed the first successful cholecystectomy in 1882, and since then the number of cholecystectomies has increased rapidly, inevitably increasing the number of complications. Iatrogenic bile duct injuries are unfortunately not rare and may have disastrous consequences and very significant long-term morbidity and mortality [1, 2]. With adherence to well-established technical principles for open cholecystectomy, the incidence of bile duct injuries remained at less than 0.5% in most of the published retrospective series [3, 4].

Introduction of laparoscopic cholecystectomy in 1987 signified a new era in biliary tract surgery. Laparoscopic cholecystectomy became the gold standard for gallstone disease and the number of laparoscopic cholecystectomies and other laparoscopic operations has rapidly increased. More specifically, the number of cholecystectomies performed annually has increased by 15-20%. Early series with large numbers of patients reported bile duct injury rates ranging between 0.5-1.5% [5], significantly increased compared with the open cholecystectomy era. More recently however, data extracted from the Nationwide Inpatient Sample show that injuries requiring biliary reconstruction occurred in less than 0.15% of patients who underwent laparoscopic cholecystectomy in the year 2000 [6].

Some of the factors implicated in laparoscopic surgery-related injuries are: the monocular view of the conventional camera, the use of the electrocautery near the triangle of Calot and the surgeon's "learning curve".

Bile duct injuries range from small postoperative bile leaks, with little clinical significance, to severe injuries and strictures of the intrahepatic ducts with devastating consequences. Injuries resulting from laparoscopic surgery are more complex than open cholecystectomy-associated injuries, frequently involve the proximal bile duct, and result in more extensive stricture formation.

We will review the types and mechanisms of iatrogenic bile duct injuries and summarize the diagnostic modalities and options for surgical management.

14.2. Types of Injury

14.2.1. Cystic Duct Injuries and Bile Leak

Bile leaks arise from three sources: the cystic duct (50%), a subvesical or gallbladder bed bile duct (duct of Luschka – 25%), or an injury to a major bile duct (25%). The incidence of laparoscopic cholecystectomy-related minor bile leaks is reported to be up to 1% [7, 8].

Cystic duct leak is the most common biliary injury associated with laparoscopic cholecystectomy. The main mechanism is failure to ligate the cystic duct, most commonly as a result of failure to safely apply the endoscopic clips. The presence of a wide and friable cystic duct, as in cases of acute cholecystitis, may result in inadequate application of the clips. The closure of the cystic duct stump may be difficult if an intraoperative cholangiogram has been performed through a short and inflamed cystic duct. In this case, the application of clips may be inadequate and ligation of the cystic duct with an "endo-loop" may be necessary.

Severe inflammation of the gallbladder and the cy-

stic duct can cause ischemic necrosis of the stump with postoperative bile leak. Any doubts regarding the blood supply and the viability of the cystic duct stump should make a surgeon particularly cautious. Laparoscopic suture ligation of the cystic duct or conversion to open procedure may be necessary in these cases.

Bile leaks cause bile collections (bilomas) or biliary fistulas. Bilomas can become secondarily infected, causing localized infection or frank peritonitis, potentially life-threatening complications. Percutaneous drainage of a biloma of any significant size is indicated to avoid secondary infection and peritonitis. Most of the bile leaks, secondary to inadequate ligation of the cystic duct stump resolve after endoscopic placement of a biliary stent, which seals the site of the leak and allows healing of the stump. Reoperation with identification and ligation of the cystic duct stump is sometimes necessary.

Excessive right upper quadrant pain or an elevated bilirubin in the immediate postoperative period should prompt investigation for a bile leak. An ultrasound or a CT scan examination of the area may detect a fluid collection, and a radionuclide imaging study [e.g., hepatoiminodiacetic acid (HIDA) scan] may demonstrate extravasation of bile in the region. Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice to confirm a suspected bile leak, and to control it by placing an endoscopic stent.

14.2.2. Extrahepatic Bile Duct Injuries

Injuries below the confluence of the two main hepatic ducts are extrahepatic, whereas injures above this level are essentially intrahepatic, because the confluence is located deep in the porta hepatis. The majority of the injuries associated with laparoscopic cholecystectomy are extrahepatic. Most commonly, the extrahepatic portion of the common hepatic duct is injured. Injuries of the extrahepatic biliary ducts occur during attempted dissection in the triangle of Calot. Inadequate identification of the structures results in injury of the common bile duct or the hepatic duct. One of these structures is most commonly misidentified as the cystic duct, and is clipped and transected during the operation. If the injury is not recognized at this stage of the procedure, the dissection continues superiorly, where the right hepatic artery may be mistaken for the cystic artery and divided. Dissecting sharply near the bile ducts or near the cystic duct-hepatic duct junction can also cause injury. In this case, the leak of bile during the procedure alerts the surgeon and indicates the likelihood of an injury.

Injuries of the extrahepatic bile ducts are either partial lacerations or complete transections. If the injury is not recognized and the dissection continues, excision of a part of the duct and loss of tissue may occur, making the repair of the injury even more challenging. In a reported series from referral centers, simple lacerations form the minority, with most of the laparoscopic injuries being severe lacerations or transections [9].

14.2.3. Intrahepatic Bile Duct Injuries

Injuries at or above the confluence of the two main hepatic ducts are essentially intrahepatic, because this anatomic area is covered by liver parenchyma. These injuries occur most frequently during dissection of the gallbladder off the liver bed, especially in the presence of severe inflammation and scarring of the triangle of Calot. The right hepatic duct is far more commonly injured than the left hepatic duct. The duct is misidentified as the cystic duct or as an "accessory" duct, clipped, and divided. Injury to the left hepatic duct occurs when misidentification of the structures results in dissection on the medial aspect of the common bile duct. Even experienced laparoscopic surgeons may encounter difficulties in dissection and identification of structures in the porta hepatis. Prompt cholangiography and a willingness to convert to open cholecystectomy may prevent a serious injury. Inability to perform cholangiography or the appearance of an "incomplete" or inadequate cholangiogram, are indications to convert to an open procedure.

A clinically relevant classification of bile duct injuries has been proposed by Bergman et al in 1996 [10]. According to this system injuries are classified in 4 major categories shown in table 14.1.

14.2.3.1. *Strictures of the Bile Ducts*

Bile duct strictures following cholecystectomy occur either early or late after the operation. The severity of the stricture may vary according to the degree and the location. They can be classified in four types according to the system described by Bismuth [11] (fig. 14.1). Grade I strictures are distal strictures located more

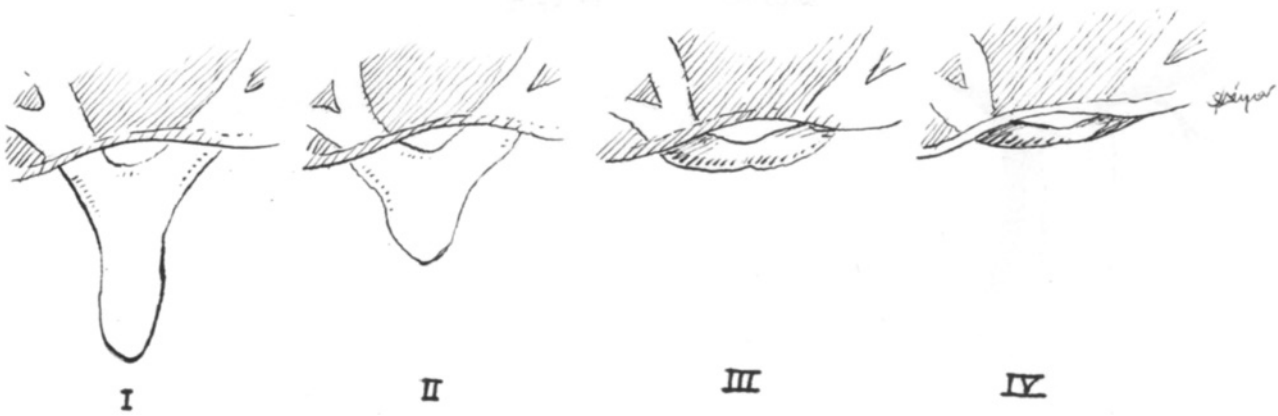

Fig. 14.1. Classification of postoperative biliary strictures according to Bismouth.

Table 14.1. Classification of bile duct injuries according to Bergman JJ et al.

Type A	Leakage from the cystic duct or peripheral hepatic radicals.
Type B	Major bile duct injury with leakage from the CBD or from an aberrant segmental extrahepatic duct or the right hepatic duct with or without concomitant stricture.
Type C	Stricture of the CBD without leakage.
Type D	Complete transection of the CBD, with or without partial resection of the bile ducts.

than 2 cm from the confluence of the left and right hepatic ducts; grade II strictures involve the common hepatic duct, less than 2 cm from the confluence; grade III strictures are within lcm of the confluence; and grade IV strictures involve the hepatic duct confluence. Chances of a successful repair and a satisfactory outcome vary inversely with the grade of the stricture.

Direct injury to the duct, clipping of the duct, thermal injury, devascularization of the duct during dissection, or inflammation and scarring secondary to bile leakage represent the main mechanisms of stricture formation. Application of a clip near the confluence of the cystic duct with the hepatic duct may cause partial or complete obstruction of the common hepatic duct. This type of stricture usually occurs early, within days or weeks of the operation. Strictures caused by secondary inflammation or thermal injury sometimes become clinically obvious months or even years after the original operation.

Ischemia is an important etiologic factor for the formation of bile duct strictures. The hepatic duct and the common bile duct receive their blood supply from axial arteries located generally at the 3 and 9 o'clock positions (fig. 14.2). Unnecessary dissection around the common bile duct during laparoscopic cholecystectomy and excessive use of electrocautery can cause damage to the feeding vessels, with subsequent formation of ischemic strictures.

Bile leak from the cystic duct or from minuscule injuries of the common bile duct can cause an intense local inflammatory response, which may become further complicated with infection. Inflammation results in fibrosis and scarring, contributing to stricture formation. Scar tissue may also result from a hematoma in the porta hepatis, if adequate hemostasis was not achieved during the original operation.

Iatrogenic strictures of the major bile ducts can be potentially devastating complications that usually require surgical repair. Endoscopic and transhepatic stenting and dilation may be used as a temporary management of a stricture to alleviate infection, jaundice, and inflammation before definitive repair is embarked upon.

14.3. Mechanisms of Injury and Risk Factors

14.3.1. Anatomic Variations

The anatomy of the biliary ducts and blood vessels in the area of hepatoduodenal ligament can vary greatly making anatomic variation the rule rather than the exception. The cystic artery usually arises from the right

Fig. 14.2. The arterial blood supply to the biliary tree.

hepatic artery, but it may also arise from the left hepatic, common hepatic, gastroduodenal, or even the superior mesenteric artery (fig. 14.3). Double or accessory cystic arteries are present in 8-12% of cases. The course of the cystic artery may also vary, usually crossing behind, but sometimes anterior to, the common hepatic duct. If the cystic artery originates from the proximal portion of the right hepatic artery or from the common hepatic artery, then it may lie close to the common hepatic duct. In this case, the duct could be injured during the dissection or the clipping of the cystic artery.

Variations of the anatomic position of the cystic duct are also common. Accessory hepatic ducts are present in approximately 15% of cases. They usually drain a portion of the right lobe of the liver and join the right hepatic duct, the common hepatic duct, or the infundibulum of the gallbladder. The duct of Luschka is a small accessory duct that may drain directly from the liver into the body of the gallbladder.

The plethora of anatomic variations in the area of the triangle of Calot dictates extreme caution during laparoscopic dissection. All structures should be recognized with certainty before being ligated and divided. Recognition of the junction of the cystic duct with the gallbladder may be difficult in the presence of inflammation. Any doubts about the anatomic position of the structures should prompt intraoperative cholangiogram and conversion to open surgery, if necessary.

14.3.2. Complicated Pathology

Acute inflammation and scarring of the triangle of Calot constitute risk factors for iatrogenic injury. Acute edematous infiltration of the tissues, as in cases of acute cholecystitis or acute pancreatitis, obscures the surgeon's view and jeopardizes the recognition of structures. In cases of long-standing chronic cholecystitis, the gallbladder becomes small and fibrosed (scleroatrophic gallbladder). As a result of the fibrosis in the porta hepatis, recognition of the structures and dissection may be extremely laborious during laparoscopic cholecystectomy, predisposing to injuries.

Involvement of the common bile duct may occur in cases of severe inflammation of the gallbladder, as it does in cases of Mirizzi syndrome or in cholecystobiliary fistula [12]. Any attempt to continue the procedure laparoscopically may cause severe injury to the common bile duct. Typical cholecystectomy may not be feasible in these cases. Conversion to an open procedure is usually necessary in order to perform cholecystectomy, chlolecystostomy, or repair of the common bile duct, as needed.

Distortion of the anatomic relationship of the common bile duct with the duodenum may also be caused by the presence of a penetrating duodenal ulcer. Inflammation in cases of acute or chronic pancreatitis can also cause difficulty in recognition of the structures in the triangle of Calot. Thorough preoperative investigation minimizes the possibility of these conditions being unexpectedly discovered during laparoscopic cholecystectomy. This being the case however, laparoscopic dissection may be considered unsafe, rendering conversion of the procedure to open necessary.

14.3.2.1. *Technical Errors*

With accumulation of experience and upon review of multiple complications, it has been shown that an inappropriate operative technique is also a predisposing factor for bile duct injuries. In this section we will present the so-called technical errors that have been identified as contributing to bile duct injury.

In order to expose structures and facilitate dissection during laparoscopic cholecystectomy, cephalad and lateral retraction of the gallbladder is necessary. Errors in the retraction technique may predispose to bile duct injuries. Excessive retraction of the gallblad-

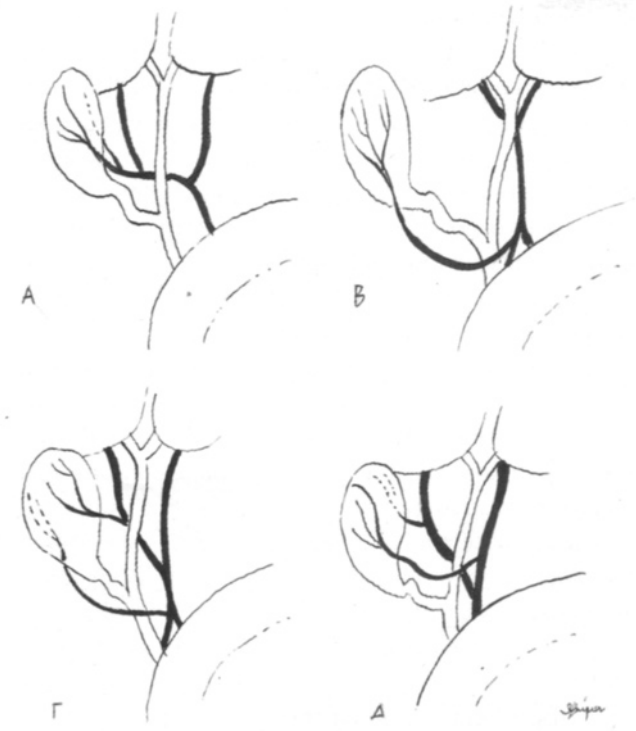

Fig. 14.3. Aberrations of the anatomy of the cystic artery: A) Arises from the right hepatic artery in 95% of cases, B) Arises from the gastroduodenal artery, C) Two cystic arteries arising from the right hepatic and common hepatic arteries, D) Two cystic arteries arising from the right and left hepatic arteries.

der may cause common bile duct injury by avulsing the cystic duct off the common bile duct. The assistant should be cautious, especially in the presence of acute inflammation or a gangrenous gallbladder where inflamed bile ducts become friable. Inadequate or medial retraction of the gallbladder predisposes to injury by obscuring the space between the common bile duct and the cystic duct.

Application of clips too close to the cystic duct-common bile duct junction may cause partial obstruction of the common bile duct with subsequent scar tissue formation and stricture. This type of injury can be avoided by clearly identifying the cystic duct-common bile duct junction before clipping. Strenuous dissection too close to the common bile duct may jeopardize blood supply with secondary formation of a stricture. Dissection should be avoided at the 3 and 9 o' clock positions of the axial vessels providing the blood supply to the duct. Vigorous dissection close to the common bile duct wall should also be avoided, again because of risk of direct injury, especially if inflammation is present. Dissection should be done close to the cystic duct-gallbladder junction, and not near the common bile duct.

The "blind" application of clips to obtain hemostasis is another frequent error. When the view of the surgeon is obscured by blood, irrigation of the area and cleaning of the laparoscope provide adequate view for identification of the bleeding vessel and hemostasis. If laparoscopic control of the bleeding is not possible, the procedure should be converted to open before significant blood loss occurs. Technical errors have been attributed to most cases of bile duct injuries [13]. Although these are more likely to occur early in the surgeon's "learning curve", major duct injuries continue to occur, even after technical competence is achieved [14].

14.3.3. Thermal and Laser Injuries

Hemostasis and dissection during laparoscopic cholecystectomy are greatly facilitated by using the electrocautery. Propagation of thermal energy depends on the relative conductivity of the tissue, which varies with the content in water and lipids. The depth of penetration into the surrounding tissues cannot be precisely controlled. Excessive use of high-intensity electrocautery may cause burn injuries to the bile ducts or late strictures by coagulating the vessels and jeopardizing the blood supply. The use of electrocautery during dissection near the common bile duct should be avoided. If the use of electrocautery is necessary for obtaining hemostasis, it should be of very short duration and low intensity. Bipolar electrocautery, which delivers energy between two points in a more controlled fashion, may be a safer technique.

The initial enthusiasm for the use of laser during laparoscopic cholecystectomy collapsed after the observation that laser can cause severe injuries with loss of tissue [15]. The use of both electrocautery and laser should be avoided near metallic clips, which conduct the temperature and can cause thermal injury to surrounding tissues.

14.4. Diagnosis of the Injury

14.4.1. Presentation of the Patient

If the injury is not recognized intraoperatively, signs and symptoms vary according to the type and severity of the injury. Patients with small leaks from the cystic duct usually present with right upper quadrant pain, caused by intraperitoneal collection of bile. Fever and leukocytosis are common findings if infection is present. Lacerations of the common bile duct result in large accumulations of bile, which causes significant peritoneal irritation with severe pain, nausea, and vomiting. Patients with postoperative biliary fistula or subhepatic abscess usually have persistent symptoms of nausea and vomiting, abdominal distention, and mild abdominal pain. These symptoms are often recognized and evaluated by the original surgeon. Physical examination reveals tenderness and guarding in the right upper quadrant. Absorption of bile from the peritoneal cavity results in elevation of total and direct bilirubin. Frank peritonitis is caused from suprainfection of bile. In these cases, the patient may present with a septic picture, including high fever, elevated white blood cell count, and positive blood cultures.

Patients with postoperative bile duct strictures, present with a picture of biliary obstruction. The time of presentation varies, but nearly 70% of patients are diagnosed within the first 6 months. If the injury is suspected at the time of surgery and the patient is regularly followed, the first finding is usually a progressive elevation of liver function tests, particularly alkaline phosphatase and bilirubin. The patient may also present with jaundice or episodes of cholangitis caused by cholestasis.

The most valuable laboratory investigation is a complete liver profile, which will show evidence of cholestasis. Total and direct bilirubin may be elevated, alkaline phosphatase is usually elevated, and the aminotrasferases may be normal or slightly elevated. If long-lasting obstruction is present, the synthetic function of the liver may be impaired, as shown by elevated prothrombin time and low albumin.

14.4.2. Imaging Studies

If a bile collection in the right upper quadrant is suspected, a computed tomography (CT) scanning of the abdomen will visualize the collection. In addition, the size of the common bile duct can also be assessed by ultrasonography (US). If the collection is small, it may be difficult to differentiate from postoperative changes or small hematomas in the subhepatic area. In these cases, hepatobiliary scintigraphy may be helpful in visualizing an active bile leak or in demonstrating a complete duct obstruction. Scintigraphy, however, cannot provide adequate anatomic definition of the injury, and further investigation will be necessary.

A magnetic cholangiopancreatography (MRCP) is a non invasive study which can visualize a leak, a stricture or a collection. MRCP can provide valuable information on planning a further investigation and choosing a management strategy.

The study of choice in patients with suspected bile duct injury is the endoscopic retrograde cholangiopancreatography (ERCP). ERCP can detect bile leaks from the cystic duct or from a lacerated common hepatic duct, bile duct strictures or retained stones . The use of ERCP also offers important therapeutic options in the management of bile duct injuries, which are discussed below.

Percutaneous transhepatic cholangiography (PTC) is a valuable tool in assessing the proximal extent of the injury and in identifying the proximal biliary stump in view of surgical correction (fig. 14.4). In cases of complete obstruction, PTC can also visualize injured segmental ducts or be used for drainage of the proximal biliary tree. The information obtained from direct visualization of the biliary tree with ERCP or PTC is essential before any surgical repair of the injury is attempted.

14.5. Management of Bile Duct Injuries

The strategy in the management of bile duct injuries depends upon two major factors: the type of injury and the time elapsed from the original operation. Advances in endoscopic and interventional techniques, offer valuable options in the treatment of complex injuries. The treatment of choice is surgical reconstruction of the injury or the strictures, combined if necessary, with endoscopic or percutaneous techniques.

14.5.1. Nonsurgical Methods

Interventional radiologic methods applied in the ma-

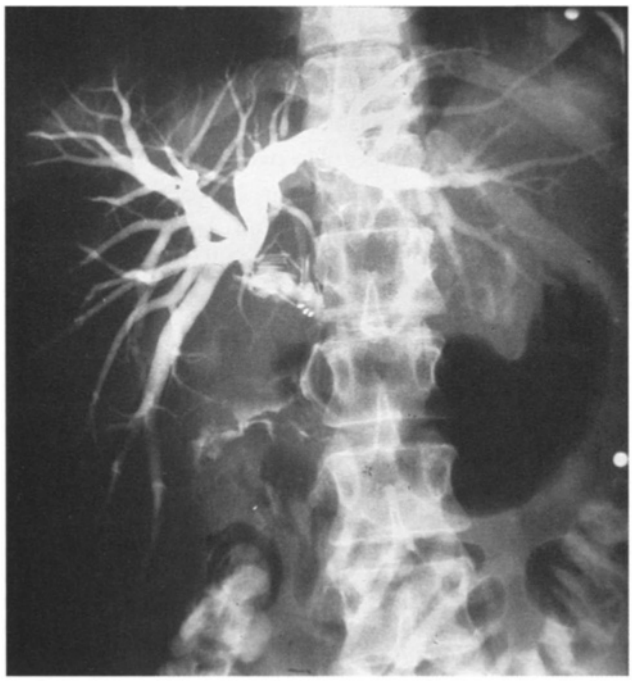

Fig. 14.4. PTC: Ligation of common hepatic duct with marked dilatation of the intrahepatic biliary tree.

nagement of bile duct injuries include PTC and the drainage of collections. CT –or US– guided drainage of bilomas must be done promptly after diagnosis. Bacteriologic examination of the fluid indicates the appropriate antibiotic coverage in cases of infection. Percutaneous catheter drainage of an infected collection is advisable before any surgical reconstruction is attempted. The transhepatic approach offers the option of draining the proximal biliary tree in cases of complete biliary obstruction. After the identification of the proximal extent of the injury, a transhepatic catheter can be placed over a guide wire, and left in place until the definitive reconstruction. Percutaneous techniques also have been used in the management of biliary strictures. Balloon dilators of various sizes are passed transhepatically over a guide wire to dilate biliary strictures. A stent is then left in place to maintain patency of the duct. Long-term results of this technique seem to be quite satisfactory [16, 17].

ERCP is a valuable tool in the diagnosis and management of bile duct injuries. Bile leaks from the cystic duct can be managed entirely endoscopically. After the site of the leak has been identified, a sphincterotomy is performed in order to lower the pressure in the common bile duct. Bile flow is pressure dependent and bile will take the path of least resistance. By lowering the pressure in the common bile duct, bile will flow preferentially distally into the duodenum and not through the cystic duct stump. Placement of a stent at the level of the leaking cystic duct may seal the leak and facilitate healing. The stent is usually removed after 3-4 weeks. The results of this technique are quite satisfactory [18]. Endoscopic dilatation of bile duct strictures can be attempted in cases of low-grade strictures and in patients who are poor surgical candidates. After a sphincterotomy is performed, a balloon catheter is advanced to the level of the stricture, and dilatation is attempted by inflating the balloon. After successful dilatation, a stent is left in place, to be removed after several weeks. The medium - and long-term results of this technique show that over 60-70% of patients remain symptom-free for long time-periods [16]. Interventional radiologic and endoscopic techniques may be used alone or in combination with surgery for the management of postoperative bile duct injuries, in selected groups of patients. Surgical reconstruction remains the gold standard in the management of iatrogenic injuries of the bile ducts.

14.5.2. Surgical Treatment

Mayo performed the first reconstruction of a post cholecystectomy injury in 1905 by anastomosing the hepatic duct with the jejunum. The goal of the operative reconstruction is to restore the continuity of the biliary tree or to re-establish normal flow of bile. The two main categories of reconstructive operations are: (1) re-establishment of the continuity of the biliary tract by directly re-anastomosing the injured bile duct, and (2) creating an anastomosis between the bile duct and the gastrointestinal tract. The type of operation depends on the type of injury, the timing of the repair, and the experience of the surgeon. The general principle dictating the strategy of repair is that the reconstructive procedure should always be performed by an experienced surgical team, in a high volume hospital. If this is not the case, the patient should be referred to another institution for definitive repair.

14.6. Repair of Injuries Recognized at the Time of Initial Surgery

14.6.1. Repair of Cystic Duct Leaks

This represents a type A injury usually with excellent prognosis. If recognized at the time of initial surgery, the procedure is converted to open. The leaking duct is recognized and safely ligated. The subhepatic area is drained with a closed suction tube.

14.6.2. Repair of Small Lacerations

Small partial lacerations of the bile ducts or small injuries that result from avulsion of the cystic duct can be repaired directly over a T-tube. The defect of the bile duct wall should be minimal, and the blood supply preserved in order to safely attempt this approach. More extensive injuries or thermal injury to the bile duct usually require Roux-en-Y reconstruction with hepatico-jejunostomy, proximal to the level of the injury.

14.6.2.1. *End-To-End Repair*

If bile duct injury is suspected at the time of the laparoscopic cholecystectomy, an intraoperative cholangiogram should be performed to confirm the injury and to delineate the anatomy of the bile ducts. The procedure is converted to open celiotomy and the injury is reassessed. If the injury involves the common bile duct, an end-to-end anastomosis of the duct may be attempted. This type of repair should be avoided, however, in cases of injury near the confluence of the two hepatic ducts. Absolute requirements for electing this procedure are: (1) no loss of bile duct tissue, (2) sufficient length of the duct to allow a tension-free anastomosis, (3) a bile duct of adequate size, (4) preserved blood supply to the two stumps, and (5) absence of infection in the right upper quadrant.

The duodenum is mobilized with a Kocher manoeuver to facilitate the approximation of the two segments. The segment of the duct that has sustained a sharp injury or has been clipped should be excised to well vascularized viable tissue. A single layer anastomosis is constructed in an end-to-end fashion by using monofilament absorbable or nonabsorbable suture material. A T-tube is usually placed in the duct with the long limb exiting through a separate site. The T-tube is removed after a few weeks. A closed system or a sump catheter can be left in place to drain any bile leaks (fig. 14.5).

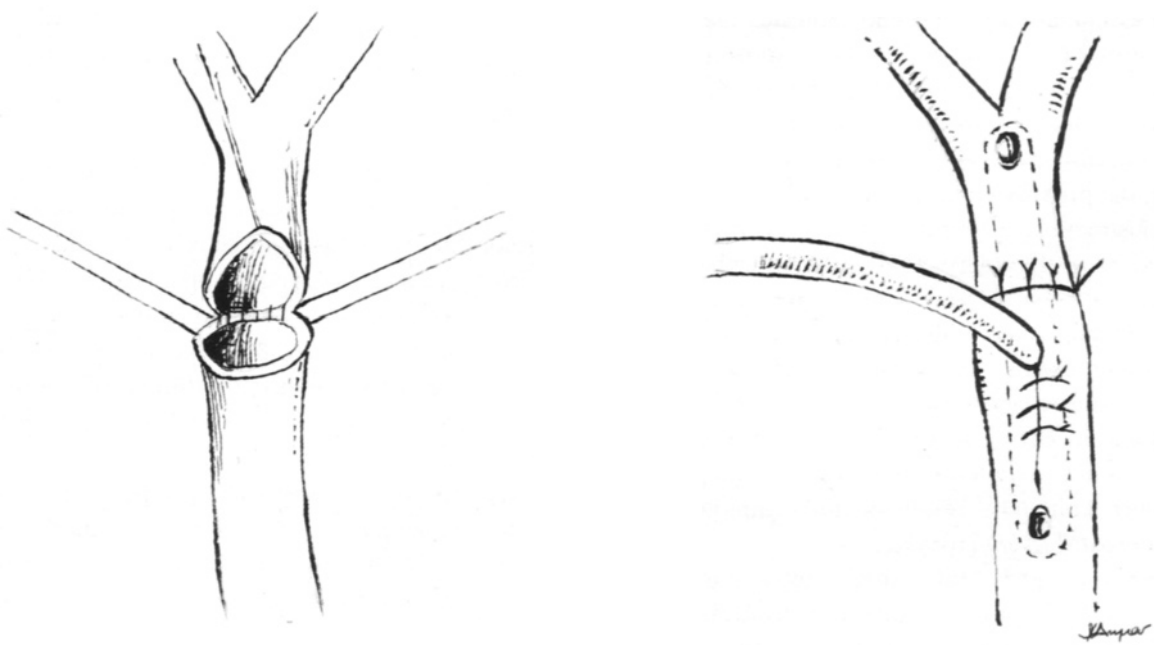

Fig. 14.5. Surgical reconstruction of an injury to the common bile duct. End to end repair over a T-tube.

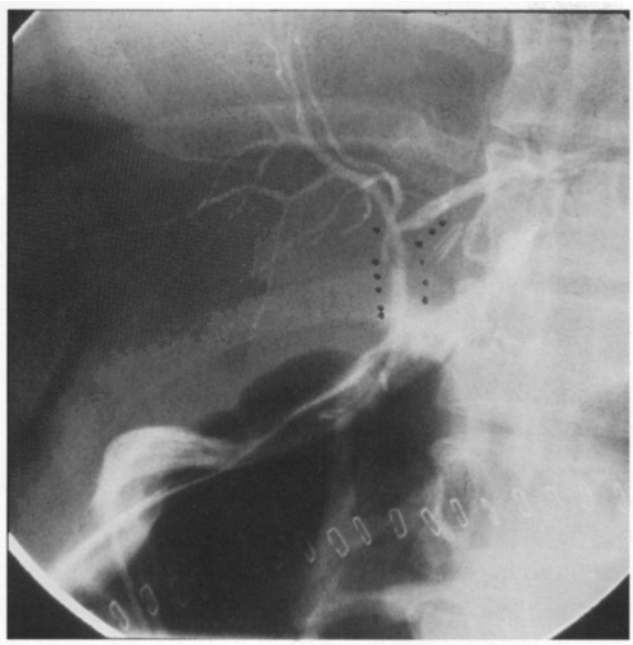

Fig. 14.6. PTC: Transection of common hepatic duct. Extravasation of contrast in the peritoneal cavity.

14.7. Repair of Biliary Strictures and Injuries Recognized Postoperatively

The majority of bile duct injuries are recognized postoperatively. Therefore, reconstruction takes place several days or even weeks after the initial operation. In a similar way, operations for biliary strictures are carried out after a significant time period has elapsed since the initial operation. As a result, inflammatory reaction or fibrosis may be found at the time of reconstruction (fig. 14.6). Drainage of bile collections and control of infection is essential before any attempt of reconstruction. The goal of the operation is to create an anastomosis between the bile duct and the gastrointestinal tract. The segment of the GI tract used for the anastomosis is either the duodenum (choledochoduodenostomy) or the jejunum (Roux-en-Y choledocho- or hepatico-jejunostomy). Using the duodenum for the anastomosis offers the advantage of endoscopic accessibility should a postoperative anastomotic stricture develop. Creation of a choledocho-duodenostomy, however, is not feasible in most cases owing to the distance between the segment of the duct proximal to the injury and the duodenum. The anastomosis is also prone to stricture formation, due to the small size of the injured bile duct, or the presence of crush or thermal injury to the duct.

14.7.1. Hepatico-Jejunostomy

This procedure is accepted as the gold standard of surgical repair for major biliary injuries and strictures.

The operation involves dissection of the area of the porta hepatis and identification of the bile ducts. The injury or stricture is identified and any devitalized or fibrosed tissue is excised. Placement of an endoscopic or transhepatic stent in the biliary duct before the operation may facilitate the recognition of the structures and the dissection. The distal bile duct is sutured and the proximal segment is debrided to healthy tissue. A Roux-en-Y loop of jejunum is used to create an end-to-side mucosa-to-mucosa anastomosis (fig. 14.7). The anastomosis can be performed in one or two layers using absorbable or nonabsorbable monofilament suture material. The use of transanastomotic stents is controversial. The use of the stent is not necessary when the distal hepatic duct or the common bile duct is used for a wide mucosa-to-mucosa anastomosis has been created [19]. For intrahepatic anastomosis near the confluence of the hepatic ducts, the placement of the stent may facilitate the creation of the anastomosis, a T-tube, or a silastic transhepatic tube can be used as a stent (fig. 14.8, 14.9). The timing of

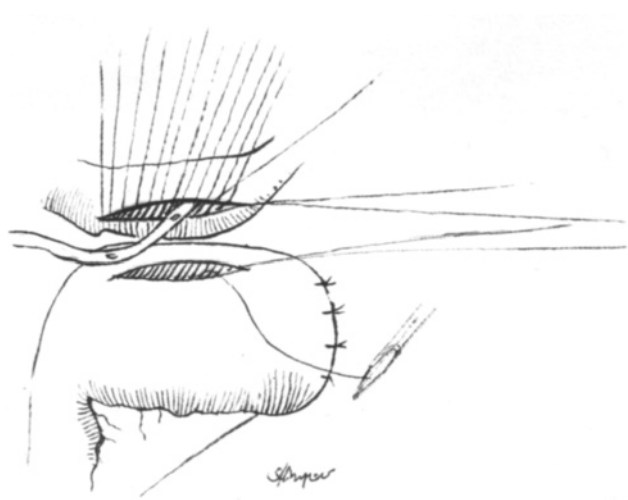

Fig. 14.7. Repair of a proximal injury. Hepatico-jejunostomy at the level of the hepatic duct confluence.

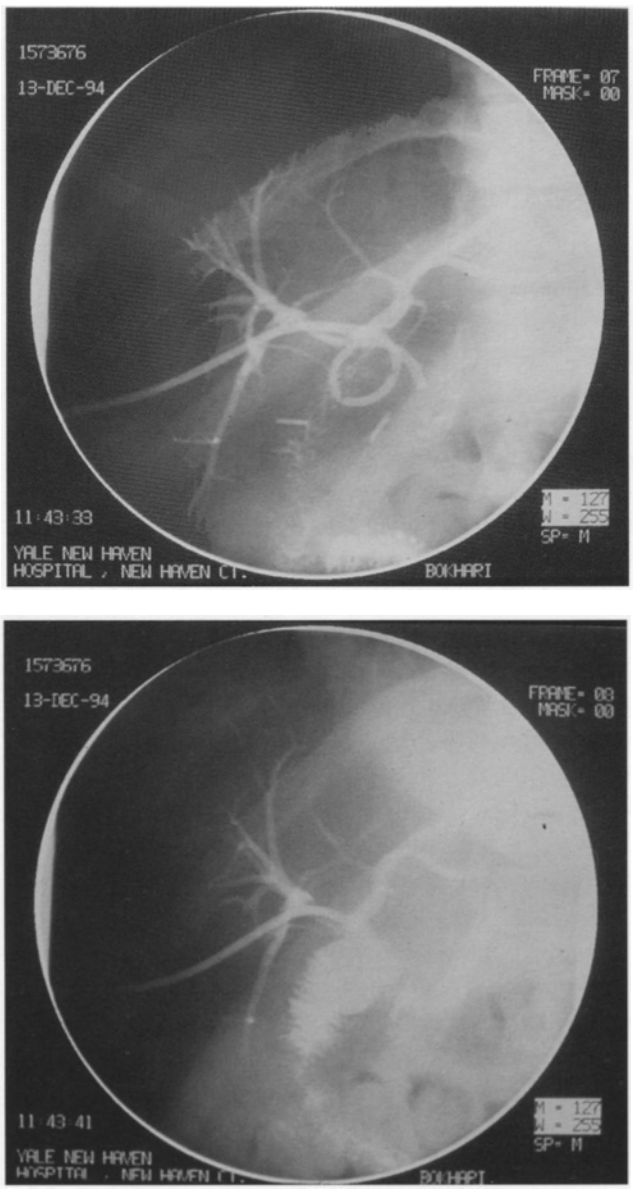

Fig. 14.8, 14.9. Hepatico-jejunostomy with placement of a transhepatic silastic tube. Contrast is flowing into the jejunal limb.

removal of the stent depends on the quality of the biliary segment used for the anastomosis. If the proximal segment of the duct is fibrosed or adequate length is not available for a mucosa-to-mucosa anastomosis, a long-term stent may be necessary. A horseshoe-shaped metallic marker or a coronary bypass type "O" ring can be sewn to the anti-mesenteric border of the Roux limb and secured to the anterior abdominal wall to allow for a transjejunal biliary intervention in the future [20]. The use of a Roux-en-Y limb of jejunum is preferable because it prevents the reflux of intestinal contents into the bile duct and minimizes the risk of cholangitis.

14.7.2. Repair of Proximal Biliary Injuries. The Hepp-Couinaud Technique

Biliary injuries or strictures located close to the confluence of the hepatic ducts or (Bismuth type III and IV) are technically difficult to repair. Often the confluence has to be debrided and an anastomosis between both the hepatic ducts and the jejunum is created. In cases of severe inflammation of the area adequate dissection or visualization of the confluence may be challenging. The use of the left hepatic duct for an anastomosis proximal to the bifurcation may be preferable in these cases because of (1) the anatomic integrity of the left hepatic duct and its branches, and (2) the left duct being more accessible than the right in the hilum of the liver.

Based on the anatomic works of Couinaud, Jacques Hepp re-described the operative technique of exposure and dissection of the intrahepatic segment of the left hepatic duct and the creation of anastomosis of the left hepatic duct with a limb of jejunum for the repair of proximal biliary duct strictures [21]. The left hepatic duct lies outside the liver parenchyma, between the caudate and the quadrate lobes of the liver. The left duct is the most anterior element of the portal triad. By dividing the hilar plate ("la plaque hilair") which Couinaud described as a "thickened part of Glisson's capsule", the left hepatic duct can be exposed. Initially, the surgeon needs to carefully dissect by the area of the hilum and to recognize the confluence of the hepatic ducts. The use of a 25 G needle to aspirate bile facilitates the identification of the ducts. An intraoperative cholangiogram is performed to delineate the anatomy. The "ligamentum teres" is divided and the cephalad retracted to expose the inferior aspect of the liver. Glisson's capsule is incised between the caudate and quadrate lobes, and the hilar plate is separated from the liver parenchyma with blunt dissection. The left hepatic duct is opened after it has been exposed, and a wide side-to-side hepatico-jejunostomy with a Roux-en-Y limb of jejunum is created (fig. 14.10). The use of a stent is optional and depends on the technica-

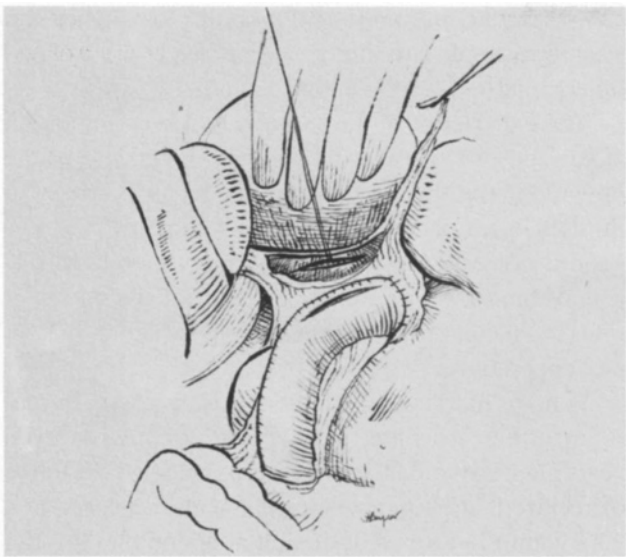

Fig. 14.10. Dissection of the hilar plate and visualization of the intrahepatic portion of the left hepatic duct to create an end-to-site hepatico-jejunostomy.

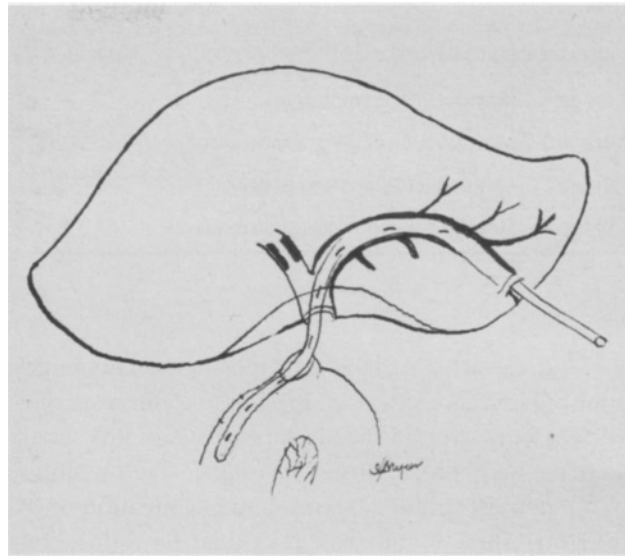

Fig. 14.11. The "mucosal graft" technique. A silastic tube is sutured to the jejunum and pulled back to bring together the jejunum and the intrahepatic portion of the left hepatic duct.

lities of each particular anastomosis and the preferences of the surgeon. The stent may be a "U"-shaped tube or a straight tube exiting through the liver or through the jejunum. The subhepatic area is drained with a closed suction or a sump drain, which is removed postoperatively, if there is no biliary drainage.

14.7.3. Mucosal Graft: The Rodney-Smith Technique

If the creation of a mucosa-to-mucosa anastomosis is not feasible, due to the inability to dissect an excessively fibrosed hilum, the mucosal graft-technique can be used to create a communication of the left hepatic duct with the jejunum. The left hepatic duct is cannulated transhepatically. The tube is advanced to the hilum of the liver and pulled out at the level of the hepatic duct confluence. The tube is subsequently introduced in the jejunal loop, through an opening and sutured to the jejunum. The transhepatic tube is pulled to place the jejunum into the hilum of the liver (fig. 14.11). The serosa of the jejunum is sutured to the Glisson's capsule with interrupted sutures. Acceptable long-term results have been reported for this technique in earlier patient series [22].

14.8. Perioperative and Long-Term Results

The operative mortality for repair of bile duct strictures is significant. In a cumulative review of 7,643 procedures performed in 5,586 patients, an overall mortality rate of 8.3% was reported [23]. More recent reviews, however, report mortality of less than 5% [24]. The number of previous attempts of repair and type of stricture significantly influences operative mortality. Operations for repair of type III and IV strictures, as well as operation performed for repair of recurrent strictures, have considerably higher mortality. Morbidity is also significant and influenced by the same factors [24]. The most common postoperative complications for operations performed for biliary reconstruction are: anastomotic leak, cholangitis, and hepatic failure.

Long-term follow up of patients undergoing biliary reconstruction is necessary due to the high incidence of recurrent stricture formation. Patients with recurrent strictures usually present with abdominal pain, liver failure, jaundice, and recurrent episodes of cholangitis. Some patients present with mild elevation of liver function tests, but remain asymptomatic. Grading systems have been developed to evaluate the outcome of patients undergoing operations for a benign biliary stricture (table 14.2).

Table 14.2. Proposed grading system for evaluation of patients after biliary reconstruction 25.	
Grade A	Normal LFT's, asymptomatic.
Grade B	Mild elevation of LFT's, asymtomatic.
Grade C	Abnormal LFTs, cholangitis pain.
Grade D	Surgical revision or dilatation required.

Mild elevation of liver enzymes is not uncommon after biliary reconstruction. Progressive elevation of liver enzymes even in the absence of symptoms should alert the surgeon to further investigate the possibility of a recurrent stricture. Ultrasound examination of the liver may show intrahepatic duct dilatation. If the bile ducts are dilated or if the patient experiences episodes of cholangitis, imaging of the biliary tree becomes necessary. If a Roux-en-Y hepatico-jejunostomy has been created, a detailed imaging of the bile ducts and the anastomosis can be achieved with percutaneous transhepatic cholangiography.

Good long-term results can be achieved in 70-90% of patients [26]. The success of the repair is inversely related to the number of previous operations for reconstruction. Other factors influencing the outcome are: the type of injury, the type of repair, and the experience of the surgeon. Operations for repair of proximal injuries present a higher incidence of recurrent strictures. For proximal, mainly type IV strictures, superior results have been reported with the Hepp-Couinaud technique. Long-term results of end-to-end primary repair of the bile duct seem to be inferior overall to the results of the hepaticojejunostomy. A failure rate of 40-50%, for end-to-end repair, has been reported in series with long patient follow up [27].

The presence of an arterial injury combined with a bile duct injury is one deserving particular attention. The incidence of an arterial injury was observed in 7% of patients who had previously undergone open cholecystectomy, in an autopsy series [28]. Although there is no data available for patients undergoing laparoscopic cholecystectomy, one could speculate that incidence may be even higher. The incidence of combined vascular and biliary injuries exceeds 20-30% in most series. Surgical reconstruction of combined arterial and biliary injuries are technically challenging. As a result, operative morbidity and mortality are higher and long term results are inferior compareed with isolated biliary injuries [29].

The experience of the surgeon is also an important factor and one that can influence the outcome of the operation. The success of the initial repair is crucial to the long-term patency of the anastomosis. If the surgeon is not experienced in performing high hepatico-jejunostomies, he or she should ask for assistance or refer the patient to a center with experience in this type of operation.

Long-term follow up of patients is necessary because recurrent strictures may appear months or even years after the initial repair. Approximately two-thirds of recurrent strictures will appear within 2 years, and 90% within five years of the initial operation [30]. If a recurrent stricture occurs, transhepatic balloon dilatation and stent placement may prove effective. Percutaneously placed angioplasty balloon catheters are used to progressively dilate the stricture. A stent is left in place after the procedure. Most patients with recurrent strictures however, will require re-operation. Re-operations for repair of recurrent bile duct strictures are generally more laborious, due to the significant amount of fibrosis present and the difficult dissection of the hilum of the liver. In this case, utilization of the left hepatic duct for the anastomosis can be an effective approach.

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CHAPTER 15

PRINCIPLES OF THE SURGICAL MANAGEMENT OF THE COMMON BILE DUCT STONES

Con. Ch. Karaliotas, S. Lanitis, G. Sgourakis

15.1. Introduction

Choledocholithiasis has always been a challenge for surgeons dealing with biliary pathology. Both diagnosis and treatment have evolved over the last years with the introduction and universal application of advanced imaging modalities as well as endoscopic and laparoscopic procedures. Consequently, the management of choledocholithiasis has been the subject of debate for several years and the classic treatment option for the management of the common bile duct stones (CBD), which traditionally was the open exploration of the CBD, is progressively less favorable as a first approach.

Currently, transabdominal ultrasound (US) and endoscopic retrograde cholangio-pancreatography (ERCP) form the mainstay preoperative imaging modalities while MRCP, endoscopic ultrasound (EUS), and spiral CT are gradually being established as potentially more accurate and less invasive tools. The indications of the intraoperative cholangiogram (IOC) remain inconclusive while, in experienced hands the intraoperative US can be an accurate tool in detecting CBD stones.

The exploration of the common bile duct (CBDE), if indicated is mainly performed using either the new established and safe laparoscopic technique or pre or post-operative endoscopic sphincterotomy (ES). The latter has proven to be particularly effective in instances such as failure of laparoscopic CBDE, surgical inexperience, unfavourable anatomy and patient selection.

Conventional open CBDE has limited but essential indications should never been looked upon as a failure. Nevertheless, it should not be the first approach as it increases morbidity which has already risen since the surgical experience in this technique has fallen into a decline [1]. Open sphincterotomy, sphincteroplasty, and choledochoenterostomy remain necessary operations for certain patients [2].

The National Institute of Health consensus in 1993 asserted that CBD stones must be detected and removed either prior, during or after cholecystectomy [3].

After the establishment of the laparoscopic cholecystectomy as the treatment of choice for gallbladder removal [3] and considering the lack of experience and equipment available at the time, exploration of the duct was passed on to the endoscopist and the ERCP with endoscopic sphincterotomy (ES) becoming the most common technique used. Later, advances in technology and increased surgical experience made laparoscopic exploration of the CBD both feasible and as effective as ERCP/ES.

A recent systemic review based on randomized control studies compared surgical versus endoscopic treatment of bile duct stones. This study revealed that laparoscopic CBD exploration is as effective as pre or postoperative ERCP/ES in clearing the duct with no differences in morbidity and mortality but with shorter hospital stay and less procedures per patient needed [3, 4]. Overall, however, the open exploration of the duct was found to be much more successful than any other combination of techniques with surprisingly less mortality than ERCP/ES and equal morbidity [3]. This does not mean that we should regress and consider the open exploration of the CBD as the first and only approach. It should, however, be considered a reliable and highly effective technique not to be forgotten and one that surgeons dealing with the biliary tree should be proficient equipped to apply when circumstances dictate.

15.2. Incidence of Choledocholithiasis

Cholecystectomy has been one of the most frequently performed surgical procedures in the world given that the presence of gallstones and symptomatic cholelithiasis are a common medical problem with an incidence of 10-20% [3-6].

The management of these patients, both in terms of the workup and treatment, is complicated in the presence of common bile stones, found in 5-20% [3, 5, 7, 8]. Furthermore, the morbidity associated with the disease is elevated, as is the cost because additional investigations, medications, therapeutic interventions and admission time are often necessary. A recent study demonstrated a 14.2% incidence of choledocholithiasis in 1.000 consecutive laparoscopic cholecystectomies with routine intraoperative cholangiogram [9].

Choledocholithiasis seems to be more common among the female population [10].

In the United States, the incidence rate for gallstones is approximately 40% in individuals over 60 years of age. In individuals undergoing cholecystectomy for symptomatic cholelithiasis, 8-15% of patients under 60 years of age have CBD stones, compared to 15-60% of patients over 60.

Fig. 15.1. Stones passed in CBD through cystic duct. (Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

15.3. Pathogenesis of CBD Stones

Gallstones have been traditionally classified as cholesterol stones and pigment stones based mainly on their chemical composition [11-13].

Cholesterol supersaturation, stasis, as well as accelerated nucleation can cause cholesterol stones. They are light brown, smooth or faceted, single or multiple. The sex of the patient, parity, obesity, weight loss, and genetics are all risk factors in the development of cholesterol stones [11, 12, 14]. In western countries, they compose 70% of all gallstones.

Pigment stones account for 30% of all gallstones [15-17].

Black pigment stones occur in conditions in which either bilirubin excretion is increased, (e.g. haemolytic disorders) or gallbladder bile stasis is pronounced (prolonged fasting and long-term parenteral nutrition). Pigment stones are more common in patients with cirrhosis and ileal disease, although the exact mechanism of stone formation under these conditions is not fully understood and are usually found in the gallbladder.

Brown pigment stones are made up of a mixture of pigment and bile lipids and are usually found in the bile ducts. They are associated with biliary stasis and bacteria infection [15-17].

CBD stones are usually "secondary" (85%) as a result of the passage of gallstones originally formed in the gallbladder through the cystic duct into the CBD (see fig. 15.1) [5]. Therefore, they have a typical spectrum of cholesterol stones and black pigment stones. Bacteria can be cultured from the surface of cholesterol and pigment stones but not from the core, suggesting that bacteria do not play a role in their formation.

"Primary" stones can also be "de novo" formed in the common bile duct (see fig. 15.2) and principally attributed to factors as bile stasis, which promotes the growth of bacteria, and chronic bactebilia. Primary CBD stones are usually soft and earthy in consistency, take the shape of the duct and have a higher content of cholesterol (Brown pigmented) 90% of which have cultures positive for bacteria even in the core of the stone. Other contributing factors include chemical and pH imbalances, increased bilirubin excretion, and formation of sludge [7, 17].

Fig. 15.2. "De novo" lithiasis of CBD.
(Modified. From "The CIBA collection of Medical illustrations" Frank Netter 1957, with permission of Novartis).

15.4. Clinical Findings

15.4.1. Cholelithiasis

Patients with cholelithiasis may be completely asymptomatic in about 85-90%. They may have moderate symptoms in 7-10% and only 3-5% of patients experience severe symptoms. The first symptom is usually (90%) biliary colic [10, 18].

The probability of developing biliary colic in the asymptomatic group is 11.9% + /-3.0% at 2 years, 16.5% +/-3.5% at 4 years, and 25.8% + /-4.6% at 10 years. The cumulative probability of developing complications after 10 years was 3.0% + /-1.8% in the initially asymptomatic group and 6.5% + /-4.4% in the symptomatic group. The probability of asymptomatic gallstones becoming symptomatic is about 2%/year [19].

15.4.2. Choledocholithiasis

The natural history of CBD stones is variable but they are more likely to cause symptoms. They can spontaneously pass into the duodenum (20%) either without causing symptoms or by causing a gallstone ileus [5] (fig. 2). They can also cause acute pancreatitis. Should they not pass, they may long remain asymptomatic or they may obstruct the CBD causing edema, spasm and fibrosis of the ductal wall and subsequent proximal dilatation of the duct and thickening of its wall [5].

An obstruction will lead to symptoms and complications that include pain, jaundice, cholangitis, pancreatitis, and sepsis [5, 17, 20, 21]. Finally it can erode to adjacent organs causing choledochoenteric fistulas [5].

The stones are found incidentally during cholecystectomy in about 7% of these cases.

Eventually CBD stones will partially or completely obstruct the CBD at some level in about 25-50% of the patients and even cause biliary infection, necessitating treatment.

A history of cholelithiasis is not essential for the diagnosis of choledocholithiasis as gallbladder stones can be asymptomatic.

The vast majority of patients present with right upper quadrant pain which is colicky in nature, moderate in severity, intermittent, transient, and recurrent and may be associated with nausea and vomiting [5].

If the pain is severe, a coexisting condition should be suspected as the primary cause of pain.

Typical obstructive jaundice with discoloration of stools and dark colored urine occurs only in 50% of jaundiced patients with obstructed CBD. Jaundice can be intermittent since the stone can flow back up into the dilated CBD when dilatation develops, allowing the edema to subside and temporarily relieving the obstruction [5].

Fever suggests infection and the classic "Charcot's triad" of fever, jaundice, and right upper quadrant pain strongly favors the diagnosis of cholangitis. Nevertheless, the full clinical picture is found only in a small percentage of these patients (19%). Overall 92% of patients present with fever, 65% with jaundice, and 42% with pain.

Five percent of cholangitis patients may present with septic shock indicating acute obstructive suppurative cholangitis. In these cases, the patient presents with the classic Raynauld's pentad which further includes mental status changes and systemic shock with hypotension [5, 6].

Generally, a dilated CBD>12 mm in combination with raised bilirubin or past history of jaundice can predict the diagnosis of choledocholithiasis up to 90-100% [22].

Gallstone pancreatitis accounts for 50% of all cases of pancreatitis and eventually 4-8% of patients with gallstones develop pancreatitis. The presentation then

differs; the pain is located in the epigastric and mid-abdominal areas, it is sharp, severe, and continuous, with radiation to the back. Bending over can alleviate the pain. Nausea and vomiting are frequently present, and approximately 15% patients report a similar previous episode.

Patients presenting with cholecystitis, biliary colic, pancreatitis, and jaundice were found to have common duct stones 7%, 16%, 20%, and 45% of the time, respectively [2] (table 15.1).

Table 15.1. CBD stones natural history and associated conditions.

CBD stones (Pass to duodenum 20%)	CBD stones remained "in situ" (80%)
• Asymptomatic • Gallstone ileus • Pancreatitis	• Asymptomatic • Obstruction of CBD – Colic – Jaundice • Pancreatitis • Cholangitis • Choledochoenteric fistulas

15.4.3. Physical Examination

There are no specific signs for the diagnosis of symptomatic choledocholithiasis.

Right upper quadrant abdominal tenderness, which is moderate in severity, is the main finding while guarding (voluntary or involuntary) or rebound is absent.

Severe tenderness, including the "Murphy sign", should suggest the presence of acute cholecystitis.

Depending on the severity and duration of CBD obstruction, the extent of the jaundice may vary.

Against a background of infection and sepsis, nonspecific systemic signs such as fever, hypotension, and flushing may be present.

15.4.4. Laboratory Studies

As most patients with CBD stones are asymptomatic, laboratory tests can be completely normal. Patients with cholangitis and pancreatitis have abnormal laboratory test values which are suggestive rather than specific.

Raised WBC (WCC) count merely indicates the presence of infection or inflammation.

Serum bilirubin (Bil) level elevations indicate obstruction of the CBD.

Serum amylase (Amyl) and lipase values are elevated in the presence of acute pancreatitis complicating choledocholithiasis. Alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels are elevated in patients with obstructive choledocholithiasis ALP and Bilirubin are elevated early in the course of the disease and in addition to AST and LDH are cumulative in predicting CBD stones. When one of these is elevated the propability for stones is 20% while when two are raised the propability increases to 40% and more than 3 raised values >50% [5].

A recent study found that GGT has overall better specificity and is the most sensitive marker. A GGT level of >90u/l indicates a high risk for CBD stones and warrants further imaging while if it is <90 u/l there is only 30% likelihood of CBD stones and can be managed expectantly [23].

Liver function tests including transaminases (serum glutamic-pyruvic transaminase (SGPT/ ALT and serum glutamic-oxaloacetic transaminase SGOT/AST) levels are elevated in patients with choledocholithiasis complicated by cholangitis, pancreatitis, or both. Prothrombin time (PT) may be elevated in patients with prolonged CBD obstruction, secondary to depletion of vitamin K (the absorption of which is bile-dependent). Blood culture results are positive in 30-60% of patients with cholangitis and usually E. Coli grows in the cultures [5].

15.5. The Surgeon's View in Perioperative Imaging Study of CBD

We can classify the available diagnostic modalities as preoperative, intraoperative and postoperative (table 15.2). Despite the fact that cholangiography remains the most reliable test for the diagnosis of choledocholithiasis, its invasive nature, associated morbidity, and cost make it not favorable for screening test of choice.

15.5.1. Preoperative Studies

15.5.1.1. *Transabdominal Ultrasonography (US)*

It is the first line diagnostic modality for the assessment of the biliary tree in cases with biliary-related symptoms because it is sensitive, noninvasive, inexpensive, and readily available. It can accurately diagnose gallbladder stones (97% in elective situations and

Table 15.2. The Surgeon's View in Perioperative Imaging Study of CBD.

Preoperative studies
- Transabdominal ultrasonography (U/S).
- Endoscopic ultrasonography (EUS).
- Computed tomography scan (CT).
- HCT-C helical computer tomographic cholangiography (same detect ability as MRCP).
- Magnetic Resonance Cholangio Pancreatography (MRCP).
- Cholangiography.
- Endoscopic Retrograde Cholangio Pancreatography (ERCP).
- Percutaneous Transhepatic Cholangiogram (PTC).

Intraoperative studies
- Intraoperative cholangiography (IOC).
- Rigid / Flexible Choledochoscopy.
- Intraoperative ultrasonography.

Postoperative studies
- T-tube cholangiography.
- ERCP.
- PTC.

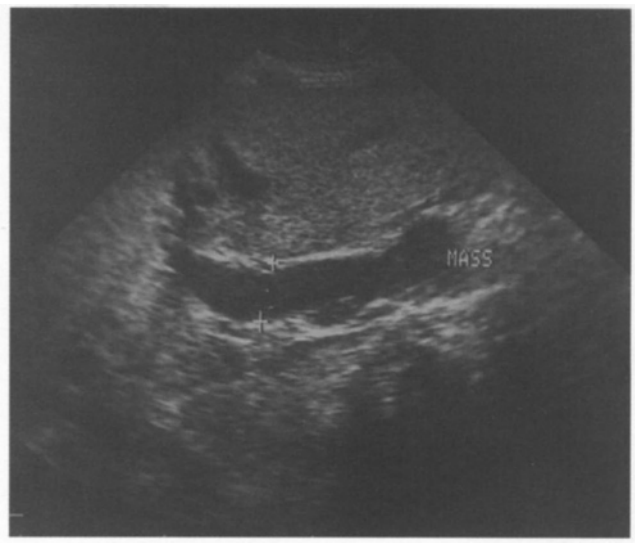


Fig. 15.3. Trans - abdominal Ultrasonography with erroneous initial diagnosis "mass in the CBD" It was a stone with a lot of sludge.

80% in the presence of acute cholecystitis), but the sensitivity in identifying CBD stones is far less (15-40%) mostly because the retro duodenal part of the CBD is hardly visible as a result of gas in the duodenum (fig. 15.3) [24]. Overall, the sensitivity in detecting common duct stones is no more than 18%-74% [6]. Diagnosis depends mostly on the presence of common bile duct dilatation (>10mm) which can be identified, with up to 90% accuracy and on the presence of echogenic foci in the CBD. A combination of CBD dilatation on U/S with an age greater than 55 and abnormal liver enzymes, can predict CBD stones up to 95% of the time [2, 5].

Nevertheless, a non-dilated duct cannot exclude choledocholithiasis and the overall usefulness of ultrasonography findings as a predictor of CBD stones is at best 15-20%.

15.5.1.2. *Endoscopic Ultrasonography (EUS)*

The reported sensitivity and specificity of CBD stone detection with the EUS is 85-100%, which is much higher than that of transabdominal U/S. Recent studies confirmed the high sensitivity and specificity as being equal to those of the diagnostic ERCP (98% and 99% respectively) [5, 6]. It can detect CBD stones as small as 5mm (fig. 15.4). This is usually not feasible with the MRCP and the Helical Computer Tomographic-Colan-

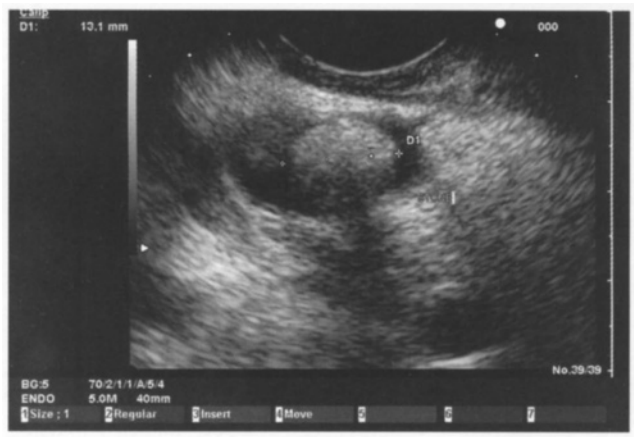


Fig. 15.4. Endoscopic ultrasonography: stone in CBD.

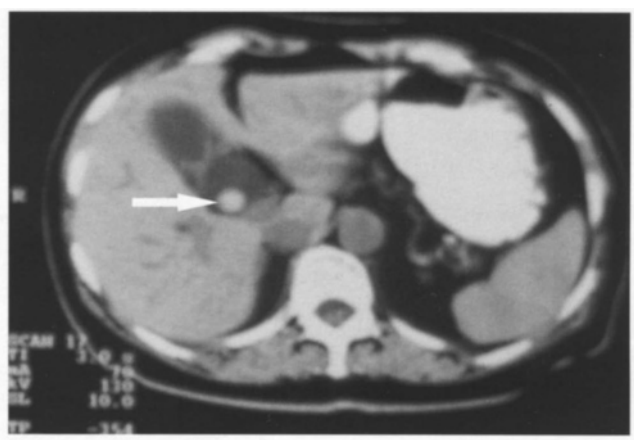


Fig. 15.5. CT of upper abdomen. Distension of Common bile duct. The arrow depicts a stone in CBD.

giography (HCT-C). It can further detect a thickened duct wall and presence of enlarged lymph nodes in the area, signs of inflammation [6]. Its major advantage is decreased morbidity as compared with ERCP. In addition, there is no need for cannulation of the CBD and no exposure to radiation is involved. However, endoscopic ultrasound is highly operator-dependent [2]. Moreover, it is more costly than transabdominal U/S, a partly invasive procedure, and not readily available since an experienced endoscopist / ultrasonographer is needed [5].

15.5.1.3. *Computed Tomography Scan (CT)*

With a sensitivity up to 50-90% [6] in the detection of CBD stones, CT scan is considered an essential tool in the evaluation of patients with jaundice (fig. 15.5).

Capable of defining the level of the obstruction, it can also demonstrate ductal dilatation, both intrahepatic and extrahepatic, and further provides information about the surrounding structures, especially the pancreas. Nevertheless, it involves radiation with all the associated risks.

Helical computer tomographic cholangiography (HCT-C) possesses the same detection ability as MRCP and a sensitivity of 95% [5, 6]. Nevertheless, it is subject to the same limitations as conventional CT.

15.5.1.4. *Magnetic Resonance Cholangio Pancreatography (MRCP)*

This is the most recently introduced diagnostic tool which was first described in 1991 [25] and seems ideal for the diagnosis of biliary pathology that cannot be otherwise accurately demonstrated with other non invasive modalities (fig. 15.6a, b). Bile duct anomalies and stones can be detected without the need for intervention or radiation, furthermore, it is 100% safe [24].

It uses a heavily weighted T2 pulse sequence which displays the non-flowing fluid in the biliary tree and pancreatic ducts [24].

MRCP combines the advantages of high accuracy (89-100%), sensitivity (81-100%), and specificity (85-100%) [24] with non-invasiveness, providing positive predictive values of 95%-100% [2]. The disadvantages include high cost, time-consumption and the lack of therapeutic possibilities of ERC [2]. In addition, certain factors such as obesity, presence of metal objects (eg, pacemakers, cerebral aneurism clips) and claustrophobia, preclude its application.

Nevertheless, despite its high cost as a diagnostic tool, it is still 5 times less expensive than ERCP and the overall cost to an institution could be reduced if a percentage of ERCPs were avoided. In the same study it has been suggested that MRCP should detect 97% of the larger stones (diameter>5mm) which are unlikely

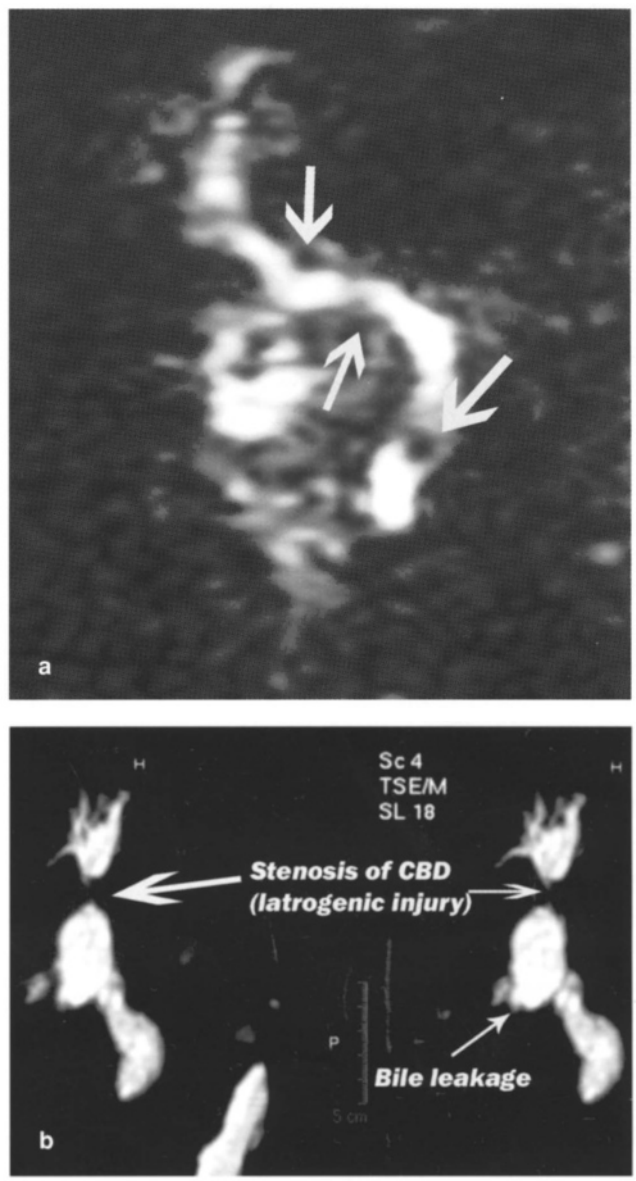


Fig. 15.6.
a: MRCP with stones in CBD.
b: MRCP solved the diagnostic problem 30 days after laparoscopic cholecystectomy. Iatrogenic injury of the CBD with stricture at the confluence. Slight bile leakage.

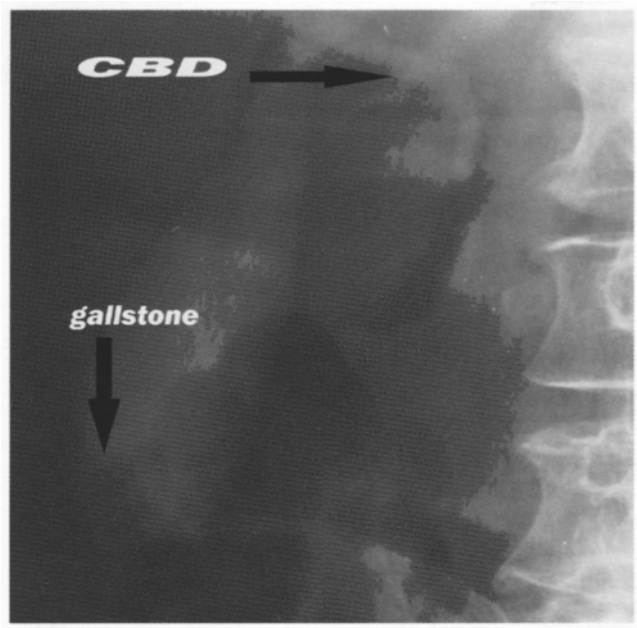


Fig. 15.7. Gallbladder stone in preoperative IV cholangiography. Today out of use.

to pass spontaneously while those that can be missed will probably pass without complication [24].

15.5.1.5. *Preoperative Cholangiography*

We are much obliged to history for referring to intravenous cholaniography (IV).

It used to be the only diagnostic tool in the form of IV cholangiography for assessing the biliary tree with minimal sensitivity and many limitations (fig. 15.7). The IV form is hardly used nowadays since the introduction of endoscopic (ERCP) as well as the percutaneous (PTC) approach which until today remain the criterion standard for the detection of CBD stones and have a sensitivity up to 95% and specificity up to 92-98% [5].

15.5.1.6. *Endoscopic Retrograde Cholangio Pancreatography (ERCP)*

It has become the diagnostic and therapeutic tool of choice in patients with choledocholithiasis since its introduction in the early 1970s (fig. 15.8 a, b, c).

According to the experience of the endoscopist the success of the procedure reaches 90-95%. The CBD is cannulated through the ampulla, in order to inject the

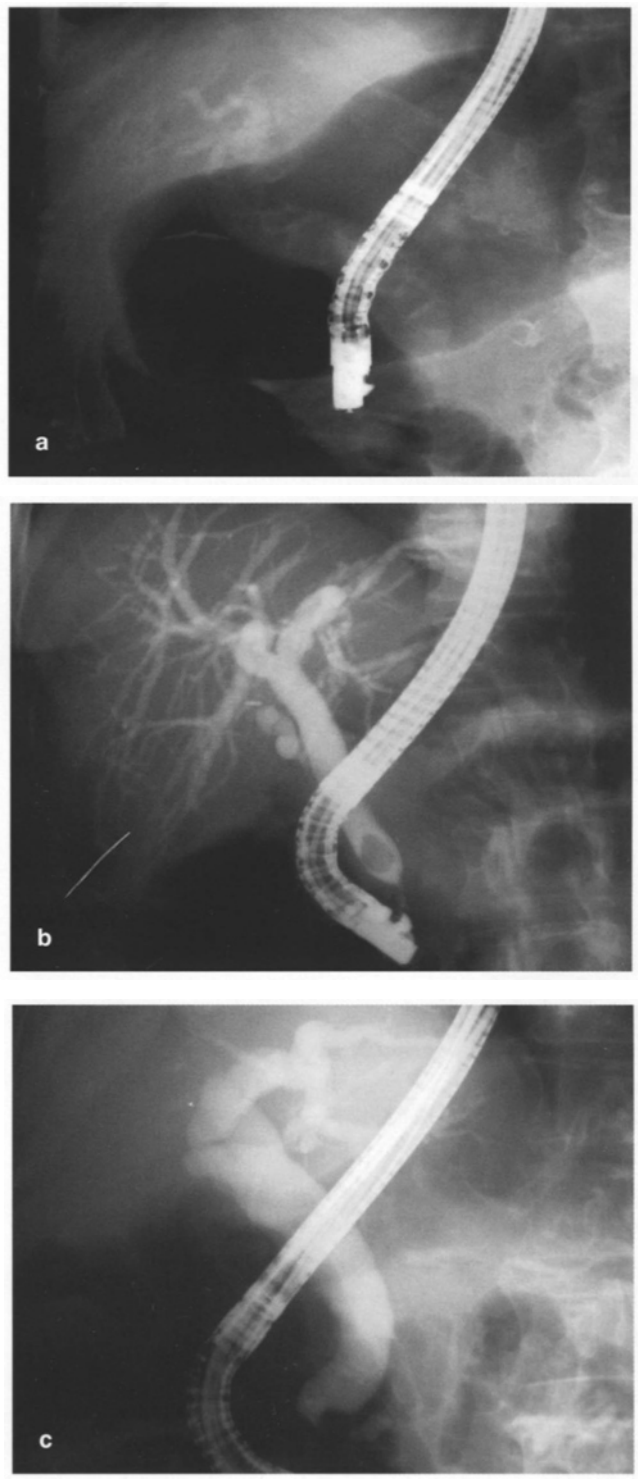


Fig. 15.8.
a. Preoperative ERCP. Common bile duct crammed with stones. Paradoxically enough the patient was appearing slight symptoms and signs.
b. Postoperative ERCP. Retained stone in the CBD after laparoscopic exploration.
c. Preoperative ERCP. Impacted stone in the ampoule.

contrast material directly to the biliary tree. In most centers, ERCP is the modality of choice when choledocholithiasis is suspected since it can combine diagnosis and treatment at the same time. It displays identical sensitivity and specificity to that of cholangiography (95% and 98%) [5]. In terms of its therapeutic application, the first ERCP achieves a success rate of about 85% which can be increased with additional procedures [26].

Nevertheless, it is not free of risks and a recent prospective study of 1177 consecutive ERCS demonstrated a 30-day morbidity rate of 15.9%, with procedure-related mortality at 1% which confirms what other authors have supported in the literature [2, 6, 24]. Major complications include hyperamylasemia and cholangitis but perforation of the duodenum and bleeding can also occur. Prophylactic antibiotics are often recommended, especially in patients with CBD obstruction.

Failure is usually due to inability to cannulate the papilla and reaches 3-10% [24].

15.5.1.7. *Percutaneous Transhepatic Cholangiogram (PTC)*

It is a second line modality and usually reserved for patients in whom ERCP is difficult or impossible to perform (eg, those with previous gastric surgery or distal obstructing CBD stone or the lack of an experienced endoscopist). It also constitutes an attractive option in patients with extensive intrahepatic stone disease and cholangiohepatitis. A long large-bore needle is advanced percutaneously and transhepatically into an intrahepatic duct and cholangiography is performed. A catheter can be placed in the biliary tree over a guidewire. Contraindications to this approach are uncorrected coagulopathy while the normal size of the intrahepatic ducts can impede the procedure difficult. Prophylactic antibiotics are recommended to reduce the risk of cholangitis [5].

15.5.2. Intraoperative Studies

15.5.2.1. *Intraoperative Cholangiography (IOC) (Tables 15.3, 15.4)*

Since it was described by Dr. Mirizzi in 1931 [27], in the era of conventional open cholecyctectomy, IOC has traditionally formed a basic step of the operation (fig. 15.9). This changed radically with the introduction of the laparoscopic approach. It has been highly debatable whether the use of routine intraoperative cholangiography (IOC) during a cholecystectomy is necessary [20, 28, 29]. While it is supported that it can provide accurate information concerning biliary anatomy and the presence of CBD stones, thereby decreasing the incidence of intraoperative bile duct injury, on the other hand it increases risk and cost by giving a false positive result (2-16%) [30] which can lead to unne-

Table 15.3. Information obtained from IOC.

- Length of cystic duct and location of its junction with the CBD.
- Size of the CBD.
- Presence of intraluminal filling defects.
- Free flow of contrast into the duodenum.
- Anatomy of the extrahepatic and intrahepatic biliary tree.

Table 15.4. Causes of procedure failure.

- Inability to cannulate the cystic duct.
- Leakage of contrast during the injection.
- Air bubbles mimicking stones.
- Quick flow of the contrast into the duodenum, luck of proper filling of the biliary tree.
- Spasm of the sphincter of Oddi.

Fig. 15.9. Intraoperative cholangiography. Large stones in the CBD. Two efforts with ERCP for clearance were unsuccessful. Laparoscopic cholecystectomy was converted to open exploration because of huge inflammation.

cessary CBD exploration in a patient without suggestion of CBD stones. Also in a prospective study it was found that about half of the positive IOC without exploration of the duct were either false positive or the stones had passed spontaneously [28, 31]. Moreover, the incidence of biliary tree injury as well as the incidence of retained stones is no different from that of patients who underwent IOC only when CBD stones were suspected clinically.

On the other hand, the incidence of unsuspected stones is about 3-7% and a routine application can help identify these patients.

Selective IOC can be performed on patients with suggestive symptoms like history of jaundice, biliary pancreatitis, dilated CBD on US and elevated LFT. However, even in such cases, ERCP or CD exploration can only revealed stones in 46-62% [28].

Nevertheless, even if CBD stones were demonstrated preoperatively, an intraoperative cholangiogram prior to a planned exploration is advisable in order to confirm that the stone is still located in the CBD and has not passed to the duodenum [20].

A recent evaluation of the factors affecting the decision for performing an IOC demonstrated that only a dilated CBD on U/S or raised bilirubin can predict the presence of CBD stones. It is suggested that the old criteria (deteriorated LFT or clinical history of jaundice and pancreatitis) not be used. In the same study a prospective analysis showed that patients with CBD <10mm, with normal LFT and no history of jaundice/pancreatitis who were not submitted to IOC, had no evidence of retained stones in a long follow up.

As a consequence, preoperative ERCP is recommended for patients having CBD dilatation and raised bilirubin while IOC for those with only CBD dilatation [28].

A postoperative ERCP has been suggested for those patients with an abnormal IOC but studies revealed that about 1/3 of those were not found to have stones in the CBD, since small stones can pass spontaneously. Therefore a more selective and less invasive approach is recommended for those patients with an abnormal IOC but normal LFTs [31].

In terms of the technique, IOC is performed by inserting a catheter intraoperatively into the cystic duct, followed by injection of diluted (50%) contrast material to outline the biliary tree. Films are taken and are assessed for the presence of filling defects, the anatomy and caliber of the biliary tree, and the flow of contrast into the duodenum. This procedure can be performed at open or laparoscopic cholecystectomy.

IOC findings have a positive predictive value of 60-75% for the detection of CBD stones.

Most of the recent studies support the limited use of IOC [28].

15.5.2.2. *Choledochoscopy*

It can be performed using either open or laparoscopic techniques (fig. 15.10). With advances in technology, small, flexible choledochoscopes with high definition can now be used through either the cystic duct or the CBD to directly visualize and even extract the CBD stones using balloon catheters and dormia basket. Furthermore, application of lithotripsy is available. Sensitivity for detection approaches 100% in expert hands. Choledochoscopy can be performed postoperatively through the tract of a T-tube about 6 weeks after the T-tube was placed.

15.5.2.3. *Intraoperative Ultrasonography (IUS)*

Special probes are used to visualize the biliary tree. It can be performed using either open or laparoscopic techniques, and results have a positive predictive value of approximately 75%. It provides better resolution than transabdominal ultrasonography and with the recent introduction of a small high frequency probe in a 6F sheath; it is now possible to perform intraluminal ultrasonography.

The reported specificity is equal, while the sensitivity is better than that of IOC [2], it is less time consuming (7 + /-3 min versus 13 + /-6 min) and no cannu-

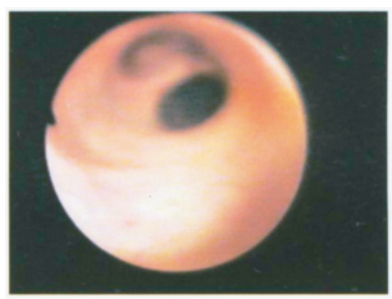


Fig. 15.10. Choledochoscopy: classical view of hepatic ducts confluence.

lation of the CBD or exposure to radiation is needed. Therefore, evaluation of the CBD by intraoperative US is a viable alternative to IOC, although most surgeons are not familiar with this technique. Being operator-dependent, the latter can limit the usefulness of this modality [2,5]. Prospective studies also showed that IUS was more sensitive for detecting stones, but that IOC was better in delineating intrahepatic anatomy and defining anatomical anomalies of the ductal system. The authors concluded that the two methods of duct imaging were complementary [2] (see also chapter 4).

15.5.3. Postoperative Studies

15.5.3.1. *T-tube Cholangiography*

Even after CBD exploration a small percentage (2-10%) of retained CBD stones can be identified, usually on routine T-tube cholangiography performed at 7-10 days postoperatively (fig. 15.11).

T-tubes are placed following CBD exploration to help in the diagnosis and management of retained stones. Various opinions have been expressed concerning T-tube management. If no obstruction is identified on the early (1st week) cholangiogram it can be removed somewhere between the 1st and 2nd postoperative week. If there is a retained stone, it can be clamped and left in place for 6 weeks. The cholangiogram is repeated after this period (small stones may pass spontaneously), and any retained stones can be removed percutaneously.

15.5.3.2. *ERCP*

This has become the modality of choice to aid in the diagnosis and treatment of retained stones, after cholecystectomy, that went undetected or were left behind to be dealt with endoscopically.

Endoscopic sphincterotomy (ES): This procedure can be performed postoperatively for retained CBD stones. Usually, stones smaller than 1 cm pass spontaneously within a few days of the sphincterotomy. For extraction of larger stones, a basket or a balloon catheter is required. Endoscopic sphincterotomy is contraindicated in patients with coagulopathy and usually in patients with a long distal CBD.

(More about ERCP in preoperative imaging as well as in treatment section).

Table 15.5. Non operative/ non interventional procedures.

- Dissolution Therapy (Ursodiol, Actigall).
- Extracorporeal shock lithotripsy (ESWL) [High rate of failure (95%) when used alone with a high complication rate (19%). Complications include biliary pain (13%), cholangitis (5%), hemobilia (5%), ileus (2.5%), and complications related to the procedure itself (13%)].

Table 15.6. Complementary procedures (lithotripsy methods).

- Mechanical (M.L.).
- Electrohydraulic Lithotripsy (E.H.L.).
- Laser Lithotripsy (L.L.).

15.5.3.3. *PTC*

This is used in patients with retained intrahepatic stones or in patients with gastric surgery, in whom ERCP is more difficult to perform.

15.6. Treatment of Choledocholithiasis

The aim of treatment is to extract or dissolve the stone which can be done using non-operative, interventional and surgical techniques (tables 15.5, 15.6). However, if this is not possible, the aim is then to provide drainage for the obstructed bile in order to improve the patient's condition while waiting for definitive surgical intervention. Non-surgical procedures can also be performed postoperatively to remove retained stones. Lithotripsy techniques are complementary to both the surgical and interventional approach.

Interventional Treatment of Choledocholithiasis (Table 15.7)

Table 15.7. Interventional procedures.

Non Surgical

a. ERCP (sphincterotomy (E.S), balloon dilatation, stenting, lithotripsy).
b. PTC (lithotripsy, choledochoscopy).

Surgical

a. Choledocholithotomy (CBD exploration and stone retrieval):
   - Open.
   - Laparoscopic.
b. Biliary drainage procedures.
   - Transduodenal sphincteroplasty.
   - Choledochoduodenostomy.
   - Roux en-Y choledochojejunostomy.

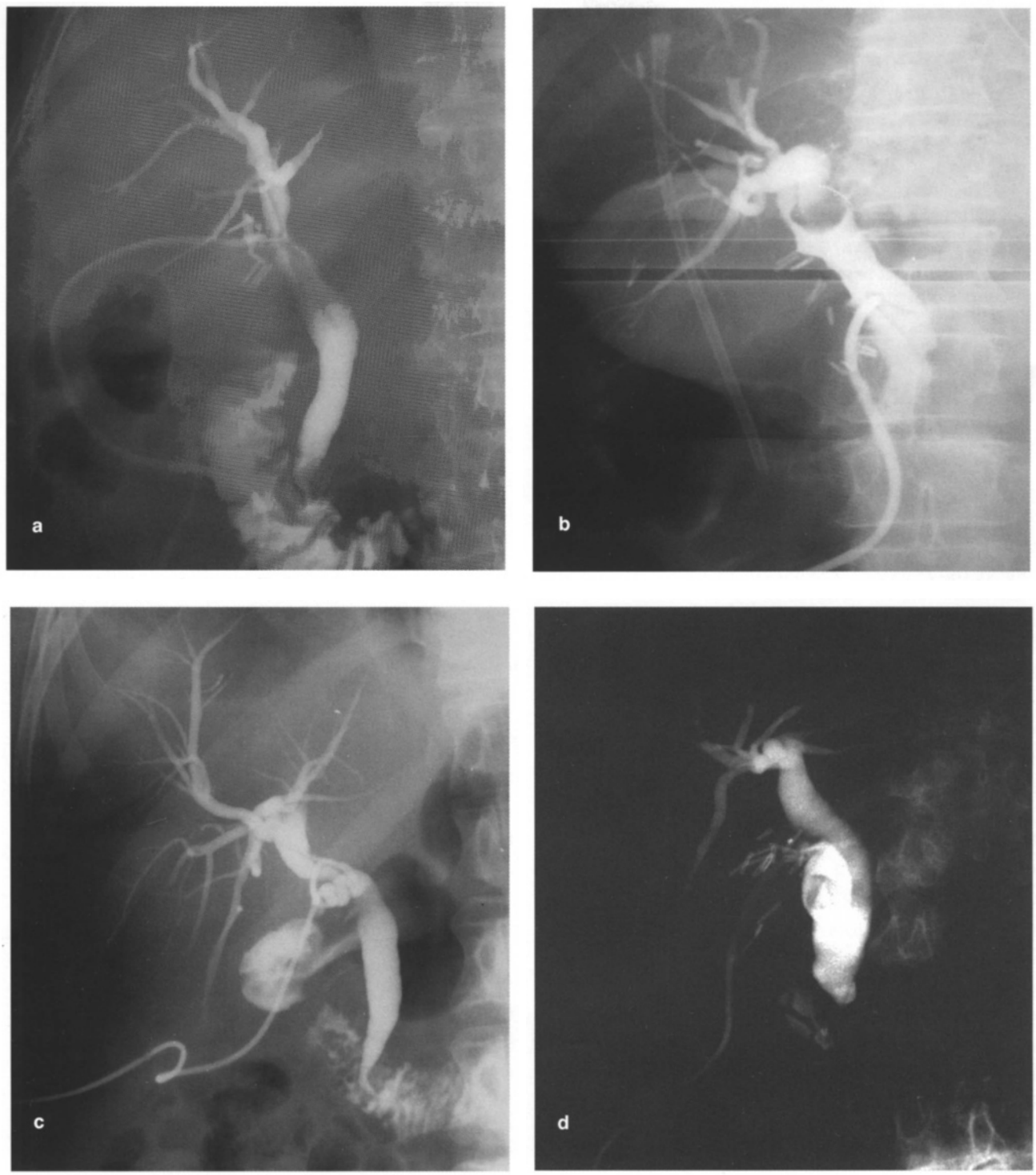


Fig. 15.11.
a. Postoperative cholangiogram via T-tube after laparoscopic exploration of CBD. Successful clearance of CBD.
b. Missed stone in CBD at the end of laparoscopic exploration. New attempt at the same time was successful.
c. Normal postoperative cholangiogram via T-tube after open exploration of CBD.
d. Normal postoperative cholangiogram via T-tube on third post-operative day after laparoscopic exploration of CBD.
The common bile duct was completely cleared, but a stone embedded in the cystic duct stump. The tightly embedded stone removed with ERCP/sphincterotomy.

15.6.1. Non-Surgical Approach

15.6.1.1. *Endoscopic Retrograde Cholangiopancreatography ERCP + /-ES*

ERCP is a sensitive and specific diagnostic tool and therefore initially is used as such. Indications include, apart from suspected or confirmed CBD stones, persistent jaundice, suspected malignancy, ascending cholangitis and pancreatitis.

Unfortunately no stones are found in 20-60% of the patients submitted to ERCP for suspected choledocholithiasis and morbidity can unnecessary increase in this group [32]. On confirmation of the presence of choledocholithiasis (initial or retained stones), various therapeutic options are available depending on the size and location of the stone(s) with a success rate of about 85%.

Usually, a sphincterotomy (E.S.) is performed in order to either retrieve larger stones (1-2cm) with a Dormia basket or a Fogarty catheter or to allow smaller ones (<1cm) to pass spontaneously usually within 48h. Smaller stones can sometimes be retrieved with an intact papilla while larger ones (>2cm) may additionally require lithotripsy or chemical dissolution.

Should stone extraction prove unsuccessful, a surgical approach (open / laparoscopic) with CBD exploration or a biliary drainage procedure, whether internal or external, can be performed.

In expert hands, the success rate of stone extraction by ERCP in cases of choledocholithiasis reaches 85-90%. Complications of sphincterotomy and stone extraction occur in 10% of cases [5]. These include bleeding (2%), duodenal perforation (1%), cholangitis (2%), pancreatitis (2%), bile duct injury (<1%), and the usual complications associated with upper GI endoscopy (2%). The mortality rate following endoscopic sphincterotomy is 1% [2, 5, 24, 32]. Endoscopic sphincterotomy is contraindicated in patients with uncorrected coagulopathy.

15.6.1.2. *Percutaneous Extraction*

This is performed after diagnostic PTC findings have confirmed the presence of CBD stones. An external biliary catheter is placed percutaneously into the biliary tree, and the tract is dilated over several weeks (2-6 wk) up to 16F size by placement of progressively larger catheters. The CBD stones are then extracted using a Dormia basket or a choledochoscope. Complementary techniques (lithotripsy) can also facilitate the fragmentation and extraction of stones. Stones or their fragments can be trapped inside a basket and passed through the sphincter of Oddi into the duodenum or retrieved through the tract. The procedure may need to be repeated for complete clearance.

The morbidity rate is approximately 10%, and the mortality rate is 1%. Complications include bleeding, duct injury, bile leakage, and cholangitis. The success rate is 75-85%. The procedure is contraindicated in patients with coagulopathy.

15.6.2. *Surgical Approach*

Traditionally, before the introduction of minimal invasive techniques, open choledochotomy and extraction of the stones (choledocholithotomy), initially described by Courvoisier in 1889 [4] had been the standard of care for the treatment of choledocholithiasis. However, surgical exploration of the CBD increases the low morbidity and mortality of the simple cholecystectomy (<0.5%) by 3-7 times. Morbidity is more elevated in positive rather than negative exploration and can be as high as 19% [33].

With the advances in technology and the experience gained in the field of laparoscopic and endoscopic surgery, the open exploration of the CBD has gradually been replaced by these techniques as a first line treatment, mainly because less interventional techniques are associated with less postoperative pain and discomfort, followed by a short recovery period and less morbidity.

Nevertheless, it remains a viable option in situations in which laparoscopy and endoscopy is contraindicated or when these modalities have failed. Although this procedure carries a low morbidity and mortality rate in young patients (<1%), the mortality rate is as high as 4% in elderly populations [33]. The most common reason for converting to open CBDE is an impacted stone at the ampulla of Vater and usually these cases require a transduodenal exploration. Open CBDE should also be considered as the initial procedure of choice if patients present with dilated CBD, multiple common bile duct stones or when minimally invasive techniques are not readily available. This entails either performing a

choledocholithotomy, choledochoenterostomy or a sphincterotomy (sphinteroplasty). Studies have shown overall similar results with either of the two operations. Therefore, surgical experience should dictate which one to perform. Some authors, however, have suggested choledochoenterostomy for CBD greater than 2 cm in diameter in order to create a large opening between the bile duct and intestine [2, 20, 34-39].

Two issues must be addressed in the surgical treatment of choledocholithiasis,

- the exploration of the CBD and
- the fate of the gallbladder.

Exploration of the CBD should include clearance of the stones and, sometimes, a drainage procedure.

Surgical methods used to achieve this goal vary and can be performed by an open or laparoscopic route. The timing and necessity of a cholecystectomy in patients with choledocholithiasis who have asymptomatic gallbladder stones remains a subject of debate.

15.6.2.1. *Choledocholithotomy (See Table 15.8)*

During CBD exploration the surgeon should be aware of the possible complications which mainly comprise injury of the bile duct during attempt to remove stones, creation of a false passage to the duodenum when probing the duct, incomplete clearance of the duct and perforation of a duodenal diverticulum.

Technically, during the exploration of the distal duct care must be taken to avoid trauma in the ampulla and subsequent pancreatitis. It is preferable to abandon manipulation of the ampulla when not feasible and proceed with duodenotomy and exposure of the ampulla in order to avoid possible CBD peroration [34].

Table 15.8. Indications for common duct exploration [5, 20, 21, 33, 34, 40, 41].

a. Chills, jaundice and Fever before the operation (in more than 90-97% of the cases there are CBD stones during the exploration).
b. Palpation of a stone in the CBD during operation (this maneuver should be done from liver hilum to the papilla after Kocher maneuver and has an accuracy of 98%).
c. Demonstration of a stone during the workup of the patient (either preoperatively or intraoperatively).
d. Acute suppurative cholangiitis.
e. Retained stones in the CBD (postoperatively are usually dealt with endoscopically or by interventional radiology. If both methods fail, operative management is contemplated).

15.6.2.2. *Exploration of the CBD: Technique*

Incision

Either technique can be adopted through a subcostal (Kocher), transverse, paramedial (Para-rectal) or midline incision. The choice depends on the patient's habitus, the operating possibilities (i.e extension of the incision) and the personal preference of the surgeon.

Exposure

Two packs should be placed, one over the first part of the duodenum and one over the hepatic flexure. In order to create a wide operating field the liver should be gently retracted superiorly before the packing. A third pack can be applied to keep the stomach and lesser omentum retracted to the left of the patient. In order to properly expose the common bile duct and accurately evaluate the presence of CBD stones a complete Kocher manoeuvre should be effected, allowing more direct control of the CBD instrumentation (fig. 15.12).

Trancystic Exploration of the CBD

This technique is used to clear the CBD of stones mostly during laparoscopic cholecystectomy, after choledocholithiasis is confirmed based on findings of IOC. The cystic duct is dissected close to its junction with the CBD, and a transverse incision is made in that area.

The CBD can be irrigated with N/S in an attempt to flush small stones through the sphincter of Oddi or out through the opening in the cystic duct. For extraction of larger stones, a Dormia basket is passed over a guidewire into the CBD under fluoroscopic guidance.

If the cystic duct is large enough or can be balloon-dilated, a flexible choledochoscope is passed and the CBD examined under direct vision.

Balloon dilatation of the sphincter of Oddi can be performed when all other techniques have failed to clear the stones. A risk exists for mild pancreatitis (3% in one series). It is indicated in the presence of small ducts, for which the risk of CBD stricture after choledochotomy is high. Independent small series report a success rate up to 80%.

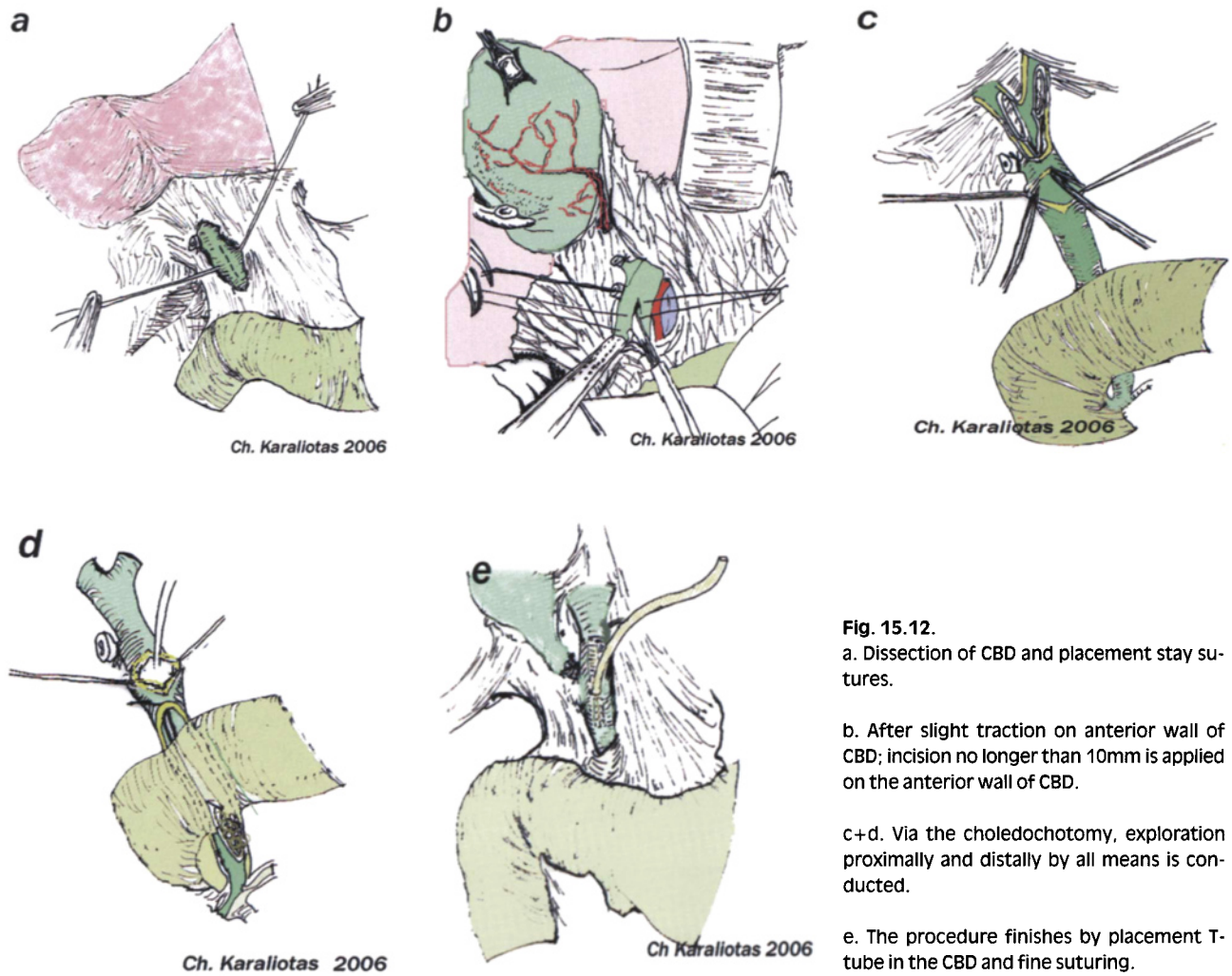


Fig. 15.12.
a. Dissection of CBD and placement stay sutures.

b. After slight traction on anterior wall of CBD; incision no longer than 10mm is applied on the anterior wall of CBD.

c+d. Via the choledochotomy, exploration proximally and distally by all means is conducted.

e. The procedure finishes by placement T-tube in the CBD and fine suturing.

Open Supraduodenal Choledochotomy

Having in mind that choledochoduodenostomy may be inevitable, the incision over the CBD should be placed in the lowermost part of the supraduodenal CBD. The more the proximal duct is left, the easier another possible procedure to the duct would be. Furthermore, the maniplulation of the choledochoscope close to the ampulla would be facilitated from a short choledochotomy – ampulla distance (approximately 7 cm) [20].

Prior to any exploration, an intraoperative cholangiogram can supply useful information regarding the size, number and location of these stones. This can be facilitated by the administration of morphine which induces sphincter spasm and visualization of the intrahepatic ducts.

A Kocher's manoeuvre permits access of surgeons fingers around the ampulla in order to gain better control of the manipulations [34, 38].

Choledochotomy is performed by placing 2 traction sutures on either side of the intended choledochotomy incision on the CBD distal to the cystic duct.

The basic operating steps are [5, 20, 34, 38]:

- Cholangiography (transcystic or using a needle through the CBD)
- Accuracy 85-98% with false positive 4% and false negative 0.2% results
- Can be replaced by intraoperative U/S offering even better sensitivity and specificity depending on the operator [5].
- Cholecystectomy (may be done later or not at all).

- Duodenal mobilization through Kocher's manoeuvre in order to gain access and palpate the distal CBD and the ampulla and exclude the possibility of an ampullary carcinoma.
- Choledochotomy incision. Should be small (1-2cm) and longitudinal to the CBD and can be done using a No 11 or 15 blade. It should be placed in the supra-duodenal area distally to the insertion of the cystic duct in the antero-medial surface of the CBD after placement of 2 guide sutures (stay sutures) one opposite the other, and application of traction. The incision can be extended using Potts angled (choledochotomy) scissors.
- Send specimen of the CBD for culture. Cultures should be obtained as a first step.
- Exploration of the CBD:
  "Milking" stones from the common hepatic duct and from the distal CBD towards the choledochotomy incision should be attempted. The left hand of the surgeon should be kept behind the duodenum and head of the pancreas during any instrumentation. At this point, there are multiple available tools and manoeuvres that may be used in order to extract the stones (table 15.9).

Nevertheless, if an impacted stone in the distal CBD cannot be safely and non traumatically removed, a sphincterotomy or sphincteroplasty should be performed.

Table 15.9. Tools/manoeuvres used to extract stones from CBD [20, 34, 38].

- Pituitary scoop with malleable handle (most effective) used to scoop and retract the stones.
- Randall stone forceps used to grasp the stones.
- Fogarty balloon inserted beyond the stone and if possible into the duodenum to mark a possible duodenotomy area. It is then inflated and retracted, deflated slightly to allow passage to the distal CBD and then re-inflated to be completely retracted and extract any stones lying between the balloon and the choledochotomy (Fogarty 1968). The balloon is then re-inserted towards the hepatic ducts and the same procedure is used.
- 10F catheter and saline irrigation in order to flush, dislodge and wash out the stones. Small stones sludge and debris can also be removed through the cystic duct in this way which avoids opening the CBD.
- 16F rubber catheter and suction when making contact with the stone.
- Metal Bakes dilators (to determine the patency of the ampulla, not larger than No 3).
- Choledochoscopy or cholangiography (usually with a balloon catheter) to ensure clearance of the duct).
- Lithotripsy (mechanical, electrohydraulic, laser).

- Check for ampullary stenosis. This can be done by passing a Bakes dilator (up to No 3) through the ampulla until a 10F rubber catheter is able to pass to the duodenum. Excessive force should never be applied in these manipulations.
- Check for residual stones.
- A choledochoscope can be used for both to confirm that the CBD is clear and to remove any retained stones. The Dormia basket can be helpful at this point to be inserted beyond/at the level of stone, to open up, catch the stone and retract.
- Balloon catheter cholangiography. Initially a Folley catheter (10F) is inserted into the hepatic duct and inflated. The contrast medium is then injected and possible residual stones can be identified. The technique can be repeated in the distal CBD before closing the choledochotomy.

T-tube Cholangiography

- Insertion of the T-tube (T-tube choledochostomy):
  It should be done in the absence of sphincterotomy [5]. The purpose of this step is to at least insert a 14F rubber tube into the CBD in order to stent the closure, decompress the CBD and allow the spasm and oedema of the sphincter to settle down after the exploration, facilitating, at the same time, post operative cholangiography (7-8 days later). In addition, we can use the tract to extract residual stones in which case a straight course is necessary while the tube traverses the abdominal wall. Limps must be shortened to avoid blocking the hepatic duct and entering the duodenum, causing siphon or inducing pancreatitis and the distal part is brought out through a stab wound in the anterior axillary line and a close suction drain is placed close to the CBD, brought out through a separate stab wound and secured in place. The choledochotomy is closed around the tube and saline is injected to assess the closure and exclude leakage. It is safe and effective but does not lack complications, which can reach 10%. It further adds discomfort to the patient, preventing them from working for as long as the T-tube remains in situ. In one controlled study, intraoperative stenting of the duct rather than using a t-tube was tried with good results [42].

- Completion cholangiogram through the T-Tube along with choledochoscopy are the most reliable methods for confirming clearance of the duct. It can also identify unsuspected injuries to the biliary tree before closure of the abdomen [20, 38, 39]. Finally, it serves as a baseline for further imaging.
- Insertion of drain; It is inserted in the right upper abdominal quadrant and could drain the area around the choledochotomy.
- Postoperative cholangiogram:

  Bile will drain freely for 5-7 days after which a cholangiogram should be obtained. If normal, the T-tube is removed in 7-8 days [34]. Some other authors suggest doing this in 10-14 days while others suggest leaving the T-tube in place for 4-6 weeks after which the cholangiogram is repeated and by which time the tract has matured and any residual stones can be removed through the tract [5]. Alternatively, other authors prefer intermittently clamping the T-Tube before the cholangiogram or hanging the collecting bag in a higher than the CBD level.

  A small-caliber duct (<6 mm in diameter) is a relative contraindication to choledochotomy.

  If the stone is impacted in the distant CBD, a sphincteroplasty allows manipulation under direct vision and is favorable to aggressive manipulations and to a possible injury to the ampulla.

  Any perforation of the CBD and trauma of the pancreas will prompt a bile leak directly to the head of pancreas and lethal pancreatitis. In such cases, diverting the bile away from the pancreas is mandatory. This can be done with a choledochotomy, suturing of the distal stump and anastomosing of the proximal with the jejunum in a Roux and Y fashion. For CBD lacerations without pancreatic trauma a suture repair with or without insertion of a T Tube is a solution.

Choledochoscopy

It is a very effective method of identifying and retrieving CBD stones when other methods have failed. In the hands of an experienced operator, it is probably the most accurate method for detecting CBD stones. When applied correctly, there is only a 0-2% chance of retained stones, a far better percentage than the usual 3%-5% of the routine exploration. Along with the completion cholangiography, it is also a reliable means for confirming complete duct clearance after a successful exploration.

There are two types of scopes: The rigid right-angle with the Hopkins rod-lens system offers the best possible image quality, it is cheaper, easier to operate, has a longer life-span and is less susceptible to damage than the flexible fiber optic endoscope. Nevertheless, the flexible scope can cover much greater distances in either direction (liver biliary branches / duodenum) and can be used to extract stones via the T-tube tract.

The instrument is inserted through the choledochotomy incision and initially advanced towards the intra hepatic ducts in order to visualize the hepatic duct, the bifurcation of the right and left hepatic duct and possibly the orifices of the secondary and even tertiary ducts. The scope can then be directed distally towards the ampulla, which looks like an inverted cone with a small orifice that opens and closes to permit the passage of the saline.

Using a liquid medium, maintained with a continuous flow of normal saline under pressure through the sidearm of the scope, the choledochoscope can be advanced into the distal and peripheral ducts, to identify CBD stones or even lesions, and retrieve or biopsy them. This can be done with a Dormia basket, fogarty biliary catheter, flexible forceps or punch biopsy instruments passed through the working channel.

15.6.2.3. *Biliary Drainage Procedures*

The available options are:

- Transduodenal sphincteroplasty.
- Choledochoduodenostomy.
- Choledochojejunostomy Roux-en-Y.

Approximately 30% of all patients requiring an open choledochotomy need a drainage procedure. Indications for a drainage procedure are: Multiple CBD stones (>4), sphincter of Oddi stenosis or dysfunction, primary CBD stones, previous choledocholithotomy, and marked CBD dilatation.

Transduodenal Sphincterotomy and Sphincteroplasty (Fig. 15.13)

Sphincterotomy consists of incising the distal part of the sphincter musculature for a distance of approxima-

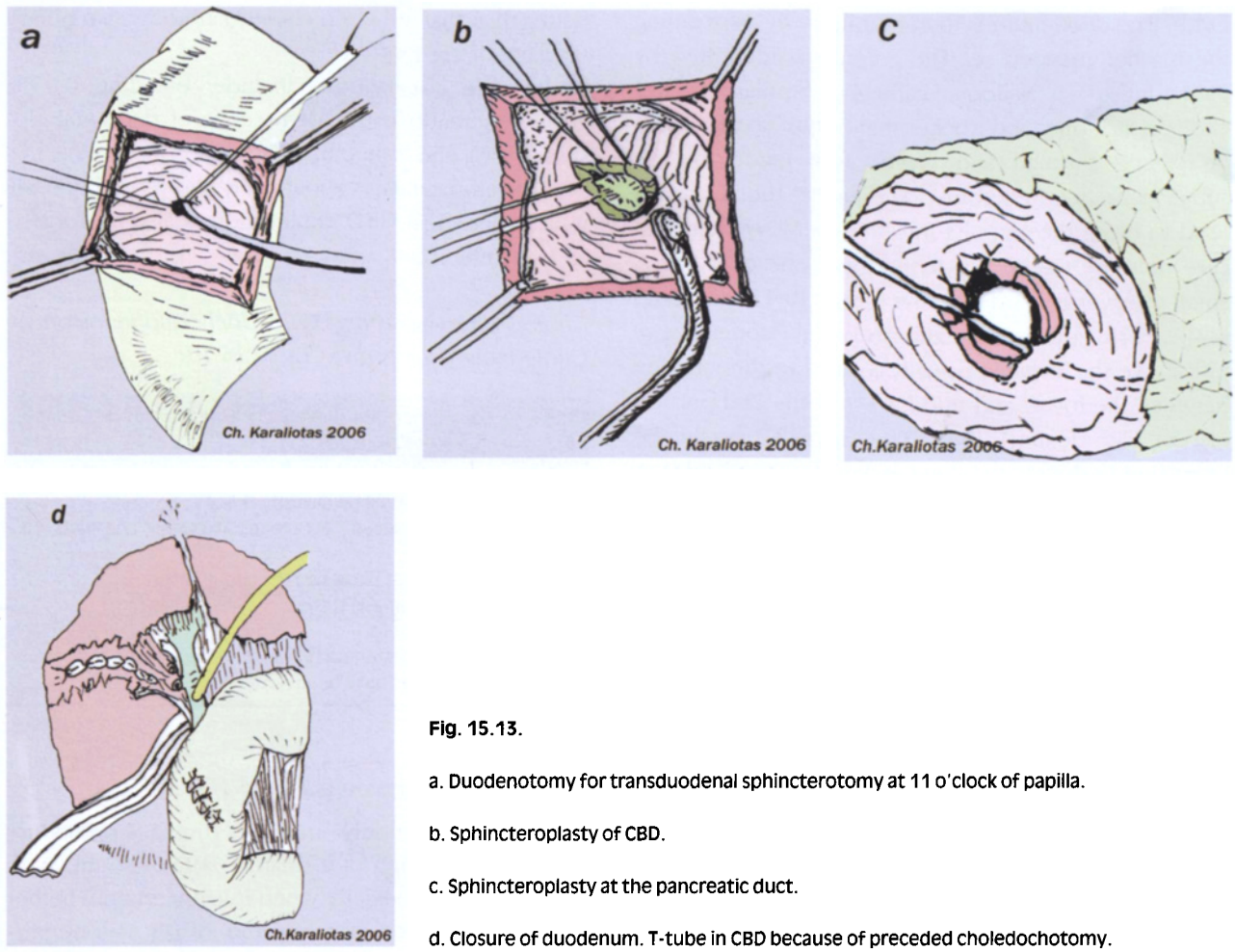


Fig. 15.13.

a. Duodenotomy for transduodenal sphincterotomy at 11 o'clock of papilla.

b. Sphincteroplasty of CBD.

c. Sphincteroplasty at the pancreatic duct.

d. Closure of duodenum. T-tube in CBD because of preceded choledochotomy.

tely 1 cm. This incision should not extend beyond the outer wall of the duodenum.

As already discussed, it is advisable to avoid using excessive force in the manipulations when we attempt to remove an impacted stone.

Intraoperative sphincterotomy is the advised alternative.

After performing a Kocher's manoeuvre, a No 4 Bakes dilator is passed into the distal CBD in order to orientate and indicate the location of the ampulla. In the area of the duodenum opposite to the palpable probe, a 4 cm lateral duodenotomy is performed and the ampulla is exposed. Using the dilator as a guide, a 10mm incision through the anterosuperior side (opposite the pancreatic duct orifice) wall of the ampulla at the 11 o' clock position is performed and if successful, there is no need for suturing the mucosa. If, however, the stone cannot be extracted, a normal sphincteroplasty should be performed [2, 34].

Sphincteroplasty

The indications for this retrograde approach to the exploration and clearance of the CBD are: the presence of stones impacted to the distal ampullary region and the presence of multiple and recurrent CBD stones. In addition, papillary stenosis and pyogenic cholingitis [43].

A sphincteroplasty requires complete division of the sphincter muscle. This creates a patulous, wide opening that is followed by suture approximation of the wall of the duodenum to the wall of the CBD [35]. During open surgery and after cholecystectomy has been completed, a Fogarty balloon catheter is passed through the cystic duct into the CBD and through the sphincter of

Oddi. The duodenum is then mobilized by performing the Kocher manoeuvre. The ampulla is identified by pal-pating the balloon catheter. Similarly, after choledocho-tomy and Kocher manoeuvre, a dilator can be passed through and serves as a guide for the subsequent duo-denotomy. Thereafter, the dilator is used to bring the ampulla into the operative field, but care must be ta-ken not to perforate the duct [2]. A small transverse duodenotomy (about 10-15 mm long) [43] is perfor-med on the anterio-lateral duodenal wall just above the ampulla (usually located in the junction between the lower and middle 1/3 of the 2nd portion of the duo-denum) [38]. The ampulla should be identified in the medial duodenal wall (80% visible). A choledochosco-pe can be used to illuminate the area of the ampulla. When the ampulla is identified, is grasped laterally with a clamp and the duct is catheterized. It is vital to know the anatomic relations of the ampulla.

Usually (80%) the pancreatic duct lies between 4 and 5 o clock position and is exposed after a small (5-6mm) incision on the superior wall of the ampulla (11 o clock position). It can then be catheterized [35].

After sphincterotomy is performed at the 11 o' clock mark, it must be carried for a distance of approximately 1.5 - 2 cm [2]. Since that it is done on the anterior-medial wall of the distal CBD and on the back wall of the duodenum, part of it is blind. Palpation of the area behind the ampulla can prevent bleeding from an anomalous artery in the area. The sphincter is progressively divided between small clamps, with sequential sutures placed 3-4mm on either side of the clamps until the proper size is achieved. At the apex of the sphincterotomy, a figure of eight suture can minimize the possible leakage from the duodenum.

Subsequently, retrograde instrumentation of the CBD can be used to extract the stones. A choledochoscope can also be used [43].

The duodenum is closed transversely or longitudinally in 2 layers as is the choledochotomy as previously described [2, 35].

A completion cholangiogram is performed through the cystic duct. The cystic duct stump is closed. The edges of the incision are sutured at the beginning of the incision and at its apex using an absorbable suture.

The success rates have been reported to be as high as 90-100%, with morbidity and mortality rates slightly better than that with open choledochotomy. No biliary strictures were reported.

Possible complications include: bleeding 0.65%, acute pancreatitis 0.60%, dehiscence of duodenal closure 0.55%, and cholangitis 0.50%.

Overall morbitity is about 2.3% and mortality 0.8% which increases if CBD exploration is also performed and a T-tube is used.

Choledochoenterostomy (Choledochoduodenostomy/ Choledochojejunostomy) (Table 15.10)

Table 15.10. Indications for Choledochoenterostomy [20, 36, 39, 41].

- Invariably the CBD must be dilated >1.5cm.
- Unsuccessfully retrieved CBD stones in elderly and high risk patient.
- Multiple or large duct stones on the above settings.
- Irretrievable intrahepatic stones.
- Stenosis of the ampulla.
- Impacted ampullary stone after failure to remove it.
- Doubt that all stones have been removed.

Choledochoduodenostomy (Fig. 15.14)

It is the most commonly employed drainage procedure usually in the setting of a dilated CBD (>1.5cm) with multiple stones especially when it is uncertain whether all stones have been removed [36, 39]. It can be performed either side-to-side or end-to-side.

In the side-to-side procedure, "sump" syndrome is a feared complication, in which food particles reflux into the biliary tree, resulting in obstruction, cholangitis, and/or pancreatitis. This complication can be diminished if the size of the anastomosis is limited to 14 mm or by preferring the choledochojejunostomy (Roux-en-Y). Overall it adds an extra 1% to mortality [5]. Other authors suggest a wide anastomosis with a stoma of >2.5cm in order to permit a free pass back of the food and decrease the possibilities for obstruction and cholangitis [36, 39]. In order to diminish the chances for Sump syndrome, closure of the distal CBD and proximal end to side anastomosis is suggested either with the duodenum or with the jejunum in a Roux-en-Y fashion [36].

Nevertheless, the most common choledochoenterostomy performed is the side-to-side choledochoduodenostomy (see complications about CBD exporation in table 15.11).

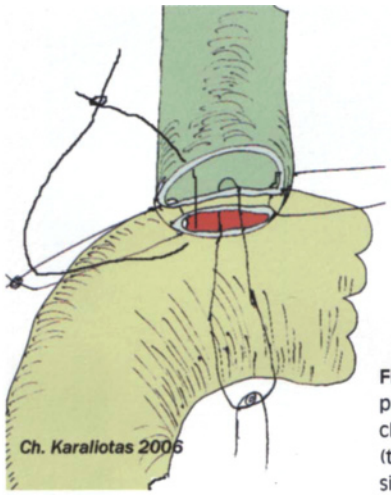


Fig. 15.14. Schematic representation of end to side choledochoduodenostomy (today for choledocholithiasis is rarely performed).

Table 15.11. Complications of CBD Exploration.

- **Bile Leak and Bile peritonitis**
  From T-tube displacement or from CBD injury.
- **Acute pancreatitis**
  From instrument trauma.
- **Increasing jaundice**
  Usually caused by the anaesthesia and liver decompensation peaking at day 10 to start decreasing thereafter.
- **Haemorrhage**
  a. Intra-abdominal Haemorrhage.
  b. Haemobilia.
- **Residual CBD stone**
  Early detection/treatment:
  If < 1 cm use a N/S flush + /-Heparine after the PO day 12 (1000N/ S with 5000u over 24 h/4-5d)

Late treatment:
Choledochoscope through the T-tube track.
ERCP.
Relaparotomy.

Technique

A generous Kocher manoeuvre is performed and the di-stal CBD is exposed. A 2-3 cm longitudinal choledochotomy is made close to the lateral border of the duodenum along with a similar-sized longitudinal duodenotomy at the corresponding location. Guy sutures can be placed in the midpoints of the medial and lateral choledochotomy incision. A "diamond-shaped" anastomosis is made with interrupted absorbable sutures (vicryl 3-0 or 4-0). The anastomosis begins with suturing the posterior and medial part of the duodenum with the distal part of the CBD and placing the knot inside the lumen. The posterior wall is done first followed by the anterior, taking care to finish the anastomosis without tension [36, 39]. As already mentioned, one potential complication from this is the "sump syndrome" caused by food or other debris caught in the distal CBD. This complication is rare (about 1%), and can be managed with ERC/ES.

Other authors have suggested end-to-side choledochoduodenostomy as well as choledochojejunostomy as alternative approaches, although endoscopic biliary access following these operations is virtually impossible.

Choledochojejunostomy

This anastomosis is performed either in continuity or preferably as a Roux-en-Y loop that is passed in a retrocolic fashion. The preferred anastomotic size is 2.5 cm. It has the disadvantage of an added anastomotic line, redering future endoscopy is impossible but has the advantage of not being associated with reflux of food particles and sump syndrome.

Isoperistaltic anastomosis is suggested while there is no difference in the way that the anastomosis is constructed (s-e, s-s, e-s,e-e).

Side to end/side anastomoses are easier to perform but they incorporate the risk of sump syndrome. It does not require circumferential dissection of the duct.On the other hand the end to end/side anastomosis eliminate the blind segment of the CBD hence the risk of developing sump syndrome. Nevertheless, for this kind of anastomosis, circumferential dissection of duct is necessary.

The jejunum is divided about 15 cm from the Treitz ligament in the area of the mesentery about 2 cm distal to the artery supplying the 2nd arcade. The incision in the mesentery is extended to reach the arteries supplying the 3rd and 4th arcade and those vessels are divided in order to mobilize the jejunum. The jejunum can then pass through an avascular area of the transverse mesocolon usually to the right of the middle colic artery in order to reach the hepatic duct. The peritoneum around the duct is divided and the CBD exposed. For a side to end/side anastomosis, the duct is divided and the distal part is over sewn. For a side to end/side anastomosis a 2.5-3.5 cm longitudinal incision in the anterior wall of the duct is made. The anastomosis is performed with one layer of seromuscular sutures placed 4mm

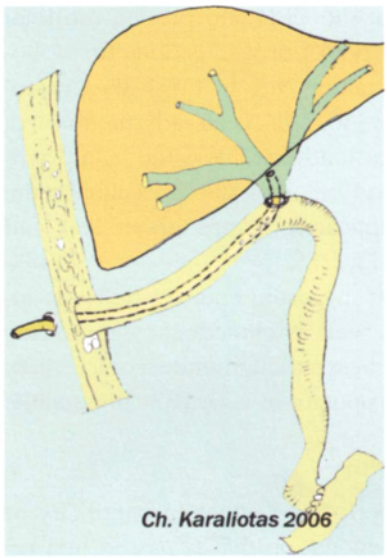
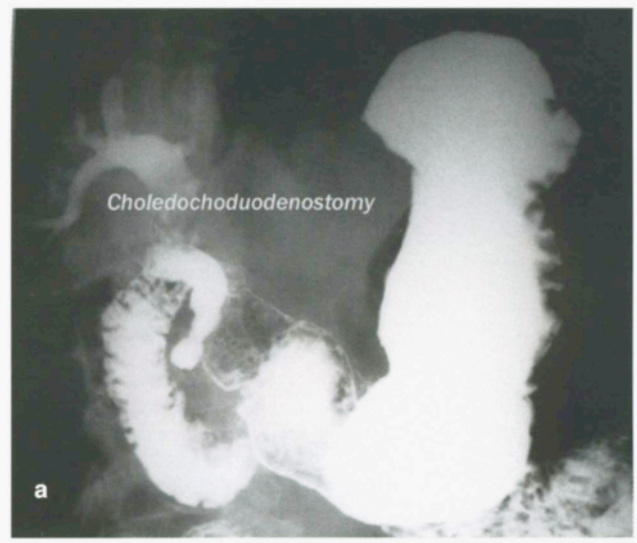


Fig. 15.15. Schematic representation of Roux-en-Y end to side choledochojejunosto my. The end of the jejunum whenever needed is brought under the skin for easier accessibility of anastomosis.



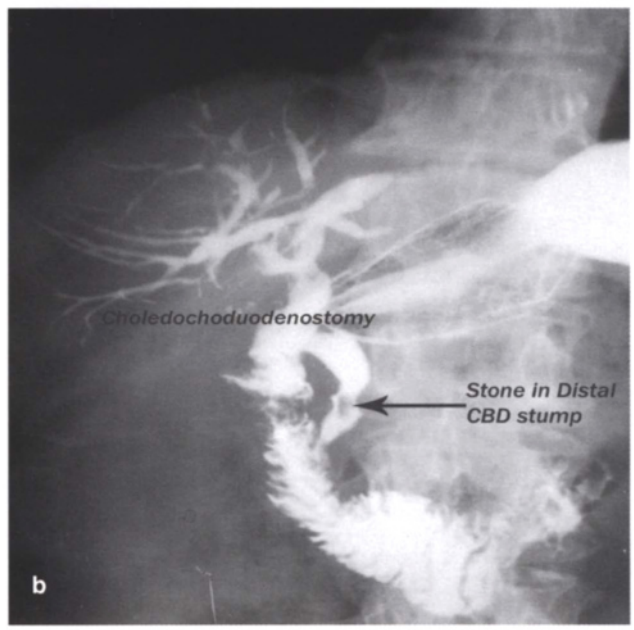


Fig. 15.16.
a. Barium meal for diagnosis of "sump syndrome" in choledochoduodenostomy.
b. Stone in blind distal part of CBD; classical case of "sump syndrome".

apart starting from the caudal and cephalad sutures and proceeding with the right and left side of the anastomosis. The Roux-en-Y jejunojejunostomy is stapled or hand sewn and the mesenteric gap is closed.

If further intervention is anticipated, the anastomosis with the jejunum is effectuated some distance away from the distal end (on the side of the jejunum) and the distal end of the loop is brought under the skin and marked allowing an endoscopy through this area if needed (fig. 15.15). Alternatively, another part of the jejunum can be brought under the skin and marked.

In the postoperative period, problems in the patency of the anastomotic ring and the function of the anastomosis are examined by MRCP or endoscopy when the last is feasible. During the past years, the checking was done by barium meal for choledochoduodenostomies (fig. 15.16) or by scintigraphies (usually 99Tc – HIDA) in the case of choledochojejunostomy (fig. 15.17).

15.7. Cholecystectomy in Patients with Choledocholithiasis

Performance of a cholecystectomy in patients with choledocholithiasis remains controversial, though recomended by most experts. However, in patients who cannot tolerate surgery well (eg, due to age, medical problems), leaving the gallbladder in situ is an option providing the organ is asymptomatic.

Cholecystectomy is not indicated for primary CBD stones.

In cases of acute cholecystitis, jaundice with firmly impacted CBD stones in an acutely ill patient the only recommended approach is to decompress the duct with a T-tube (Williamson 1990).

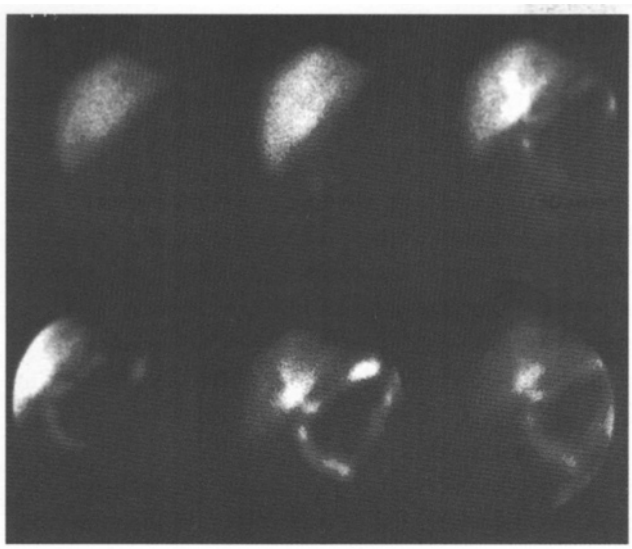


Fig. 15.17. Cholescintigram with 99Tc-HIDA, for evaluation of a choledochojejunosomy function which works properly.

15.8. Postoperative Care

T-tube: it must by gravity drain freely to a plastic bag until the postoperative cholangiogram (day 5-7) which if normal and if free flow is demonstrated the T-tube can be clamped and removed at postoperative day 9-21.

A tube cholangiogram helps assess for the presence of retained stones, the status of the sphincter of Oddi, the architecture of the biliary tree, and the condition of the anastomosis. This study is best performed under fluoroscopic guidance in the radiology department.

- *Antibiotics:* patients must be covered perioperatively.
- *Drain:* should be removed after 4-5 days unless drainage is excessive.
- *Laboratory data:* serum bilirubin, amylase levels and liver enzymes are measured in the postprocedure period as part of follow-up care.
- *Further outpatient care:*
  Serum bilirubin levels and liver enzymes are measured in the postprocedure period as follow-up care.

Management of retained stones: Extraction (or consideration of lithotripsy) of retained stones is performed 6 weeks after placement of a biliary drain or catheter, when the tract is mature. Dissolution of the stones using monooctanoin is another option.

15.9. Lithotripsy as a Complimentary Modality for the Management of the Common Bile Ducts

As already discussed, choledocholithiasis is nowadays managed with minimal invasive techniques preserving open exploration for cases where these modalities fail to remove the stones or for cases when common bile stones are identified during an open procedure.

Lithotripsy can be used complementary to both surgical and non surgical treatment modalities in order to increase the success rate and decrease the percentage of retained stones.

Endoscopic sphincterotomy (ES) and extraction of stones using basket or balloon catheter can effectively treat more than 80% of all CBD stones (80-90%) with a complication rate of less than 10% [44, 45]. Nevertheless, the success rate declines with the increase in the stone size. Stones larger than 1.5 cm must be fragmented before they can be extracted [8]. Hence, for those stones which cannot be initially extracted, mechanical lithotripsy (ML) is the method of choice as a next step with success rates reported up to 88-92% [8, 44].

Nevertheless, even this method can be difficult or impossible when very large, impacted, or very hard concretions, are present in the CBD. Laser lithotripsy (LL), Electrohydraulic Lithotripsy (EHL), and ESWL constitute alternative options, with success rates of 80% to 95%, particularly indicated for elderly patients and patients with an elevated surgical risk.

Unfortunately these methods are not widely available and usually stenting is used for immediate stone therapy, which of course cannot be used as a definitive treatment apart from selected cases [46].

The available intracorporeal Lithotripsy techniques are:

- Mechanical Lithotripsy (M.L.).
- Electrohydraulic Lithotripsy (E.H.L.).
- Laser lithotripsy (L.L) (table 15.12).

Table 15.12. Criteria for application of lithotripsy techniques are [44].

(a) Size of the stone (>2cm).
(b) Complete obstruction of the lumen.
(c) Impacted stones.
(d) Intrahepatic stones located high in the biliary tree.
(e) Stones above narrow or angulated part of the ducts.

These techniques require near contact with the stone. Usually this is accomplished via T-tube track, percutaneous, transhepatic or endoscopic retrograde approaches. Nevertheless, in the open exploration of the duct, these techniques can be successfully applied and cholangioscopy or choledochoscopy can be used for direct visualization of probe placement for lithotripsy in order to minimize the risk of duct damage.

15.9.1. Mechanical Lithotripsy

Mechanical lithotripsy systems were introduced in 1982 [47, 48] and since then they have become effective and relatively easy to use with reported efficacy rates in excess of 90% [8, 49-52]. A low-cost modality, it can add a further 4-8% success to the common methods of stone extraction [45].

The lithotripter consists of a large hard-wire basket with an additional spiral sheath which is advanced in the biliary tree to reach the position of the stones. The basket is then pulled back to the external hard duct of the lithotripter and the cranking mechanism is used to fragment the stones [45, 53]. Usually pneumatically driven projectiles strike a metallic probe on a calculus and proving perticularly useful with large and hard stones. Commonly, the created fragments require extraction with either an endoscopic basket or grasper.

These devices work best when they are used through a rigid endoscope and can be associated with stone migration during treatment. Nevertheless, a flexible pneumatic lithotripsy probe is available [8, 45, 54].

Failure is usually due to stones >3 cm that cannot be captured with the lithotripter basket especially when they occupy the whole lumen of the duct. Nevertheless, even larger stones can be partially captured and gradually fragmented [45]. Other contributing factors leading to failure of this technique are multiple large stones preventing the opening of the basket, or extremely hard stones causing the basket to break [8]. In conclusion, mechanical lithotripsy can be cumbersome in about 10% of all cases, time consuming, or ineffective. In such cases, additional methods such as extracorporeal shock wave, intracorporeal electrohydraulic, or laser induced lithotripsy are recommended [55].

15.9.2. Electrohydraulic Lithotripsy (E.H.L.)

EHL is an effective way of managing difficult CBD stones with fragmentation rates of 96% and final stone clearance rates of 90% with few complications [44].

EHL probes deliver energy via 2 coaxial electrodes (Bipolar Electrode) in an aqueous medium. Ignition creates a small spark of high temperature that vaporizes a small volume of water into a gaseous bubble. The bubbles expand circumferentially as hydraulic shock waves. The shock waves are produced only between the two electrodes, they last 2-4 μs each and their voltage is between 1000-2000 v. Usually the bursts happen at a frequency of 5-6 shocks per sec and with an average of 5-10 bursts per stone fragmentation [44]. A continuous infusion with N/S is mandatory. The electrode should be in close apposition to the surface of the stone so that energy is absorbed only by the non-flexible stones precipitation their fragmentation. Therefore, direct visual control is required in order to avoid bile duct perforation because of contact of the probe with the duct wall [56].

Power is proportional to the diameter of the probe. EHL lithotripsy can damage adjacent tissues so care must be taken not to touch the CBD walls in order to avoid the risk of perforation.

After the stone is fragmented the stone chips are removed from the duct by common measures (balloon, basket) [44, 45, 54, 57-59].

Failures are usually attributed to an extremely large stone. In addition, when the CBD is full of multiple stones, the technique may similarly fail. It is not free of complications since there is a potential risk of haemorrhage, perforation of the duct as well as late stricture of the duct. Despite excellent results, complications up to 22% have been described and including haemobilia, perforation of the duct, acute pulmonary embolism, and haemothorax [60].

Nevertheless, it is considered to be the safest and most effective mechanical method as well as less time consuming and the least expensive. The consistency of the stone is not a factor affecting the outcome [54, 57-59].

15.9.3. Laser Lithotripsy (L.L.)

The success rate of this technique is reported to be between 82-90% [56].

Laser lithotripsy was first described by Orii et al in 1981 [61].

The first generation lasers were ineffective in stone fragmentation and posed a high risk of thermal bile duct injury. At that time, the continuous-wave Nd:YAG laser was used successfully in 2 patients. The best form of laser used is the o Nd:YAG laser with continuous current (energy 2j and pulse duration 10 ms) but the initial wavelength caused increased wall temperature incurring a high risk of damaging the ducts so it was not successfully applied to the lithotripsy.

The second generation lasers are based on pulsed dye laser technology delivering low energy in pulses thus minimizing the risk of injury and generating a mechanical shock wave as the plasma expands and collapses on the stone surface.

The light wavelength yielding the best results is the 504 nm. Research suggested that the 504-nm coumarin pulsed dye laser was a nonthermal safe laser. It uses a light energy of 504 nm delivered in a pulsatile fashion with a pulse duration of 1,5 - 2 μs and energy of 60-120 mj through optical quartz fibers. This produces plasma between the tip of the fiber and the calculus, fragmenting stones with a photo acoustic effect [61].

Therefore, light energy which is converted to mechanical energy is used to successfully fragment the stones. In this way, damage to the tissues is avoided.

The deliverable energy is limited by fiber diameter, with the smallest fibers (200-μm fiber) only able to deliver 80 MJ, which is often not sufficient to fragment the hard stones. In addition, this laser energy has little effect on cystine calculi; 504 nm of light energy passes through this crystal rather than creating the aforementioned plasma on the surface.

Even with the smallest fibers, the energy delivered is usually sufficient to fragment most stones into fine dust and small pieces irrespective of composition.

The 504 nm Coumarin Pulsed dye Laser is a safe and effective widely used laser but perforation of the duct has been reported in up to 11.1% after 50 consecutive pulses with energy of 60 mj and in up to 44,4% with energy of 120 mj [49, 50].

Advancing laser technology has led to the development of the holmium:YAG (yttrium-aluminum-garnet) laser, which is a thermal laser using 2150-nm wavelength of light. It works with a photothermal mechanism when is used in saline irrigant. Energy is delivered in a pulsatile fashion through low-water density quartz fibers. A vaporization bubble formed at the tip of the fiber confines the thermal effect of this laser when this is applied within a water-based medium. Its energy is rapidly absorbed by water, creating a vaporization bubble that has minimal effects on adjacent tissue 2-3 mm from the fiber tip. These qualities result in minimal tissue trauma. With this laser energy, calculi can commonly be sculpted into extractable fragments or pulverized into dustlike particles that pass easily from the biliary tract while hazardous cavitation bubbles or shock waves are not produced. In 1995, Matsuoka presented the first clinical series of endoscopic lithotripsy with this wavelength and found it to be safe and efficient in treating ureteral stones [62]. Later it was applied in the management of the choledocholithiasis [61]. As opposed to the coumarin pulsed-dye laser, holmium laser lithotripsy produces smaller fragments that can be, in part, irrigated from the ducts.

The holmium:YAG laser is an effective multidisciplinary lithotripter with a fragmentation rate >90% [61], but it can be used only under cholangioscopic control, limiting its use to centers who have the equipment and the expertise to use them.

In terms of the technique, from the work channel of the choledochoscope, under direct vision (increases the rate of complete clearance of the duct and decreases the complication rate) the lithotripter is introduced, approaches and closely apposes the stone and the laser is fired resulting in stone fragmentation. The CBD is then irrigated with N/S and the stone chips are removed. Laser lithotripsy is the safest method described [54, 57-59].

Laser lithotripsy using smart laser systems such as the rhodamine 6G dye laser and the frequency double pulse Q switched neodymium YAG laser (FREDDY) can simplify the treatment of these difficult bile duct stones. Effective stone fragmentation is accompanied by only low tissue alteration.

The rhodamine 6G-dye laser allows blind fragmentation of these stones by exclusive insertion of a 7-F metal marked standard catheter into the bile duct by standard duodenoscopes using intermittent fluoroscopy.

FREDDY uses a piezoacoustic stone/tissue discrimination system which can achieve a fragmentation efficiency comparable to that of the rhodamine 6G dye laser at about one third of the cost system [55].

The need for application of lithotripsy under direct vision is overcome with the introduction of the optical

stone tissue detection system (oSTDS) which automatically cuts off the emitted laser pulse, if no contact between fiber tip and stone is established by the detector [55]. This is done using a fraction of the energy of the laser pulse (about 1-2%) to induce specific fluorescence on the surface of the target in front of the distal fibre end which when transmitted back and analyzed (qualitative and quantitative) can differentiate between stone material and tissue. In this way the laser pulse can be cut off 190 ns after its release and even in case of bad application only 5-8% of the total energy of the 2.5 ns (2500 ns) laser pulse is delivered until the beam is cut off. increasing the safety of laser lithotripsy under unfavorable or even blind viewing conditions [55].

15.10. Management of Retained Stones After Cholecystectomy

15.10.1. Incidence

After cholecystectomy the incidence of retained or recurrent calculi overall is 1-2%. In patients who had CBD exploration that percentage is less than 5% and after a second operation on the biliary tree increases to 20% [14, 41].

Other authors report the incidence of retained CBD stones postoperatively to be about 14% after open operation [63] ranging from 5% to 15% [64] and about 8% following laparoscopic surgery [63].

After endoscopic approaches the incidence of retained stones is between 5-10% usually because the stones are either too big or impacted [56].

In such cases the same principles in diagnosis and management as the ones described for the initial management of the CBD stones can be applied.

15.10.2. Management of Retained Stones (<5%) [20, 21]

The management of retained stones after cholecystectomy is a problem mostly managed by the endoscopist. Nevertheless, in cases where these techniques fail or they are not feasible there is a role for open CBD exploration.

The treatment options include extraction of the stone or bypass/biliary-enteric rainage.

Optimization of the patient is vital and antibiotics can reduce complications if given perioperatively in high-risk patients. Vitamine K should be administered to a jaundiced patient [76].

15.10.3. Stone Extraction

- Extraction through the T-tube with or without the use of the choledochoscope (success rate 95%).
- Dissolution of small stones using solvents through the T-tube.
- ERCP sphincterotomy (success up to 85% with a complication rate up to 5-10% haemorrhage, pancreatitis, cholangitis, perforation and mortality up to 0.5-2% and long term complications like stenosis up to 10%).
- Biliary lithotripsy.
- Open surgery (mortality <2%) and either reexploration or biliary enteric drainage with the latter being a better option when stricture of the distal duct, marked dilatation, multiple stones and an inability to remove them all is the case.

15.10.4. Biliary Enteric Drainage

15.10.4.1. *Indications*

- Stricture of the distal duct or sphincter of oddi.
- Inability to remove all stones from the duct.
- Multiple stones or primary CBD stone.
- Marked dilatation of the duct (>2 cm).
- Second reoperation.

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CHAPTER 16

LAPAROSCOPIC COMMON BILE DUCT EXPLORATION

Con. Ch. Karaliotas, G. Sgourakis, Th. Christofides, S. Lanitis

16.1. Introduction

Choledocholithiasis is predictable in 8 and 15% of patients undergoing laparoscopic cholecystectomy, the percentage increasing with age. After the advent of laparoscopic cholecystectomy, endoscopic retrograde cholangio-sphincterotomy (ERCS) had essentially replaced open surgery for safe and effective common bile duct stone extraction, despite its significant morbidity and mortality. The performance of laparoscopic cholecystectomy and laparoscopic intraoperative cholangiography combined with technological advances in equipment and instruments made laparoscopic common bile duct exploration the next logical sequential step in cases of choledocholithiasis.

Although this is a matter of controversy, we share the belief that intraoperative cholangiography should only be performed in selected cases, where choledocholithiasis is suspected [1]. As stated in the literature, intraoperative cholangiography can be accomplished in 65 to 98% of cases with a less than 5% false positive or negative rate [2]. Imaging with digital subtraction and amplification and/or intraoperative ultrasound [3] is of great assistance in detecting CBD lithiasis and anatomical abnormalities.

Large prospective randomized trials [4, 5] have notably documented the advantages of laparoscopic common bile duct exploration with results comparable to that of endoscopic CBD stone removal. ERCP should be performed only in cases of elderly patients with suppurative cholangitis. The spectrum of laparoscopic treatment options is presented below.

16.1.1. Trancystic Laparoscopic CBD Exploration (Fig. 16.1)

The trancystic approach is the most widely held method engaged at present for common bile duct stone retrieval. Intraoperative management obviously includes cholangiography or an intraoperative sonographic study [6] which dictates the approach of ductal access (trancystic or choledochotomy) and the choice of equipment to successfully accomplish stone extraction. Certain characteristic criteria are pivotal to the decision making process (table 16.1) [4]. Findings such as stone diameter > 6 mm, intrahepatic stones, number of stones ≥ 4, cystic valves, stone in the proximity of cystic duct insertion to the CBD, cystic duct diameter < 3 mm and posterior or distal entrance of the cystic duct will preclude the performance of trancystic approach while CBD diameter <8 mm and marked inflammation significantly discourage choledochotomy [7].

Table 16.1. Criteria impeding decision making for trancystic exploration.

- Stone diameter >6 mm.
- Intrahepatic stones.
- Multiple stones in CBD.
- Valves in cystic duct.
- Anatomical variations of entrance and course of cystic duct:
  - Spiral long course of cystic duct.
  - Very low entrance of cystic duct in CBD.
  - Posterior course and entrance of cystic duct.

Some of the above mentioned findings are only relative contraindications for those experienced surgeons mastering the technique. A minimum 2 mm inner diameter of the cystic duct, which could be dilated twice as much, is mandatory to allow the insertion of instruments.

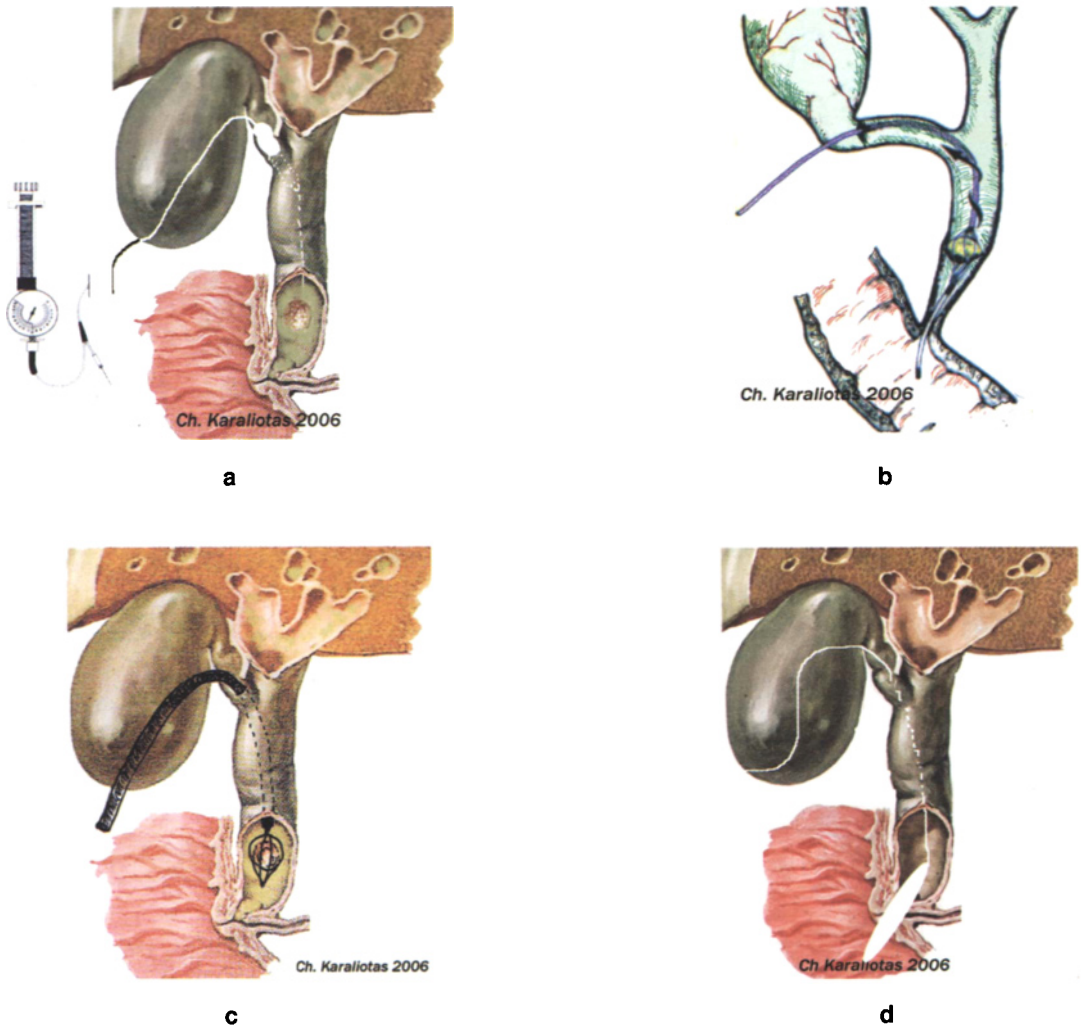

Fig. 16.1. Trancystic exploration.
a. Dilatation of cystic duct is performed in order to pass instruments via cystic duct into common bile duct. Glugagon 1mg is i.v. given to the patient for sphincter relaxation.
b. Technique of blind wrapping and trapping of CBD stone among Dormia basket wires.
c. Alternative technique of wrapping and trapping of CBD stone with direct visualisation by choledochscopy.
d. At the end of complete clearance of CBD, may be needed dilatation of sphincter of Oddi. This is performed under fluoroscopy and indicated only for small stones.

In addition to the four trocars used in the established set-up for laparoscopic cholecystectomy, a fifth trocar is placed in the right subcostal area paralleling the axis of the cystic duct.

It is not uncommon for a variety of noncholedochoscopic manoeuvres to clear the duct before choledochoscopy is employed. When cholangiogram demonstrates no flow into the duodenum, due to small stones or debris, the administration of 1 or 2 mg of Glucagon IV injection or intraductal injection of 3 to 4 mL of 2% lidocaine (without epinephrine) mixed with the contrast material, relax the smooth muscle fibers of the sphincter of Oddi, thus clearing the duct [8]. A small stone without clinical or laboratory significance will spontaneously pass to the duodenum.

The flashing of CBD through cholangiocatheter might also be a complementary procedure with successful outcome. Low pressure balloon tipped Fogarty catheters

or stone retrieval Dormia or Segura type baskets inserted through the cholangiogram sleeve with or without fluoroscopic guidance (fig. 16.2.) can also be conducive to duct clearance. It is essential that the basket is not advanced too far into the CBD otherwise "arrest" of the ampulla may ensue. Pancreatitis or perforations of the CBD are potential complications.

The inner cystic duct diameter should be large enough to allow passage of the scope and if necessary, the cystic duct can be dilated with awareness, using curved forceps, mechanical graduated dilators over a flexible guide wire or pneumatic high pressure angioplasty balloon dilators advanced similarly over a guide wire. This must be done smoothly to avoid injuring the CBD. The choledochoscope is inserted through the small incision on the cystic duct made for the intraoperative cholangiography, either from the sleeve of the cholangiocatheter or through the medial epigastric port. Forceps manipulation or introduction of the scope over a guidewire facilitates insertion of the instrument into the CBD.

Laparoscopic CBD exploration via the trancystic approach using a small cholangioscope (2.1 to 3.2 mm in diameter with a 1 mm working channel), involves Fogarty catheters, Dormia-Segura wire baskets, and lithotriptor probes.

Attention must be paid to avoid lacerations of the CBD during stone retrieval. In selected cases the cystic duct incision may be extended by advancing scissors and cutting the cystic duct longitudinally en route for CBD in order to accommodate the choledochoscope or to permit removal of a larger stone. If this is the case then closure of the duct invariably necessitates suturing after T-tube placement. Ureteral catheters are highly practical for confirming the patency of the ampulla.

Trancystic approach is successful in 85 to 90% of the cases [9,10,11]. It is rather unfeasible in cases of hepatolithiasis to advance the instruments proximally (due to the acute angle of entrance of the cystic duct into the CBD), although employing inferior traction on the gallbladder infundibulum has been reported to be effectual. Stones impacted in the ampulla can dealt with by lithotripsy under direct vision taking great care to keep the CBD wall out of harm's way. A completion cholangiogram must be carried out in all cases.

Oral intake is resumed as soon as tolerated and in the absence of biliary drainage, the patient is discharged the following day. When a trancystic biliary drainage catheter is left in place a cholangiogram is performed on the first or second postoperative day and the drain is clamped. In cases of poor duodenal drainage

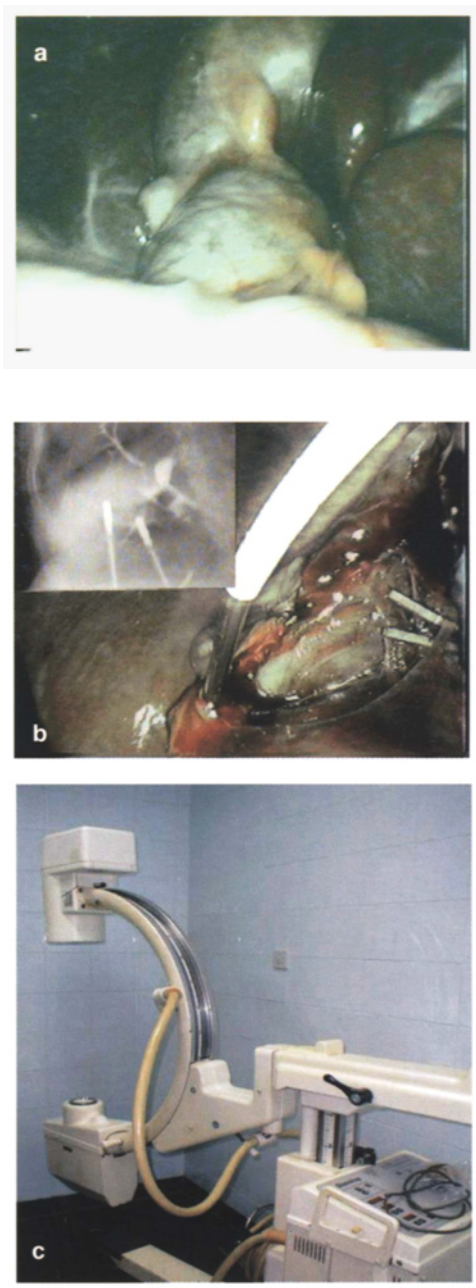

Fig. 16.2.
a. A very wide dilatation of CBD. Indication for laparoscopic choledochotomy.
b. Intraoperative cholangiography. The catheter and the cholangiogram.
c. C-arm for intraoperative fluoroscopy and cholangiography.

the catheter is left open and removed after 3 or 4 weeks. A final cholangiogram is mandatory before removal.

If drainage is required for the management of retained stones, a transcystic transpapillary 2 to 3 mm catheter can be introduced through the cystic duct and left in situ. Now a new-established tract is forming by waiting for a period of 5-6 weeks before any attempt can be made to introduce a guide-wire and retrieve any retained stones [12]. The most distressing complication is CBD injury and the immediate identification of which is crucial to a better outcome.

The method is secure, is productive and cost effective, but commands technical expertise and familiarity with the equipment.

16.2. Transcholedocal Laparoscopic CBD Exploration

A transcholedochal laparoscopic CBD exploration should be performed in cases when the cystic duct is < 3 mm in diameter or friable, the stones are very large, the CBD is dilated or the transcystic approach has failed (table 16.2).

Table 16.2. Criteria enabling decision making for transcholedochal CBD exploration.

- Cystic duct diameter <3mm.
- Friable cystic duct.
- CBD diameter > 8mm.
- Large stones in the CBD.
- Previous efforts for transcystic exploration failed.

16.3. Non-Choledochoscopic Manoeuvres

After verification of CBD lithiasis in intraoperative cholangiography, lateral and upward traction on the gallbladder facilitates stability of the CBD through the intact cystic duct. An additional port is inserted to the left midclavicular line at the level of the umbilicus. The peritoneum and fascial layer over the CBD is divided. Dissection of the proper hepatic artery or its right branch, in the event of these vessels traversing the bile duct is mandatory for the choledochotomy. The anteriorly exposed supraduodenal segment of the CBD is incised initially at a distance of less than 1 cm and elongated subsequently as mandated. Occasionally a stone pops out with a spurt of bile while incising the CBD (fig. 16.3 a-b).

The CBD distal to the choledochotomy is manipulated bluntly from below upward using two instruments in order to extricate occluding stones. This straightforward manoeuvre is successful in a number of cases [13].

A deflated balloon catheter is subsequently advanced through the choledochotomy with the assistance of atraumatic forceps into the duodenum. The balloon is then inflated and pulled out blindly to dislodge stones detected in the cholangiogram (fig. 16.4 and 16.5). We have found this step of action to be particularly successful for larger stones. Smaller stones can also be extracted by using forceful irrigation of the CBD

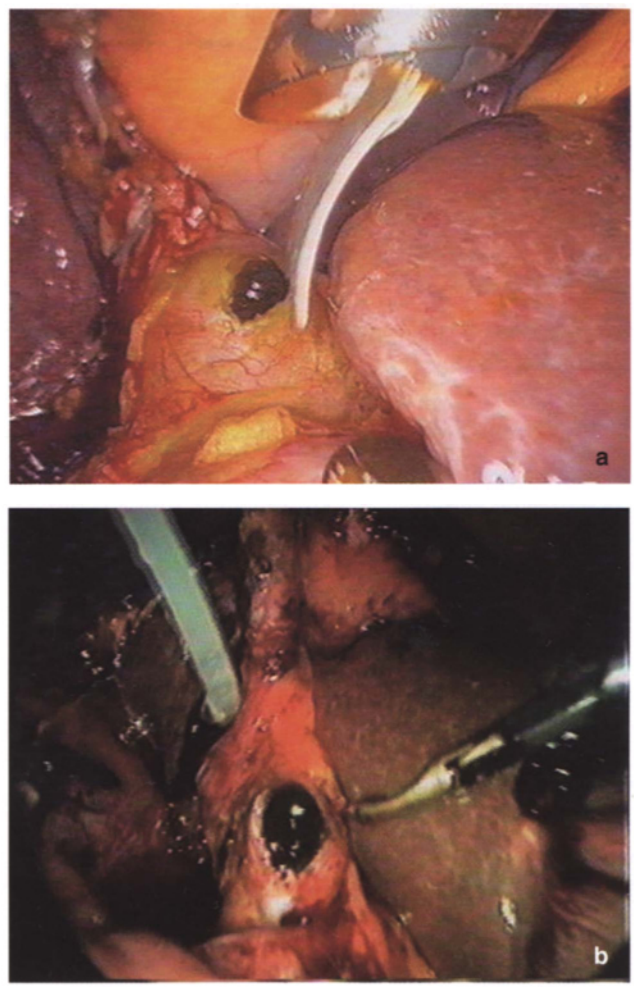

Fig. 16.3. a-b. Stones pop out after choledochotomy in two different cases.

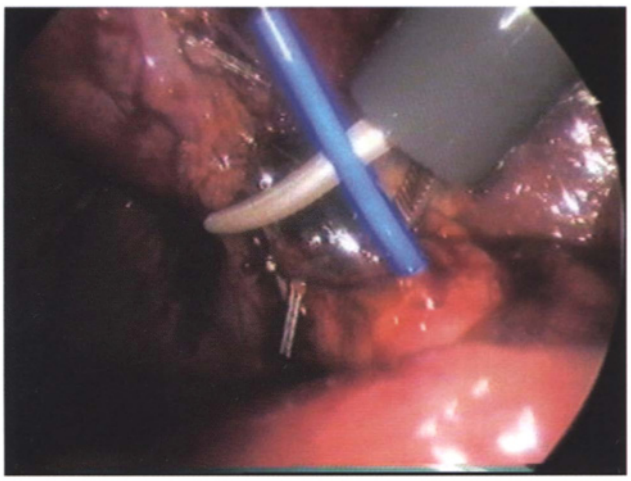

Fig. 16.4. Stone removed by dragging the ballon blindly.

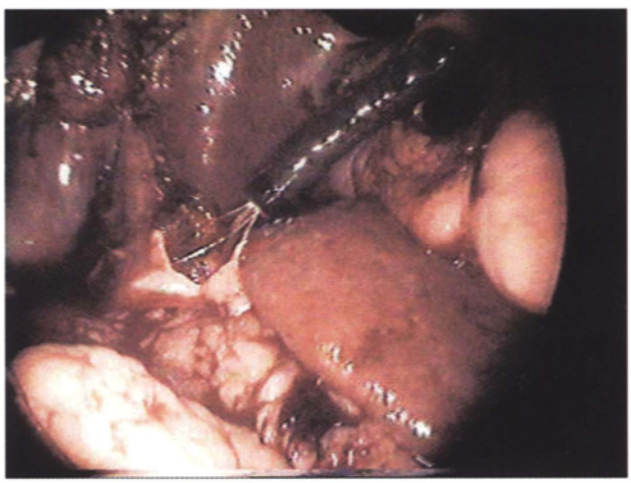

Fig. 16.5. Stone removed by dormia via choledochoscope.

through an inserted silastic catheter or the sucker tip, to which they adhere.

16.4. Choledochoscopy

When all non-choledochoscopic measures have been tried a visually guided extraction of the remaining stones follows. The 5.5 mm flexible choledochoscope is inserted from the right subxiphoid port. Copious saline irrigation of the CBD is indispensable. Stone removal is accomplished through Dormia or Segura type wire baskets or balloon-tipped Fogarty type catheters. Intraductal electrohydraulic lithotripsy or laser fragmentation is used cautiously to fragment a very large impacted stone. Visually guided extraction proved successful in 87.5% in our series [1].

In complicated cases with severe pericholecystitis or perforation, intraoperative ERCP permits recognition of the CBD and verifies the existence of CBD calculi. A sphincterotomy can be carried out and, as judged appropriate, a stent can be inserted to guarantee CBD drainage with minimal morbidity. Kocher manoeuvre, namely mobilization of the duodenum and head of pancreas or even laparoscopic choledochoduodenostomy, is necessary in cases of large occluding calculi where endoscopic treatment has failed or in the presence of a heavy stone load [14]. Conversion to open surgery is obligatory when lack of experience so dictates.

After stone extraction a completion choledochoscopy is performed and the biliary tree is examined in its entirety for retained calculi or debris. There is a degree of difficulty attached to the adequate visualization of the the ampullary region (Fig. 16.6, 16.7).

T-tube or cystic duct stump drainage with primary closure of the bile duct is employed for decompression of the extrahepatic biliary tree from its transient obstruction due to edema at the lower end of the CBD

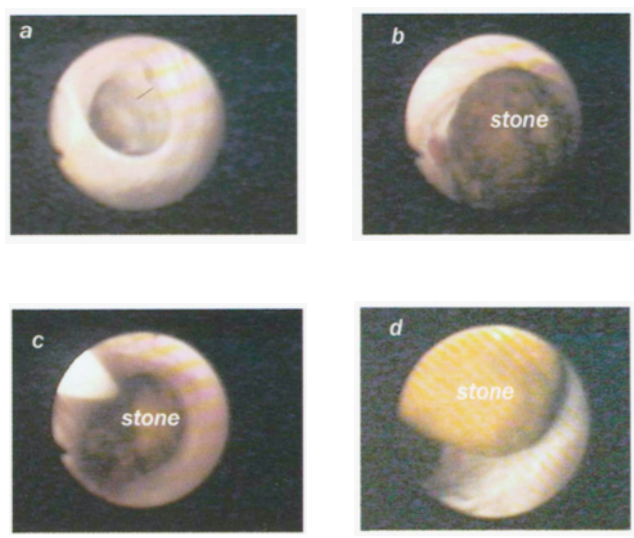

Fig. 16.6.
a. Choledochoscopy procedure at the beginning.
b. Choledochoscopy meets a pigment stone.
c. A Dormia basket catheter passes behind the pigment stone for trapping it.
d. Cholesterole stone during choledochoscopy.

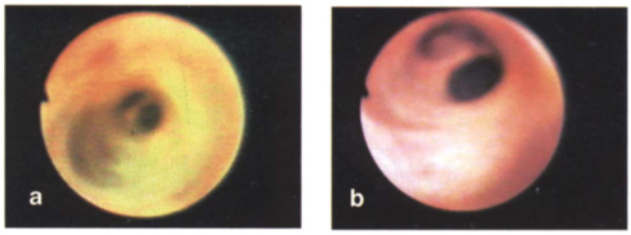

Fig. 16.7. Choledochoscopy: two different view of the common bile duct inside, by choledochoscopy.
a. Distal view of CBD.
b. Proximal view of common hepatic duct.

(fig. 16.8). Noteworthy is that an increasing number of reports in the literature support the primary closure of the bile duct without drainage for selected cases [15]. The length of the transverse limb of the T-tube should be roughly twice the length of the CBD opening. Closure of the choledochotomy is completed with interrupted 4/0 absorbable sutures involving non-cutting needles using intra- or extra-corporeal knots followed by a fluorocholangiogram to ensure that complete duct clearance has been achieved.

Postoperative bile leakage is frequent and is addressed by the insertion of a subhepatic drain. Bile drainage beyond 48 hours is twice as common after T-tube drainage than cystic duct drainage (15% vs 7% in our series) contributing, partly, to the longer hospital stay in the former group of patients (9 vs 7 days in our series).

Cholangiography is usually carried out on the fifth postoperative day. The cannula is removed the following day (longer in elderly patients and diabetics), should no bile leak be documented. Occasionally, a residual stone is depicted in the completion fluorocholangiogram. According to our practice there are two possible ways of dealing with this. Either, a guidewire is introduced through the cannula into the duodenum, as an endoscopist guide for eventually sphincterotomy and stone extraction, or retained stones can be extracted by interventional radiologists after the tract has matured.

The administration of CBD infusion of stone solvents has proved rather disappointing. Extracorporeal shock wave lithotripsy [16] or anterograde sphincterotomy and direct approach of the papilla through endoscopic duodenotomy [17] can be considered as alternative options.

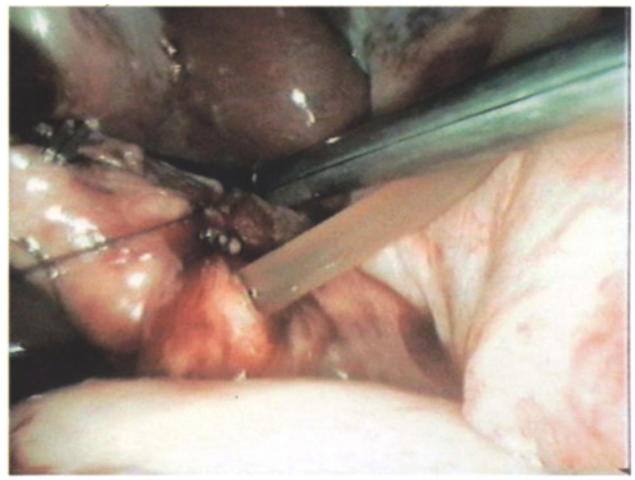

Fig. 16.8. T-tube and choledochotomy suturing.

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CHAPTER 17

ENDOSCOPIC MANAGEMENT OF COMMON BILE DUCT STONES

Kon. Goumas, A. Poulou

17.1. Introduction

The management of patients with common bile duct stones was always challenging and the introduction of endoscopic retrograde cholangiopancreatography (ERCP), three decades ago, had a major influence in the overall treatment. The profound advantages of ERCP vs open or laparoscopic surgery, established it as the predominant method for the treatment of choledocholithiasis. Endoscopic sphincterotomy of the main duodenal papilla, in combination with a number of older and innovative techniques for stone fragmentation and extraction, is nowadays considered the cornerstone of the endoscopic treatment for patients with common bile duct stones. Recent advances in radiologic imaging, such as magnetic resonance cholangiopancreatography (MRCP) and laparoscopic surgery are struggling to compete with ERCP, however ERCP continues to be a first line method in treating choledocholithiasis.

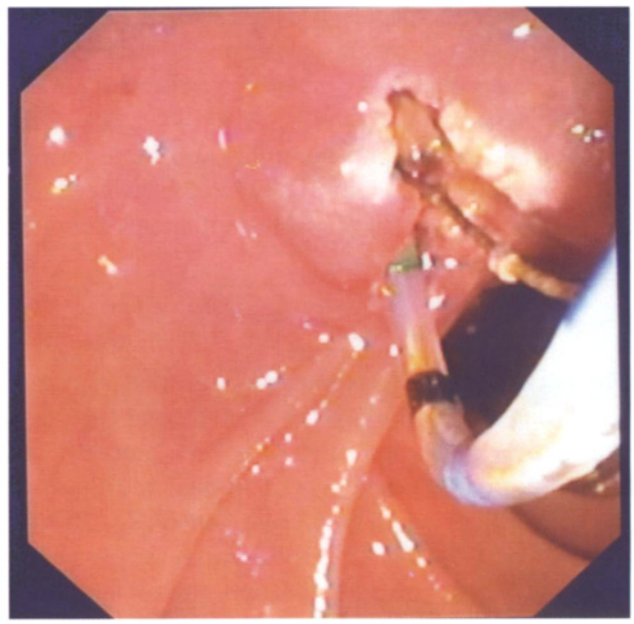


Fig. 17.1. Endoscopic view of the endoscopic sphincterotomy.

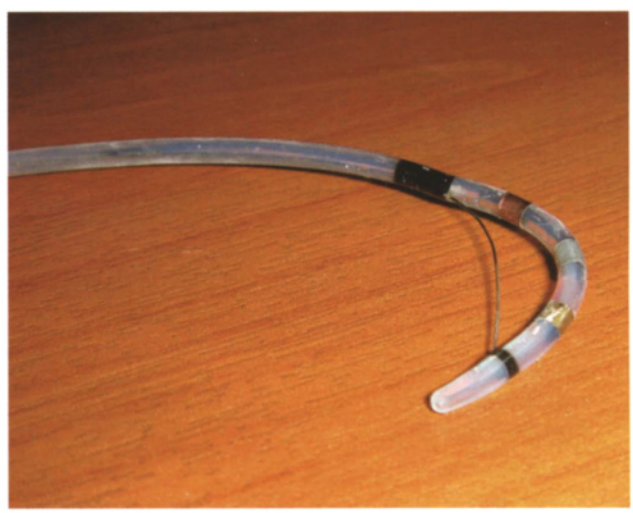


Fig. 17.2. Standard sphincterotome.

17.2. Endoscopic Sphincterotomy

17.2.1. Standard Technique

Sphincterotomy is a procedure during which incision of the papilla and the muscles of the sphincter of Oddi occurs, in order to broaden the distal part of the common bile duct (fig. 17.1).The procedure is performed using a sphincterotome, which consists of a Teflon catheter with a cautery wire exposed near its tip. The Demling-Classen sphincterotome (pull-type papillotome) is the most frequently used (fig. 17.2), although there are numerous variations of this basic type papillotome [1]. After correct orientation of the papilla with

a side viewing duodenoscope, the sphincterotome is introduced into the bile duct while its position at the papilla and within the duct is monitored both endoscopically and fluoroscopically. Subsequently, the sphincterotome is retracted until one half to two thirds of its cutting-wire length is visible outside the papilla. When tension is exerted on the cutting wire, the roof of the papilla comes in contact with it. Applying intermittent bursts of diathermic current, forms the incision in ranging length from 0.5 to 1.5 cm, depending mainly on the local anatomy and the size of the stone to be extracted [2]. The cutting wire should track directly up the middle of the papilla, usually between 10 to 12 o' clock position in the visual field. In patients with Billroth II gastrectomy or gastric bypass with Roun-en-Y, the orientation is rotated 180° to the upside down position and biliary sphincterotomy may be performed by use of a needle-knife over a previously placed biliary stent or by use of a rotatable papillotome (orientation to 6 o'clock).

17.2.2. Complications

The safety of sphincterotomy has been well documented during the last thirty years. A short-term complication rate of 5.4% associated with 0.3% mortality has been reported by Coppola et al, in their retrospective study [3]. Bleeding (2.4%), acute pancreatitis (0.5%), perforation (0.4%) (fig. 17.3) and acute cholangitis (1.3%) were the most frequent and significant complications (table 17.1). Surgical intervention due to post-sphincterotomy complications was reported in 0.9%. Post-sphincterotomy complication rate is directly related to several risk factors (table 17.2). Freeman et al [4], reported that a suspected sphincter of Oddi dysfunction, younger age, pre-cut sphincterotomy, difficult cannulation and repeated injections of contrast medium in the pancreatic duct were associated with an increased rate of acute pancreatitis. Apart from this deduction, they concluded that patients previously suffering from coagulation disorders and receiving anticoagulation therapy within three days preceding the procedure or experiencing cholangitis prior to the procedure, as well as active bleeding during the procedure, combined with the limited experience of the endoscopist, were factors that related to a higher rate of post-sphincterotomy hemorrhage. In this study, the investigators prospectively collected data from 2347 patients who had undergone endoscopic biliary sphincterotomy, concluding that the overall complication rate was 9.8%.

Moreover, after a multivariate analysis of risk factors for sphincterotomy complications, Freeman et al [4] made the assumption that limited experience of the operator is a significant risk factor. There was a significant increase in the number of difficult and failed can-

Table 17.1. Complications of endoscopic sphincterotomy.

A. Early complications
• Bleeding
• Perforation
• Acute pancreatitis
• Acute cholangitis
B. Late complications
• Recurrence of stones
• Papillary stenosis

Table 17.2. Risk factors affecting the post-sphincterotomy complications rate.

- Sphincter of Oddi dysfunction
- Younger age
- Precut sphincterotomy
- Extension of sphincterotomy
- Difficult cannulation
- Repeated pancreatic injections of contrast medium
- Preprocedure coagulation disorders
- Preprocedure acute cholangitis or acute pancreatitis
- Limited endoscopist's experience
- Allergy to contrast medium

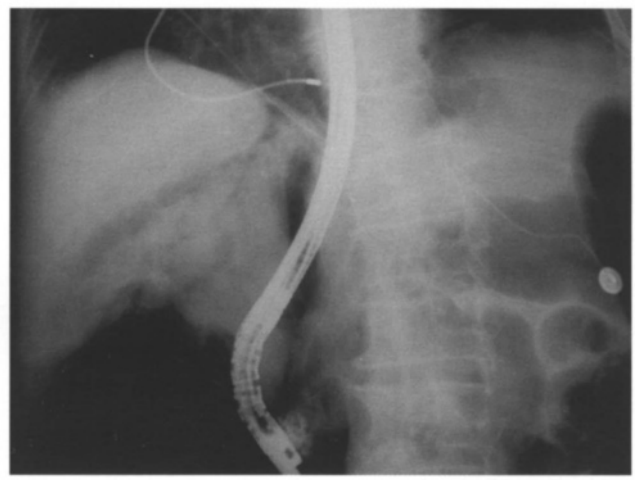


Fig. 17.3. Post-endoscopic sphincterotomy perforation of the duodenal wall. Note the subphrenic and perihepatic presence of intra-abdominal air.

nulations, pancreatic injections as well as post-sphincterotomy complications, when the performing endoscopist had an average of less than one sphincterotomy procedures per week. In the retrospective study by Coppola et al [3], there was a statistically significant reduction in complication rates correlating with increased operator's experience for the specific procedure. The complication rate decreased from 10.3% during the initial 2 years, to 2.1% during the final 2 years of the 8-year study.

17.2.3. Complications Prevention and Management

Pancreatitis, hemorrhage, perforation of the duodenal wall and cholangitis are the most frequent complications of endoscopic sphincterotomy and they usually become manifest within 12 to 24 hours, although pancreatitis and cholangitis may appear later.

Late complications of sphincterotomy include recurrent stone formation (fig. 17.4) as well as papillary stenosis which is manifested with biliary colic, cholangitis and biliary pancreatitis, especially in patients with a gallbladder in situ, a large bile duct and those with periampullary diverticuli [6]. Sphincterotomy alone does not predispose to an increased risk of cholangitis neither to an increased risk of bile duct or gallbladder cancer development [7]. Most of the early and late complications of sphincterotomy, with the exception of acute pancreatitis, can be managed effectively by means of ERCP [1].

Recently, a new high-frequency current generator with an automatically fractioned cutting function (endocut, Erbe), (fig. 17.5) has shown promising results in reducing the risks of bleeding and perforation from sphincterotomy. Compared to a standard generator for sphincterotomy, the Erbe endocut generator showed a significant reduction in the rates of bleeding (26% vs 4%; $p = 0.002$) and uncontrolled incisions (36% vs 2%; $p < 0.001$) [5].

Pancreatitis remains the major complication from ERCP procedure. Many studies have examined the prevention of post-ERCP pancreatitis by means of specific drugs, but they are not widely approved and may not be truly effective. Gabexate [8], somatostatin [9], ulinastatin [10] and other protease inhibitors [11] have shown promising results but there are no guidelines for the use of these agents. Unfortunately large studies demonstrated that most drug agents promising the prevention of post-ERCP pancreatitis have been proven ineffective [12].

Stenosis of the biliary orifice after endoscopic biliary sphincterotomy (EBS), which was performed for common bile duct stone removal, has been estimated to develop in 1% to 2.5% of cases [13]. This figure may

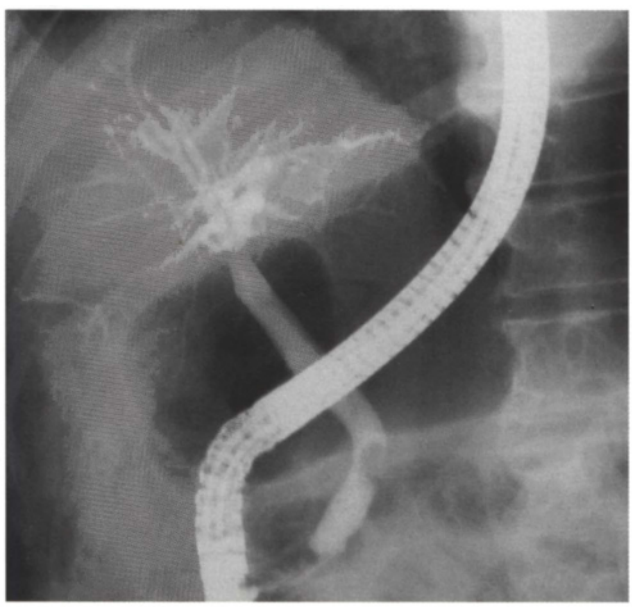


Fig. 17.4. Retrograde cholangiogram demonstrating recurrence of choledocholithiasis, 4 years after the initial endoscopic sphincterotomy.

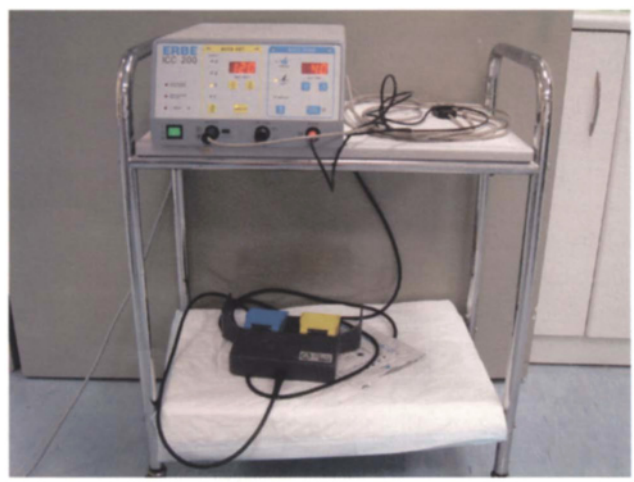


Fig. 17.5. High frequency current generator with an automatically fractioned cutting function (Endocut, ERBE) used for safer endoscopic sphincterotomy.

reach 16% when EBS is performed for sphincter of Oddi dysfunction [14]. It has been reported that endoscopic dilation and multiple stent placement achieved stricture resolution [15]. Endoscopic follow-up treatment consisted of the sequential insertion of an increasing number of plastic stents with larger diameter, in 3-month intervals till stricture resolution.

17.2.4. Difficult Bile Duct Cannulation

The inability to achieve selective cannulation of the bile duct is probably the most frustrating and humbling experience for the endoscopist. Even in the most experienced hands, cannulation of the appropriate duct may fail in 5-20% of the cases [16]. Luckily, there are methods that have been developed to increase the likelihood of biliary access using a variety of precut techniques [17] with success rates greater than 90%. The use of a needle-knife catheter [18] the papillary septotomy using a standard sphincterotome [19] and the use of a pancreatic duct stent [20] are some of the most common techniques facilitating difficult bile duct cannulation. Compared to other techniques, the disadvantage of using a needle-knife catheter is the increased occurrence of complications.

17.3. Balloon Sphincteroplasty

Balloon sphincteroplasty was introduced in the mid 90's as an alternative to sphincterotomy. The main advantage of balloon sphincteroplasty is the preservation of the sphincter [21]. After a diagnostic ERCP is performed, a deflated high pressure hydrostatic balloon catheter is positioned across the papilla. The balloon (of 6 to 8mm diameter) is inflated with radiopaque medium, until the "waist" corresponding with the biliary sphincter disappears on fluoroscopic monitoring (fig. 17.6). Biliary sphincter dilation permits the removal of only small stones, while the extraction of larger stones requires a previous mechanical lithotripsy [21, 22]. It is worth mentioning that the long-term consequences of sphincteroplasty on sphincter's function are unclear at this time.

The drawback of sphincteroplasty compared to sphincterotomy is the high rate of post-dilation pancreatitis, associated with a significant mortality rate re-

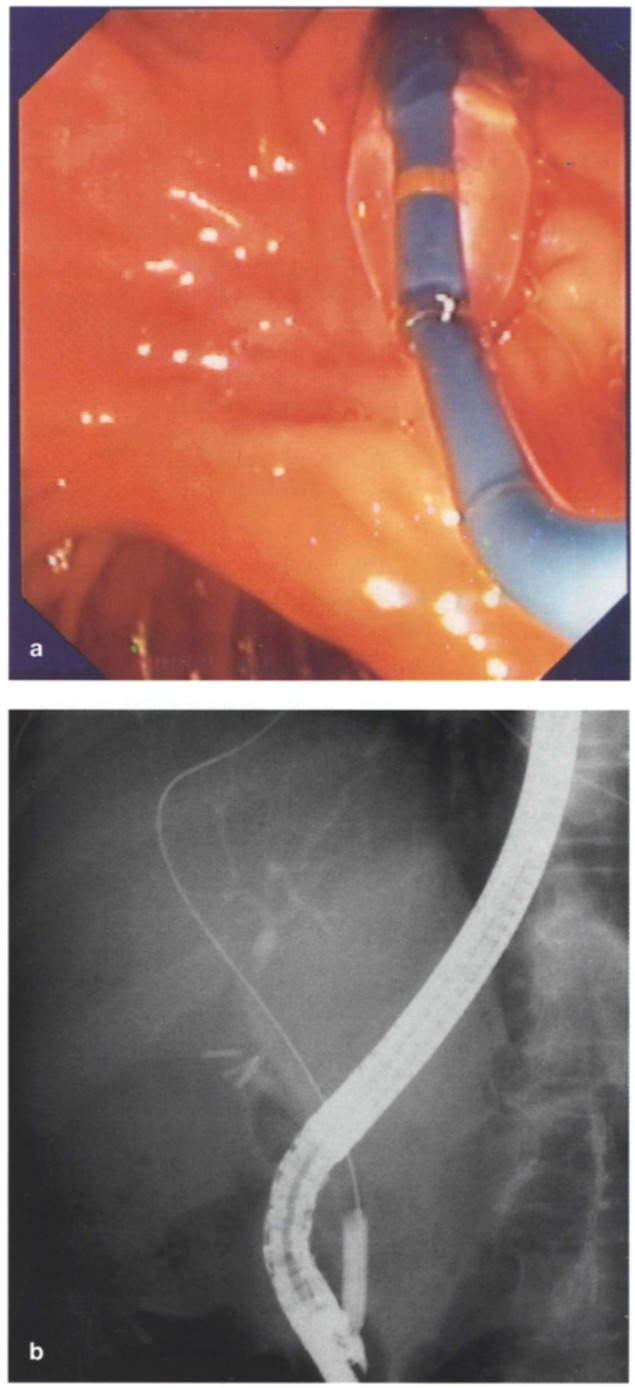


Fig. 17.6.
a. Endoscopic view of a high pressure hydrostatic balloon catheter of 8mm in diameter, which has been placed and inflated across the biliary sphincter in order to perform a sphincteroplasty.
b. Retrograde cholangiogram of a patient with liver cirrhosis showing the same hydrostatic balloon dilation catheter fully inflated across the biliary sphincter. The patient's severe coagulation disorders did not permit the performance of a safe sphincterotomy for the management of his biliary microlithiasis.

ported [23]. However, Bergman et al [24] and others [25, 26] did not demonstrate an increased incidence of pancreatitis in patients undergoing sphincteroplasty. Sphincteroplasty could replace sphincterotomy in selected patients, e.g. patients with coagulation disorders. At present, the general consensus is that sphincteroplasty should be limited to study protocols until its risks are better defined.

17.4. Effectiveness and Technical Aspects of Endoscopic Stone Extraction

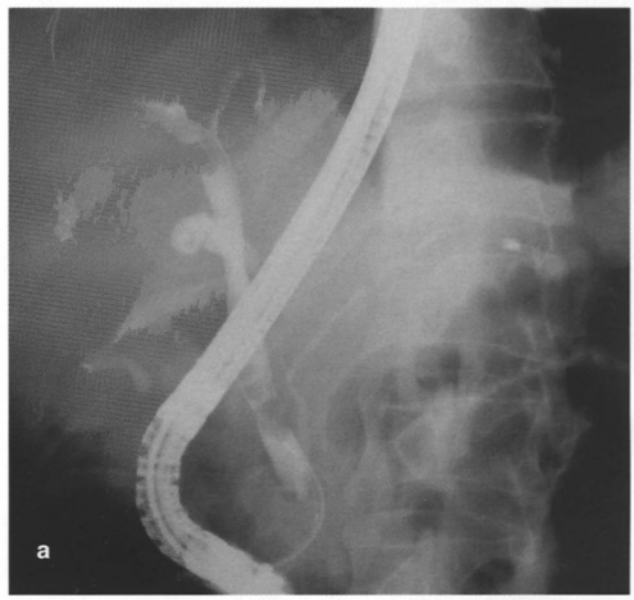
After endoscopic sphincterotomy, 85% to 90% of CBD stones can be extracted with Dormia basket or balloon catheter [27] (fig. 17.7, 17.8, 17.9), while for sphincteroplasty, a similar effectiveness has been reported for CBD stones measuring 8mm approximately [21, 23]. The Dormia basket provides better traction than the balloon catheter and is preferable for the removal of a large stone (>1 cm). The balloon catheter is advantageous for the extraction of small stones and sludge because it occludes the bile duct lumen after inflation. In the case of multiple medium-size CBD stones, both devices are equally effective in their removal [2].

Stone impaction (fig. 17.10) represents the main reason for the failure of a CBD stone extraction. To avoid it, careful assessment of the sphincterotomy size is needed. Moreover, several technical tips help prevent stone impaction e.g. the usage of balloon catheter over a guide wire for multiple small stones extraction and use of dormia basket for larger stone removal is strongly recommended [2].

17.4.1. Mechanical Lithotripsy

Large stones (d > 1.5 cm), multiple and impacted stones or those located proximal to a stricture have been called "difficult" stones because their extraction without fragmentation, sometimes is not possible. CBD stones fragmentation can be achieved by mechanical or shock wave lithotripsy. Among them, mechanical lithotripsy is the simplest and most cost effective method. The success rate varies from 68% to 100% depending on the stone size. The most desirable result for mechanical lithotripsy can be achieved with stones of less than 3 cm diameter [28].

There are two types of mechanical lithotripters that are used, depending on whether lithotripsy is performed on an emergency or an elective basis [2] (fig. 17.11). Failure to extract the stone with a Dormia basket, in some cases, results in impaction in the bile duct of both the basket and the captured stone in it. In a situation like this, the "emergency"-type lithotripter, which consists of a flexible coil sleeve and a cranking



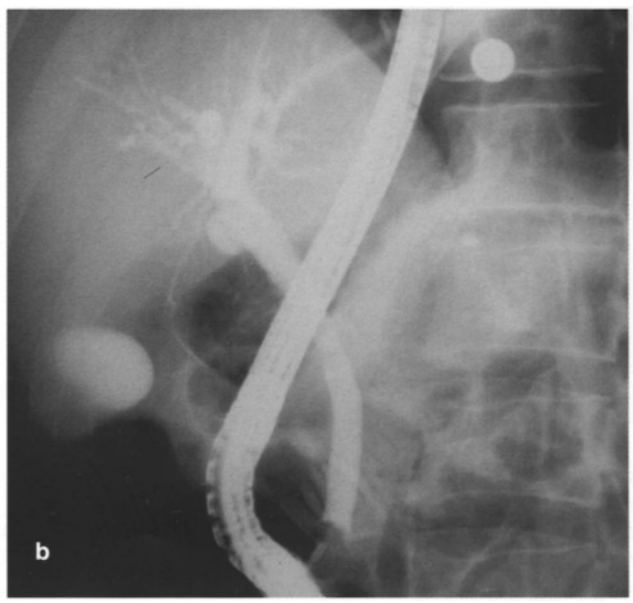


Fig. 17.7.
a. Retrograde cholangiogram of a patient with bile duct stones.
b. The same patient after complete endoscopic removal of the bile duct stones. Note the balloon catheter for stone extraction, inflated at the distal end of the common bile duct.

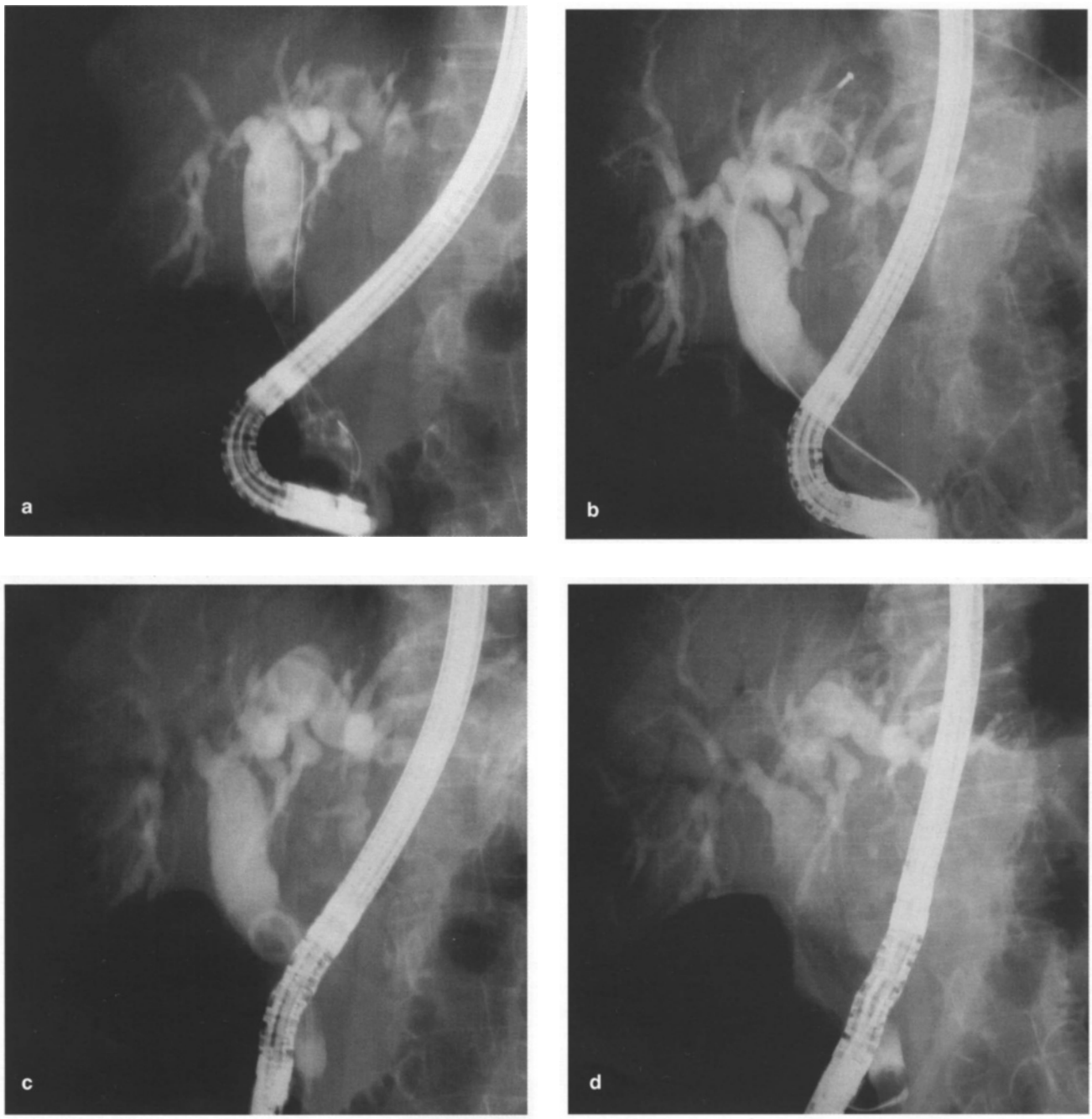
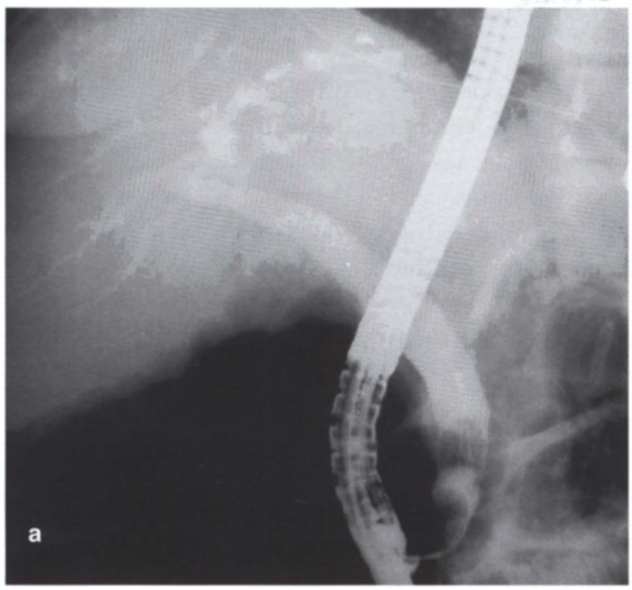


Fig. 17.8. Serial retrograde cholangiogram demonstrating complete clearance of the biliary tree from multiple intra- and extrahepatic stones, during two ERCP sessions.
a, b. Clearance of the extrahepatic bile ducts from stones. A pig-tail plastic stent has temporarily been inserted into the common bile duct to protect from a further stone impaction at the distal common bile duct.
c, d. Clearance of the intrahepatic biliary tree (left hepatic duct) from stones using basket and balloon catheters.



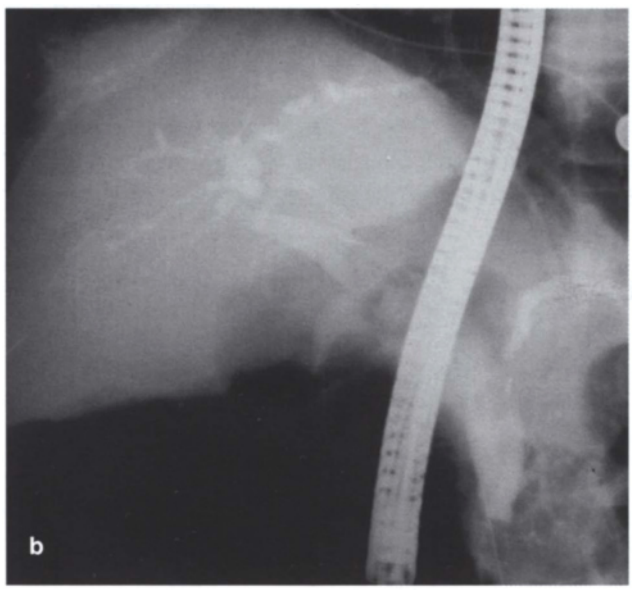


Fig. 17.9.
a. Common bile duct stones demonstrated at ERCP with a Dormia basket inserted into the bile duct. A stone has been captured in the basket.
b. Retrograde cholangiogram of the same patient showing complete bile duct clearance from stones, using a balloon catheter for stone extraction.

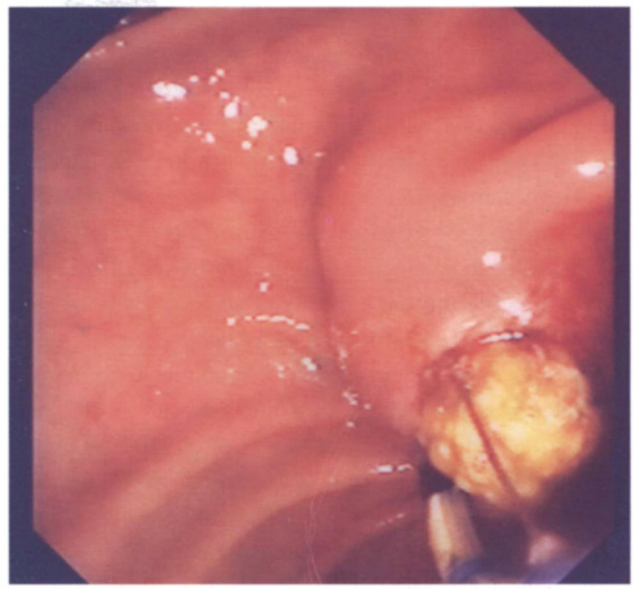


Fig. 17.10. Endoscopic view of a stone extraction. The stone was impacted at the main duodenal papilla. After a small sphincterotomy, the stone automatically fell in the duodenal lumen.

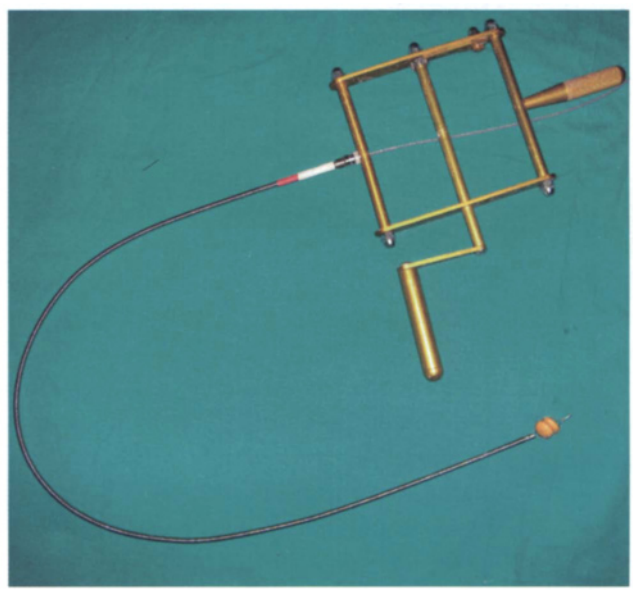


Fig. 17.11. Mechanical lithotripter with a flexible wire sheath containing a Dormia basket wire.

handle, is used. After the basket handle is cut-off with a pair of pliers, the endoscope is removed. The metal sleeve is inserted over the basket catheter until it comes in contact with the stone and together with the basket wires are attached to the lithotripter handle. After forceful traction on the basket wires the stone is usually fragmented against the lithotripter sleeve. Sometimes, the basket may fracture, rather than the stone. Fortunately only in a few and rare cases, the basket Teflon sheath may slip back, leaving the basket wire uncovered. Subsequent traction may cause injury of the mucosa at pressure points, such as the papilla, gastric angularis fold or cardia [2]. The "elective"-type lithotripter consists of a special crushing basket in a Teflon sheath and an outer flexible metal sheath. When the need for lithotripsy is evident, the use of the "elective"-type lithotripter is preferable. It is used through the working channel of a duodenoscope and is suitable for intraductal mechanical lithotripsy. However, during a forceful lithotripsy, the thinner metal sheath of the "elective"-type lithotripter could buckle and cause damage to the endoscope working channel.

17.4.2. Intraductal and Extracorporeal, Shock Wave Lithotripsy

When mechanical lithotripsy fails, shock wave lithotripsy could be useful for the effective fragmentation of CBD stones. Shock waves can be delivered within the bile duct (intraductal shock wave lithotripsy) or by an extracorporeal generator (extracorporeal shock wave lithotripsy).

During intraductal shock wave lithotripsy, the shock waves are generated at the tip of a flexible lithotripsy probe using electrical (electrohydraulic lithotripsy) or light energy (laser lithotripsy) [29, 30]. The lithotripsy probe is inserted into the bile duct through the working channel of a cholangioscope and fragmentation of the stone is achieved by delivering shock waves on the stone's surface, under cholangioscopic guidance. The success rate of this method is high (>90%) [31, 32]. Intraductal shock wave lithotripsy is a costly method and requires two endoscopists, experienced in using the mother-baby scope system. The major risk of this method is bile duct injury from a misdirected shock wave pulse. A novel laser device, with an automatic stone recognition system, has been reported to be safe and effective for CBD stones lithotripsy, under fluoroscopic guidance [33].

Extracorporeal shock wave lithotripsy has also been used for the fragmentation of CBD stones [34]. However, multiple sessions are usually needed for complete fragmentation of the CBD stones. Moreover, after lithotripsy, endoscopic clearance of the bile duct from stone fragments is mostly unavoidable.

17.4.3. Common Bile Duct Stenting for Difficult Stones

In patients with difficult stones, temporary placement of a biliary stent, in order to maintain biliary drainage, is very useful in short term (fig. 17.8). Sometimes, the combination of stent placement and oral administration of ursodeoxycholic acid may result in disintegration of the CBD stones [35]. Nevertheless, the long-term stenting of the bile duct for choledocholithiasis is not recommended for the majority of this group of patients, due to high morbidity and mortality rate, mainly from sepsis [36]. However, there is always a small percentage of patients considered at high risk for surgical management and for whom judicious conservative management of the in situ gallbladder is justifiable.

17.5. The Role of ERCP in Combined Choledocholithiasis and Cholelithiasis

When patients present with the combined problem of symptomatic cholelithiasis and choledocholithiasis there are two questions to answer: (1) what is the best method for clearing the bile duct and [2] what should be done with the gallbladder? In the recent past several options were considered in order to manage this problem, e.g., laparoscopic cholecystectomy with laparoscopic bile duct exploration; laparoscopic or open cholecystectomy followed by postoperative ERCP; preoperative ERCP followed by cholecystectomy (laparoscopic or open).

Laparoscopic approach for all stones (bile duct and gallbladder), is an appealing single-stage method to manage the gallbladder and CBD lithiasis. Overall, the results of laparoscopic bile duct exploration in specialized centers have been impressive, with reported success rates from 76% to 96%, complication rates from

8% to 17% and conversion to open choledochotomy from 4% to 10%. Approximately 5% of patients have retained stones after laparoscopic bile duct exploration [37-40]. While there is evidence that elective and emergent clearance of the bile duct by ERCP had advantages over open bile duct exploration, the comparison of ERCP therapeutic approach with laparoscopic bile duct clearance is much more equivalent in the elective setting [40]. In practice, however, laparoscopic common bile duct exploration is time consuming, technically demanding and is not always available as it is depending on local expertise.

The role of ERCP in the management of acute calculous bile duct disease in the presence of cholelithiasis, still remains central and optimal worldwide. All CBD stones could be managed pre- or postoperatively by the endoscopist. However, this strict therapeutic strategy should be more flexible and should rely on an accurate selection of patients. Several investigators have evaluated the value of clinical, biochemical and sonographic indicators to predict the presence of CBD stones [41-44]. Only clinical jaundice and abnormal imaging have high sensitivity and specificity in selecting patients for preoperative ERCP. Other clinical and anatomical criteria that favor preoperative endoscopic stone extraction are acute cholangitis or pancreatitis, stone size larger than 0.8 cm, stones located in the common hepatic duct, multiple stones and anomalous bile duct anatomy [2]. It is conceivable that the widespread use of MRCP, which has shown impressive results [42], will lead to a more accurate preoperative selection of patients undergoing ERCP [45].

Following endoscopic bile duct clearance, the decision to leave the gallbladder in situ and follow the patient expectantly, compared with routine laparoscopic cholecystectomy has been examined in several studies in the past [40, 46-49]. Biliary events after endoscopic duct clearance with gallbladder left in situ, in patients considered at high risk for open or laparoscopic cholecystectomy, were quite frequent, sometimes clinically serious and most of them occurred within the first year of follow-up. Therefore the majority of patients after successful endoscopic bile duct clearance should undergo laparoscopic cholecystectomy as early as possible in order to reduce the risk of further biliary events. However, in practice, there is always a small group of patients considered at high risk for surgical management. In these patients, judicious conservative management of the in situ gallbladder as well as symptomatic treatment of subsequent biliary events, is justifiable.

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CHAPTER 18

CURRENT CHANGES IN BILIARY REOPERATIONS FOR BENIGN LESIONS

E.J. Papaevangelou, A. Papaevangelou-Nomikou

18.1. Introduction

Over the last decades and up-to-the present time, surgical reapproach to the biliary tree for benign lesions remain one of the main topics in surgery. Reoperations are necessary for:

a. retained or recurrent stones in the biliary tree,
b. stenosis at the level of sphincter of Oddi,
c. malfunctioning previous bilio-digestive anastomoses,
d. strictures and stenoses of the biliary tree - an entity which represents the most interesting point of biliary reoperations,
e. intrahepatic lithiasis, cystic duct syndrome etc.

18.2. Retained or Recurrent Stones

Retained or recurrent stones used to be the most common reason for biliary reoperations [1]. Not any more! In 2002, Huttl et al presented a nationwide survey in Germany, with 8433 choledochotomies out of 98482 cholecystectomies. This percentage of CBD explorations decreased continuously from 7.4% in 1991 to 3.8% in 1996 [2]. Currently, this percentage is closer to zero, due to the fact that interventional radiologists, gastroenterologists and surgeons visit the common bile duct by means of endoscopic retrograde cholangiography (ERCP).

Interventionists actually have a very large experience in ERCP, consequently, they are assigned with the exploration of the common bile duct at present.

The rate of common bile duct lithiasis has declined over the last decade. Overlooked and complicated cases have almost disappeared.

As soon as early symptoms of cholelithiasis appear and diagnosis is confirmed patients promptly proceed to surgery.

It is probable that lithiasis begins from the gallbladder, with small stones immigrating from there to the CBD through the cystic duct.

In recent years, laparoscopic "invasion" offers a better and safe approach to the extrahepatic biliary ducts, even in cases of acute cholecystitis. Laparoscopic surgery approaches the gallbladder, the cystic duct and the choledochus in a very clear way. The cystic duct is always dissected down to its convergence with the common bile duct, and offers two possibilities:

a. to perform an intraoperative fluoroscopic cholangiography in order to detect the condition of the biliary tree and find possible lithiasic elements within it [2], and
b. to clear the CBD from stones, at a rate exceeding 66%, according to Nathanson's experience across seven metropolitan hospitals in Australia [3].

Intraoperative cholangiography is not required in:

a. cases with preoperative ERCP,
b. severe cholangitis or pancreatitis,
c. common bile duct of diameter less than 6 mm (with the exception of cases of microlithiasis).

In this study, attention was focused on the decompression drainage of the CBD, mainly in cases of edematous ampulla due to instrumentation or stone impaction. This policy minimizes complications that followed conventional choledochotomy, bile leak, pancreatitis and general morbidity [4].

Conversion from laparoscopic to open surgery -al-

though subject to extended difficulties– remains a strong weapon for biliary surgeons. According to Suter et al, the conversion rate is as high as 15% [5] and mainly involves cases of acute cholecystitis. Conversion to open surgery leads to prompt recognition, facilitating restoration, of the "surgical accident". This rate, mentioned by Suter, is actually very high for experienced laparoscopic biliary surgeons, even in cases of elderly patients where acute cholecystitis increases the likelihood of conversion to open surgery and the probability of injury.

Conversion grants immediate treatment success, as defined by "John Hopkins criteria". Roux en Y hepatico-jejunostony, offers the best surgical choice [6].

In recent years laparoscopic cholecystectomy has been widely accepted, all over the world. It offers better approach to the gallbladder, even in cases with inflammation, adhesions and fibrosis and leads to a better view of the Callot triangle. Open surgery, is no longer first choice for biliary operations [7].

The diagnostic armamentarium increases the understanding of the condition of the patient's biliary tract and includes B-mode ultrasonography, CT or MRI, intraoperative cholangiography, micro-choledochoscopy and intraoperative ultrasonography. However, these methods have not been applied with intent to cure since postoperative endoscopic retrograde cholangiography (ERCP) can offer comprehensive knowledge of the condition of c.b.d and at the same time allows the removal of biliary stones [3]. Clinical and radiologic information such as jaundice, pancreatitis, small gallbladder stones, short or wide cystic duct and common bile duct dilatation is of great importance. Due to its simplicity and reliability micro-choledochoscopy is superior to other methods in treating residual bile duct stones. Two decades ago, retained or recurrent stones of the CBD were regarded as a significant problem in biliary reoperations.

Today, this problem no longer exists since the common bile duct is easily and effectively approached by ERCP. Retained stones? So what!! [3]. Choledocholithiasis false negative rate and retained or recurrent stones cease to pose a problem in biliary surgery. This probably accounts for laparoscopic CBD exploration not being considered significant in German surgical practice [2]. This, in no way excludes laparoscopic choledochotomy from being of major importance in the years to follow.

18.3. Stenosis of the Sphincter of Oddi

In recent years this disorder has virtually disappeared. Although there were many doubts about the existence of such a stenosis of the sphincter, it seems that some authors have recognized stenotic alterations with anatomopathological findings of connective tissue proliferation on the specimen taken out when sphincterotomy with sphincterolpasty and wedge excision of a part of the sphincter was undertaken.

So, stenosis of the sphincter of Oddi is considered to be due to:

a. remaining calculi at the lower end of the CBD,
b. bougies' dilatation of the sphincter in an effort to permit easy passage or stones from the CBD to the duodenum,
c. impacted stones to the lower CBD, resulting in destruction of the sphincteric mechanism, and
d. traumatic local injuries of the sphincter during ERCP manipulations.

Nowadays, few if any, surgeons worry about the situation of the sphincter of Oddi.

The used instruments, dilatators or bougies, choledochotomies and exploration of the CBD, overpass the sphincter without any special effort.

18.4. Malfunctioning "Low" Bilio-Digestive Anastomoses

Many of the biliary surgeons used to complete a choledochotomy and choledochal exploration by constructing a bilio-digestive anastomosis, namely choledocho-duodenal or choledocho-jejunal anastomosis. It is always necessary to establish a large anastomosis, exceeding 1 cm, mainly when the common bile duct is quite large.

Reoperations were imposed when anastomoses were not working satisfactorily:

a. in cases of disfunction, without stenotic phenomena,
b. in cases of stenosis that allows the retrograde passage of the duodenal or jejunum contents into the common bile duct, causing a mild or severe cholangitis which cannot be adequately explained.

Reoperations for malfunctioning bilio-digestive anastomoses are not seen any more due to the fact that, this kind of anastomoses is not standard practice nowadays. French studies refer to "anastomoses cholechoduodenales basses" meaning sphincterotomies with those few extra stitches that follow spincteroplasties.

18.5. Benign Strictures of the Biliary Tract

This group of lesions constitutes the main reason for open surgery, one that is realistically difficult nowadays. In almost all cases, strictures are the result of traumatic injuries of the common bile duct and its branches, during cholecystectomies. Iatrogenic stenoses have various etiologies. Bismuth's classification, depending on the level and degree of stricture, is still generally accepted [8]. Patients present various signs and symptoms depending on the moment the lesion is detected. The treatment largely depends on such timing. Roux-en-Y bilio-digestive anastomosis, namely hepatico-jejunostomy is the method of choice and should only be performed by experienced and well trained surgeons. It is necessary to respect the following principles [9]:

a. good exposure of the operating field,
b. internal drainage of the intra-hepatic stenosis,
c. radiological imaging of the situation of the biliary tree,
d. meticulous mucosa to mucosa anastomosis in order to reduce the probability of a new anastomotic stenosis,
e. trans-anastomotic stents are not necessary,
f. a blind subcutaneous jejunal loop is, sometimes, recommended and good enough to permit dilatation of the anastomosis, in cases of future stenosis.

Preoperative transcutaneous insertions of stents, e.g. in cases of malignancy, are not recommended, because surgery follows detection of stenosis in almost all cases. As already mentioned, bile duct injury with subsequent biliary stenosis is always iatrogenic and is 0.1 to 0.5% among biliary operations [10-13]. Roslyn found 0.2% of bile duct injuries, among 42472 biliary operations in U.S.

Our personal experience includes 148 cases of biliary reoperations among 4110 biliary operations (3.6%). 14 reoperations were performed for iatrogenic biliary stenoses with formation of Roux en Y bilio-digestive anastomosis. Injuries of bile ducts occured often during the first years of laparoscopic surgery, but experience led to a significant decrease in the rate of injuries making it unquestionably safer today [10].

Decision for reoperation follows the efforts of intervensionists, like transhepatic image guided or endoscopic balloon dilatation, and application of intrabiliary stents.

18.6. Reoperations for "Postcholecystectomy Syndrome"

This entity describes the presence of symptoms after cholecystectomy. Cases for biliary reoperations comprise: residual or reformed gallbladder stump cholelithiasis, neuroma of the cystic duct, hepatolithiasis, choledocholithiasis, sclerosing cholangitis, strictures, trauma, dyskinesia, fistula, oddi stricture, pancreatic stone, chronic pancreatitis, retained gallbladder pouch, suture granulomas and cystic duct mucocele [14].

Surgical therapy should be directed at the specific cause. Some patients who present with no identifiable etiology and an unyielding exploration may respond to shpincteroplasty to both bile and pancreatic ducts. If after complete evaluation (including ERCP and shpincterotomy), a patient has incapacitating right upper quadrant pain, the treatment of choice is transduodenal shincteroplasty and septoplasty providing the head of the pancreas is not hard and fibrotic, in which case choledochoduodenostomy may prove valuable [14].

18.7. Reoperations for Cases with "Cystic Duct Syndrome"

Though rare, this is a well-known entity that refers to a long cystic duct stump containing stones after previous cholecystectomy. Patients suffer from hepatic colics. Open or laparoscopic surgery involves removing the portion of the cystic duct left behind.

18.8. Conclusion

So, what is left today to be included in biliary reoperations?

a. Iatrogenic lesions to the main biliary duct and its branches, such as parietal traumatic lesions with bile leak, occlusion due to ligatures, transection of biliary ducts, clips to stop hemorrhage and involving parts of the biliary tree,
b. recurrent or retained stones where ERCP fails to evacuate the common bile duct after two consecutive efforts,
c. reoperations concerning the lower part of the CBD and mainly the Oddi's Sphincter,
d. malfunctioning bilio-digestive anastomoses with cholangitis.

Current changes of biliary reoperations today include reoperations following injuries of the biliary tree. All other reasons have disappeared.

Laparoscopic surgery resulted in an easier cholecystectomy, with a better approach to the extrahepatic biliary ducts, respecting the common bile duct and its branches and recognizing abnormalities of the biliary tree or potential surgical "accidents", immediately during the initial surgery.

ERCP considerably changed the surgical practice of the common bile duct, by permitting easy and effective entrance and at the same time, the removal of stones.

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CHAPTER 19

OTHER BENIGN BILIARY DISEASES AND LESIONS

G. Sgourakis, Th. Mitellas, Con. Ch. Karaliotas

19.1. Mirizzi's Syndrome

Mirizzi's syndrome is a rare entity that causes extrahepatic biliary strictures and occasionally an apparent tumor at the liver hilum associated with cholelithiasis, a condition that occurs in no more than 0.5% of cholecystectomies [1]. An impacted calculus in the gallbladder ampulla or in the cystic duct may cause direct pressure or edema (type I), or sporadically may erode through the wall of the cystic duct and into the common hepatic duct (type II) resulting in a colecystocholedochal fistula and causing in this way the obstruction of the common hepatic duct [2]. A cystic duct remnant calculus causing Mirizzi's syndrome is exceedingly rare [3].

Abnormal liver function tests and occasionally jaundice (produced by both extrinsic compression and intrinsic calculus obstruction) may give some evidence which differentiates patients from those suffering from acute cholecystitis, but patients may also present with sepsis or an empyema of the gallbladder and this may lead the surgeon to diagnose Mirizzi's syndrome as cancer. Seldom is the diagnosis made at the time of cholecystectomy.

Ultrasonography discloses dilatation of the proximal biliary tree including the common hepatic duct above the bladder neck and an abrupt change of the caliber of the common hepatic duct or a decompressed gallbladder with stones involving the common hepatic duct. This latter finding is highly suggestive of the existence of the syndrome. ERCP discloses a cicatricial stenosis of the common hepatic duct beyond the dilatation of the proximal biliary tree and may disclose a fistula between the gallbladder and the common hepatic duct (type II). It further permits endoscopic stent placement for jaundice relief. PTC is considered by some authors the radiologic method of choice for the preoperative diagnosis as it will clearly delineate the obstruction, the stone and the presence of a fistula.

The diagnostic workup points toward exclusion of the diagnosis of bile duct or gallbladder cancer, however both conditions may coexist. Mirizzi's syndrome should be included among the few benign disorders which can yield high elevations in the CA19-9 [4]. A smooth, lessening stricture is more suggestive of a benign pathology. On the contrary a prominent mass or lymphadenopathy would be more in accordance with cancer. CT scanning and laparoscopic ultrasound may be of assistance [5-7] in outlining the stricture, ruling out tumor dissemination and defining vascular invasion. The typical CT features are dilatation of the biliary tree above the neck of the gallbladder with a normal tree below. Visualization of the cystic duct joining the common hepatic duct may disclose an impacted stone in the cystic duct or in the gallbladder neck. A targeted biopsy may substantiate a malignant diagnosis.

Percutaneous treatment of the Mirizzi's syndrome with electrohydraulic lithotripsy (EHL) under cholangioscopic control and endoscopically with EHL or via laser shock-wave lithotripsy, under cholangioscopic guidance has been described in case reports [8].

Laparoscopic cholecystectomy has been conveyed for type I Mirizzi's syndrome [9, 10]. The regular methodology for type I Mirizzi's syndrome is to perform an open cholecystectomy in order to permit sufficient assessment of the related stricture. Intraoperative cholangiography (IOC) should be carried out (fig. 19.1, 19.2, 19.3), and in those patients with unrelenting strictures a hepatico-jejunostomy should be executed. For type II Mirizzi's syndrome patients the optimal approach is cholecystectomy and hepatico-jejunostomy [2] while

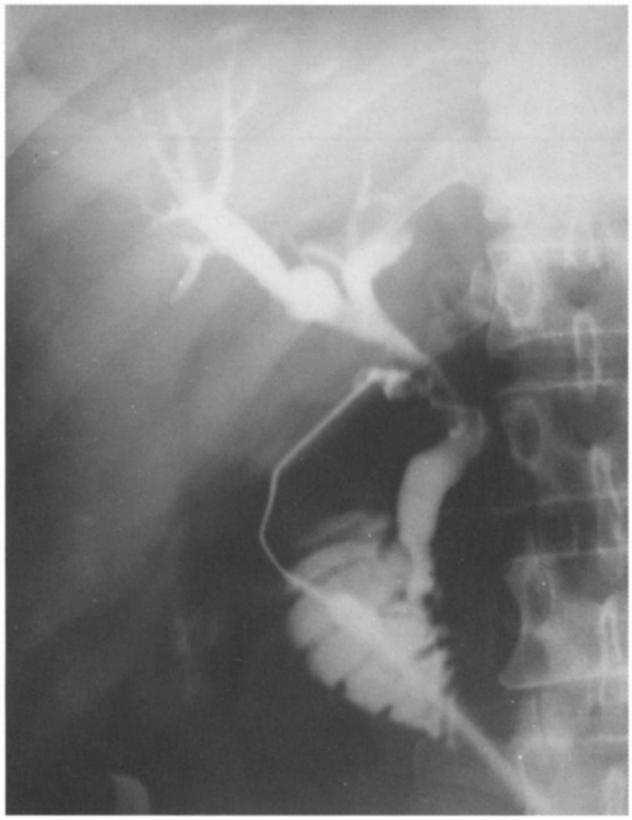

Fig. 19.1. IOC: Pressure on common bile duct. Mirizzi syndrome.

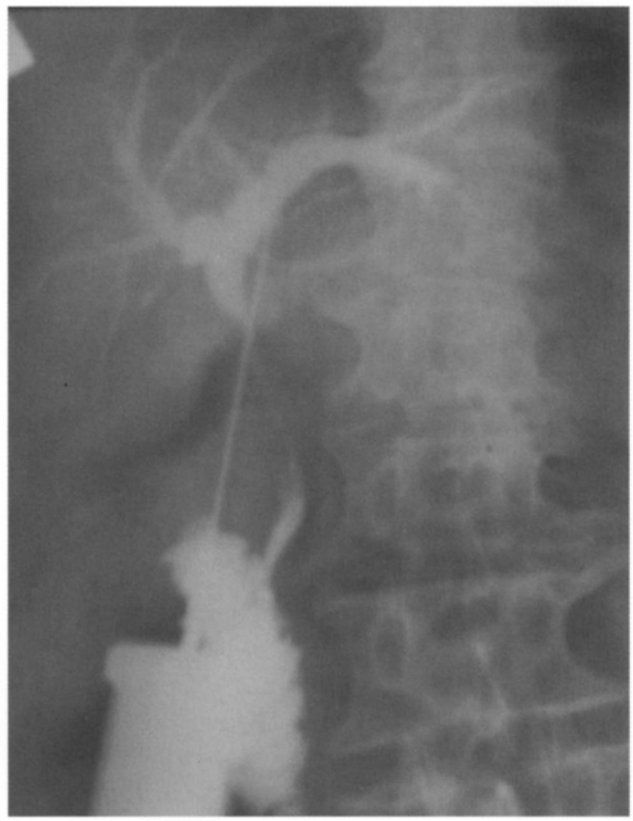

Fig. 19.3. IOC: Erosion of common hepatic duct, Mirizzi syndrome Type II.

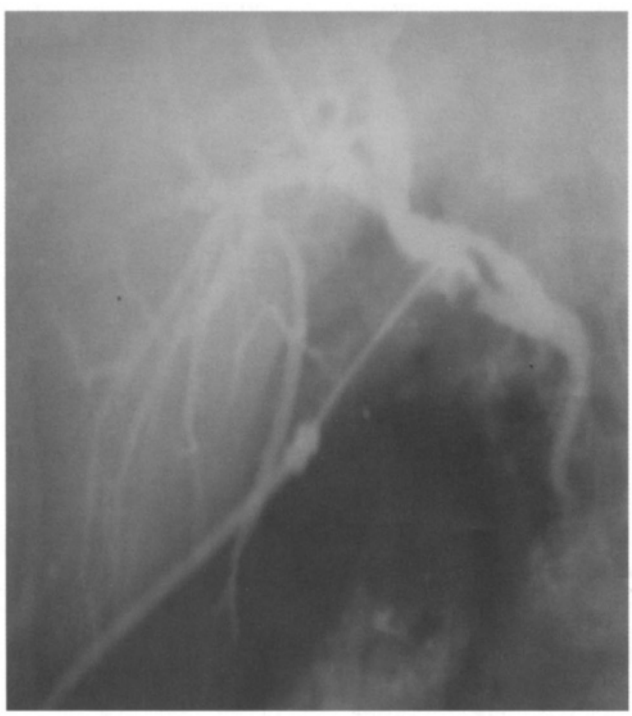

Fig. 19.2. IOC: Pressure on common bile duct. Mirizzi syndrome.

common bile duct rebuilding using Hartmann's pouch grafts and T-tube insertion have been described. Patients with fistula sizes of less than one-third of the common bile duct diameter undergo choledochoplasty with 5 mm cuff of the gallbladder, and patients with fistula sizes between one-third and two-thirds of the diameter of the common bile duct undergo choledochoplasty with 10 mm cuff of the gallbladder. Patients with fistula sizes of more than two-thirds of the common bile duct diameter undergo Roux-en-Y hepaticojejunostomy [11]. Long-term results of this pioneering advancement are expected.

19.2. Functional Disorders of the Biliary Tract

Sphincter of Oddi dysfunction emerges in less than 1% of patients after cholecystectomy and in 14% of patients argumentative of postcholecystectomy symptoms [12].

Sphincter of Oddi dysfunction can engage abnormalities in the biliary sphincter, pancreatic sphincter, or both.

19.2.1. Gallbladder Dysfunction

The principal symptom of gallbladder dysfunction is pain of biliary type. At present, the only objective feature is diminished gallbladder emptying. Biliary pain in the absence of gallstones is approximately to 2.4%, as stated in a ultrasonographic study [13]. Modified Rome diagnostic criteria concerning specification of the duration, number of episodes of pain, and the time within which they occur and of the established functional abnormality are applied for documentation of gallbladder dysfunction [14].

A conservative regimen consists of altering gallbladder motility by use of motility agents or ursodeoxycholic acid which deteriorates motor function or reduction of pain and inflammation with non-steroidal anti-inflammatory drugs. The diagnostic algorithm includes the following steps: Abnormal gallbladder emptying (<40% ejection) in CCK-cholescintigraphy implies gallbladder dysfunction. In the case of normal emptying, microscopic examination of bile to detect cholesterol crystals and bilirubinate, magnetic resonance cholangiography, ERCP or endoscopic ultrasound to establish the diagnosis of lithiasis should be the next step. If there is not an apparent reason for diminished emptying, cholecystectomy is suggested. Absence of common bile duct stones or other significant pathology prompts for sphincter of Oddi's manometry which will disclose patients as potential candidates for sphincterotomy.

19.2.2. Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction may effect either biliary or pancreatic disorders and has been more frequently described following cholecystectomy for assumed gallbladder pain. Up to 90% of patients with idiopathic recurrent pancreatitis demonstrate a spectrum of sphincter of Oddi manometric disorders (increased basal pressure, increased amplitude and frequency of phasic waves, a paradoxical response to CCK and an increased number of retrograde waves) and it is stated that motility disorders of the sphincter of Oddi may be associated with episodes of pancreatitis [15]. Postcholecystectomy patients with biliary-type sphincter of Oddi dysfunction have been classified in three types [16]:

- Type I patients with a history of pain, elevated liver function tests, delayed contrast emptying, and a common bile duct diameter ≥12 mm at ERCP.
- Type II patients present with a history of pain and only one or two of the above mentioned findings (fig. 19.4).
- Type III patients with a history of only recurrent biliary-type pain and none of the above findings.

The prevalence of sphincter of Oddi dysfunction varies among groups, being maximum in type I (65-95%), moderate in type II (50-63%) and least in type III (12-28%). In opposition, the probability that biliary pain is apparent as a manifestation of the syndrome of chronic functional abdominal pain is higher in type III patients and lower in type I [14].

Diagnostic work up includes all the modalities in the biliopancretic field and diagnosis is established by exclusion of other causes of abdominal pain. There is usually delayed drainage of contrast at ERCP, in the first two types of sphincter of Oddi dysfunction and manometry should be set aside for those patients in whom the diagnosis remains unclear.

Hormones such as CCK and glucagon, calcium channel blockers, nitrates, octreotide and botulinum toxin have been used in the terms of conservative treatment but long-term results are unspecified [17-20]. Sphincterotomy for sphincter of Oddi dysfunction seems effectual in those patients with an elevated sphincter of Oddi basal pressure (>40 mmHg), but is not superior

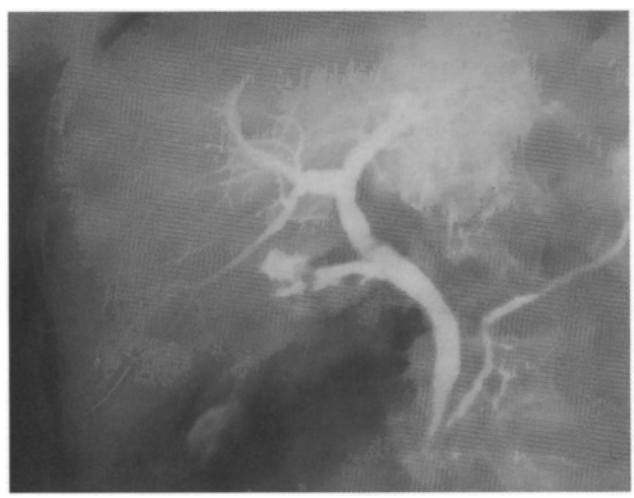

Fig. 19.4. IOC: Sphincter of Oddi dysfunction Type II. Simultaneous retrograde pancreatography.

to placebo therapy in those patients with a normal basal pressure. [21] Surgical sphincterotomy is indicated in cases of endoscopic sphincterotomy failure. Sphincter of Oddi stenosis should also be treated by endoscopic sphincterotomy.

19.2.3. Pancreatic-Type Sphincter of Oddi Dysfunction

There is a more apparent form (approximating Biliary-type I sphincter of Oddi dysfunction) of pancreatic-type sphincter of Oddi dysfunction that may exhibit classic pancreatitis presentation with epigastric pain, which frequently radiates to the back, and elevated serum amylase. In its less noticeable form (approximating Biliary-type III sphincter of Oddi dysfunction), the pain is as described above but there is no abnormality in pancreatic enzymes. Total division of the sphincter through open transduodenal or endoscopic approach by means of sphincteroplasty and septectomy is a high yielding treatment [22].

19.3. Acalculous Cholecystitis

Acute inflammation of the gallbladder can arise in the absence of gallstones. Aetiology varies among several disease entities: 1) diminished motility and deprivation of food intake in cases of trauma, burns, total parenteral nutrition, surgery, anesthesia and drug addiction, 2) lessening blood flow of the cystic artery in congestive heart failure, coronary artery bypass surgery, arteriosclerosis, polyarteritis nodosa, systemic lupus erythematosus, diabetes, shock, cryoglobulinemic vasculitis, antiphospholipid antibody syndrome, Churg-Strauss syndrome and X-linked hyper-immunoglobulin M syndrome 3) blockage of the cystic duct by extrinsic inflammation, metastases, lymphadenopathy and 4) infection in cases of salmonella, cholera, Kawasaki syndrome, hepatitis A virus, plasmodium falciparum, dengue virus, varicella-zoster virus, cytomegalovirus or cryptosporidia in AIDS, candida, leptospirosis and scrub typhus infections.

Gallbladder distention with bile stagnation and ischemia, coagulation factors and prostaglandins may also have roles in the disease process. Histology reveals serosal and muscular edema, with erratic thrombosis of venules and arterioles [23].

Clinical presentation is identical to that of acute cholecystitis, should the patient be alert but the prevailing clinical manifestation is driven by the patient's underlying critical condition. Fever, leucocytosis and abnormal values of alkaline phosphatase and bilirubin prompt for investigations in the unconscious patient.

Ultrasonography is the usual modality of choice that visualizes the distended wall-thickened gallbladder, echogenic sludge, pericholecystic fluid, and a potential abscess formation. CT scan shows a similar sensitivity. Serial images from a Tc-99m-IDA scan show normal hepatic uptake of radiotracer with normal visualization of common duct and bowel but the gallbladder is not visualized. Intervention in acalculous cholecystitis is imperative. Percutaneous ultrasound or CT-guided or open cholecystostomy is performed on critically ill patients for both diagnostic and therapeutic reasons with great success and, should this be possible, cholecystectomy is performed after the patient has recuperated from the underlying critical pathology.

19.4. Biliary Intrahepatic and Common Bile Duct Cysts in Adults

Biliary cysts consist of cystic dilatations of the extrahepatic and or intrahepatic biliary tree.Women are affected three to eight times more often than men. Approximately 50% of the patients become adults by the time diagnosis is established.

The pathogenesis of choledochal cysts is mostly attributed to a congenital etiology or a congenital predisposition. An anomalous junction of the common bile duct with the pancreatic duct has been stated as the causative factor in 90% of patients according to the study of Miyano and Yamataka [24]. An anomalous pancreatobiliary junction is regarded as the insertion of the pancreatic duct to the common bile duct 1 cm or more proximal to the point where the common bile duct reaches the ampulla of Vater. Inflammation and weakening of the biliary walls ensues after activation of the pancreatic proenzymes in the alkaline environment to which pancreatic secretions and enzymes reflux. Defects of the developing bile ducts during organogenesis have also been incriminated.

Choledochal cysts are lined with cuboidal epithelium and are classified into five types as firstly described by Alonso-Lej and lately refined by Todani in 1977 [25].

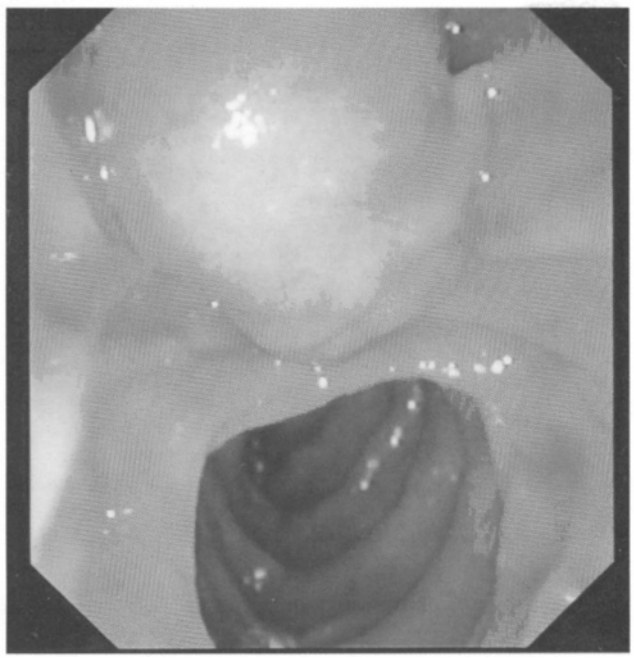

Fig. 19.5. Endoscopic view of choledochal cyst Type III.

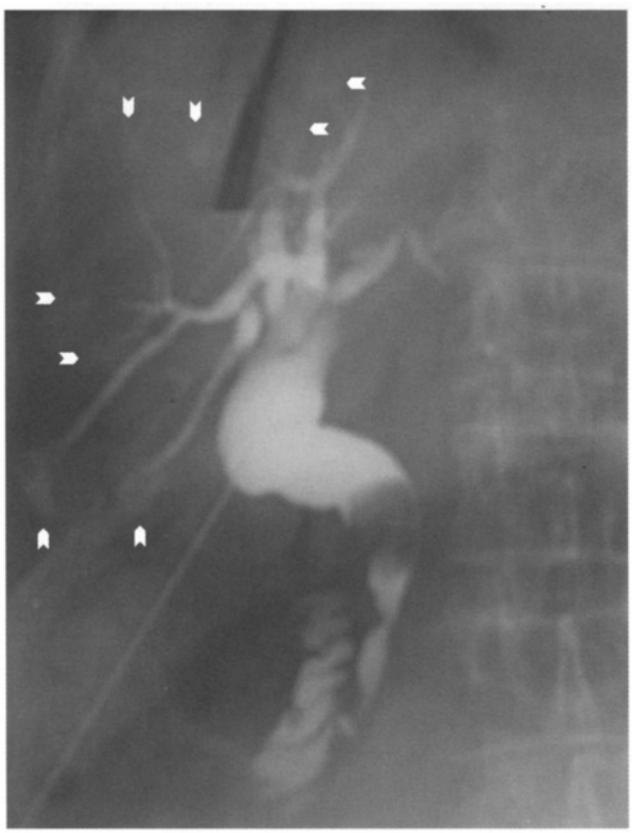

Fig. 19.6. Caroli's disease and CBD lithiasis. Arrowheads depict intrahepatic cystic dilatations.

Type I: cysts consisting the 80-90% of the cases are saccular or fusiform dilatations of the entire common hepatic and common bile ducts or a part of each. Type II: diverticula or protrusions impelled from the common bile duct wall connected to the common bile duct by a slender pedicle. Type III or choledochocele: cysts in the intraduodenal portion of the common bile duct (fig. 19.5). Type IVA/B: numerous dilatations of the intrahepatic and extrahepatic biliary tract (IVA) multiple dilatations only in the extrahepatic biliary tract (IVB). Type V or Caroli disease: multiple dilatations of the intrahepatic biliary dactules in both hepatic lobes with in between strictures, stones, obstruction and predisposition for cholangitis. The left liver lobe is most prevalently affected in case of unilobar presentation (fig. 19.6).

The most usual clinical manifestation in adults is vague epigastric or right upper quadrant abdominal pain. A percentage of 10-20% of adult patients are admitted with abdominal pain, jaundice and a palpable right upper quadrant abdominal mass. Bile duct stone formation, hepatic abscesses, pancreatitis, cirrhosis and portal hypertension may ensue in the long run, due to enduring biliary obstruction and recurrent cholangitis.

Ultrasonography is the initial imaging modality in patients with choledochal cysts. A cystic extrahepatic mass is depicted and occasionally, the specific type of cyst may be recognized. Ultrasound may also disclose concurrent pathology as common bile duct stones, dilatation of intrahepatic biliary tree, and thrombosis of the portal vein, biliary neoplasms and hepatic abscess. A complementary study is regularly needed in order to to assess the biliary anatomy and to plan the appropriate surgical treatment. CT is highly accurate and also contributes to surgical planning. A dilated cystic mass with clearly delineated walls is typically demonstrated (fig. 19.7).

A water-like attenuation is produced by the contained bile. A thickened cyst wall implies that several episodes of cholangitis have occurred. CT cholangiography has been reported recently but this modality has yet to be evaluated. False-positive and false-negative results are rare. ERCP enlightens the course of pancreatic duct and the distal extent of the choledochal cyst additionally to the information yielded, concerning the epithelium of the cyst and the presence of related tumors or strictures (fig..19.8, 19.9). MRI and MRCP pro-

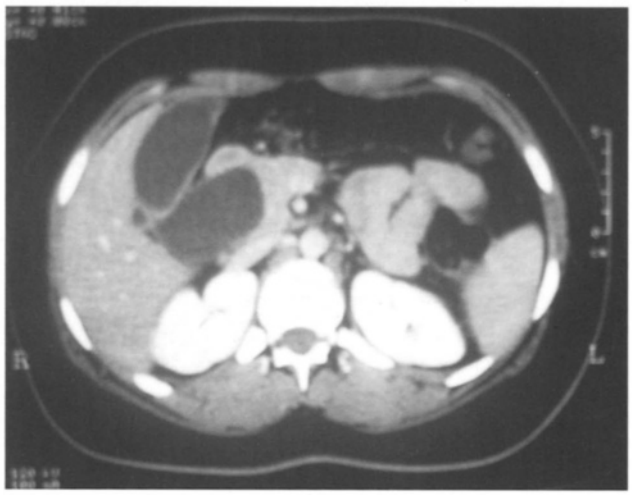

Fig. 19.7. CT scan. Common bile duct cyst. Type I.

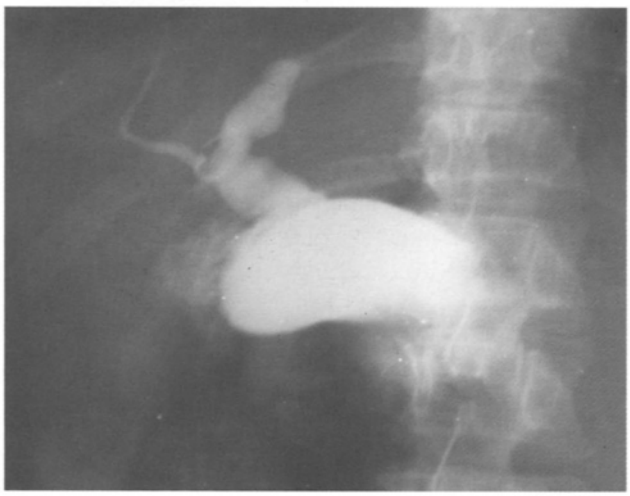

Fig. 19.8. ERCP. Common bile duct cyst. Type II.

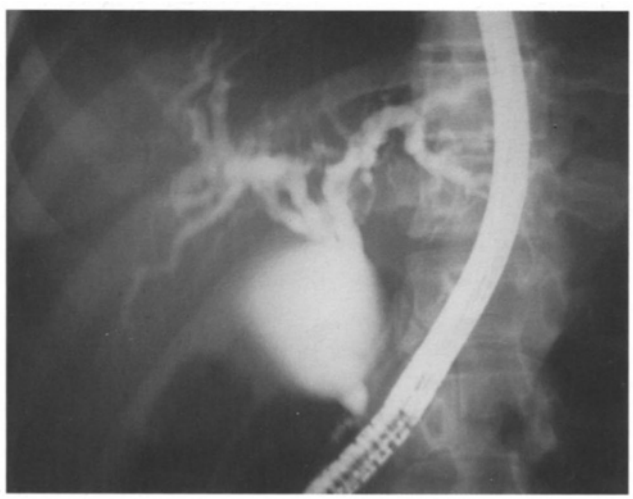

Fig. 19.9. ERCP. Common bile duct cyst. Type I.

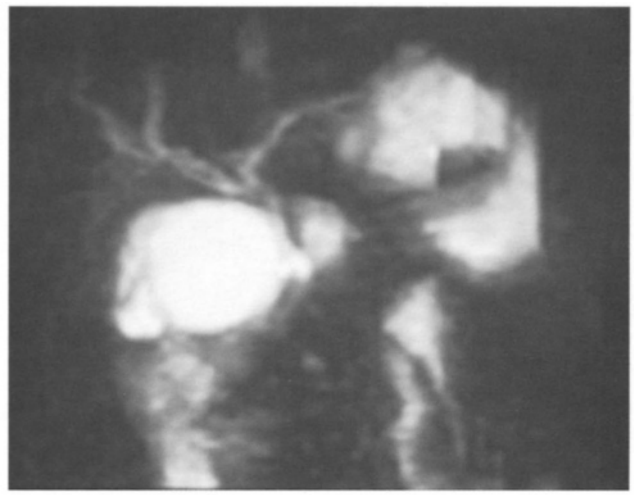

Fig. 19.10. a. MRCP. Common bile duct cyst. Type II.

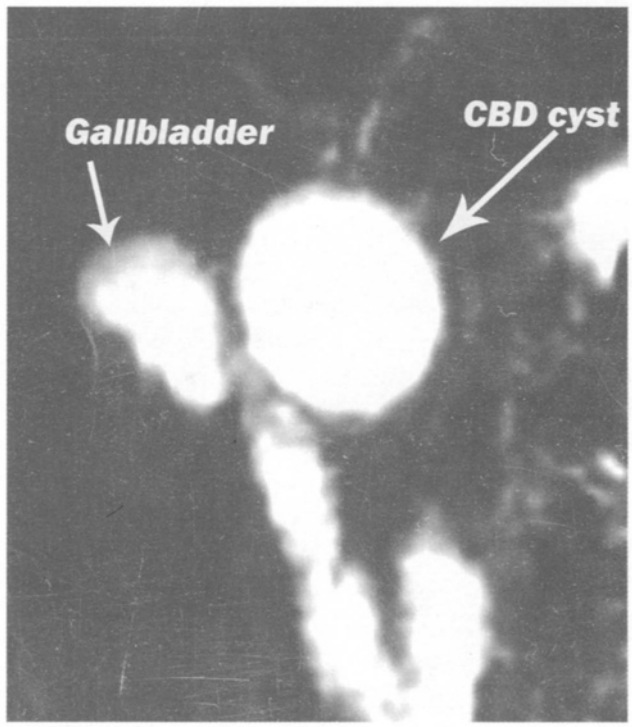

Fig. 19.10. b. MRCP. CBD cyst. Type II.

duce remarkably strong signals on T2-weighted images (fig. 19.10a, 19.10b). The diagnostic accuracy is between 82-100%. Anomalies of the pancreatic duct and the long common channel are clearly well visualized. Kim et al found that MRCP and ERCP share the same overall diagnostic accuracy [26]. The differential diagnosis between choledochal cyst, pancreatic pseudocyst

and other cystic pancreatic lesions may be difficult by MRI alone. Small gallbladder neoplasms may elude the diagnosis. Hepatobiliary scintigraphy can assure fairly good accuracy but it should be complemented by other modalities.

Development of cholangiocarcinoma in the context of the presence of a choledochal cyst is approximately 15% in adults, and complete excision of the cyst is obligatory. An increased risk for development of cholangiocarcinoma, persists even after total excision of the cyst.

Total excision of the cyst and a Roux-en-Y biliary-enteric anastomosis is performed in type I cysts. Type II cysts are completely excised, with a primary closure of the common bile duct over a T-tube (fig. 19.11 and 19.12). Endoscopic intervention and sphincterotomy is reserved for those choledochoceles ≤ 3 cm in diameter while larger ones frequently related with partial duodenal obstruction are excised by a transduodenal approach with reimplantation of the pancreatic duct into the duodenum should its insertion be found within the cyst. In type IV disease the dilatated extrahepatic duct is entirely removed, and a Roux-en-Y biliary-enteric anastomosis is performed. Interventional radiology plays a major role in cases of IVB disease where ductal strictures, hepatolithiasis, or abscesses are evident. Resection should be considered when the location of the cysts is restricted to specific hepatic segments or a hepatic lobe. For types I, II, and IV cholecystectomy is also performed. Lobectomy is the treatment of choice in unilobar extension of Caroli disease. Liver transplantation should be considered in patients with bilobar disease and concurrent biliary cirrhosis or portal hypertension. Kaneko et al [27] proposed external biliary drainage in patients presenting with prolonged abdominal pain, jaundice, and vomiting caused by protein plugs or proteinaceous debris to relieve the signs and symptoms.

19.5. Biliary Strictures Mimicking Malignancy

Benign biliary pathology thought to be malignant is repeatedly found in resected specimens of the pancreatic head. Some of these disease entities are reported below.

Fig. 19.11. CBD cyst of type I.

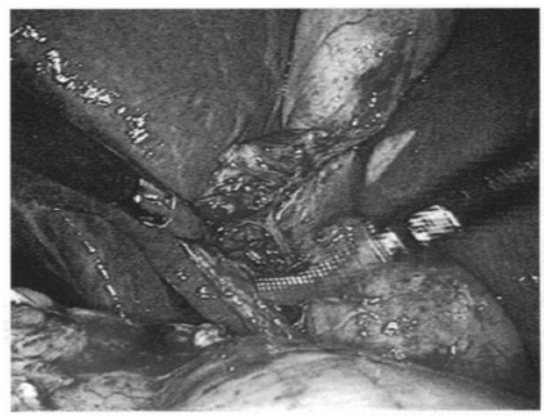

Fig. 19.12. CBD cyst of type I.

19.5.1. Autoimmune or Lymphoplasmacytic Sclerosing Pancreatitis

Autoimmune pancreatitis (AIP) or lymphoplasmacytic sclerosing pancreatitis is an infrequent variety of chronic pancreatitis depicted by discontinuous bouts of abdominal pain associated with pancreatic ductal narrowing and parenchymal edema on CT scan and occasional intra-pancreatic biliary stenosis or coexistence of biliary lesions (sclerosing cholangitis similar to primary sclerosing cholangitis) on endoscopic retrograde cholangiopancreatographic (ERCP) images. Abraham et al [28] documented 11 out of 442 Whipple resections that had been performed for a clinical suspicion of malignancy that proved to be finally lymphoplasmacytic sclerosing pancreatitis cases. A percentage of 2.5-5% of all pancreaticoduodenectomies for suspected pancreatic adenocarcinoma are performed in the setting of AIP and a proportion of these patients will result to

either biliary anastomotic strictures or intrahepatic strictures following resection.

Lymphoplasmacytic infiltration is repeatedly present in peripancreatic retroperitoneal tissue, extrahepatic bile duct, gallbladder, liver, gastric mucosa, salivary gland and lymph nodes [29, 30].

Autoimmune pancreatitis is related to other autoimmune entities such as Sjogren's syndrome, Riedel's thyroiditis, tubulointerstitial nephritis, retroperitoneal fibrosis, sarcoidosis, ulcerative colitis, primary sclerosing cholangitis, rheumatoid arthritis and type 1 diabetes mellitus [31].

The Japan Pancreas Society has proposed the following diagnostic criteria for the diagnosis of AIP: diffuse main pancreatic ductal narrowing and irregular walls involving at least 1/3 of its length and diffuse parenchymal edema, elevated levels of serum IgG4 or the presence of autoantibodies (ANA, ALF, ACA-II and Reumatoid factor) and/or demonstration of fibrotic changes with lymphocytic and plasma cell infiltration of the pancreas on histological examination [32].

The histologic features characteristic of AIP are diffuse fibroinflammatory infiltrates that can involve both the pancreatic ducts and acinar parenchyma with dense periductal inflammation rich in lymphocytes and plasma cells, ductal epithelial damage, focally dense fibrosis, and perivascular inflammatory cell aggregates (periphlebitis) [33].

The diagnostic work up of patients with diffuse pancreatic swelling on CT should also encompass the measurement of serum IgG4 (the cutoff value of 135 mg/dL was found by Hamano et al to be 95% sensitive and 97% specific for the differential diagnosis of AIP versus pancreatic cancer [34]). An ERCP should also be directed to weigh up for the presence of a sclerosing pattern and lymphoplasmacytic infiltration with benign pancreatic ductal epithelium on fine needle aspiration. An absolute symptomatic and radiographic resolution often results following a 4 weeks of glucocorticoid regimen [35].

19.5.2. Inflammatory Pseudotumor

Inflammatory pseudotumour emulates malignancy of the bile ducts and hilar strictures accounting for 8% of cases in patients undergoing surgery for presumed malignant hilar obstruction [36]. Cholangiography is highly reminiscent of a malignant stricture. Some patients with a benign disease of this kind are liable to inappropriate treatment, unless they are subjected to curative resection. Steroids have been successfully applied for treatment.

19.6. HIV Cholangiopathy (AIDS Cholangiopathy)

HIV cholangiopathy is a secondary sclerosing cholangitis that develops in severely immunosupressed patients which develop a wide variety of cholangiographic alterations, associated with an assortment of clinical symptoms. As stated by Cello et al 45% of patients with AIDS and lasting diarrhea were found to have cholangiographic changes regardless of the absence of biliary symptoms [37].

The disease is presumably associated with infections of the entire biliary tree by opportunistic organisms. As stated by Benhamou et al [38] as high as 23% of patients with HIV cholangiopathy were contaminated by both Cytomegalovirus and Cryptosporidium.

Mycobacterium avium intracellulare, C. albicans, microsporidia, herpes simplex virus, Cyclospora, Isospora, Cryptococcus and giardiasis have also been incriminated [39]. In about 50% of cases the offending pathogen is not identified while of a better yield is the sampling of bile along with the biopsy of the papilla and duodenum at ERCP.

Symptomatic patients may manifest epigastric or right upper quadrant abdominal pain radiating to the back, fever, nausea, vomiting. The serum alkaline phosphatase level may be elevated up to six times the normal value. The serum bilirubin may be elevated to some extent. The serum aspartate transaminase and alanine transaminase levels may be elevated up to two to three times the normal value. The rise in liver function tests may also be attributed in drug interactions or viral hepatitis. The CD4 lymphocyte count is commonly less than 100/mm^3 [40], while values exceeding 200/mm^3 are exclusive of HIV cholangiopathy.

HIV cholangiopathy comprises several pathologic entities such as secondary sclerosing cholangitis, papillary stenosis, and extrahepatic biliary strictures [41].

Ultrasonography has a sensitivity of 75% and depicts dilation of the intrahepatic ducts and the common bile

duct, thickening of the common bile duct and distention and wall thickening of the gallbladder.

Cello et al [37] has clearly illustrated the cholangiographic ERCP findings, comprising of papillary stenosis alone in 28% of patients and along with intrahepatic changes of sclerosing cholangitis in 49%, sclerosing cholangitis alone in 12%, and a long extrahepatic stricture in 10%. Other authorities report that 53% of patients have pancreatic ductal changes although there is no impact in respect to risk factors for acute or chronic pancreatitis.

Endoscopic sphincterotomy efficiently relieves pain within approximately 12 months in patients with papillary stenosis with or without intrahepatic ductal disease although the abnormal liver function tests commonly remain so. Biliary strictures may respond to stenting, but surgery is of a low yield since the cumulative one-year survival for HIV cholangiopathy is approximately 40% [42]. Medical treatment directed at a specific organism does not increase the likelihood of a successful outcome.

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CHAPTER 20

CHOLANGITIS

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20.1. Introduction

Cholangitis is an infection of the biliary ductal system. It is a result of bacterial infection superimposed on partial or complete obstruction of the biliary system. The original description of cholangitis, by Charcot in 1877 [1], alluded to inflammation and the symptoms now known as "Charcot's triad" (intermittent chills and fever, jaundice and abdominal pain). In clinical practice, the term "cholangitis" is used to refer to the signs and symptoms produced by bacterial inflammation of the biliary duct system, without regard to the presence or absence of inflammatory changes within the walls of the bile ducts or the parenchyma of the liver. Bacteria can be present within the biliary tract (bacterbilia) without clinical symptoms and the bile of asymptomatic patients can harbor many bacteria if the biliary tree is otherwise normal. Thus, bacteria in bile, increased biliary pressure, and invasion of bacteria into the bile ducts and liver tissue are all important in the development of cholangitis.

When biliary stasis occurs, elevated intraductal pressure leads to bacteraemia and about 50% of the patients have positive blood cultures [2]. The origin of bacteria in bile is unclear, but the most acceptable theory is that small numbers of bacteria normally pass into the portal venous system from the intestine, enter the liver, and are phagocytosed by the reticuloendothelial system. When a foreign body or other lesion is present within the biliary duct system, colonization of bile by bacteria is frequent. Clinical cholangitis develops when bacteria are released from the biliary duct system into the circulation, which occurs when pressure within the system is sufficiently high. Either complete or partial obstruction of the biliary tract may result in increased intraductal pressure [2, 3].

The disease can present a wide range of severity, from low grade fever to severe sepsis with frank pus within the biliary tree, which is also known as acute suppurative cholangitis [4]. Cholangitis should be considered a clinical entity common to a variety of lesions that can produce partial or complete obstruction of the bile duct system. When the diagnosis of cholangitis is made, appropriate tests must be done to find the associate lesion and the proper management.

20.2. Acute Suppurative Cholangitis

The term suppurative cholangitis is used to describe the septic type of cholangitis. However, not all patients with this severe type of cholangitis have pus in their bile ducts and not all the patients with pus in their bile ducts have septic manifestations. Therefore, the term "acute suppurative cholangitis" describe the presence of pus into the biliary system and not the patient at the most severe end of this clinical spectrum [5]. The concept of a spectrum of cholangitis is important because the degree of severity as manifested clinically, determines the appropriate therapy, as well as the rapidity with which therapy must be instituted.

In the past, about 80% of cases of acute cholangitis were related to choledocholithiasis. Today, due to the increase in endoscopic and radiological intervention and prolonged survival in patients with malignant disease, most cases with cholangitis are related to malignant biliary obstruction and the interventional procedures. Other common etiologies are listed in table 20.1 [4].

The infective organism is usually one of the gut flora and gram-negative bacilli are commonly encountered. These include Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas, Streptococcus, Proteus and Enterobacter species. Anaerobes

Table 20.1. Possible aetiology of acute cholangitis

Billiary stones
• Choledocholithiasis.
• Hepatolithiasis (recurrent pyogenic cholangitis).
• Mirizzi syndrome.
Benign biliary condition
• Benign stricture.
• Anastomotic stricture.
• Ampullary stenosis.
• Choledochal cyst.
• Periampullary diverticulum.
• Primary sclerosing cholangitis.
Malignant stricture
• Cholangiocarcinoma.
• Carcinoma of pancreas.
• Carcinoma of ampulla.
• Carcinoma of gallbladder.
Indwelling tubes or stents
• Cholangiography.
• T-tube.
• Percutaneous transhepatic.
• Endoscopic retrograde.
Parasitic infestation
• *Opistorchis sinensis.*
• *Ascaris lumbricoides.*

including Bacteroides and Clostridium species can be detected in about 25% of patients. In about 20% of patients, two organisms are isolated but there are rarely more than two [4].

20.2.1. Diagnosis

The diagnosis of acute cholangitis should be considered in all patients who present with any of the triad symptoms of fever, jaundice, or right upper quadrant pain. The presence of known choledocholithiasis, a history of biliary surgery, an indwelling biliary catheter or recent endoscopy should increase clinical suspicion.

The classic presentation of acute cholangitis is Charcot's triad (fever, jaundice and right upper quadrant abdominal pain). The mentioned triad is rarely accompanied by shock and mental confusion (Reynold's pentate), although one or more of these features may be absent. Charcot's triad is present in only 50% to 70% of the patients [4]. The most frequent symptom is fever, which is present in over 90% of the patients. Abdominal pain occurs in about 80% of the patients and clinical jaundice occurs in similar incidence. Jaundice and mild to moderate right upper abdominal tenderness are seen in as many as two-thirds of patients. Other possible presenting symptoms include paralytic ileus and systemic manifestations of sepsis. Differential diagnosis of the principal abdominal conditions that confuse with acute cholangitis are acute cholecystitis, acute pancreatitis, acute hepatitis, liver abscess, acute pyelonephritis and perforated peptic ulcers. Moreover, acute pyelonephritis can mimic the pain and fever of cholangitis, and the intermittent spiking fevers of cholangitis can be mistaken for bacterial endocarditis. Right lower lobe pneumonia can present primarily with abdominal pain and mimic also an episode of acute cholangitis.

20.2.2. Laboratory Findings

Blood tests may present leucocytosis, elevated C-reactive protein and elevation of the serum bilirubin, alkaline phosphatase and transaminases. A minority of patients will present leucopenia, often a manifestation or overwhelming gram-negative sepsis. Serum amylase may be elevated in about one-third of the patients and is marked by raised in about 10% of the patients when concomitant acute pancreatitis is present [4]. During the process of laboratory work-up, blood cultures as well as bile cultures (in case of PTC or ERCP) are sending to microbiology lab to isolate infective organisms.

20.2.3. Radiological Investigations

Ultrasonography (U/S) may show dilated bile ducts, but is insensitive in diagnosing distal common bile duct stones or establishing the exact cause of cholangitis. This technique detects the presence of gallbladder stones but it can only detect about 35% of the choledocholithiasis [4]. Compared with U/S, computed tomography is more effective in demonstrating the cause and the level of biliary obstruction. Direct cholangiography, including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP), is particularly useful in the diagnosis and management of the patient suspected of having biliary obstruction causing acute cholangitis (fig. 20.1). ERCP is achievable in 85-90% of the patients and can detect extra hepatic biliary obstruction if it is present [6]. Direct cholangiography is not a contraindication in acute cholangitis. However, due to the fact that can exacerbate the disease leading to severe sepsis, should always be combined with therapeutic drai-

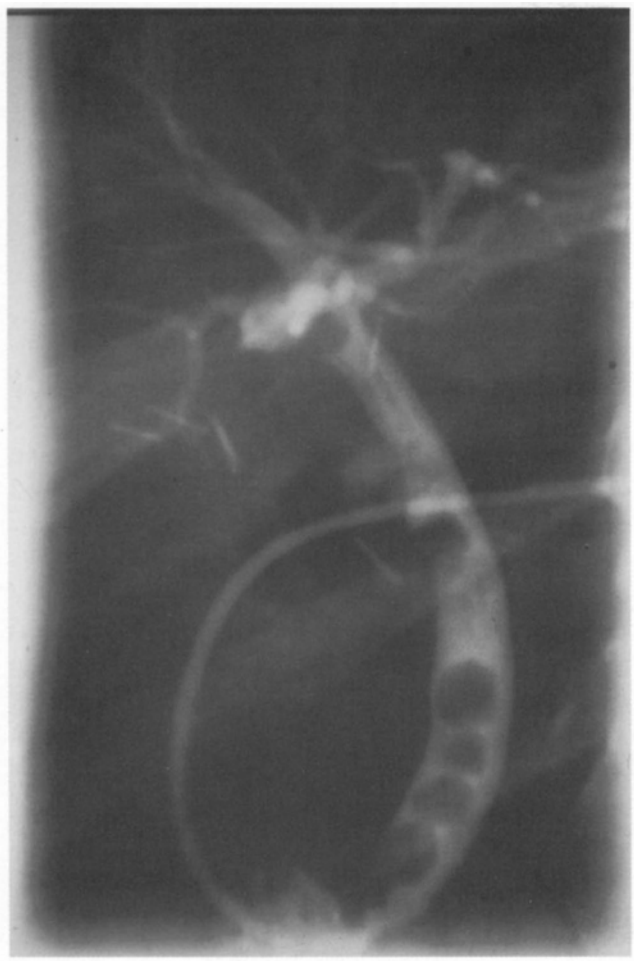


Fig. 20.1. Endoscopic studies in choledocholithiasis and cholangitis (AAP). Retrograde cholangiogram showing common bile duct (CBD) stones.

nage procedure whenever biliary obstruction is demonstrated, and systemic antibiotics should be administered prior to these procedures. Magnetic resonance cholangiopancreatography (MRCP) unlike ERCP, is a noninvasive method and can be a useful tool to complete the diagnostic steps in patients with acute cholangitis if ductal cannulation by ERCP is unsuccessful or incomplete.

20.2.4. Management

Initial management includes supportive care and antibiotics. The majority of patients (70-85%) will respond to these measures within 24-48 hours [4,6]. Patients presented with systemic signs of severe infection may require intensive care unit monitoring and inotropic agents to support blood pressure. Broad-spectrum intravenous antibiotics are required, which should be able to cover especially gram-negative gut-derived organisms. A reasonable choice for initial antibiotic treatment of acute cholangitis is Ticarcillin and Clavulanate or Piperacillin and Tazobactam, and in severe cases Imipenem-Cilastatin. Response to initial management is usually measured by clinical improvement and normalizing liver function tests. In patients who respond to antibiotics and supportive treatment, definitive treatment can be delayed until the patients have recovered from cholangitis. However, approximately 15% of patients will not respond and require immediate ductal decompression [6]. Biliary decompression may be performed endoscopically (ERCP), or via percutaneous transhepatic route (PTC) depending on the level and nature of the biliary obstruction. Before the advent of interventional radiology in therapeutic endoscopy, surgical decompression was the only treatment for these patients. Surgical interventions in cases of choledocholithiasis include stone extraction, T- tube insertion, or bilioenteric bypass. Open surgery however has been associated with high morbidity and mortality.

Endoscopic biliary drainage and stone extraction has become the optimal mode of treatment for many patients with various conditions including acute cholangitis (fig. 20.1). This method may include also endoscopic sphincterotomy and/or simply placement of an endoscopic biliary stent in the heamodynamically unstable patient. In experienced hands successful endoscopic common bile duct stone clearance can be achieved in more than 90% of patients. Biliary drainage via PTC for patients with acute cholangitis could achieve a successful rate close to 100% with a complication rate less than 10% and mortality around 5% [4]. The major advantage compared to endoscopy or surgery is that there is no need for anesthesia or systemic sedation, which can result in hemodynamic instability and respiratory complications. The disadvantage includes the need to puncture the liver, which may result in serious complications (in patients with severe sepsis, clotting derangement and thrombocytopenia) such as bile peritonitis, hemoperitoneum and hemobilia.

As mentioned, the selection of which procedure to perform should be based on the level and nature of the biliary obstruction. Choledocholithiasis and cholangitis associated with periampullary malignancies are best

approached endoscopically. In patients with a proximal perihilar obstruction or a biliary-enteric anastomotic structure, percutaneous drainage may be the preferred route of decompression. If cholangitis is secondary to a tumor, the initial step is endoscopic/transhepatic decompression. After resolution of inflammatory signs, the tumor is evaluated for resectability and further treatment is planned electively. In cases in which either endoscopic or percutaneous biliary drainage is not possible, common bile duct exploration and a T-tube placement remains a life saving procedure. Unfortunately, the mortality in these critically ill patients is considerable higher (up to 40%) than for patients successfully managed endoscopically [4].

20.2.5. In Conclusion

Acute suppurative cholangitis is a serious infective condition of the biliary tract that requires emergency treatment. Therapeutic endoscopy and interventional radiology has significantly improved the morbidity and mortality in these patients. Endoscopic treatment plays a major role in both the acute phase and the definitive treatment in case of choledocholithiasis. However, if endoscopic intervention is unsuccessful, surgical or radiological intervention must be performed before further deterioration. The definitive treatment depends on surgical risks of the patients and the availability of endoscopic and surgical expertise at different centers.

20.3. Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis (RPC) is a clinical syndrome characterized by repeated infections of the biliary tract by pus forming bacteria. The term RPC was used by Cook in 1954 and the synonymous associated with this condition includes Asiatic cholangiohepatitis, Oriental cholangiopetatitis, Hong Kong Disease, Chinese biliary obstruction syndrome and Primary cholangitis [7, 8]. Although the disease is prevalent in Southeast Asia, easy of travel and migration have meant that this condition is now encountered in Western countries more often.

Unlike gallstone disease seen in Western countries which affects group of patients in their 40s and 50s, RPC typically afflicts a younger group of patients with a peak age of 20 to 40 years old, is equally common in males and females and there is a strong association with malnutrition. However, shifts of the peak age incidence to an older age group have been noted in recent years. These elderly patients were those afflicted by the disease when young, survived the attacks of acute cholangitis, had one or more biliary operations and presented again with recurrent acute cholangitis, biliary cirrhosis, or liver failure.

20.3.1. Pathogenesis

The disease is characterized by recurrent primary bacterial infection of the biliary tree, resulting in extrahepatic and intrahepatic duct stricture, bile stasis, and subsequent stone formation and may be associated with parasites. The infection of the biliary tree with bacteria that possess beta-glucuranidase activity is likely the critical event in those patients. In the presence of b-glucuranidase, bilirubin glucuronide is hydrolyzed into free bilirubin and gluconic acid. This free bilirubin can then form insoluble calcium bilirubinate pigment stones after combination with calcium. Infection of normal bile with bacteria with intense glucuranidase activity, such as E. coli, gives rise to the multiple stones formation and recurrent episodes of cholangitis classically seen in RPC [9]. Along with Klebsiella species, these are the two most common organisms isolated from the bile in these patients [7]. The overall positive bile culture rate has been reported to be as high as 87%. In addition, in the acute stage of the disease, 39,5% of the patients have a positive portal blood culture, while the positive supraduodenal lymph node culture rate is 38,1% [10]. However, in a non-obstructed biliary system, bacteria excreted into the bile will not usually give rise to infection and episodes of cholangitis. Thus, an obstruction produced by parasites (Clonorchis Sinensis now known as Opistorchis sinensis, or Ascaris lumbricoides) can initiate the sequence of events, leading to the formation of intrahepatic pigment stones [11]. Biochemical analysis of these stones revealed a bilirubin content of 40.2-57% and a cholesterol content of 2.9-25.6%. This differs greatly from cholesterol stones which are common in western countries, which contain >90% in cholesterol and only 0.02-5% bilirubin [9]. There are two types of pigmented stones, black and brown which are seen in RPC. Stones are found in 90% of patients and the most common site of occurrence is the common hepatic duct or bile ducts (50%). In 25% of all

patients with RPC, stones are found only in the intrahepatic ducts, with 4 to 1 preponderance of left to right, and only 15% of the patients have stones in the gallbladder [10].

The hypothesis of biliary infection as the cause of RPC, indicates that the initiating process is the establishment of enteric flora via the portal venous system from bowel origin into the intrahepatic biliary tree. The reasons for the breakdown of normal host defense mechanisms may be that (1) the organisms are particularly virulent, (2) the bowel wall is injured (eg by enteric infection), thus allowing a larger than normal load of organisms to enter the blood-system, (3) the metabolic activities of the hepatocytes have been altered (eg by malnutrition) to produce bile that lacks or is reduced in bactericidal properties, or that is increased in lithogenicity and (4) the biliary tree is damaged-obstructed by the presence of parasites to increase its susceptibility to infection. The most likely cause, is the establishment of bowel organisms in the liver and biliary tract of a compromised host, because there are little data to support the first possibility and RPC is also found in countries where parasitic infestation is not endemic. However, this does not explain one of the main pathologic features of RPC, ie the significant preponderance of the left liver lobe. One possible explanation may be the selective distribution of portal blood within the liver. Another explanation is that the more oblique course of the left hepatic duct results in poorer drainage of the left ductal system as compared to the right hepatic duct, thus leading to increased incidence of stone formation [8, 12].

The pathological hallmark of RPC is the steadily progressive, recurrent cholagiohepatitis with periportal fibrosis. In the acute stage, neutrophils infiltrate the portal triad and also are found in the small bile ducts. The infection process leads to destruction of these small ducts and adjacent liver parenchyma, leading to microabscesses formation. These microabscesses may continue to enlarge and coalesce into multiple pyogenic abscesses. Resolution results in intense fibrosis and larger ducts can become irregular and short segments of relative stricture can occur along the duct. These structures are most frequently encountered at the site of duct confluence. Recurrent attacks of infection led to permanent damage of the duct wall and the ducts remain dilated. This chronic inflammatory cell infiltration of the portal tract, in severe and persistent cases, results in bridging fibrous band developing between portal tracts and replacement of the liver by fibrous tissue. The affected lobe of the liver, usually the left, is normally atrophic with compensatory hypertrophy of the remaining lobe. The affected lobe can be so destroyed and transformed in a cavernous biliary sac filled with biliary mud, stones, parasites and pus. These repeated inflammatory damage to the ductal epithelium from the attacks of cholangitis can lead to atypical epithelial hyperplasia, dysplasia and eventually to cholangiocarcinoma [13].

20.3.2. Clinical Presentation

Patients with RPC are typically young thin and are almost invariably of a lower socio-economic status. Most have had previous episodes of cholangitis, which are usually increase in frequency and severity with the passage of time. The chief complaints are abdominal pain, fever and jaundice (Charcot's triad). Often the fever is associated with chills and is preceded by rigors. Jaundice is mild, since biliary obstruction is usually incomplete and a history of tea-colored urine is usual. Nausea is present with pain, but vomiting is rare. Physical examination may reveal signs of scars of previous surgery. There is tenderness with a degree of guarding in the right upper quadrant or the epigastrium. If the latter is marked, a left lobe abscess must be suspected. The liver is enlarged in 60% of patients, but this finding may be masked by abdominal guarding due to an underlying abscess. Acute pancreatitis is associated with RPC in 10% of patients. Signs of generalized peritonitis are present in 5% of patients and may be caused by rupture of a diseased gallbladder or liver abscess or because of severe acute pancreatitis [12]. These complications are associated with septic clinical condition, and/or the development of worsening hemodynamic parameters which becomes rapidly fatal, unless surgical intervention is immediately undertaken to decompress the biliary system.

20.3.3. Laboratory Findings

Routine laboratory tests do not differentiate patients with RPC from those with other causes of biliary obstruction and infection. Thus, there is a leucocytosis, elevation of liver function tests, mild thrombocytopenia,

while a number of patients have a concomitant mild derangement of clotting profile with a prolonged prothrombin time. When serum amylase is elevated, a stone impacted at the lower end of the common bile duct must be suspected. Stool examination for parasites,as well as blood cultures should be performed.

Additionally investigations are necessary in these patients to define the exact location of all stones and structures as well as ductal anatomy before the definitive treatment. Ultrasonography can recognize intrahepatic stones, and may show features of biliary obstruction, pneumobilia, liver abscess or pancreatitis. However, some stones in RPC may form casts within the intrahepatic ducts, leading to the stones being missed by ultrasonography [8]. Computed tomography (CT) can provide images of the dilated intra and extrahepatic ducts, even if they are filled with sludge or pus, with the advantage of less interference by bowel gas, surgical scars and observer bias. In addition, computed tomography can differentiate intrahepatic stones from pneumobilia, provides accurate topographic localization for drainage of liver abscess and detects segmental ductal involvement in cases of complete obstruction of the bile ducts, which is necessary before liver resection as therapeutic procedure is undertaken. Scans with and without contrast is mandatory, as stones are easier to detect on no contrast scans, whereas subtle intrahepatic biliary dilatation is more easily delineated on a contrast scan. Direct cholangiography, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) are the most accurate way to define biliary ductal anatomy by depicting strictures, calculi, and ductal ectasia. ERCP is the preferable method since it is both diagnostic and therapeutic (drainage of the biliary system). When a stone or stricture prevents the filling of the intrahepatic ducts or when it is technically impossible to perform an ERCP due to previous biliary-enteric by pass surgery, PTC under ultrasonography guidance is performed. Magnetic resonance cholangiography (MRCP) has been shown to be better than ERCP/PTC for accurate topographic evaluation of RPC, because it is able to depict all the biliary tree, despite obstruction or stenosis [8]. In addition, it is a non-invasive investigation and is comparable to ERCP in diagnosing choledocholithiasis.

Radiographic features of conditions that have to differentiate from RPC are sclerosing cholangitis (biliary duct strictures are more peripherally, lack of stones), choledochal cysts and Caroli disease.

20.3.4. Management

About 70% of the patients with repeated attacks of acute cholangitis improve on conservative therapy [12]. Urgent therapeutic interventional procedures needs to be applied in cases such as those with peritonitis secondary to perforated gangrenous gallbladder, complicated liver abscess or those with septic profile despite the conservative treatment. Definitive surgical procedure is considered when patients recover after conservative treatment and depends on the frequency and severity of attacks of acute cholangitis, presence of biliary strictures, the indication for liver resection, dysplastic changes of biliary strictures (cholangiocarcinoma) and the presence of comorbid medical conditions.

The initial management is to control the underlying infection and involves intravenous fluid replacement, analgesics, administration of antibiotics after blood culture, and nasogastric aspiration. Patients who fail to respond, with severe attack of cholangitis, undergo ERCP for decompression of the biliary system. If this is not feasible due to obstructing duct stone or stricture, a percutaneous transhepatic biliary drainage of the obstructed biliary ducts can follow. If a large liver abscess is present, this can be drained percutaneously under ultrasound or CT guidance. Small multiple abscesses usually respond to antibiotic treatment and biliary decompression. No attempt is made, to perform a full cholangiogram or to remove all calculi from the biliary system during the severe attack of cholangitis. An excessive contrast injection during these interventions may result in cholangiovenous reflux which can lead to septicemia.

If there is no improvement after non-operative interventional procedures, due to undrained biliary system or individual liver segment, urgent surgery must be considered. Urgent surgery can be undertaken also when the patient is presented with peritonitis as a result of gangrenous cholecystitis or ruptured liver abscess. The principles of emergency surgery are decompression of the obstructed biliary system by a limited exploration of the bile duct and insertion of a T-tube. Stones that can be extracted easily are removed. Following gently irrigation with saline of the common bile

duct (CBD), the biliary system is explored. Any tight strictures in the left or right hepatic duct should be dilated gradually, until there is free flow of infected bile. A stone impacted at the lower and of the common bile duct, can be removed by transduodenal sphincteroplasty in the presence of acute pancreatitis or by electrohydraulic lithotripsy under choledoscopic guidance. A large T-tube is inserted into the common duct at the end of exploration which affords a percutaneous route for endoscopically intervention when the patient has recovered. Large palpable liver abscesses are drained intra-operatively. A cholecystectomy is performed only when it is grossly distended or there is evidence of cystic duct obstruction, empyema or gangrene of the gallbladder. Emergency operations are usually inadequate in terms of stone clearance and the type and the duration of the operation are limited by the stability of the patient. In addition, surgeons are frequently unable to perform optimal procedures because of insufficient knowledge of the location of stones and strictures.

Definitive management depends on the extent of the intrahepatic disease and the degree of hepatic fibrosis. Principles of elective definitive surgery comprise the removal of intrahepatic and extrahepatic stones, the establishment of satisfactory drainage of the affected segment of the biliary tree and whether liver resection has to be performed.

However, once the patient has recovered from an acute attack of cholangitis, more definitive treatment via the endoscope or under radiological guidance can be performed. For those patients with stones in the CBD, endoscopic sphincterotomy with stone extraction is effective and comparable to surgical sphincteroplasty. Intrahepatic strictures can be also be dilated endoscopically to allow complete removal of the intrahepatic stones and long segmental strictures which are likely to restenose can be stented successfully. In patients where the endoscopic approach has failed, percutaneous route (PTC) can be combined with endoscopy to achieve stone clearance or stricture dilatation. Intrahepatic strictures can also be dilated or stented through a percutaneous transhepatic biliary drainage catheter under fluoroscopic screening or choledoscopy. In patients who underwent acute surgical intervention and T-tube insertion into the common duct, interventional approach through the T-tube tract into the biliary system can be also achieved. The main complications of dilatation therapy include septicemia, haemobilia and stricture recurrence.

When definitive surgical intervention is required, it is mandatory to have complete preoperative investigations of the biliary tract and a complete knowledge of the location of stones, strictures and the extend of the intrahepatic disease. Cholecystectomy is always performed, since histologically it shows inflammation, although rarely contains stones. In the presence of predominantly extrahepatic disease a choledochotomy is performed. The common bile duct and the main and segmental intrahepatic ducts are examined carefully with intraoperative choledochoscopy and stones can be removed with stone forceps and irrigation. The placement of a large T-tube following the exploration will allow post-operative interventional procedures and residual stones can be easily removed. In the presence of intrahepatic stones which are difficult to extract due to ductal strictures, a direct hepatotomy can be performed to remove the stones. Stones in segmental bile ducts that cannot be retrieved easily may require electrohydraulic lithotripsy through the working channel of the flexible choledochoscope. It is not always possible to clear the intrahepatic duct stones completely. Small stones or fragments can be drained, provided that an adequate biliary drainage is constructed. In the presence of a proximal biliary tract stricture (common bile duct) or when the common duct is extremely dilated and fibrotic, a hepaticojejunostomy type anastomosis can be performed. This provides a widely patent anastomosis for biliary drainage and for small stones to fall freely into the loop of bowel. In addition, the closed end of the Roux loop tacked to the peritoneal surface of the abdominal wall can provide a permanent access route to the biliary tract. The location of the hepaticojejunal anastomosis depends on the site of the stricture of the common duct and the ease of exposure of the bile duct. It can be constructed at the common bile duct, common hepatic duct, left hepatic duct or the left lateral segmental duct.

Hepatic resection is only performed for those with recurrent and localized severe disease. Usually the disease is located to the left lateral segment which can be atrophic with cavernous transformation of the bile ducts, or with an abscess. Hepatectomy is performed also to remove the underlying stricture which has the potential to turn malignant. Liver resection of the right

lobe disease is unusual. The overall operative mortality in hepatic resection is ≤2%, but the morbidity (infection, subfrenic collections) from operating on an underlying septic condition is ≈30% [8]. Despite multiple operations, RPC patients can develop secondary biliary cirrhosis and liver failure and the only available treatment in these patients is liver transplantation.

20.3.5. In Conclusion

RPC is a clinical syndrome characterized by repeated infections of the biliary system by pus-forming bacteria. Medical treatment is ineffective and surgical treatment is not satisfactory. The long-term goal of therapy is to extract stones and debris and relieve strictures. It may take several interventional procedures and may require a Roux-en-Y hepaticojejunostomy for biliary drainage. Hepatic resection should be performed whenever indicated. Recurrences are common and the prognosis is poor once biliary cirrhosis and liver failure has developed and the only treatment in these patients is liver transplantation.

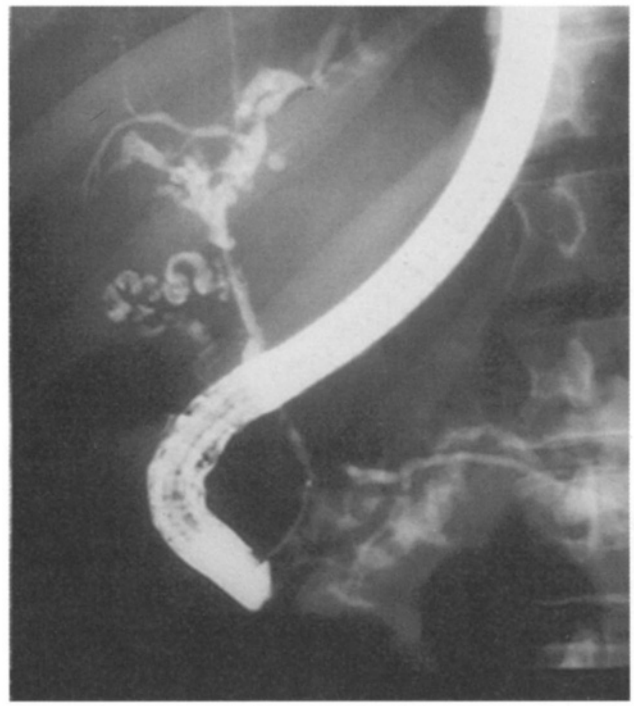


Fig. 20.2. Cholangiogram demonstrating diffuse involvement of intrahepatic and extrahepatic bile duct in a patient with primary sclerosing cholangitis (AAP).

20.4. Primary and Secondary Sclerosing Cholangitis

Sclerosing cholangitis is a rare inflammatory biliary tract disease characterized by fibrotic strictures involving the intrahepatic and extrahepatic biliary tree. It is a progressive disease that eventually results in secondary biliary cirrhosis. The term "sclerosing cholangitis" was first used in 1954 by Castleman and later by Schwartz and Dale in their 1958 review article, although the syndrome was first reported by Hofman in German literature in 1867 [14]. The disease was considered a rare disorder before the advance of the interventional procedures. The introduction of endoscopic retrograde cholangiography and percutaneous transhepatic cholangiography has led to an increase in the identification of patients with the characteristic cholangiographic findings of sclerosing cholangitis (fig. 20.2). The diagnosis of "Primary sclerosing cholangitis" (PSC) requires the presence of multifocal strictures and beading of the intrahepatic and/or extrahepatic biliary tract in the absence of other precipitating causes. Even with associated calculi, the disease may be primary with secondary formation of calculi. In cases where disease is caused by biliary stones, acute cholangitis, previous biliary surgery or toxic agents, the term "Secondary sclerosing cholangitis" is used.

Primary sclerosing cholangitis progresses slowly in most patients with over a 10 to 15 year period and usually leads to cirrhosis, portal hypertension and liver failure. The mean age of presentation is of 40 years old and men are affected twice as commonly as women. Many consider PSC to be an autoimmune reaction because it is associated with other autoimmune diseases, such as ulcerative colitis, retroperitoneal or mediastinal fibrosis, and Riedel's thyroditis. More than one half of patients are symptomatic when diagnosed and approximately 75% of patients with PSC have inflammatory bowel disease [14]. PSC may precede or follow the bowel disease and progression of one is unrelated to the other.

20.4.1. Pathogenesis

The cause of PSC remains unknown, despite that a variety of factors have been incriminated in the disease process. These include bacteria and viruses, chemicals

and drugs, ischemic damage and genetics abnormalities of immunoregulation, all of which can produce injury to the biliary tract resulting in diffuse strictures similar to primary sclerosing cholangitis. However, no specific data exist to distinguish PSC from sclerosing cholangitis secondary to these causes. Recent studies have focused genetic and immune factors as the most likely etiologic agent in these patients, although the disorder is not inherited in any distinct pattern. There are familial occurrences of PSC as well as an association between PSC and HLA-B8, DR3, DR2 and DR4 [14]. Patients with PSC have signs of abnormal immunoregulation, including infiltration and destruction of bile ducts by lymphocytes, hypergammaglobulinemia, perinuclear autineutrophil cytoplasmic antibodies and anticolon epithelial antiantibodies. PSC along with other disorders of immunoregulation, including inflammatory bowel disease, thyroiditis and type 1 diabetes, is commonly associated with HLA haplotype B8/DR3 [15, 16]. Patients with PSC have several abnormalities in cellular immunity including low values of circulating suppressor T-cells, whereas the number of suppressor T and helper T-cells are increased in the portal tracts [14].

20.4.2. Diagnosis

Before the diagnosis of PSC is established, other diseases that cause secondary sclerosing cholangitis need to be excluded. These include chronic bacterial cholangitis secondary to bile duct strictures or choledocholithiasis, previous biliary surgery, posttraumatic choledochal cysts, cholangiocarcinoma, infections, cholangiopathy associated with AIDS (Cytomegalovirus infection or Cryptosporidiosis) (fig. 20.3 & 20.4), toxic and ischemic insults [17]. These lesions can generally be excluded by the past medical history and reviewing the cholangiographic findings and bile duct cytology and biopsies.

The diagnosis of PSC is suggested by clinical presentation associated with cholestatic liver function test abnormalities. In patients with clinical apparent disease there is no specific or pathognomonic symptom or signs. The usual presentation includes cholestatic jaundice, pruritus, fatigue and right upper quadrant pain. Fever and marked abdominal pain are uncommon, especially without preceding biliary tract manipulation. In several patients with ulcerative colitis, abnormal liver function tests found on routine testing lead to the diagnosis. The clinical course is characterized by relapses and remissions, but in most cases the disorder is progressive. Jaundice, hepatomegaly and splenomegaly are the most common clinical signs of advanced disease. A small percentage of patients will present with signs and symptoms of liver failure, including portal hypertension, bleeding oesophagogastric varices and ascites.

20.4.3. Laboratory Findings

Elevations of serum alkaline phosphatase and bilirubin are the most common laboratory findings. The levels of bilirubin often fluctuate with respect to the remissions and exacerbations of the disease and the extend of hepatic injury. Serum albumin and prothrombin time are often normal until late in the course of the disease. Autoantibodies are present in less than 10% of patients and a small number of patients with PSC have positive results for antimitochondrial antibodies.

The clinical presentation and elevation of alkaline phosphatase and bilirubin may suggest the diagnosis, but this is usually confirmed by cholangiography (fig. 20.5). ERCP is the preferred procedure because of difficulties in cannulation of the intrahepatic ducts by the percutaneous transhepatic route, as they are usually nondilated and fibrotic. In addition, ERCP offers the advantage of visualizing the pancreatic duct. Magnetic resonance cholangiopancreatography (MRCP) in increasingly being used as a noninvasive method of diagnosis. Differences in the techniques were observed, in that more bile duct stenosis and pruning were seen with ERCP and more skip dilatation with MRCP ($p<0,0001$) [18]. Overall, the results suggest that MRCP can become the diagnostic method of choice in PSC and that ERCP can be reserved for the group of patients with a diagnostic doubt after MRCP. Typical cholangiographic findings are multifocal strictures involving both the intra- and extra-hepatic biliary tree, although only one of these systems may be involved. Despite the presence of diffuse disease in the majority of patients, the hepatic duct bifurcation is the most severely affected segment. Involvement of the extrahepatic ducts alone, without intrahepatic involvement occurs in 5%-10% of patients with PSC, and strictures limited to the intrahepatic ducts occur in less <5%. Intervening segments of normal or slightly dilated bile ducts between the strictures produce the classic beaded appearance. Mar-

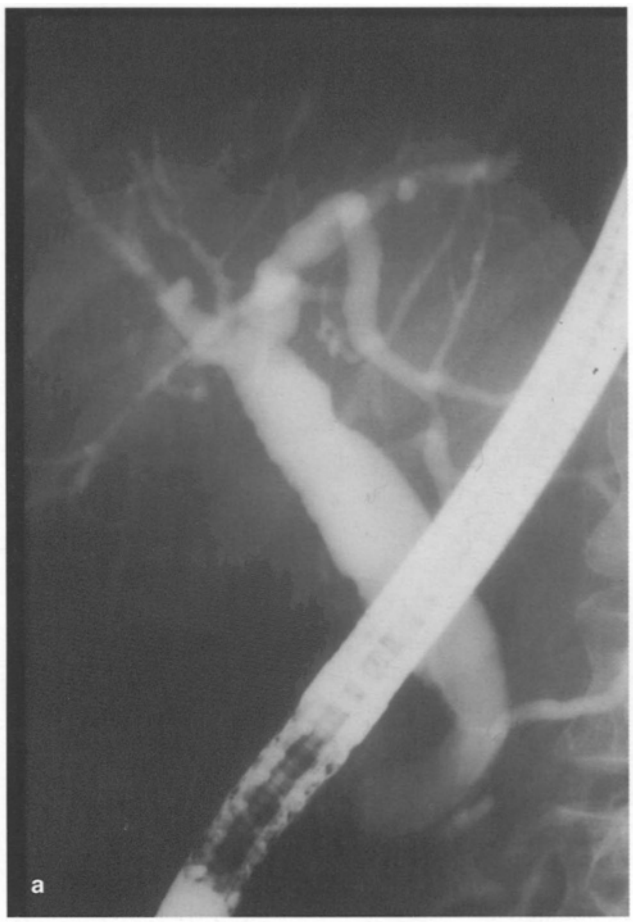
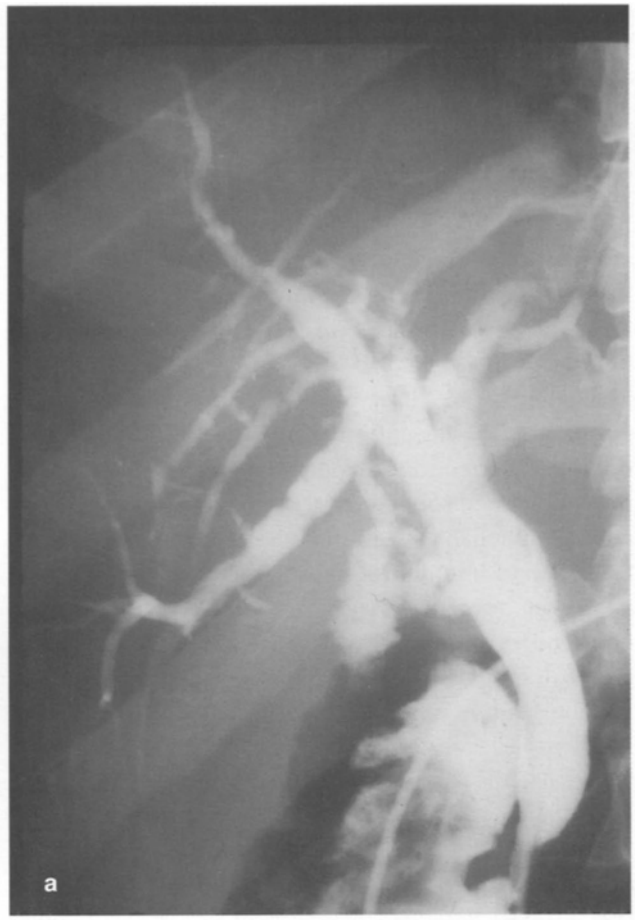


Fig. 20.3.
a. Endoscopic cholangiogram in a patient with AIDS and sclerosing cholangitis (AAP).
b. Colon biopsy showing cytomegalovirus enteritis in the same patient (H & E, x100).



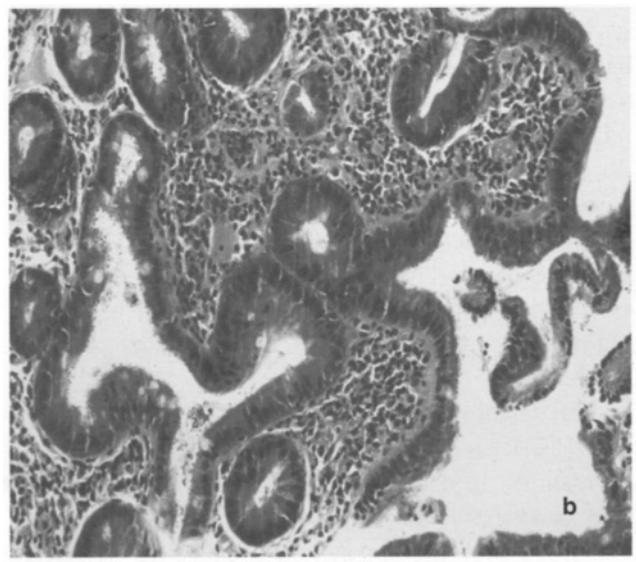


Fig. 20.4.
a. Endoscopic cholangiogram in a patient with AIDS and sclerosing cholangitis (AAP).
b. Intestinal biopsy showing infection with cryptosporidium (H & E, x100).

kedly dilated bile ducts, polypoid masses within the bile ducts or progressive stricture formation on serial cholangiograms are suggestive of a complicating bile duct carcinoma. Pancreatic duct abnormalities have been reported in 8% to 50% of patients with PSC although they seldom have symptoms of pancreatitis [19, 20].

20.4.4. Pathology

A liver biopsy may not be diagnostic, but is important to determine the degree of hepatic fibrosis and the present of cirrhosis for staging the liver disease to determine the prognosis. The most consistent abnormality is the absence of interlobular bile ducts in the portal tracts. An infiltrate of plasma cells, neutrophils and eosinophils in these tracts is characteristic. PSC is staged histologically according to the staging system based on the extent of inflammation and fibrosis on liver biopsy, proposed by J.Lwdwing [21]. In stage 1, inflammation and fibrosis are confined to the portal tracts. Stage 2 is characterized by periportal fibrosis with or without periportal hepatitis. Stage 3 is characterized by portal- to portal bridging with the formation of fibrous septae. Bile ducts are severely damaged or absent and cholestatic changes are prominent in periportal and periseptal hepatocytes. Cooper-protein complexes are present within lipolysosomes adjacent to the nucleus in damaged hepatocytes. In stage 4, biliary cirrhosis develops and the histologic changes are difficult to distinguish from primary biliary cirrhosis. Microscopic examination of the extrahepatic bile ducts shows a diffuse inflammatory infiltrate composed predominantly of lymphocytes and plasma cells with epithelial ulceration. Neutrophils are seen within lumens of gland like structures. The extensive fibrosis of the wall with entrapment of gland like structures may simulate adenocarcinoma.

Occasionally, inflammatory changes involving interlobular bile ducts are present in biopsies obtained from patients with cholestatic liver function tests but a normal cholangiogram. These patients are considered to have "small-duct PSC" (former by called "pericholangitis") and have a significantly better survival compared with patients with large-duct PSC, the majority of whom progress to chronic liver disease. Although the clinical symptoms and signs and the age of presentation of small-duct and large-duct PSC are similar, the clinical course is much more benign in the small-duct group, the majority of patients do not progress to large-duct disease and no patients develop cholangiocarcinoma [22]. Therefore, the small-duct PSC is a new clinical entity and in the majority of cases does not represent an early form of classical PSC.

20.4.5. Associated Diseases

Numerous diseases have been associated with sclerosing cholangitis. A strong association exists between inflammatory bowel disease, primary ulcerative colitis, and sclerosing cholangitis. The incidence of ulcerative colitis in patients with sclerosing cholangitis is 75% [14]. Conversely, the prevalence of sclerosing cholangitis in patients with ulcerative colitis ranges from 2.5% to 7.5% [23, 24]. The activity of either disease does not affect the activity of the other and both diseases can be presented concurrently, although symptoms of ulcerative colitis usually predate the development of sclerosing cholangitis. In the presence of PSC, ulcerative colitis almost always involves the entire colon, whereas left-sided colitis is more common in patients without PSC.

The development of cholangiocarcinoma will complicate the clinical course of 10-20% of patients with PSC. Between 10% and 30% of patients undergoing liver transplant have incidental cholangiocarcinoma in the hepatectomy specimen [25]. Cholangiocarinoma can present any time during the disease process and not correlate with the extent of sclerosing cholangitis or the development of liver failure, but frequently follows on aggressive course of the disease. The bile duct cancer is most often extrahepatic and commonly occur near the hepatic duct bifurcation [26]. This site is also a common position for dominant benign strictures in PSC, making the diagnosis of bile duct cancer a great challenge. When the diagnosic modalities of brush cytology, DNA analysis, serum Ca 19-9 and serum CEA were all combined, a diagnostic sensitivity of 88% and specificity of 80% were reached [27]. Evaluation with endoscopic ultrasound and endosonography-guided fine needle aspiration of undiagnosed hilar strictures suspicious for cholangiocarcinoma when it is technically feasible has an accuracy, sensitivity and specificity of 91%, 90% and 100% respectively [28].

The incidence of gall bladder cancer is also increased in patients with PSC, and screening is advocated by some groups with early cholecystectomy for gallbladder polyps. They also support the evolving con-

cept of biliary dysplasia as the initial step in the development of carcinoma in the biliary tree and gallbladder in PSC [29].

20.4.6. Management

No known specific medical therapy is effective for PSC. A variety of immunosuppressive, anti-inflammatory and antibiotic agents have been used to treat PSC. The most encouraging results suggest that ursodeoxycholic acid significantly improves serum liver function tests and liver histologic appearance, but unfortunately with no significant difference in clinical outcome [30].

Nonoperative interventions, as ERCP with balloon dilatation and temporary stenting where technical possible, is preferred to percutaneous transhepatic cholangiographic intervention in the management of symptomatic dominant extrahepatic strictures. These measures have given short-term improvements in symptoms and serum bilirubin levels and long term improvement in only less than one half of the patients [14, 31]. Surgical management with resection of the hepatic duct bifurcation and hepatico-jejunostomy, can improve jaundice in select group of patients without cirrhosis or significant intahepatic biliary disease. This operation in selected patients can preclude or delay the need for hepatic transplantation and moreover does not eliminate or influence the results of hepatic transplantation. In addition, this form of surgical therapy has greater and longer biochemical improvement, better survival until death or liver transplantation, and a lower incidence of cholangiocarcinoma than in patients treated medically or with endoscopic dilation.

The role of biliary surgery in PSC, however, has decreased considerably with the excellent results of liver transplantation in patients with advanced liver disease and end-stage PSC. The timing of transplantation in patients with PSC should be considered before the disease is too advanced. Primary indications for referral for liver transplantation include bleeding due to esophageal varices or portal gastropathy, intractable ascites (with or without spontaneous bacterial peritonitis), intractable pruritus, severe muscle wasting or persistent elevations in serum bilirubin. The presence of known malignancy or preoperative recognition of cholangiocarcinoma results in patients being refused transplantation due to poor results postransplant. However, an incidental finding of cholangiocarcinoma in the explanted liver specimen does not usually portend a poor prognosis. Biliary strictures in the transplanted liver are a post-transplant problem in patients with PSC, along with histologic features on post-transplantation liver biopsy consistent with recurrence of the disease. Possible causes of the strictures are the recurrence of PSC, bile duct ischemia, chronic rejection, cholangitis and chronic immunosuppression. PSC recurs in 10% to 20% of patients and may require retransplantation [32, 33].

20.4.7. In Conclusion

PSC is a chronic progressive disease and is characterized by diffuse bile duct strictures, chronic cholestasis and frequent association with ulcerative colitis. The diagnosis is confirmed on cholangiography. The disease is slowly progressive over a 10-15 year period and is complicated by cirrhosis and portal hypertension. The disease has an increased incidence of bile duct cancer. There is no medical therapy that is effective in the treatment of PSC. Endoscopic dilation and stenting or surgical drainage procedure is the optimal treatment of symptomatic dominant biliary stricture. In patients with PSC and advanced liver disease, liver transplantation is the only option of treatment.

20.5. Fibrosis of Papilla-Papillitis

Papillitis is an acute inflammatory disorder involving the mucosa overlying the major duodenal papilla, whose circular fibers regulate the flow of bile and pancreatic ducts into the duodenum [34]. Spasm or inflammatory changes of this papillary musculature may have a variety of clinical manifestations. The biliary or pancreatic system or both, will be involved to the degree of outflow obstruction of their respective ductal systems within the papillary complex [35]. Stenosis of the distal portion of the common bile duct by fibrosis was first described by Florcken in 1912. Fourteen years later, Del Valle and Donovan described patients with partial or complete choledochal obstruction and termed the process "sclerosing choledocho-odditis". Hess found that papillitis may affect the biliary and pancreatic ductal systems independently or in combination, although isolated involvement of the pancreatic duct was rare in his experience [35].

Chronic recurrent inflammation may induce an inflammatory infiltrate to extensive and severe fibrosis

leading to papillary stenosis. This situation usually develops in association with cholelithiasis from repeated passage of small stones or sludge, iatrogenic injuries during common bile duct exploration or infection [36, 17]. Such cases are referred to as secondary papillitis, considering that the basic process affecting the biliary tract also involves the choledochoduodeodenal junction. Even though most cases result from stones or traumatic choledochal instrumentation, cases of idiopathic papillary stenosis have been reported and are called primary papillary stenosis or primary papillitis, which is an inflammatory stenosis of the papilla without biliary tract disease [37].

20.5.1. Diagnosis

Most patients with papillary stenosis are middle-aged women and many have had cholecystectomies. The most frequent presenting complaint is biliary colic. Other symptoms may be those of obstructive jaundice, cholangitis, and pancreatitis. Jaundice or cholangitis rarely occurs as a primary presentation. Papillary stenosis in combination with stasis also may lead to formation of common duct stones. Pancreatitis is usually mild and recurrent without accompanying signs of pancreatic inflammation or hyperamylasemia and is considered part of this syndrome [36].

20.5.2. Laboratory Findings

Pathologic changes of the papilla may vary from an inflammatory infiltrate to extensive and severe fibrosis, and no true correlation exists between histology and symptomatology. Acute inflammatory changes and distortions of glandular architecture may be found in normal persons older than 50 years of age [38]. Papillary stenosis can be a result of organic stenosis or functional obstruction (i.e. biliary dyskinesia – other motility disorders) and differentiation is frequently difficult. A dilated common bile duct that is difficult to cannulate with delay emptying of the contrast are useful diagnostic features. Certain cholangiographic findings suggest papillary stenosis, (1) narrowed distal (intraduodenal) common bile duct (CBD) segment, (2) dilated CBD or pancreatic duct and (3) delayed contrast drainage from the biliary (>45min) or pancreatic duct (>10min) [36]. Ampullary manometry (the most useful diagnostic tool) and special provocation tests are available in specialized units.

20.5.3. Management

If the diagnosis is well established, endoscopic sphincterotomy is the treatment of choice, with success rate of more than 95%. The incident of recurrent stenosis after endoscopic sphincterotomy is 11,5% [39]. In patients with recurrent pancreatitis, balloon dilatation of the pancreatic sphincter is recommended.

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CHAPTER 21

CANCER OF THE EXTRAHEPATIC BILIARY TRACT

CALLBLADDER CARCINOMA

G. Karatzas, E. Misiakos

21a.1. Incidence

Gallbladder carcinoma (GBC) is a rather rare malignancy associated with a rapidly lethal course independent of any kind of treatment. The high mortality rate associated with the disease is due to the early silent growth of the tumor with a late presentation, an early occurrence of lymph node spread, and an anatomic relation to the porta hepatis [1]. It is considered as the most common biliary tract malignancy and the fifth most common gastrointestinal cancer, pancreatic cancer occurring about five times as frequently [2]. In general, the incidence of GBC seems to be increasing in the Western World. A recent study from France reported an annual incidence of 0.6 cases per 100,000 men and 1.7 cases per 100,000 women [3]. In the US it accounts for approximately 7,100 new cases and 3,500 deaths per annum [4].

GBC predominantly occurs in elderly females, the incidence increasing with age: the majority of patients are over 50 years of age and the peak incidence is 70-75 years [5]. There is evidence that in some countries mortality from the disease is decreasing in parallel with the increasing use of cholecystectomy. This was the case in US, Canada and G. Britain in the decade 1977-1987, when a decline in mortality from this cancer was noted [6].

GBC has large geographic and ethnic variations, with areas of high prevalence scattered throughout the globe 7, 8]. Bolivia and Chili have the highest incidence rates in the world (15 and 13 per 100,000 population, respectively) [9]. Intermediate incidence rates (3.7-9.1 per 100,000 population) were reported form North-Eastern Europe (Poland, Czech Republic), India, and Israel [10, 11, 12]. Relatively low incidence rates (<3 per 100,000 population) were reported in the UK, Spain, and New Zealand [7, 11]. In the US, the overall incidence of GBC is quite low, at 1.2 per 100,000 [13, 14]. However, certain subpopulations in the US have high incidence rates, such as the American Indians, followed by the Hispanics [15, 16]. On the contrary blacks have approximately 50% lower incidence rates than those for whites [7].

21a.2. Risk Factors

There is an established association between cholelithiasis and GBC, although a cause-and-effect relationship between them has not been proven. The high rate of incidence of this tumor in several ethnic groups and the female predominance correlate closely with variations in the incidence of cholelithiasis [17].

Indeed, cholelithiasis is encountered in more than 90% of cases of gallbladder cancer [18]; in addition, most cases with gallbladder cancer are associated with multiple and large stones (> 3 cm), which is probably a reflection of the long-term presence of gallstones [19]. Chronic mechanical damage and inflammation of the gallbladder mucosa produced by the stones leads gradually to dysplastic changes and neoplastic transformation [20]. However, as the majority of GBC are not squamous cell carcinomas, but are adenocarcinomas malignant transformation of gallbladder adenomas or adenomyomatosis is also a substantial possibility [21, 22].

Although cholelithiasis is found in 80% of GBC cases in Western countries, in countries of the Far East, such as Korea, only 30% of GBC cases are associated with lithiasis [23]. Anomalous union of the pancreatobiliary duct, being quite frequent in East Asia, may play a role in the pathogenesis of GBC in these areas [24]. Alterations in bile composition, gene mutations, and epithelial cell proliferations may contribute to the pathogenesis of GBC [20, 25, 26].

Malignant transformation of benign tumors of the gallbladder has only rarely been reported; however, a direct relationship between adenoma, carcinoma in si-

tu, and invasive carcinoma of the gallbladder has been demonstrated [17]. For that reason polypoid lesion of the gallbladder may have a malignant potential, especially if they are greater than 10 mm in diameter. If diagnosed, cholecystectomy is indicated even in the absence of stones [27]. Small polyps need to be removed only if they cause symptoms or coexist with gallstones.

There are two other pathologic conditions associated with the development of carcinoma: cholecystoenteric fistula and porcelain gallbladder. There is an increased incidence of development of GBC in patients who have had a cholecystoenteric fistula; the tumor may develop one to two decades later [28]. Nonetheless the incidence of GBC associated with a calcified or porcelain gallbladder is increased; in the 60s it was believed to range from 12.5 to 61% [29]. Recent reports have demonstrated an incidence of about 5% [30], and it is higher in gallbladders with selective mucosal calcification than in those with complete mucosal calcification [31].

The chronic typhoid carrier state has been proven to be another significant risk factor for the development of GBC [32]. In addition to the carrier state, bile stasis, deconjugation of bile acids, production of mutagenic stasis in the bile, and increased concentration of free radicals in the gallbladder are other possible factors implicated in the pathogenesis of GBC [20]. Nevertheless, the deficiency of certain micronutrients and antioxidants, such as selenium (Se), zinc (Zn), copper (Cu), manganese (Mn), ascorbic acid (vitamin C), and a-tocopherol (vitamin E) have a significant association with the development of GBC [33]. The major mechanism by which such dietary compounds may affect carcinogenesis includes antioxidation, changes in carcinogen metabolism, promotion of differentiation and growth inhibition, and immunologic modulation [34, 35, 36].

21a.3. Genetics

Adenoma and dysplasia of the gallbladder mucosa are considered as precancerous lesions. Unfortunately the precise molecular mechanisms of the progression of GBC are still unknown. Loss of heterozygosity (LOS) may be associated with the development of dysplasia and the malignant transformation of GBC. Microsatellite instability (MI) has a limited role in the development of GBC. Gene alterations of dominant oncogenes (K-ras), and tumor suppressor genes (*p53*, and *p16*) play an important role in the malignant changes of dysplasia [37, 38]. Loss of the p53 tumor suppressor gene function is one of the first events in tumigenesis. In addition a pathway from p53 regulating vascular endothelial growth factor (VEGF) induces angiogenesis in human GBC, which plays an important role in tumor progression and metastasis [39].

Methylation of 5' gene promoter regions, a major mechanism for silencing several tumor suppressor genes, is involved in the pathogenesis of GBC. Analysis of the methylation frequencies in GBC revealed several genes (*3-OST-2*, *CDH13*, *CDH1*, *RUNX3*, *APC*, *RIZ1*, *HPP1* and *p16*) involved in the development of GBC. The finding of gene methylation in gallbladders with chronic inflammation suggests that this phenomenon may be an early event in the malignant transformation of the gallbladder mucosa [40].

21a.4. Pathology

A variety of histological types of gallbladder carcinoma occur, all of which exhibit similar patterns of growth or clinical presentation and natural history. Macroscopically GBC may present as a mass lesion, either protruding in the gallbladder lumen or as a flat variety; the protruding tumors may be papillary or nodular [41]. CGB exhibit two patterns of growth: *infiltrating* and *fungating*. The infiltrating tumors are more common, histologically scirrhous, and appear as a diffuse thickening and induration of a significant part of the gallbladder wall, which may involve the entire gallbladder. The fungating tumors grow into the lumen as a cauliflower-like mass invading the gallbladder wall at the same time. The central portion may be ulcerating, hemorrhagic or necrotic. The most common sites of involvement are the fundus, neck and lateral walls [42].

Histologically, adenocarcinoma, the most common histological type, is found in 80% of cases. Adenosquamous carcinoma occurs in 3%, undifferentiated carcinoma in 6%, and mixed tumor (with glandular and squamous components) or adenoacanthoma in 1% [17].

The tumor spreads mainly by local invasion of the liver and other surrounding organs such, as the duo-

denum, hepatic flexure of the colon, omentum, and the abdominal wall. The common hepatic duct is frequently infiltrated, especially by tumors of the gallbladder neck or the Hartman's pouch. In this case, GBC presents with obstructive jaundice mimicking the clinical presentation of hilar cholangiocarcinoma. Penetration of the gallbladder fossa by the tumor may arise at an early stage by either direct invasion or by hematogenous spread through the cholecystic veins draining the gallbladder wall into the liver [17]. Lymphatic spread may occur through the lymphatics to the lymph nodes of the cystic duct, the common bile duct and the pancreaticoduodenal region. Hematogenous spread to distant organs such as the liver, lungs, pleura etc., does not occur until the tumor is locally advanced.

Histological classification and staging of GBC is done on the basis of the Tumor Node Metastasis (TNM) classification (table 21a.1) and in accordance with the American Joint Committee on Cancer staging system [43] (table 21a.2), and depends on the size of the tumor, its location, the presence of dysplasia, the degree of differentiation, and the degree of invasion of the gallbladder wall. These factors guide surgical options in the management of GBC and predict the clinical outcome after surgery [20].

Table 21a.1. TNM classification of GBC.

Tumor	
Tx	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1a	Tumor invades lamina propria
T1	
Tib	Tumor invades mascular layer
T2	Tumor invades the perimuscular connective tissue
T3	Tumor perforates the serosa or directly invades one adjacent organ, or both (extension 2 cm or less into liver)
T4	Tumor extends more than 2 cm into liver, and/or into two or more adjacent organs
Node	
Nx	Regional lymph nodes cannot be assessed
No	No regional lymph node metastasis
N1	Metastasis in hepatoduodenal ligament
N2	Metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes
Metastasis	
Mx	Distant metastasis cannot be assessed
Mo	No distant metastasis
M1	Distant metastasis

Table 21a.2. American Joint Committee on Cancer staging classification.

Stage	Tumor (T)	Lymph nodes (N)	Metastasis (M)
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0 N1	M0
Stage IVA	T4	N0 N1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Tis, tumor *in situ* (T).

21a.5. Clinical Manifestations

No symptoms or signs are specific for GBC. Carcinomas in situ or not penetrating the gallbladder wall are usually asymptomatic. Any symptoms present in these cases are attributable to gallstones, and may range from mild dyspepsia or biliary colic to acute or chronic cholecystitis. In these cases diagnosis is made if cholecystectomy is performed for symptomatic cholelithiasis [17].

The development of a malignant tumor in patients with pre-exisiting biliary symptoms may produce a noticeable change in symptoms. Early invasion of the serosa and the gallbladder fossa may produce a visceral-type dull pain in the right hypochondriac region referred to the right scapula. Invasion of the gallbladder neck or cystic duct may produce obstructive symptoms. At late stage GBC produces non-specific systemic features, such as anorexia, malaise, weight loss, nausea and vomiting. In addition, invasion of the common hepatic duct produces compression of the common bile duct and obstructive jaundice. Other findings such as abdominal mass, duodenal obstruction and ascites suggest advanced disease [44]. Jaundice is accompanied by a visceral type pain in the majority of advanced cases, which may be useful to differentiate this disease from periampullary carcinoma. The presence of a palpable gallbladder at physical examination always indicates advanced disease.

21a.6. Diagnostic Methods

Because of the atypical clinical presentation and the insidious progress of the disease, preoperative diagnosis has always been difficult at least in the early stage.

However, the advent of new investigational techniques combined with a high index of clinical suspicion may help in the preoperative diagnosis in the majority of advanced cases.

Hematological and biochemical parameters may provide some help in diagnosis. A mild anemia is often present and should rise suspicion when investigation indicates benign biliary disease. Interestingly, in early non-jaundiced cases, the serum alkaline phosphatase may be elevated. This may be due to invasion of the gallbladder bed, cholangitis, obstruction of a hepatic duct, or liver metastasis [17].

Ultrasonography is a practical tool for the detection of a gallbladder mass. It may indicate polypoid lesions, which are usually benign if they have a diameter not exceeding 1 cm. However, most polypoid lesions greater than 1 cm may be malignant and should be treated with cholecystectomy [45, 46]. Unfortunately, ultrasonography may miss most early cases of GBC-only around 30% of early cases can be diagnosed preoperatively by ultrasonography [44, 47].

In more advanced-stage tumors, multiple imaging techniques such as ultrasonography, computerized tomography (CT), and magnetic resonance imaging (MRI) can detect the primary tumor and indicate any invasion of adjacent structures and metastatic lesions. Ultrasonography allows correct diagnosis in 70-80% of advanced cases [48]; it may also indicate liver infiltration or intrahepatic ductal dilatation. A CT scan is helpful both in diagnosis and staging. However, despite the increased accuracy of CT scan in the preoperative diagnosis of GBC, the extent of the disease is often underestimated. The most common causes of understaging GBC preoperatively are small hepatic metastases, microscopically involved regional lymph nodes and undetected peritoneal carcinomatosis [44, 49].

Selective hepatic angiography is useful in diagnosing resectable disease [20]. Computerized tomography angioportography or MRI has the advantage of demonstrating the vascular details of the area of the neoplasm [50, 51].

Among the cholangiographic techniques percutaneous transhepatic cholangiography (PTC), and endoscopic retrograde cholangiopancreatography (ERCP) are the most useful in diagnosing GBC and its spread into the biliary tree. PTC in the jaundiced patient may show changes within the intrahepatic bile ducts suggestive of GBC. Distortion, stricturing, or obstruction of the bile ducts draining the hepatic segments adjacent to the gallbladder fossa may be shown. ERCP is mainly useful for non-jaundiced patients with biliary symptoms, in the absence of dilated intrahepatic biliary ducts. When it is done for the jaundiced patient the usual finding will be obstruction of the common hepatic duct with non-filling of the gallbladder [17]. ERCP may also demonstrate an anomalous junction of the pancreatico-biliary ducts, providing the opportunity of brush cytology and biopsy of the lesion extending to the common bile duct or the duodenum [20].

Fine needle aspiration cytology guided by ultrasound or CT may provide diagnosis of malignancy if a mass lesion in the abdomen is under investigation. This technique is useful for GBC, when non-operative methods of palliation are under consideration to relieve obstructive jaundice. In other cases when diagnosis is in doubt, diagnostic laparoscopy is routinely performed before exploratory laparotomy for patients with suspected GBC. Any suspicious findings should be biopsied, especially peritoneal or hepatic masses. If ascites is present, a fluid specimen should be obtained for cytologic examination. The laparoscopic detection of inoperable GBC spares the patient an unnecessary laparotomy [44, 52].

21a.7. Surgical Treatment

Surgery is the only effective treatment for GBC and provides these patients the prospect of relatively long-term survival. The surgical approach depends largely on the mode of presentation and extent of the disease. GBC patients present in one of the three ways:

- As an incidental finding at the time of cholecystectomy.
- As a resectable biliary tract malignant tumor.
- As an advanced intrabdominal malignancy.

Each of the three possibilities will be analyzed in terms of surgical approach or any other palliative measures required.

21a.8. Incidental Finding at Cholecystectomy

Since the era of open cholecystectomy, it was well known that the diagnosis of GBC is incidentally made in about 27-41% of cases during or after cholecystectomy performed for benign biliary disease [17, 53 and 54]. Today, in the age of laparoscopic surgery, GBC is unexpectedly found during or after laparoscopic cholecystectomy, in 0.3% to 0.5% of cases, in Western countries [55, 56]. In Japan the percentage is slightly higher (0.8 to 0.9%) [52, 57]. Most of the cases unsuspected preoperatively belong to stages pT1 and pT2 [58].

The possibility of tumor implantation to the abdominal wall has been a matter of debate. Some authors have stated that it did not increase after laparoscopic surgery [59, 60]. However, others support that pneumoperitoneum with carbon dioxide (CO2) may promote the dissemination of malignancy [61]. Furthermore, excessive manipulation of the gallbladder during laparoscopic cholecystectomy and bile spillage may significantly affect prognosis in patients with unsuspected GBC [62]. Indeed, it has been reported that the incidence of port-site recurrence increased from 9% in cases without intraoperative gallbladder perforation to 40% in patients with documented perforation [63]. Although most of the port-site recurrences occur at sites through which the specimen was removed, they do not always develop at the removal port-sites [55]. The use of a protective retrieval bag for the extraction of the gallbladder is always suggested; however, this does not exclude intraperitoneal seeding. It is also mandatory to avoid perforation of the gallbladder and bile spillage in the surgical field during laparoscopic cholecystectomy [64].

The diagnosis of a tumor confined in the gallbladder is made when the excised gallbladder is opened immediately after removal, or during histological examination of the surgical specimen by the pathologist. A removed gallbladder should be opened before closure of the abdominal wounds and any suspicious lesion should be sent for frozen-section examination [17]. If a tumor is discovered the surgical strategy is best determined by the diagnosed T stage of the disease [65]. Patients with GBC confined to lamina propria (pT1a) have excellent prognostic features and can be cured by cholecystectomy alone [66, 67]. If the tumor invades the muscular layer (pT1b) the possibility of lymph node metastasis is 16% [68] and the lymphatic, venous, and perineural infiltration is up to 50% [69]. It is not clear whether a simple cholecystectomy, as supported by some author, is sufficient at this stage [53, 58, 66, 67]. In contrast, others recommend an "extended cholecystectomy", as offering a better long term survival [65, 68 and 69]. Extended cholecystectomy involves wedge resectioning of the liver segments IVb and V at least 3 cm in depth from the gallbladder bed, together with regional lymphadenectomy. The latter includes the nodes of the first (N1) level, i.e., the nodes of the cystic duct, portal vein, hepatoduodenal ligament, and the liver hilum, and the second level (N2), i.e., the nodes around the pancreatic head, duodenum and celiac artery (fig. 21.1) [17, 65]. When patients with T1 are incidentally diagnosed after a simple cholecystectomy and the surgical margins are free of disease, then cholecystectomy is a sufficient operation for this group of patient [65, 70]. However, if the cystic duct margin is positive, these patients should be subjected to a repeat resection of the cystic duct stump or common bile duct resection and biliary reconstruction [70, 71, 72].

T2 tumors may be also incidental histologic findings after cholecystectomy. Up until the 1980s the treatment of choice for these patients was simple cholecystectomy. However, in the last fifteen years, many studies have reported that the incidence of lymph node metastasis may be as high as 39-54% [73, 74] and the incidences of lymphatic, venous and perineural

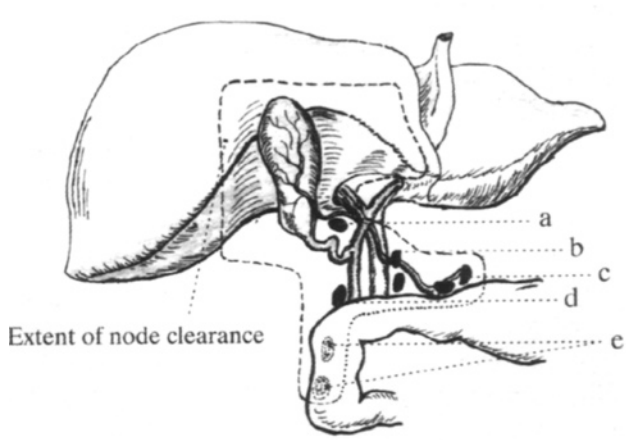

Fig. 21.1. Extent of lymph node clearance (a, d, c, d, e) in resectable gallbladder tumor.

invasion are also very high [65, 75]. Besides, the positive surgical margin status is reported as 24% after simple cholecystectomy for this subgroup of patients. Therefore, the most acceptable operation for T2 tumors is extended cholecystectomy, including the first and second level nodes [65]. Especially among patients with inapparent pT2 tumors incidentally found at simple cholecystectomy, those with subserosal invasion >2 mm, or with positive surgical margins are suitable candidates for radical resection, since they have a substantial survival benefit from a more extensive operation [53, 76].

21a.9. Resectable Malignant Tumor Preoperatively Suspected or Confirmed

Although the correct preoperative rate of diagnosis of GBC remains very low, over one-third of patients present with obstructive jaundice, many of whom will be correctly diagnosed as having malignant tumor of the biliary tract. Preoperative investigation with ultrasonography, CT scan, MRI cholangiography and angiography, and patient's parameters, such as age and clinical status, can determine whether the patient is a suitable candidate for radical surgery or not (fig. 21a.2, 21a.3).

Stage II-IVa GBCs can be treated with radical surgery. For patients with stage II disease, extended cholecystectomy is the most reasonable operation. For patients with stage III, extended cholecystectomy could be a sufficient operation [77]. For these patients the likelihood of a positive lymph nodes of first and second level, and also lymphatic, venous, or perineural invasion are extremely high. A survival benefit has been obtained with extended lymphadenectomy, since this operation offers a 16% 5-year survival rate, compared with no 5-year survival after simple cholecystectomy [65].

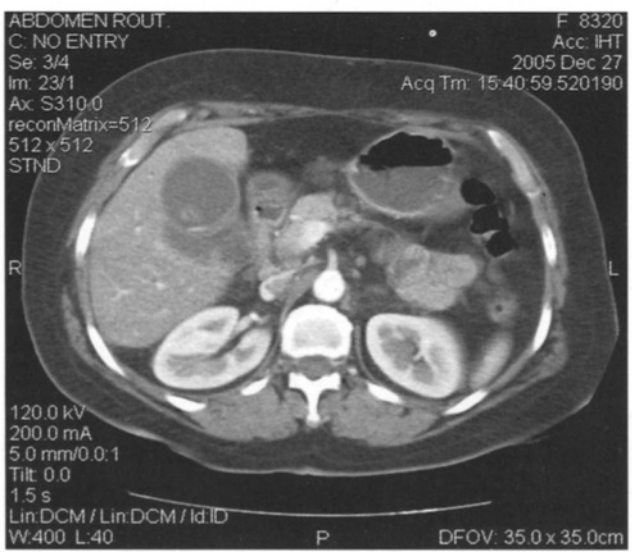

Fig. 21a.2. CT in gallbladder cancer with stones.

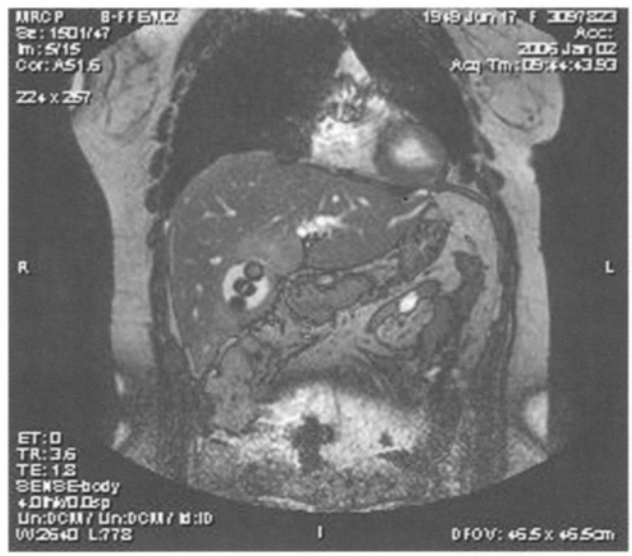

Fig. 21a.3. MRI of the patien of the previous figure (21.1) with gallbladder cancer and stones.

For patients with locally advanced disease, extended cholecystectomy is not a sufficient operation. Extended resections, including resection of the extrahepatic bile duct and/or bowel resections for direct involvement of the duodenum, small bowel, or colon are recommended, as all known disease can be removed with such an operation [44, 72]. Extended right hepatectomy can be performed when the right portal triad is involved by direct extension of the primary tumor. Several Japanese groups suggest combined major hepatic and pancreatic resections, the so-called hepatopancreatoduodenectomy with survival benefit for patients with stage III or IVa [78, 79]. This operation is the optimal strategy in the treatment of advanced GBC, according to Japanese surgeons [77]. Surgical benefits may be obtained for patients with peripancreatic lymph node metastases or perineural invasion. How-

ever, a minimal likelihood of cure exists when the tumor has massively invaded the bile duct and regional lymph nodes [77]. Western surgeons, on the other hand, have not adopted this aggressive operation for GBC. Extension of regional lymphadenectomy to paraaortic nodes has been suggested, but this does not seem to add any survival benefit for cases with involvement of celiac, superior mesenteric, or paraaortic lymph nodes [44, 80].

For those patients with non-resectable lesions, some form of palliative procedure should be applied. A considerable number of patients need palliation for jaundice or cholangitis, as well as gastric outlet obstruction. Palliative procedures commonly performed for jaundice include Roux-en-Y or jejunal loop anastomosis with common hepatic duct, left duct, segment III or Longmire bilioenteric anastomosis [20]. Segment III bypass is preferred by most authors despite the increased morbidity rate-50% in several series [81]. Malignant obstruction of this anastomosis does not occur until a late stage and prolonged relief of jaundice is usually obtained. The procedure is recommended even for patients with obstructed hepatic duct confluence, provided severe cholangitis is not present [82].

Symptoms of gastric outlet obstruction are present in up to 30% of patients with advanced GBC. Gastrojejunostomy is the preferable procedure to relieve symptoms [20]. The procedure has a mortality rate of 7% and morbidity of 42% [83]. When gastric outlet obstruction coexists with biliary obstruction, the morbidity and mortality are much higher.

For elderly and debilitated patients with advanced disease radiological or endoscopic stenting is an option for palliative treatment. However, endoprosthesis insertion carries a significant morbidity and mortality rate. Tube blockage or displacement, recurrent cholangitis, although less common with the newer expandable metallic stents, remain a serious problem [17]. In a meta-analysis of biliary bypass versus biliary stenting, long-term results did not show any significant advantage of one over the other [84]. However, bypass surgery allows patients to return home without stents and tubes, and without further requirement for repeated interventions, offering a better quality of life.

21a.10. Advanced Malignancy

When there is clinical or radiological evidence for advanced malignancy, such as large abdominal mass, ascites or distant metastases, a choice between surgical palliation or chemotherapy should be made. Laparotomy alone, often performed in the past to assess the stage of the disease, and/or feasibility of surgical palliation, carries a significant morbidity and mortality rate and should therefore be

Avoided [20, 85]. Laparotomy for biopsy alone is no longer justified, since percutaneous fine needle cytology can yield a positive diagnosis in the majority of cases [17].

Chemotherapy seems to have little effect in patients with advanced GBC. The most commonly used drug for chemotherapy is 5' fluorouracil (5-FU). A bolus injection of 5-FU has yielded response rates ranging from 10 to 24% [86]. Another drug used for the treatment of inoperable GBC is mitomycin C [87]. Cisplatin has also been used in combination with 5-FU for unresectable lesions and for resected lesions with recurrence [88]. The role of regional chemotherapy has not been fully investigated in GBC. Japanese authors have shown satisfactory response rates in downstaging tumor by preoperative systemic or regional chemotherapy [88, 89]. Nonetheless superselective intra-arterial chemotherapy with mitomycin for GBC may have a satisfactory response rate and may yield a significantly better patient survival [90] .

The role of radiotherapy in the treatment of GBC has not been well defined. However, in several centers postoperative radiotherapy and/or adjuvant radiochemotherapy is commonly used for advanced GBC [83]. Intraoperative radiotherapy in patients with malignant bile duct obstruction due to GBC may produce resolution of biliary strictures, without prolonging long-term survival [17, 91].

External beam irradiation has also been suggested after apparently curative surgery with encouraging results [92]. In general, chemotherapy and radiotherapy have yielded disappointing results in the treatment of advanced GBC, because most of the patients undergoing these forms of treatment have already disseminated malignancy.

21a.11. Prognosis

The overall outcome of the disease is dismal with the overall 5-year survival rate being less than 5% and a median survival of 5 to 8 months. Classical reports from the 1970s had introduced an almost total pessimism regarding any possibility of effective therapy for GBC. Piehler and Circhlow [93] analyzed 58 [36] cases with GBC from 1960 to 1978 and found a one-year survival of 11.8% and 5-year survival of 4.1%. The best survival was achieved in patients with incidentally found tumors at cholecystectomy specimens-even in this group of patients the 5-year survival was only 14.9%. Only 25% were operated on with curative intent and of these only 16.5% survived 5 years. A recent report from France recorded similar results [94]: the median survival being only 3 months, the 5-year survival 5% and the one year survival 14% among 724 patients with GBC. They did not observe any substantial difference among the different surgical procedures and they concluded that there was no progress in the treatment of GBC.

In the pastone or two decades, a more positive approach has prevailed in the treatment of GBC, due to advances in surgical techniques, which has allowed the successful performance of extended resections [94]. Indeed, the low morbidity achieved in the recent years by extended operations involving the liver, bile duct, and pancreas has contributed to a change in our attitude regarding treatment of this cancer [44, 68, 73, 94].

The surgical strategy and associated prognosis depends on the stage of the disease.

Patients with T1 disease incidentally diagnosed after a simple cholecystectomy do not usually require any further surgery and the 5-year survival rate is 95% [95]. Despite the fact that a number of reports of early recurrence after simple cholecystectomy for T1 tumors have been published [94, 96], there is no justification for more extended resections, with their higher morbidity and mortality rates, for these tumors.

Patients with T2 tumors are candidates for extended cholecystectomy, as this exterminates any spread of the disease by local invasion or via lymphatics [94, 95]. A radical second resection provides a significant survival benefit mainly for patients with deep subserosal invasion (>2 cm) [76], or for patients whose surgical margin was cancer positive at the initial cholecystectomy [53]. In these patients post-resectional 5-year survival rate ranges from 50% to 60%.

The surgical attitude towards locally advanced tumors (T3 and T4) remains controversial. The long-term outcome of patients with T3 tumors is generally poor, since spread of the residual tumor makes it difficult to remove cancer cells completely. However, the reduction in the short term morbidity and mortality rates after major hepatobiliopancreatic surgery has allowed the appliance of extirpative operations in the management of GBC. Frena et al [94] reported a one-year actuarial survival rate of 53.8% in a small number of patients with T3 and T4 tumors who were treated radically with major surgery. Cubertafond et al [85] reported that no patients with T3 and T4 tumors survived more than 36 months after extensive surgery. On the other hand Japanese surgeons reported more encouraging results. Toyonaga et al [53] reported that radical second resection lengthened the median survival time from 7 to 15 months in a small number of patients with T3 tumors. Miyazaki et al [97] reported that the mean survival of patients with T3 and T4 tumors after curative resection was approximately 2 years, whereas after noncurative resection it was only 4 months. Other authors report 5-year survival rate for stage III and IVA disease (Table 2) to be 33-57% and 17-33% respectively, after extensive surgery [73, 98, 99]. In addition, Todoroki et al [100] have shown that radical resection improves the prognosis even for stage IV disease, provided that gross tumor resection is combined with radiotherapy. This suggests the additive role of surgery and adjuvant therapy in changing the natural history of GBC4.

According to AJCC classification [101] GBC patients are subdivided into two groups, those with stage I or II disease, in whom cancer is confined to the gallbladder (T1-T2, N0) and is amenable to radical resection, and those with stage III or IV, the majority of patients, in whom there are already regional (N1) or remote (N2) lymph node metastases, indicating disseminated disease. In the second group of patients surgery can only be palliative. According to Frena et al [94] one and 5-year survival rates of stage I-II patients are 100% and 75% respectively, whereas survival rates for stage III and IV patients are only 59.9% and 0%, respectively. This indicates that the presence of positive lymph nodes in GBC dramatically affects survival. Patients with N1

disease should also be offered resection with curative intent- though not feasible, because this has been proven to yield a better life expectancy in patients with stage III (T3N1M0) and stage IV (T4N1M0) disease (66.6% one-year survival). Palliative surgery in these patients could not offer any chance for survival at one year [94].

The outcome for stage IV patients (mainly stage IVB) remains disappointing. In these patients radical resection is not applicable. Palliative surgery may offer temporary symptomatic relief from symptoms, but cannot prolong survival. Lai [102] reported that the result for stage IV patients was poor. All patients died within a few months with the exception of one patient who survived for 16 months. Adjuvant treatment targeting locoregional disease such as radiotherapy and/or systemic chemotherapy is often used without having any substantial impact on disease survival [103].

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BILE DUCT CANCER

G. Karatzas, E. Misiakos

21b.12. Incidence

Cholangiocarcinoma (CCA) is the primary cancer of the biliary tree. It is broadly divided into intrahepatic, extrahepatic hilar tumors and extrahepatic distal bile duct tumors, according to its anatomic distribution within the biliary tree [1]. It is an epithelial neoplasm, adenocarcinoma in most cases. Although it comprises about 10%-15% of hepatobiliary neoplasms, its incidence is increasing globally [2, 3]. The annual incidence of CCA is approximately 1.0 per 100,000 in the United States, 7.3 per 100,000 in Israel, 6.5 per 100,000 among American Indians, 5.5 per 100,000 in Japan [4], and 2 per 100,000 in England and Wales [5]. However, this increase is mainly due to a sharp rise in the incidence of intrahepatic cholangiocarcinoma, whereas the incidence of extrahepatic cholangiocarcinoma seems to have declined the last two decades [6]. Using the Surveillance Epidemiology and End Results (SEER) database, which represents 10-14% of the total US population, the age adjusted incidence of intrahepatic CCA has increased by 165%, from 0.32 per 100,000 population during 1975-1979 to 0.85 per 100,000 during 1995-1999 [2, 12]. This rise occurred across all age groups, especially those older than 65 years, and in both sexes. In addition, the rising incidence does not seem to be plateauing, as would be expected if it were due to an improvement in diagnostic techniques, such as computerized tomography (CT), magnetic resonance imaging (MRI), or endoscopic retrograde cholangiopancreatography (ERCP), which have gained wide acceptance during the last one-two decades [2, 5]. The incidence of intrahepatic CCA varies widely across the world: it is more common in Asia, especially in northeast Thailand (96/100,000 in men and 38/100,000 in women), probably due to the high prevalence of liver fluke infestations [2, 6].

Incidence and mortality rates for extrahepatic CCA seem to be declining worldwide [2, 13]. According to SEER data, the US age-standardized mortality rates for extrahepatic tumors dropped from 0.6 per 100,000 population in 1979 to 0.3 per 100,000 in 1998. Also the age-standardized incidence rates decreased from 1.08 per 100,000 to 0.82 per 100,000 in the same period [2, 14]. The data for extrahepatic CCA are more difficult to obtain due to the fact that gallbladder cancers are often combined with extrahepatic CCA for coding purposes [15].

21b.13. History

CCA has been recognized for more than 100 years. The first 18 cases of extrahepatic bile duct cancer were initially reported by Musser [7] in 1889. Since then two major cumulative reports have been published: one by Stewart et al in 1936 [8], who reviewed 306 cases of extrahepatic bile duct cancer and one by Sako et al [9], who found 570 additional cases in the literature, from 1935 to 1954. The first cases of intrahepatic CCA have been reported by Altemeier in 1957 [10]. Klatskin in 1965 [11] reported the first case series of patients with tumors of the hepatic duct bifurcation-from this report the term "Klatskin tumor" originated. After a decade the French surgeon H. Bismuth classified hilar CCA according to location in the biliary ducts [16, 17]. More recent advances include progress in the understanding of tumor genetics, the improvement in diagnostic techniques and more aggressive surgical approaches including radical resection and liver transplantation [4].

21b.14. Risk Factors

The precise cellular origin of CCA remains unknown. However, there is experimental evidence that certain carcinogens may induce neoplastic differentiation of liver stem cells resulting in CCA [4]. There are several risk factors, which are implicated in the pathogenesis of this tumor. Most of them seem to be associated with chronic inflammation of the biliary epithelium.

21b.14.1. Hepatolithiasis

Cholelithiasis is present in up to one third of patients with CCA [4, 16], which is not dramatically different from what should be expected in an elderly population. Therefore there should be an association between cholelithiasis and cholangiocarcinoma; however a clear

cause-and-effect relationship has not been established. In contrast, hepatolithiasis is a definitive risk factor for CCA. Although rare in the west, hepatolithiasis is endemic in certain parts of East Asia, and is associated particularly with peripheral intrahepatic CCA [2]. Up to 10% of patients with intrahepatic biliary stones develop this tumor [17]. In Taiwan, up to 70% of patients with CCA undergoing surgery have hepatolithiasis, and in Japan this figure is 6-18% [18, 19]. Biliary stones may cause bile stasis, which predisposes to recurrent bacterial infection and inflammation of the biliary tree, a potential predisposing factor for the development of CCA [15]. The cancer risk is apparent with biliary stones, even in the absence of secondary infestation with liver flukes [4].

21b.14.2. Parasitic Infection

For almost four decades, a pathogenic association has been detected between the liver fluke *Clonorchis sinensis* and cholangiocarcinoma [20, 21]. Clonorchiasis is common in Asia, where the ingestion of raw fish is common. This parasite gains entry through the host duodenal mucosa. It mainly inhabits the human intrahepatic, or less commonly the extrahepatic biliary ducts. The adult worms measure up to 25 mm long, and they may obstruct the bile flow and cause periductal fibrosis and hyperplasia, which are conditions predisposing to CCA [4]. Another liver fluke, *Opisthorcis viverrini* has been implicated more recently in the pathogenesis of CCA. Most epidemiological data are from Thailand, which has the highest incidence of CCA worldwide (87 per 100,000 population) and where almost 7 million people have opisthorchiasis [22, 23]. Adult worms also inhabit and lay eggs in the biliary system producing inflammation predisposing to CCA. Ingestion of nitrosamines may also play a role in the increased incidence of CCA in this region.

21b.14.3. Congenital Biliary Cysts

Congenital anomalies of the biliary tree associated with choledochal cysts, Caroli' syndrome, or congenital hepatic fibrosis carry a 15% risk of malignant transformation after the second decade at a mean age of 34 years [24]. The overall incidence of CCA in patients with untreated cysts is up to 28% [25]. Patients with cystic dilatations of the bile duct who have CCA usually present two decades earlier than patients with sporadic CCA [4]. One explanation for the origin of choledochal cysts and the subsequent formation of CCA is the finding of a high entry of the pancreatic into the extrahepatic biliary tree in these patients [26, 27]. It is evident that reflux of pancreatic secretions into the bile duct may cause malignant changes of the bile duct epithelium. Additional factors may include biliary stasis, activation of bile acids, and deconjugation of carcinogens. Bile duct adenomas and biliary papillomatosis are also predisposing conditions for the development of CCA. It is believed that individuals who are heterozygous for bile salt transporter polymorphisms have an increased predisposition to malignant transformation after exposure to factors producing chronic inflammation in the biliary tree [15].

21b.14.4. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is the most known predisposing condition for CCA in the Western countries. CCA rates of 8-40% have been reported in patients with PSC in clinical studies and necropsy specimens [2]. Furthermore previously unrecognized CCA has been noted in 9 to 36% of patients undergoing orthotopic liver transplantation for PSC [28, 29]. These patients develop malignancy within 2 years of the diagnosis of PSC. Two thirds of patients with PSC have associated inflammatory bowel disease, especially ulcerative colitis [30]. An association between ulcerative colitis and CCA has been established according to some authors [31, 32]. The incidence of CCA in patients with ulcerative colitis ranges from 0.14% to 1.4%, which is a figure 400 to 1000 times greater than the one in the general population. However, there are more recent studies which could not establish an association between the risk of CCA and the presence or severity of inflammatory bowel disease [30, 33].

21b.14.5. Chemical Carcinogens

Several chemical carcinogens and drugs have been implicated in the pathogenesis of CCA. Thorotrast, a radiological contrast agent widely used in the 1930s and 1940s was banned in the 1960s for its carcinogenenic properties; it causes microsatellite instability, followed by clonal expansion of cholangiocytes and inactivation of hMLH1 [34]. This agent has been stron-

gly associated with the development of CCA many years after exposure, increasing the risk to 300 times that of the general population [2, 35]. Chemicals that may potentially cause CCA include several by-products of the rubber and chemical industries, including dioxins and nitrosamines [36], asbestos [37], and polychlorinated biphenyls [38]. In particular nitrosamines found in cured meat have been associated with carcinogenesis of CCA [4]. Drugs also implicated in the pathogenesis of CCA include isoniazid, methyldopa, and oral contraceptives [4, 39]. Alcohol and smoking are also implicated in the pathogenesis of CCA [40].

21b.14.6. Viral Hepatitis

Hepatitis B and C viruses have been linked to CCA development. A prospective controlled study from Japan reported a 3.5% risk of developing CCA at 10 years in patients with hepatitis C cirrhosis, which is a figure 1000 times greater than that in the general population [41]. In another study from Italy, 23% of patients with CCA were positive for hepatitis C virus antibodies and 11.5% were positive for HbsAg antigen, compared with 6% and 5.5% of control subjects, respectively [42]. Hepatitis C virus is a well established risk factor for hepatocellular carcinoma and both cholangiocytes and hepatocytes have the same progenitor cell, indicating a possible role of for the virus in the pathogenesis of CCA as well. Furthermore, RNA form hepatitis C virus has been detected in CCA tissue in a Chinese study [43].

21b.14.7. Dietary and Other Factors

A recent study performed in Japan, the Japan Collaborative Cohort Study, has evaluated risk factors for CCA and gallbladder carcinoma (GBC) [44]. According to this study, high intake of fried food was a factor that significantly elevated the risk of the diseases, whereas high intake of boiled beans had a significant preventive relation to the diseases in females. Similarly, high consumption of fish had a preventive relation to CCA in males and GBC in females. Other factors, such as history of blood transfusion and constipation-bowel movements less than once per 6 days, elevated the risk of the diseases.

21b.15. Molecular Pathogenesis

It is generally accepted that the milieu of chronic biliary inflammation and cholestasis leads to the production of cytokines and reactive oxygen species, which causes irreversible DNA damage [45] at the cellular level. As every cancer, CCA possesses molecular mechanisms to promote growth and proliferation, avoid apoptosis, and invade surrounding tissues and produce metastases [6]. Several studies have shown abnormal expression of the K-ras oncogene in 21-100% of cases and the p53 tumor suppressor gene in 37% of cases [46]. In addition, it has been shown that the inactivation of p16 is an early step in the carcinogenesis of intrahepatic CCA arising in hepatolithiasis [47]. Increased expression of c-met and c-erbB-2 proto-oncogenes has been shown and most likely promote the metastatic potential of the intrahepatic CCA [48]. Interleukin 6 (IL-6) [49] and increased cyclooxygenase isoenzyme expression [50] are also related to autologous proliferation signaling in intrahepatic CCA. Indeed selective Cox-2 inhibitors have been shown to inhibit CCA cell growth in experimental or in vitro models [51]. Several anti-apoptotic proteins, such as mcl-1 and Bcl-xl, are also expressed [52]. It has also been shown that Ecadherin, a-catenin, and b-catenin, proteins normally expressed in biliary cells, are gradually down-regulated during neoplastic transformation in a manner that expresses the tumor grade and invasiveness [53].

Several other genes, such as RAB27B, TIMP3, and EMP2 were found upregulated in tumors with lymph node involvement [54]. In addition VEGF-C, a lymphangiogenic factor, has been shown to play an important role in the lymph node metastasis of intrahepatic CCA [55]. Continuous research in the field of tumorigenesis of CCA will doubtless contribute to the development of diagnostic and therapeutic strategies for this type of cancer.

21b.16. Location

According to its location in the biliary tree, CCA is classified into intrahepatic and extrahepatic type. The intrahepatic tumors are classified macroscopically into four growth types: 1) mass forming, 2) periductal infiltrating, 3) mass forming plus periductal infiltrating, and 4) intraductal [56].

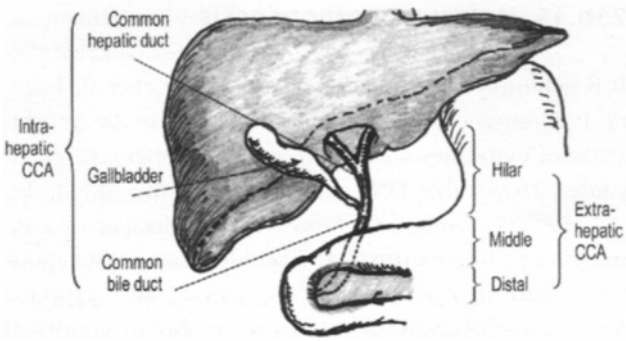

Fig. 21b.4. a. Anatomical locations of extrahepatic biliary tumors.

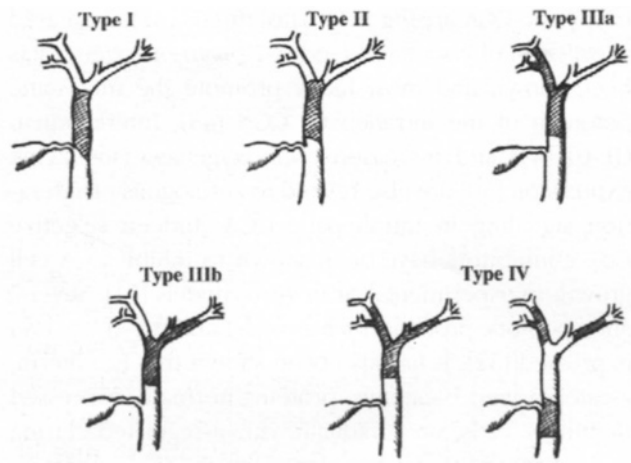

Fig. 21b.4. b. Bismuth classification for the extrahepatic cholangiocarcinoma.

The extrahepatic tumors are further divided into: 1) hilar or Klatskin, 2) middle, and 3) distal tumors (fig. 21b.4 a). Klatskin tumors represent approximately 60% of all extrahepatic tumors [6]. Bismuth and Corlette have classified all hilar CCA into 5 major types according to the biliary segment affected by tumor (fig. 21b.4 b). Type I affects the common hepatic duct. Type II affects the common hepatic duct and the confluence of the right and left hepatic ducts. Type III involves the common hepatic duct and either the right or left hepatic duct. Type IV involves the confluence of the hepatic ducts and extends to both the right and left hepatic ducts or involves multifocal bile duct tumors (fig. 21b.5).

Macroscopically, extrahepatic CCA presents as sclerosing, nodular, or papillary phenotypes [56]. The sclerosing type is the most common; it is characterized by annular thickening of the bile duct wall due to infiltration of the periductal connective tissue.

21b.17. Pathology and Staging

Adenocarcinoma accounts for more than 95% of CCA, whether it is extrahepatic or intrahepatic. Other histologic types of CCA have been reported, including squamous or mucoepidermoid carcinoma, papillary carcinoma, leiosarcoma, rhabdomyosarcoma, cystadenocarcinoma, carcinoid tumor etc [4, 6, 57, 58].

Poorly differentiated CCA is not uncommon and is characterized by scarce malignant cells dispersed in a fibrous stroma. However, in well differentiated adenocarcinoma it is often hard to distinguish the presence of malignancy, since the distinction between inflammatory reaction of bile duct epithelium and malignancy is difficult, especially in the presence of biliary stasis and/or sepsis. The presence of at least two of the following characteristics confirms the diagnosis of CCA: 1) variation of nuclear size, 2) formation of distended intracytoplasmic lumina, 3) positive reaction to carcinoembryonic antigen (CEA). 4) neural invasion [59].

CCA staging is based on the tumor-node-metastasis (TNM) classification of the American Joint Commission on Cancer or the Union Internationale Contre le Cancer (AJCC/UICC) [60]. Today we follow the 6th Edition of the AJCC/UICC staging system [61, 62] which is analyzed in tables 21b.3 and 21b.4. In Japan a more complex system has been introduced by the Japanese Society of Biliary Surgey (JSBS), containing more precise description of tumor invasion of adjacent organs and blood vessels [63].

21b.18. Clinical Presentation

CCA usually appears after the 4th decade of life. This cancer is often silent for long periods of time. During the prodromal period, which may last from 1 to 120 months there may be anorexia and malaise and modest weight loss. Some patients, though completely asymptomatic, are diagnosed early during an investigation based on an isolated rise in serum alkaline phosphatase level [6]. This occurs because lobar or segmental ductal

Table 21b.3. TNM classification of extrahepatic CCA.

Tumor		
	Tx	Primary tumor cannot be assessed
	Tis	Carcinoma *in situ*
	T1	Tumor confined to the bile duct histologically
	T2	Tumor invades beyond the wall of the bile duct
	T3	Tumor invades the liver, gallbladder, pancreas, and or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)
	T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall.
Node		
	Nx	Regional lymph nodes cannot be assessed
	No	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Metastasis		
	Mx	Distant metastasis cannot be assessed
	Mo	No distant metastasis
	M1	Distant metastasis

Table 21b.4. American Joint Committee on Cancer staging classification [61].

Stage	Tumor (T)	Lymph nodes (N)	Metastasis (M)
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Tis, tumor *in situ* (T).

obstruction is commonly incomplete [64]. Other patients with papillary tumors may present with unexplained iron deficiency anemia, due to continuous bleeding or with intermittent fever. Occasionally an abdominal mass may be the only finding in asymptomatic patients. These nonspecific symptoms are common for tumors arising within the intrahepatic ducts of the liver parenchyma.

In extrahepatic CCA the leading symptom is painless obstructive jaundice accompanied by pale stools, dark urine and pruritus [6]. In some cases there may be an initial attack of jaundice indicating the presence of malignancy, and in patients with periampullary lesions there may be intermittent jaundice. Intermittent jaundice may also occur in the rare case of intrahepatic or hilar papillomatous lesions [65]. However, progressive and unremitting painless jaundice is the predominant symptom in most cases. Cholangitis is an unusual presentation.

Biliary pain is almost never present in mid and high bile duct tumors, in the absence of biliary lithiasis. However, a dull pain may be present in periampullary lesions, even in the absence of stones. However, gallstones or common bile duct stones may coexist with CCA. Therefore meticulous preoperative investigation of any obstructing lesion is essential lest an underlying malignancy is overlooked [64].

Physical examination reveals evident obstructive jaundice together with a modest painless enlargement of the liver, usually without a prominent liver mass. Ascites may be present in advanced cases with liver involvement. Cachexia and weight loss are usually present.

21b.19. Investigative Techniques

At presentation most patients with obstructive jaundice due to CCA will have a total serum bilirubin level greater than 10 mg/dl. The liver enzymes alkaline phosphatase and gamma-glutamyl transpeptidase are also elevated, but it is uncommon for the transaminase concentrations to also increase. Increased serum levels of alkaline phosphatase with a normal bilirubin may be present in case of an asymptomatic intrahepatic CCA [6]. Mild anemia is common together with a mild hypoalbuminemia and/or prolonged prothrombin time, due to malnutrition or depressed hepatic synthetic function [4]. There are no specific tumor markers for CCA. Carcinoembryonic antigen (CEA) has unsatisfactory sensitivity and specificity for cholangiocarcinoma [46]. Serum CA 19-9 and CA 50 may be elevated in patients with CCA, but levels may drop as biliary obstruction is relieved. In a series of patients without PSC, the sensitivity of CA 19-9 concentrations of more than 100 U/mL in diagnosing CCA was estimated as 53% [66].

Radiologic evaluation is essential for diagnosis, study of the extent of the disease and planning of treatment. The primary investigation for a suspected CCA is a transabdominal *ultrasound* scan, which may localize the site of obstruction, diagnose coexistent biliary lithiasis, and detect bile duct dilatation. In the case of proximal (hilar) lesions, intrahepatic duct dilatation with normal diameter extrahepatic ducts is usually

seen. In the case of distal lesions, both intrahepatic and extrahepatic ducts are dilated [67].

Standard *computerized tomography (CT)* can visualize the tumor in only 40% of cases [68]. Bolus-enhanced CT scans can detect the tumor in 59% of cases (fig. 21b.5 a, 21b.5 b) [4]. In case of extrahepatic CCA, the primary lesion is usual-ly not visible [69], whereas the effect of tumor obstru-ction on the bile ducts (ie, dilation) and the hepatic lobes (ie, atrophy/hypertrophy) is seen [6]. Intrahepatic CCA usually presents with delayed venous phase enhancement of a hypodense lesion after contrast administration. Today, contrast-enhanced, triple phase, *helical CT* can easily detect intrahepatic CCAs of greater than 1 cm, defining the level of biliary obstruction and the presence of lymphadenopathy [70].

Magnetic resonance imaging (MRI) has been proven more sensitive than CT in detecting these small tumors [4]. MRI and CT are the principal approaches to visualizing peripheral tumor growth [71]. On cross-sectional MR imaging, CCA appears as a hypointense signal on T1-weighted images and as a moderately intense lesion on T2-weighted images. *Magnetic resonance cholangiopancreatography (MRCP)* has several advantages over conventional CT in delineating the biliary system. This technique can provide a three-dimensional computerized reconstruction of the biliary tree, the anatomy of the tumor, invasion of liver parenchyma, vessel encasement, local lymphadenopathy, and distant metastases [72]. The non-invasively acquired cholangiographic images obtained at MRCP are comparable to invasive cholangiography (endoscopic retrograde cholangiopancreatography [ERCP] and percutaneous transhepatic cholangiopancreatography [PTC] in detecting the level and characteristics of biliary obstruction [73]. With MRCP undrained bile ducts can be delineated without injection of contrast, thus avoiding the possibility of cholangitis [72]. For the above reasons MRCP has become the imaging method of choice in defining the morphology and extent of biliary tumors and assessing respectability.

However, recently the multi-slice three dimensional *spiral CT cholangiography (3-D CTC)* has been introduced as an accurate technique for the imaging of the biliary tree.

In a recent study 3-D CTC was found superior to conventional CT and ultrasonography in the diagnosis

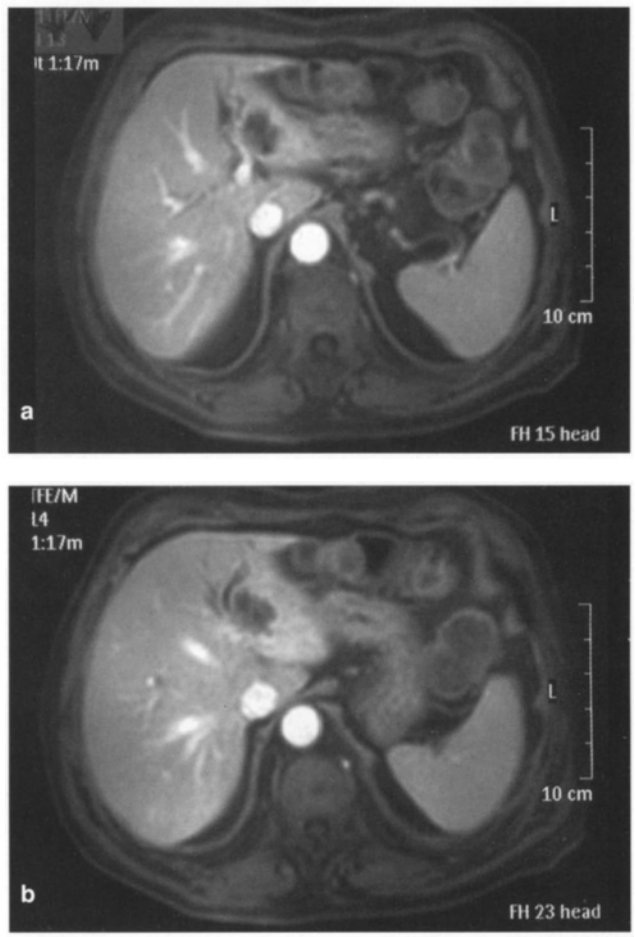

Fig. 21b.5. a-b. Two differences sections of CT in a patient with intrahepatic cholangiocarcinoma.

of extrahepatic and hilar CCA, and equivalent to ERCP in the diagnosis of hilar CCA [74]. Another prospective study comparing 3-D CTC with MRCP concluded that 3-D CTC is almost equivalent to MRCP for the imaging of biliary obstruction, and therefore can be used in individuals for whom MRI is contraindicated [75].

Positron emission tomography (PET) provides metabolic information of tumors rather than anatomic data on tumor location. In a study by Wakabayashi et al, 2-deoxy-[18F] fluoro-D-glucose (FDG) PET has been shown to have a sensitivity and specificity of 90 and 78% respectively, in diagnosing CCA, compared to 86 and 56% for CT scanning and 64 and 100% for cytological examination of bile [76]. In another study by Petrowsky H, et al [77], a novel fusion technique of combined PET and CT scan has been shown as an

accurate method in diagnosing the primary intra- and extra hepatic CCAs. The technique can detect nodulal CCAs as small as 1 cm, but it is less accurate for infiltrating tumors [78]. It was also valuable in detecting unsuspected distant metastases, which are not diagnosed by standard imaging modalities. Therefore, the PET/CT staging may have an important impact on selection of appropriate treatment.

The two invasive cholangiographies are of great value in the diagnosis of CCA. *ERCP* and *PTC* can delineate the location of the malignant stricture and present the precise imaging of the biliary tree, but have, as main disadvantages, the risk of biliary leakage, duodenal perforation, bleeding, and pancreatitis. The choice between ERCP and PTC is largely dependent upon local expertise, and failure of one or other technique. For example ERCP may fail to efficiently delineate the proximal lesions; for the latter PTC is the procedure of choice [15]. ERCP also offers the advantage over non invasive tests in that tissue samples can be obtained by brush cytology. However, the sensitivity of brush cytology for diagnosing CCA has been poor [69]. The sensitivity of the method could be increased by new analysis techniques, such as *fluorescence in-situ hybridization* and digital image analysis [69]. In a large study the sensitivity of fluorescence in-situ hybridization was significantly better than that of routine brush cytology, although specificity was lower for the detection of malignancy in biliary tract strictures [79].

Endoscopic Ultrasound with fine-needle aspiration *(EUS-FNA)* has emerged as an alternative technique to ERCP brushings for establishing the cytological diagnosis of CCA. EUS can be useful in detecting local lymph node enlargement and allows fine-needle aspiration of the tumor mass or the local lymph nodes. EUS-FNA has a greater sensitivity for identifying malignancy than ERCP with brushings, as concluded in large studies [80, 81]. However, in another study EUS was found superior to ERCP when a pancreatic tumor was found to be the cause of a biliary stricture, whereas ERCP was superior if a biliary malignancy was suspected [82].

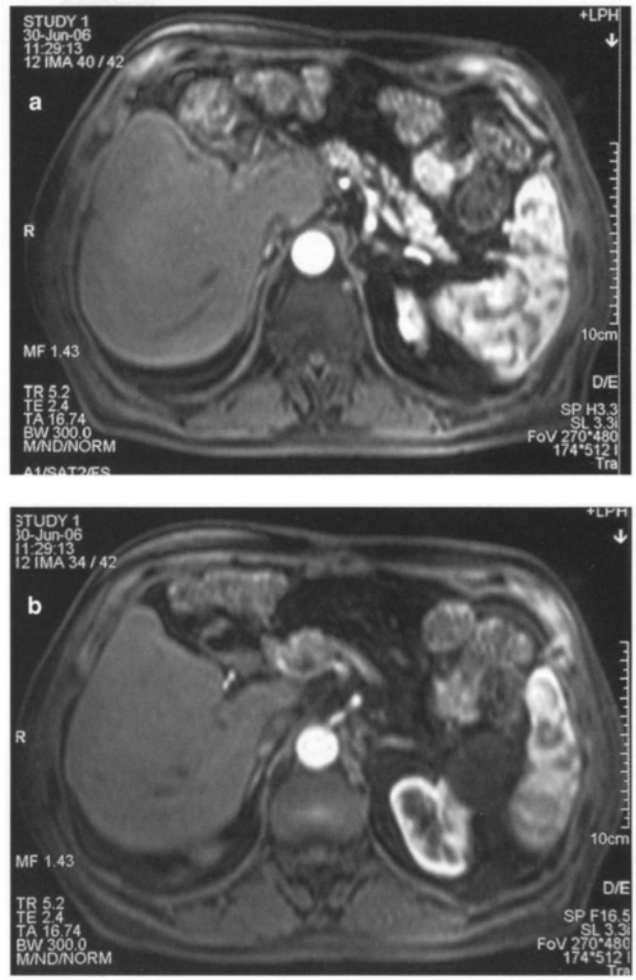

Fig. 21b.6. a-b. CT sections in the patien with cholangiocarcinoma after left hepatectomy.

21b.20. Surgical Treatment

21b.20.1. Preoperative Assessment

A complete surgical resection with histologically negative resection margins is the only hope for cure for CCA patients (fig. 21b.6 a-b). However, only a minority of patients are suitable candidates for surgical resection. Therefore, preoperative assessment of resectability is mandatory and should be done by a specialist surgical team. Both patient and tumor factors should be considered pre-operatively. First the general medical condition of the patient in terms of cardiac, respiratory and renal function should be considered before surgery. Second in patients with obstructive jaundice, the pathophysiological abnormalities associated with this condition such as disturbances in hepatic, pancreatic and immune function, the hemostatic mechanisms, the gastrointestinal barrier, and wound healing should be taken into account [83].

Table 21b.5. Criteria of nonresectable CCA [84].

1. Involvement of hepatic duct up to secondary biliary radicals bilaterally.
2. Encasement or occlusion of the main portal vein proximal to its bifurcation.
3. Atrophy of one hepatic lobe with encasement of contralateral portal vein branch.
4. Atrophy of one hepatic lobe with contralateral involvement of secondary biliary radicals.
5. Distant metastases (peritoneum, liver, lung).

During preoperative evaluation, almost one third of cases will be considered as unresectable. Table 21b.5 lists the criteria for nonresectable CCA [6, 84]. In addition, at laparoscopy, 25 to 30% of patients who were thought to be candidates for radical surgery will be found to have unresectable disease (*about Surgical treatment see more details in chapter 22 and in the section III concerning hepatectomies*) [85].

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ENDOSCOPIC PALLIATIVE MANAGEMENT OF THE MALIGNANCIES OF THE BILIARY TRACT

Kon. Goumas, A. Poulou

21c.21. Introduction

The main causes of malignant obstruction of the main biliary duct are ampullary carcinoma, cholangiocarcinoma, adenocarcinoma of the pancreatic head and carcinoma of the gallbladder. During diagnosis, most of these tumors usually have locally advanced disease or distant metastases. Nevertheless, in such cases if an accurate tissue diagnosis is obtained, preferably without the need of laparotomy, it helps us plan further management [1]. Biliary duct lesions are not always readily accessible to biopsy and cytological techniques have therefore become the initial diagnostic modality in many cases. Brush cytology performed at endoscopic retrograde cholangiopancreatography (ERCP) has now become the preferred initial method of pursuing tissue diagnosis in many patients with biliary strictures, providing a diagnostic sensitivity of 59% (range 42-85%) [2]. Percutaneous radiologically guided fine needle aspiration (FNA) is an accurate diagnostic technique but it is operator-dependent and requires a sufficiently distinct mass lesion for targeting. Endoscopic ultrasound-guided FNA biopsy has shown very promising results in diagnosing cholangiocarcinoma, but is not yet a widely available diagnostic modality [3, 4]. It is also expected that the wider availability of cholangioscopy using the mother-baby endoscope system, as well as other innovative methods, such as intraductal ultrasound with tissue acquisition, will increase the diagnostic accuracy in suspected cases of biliary malignancies [5].

21c.22. Endoscopic or Surgical Palliative Management?

Surgical operation is still the treatment of choice for malignant biliary neoplasms. However, only a minority of patients are candidates for radical surgical resection in the time of diagnosis. The main causes of unresectability are locally advanced tumors and metastatic disease, as well as the advanced age that these patients have, accompanied by other serious co-morbidities, which increase the postoperative morbidity and mortality. As a result, in the majority of patients suffering from malignant biliary neoplasms, only palliative treatment would be advisable at the time of diagnosis [1]. Most common complications requiring palliation are primarily obstructive jaundice resulting from neoplastic compression or invasion of the common bile duct and secondarily intestinal obstruction.

There are three options for palliative treatment in patients with malignant billiary stenosis, endoscopic or percutaneous-transhepatic stenting and surgical by-pass.

Endoscopic stenting techniques are considered today as the first line treatment in cases of inoperable or unresectable tumors involving the biliary tree. When the endoscopic stenting technique fails, the percutaneous-transhepatic route must be taken into consideration. Compared to surgical by-pass, the endoscopic palliative management of patients with malignant biliary obstruction is preferable. A lower early complication rate, a shorter initial hospital stay and a lower cost for the endoscopic treatment groups have been reported in several retrospective studies [6, 7]. Late complications, mainly due to stent dysfunction, occur more frequently in patients treated endoscopically [8, 9]. However, despite readmissions for stent occlusions and cholangitis, the total hospital stay was shorter in the endoscopically treated patients compared to those subjected to surgery. The majority of studies have shown that the survival and the successful relief of jaundice were similar when comparing surgically and endoscopically treated patients. Results of a meta-analysis suggest that endoscopic approach is advantageous in patients surviving less than 6 months while surgery is preferable in patients with a longer survival [10]. The type of endoscopic stent that should ideally be used, will be discussed later in this chapter.

In daily practice, many patients with surgically curable biliary malignancies undergo preoperative biliary stenting because of practical reasons such as delay in scheduling surgery, referral of patients to specialized surgeons, psychological support of patients etc. However, the usefulness of preoperative stenting in this group of patients has not been established. The effect

of this procedure on postoperative morbidity and mortality remains controversial with some trials founding no effect [11], whereas both increase and decrease in postoperative mortality and morbidity rate have been reported [12, 13]. In a recent meta-analysis no evidence was found of either a positive or adverse effect of preoperative biliary stenting, on the outcome of surgery in patients undergoing pancreaticoduodenectomy for pancreatic cancer [14].

The question of whether or not palliative endoscopic stenting improves or not the quality of life (QOL) in jaundiced patients with inoperable or unresectable biliary malignancies, is difficult to satisfactorily answer, because few studies have addressed this question. Huibregtse suggested that improvement in clinical jaundice, itching, dyspepsia, anorexia, level of activity and feeling of well-being could be anticipated by performing internal biliary drainage [15]. In a recent prospective study, 50 patients with inoperable or unresectable malignancies involving the biliary tree were included [16]. One month after endoscopic stenting, improvement in bilirubin level (<14 mg/dl) was associated with significant improvement in social life and mental health.

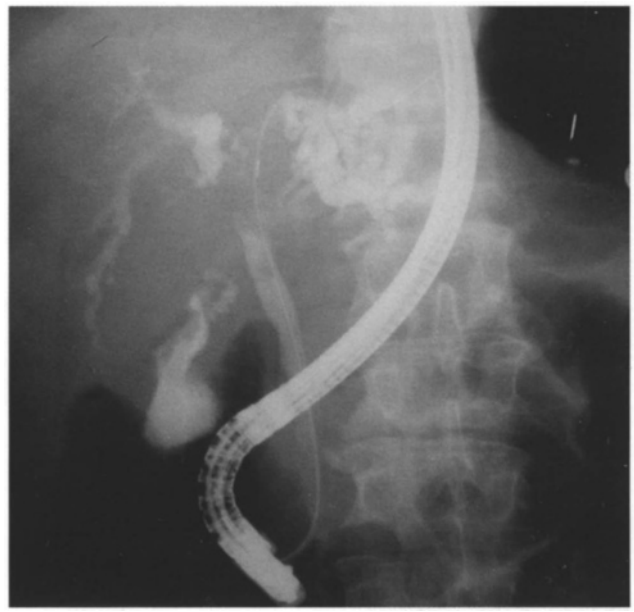

Fig. 21c.7. Hilar cholangiocarcinoma obstructing both the right and the left hepatic ducts. A guidewire has been placed at ERCP across the biliary stricture after deep common bile duct cannulation.

21c.23. Technical Aspects

21c.23.1. Technique of Biliary Stenting

A complete cholangiogram is mandatory to identify the location and extent of the stricture. To avoid forceful contrast injection during ERCP and a subsequent cholangitis, especially in hilar strictures involving the main hepatic confluence, a preliminary Magnetic Resonance Cholangiopancreatography (MRCP) could provide reliable imaging information. After deep selective cannulation of the common bile duct (CBD), usually with a double lumen sphincterotome, a guidewire is manipulated through the stricture and advanced into the obstructed bile ducts (fig. 21c.7). In patients without coagulation disorders, most endoscopists usually perform a sphincterotomy which facilitates the procedure of stent insertion, especially when more than one stent is to be used. Hydrophilic guidewires are preferable because of their higher efficacy in passing strictures, compared with Teflon coated guidewires [17]. After tissue sampling by brush cytology or specially designed endoluminal forceps, hydrostatic dilation of the stricture with bougies or dilating balloons is performed, in some cases where the strictures are very tight.

A plastic guiding catheter is then advanced over the guidewire and the plastic stent is pushed over the complex guidewire-guiding catheter, using another coaxial pushing catheter. Self-expandable metal stents are placed over the guide wire alone. When two plastic stents are to be inserted (e.g. hilar strictures), it is advisable to place the first into the left hepatic duct, facilitating the insertion of the second stent into the right hepatic duct system. When placing multiple metal stents, it is mandatory to first place all guide wires, in order to retain access to the opposite side once the first stent has been delivered [17].

The technical success rate of the procedure is about 90%, depending mainly on the experience of the endoscopist. After technically completing stenting of the bile ducts, a more than 80% clinical improvement of the patient should be expected. The most common causes of stent placement failure are tumors either obstructing the duodenum or actually involving the bile duct orifice.

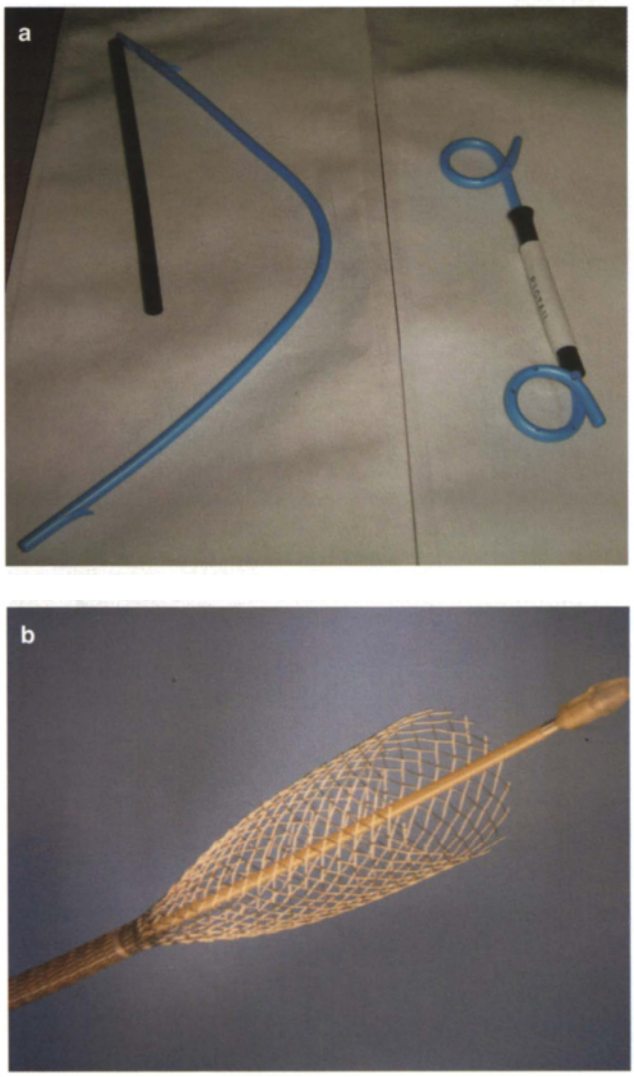

Fig. 21c.8. The two main types of biliary stents.
a. Polyethylene (plastic) stents. Several shapes of plastic biliary stents are available for use at ERCP (e.g., straight, pigtail etc).
b. Metal stent (Wallstent, Boston Scientific-Microvasive) partially released from its catheter.

21c.23.2. Types of Biliary Stents

There are two main types of biliary stents available, namely the plastic and the expandable metal ones (fig. 21c.8). Each type of biliary stent shares distinct technical characteristics as well as advantages and drawbacks. The endoscopist should be able to select the most suitable stent, according to the biliary stricture characteristics as well as the patient's expected survival.

21c.23.2.1. *Plastic Stents*

The first endoscopic insertion of a 7-French plastic stent was described by Soehendra and Reynders-Frederix in 1980 [18]. Today, plastic biliary stents still represent a valid therapeutic option for the palliative management of malignant biliary strictures (fig. 21c.9, 21c.10).

The main problem of plastic stents is their short patency rate due to clogging (fig. 21c.11), leading to recurrent jaundice and cholangiitis. Obstruction of plastic stents commences with the development of a biofilm from bile and bacteria on the luminal surface of the stent. Although several strategies have been attempted to prevent stent clogging, the problem remains unsolved [19-24]. Most of these methods while initially successful in vitro, have been proven unsuccessful in vivo.

Stent patency is also influenced by its luminal diameter. Stents of large diameter (10 or 11.5 French) remain patent for a significantly longer period of time compared with thinner stents (7 or 8.5 French) [25, 26], whereas no patency differences have been shown between the 11.5 French-stents and the 10-French-stents [27]. Therefore, 10-French-stents are the most appropriate and effective plastic stents for use in cases of malignant biliary obstruction. The length of plastic stents may vary from 5 cm to 15 cm and its choice depends on the stricture location. Whether stent exchange should be scheduled every 3 months or whenever the clinical or laboratory signs indicate stent clogging, increasing the risk of severe cholangitis is still a matter of debate. Although recent data are inconclusive [28], scheduled stent exchange is advisable in patients who live away from referral centers [29].

The migration of stent, proximally or distally, occurs approximately in 3 to 6% of the cases [30], causing stent dysfunction or damage to the duodenal wall. In most cases, the migrated stent can be removed endoscopically [17].

21c.23.2.2. *Metal Stents*

Self-expandable metal stents (SEMS) were developed to overcome the frequent short-term dysfunction of plastic stents, mainly due to their clogging. They have been used from 1989 and several types of them are available. The most common types of SEMS used in western countries include the Wallstent (braided stain-

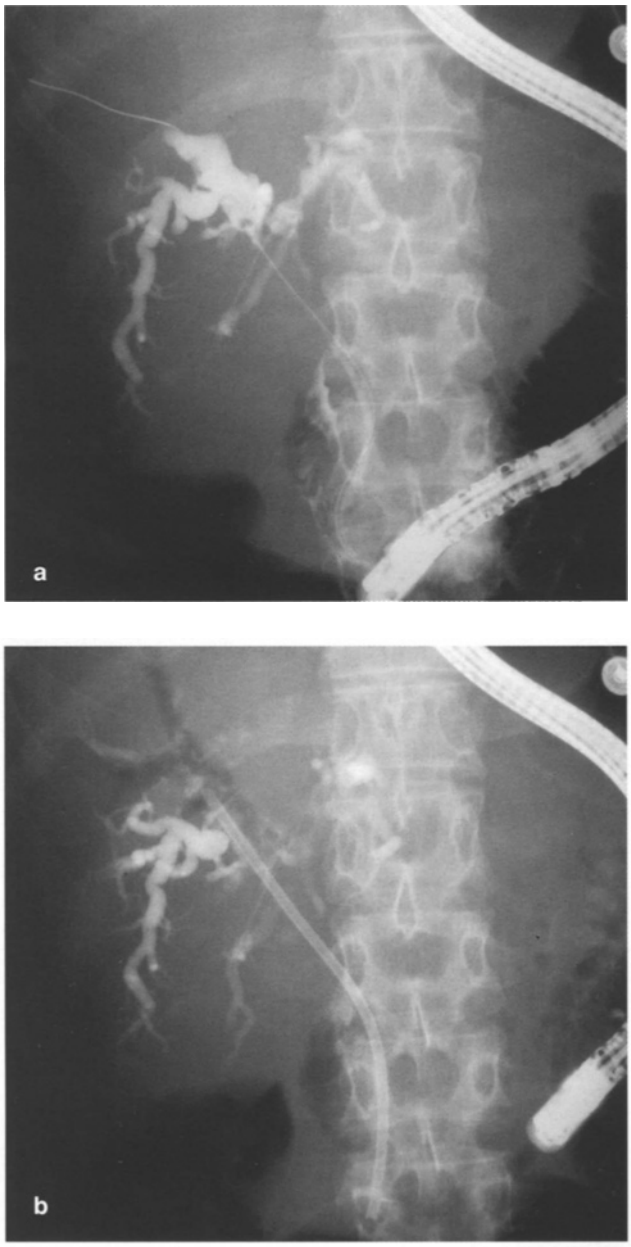

Fig. 21c.9.
a. Type III. Hilar cholangiocarcinoma (Bismuth classification).
b. A plastic 10-French stent has been placed at ERCP across the biliary stricture, draining the more dilated right hepatic duct system.

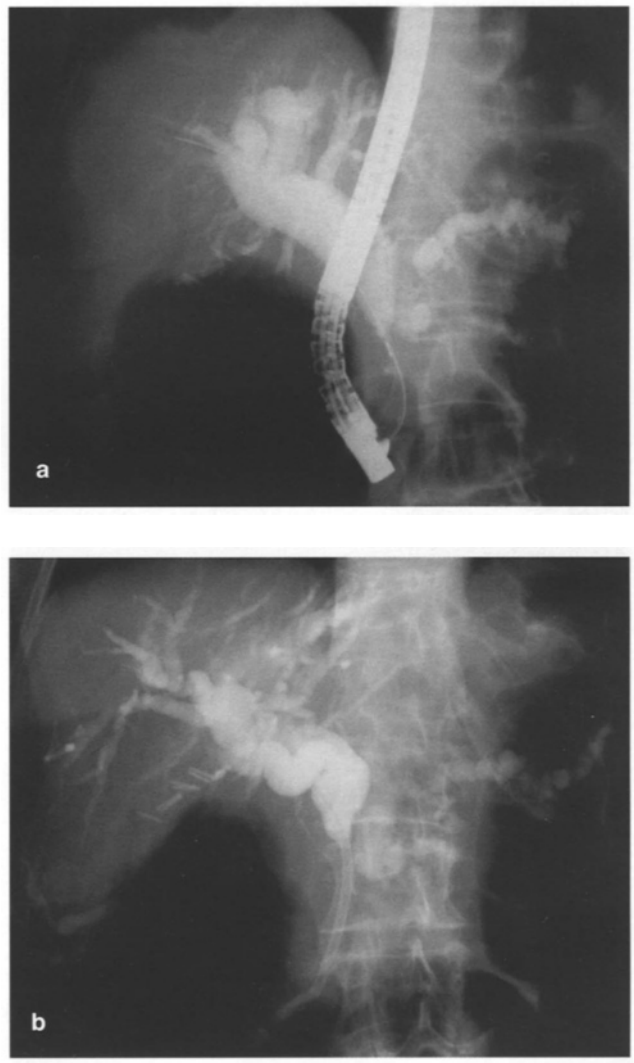

Fig. 21c.10.
a. Retrograde cholangiopancreatogram of a pancreatic head adenocarcinoma obstructing both the distal bile duct and the pancreatic duct («double duct sign»).
b. A plastic 10-French stent has been endoscopically introduced across the biliary stricture into the dilated part of the bile duct. Plastic stents may be used preoperatively, before radical surgery, but they also represent a valid therapeutic option for the palliative management of malignant biliary strictures, in patients with an expectancy of living no more than 6 months.

less steel) (Boston Scientific Natick, MA), the Diamond Ultraflex (braided Nitilol) (Boston Scientific, Natick, MA), the Zilver Stent (laser cut Nitilol) (Wilson Cook, Winston-Salem, NC) and the Memotherm (braided Nitilol) (Bard Inc, Billerica, MA) [17]. All these stents are assembled over a 7 to 8 French delivery catheter with radiopaque markers facilitating their precise release within the bile ducts. When fully expanded, SEMS reach a diameter of 30 French and they provide a patency rate significantly higher than that of plastic stents [31, 32] (fig. 21c.12, 21c.13). No significant differences concerning the patency and effectiveness were found

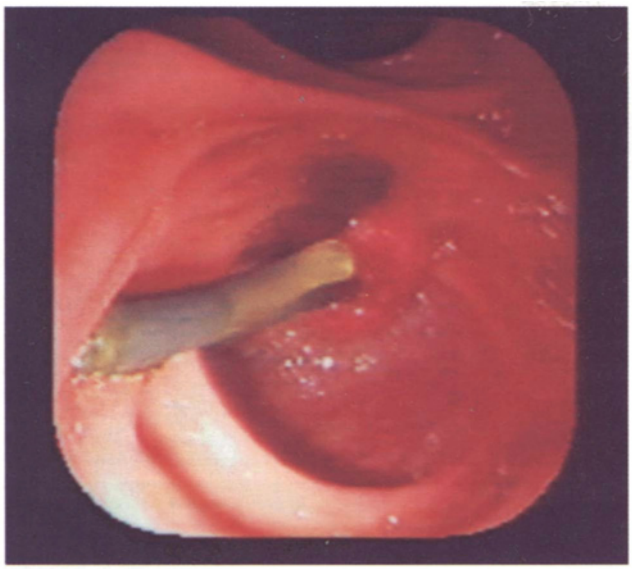

Fig. 21c.11. A plastic biliary stent occluded due to clogging, 3 months after its placement, in a patient with inoperable distal biliary malignancy.

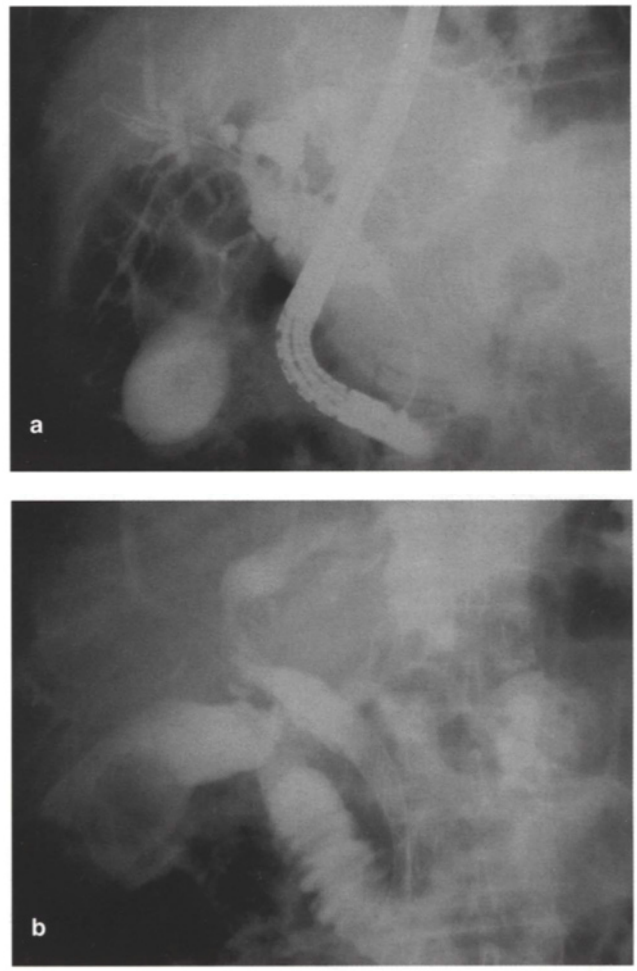

Fig. 21c.12.
a. Malignant bile duct stricture in a patient with unresectable cholangiocarcinoma.
b. A metal self-expandable stent has been placed across the same stricture for palliation of jaundice.

between the Wallstent and the Ultraflex Diamond stent at a mean follow-up of 228 days, in patients with distal malignant biliary obstruction [33].

SEMS may also be obstructed by neoplastic tissue ingrowth through their mesh in an overall occlusion rate of 22% to 33% [31, 33] (fig. 21c.14). Neoplastic tissue overgrowth together with bile and sludge may also contribute to stent occlussion. Due to their incorporation in the neoplastic tissue, uncovered SEMS can not usually be removed. To overcome SEMS dysfunction, caused by neoplastic tissue ingrowth or overgrowth, diathermic cleaning of neoplastic tissue may be tried endoscopically. Alternatively, one or more plastic stents, or a second metal stent may be inserted inside the initial one [34].

Covered SEMS have been recently developed for stent protection against tumor ingrowth. Although these stents have a lower occlusion rate (≈ 14%) [29] when compared to uncovered SEMS, they are also more prone to migration. Another disadvantage of covered SEMS is that they cannot be used in intrahepatic bile ducts. Using uncovered SEMS there is no risk of occluding the cystic, pancreatic or intrahepatic duct orifice [35].

21c.23.3. Choice of Appropriate Stent

When choosing the more appropriate stent for an individual patient with malignant biliary obstruction, stent properties and patient's clinical and anatomical individual characteristics should be taken into account. Plastic stents tend to be occluded on average after 3 or 4 months and have a substantial proportion of migration. On the other hand, SEMS are more expensive, their precise placement is more difficult, they also can be blocked, mainly by ingrowth of neoplastic tissue, and most of them are not removable.

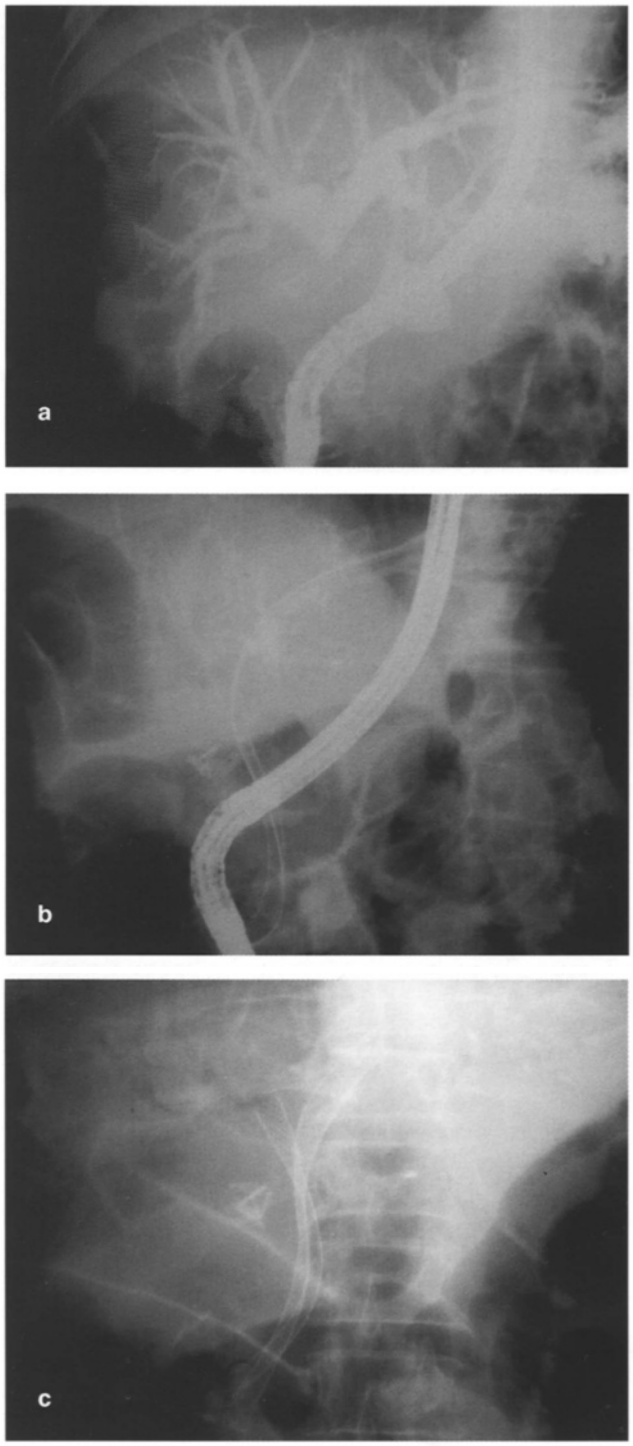

Fig. 21c.13.
a. Proximal malignant stricture of the common hepatic duct due to a locally advanced carcinoma of the gallbladder.
b. A Wallstent has been placed through the stricture into the right hepatic duct. Note a guidewire previously inserted into the left hepatic duct.
c. A second Wallstent has been placed into the left hepatic duct over the guidewire in the same patient.

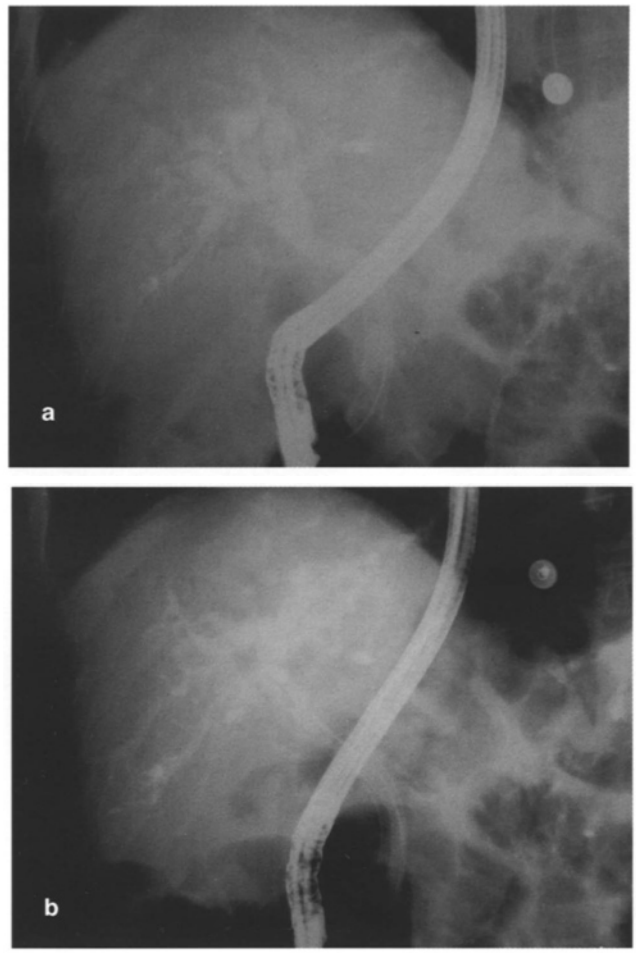

Fig. 21c.14.
a. An uncovered biliary Wallstent obstructed by neoplastic tissue ingrowth, 14 months after its placement, in a patient with a common bile duct cholangiocarcinoma.
b. To overcome the dysfunction of the obstructed metal stent, a second Wallstent has been inserted inside the initial one.

Plastic stents are equivalent to SEMS in relieving jaundice, have a similar percentage of complications related to placement and overall survival, whilst also contributing to a reduced hospital stay and reduced average number of repeated procedures due to stent dysfunction. As for the reduced overall cost percentage favors SEMS [32, 36-38]. However, it should be noted that use of a metal stent could be cost-effective only in patients surviving for more than 6 months [38]. Kaassis et al showed that the absence of liver metastases is a good indicator for favoring SEMS placement [39].

Conclusively, patients with inoperable or unresectable bile duct malignancies and an expected survival of more than 6 months should be managed either using SEMS or with a surgical bypass of the biliary stricture while the use of plastic stents should be reserved for patients with an expected survival of less than 6 months. Moreover, patients with inoperable or unresectable malignant tumors of the main hepatic ducts confluence should be managed either by the endoscopic or the percutaneous-transhepatic route techniques, aiming at complete drainage and avoiding sepsis [40, 41].

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CHAPTER 22

OPERATIONS OF THE BILIARY TRACT. TECHNICAL ASPECTS

J. Bramis, I.P. Gomatos, M.M. Konstandoulakis

22.1. Introduction

The dramatic improvement in hepatobiliary surgery over the past four decades has been one of the important advances in surgery. Increasing numbers of hepatobiliary operations are being performed by better-trained hepatobiliary surgeons, who have learned the techniques from their predecessors and made further improvements. These procedures are indicated for benign and malignant diseases of the common bile duct, hepatic ducts, liver and pancreas; are performed in the pediatric population; and may be life saving during the course of an emergency laparotomy for injury within the hepatoduodenal ligament or the liver hilum. Moreover, with the evolution of newer endoscopic, radiologic and minimally invasive techniques, the results obtained by the time-honored open approach are constantly challenged and at times improved. Hence, the hepatobiliary surgeon not only needs to be aware of the indications and contraindications, advantages and disadvantages and technical aspects of each single open approach, but he/she also needs to have detailed knowledge of the newer techniques, in order to be better prepared to individualize treatment for each patient.

22.2. Preoperative Evaluation

All patients undergoing biliary operations need to have a "road map" of the biliary tree before reconstruction is undertaken. Invasive procedures –such as endoscopic retrograde cholangiography or, more frequently, percutaneous transhepatic cholangiography– and noninvasive procedures –such as magnetic resonance cholangiography– are used to identify clearly the anatomy that may be difficult to delineate intraoperatively. Application of these imaging modalities depends on the suspicion of the location of the stricture/tumor; high (proximal) stenoses are best studied by percutaneous transhepatic cholangiography and low (distal) stenoses by endoscopic retrograde cholangiography. Patients with contrast allergies are evaluated by magnetic resonance cholangiography, although we prefer the greater resolution of the former tests. Other studies, such as computed tomography and ultrasonography, are complementary and useful for special situations such as clarifying tumor extension or documenting the presence of a biloma.

22.3. To Stent or Not to Stent

In cases where surgical intervention is not readily available as well as in patients not amenable to an operation, endoscopic biliary stenting has become a routine procedure in the management of malignant disease. Endoscopic techniques (ie, sphincterotomy, balloon dilatation, temporary stenting) have also been used in many patients with benign biliary obstruction due to postoperative strictures, primary sclerosing cholangitis, unremovable stones, and obstruction due to chronic pancreatitis, papillary stenosis, and the sump syndrome. Patients with obstruction at the liver hilum pose difficult management challenges for endoscopic, surgical, and radiological intervention. The problem is to achieve drainage of all obstructed ducts. Currently, it is technically possible to place two (or even three) conventional plastic stents during an endoscopic retrograde cholangiopancreatography, using multiple guidewires and adjunctive dilatation manoeuvres. Stents come in

two basic types: plastic stents with an outer diameter up to 12 Fr and self-expanding metal stents of outer diameter up to 30 Fr. Self-expanding metal stents are easily applied in case of malignant biliary obstruction and have complication and peri-procedural mortality rates similar to plastic stents. Given their cost, they can be recommended for patients expected to survive beyond six months. Biliary stents have also been placed to relieve benign biliary obstructions. The techniques of stent placement are identical to those involved in patients with malignant disease, except that self-expanding metal stents are used only in exceptional circumstances. All existing plastic biliary stents occlude eventually, so they should be used only on a temporary basis and be changed or removed after three to four months, as a routine practice.

The most common indications for transhepatic biliary drainage are a history of biliary-enteric anastomosis, significant duodenal or esophageal disease, prior failed endoscopic intervention, and, in some cases, high obstructions and biliary leaks. Contraindications include uncorrectable coagulopathy (INR greater than 1.5 and platelet count below 50,000) and ascites. The ideal entry site to the ducts is peripheral enough, thus allowing space for the drainage catheter above the obstruction and a smooth, direct course. The only firm indication for placement of an internal metallic stent is the palliation of an unresectable malignant biliary obstruction. Contraindications to stent placement include benign biliary obstruction, active cholangitis and biliary obstruction with concurrent bowel obstruction. Once the stent occludes, treatment options may be very limited. Surgical bypass may no longer be an option, because a surgically accessible duct above the stent may not be available.

22.4. General Principles - Exposure

Proper exposure is crucial to the safety, ease and efficiency of any operative procedure. This is a rule for hepatobiliary procedures too, because of the size and location of the liver and its proximity to major vascular structures. Surgeons have developed numerous abdominal and thoracic incisions to provide adequate access to the entire surface of the liver. A complete dissection of the liver's ligamentous attachments can provide an even better exposure by achieving increased mobility of the organ and the surrounding viscera. Most right-sided resections (segments V-VIII and trisegmentectomies) are best carried out with the patient in a slightly left-side decubitus position, with a bag or roll used to elevate the right side 15-30 degrees. Medial or left-sided resections (segments II-IV) and biliary procedures are usually most easily performed with the patient in the supine position. The surgeon can choose from a number of incisions according to the planned procedure. The upper midline incision is being favored by most surgeons for traumatic liver injuries [1] and by some surgeons for elective cases on the biliary tract and left lobe of the liver. This incision provides limited access to the right side of the liver, may provide limited exposure in obese patients or those with a short distance between the xiphoid and the umbilicus, and has a significant incidence of ventral herniation postoperatively [2]. Paramedian, Kocher and interneural right upper quadrant incisions are also being popular for some biliary procedures, but they have only limited usefulness when parenchymal liver transection is required because they allowed only limited exposure of the liver. The bilateral subcostal incision is the most popular incision among hepatobiliary surgeons [3, 4]. This incision is ideal for exposure of the supra-, retro- and infrahepatic vena cava, excellent exposure of the porta hepatis, and room for complete mobilization of the liver, if necessary.

Beginning any right upper quadrant procedure with an 8 to 10 cm incision approximately 3-4 cm (two fingerbreadths) inferior to the right costal margin, allows quick and easy assessment of the upper abdomen for the presence of metastases, the extent of local pathology, resectability and any abnormal anatomy. Then, the incision can be extended to the right and left subcostal regions, since is necessary for providing improved exposure. Alternatively, laparoscopy may allow a quick, minimally invasive assessment of peritoneal metastases and, combined with laparoscopic ultrasonography, can provide more details about the number and location of hepatic tumors and their resectability. A perpendicular midline extension to the xiphoid also improves mobilization of the thoracic and anterior abdominal walls, especially in patients with narrow costal angles. In this respect, excision of the xiphoid may prove useful. Once the initial celiotomy is completed, the ligamentum

teres hepatis (round ligament) within the falciform ligament can get ligated and divided. This permits a complete opening of the wound and placement of the surgeon's choice of self-retaining retractor.

Once the retractor is in place, the liver can be further mobilized by the division of the ligamentous attachments superiorly and posteriorly. These suspensory ligaments, including the left and right triangular ligaments and the anterior and posterior coronary ligaments, form a triangular or diamond-shaped area along the posterior aspect of the liver that communicates with the bare area of the liver and contains the retrohepatic inferior vena cava and hepatic veins. Careful division of these ligaments enables the elevation and rotation of the liver, so as to provide access to the posterior right lobe of the liver, the retrohepatic cava, the right adrenal gland and the right adrenal vein. Before any resection, the easy visualization and access to these structures provides a safe means of achieving sufficient vascular control. Access to and control of lesser hepatic veins, emptying into the retrohepatic inferior vena cava, can be achieved. However, hepatic rotation must be carefully performed, not only because the liver can be damaged with compression against any of the sharp retractor blades, but also because the liver might fracture, especially in patients with a friable or fatty liver.

22.5. Hilar Dissection

Extrahepatic dissection and control of the porta hepatis vessels and bile ducts facilitates resections of lesions situated in close apposition to hilar structures, as well as other major hepatic resections, by limiting bleeding and ensuring that the remaining liver is fully vascularized and has adequate biliary drainage. Furthermore, it creates all the conditions required to safely create a tension-free bilio-enteric anastomosis. In general, the bile duct occupies the anterior right porta hepatis.

Regarding the anatomy of the hilar region, at the inferior liver edge is a confluence of a transversely oriented left hepatic duct and a more axially oriented right hepatic duct, which descends alike the common hepatic duct to join the cystic duct at the inferior border of the triangle of Calot and become the common bile duct. Commonly, the proper hepatic artery approaches the liver in the left anterior porta hepatis and branches into right and left hepatic arteries, in the hepatic hilum. The right hepatic artery usually passes posterior to the common hepatic duct (85%) before entering the liver. The portal vein lies in the posterior porta hepatic and its primary bifurcation is at the inferior edge of segment IV. A significant variability exists in the arterial and biliary anatomy that needs to be anticipated and defined during dissection of the porta hepatis. A replaced right hepatic artery may arise from the superior mesenteric artery and ascend in the right posterior porta, behind the common hepatic duct and common bile duct in 20% of patients. With similar frequency, a replaced left hepatic artery may arise from the left gastric artery and cross the gastrohepatic ligament to enter the left liver outside the porta hepatis. Wide variation in the locations of sectoral bile ducts and their confluences may be seen; for example, major sectoral ducts of the right liver may join the left hepatic duct peripheral to the primary bifurcation or may descend in the porta to join the common hepatic duct or common bile duct distally.

Hilar dissection for liver resection generally begins with cholecystectomy and exposure of the triangle of Calot to facilitate early identification of the common hepatic duct-common bile duct junction. Further incision across the peritoneum of the porta hepatic permits the progressive exposure and isolation of the primary branches of the hepatic artery and hepatic duct at the hilum of the liver. In cases, exposure of the hilar structures is improved by the incision of Glisson's capsule and elevation of segment IV (quadrate lobe). This dissection within the hilar plate can be carried out peripherally to gain control of segmental vascular and biliary branches, since it is necessary for the anticipated parenchymal resection. Lobar or sectoral divisions of the portal triads, enveloped in a sheath of fibrous tissue originating from Glisson's capsule, can be defined during parenhcymal dissection and ligated en masse. Care is exercised during dissection to avoid injury of the hepatic ducts by diathermy and of the right hepatic artery, which might cross in front of the common hepatic duct. Exposure and control of portal vein branches may be easier after bile duct and hepatic artery branch ligation and division. Additionally, portal vein isolation is facilitated by full mobilization of the liver and rotation of the liver to the left, in order to better expose the right posterior aspect of the porta hepatis.

When a right lobectomy is indicated, the goal of hi-

lar dissection is to secure and divide the right hepatic artery, right portal vein and right hepatic duct, ensuring at the same time the normal blood flow to and bile drainage from the left lobe of the liver. In the middle of the inferior surface of the right lobe of the liver, situated between the anterior and the posterior segment of the right lobe, is an upside down V-shaped inlet that allows the right hilar vessels to enter the liver. This is where the dissection begins. Removing the visceral peritoneum from the right side of the gallbladder fossa posteriorly around the porta hepatis exposes the right side of the hilar vessels. The areolar tissue is filled with nerves and vascular lymphatics, which are best ligated or electrocoagulated. Approaching the hilum of the liver, the hepatic artery bifurcates first, followed by the portal vein and then the hepatic duct. Usually, these structures are divided in that same order: artery, vein, and duct. The right hepatic artery or several branches of it are easily isolated. In continuity, the arteries are double ligated on the patient side and single ligated on the specimen side with 2-0 silk ligatures. When cutting a vessel between ties, we leave 75% of the vessel on the patient side and 25% on the specimen side.

Occasionally, liver resection is part of the management of a proximal bile duct tumor. Exposure of these vascular structures can be difficult, because of the close proximity of the hilar biliary tumor and the hepatic artery, the portal vein and their branches (fig. 22.1). Circumferential dissection and division of the common bile duct distally allows reflection of the anterior of the CBD and CHD with adjacent neural and lymphatic tissues to skeletonize the hepatic artery and portal vein cephalad towards the hilum of the liver [5].

Anatomic resections are significantly distorted in cases of liver or biliary reoperations or massive hepatobiliary lesions. Significant variability of the anatomy of the porta hepatis can arise if the liver has undergone sectoral or lobar atrophy and/or hypertrophy. In patients with adhesions and scarring from previous surgery in the porta hepatis, dissection of the hepatoduodenal ligament can be tedious. Careful division of the adhesions between the hepatic flexure of the colon and the liver, mobilization of the duodenum and intermittent palpation of the region of the porta hepatis to identify hepatic artery pulses can facilitate approaching the hepatoduodenal ligament from the right, in anticipation of exposing the common bile duct as an initial landmark.

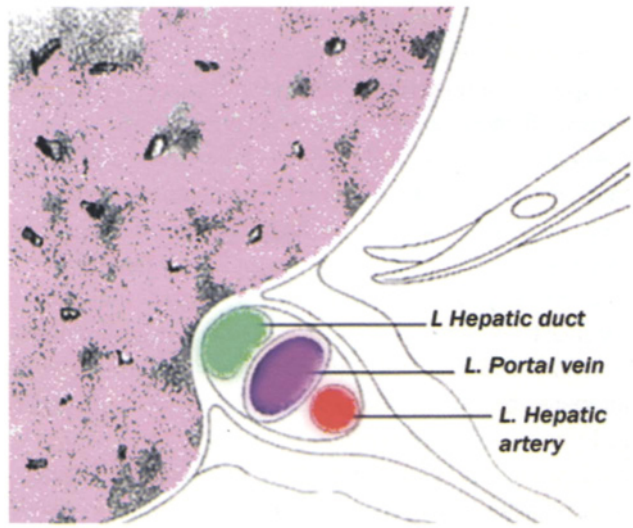

Fig. 22.1. Hilar dissection.

22.6. Biliary Tract Reconstruction

There remains considerable disparity in the reported cases with regard to the incidence of biliary complications after biliary tract surgery. Many technical issues, such as the method of dissection, selection of suture and mode, and the use of stenting tube, are still under discussion. Duct-to-duct has the following advantages over Roux-en-Y choledochojejunostomy:

1) no need for intestinal manipulation, since it serves as an anatomic barrier against the reflux of enteric contents into the biliary tract, and it may theoretically decrease the risk of ascending cholangitis; the morbidity is also reduced even when early anastomotic leakage occurs;
2) it is technically faster and easier than Roux-en-Y and
3) the physiologic bilio-enteric continuity enables good endoscopic access postoperatively.

In cases of liver transplantation, the afore mentioned reasons support the superiority of duct-to-duct reconstruction. However, in cases of benign or malignant bile duct lesions, when segmental resection of the biliary tract is required, situation differs a little.

Sixty percent of the arterial supply for the bile duct comes from the caudal side through periduodenal arteries, 38% from the cranial side and only 2% from the hepatic artery itself. The 3 o'clock, the 9 o'clock, and the retroportal arteries give rise to multiple arteriolar branches, which form a free anastomosis within the wall of the bile duct. Preservation of periductal microcirculation in the hepatic duct and excellent hepatic artery reconstruction may be a key factor for successful duct-to-duct anastomosis.

Hilar dissection is carefully performed to preserve adequate blood supply of the hepitocholedochal arterial plexus. The 2 distinct intramural arteries (3 and 9 o'clock arteries) and the bile duct is divided above the hilar bifurcation for highly located biliary stenoses. After completion of vascular anastomosis, biliary anastomosis is performed with 6-0 polydioxanone absorbable monofilament suture. The anastomosis procedure starts at the posterior wall with interrupted or continuous suture, after which the anterior anastomosis is completed. In some cases, a 4 French polyethylene tube is inserted for anastomotic decompression (fig. 22.2).

22.7. Parenchymal liver transection

In patients with malignant hilar lesions extending directly to the liver parenchyma, a final phase of liver resection with parenchymal division is often required

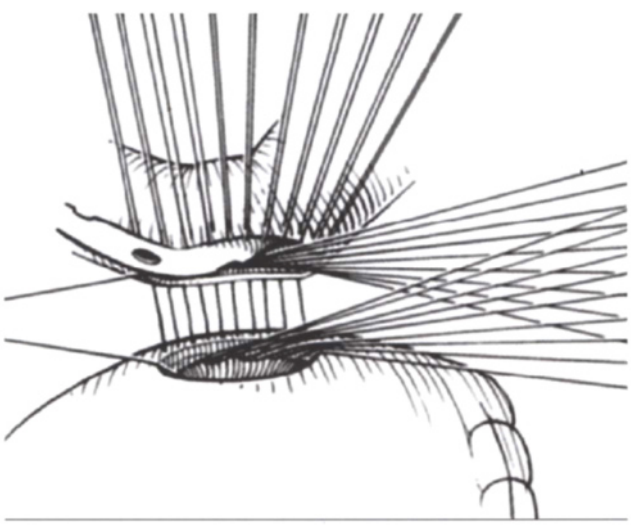

Fig. 22.2. Hepaticojejunostomy technique. Piercing the sutures.

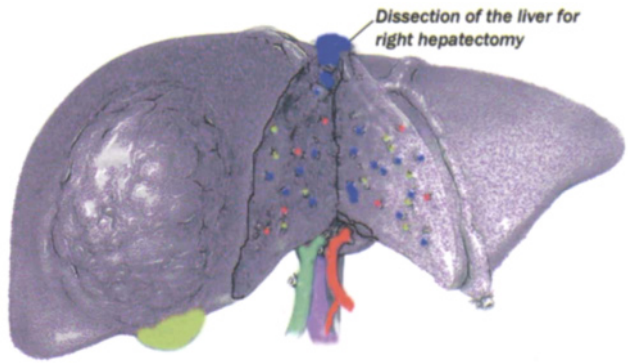

Fig. 22.3. Parenchyma liver transection.

(fig. 22.3). There are several techniques that have been developed to facilitate this stage of the procedure. Because of the extensive vascular and bile duct network within the liver, the goal of parenchymal division is to expediently dissect and ligate hepatic vessels and bile ducts, in order to complete the transection having minimal blood loss. Portal venous tributaries are enveloped by Glisson's capsule, making them somewhat resistant to traumatic injury during the parenchymal transection. On the contrary, hepatic venous branches may be thin walled and can be more easily avulsed during manipulation. The specific techniques used to dissect hepatic tissue away from vessels and bile ducts, depend on the surgeon's preference and experience and on the technology available within the surgeon's hospital setting. Temporary hepatic inflow occlusion (Pringle clamping), selective vascular isolation or complete vascular isolation are selectively used to lessen blood loss during parenchymal division.

Finger fracture (digitoclasia) parenchymal division has been the most widely used and is perhaps the simplest technique for parenchymal division in liver resection [6]. This technique is performed by initially incising the liver capsule along the planned resection plane, usually with electrocautery. After the liver capsule has been incised, the dissection is initiated with a blunt instrument (e.g., scissor tip or blunt clamp) by working through the parenchymal tissue. Vessels and bile ducts can be individually identified, encircled and either suture ligated or divided with surgical clips. Many surgeons prefer to suture ligate ducts and larger vessels on the remnant liver side of the division and use surgical clips only on the specimen side, because clips may be-

come dislodged during liver manipulation as the resection proceeds. Finger fracture techniques can also be combined with other methods of parenchymal division. The advantages of the finger fracture dissection technique are its simplicity and speed. This technique does not require sophisticated instrumentation that may be unavailable in some operative centers.

The ultrasonic dissector (CUSA), the Hydrojet, the dissecting sealer (Tissue-Link) and, the more recently developed, saline-linked cautery [7] represent the more popular advances from the classic finger fracture or the clamp crushing technique [8]. None of these instruments alone adequately addresses both precise parenchymal division and complete hemostasis-biliostasis. The specific role of these emerging technologies in liver resection and their cost-effectiveness have not yet been fully defined, but remain an area of active investigation at many centers.

In our department, liver parenchymal dissection is performed by a closed Metzenbaum scissors. Each time less than 1 cm of liver parenchyma is compressed by the scissors. A back and fourth motion of the scissors, while squeezing the tissue, disrupts normal liver easily and sharply, skeletonizing vascular and ductal structures. All minor structures (< 5mm) are ligated using metal clips. Major intrahepatic vascular or ductal structures (≥ 5mm) are carefully dissected and exposed in order to optimize secure ligation and also prevent devascularization of the surrounding liver tissue. Minor bleeders or biliary radical orifices are sutured with 6-0 PDS or suture ligated with 4-0 silk whenever possible.

22.8. Operations of the Biliary Tract

22.8.1. Hepaticojejunostomy - Indications

Hepaticojejunostomy is a common procedure, representing a time-honored and still enduring procedure in the day-to-day general surgical practice of most hepatobiliary surgeons. Currently, hepaticojejunostomy is being used more frequently with the advent of laparoscopic cholecystectomy and its higher rate of bile duct injuries. Other significantly, though less common indications for hepaticojejunostomy include biliary fibrosis produced by chronic pancreatitis, penetrating trauma of the porta hepatis, previous bilio-enteric operations with subsequent stricture formation, choledochal cyst resections and other causes of iatrogenic biliary trauma, such as gastrectomy, pancreatic and hepatic resections, portal decompressive procedures and liver transplantation. Malignant conditions such as cholangiocarcinomas and carcinomas of the gallbladder infiltrating the common bile duct or hepatic ducts may also be indications for performing hepaticojejunostomy as the final step of the resective procedure or as a palliative attempt to relieve jaundice in cases of unresectability. Increased success rates from centers of excellence base their improved results over the last decade on sound knowledge of biliary anatomy, meticulous surgical technique and intraoperative flexibility to adapt to the anatomic variants found. Drainage tubes, stents, interventional radiologic techniques and improved postoperative care have also played a role in the improved outcomes.

22.8.2. Hepaticojejunostomy - Operative Principles

In patients with malignancy, the cystic duct is doubly ligated proximally and the gallbladder is retracted laterally. The hepatic duct confluence is seen anteriorly, in front of the retractor, and is minimally obscured by segment IV of the liver. Adequate exposure is critical for creating a secure anastomosis; the usual lymphadenectomy performed with cancer resections aids in the exposure of the bile duct. The intraoperative exploration includes the following principal steps: sonography of the liver, perihilar palpation to confirm the tumor localization, exploration of the lymph nodes and exploration of the hepatic artery and portal vein. Distant metastases, including liver metastases, positive lymph nodes (frozen section) beyond the common hepatic artery and involvement of the hepatic artery or the portal vein, exceeding the extrahepatic portion of the liver lobe to be left, are generally considered contraindications against resection.

For laparoscopic bile duct injuries, the surgeon should look for the stenosing clip or ligature in the same region of the confluence; if the patient has a transhepatic stent, this will help in the localization of this structure. Otherwise, some dilatation of the bile ducts is applied, which makes the common bile duct more noticeable. In doubtful cases, the insertion of a fine needle (18G-20G) into the dilated structure will con-

firm the suspicion if bile is retrieved. Some surgeons often use transhepatic stents. Although it is not a routine, it may help with intraoperative identification of the biliary stump. Other benefits can be the conduction of contrast studies in the postoperative period, for assessing the patency of the anastomosis and the performance of perfusion/manometric studies for assisting in the outpatient management of these patients. If the anastomosis is going to be stented (in case when postoperative stenosis is highly probable), a Bakes dilator is introduced into the bile ducts, passed bluntly through the liver substance and retrieved on the anterior surface of the liver. A threaded guidewire is then attached to it and drawn through the biliary tree; a tubular stent is then passed into biliary anastomosis. Plastic stents are always preferred for benign bile duct strictures.

Incision of the hilar plate is critical for a successful operation. The density of the vasculobiliary sheath (as the elements of the portal triad are exiting the liver) increases at the level of the main pedicles, forming a surrounding structure anteriorly and posteriorly. To expose the hepatic ducts (especially the left hepatic duct), the hilar plate is incised and elevated, giving the surgeon access to the entire anterior portion of the hepatic ducts. On mobilization of the right hepatic artery, dissection into the space between the right hepatic duct and right hepatic artery beyond the proposed point of division of the right hepatic duct is not made, in order to protect blood supply to the right hepatic duct arising from the right hepatic artery (although this is not true for the majority of cases). Active arterial bleeding from the hilar plate is controlled using 6-0 prolene sutures.

Once the resected specimen has been removed from the operative field, the chosen limb of jejunum is passed in a retrocolic fashion, in order to have access to the base of the liver. We usually select the most proximal jejunal loop that lies without tension in the right upper quadrant and tailor it to obtain a 50 cm Roux-limb (fig. 22.4, 22.5, 22.6). After the jejunum is transected with staples, passage through the transverse mesocolon is necessary. This manoeuvre is greatly facilitated by lifting the transverse colon as a whole and transilluminating its mesentery from behind. This area (typically to the right of the middle colic vessels) is consistently free of vascular structures and an aperture can be created in the mesocolon for jejunal passage. The mesoco-

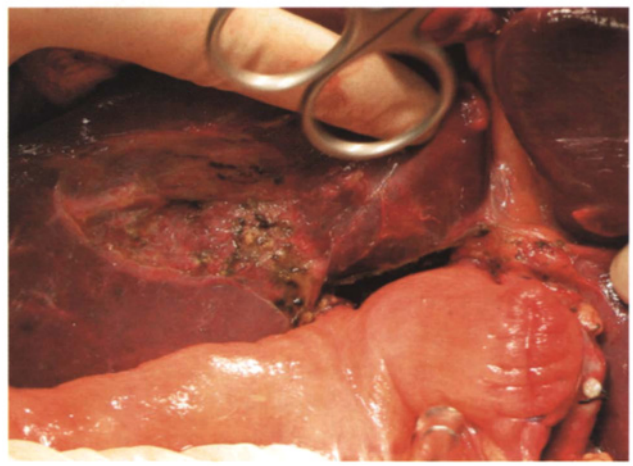

Fig. 22.4. Anterior view of two separate hepaticojejunostomies (left and right hepatic duct following resection for Klatskin tumor.

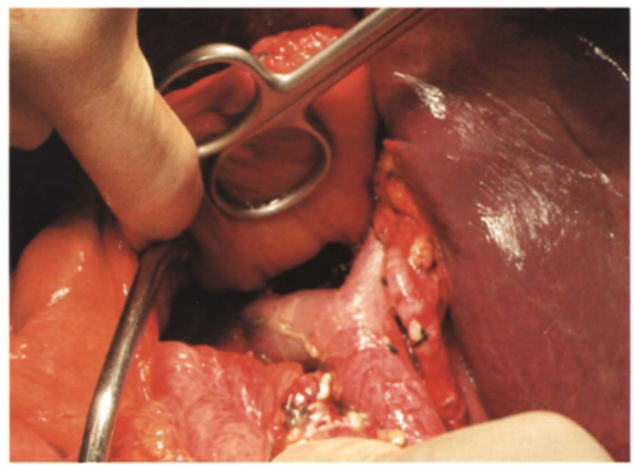

Fig. 22.5. Anterior view of two separate hepaticojejunostomies.

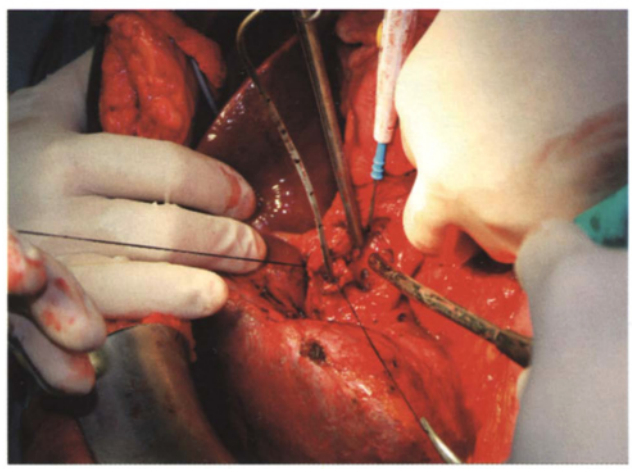

Fig. 22.6. Right liver atrophy in a patient with concomitant right hepatic artery and right hepatic duct flush ligation. Selective canullation of the right and left hepatic duct

lon is closed around the jejunum with interrupted stitches of 3-0 silk. We prefer retrocolic reconstructions because they do not add additional intestinal length, do not create open spaces for potential hernias, and the jejunal mesentery will not be exposed to tension from a distended colon. The defect left, after the resection at the confluence of the bile ducts, can be expanded bilaterally with more emphasis to the left to create a wider side-to-side anastomosis with the jejunum. The jejunum is opened to such a width that will eventually mirror the final defect in the bile duct. Therefore, the bowel incision is typically smaller for producing a better match, since it enlarges as the anastomosis is created. Bleeding from the cut edge of the jejunal opening is controlled by diathermy that is set at lower power than usual.

Of course, when dealing with malignant tumors, it is sometimes necessary to resect the confluence of the bile ducts. The resection margins of the bile ducts are always investigated by frozen section. If the hepatic ducts are separated, it is wise to approximate them for increasing the width of the actual anastomosis.

The key to successful outcome remains the same: a tension-free, meticulous mucosa-to-mucosa anastomosis. The anastomosis is started by placing the corner stitch first at the left side of the duct. The technique described previously by Blumgart [9] is used with interrupted absorbable suture, size 4-0 or 5-0. Half of the anterior row is constructed first, taking only the initial bite on the bile duct side. The sutures (with needles still attached) are placed under mild tension with a spring keeper. This manoeuvre lifts the duct and facilitates the construction of the posterior row anastomosis. When the time comes to complete the anastomosis, intercalating suture colors in the incomplete anterior row will significantly aid. The posterior row is started on the left side. Tissue bites include the jejunal mucosa and several millimeters of bile duct with the sutures tagged. Once the posterior row of sutures is placed, they are tied starting on the patient's right side with the knots inside the anastomosis, to enhance the mucosal approximation. After the back row is secured, the stent, if indicated, is slid into the jejunal limb [10]. The last half of the anterior row sutures is started by incorporating the jejunal mucosa. The sutures are tied.

For acutely damaged ducts, anastomosis to the bowel is usually made with a single layer of 6-0 absorbable sutures that are tied extraluminally. For the corner and penultimate stitches, we prefer 6-0 prolene with the knots tied outside the lumen of the anastomosis. If the lumen is small (< 5 mm), all the other posterior-row sutures are completed using 6-0 prolene double-needle sutures with the knots outside. Otherwise, absorbable 6-0 PDS sutures are used with the knots placed inside the lumen, since it is difficult to obtain close approximation of the ductal and jejunal wall in a large duct with the knots tied outside. The distance between sutures is about 1 mm. In anastomoses smaller than 1 cm, a T-tube or stent should be placed across the anastomosis, in an attempt to prevent late stricture formation.

Some surgeons advocate the placement of several 3-0 silk stitches between the jejunal limb (seromuscular) and the capsule of the liver, to help relieve the tension on the anastomosis. However, this is not a common practice in our department. Care must always be taken to completely occlude the defect in the mesocolon, for avoiding internal hernias. When the right and left hepatic ducts cannot be brought together, as is the case of patients with resected hilar cholangiocarcinoma, two separate anastomoses are required. Alternatively, in cases where there are two hepatic duct openings adjacent to each other, they are sutured to form a single hole. The septum between the reconstituted ducts is divided vertically and the gap is sutured using 6-0 PDS. Simply joining the medial wall creates tension and narrowing of the lumen. The newly created septum, when divided vertically and sutured transversely, creates a large opening. The intestinal anastomosis is then completed in a standard end-to-side or side-to-side (sutured or stapled) fashion. A soft silastic drain is placed in the subhepatic space, close to the anastomosis, and the abdomen is closed after irrigation.

22.9. Choledochoduodenostomy - Indications

Choledochoduodenostomy is indicated for choledocholithiasis, ampullary stenosis, chronic pancreatitis (once the possibility of a resectable malignant obstruction is excluded), unresectable malignant neoplasms causing biliary obstruction, operative injuries to the biliary tree and chronically dilated bile ducts. In cases of choledocholithiasis, choledochoduodenostomy is used to clear

bile ducts, particularly if multiple stones are present, mainly for allowing the passage of any retained calculi. In patients with impacted stones at or near the ampulla or an ampullary stenosis the intraoperative cholangiogram shows little or no flow of dye into the duodenum. However, it is difficult to determine with certainty whether an impacted stone or just ampullary stenosis is the case. Persistence in removing the impacted stone or passing the exploring instrument or even the choledochoscope into the intrapancreatic portion of the common bile duct carries a high risk of producing a "false passage", perforating the wall of the duodenum or common bile duct or even traumatizing the pancreas, leading to severe pancreatitis. Under these circumstances and in the presence of a dilated common bile duct (more than 15 mm in diameter), choledochoduodenostomy is a definitive, safe and prompt solution.

If injury of the distal common bile duct is not discovered at the time it occurs, it becomes unsuitable for use in the reconstruction [11]. Therefore, a choledochoduodenostomy cannot be done. Reconstruction must be performed using the common hepatic duct, often at the confluence of the two main hepatic ducts, suturing it to a Roux-limb of jejunum. However, choledochoduodenostomy may occasionally be useful in the surgical treatment of injuries to the common bile duct. Specifically, if the injury is detected at the time of surgery, is located in the distal common bile duct and the common bile duct happens to be dilated to 16 mm or more, then the injury may be amenable to repair with a choledochoduodenostomy. Moreover, if the common bile duct was completely ligated at operation, resulting in a dilated common bile duct (>15 mm in diameter), the anatomy may be suitable for reconstruction by a choledochoduodenostomy with the expectations for very good long-term results.

22.9.1. Choledochoduodenostomy - Technical Aspects

Under general endotracheal anesthesia, a right subcostal incision is made (although an upper midline incision is also reasonable). The duodenum, the supraduodenal portion of the common bile duct and the gallbladder are carefully inspected, palpated, and scrutinized for abnormalities. The diameter of the common bile duct is measured, to be at least 16 mm to allow construction of a choledochoduodenostomy with an opening no smaller than 14 mm in diameter.

Initially, the gallbladder is removed. Because the first and fourth portions of the duodenum are fixed, in most patients it is necessary to mobilize the second and third portions for facilitating cephalad displacement of the duodenum, which allows the second portion to reach the anterior surface of the distal common bile duct, thus attaining a tension-free anastomosis. Kocherization of the duodenum is performed by an incision along the lateral border of the second portion of the duodenum, elevation of the posterior aspect of the duodenum and head of the pancreas, by blunt dissection and partially exposition of the anterior surface of the inferior vena cava.

In general, the incision in the duodenum must be placed at or near the junction between the first and second portions and slightly posterior; the incision in the common bile duct is made as distal as possible. The surgeon, then, selects the type of anastomosis: end-to-side or side-to-side. Due to the reluctance to completely transect the common bile duct to do an end-to-side choledochoduodenostomy, most surgeons favor a side-to-side anastomosis, a procedure which requires more extensive mobilization of the duodenum. Choledochoduodenostomy must be constructed with precise suturing (under optical magnification) using double-armed 5-0 polypropylene suture with small atraumatic needles in a continuous running fashion, with the same technique and care used for anastomosing small arteries and veins.

For an *end-to-side choledochoduodenostomy,* the common bile duct is transected as distal as possible, for attaining an anastomosis without tension. Two stay sutures are placed at each corner of the anastomosis. The sutures are gently pulled to temporarily approximate the incisions made in the side of the duodenum and the end of the transected common bile duct. Careful scrutiny at this point is important to check whether their size matches and approximation occurs without tension or twisting. The running suture is then initiated, with the first suture placed in the posterior lip of the anastomosis, exactly in the middle of each luminal opening. This continuous technique is performed from inside the lumen, placing each suture at a 90° angle to the tissue, first running one end toward its respective corner, then running the other end toward the oppo-

site corner, both of them finishing at the point where the stay sutures had been previously placed. To facilitate optimal vision of the posterior lip of the anastomosis, each loop of the running suture is left loose. Once each suture has reached its respective corner, the needles are brought outside the lumen and the loose loops of the running suture are tightened by gently pulling simultaneously at each corner, under direct vision, with caution to avoid excessive tightening which constricts the anastomosis. To avoid this occurrence, the two stay sutures placed in each corner are tied at this point. The anterior lip of the anastomosis is then completed by running each end of the suture, again leaving the loops loose to facilitate the placement of each successive stitch, again meeting in the middle of the anastomosis. The ends of the anterior suture are tightened using a fine nerve hook and tied with at least eight knots.

For a *side-to-side choledochoduodenostomy,* the incision in the common bile duct must be planned carefully, to facilitate accurate apposition with the duodenum. Depending on the relationship between the two organs, the incision can be transverse or oblique. This type of anastomosis is constructed in a similar fashion as the one described for the end-to-side choledochoduodenostomy, with the difference that the stay sutures are positioned in the superior and inferior corner of the scheduled anastomosis. A single layer of polypropylene suture is sufficient to create a waterproof anastomosis; of course, it is possible to use two layers as well. The anastomosis should be carefully examined for bile leakage, the completed anastomosis should have a diameter of at least 14 mm, while a T-tube or stent is not needed. It is advisable to drain the area in proximity to the anastomosis with one or two soft drains connected to a closed vacuum suction system. In the rare occasions in which jaundice persists for five or more days after the operation, an upper gastrointestinal series is the simplest test to assess the patency and continence of the constructed anastomosis.

22.10. Operative Bile Duct Drainage Via Segment III – "The Round Ligament Approach"

The round ligament approach is indicated as palliative relief of obstructive jaundice, usually caused by a neoplastic process involving the proximal hepatic duct or its bifurcation, not amenable by PTC or ERCP. It is contraindicated in patients with extensive left lobar metastases, malignant involvement of the second order left hepatic ducts, left lobar atrophy due to left hepatic artery or portal vein occlusion and infection of the obstructed right hepatic biliary tree [12].

As stated by Couinaud, even when the connection between the right duct and left duct is interrupted, simple diversion of the left duct provides sufficient drainage. An intraoperative cholangiogram, cannulating the exposed left duct, is important to define the anatomical ductal pattern and ensure that the biliary-enteric anastomosis will drain the entire left lobe of the liver. The goal of the operation is to decompress the biliary tree by constructing a biliary-enteric anastomosis between a defunctionalized jejunal loop and the left hepatic duct proximal to its junction with the right main duct and distal to its bifurcation to liver segments II and III. The operation begins with dissection and exposure of the biliary duct, by partially resecting the left lobe of the liver, moves on to construction of a defunctionalized jejunal loop (e.g. a Roux-en-Y jejunal loop) and ends with construction of the biliary-enteric anastomosis.

The round ligament approach was first described in 1957 by Soupault and Couinaud [13] who proposed a transcissural approach to identify the segment III duct, by following the round ligament into the recessus of Rex in the umbilical fissure. The left portal vein divides into the umbilical portion (which continues into the round ligament) and the left branch. The left branch runs in an anteroinferior plane and does not need to be dissected. Because the entire operation is conducted proximal to the main hepatic duct, the liver hilus is left intact.

In adopting the round ligament approach, it is necessary to open the umbilical fissure to a depth usually of 5 to 6 cm for exposing the segment III duct. In some patients the space to fashion an anastomosis is considerably constrained in the recess of the umbilical fissure. In recognition of this problem, we recommended an end-to-side rather than a side-to-side anastomosis. However, a side-to-side anastomosis should be advocated in cases where bile duct wall blood perfusion is expected to be compromised.

The operation is performed through a bilateral subcostal incision. After entering in the abdominal cavity,

the inferior surface of the liver and the hilar region are exposed. This manoeuvre is facilitated by dissecting the falciform ligament to the level of the vena cava and bringing the liver forward by placing one or two laparotomy pads between the liver and the diaphragm. Intraoperative Doppler ultrasonography is used to identify the dilated segment III duct and to estimate its depth within the liver parenchyma. Then, the round ligament is retracted downwards and to the right, exposing the umbilical fissure between segments III and IV.

Using the Metzenbaum scissors or the Cavitron Ultrasound Aspirator (CUSA), the fissure is extended to the left of the falciform ligament and the liver split in a relatively avascular parenchymal plane. The left margin of the round ligament is freed down to the recessus of Rex, where the segment III branch of the portal vein is easily identified.

Alternatively, the thin layer of liver parenchyma lying anterior to the round ligament and joining segment IV to segment III is transected with electrocautery with a right-angle clamp placed in the space between the round ligament and liver parenchyma. Parenchymal bleeding will rarely need to be controlled with mattress sutures.

The segment III bile duct is identified, often lying in a vertical plane posterosuperior to the vein. Using ultrasonography, the course of the duct is followed into segment III for a distance of 4 to 5 cm. The CUSA is used to core out the liver parenchyma, which overlies and surrounds the bile duct. This creates a saucer-shaped concavity, with walls that slope down gradually from the liver capsule to the edge of the bile duct. The bile duct lies superficial to the vascular structures, at a depth of 2 to 3 cm from the liver capsule, and thus the vascular pedicle to segment III is not compromised by this manoeuvre. This creates an adequate space to fashion a tension-free and long cholangiojejunostomy.

If the CUSA is not available, the round ligament is dissected from the liver by traction anteriorly and superiorly with a clamp, dividing the portal vein branches that run between the ligament and liver segment III. These branches vary in number and caliber. We prefer to suture ligate the branches at their portal aspect and use a clip or a simple ligature for the parenchymal aspect. This procedure separates the round ligament from the liver parenchyma and exposes the vasculobiliary sheath between the hilum and the recessus of Rex. When the bile duct is markedly dilated, it is easily recognizable under this sheath of connective tissue. If the sheath is particularly thick, it must be sharply divided with the scissors, so the left duct can be visualized. Localization of the bile duct can be confirmed by puncture with a small-gauge needle.

Intraoperative cholangiography by direct cannulation of the exposed duct can be performed to assess the anatomy.

The duct must be dissected for a length of one to 1.5 cm. This dissection should not be circumferential, for preventing devascularization of the duct and avoid injury to other bile ducts draining segments IV or II. The anatomy of these ducts is extremely variable and, remaining in an anterior plane, minimizes the risk of injury, particularly because the duct's anterior surface will be used for the biliary-enteric anastomosis. Once the left duct has been exposed, a defunctionalized jejunal loop is constructed in a Roux-en-Y fashion, approximately 40 to 50 cm long. The defunctionalized jejunal loop is brought to the liver hilum through a retrocolic tunnel. After two stay sutures are placed on the anterior wall of the exposed bile duct, a longitudinal incision of about one cm in length is performed. A mirror-image longitudinal incision is created on the antimesenteric side of the jejunal loop. All of the posterior sutures are placed and tied, with the knot left inside the lumen. The anterior sutures are placed and tied with the knots on the outside. Monofilament reabsorbable suture is preferred. Two drains are placed in the perianastomotic region and the abdominal cavity is closed.

22.11. The Rodney - Smith Procedure

The Roux-en-Y mucosal graft operation, or else Rodney Smith procedure, is an alternative method of anastomosis of jejunum to a high bile duct stricture (benign or malignant). The procedure entails dissection of the subhepatic space and exposure of the hilar region. Pathologic tissue is excised and a sutureless anastomosis of jejunal mucosa to the bile ducts is performed. After removal of a disc of seromuscular coat of jejunum, a transhepatic tube is introduced into the jejunum and sutured in place. Traction on the tube subsequently draws the mucosal pocket upward into contact

with the intrahepatic duct lining. The edges of the jejunum are then fixed to the capsule of the liver and the jejunojejunal anastomosis is completed. In our department we have abandoned this procedure for the sake of a "simple" hepaticojejunosotmy.

22.12. The Longmire Procedure

The Longmire is a less commonly performed alternative procedure for high bile duct lesions-strictures and is useful in patients with left liver atrophy. It involves removal of the left lateral lobe of the liver (segments II and III), exposing the dilated respective segmental ducts. A Roux-en-Y limb is then anastomosed to Glisson's capsule around the exposed ducts.

22.13. Specific Conditions

22.13.1. Bile Duct Injuries

Common anomalies responsible for bile duct injuries include those of the cystic duct and its insertion into the common hepatic duct e.g. long parallel course with the common hepatic duct or a spiralling cystic duct opening on the medial aspect of the common hepatic duct. Anomalies of the right hepatic duct e.g. low insertion on to the common hepatic duct, right anterior and posterior sectoral hepatic ducts, anomalies of the right hepatic artery and aberrant vessels coursing along the common bile duct are other important examples.

The most common site of injury of the bile ducts is the common hepatic duct at the level of the cystic duct ascent. From this point of view, right hepatic duct injuries are the most frequent, quite often involving a concomitant right hepatic artery ligation, causing right liver atrophy along with the resulting biliary strictures.

Bismuth has classified postoperative strictures of the bile ducts in five categories [14], a classification which vastly interferes both with the selected type of surgical repair and the patient prognosis:

Type 1: Stricture >2 cm from the confluence of the hepatic ducts.
Type 2: Stricture <2 cm from the confluence, with remnant of the common hepatic duct.
Type 3: Stricture flushes with the confluence intact.
Type 4: Stricture involves the confluence.
Type 5: Stricture involves an aberrant right sectoral hepatic duct, with or without a concomitant common hepatic duct stricture.

If the bile duct has been neatly incised, end-to-end anastomosis or ductoplasty should be performed using 6-0 absorbable, closely spaced, interrupted sutures taking care to place the knots extraluminally, if possible. Some surgeons perform the repair over a T-tube, which exits the duct through a choledochotomy separate from the anastomosis.

If the duct has been crushed, more than 1 cm has been lost. If a transection is high in the hilar region of the duct, the damaged segment of the duct should be excised and choledochoenterostomy should performed. For high level strictures (Bismuth 2-4) anastomosis is made between the cut end of the hepatic ducts and the side of a Roux-en-Y limb of jejunum. For low-level strictures (Bismuth 1), choledochoduodenostomy can be performed after mobilization of the duodenum with a wide Kocher manoeuvre. Technical details of the respected operations have been presented in previous respective paragraphs.

22.13.2. Congenital Choledochal Cysts

Choledochal cysts are thick walled cystic dilatations of the bile ducts that are devoid of epithelial lining. Cysts may be localized to one segment of the extrahepatic biliary duct system or may involve the entire extrahepatic and intrahepatic biliary tree. These cysts result in stasis of bile, presenting the classic clinical symptoms of right upper quadrant pain, mass and jaundice. Other patients present with cholangitis or peritoneal sepsis-related bacterial contamination of bile or even rupture of the cyst. Malignant degeneration of the endothelial lining is reported in 20% to 50% of patients. Regarding the anatomic classification of choledochal cysts, in 1977, Todani et al. [15] modified the classic Alonso-Lej classification by adding 2 new types (types IV and V) (*see previous chapter*).

Treatment of choledochal cysts is surgical, with the exception of type V, with multiple intrahepatic cysts, which can benefit from medical management for variable periods of time. Total excision of the cyst in types I, II, and IV, followed by reconstruction of the biliary tree with hepaticojejunostomy in a Roux-en-Y

fashion, has been widely accepted as the procedure of choice in treating choledochal cysts. This procedure implies an excision of the distal terminal choledochal duct. Consequently, the procedure blocks the reflux of pancreatic enzymes into the biliary tract, therefore decreasing the incidence of carcinoma of the bile duct. With type III choledochal cysts, the general approach is one of lateral duodenotomy with unroofing of the choledochocele, so as to drain the bile duct and pancreatic duct directly into the duodenum. The two ductal openings should be carefully examined for determining whether ductoplasty is required. In patients with type IV choledochal cysts with intrahepatic cysts, each case is individually evaluated and the principle of adequate bile drainage is taken into account. Excision of the dilated extrahepatic bile ducts to the porta hepatis, with hepaticojejunostomy at the level of the hilum, may provide good biliary drainage and effective decompression of the intrahepatic cysts. If the intrahepatic cysts are localized in a small portion of the liver, partial hepatectomy may be required.

With regard to type V choledochal cysts, patients with localized disease may benefit from a hepatic lobectomy. If the disease is diffuse, involving both lobes of the liver, treatment is palliative and liver transplantation may be required [16].

22.13.3. Hilar Tumors

Tumors of the bile duct, cholangiocarcinomas, are an uncommon malignancy in the United States, with fewer than 5000 cases diagnosed each year [17]. The majorities of these are diagnosed in elderly patients and, if left untreated, patients will rarely live more than 6 months [18]. Most of these tumors are adenocarcinomas. Intrahepatic cholangicarcinomas account for 10% of all cholangiocarcinomas, hilar cholangiocarcinoma for 25%, and extrahepatic cholangiocarcinoma for 65%. Population based studies indicate that the overall 5 year survival rates for extrahepatic cholangiocarcinoma has increased from 11.7% from 1973 to 1977, to 17.3% in the years from 1983 to 1987 [17]. Surgery still remains the primary curative modality in the treatment of cholangiocarcinomas, though most patients are not in condition to undergo curative resection. The causes that preclude curative resection include: (1) hepatic ductal extension preventing complete resection, (2) soft-tissue extension (hepatic parenchyma at the hilum or unresectable vascular involvement) and (3) distant metastases (either distant nodal disease [N2] or systemic metastases).

22.13.4. Operative Strategy for Hilar Cholangiocarcinoma

The modified Bismuth-Corlett classification system for hilar cholangiocarcinoma is a more anatomic description of the location of the tumor [19]. It groups hilar tumors based upon their extension into the hepatic ductal system:

Type I: Below the confluence of the right and left hepatic ducts.
Type II: Confined to the confluence of the right and left hepatic ducts.
Type IIIa: Extension into the right hepatic duct.
Type IIIb: Extension into the left hepatic duct.
Type IV: Extension into the right and left hepatic ducts.

This system provides an anatomic classication that can guide therapy (either resectional or palliative), but does little to describe those patients who are surgical candidates, or to provide prognostic information about each subset.

Although long-term survival following treatment for hilar cholangiocarcinoma is uncommon, only those patients treated with surgery ever achieve this chance for long-term survival. Perhaps in the future, systemic therapy will become more effective, to allow prolonged survival in those patients who are not surgical candidates. Current therapy, however, is relatively ineffective and patients with either N2 or M1 disease are incurable.

In most studies that have examined survival following resection of hilar cholangiocarcinoma, the presence of positive histologic margins remains one of the most important predictors of poor outcome [20, 21]. In fact, survival of patients who undergo resection but are left with positive histologic margins is only slightly better than that of patients who do not undergo resection at all. The median survival of patients who undergo a curative resection and have histologically negative margins may be two to three times the rate of those patients whose margins of resection are positive. Therefore, long term survival is really only achieved in

patients who undergo curative resection in which the margins of resection are histologically negative.

Despite these studies demonstrating the prognostic signicance of margin status on outcome, only few other studies have clearly reported the location of the positive margin. Evidence from examining the effect of performing hepatic parenchymal resection in addition to the biliary resection, and the incidence of positive histologic margins, indicates that the proximal bile duct (or less likely, the proximal soft-tissue margin) is the culprit. Recent studies have reported an inverse correlation of the performance of a hepatectomy with the extending of positive histologic margins in the resected specimen [21, 22, 23]. In reports with infrequent performance of major hepatic resection (<30%), the incidence of positive margins was usually in excess of 60%, whereas in those reports of frequent performance of major hepatic resection (>60%) the incidence of positive margins decreases to less than 30%. These data strongly suggest that curative resection with histologically negative margins requires a hepatic resection in a signicant portion of patients with hilar cholangiocarcinoma.

This association of hepatic parenchymal resection, negative histologic margin and survival benefit becomes even clearer when the data of combined caudate lobe resection are examined. The biliary ductal drainage of the caudate lobe enters the common hepatic duct near the posterior aspect of the confluence of the right and left hepatic duct. It has been increasingly recognized that hilar cholangiocarcinoma frequently extends into the biliary ductal radical of the caudate lobe, and that the failure to resect this may contribute to a positive histologic margin and poorer overall survival. In contrast, the limited studies that have compared survival outcomes based on the performance of a caudate resection, as part of a curative resection for hilar cholangiocarcinoma, observed increased survival in the group that underwent caudate lobe resection [24, 25]. Nimura et al. [24] first reported, in a series of 91 patients, that histologically negative margins were obtained in 86% of patients when a caudate lobe resection was performed, achieving a median survival of 33 months. Although it is unlikely that a prospective trial will ever be done to specically determine the benet of caudate lobe resection, anatomic data indicate that the caudate bile ductal branch is a frequent source of positive margins following bile duct resection alone. It is therefore imperative to add caudate lobectomy to resection of hilar cholangiocarcinoma, in order to optimally ensure histologically negative margins.

Two major aspects of surgical radicality are the performance of major vascular resection as well as the extent of nodal dissection. Because extended hepatic parenchymal resection increases the likelihood of achieving histologically negative margins of resection, perhaps it is possible this same philosophy to be extended to the vasculature of the porta hepatis. The data supporting the inclusion of major vascular resection, particularly the portal vein, are limited [26, 27]. Neither perioperative morbidity, nor mortality were increased after major portal venous resection and reconstruction, but the published series are small in numbers and come from centers with an extensive experience in complex hepatobiliary surgeries. Current guidelines support major vascular resections if the expertise is available, since the provision of a curative resection with histologically negative margins remains the only hope of long-term survival to the patient.

As to the nodal dissection, Kitagawa et al. determined the location and incidence of nodal metastases in 110 patients with hilar cholangiocarcinoma [28]. The most commonly involved nodal basin was the pericholedochal (43%), followed by the periportal nodes (30.9%) and the common hepatic nodes (27.3%). The celiac and superior mesenteric lymph nodes were rarely involved, suggesting that dissection of the primary tumor along with the lymph node-bearing tissue of the porta hepatis extending to the common hepatic artery is sufficient for staging as well as disease control.

The principles of hepatic duct resection and biliary reconstruction have already been presented in previous paragraphs. Since the performance of extended liver resections (trisegmentectomies) are often required to achieve microscopically negative soft tissue margins in patients with advanced type IIIA and IIIB hilar cholangiocarcinomas, we will present the basic surgical principles for a right and left trisegmentectomy.

22.13.5. Right Trisegmentectomy for Hilar Cholangiocarcinoma

Laparotomy is performed through an upper midline incision with bilateral subcostal extensions. The distal

bile duct is divided in the pancreas. Skeletonization resection of the hepatoduodenal ligament, including dissection of the regional lymph nodes, is performed from the duodenum to the liver. The right hepatic artery is divided. Then, at a more superior level, the right portal vein is divided and the defect is closed with a continuous suture. Portal vein resection and reconstruction by end-to-end anastomosis, after complete dissection of the transverse portion of the left portal vein, is performed in cases where the portal bifurcation adheres to and cannot be freed from the tumor during skeletonization resection of the hepatoduodenal ligament.

After mobilization of the right liver, a number of short hepatic veins are ligated and divided from the caudal to cranial direction, as the right lobe is retracted anteriorly and to the left. The right hepatic vein is encircled extrahepatically by cautious dissection, clamped with vascular clamps, divided, and sewn with a continuous suture. All vena caval tributaries -except the middle and left hepatic veins- are ligated and divided because the caudate lobe will be totally resected.

The transverse portion of the left portal vein usually gives off several branches to the caudate lobe. These small ramifications are ligated and divided, so that this portion is dissected free from the hilar plate. Next, the umbilical portion of the left portal vein is exposed by dissecting the serosa of the umbilical fissure. When the umbilical fissure is concealed by fusion of the inferior lips of the medial and the lateral sections of the left liver, this liver bridge is divided.

The portal branch of segment 4 is ligated and divided at its origin. Two or 3 other small ramifications feeding the caudal part of segment 4, are also ligated and divided. Next, the umbilical plate is exposed behind the umbilical portion of the left portal vein, as the round ligament is pulled down caudally and to the left. All of the small portal branches arising from the cranial side of the umbilical portion are carefully ligated and divided. The proximal side of the ligamentum venosum is ligated and divided at the cranial side of the elbow of the left portal vein. Thus, the cranial side of the umbilical portion of the left portal vein is completely detached from the umbilical plate. This dissection produces a demarcation along the "left" side, not the right side, of the falciform ligament. This demarcation is usually encountered after pedicle occlusion of the segments 2 and 3 in left lateral sectionectomy.

Normally, the left hepatic artery originates from the proper hepatic artery, reaches caudally to the base of the umbilical portion of the left portal vein and enters the base of the umbilical fissure to the left of the umbilical portion. This anomalous distribution of the left hepatic artery creates a technical problem, since its presence compromises the detachment of the artery from the left hepatic duct. Albeit with difficulty, the dissection is possible. The liver dissection is carried out along the demarcation line (on the left side of the falciform ligament), thereby transecting the middle hepatic vein at the confluence of the left hepatic vein. Next, as the umbilical portion of the left portal vein is retracted to the left, the bile ducts of the left lateral section are divided at the left side of the umbilical portion of the left portal vein, proximally to the confluence of the bile ducts from segments 2 and 3 after carefully detaching these bile ducts from the left lateral sectional branches of the left portal vein.

Bilioenteric continuity is reestablished by Roux-en-Y hepaticojejunostomy with the jejunal limb brought to the hepatic duct via the retrocolic-anteduodenal or the retrocolic-retrogastric route. All anastomoses are performed with mucosa-to-mucosa alignment, by interrupted sutures using 5-0 or 6-0 polydioxanone (PDS, Ethicon, Tokyo, Japan), and drained externally by a 6-Fr polyvinyl chloride tube (PTBD tube, Hakko, Chikuma, Japan) introduced via the transhepatic or transjejunal route. The tubes are usually removed 3 weeks after hepatectomy.

22.13.6. Left Trisegmentectomy for Hilar Cholangiocarcinoma

This procedure is required for hilar lesions originating in the left lobe of the liver and extending across the interlobar plane into the anterior aspect of the right lobe (segments V and VIII). Candidates for this procedure must have no disease involvement in segments VI and VII. The caudale lobe (I) may be left in situ or may be removed en bloc with left lobe structures, as needed for complete tumor removal. The procedure is initiated with division of the left hilar structures as in left hepatic lobectomy. Additionally, the cystic duct and artery are divided to open the plane anterior to the right hilar structures. After the hepatogastric and left triangular ligaments are divided, the liver is rotated

from left to right for exposing the cleft between the caudate lobe (segment I) and the left lateral segments (II and III). This cleft can be opened with cautery to serve as the posterior parenchymal transection plane. Alternatively, if the caudate lobe (I) is to be removed with the specimen, then the lobe is mobilized from the anterior wall of the IVC by dividing the multiple small hepatic vein branches. With further dissection in this cephalad portion of the cleft (between segments I and II) and at the level of the suprahepatic vena cava, the insertion of the common trunk of left and middle hepatic veins into the IVC can be encircled and divided between clamps or by the use of a stapling device. This technique may also be applied to encircle the left hepatic vein alone, as is done in left hepatic lobectomy. The entire left lobe of the liver has now been devascularized while keeping segments V and VIII in the right lobe vascularized. Once the left and middle hepatic veins have been divided, the liver can be rotated further downward and to the right to expose the drainage of the right hepatic vein into the IVC. The plane of parenchymal transection is along the anteromedial aspect of the right hepatic vein, which severs venous drainage of segments V and VIII, while preserving drainage of segments V1 and VII posteriorly. As parenchymal division continues in this plane downward between the anterior and posterior sectors of the right lobe, a short period of hilar inflow occlusion will reduce blood loss from segments V and VII, which retain their inflow. At this point the separation of the right anterior and posterior sectoral vessels and bile ducts is encountered. Periodic reassessment of the appropriate dissection plane is guided by constant reference to the right hilar structures, exposed by earlier division of the cystic duct and artery. The vascular and biliary structures serving the right anterior sector (segments V and VIII) are now divided, followed by any remaining liver parenchyma, to remove the complete specimen. A careful search is made for sites of bile leakage or hemorrhage. Closed suction drainage and/or omentum are placed along the resection margin before closure.

22.13.7. Conclusion

Successful hepatobiliary surgery represents the culmination of a challenging and often difficult clinical decision process, and, therefore, it is imperative for surgeons to be familiar with current therapies available for these patients and their potential complications. Nowadays, technical refinements and advances in imaging, aneasthetic, minimally invasive and endoscopic approaches, allow us to overcome long standing problems in the diagnosis and management of malignant as well as complex benign hepatobiliary disorders. Although the role of a multidisciplinary hepatobiliary team is significant, still, surgical technique, skills and intraoperative decision-making represent the ultimate parameters contributing to a favorable clinical outcome. In this respect, attainment and attachment to solid operative principles continue to guarantee the patients' welfare.

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SECTION 3

Chapter 23: Imaging Studies of the Liver

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CHAPTER 23

IMAGING STUDIES OF THE LIVER

L. Thanos, S. Mylona

23.1. Introduction - Plain X-Ray

Thirty years ago, the imaging investigation of the liver and the biliary tree began with the plain x-ray. Nowadays it is considered less valuable since the ultrasound has become the modality of choice for their initial examination. The liver casts an appreciable shadow on a simple X-ray film. The hepatic shadow appears homogenous and is mostly formed by the right lobe. It is delineated at the right quadrant of the abdomen, though modified by individual variations of shape and orientation. Its outline is deduced due to contrast differences between the right lobe and the right hemidiaphragm and lung above, the preperitoneal fat line laterally, and the extraperitoneal fat and the kidney below. The liver lies approximately at the level of fifth intercostal space at the midclavicular line. The lower border extends to or slightly below the costal margin and should not cross the right psoas margin. The lower anterior edge of the liver that is the one clinically palpated is not directly seen on a plain film, but the gas in the right colon usually indicates its position.

The left lobe of the liver is not easily seen in the plain x-ray, since it is smaller and centrally located. Gas in the stomach may likewise suggest its position. An inferior tongue-like extension from the lateral margin of the right lobe of the liver indicates Reidel's lobe, frequently found in asthenic women.

Normally, the biliary radicles and the gallbladder are not visible in a plain film (fig. 23.1).

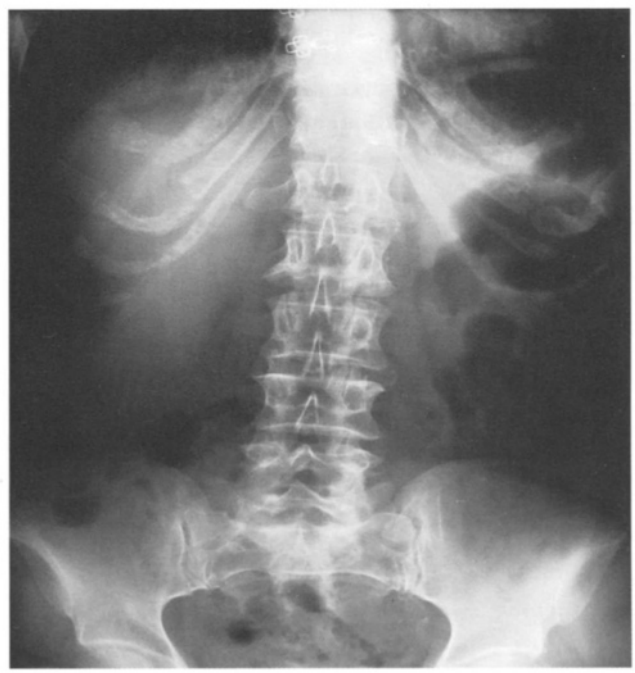

Fig. 23.1. Normal abdomen plain X-ray film.

23.2. Ultrasonography

The liver is the largest organ in the human body. Sonographic evaluation is often requested to assess hepatic abnormality as the liver is frequently involved in systemic and local disease. In addition, ultrasound remains the initial screening tool of choice for evaluating the gallbladder and the bile ducts. A modality with high sensitivity and accuracy, it has no ionizing radiation, and is fast, flexible and portable.

It can assess position, size, margins and architecture of the hepatic parenchyma. The normal hepatic parenchyma appears homogenous with moderate echogenicity. The liver is hypoechoic compared to the spleen, and hyperechoic compared to the kidney. An accurate assessment of liver size is difficult with ultrasound because of the limited field of view. Gosink [1] proposed to measure its length at the midhepatic line. In 75% of individuals a liver length of greater than 15.5 cm signifies hepatomegaly. Niderau et al [2] measured

the liver at the midclavicular line and midline. They found that organ size increases with height and decreases with age. The mean longitudinal diameter in the midclavicular line is 10.5 with SD = 1.5 cm and the anteroposterior diameter, at the same level, is 8.1 with SD = 1.9 cm [3].

As ultrasound allows evaluation of the liver anatomy in multiple planes, the radiologist can precisely localize a lesion to a given segment for the surgeons according to Couinaud's (most used in Europe) or Bismuth's anatomy (most used in north America). The left, middle, and right hepatic veins divide the liver into four sectors (segments for Bismuth) (fig. 23.2), which are further subdivided into cranial and caudal segments (subsegments for Bismuth) by the plane of portal vein. Each segment has its own blood supply (arterial, portal, hepatic venous), lymphatics and biliary drainage. The portal triad (portal vein, hepatic artery, bile duct) runs through the center of each segment, encompassed by the hepatic vein. In regard to tumors, color duplex sonography in combination with the gray-scale harmonic contrast-enhanced technique is proved to be very useful [4].

Normal peripheral bile ducts and hepatic artery branches are too small to be imaged on ultrasound, thus the portal triad is formed practically by the portal vein which is contained within a sheath of connective tissue allowing the echogenic wall in the portal vein to be viewed sonographically. The portal veins differentiate from hepatic veins, which are also imaged on ultrasound, because the latter have an almost imperceptible wall and different course. They run from the boundaries of each segment towards the inferior vena cava.

The porta hepatis lies in the inferior surface and consists of three vessels: the main portal vein, the common bile duct and the hepatic artery (fig. 23.3). The common bile duct and hepatic artery are located anterior to the portal vein. Normally, the diameter of the portal vein is less than 15 mm.

The size of the common bile duct (CBD) is the most sensitive means of distinguishing medical from surgical jaundice. The literature contains discrepant reports regarding the normal diameter of the CBD (from 4 mm to 8mm) [5, 6]. It is still unclear in literature whether the CBD dilates with age [7] or after cholecystectomy [6, 8]. A simple rule is to rate a CBD up to 10 mm as normal in elderly patients and in postcholecystectomy patients. Measurements recorded during X-ray procedures (e.g., transhepatic cholangiography, ERCP), are greater than the corresponding sonographic measurements due to radiographic magnification. The diameter of intrahepatic bile ducts is considered normal up to 2 mm, or no more than 40% of the diameter of the accompanying portal vein [9].

Normally, the gallbladder appears as an anechoic

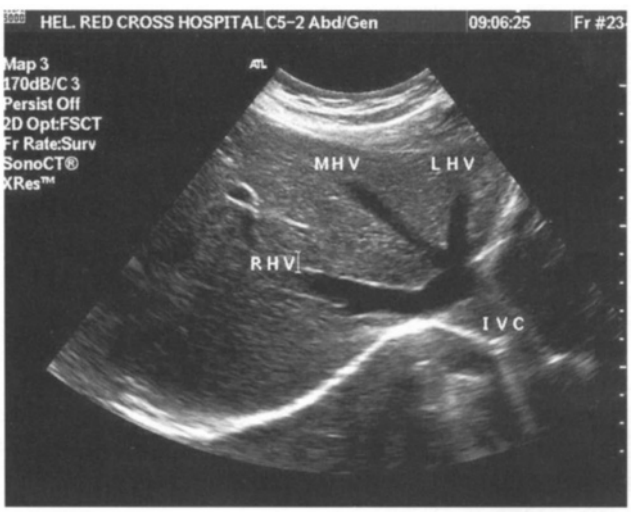

Fig. 23.2. Normal sonographic liver parenchyma appearance. The hepatic veins (HV) divide the liver into four sectors or segments and form the inferior vena cava (IVC).

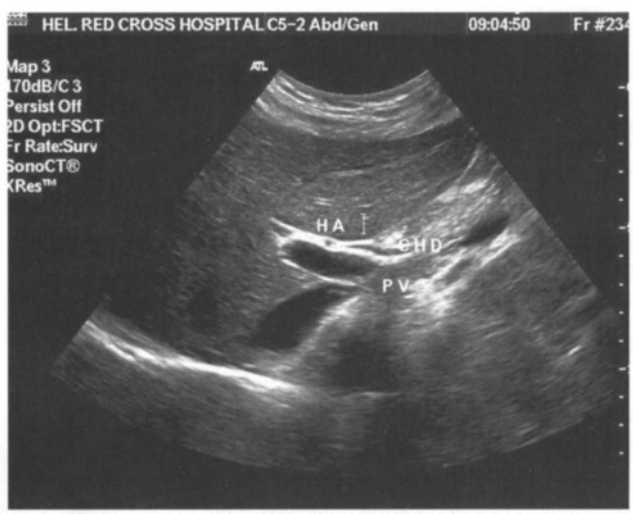

Fig. 23.3. Porta hepatis. Notice the common hepatic duct (CHD) and the portal vein (PV) parallel to each other. The hepatic artery (HA) is small circle between them.

typically ovoid structure with an echogenic pencil-thin line wall whose thickness should not exceed 3 mm. Although the gallbladder neck has a fixed anatomic relationship to the main lobar hepatic fissure and the undivided right portal vein, the anatomic position of its fundus varies greatly from each individual to another [10], as does the normal size and shape. In general terms, if the gallbladder transverse diameter is greater than 5 cm and rounded in shape, it is considered hydropic [11]. On the other hand if its diameter is less than 2 cm is likely to be abnormally contracted. The gallbladder volume is calculated from the formula [V= 0.52 (L - W - H)] [12].

Its typical ovoid shape frequently varies because of folding and kinking (e.g. Phrygian cup deformity, junctional fold) [13]. These folds can be mistaken for calculi and/or polyps. The lack of visualization of the gallbladder can be attributed to many causes, one being the variation of a "mobile" or "floating" gallbladder caused by a lax or incomplete peritoneal reflection [14].

Color duplex sonography (CDS) allows examination of the arterial and venous supply of the liver. The use of CDS can identify the celiac trunk and each branch with its normal variants and possible anomalies (arteriovenous malformations, aneurysms). The common hepatic artery, the proper hepatic artery, the right, middle, and left hepatic arteries are examined. Aneurysms are easily detected with CDS even when at an atypical site, thereby enabling elective surgery or embolization to be planned. Additionally, CDS is appropriate for subsequent monitoring of progression and outcome [15]. As regards the venous system, CDS can assess the appearance, normal diameter (IVC: 2-3 cm, Portal Vein: 0.8-1.3 cm), and possible variants, collaterals and arteriovenous malformations. It can evaluate the blood flow of IVC, hepatic, and portal veins also (fig. 23.4). Color duplex sonography can detect venous or portal thrombosis and obstruction, and evaluate liver perfusion with sufficient accuracy [16]. Furthermore, CDS can evaluate portal hypertension detect of collaterals, and visualise the umbilical vein (the most sensitive indicator of portal hypertension) [16]. In Budd-Chiari syndrome, the obstructed hepatic veins and the cause of obstruction are visible. In cases of treatment with transjugular portosystemic shunts (TIPS), CDS can detect normal function and possible complications.

Sonography is the first choice modality in case of trauma. Since the liver is the second most frequently injured solid organ, it can be used to detect intraperitoneal and subcapsular fluid collection and major parenchymal damage.

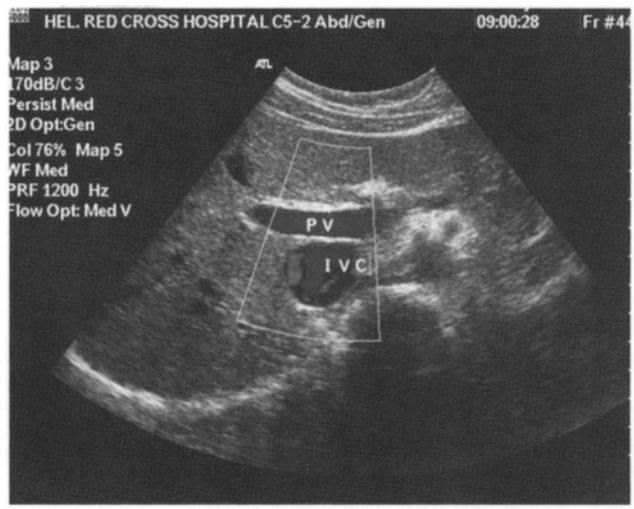

Fig. 23.4. Color sonography indicates the flow into the inferior vena cava (IVC) and the portal vein (PV).

In case of hepatic or biliary surgery ultrasound can be used for preoperative assessment. If liver biopsy is necessary, it is a perfect real time modality in the percutaneous guidance of the needle. Postoperatively, or post chemoembolization, sonography detects any possible complication and serves, in case of abscess or biloma formation, as guided modality in percutaneous drainage.

Ultrasound is used preoperatively in liver transplantation to assess the organ (parenchymal and vascular status) and the whole abdomen, and to detect any finding that may alter patient selection. Post transplantation it further serves in the assessment of liver parenchyma, evaluation of bile ducts and vascular patency and assessment of possible fluid collections.

In instances of non surgical hepatic carcinoma and metastatic disease sonography is a guided modality for percutaneous thermal radiofrequency ablation.

23.3. Computed Tomography

Computed Tomography (CT) is a standard imaging modality for the liver. It is principally used for the

evaluation of liver tumors, but can also provide useful information for a great number of other diseases. In comparison to ultrasound, it offers superior evaluation of the liver that is frequently required preoperatively. It requires minimal cooperation from the patient and compared to MRI presents a more reliable image of higher quality.

Normal liver parenchyma should appear homogenous, without any focal lesions and with a well defined surface. It has attenuation of 55 to 65 HU. In diffuse fatty infiltration each 10% increase in proportion of fat decreases its attenuation approximately 15 HU [17]. In the unenhanced CT scan the vessels within the normal liver appeared of low attenuation, round, oval or lengthwise in shape. The falciform ligament can be visualized.

In CT scans, the liver is divided according to either Couinaud's or Bismuth's anatomy.

CT scanning of the liver is usually a part of an abdominal examination (upper or complete). A noncontrast scan is required only in a few pathologic conditions such as traumatic hemorrhage, fibrosis in cirrhosis, calcifications, hemochromatosis, and in assessment of hypervascular tumors, some of which are better demonstrated (<5%) [17]. CT scanning assessment of the liver is always performed after use of intravenous contrast material. In most cases, such as known malignancies giving hypovascular matastases e.g. colorectal cancer, where 75-80% of hepatic blood comes from the portal vein, imaging in the portal venous phase is deemed sufficient [17, 18]. The liver in this phase (60 secs - 70 secs after the contrast material injection) has a homogenous and high uptake of the contrast material and the lesion-to-liver contrast is better seen (fig. 23.5a). The portal vein at the porta hepatis and its intrahepatic ramification are delineating in this phase. Multidetector CT can easily delineate hepatic venous anatomy and accurately identify normal venous variants. Hepatic vein mapping is also important prior to liver resection or transplantation, as the course of the middle hepatic vein determines the plane for formal right or left hepatectomy and allows preoperative prediction of the postoperative liver volume [17].

It is often necessary to perform delayed scans. An early delayed scan in 3 mins to 5 mins after contrast material injection shows better hemangiomas and small cysts. A late delay scan in 10 mins to 15 mins identifies small cysts and tumors with a large fibrotic component (e.g., cholangiocarcinoma, encapsulated HCC, some nodular NHL – Non-Hodgkin's Lymphoma) [17].

In instances where hypervascular lesions are suspected, partial liver surgical resection is planned or in a pre-surgery screening in case of malignancy that causes metastatic liver disease, an arterial phase (20 secs - 30 secs after the contrast material injection) is requested in addition to the standard portal phase (fig. 23.5b). In this phase the liver contrast material uptake is less as hepatic artery offers only the 20%-25% of its supply. The hepatic artery and its branches are delineating in this early phase [17, 18]. The CT can be further used in this phase to diagnose a variety of arterial pathologies,

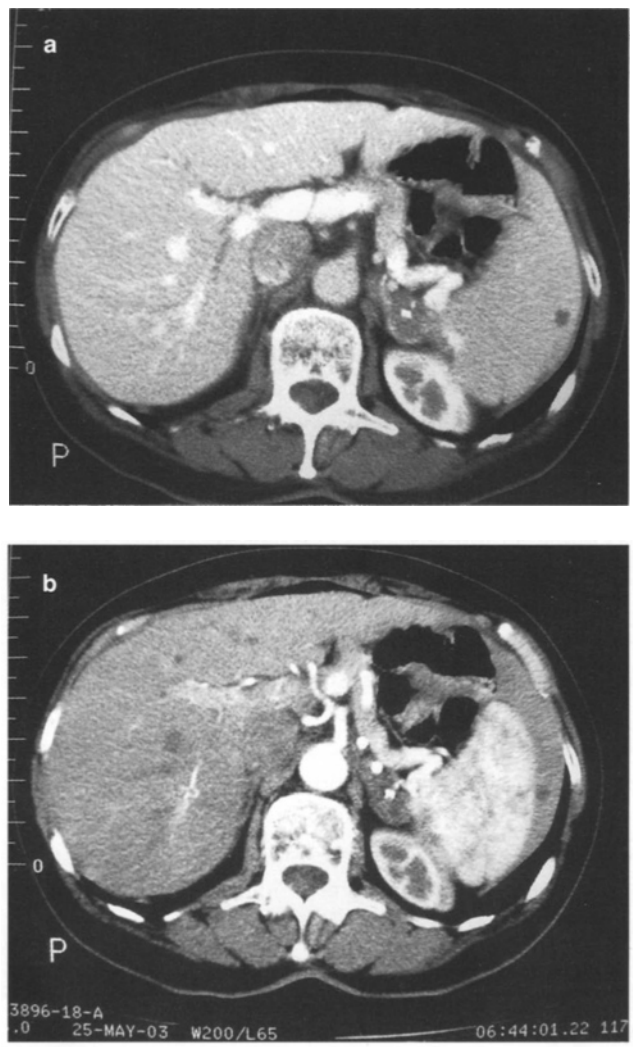

Fig. 23.5. a) Arterial phase b) Portal phase. Enlarged liver left lobe which envelopes spleen. A tiny cystic lesion is seen.

including aneurysm and pseudoaneurysm of the hepatic artery and hepatic infarctions. An early arterial phase is helpful for pre-surgery 3D reconstruction of the arterial supply but rarely increases tumor detection [19].

The intrahepatic biliary tree branches are rarely visualized in pre and post contrast CT scanning. Their course is parallel to portal vein ramifications and new technology equipment may allow their visualization as low attenuation foci [20]. Only the ducts with diameter 2 mm-3 mm appear on noncontrast CT scans, and ducts with 1 mm-2 mm diameter on contrast images [21]. The common bile duct (CBD) and the common hepatic duct (CHD) appear as rounded water attenuation structure at the porta hepatis [22]. Their wall, if identified, is hyperdence and has a thickness of less than 1.5 mm. The CBD begins from the liver hilum and gradually taper in diameter as it runs towards the ampulla of Vater within the hepatoduodenal ligament. Its normal diameter is up to 5 mm; 6 mm to 7 mm is considered marginal [21]. After cholecystectomy or in elderly individuals, diameters up to 10 mm are still considered normal. After IV injection of contrast material, both CHD and CBD are better demonstrated as low attenuation circles against the contrast enhanced hilum vessels and pancreatic parenchyma, respectively.

The gallbladder is round or ovoid homogenously hypoattenuating structure (0 to 15HU) with a size up to 50 ml and a well defined thin wall, less than 3 mm on noncontrast CT scans, located at the inferior border of the liver between IV and V segments. The cystic duct has a diameter less than 2 mm, and usually is not seen [21].

With modern equipment, the visualization of biliary tree anatomy is improved and anatomical variations, strictures, and small masses can be identified.

Prior to liver transplantation, intra- and extrahepatic vascular road mapping may not only prove essential to the technical success but may also decrease the incidence rate of vascular complications. Moreover, it is of great help in the curative partial liver resection in patient with malignant tumors, as it delineates the relationship of tumor to adjacent vessels, and estimates the tumor-free margin thus avoiding wrong surgical procedures [18]. In addition, it ensures an adequate intra-arterial chemotherapy infusion pump position within the desired artery.

The development of intra-arterial contrast injection techniques improved detection of liver lesions, namely CT hepatic arteriography (CTHA), first described by Prando et al [23] and CT arterial portography (CTAP). These are interventional procedures and must not be used as screening tools. In CTHA a catheter placed under fluoroscopic guidance into the main hepatic artery, allows direct contrast material infusion during CT scan. It is mostly performed in surgical candidates with liver cirrhosis and suspected HCC and nowadays often in conjunction with spiral CTAP [24]. In CTAP the contrast material is injected directly into the superior mesenteric artery or splenic artery. This results in a tremendous enhancement of normal liver parenchyma due to selective delivery of contrast into the portal venous system [24, 25]. It is used in planning partial hepatectomy (to exclude tumors in residual liver segments, detection rate greater than 90% for lesions ≥1 cm in diameter, but is of very limited specificity because all lesions appear as hypoattenuating [18]). Cirrhosis and large tumors can limit its effectiveness.

One of the new multidetector row CT applications is CT angiography. Nowadays, there is the tension to replace the standard diagnostic digital angiography to depict vascular anatomy [26]. CT angiography provides the surgeon with information regarding the anatomy of the celiac trunk, hepatic arteries, hepatic and portal venous system before liver resection or transplantation, helps the planning of chemoembolization, and enables surgical implantation of chemotherapy catheters by depicting the anatomy of the gastroduodenal artery and the origins of proper, left, middle, and right hepatic arteries (fig. 23.6). In post-liver transplantation it serves in the detection of hepatic arterial complications [27]. The venography can also identify the venous system, helping to visualize hepatic and portal ve-

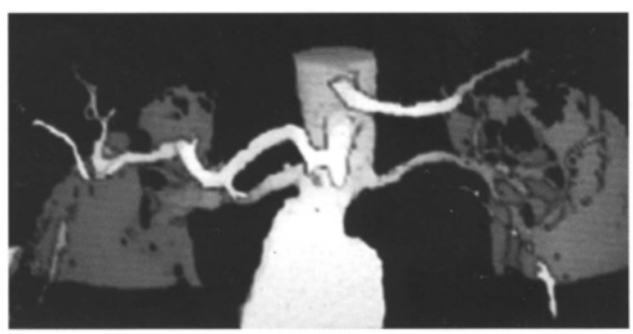

Fig. 23.6. CT arteriography.

nous major variations and to identify portosystemic collaterals in case of individuals with portal hypertention [28].

Another modern CT application is CT cholangiography which involves oral or IV administration of cholangiographic contrast material to opacify the biliary tract. Using inner surface of the biliary system can be appraised by using virtual endoscopy combined with virtual CT cholangioscopy [21]

Virtual hepatectomy can be performed with multidetector row CT. This technique enables the surgeons to plan the extent of hepatic resection, estimate the liver volume to be ablated and predict, in combination with hepatic laboratory tests, the function of the remaining hepatic parenchyma [29].

CT is also the modality of choice for classification of known hepatic or biliary trauma. According to clinical and imaging findings, 20%-40% of patients can be conservatively managed.

CT further serves in the follow-up of hepatobiliary surgery in malignancies, and in postoperative complication (bilomas, abscesses, hematomas) as a guiding modality for percutaneous drainage.

Where primary or metastatic hepatic tumors cannot be managed surgically, CT-guided tumor ablation provides a minimally invasive alternative therapy.

23.4. MRI of the Liver

Although MRI is not a first line routine examination for the evaluation of the liver pathology it is more sensitive in characterizing various lesions, detecting the smallest of them and helps in confirming diagnosis in cases where ultrasound and CT are unequivocal. Its use in gallbladder diseases is limited. As for the billiary tree the most useful and familiar procedure is MR cholangiopancreatography (MRCP) (fig. 23.7). This procedure in a 3D reconstruction which visualises the common hepatic duct and its main branches as well as the common bile duct, providing amenable pathology information [30].

The current standard MR imaging examination of the liver includes a combination of T1- and T2- weighted sequences followed by the acquisition of dynamic contrast-enhanced T1- weighted images following injection of a rapid bolus of gadolinium chelate (fig. 23.8a, 23.8b, 23.8c). T1 weighted images give information on density and spatial resolution, whereas T2 weighted images differentiate normal liver parenchyma from tissues with high water content, thus distinguishing benign from malignant lesions. A normal liver usually has similar or higher signal intensity on T1 weighted images compared with muscles [31]. Highly concentrated bile, as in fasting patients, appears hyperintense, whereas when diluted it appears hypointense on T1 weighted images [32].

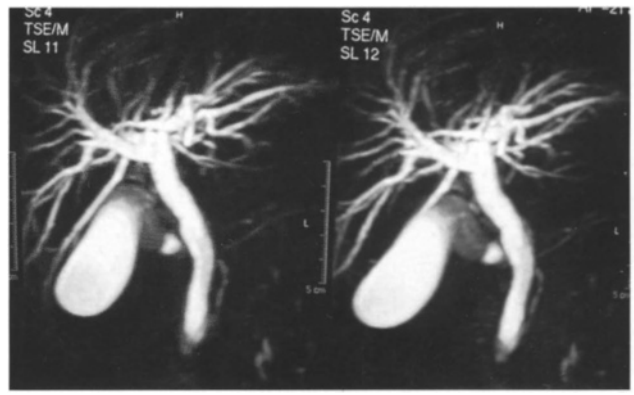

Fig. 23.7. MR cholangiopancreatography.

The combination of in -phase and opposed- phase T1 weighted gradient echo (GRE) is useful in demonstrating fatty tissue. They serve to diagnose. diffuse or focal fatty infiltration, and the presence of lipid within a liver tumor. A dynamic GRE T1 weighted series after intravenous injection of gadolinium chelate is used when lesion characterization is required, and may prove superior to unenhanced T2 images in the early detection of small liver lesions [33]. Rapid dynamic gadolinium enhanced GRE T1 images are useful in demonstrating the vascular structures and differentiating hypoattenuated lesions from hyperintense blood vessels.

In T2 waited images normal liver parenchyma appears low-to-intermediate signal intensity [33]. For better visualization and characterization of liver parenchyma fast or turbo spin echo techniques (FSE) are preferred as they give higher contrast between fat and iron or other metals, differentiating embolization coils or IVC filters [34]. For better characterizations of liver cysts and haemangiomas, heavy T2-weighted images are used [35].

Fat suppression techniques on both T1- and T2-

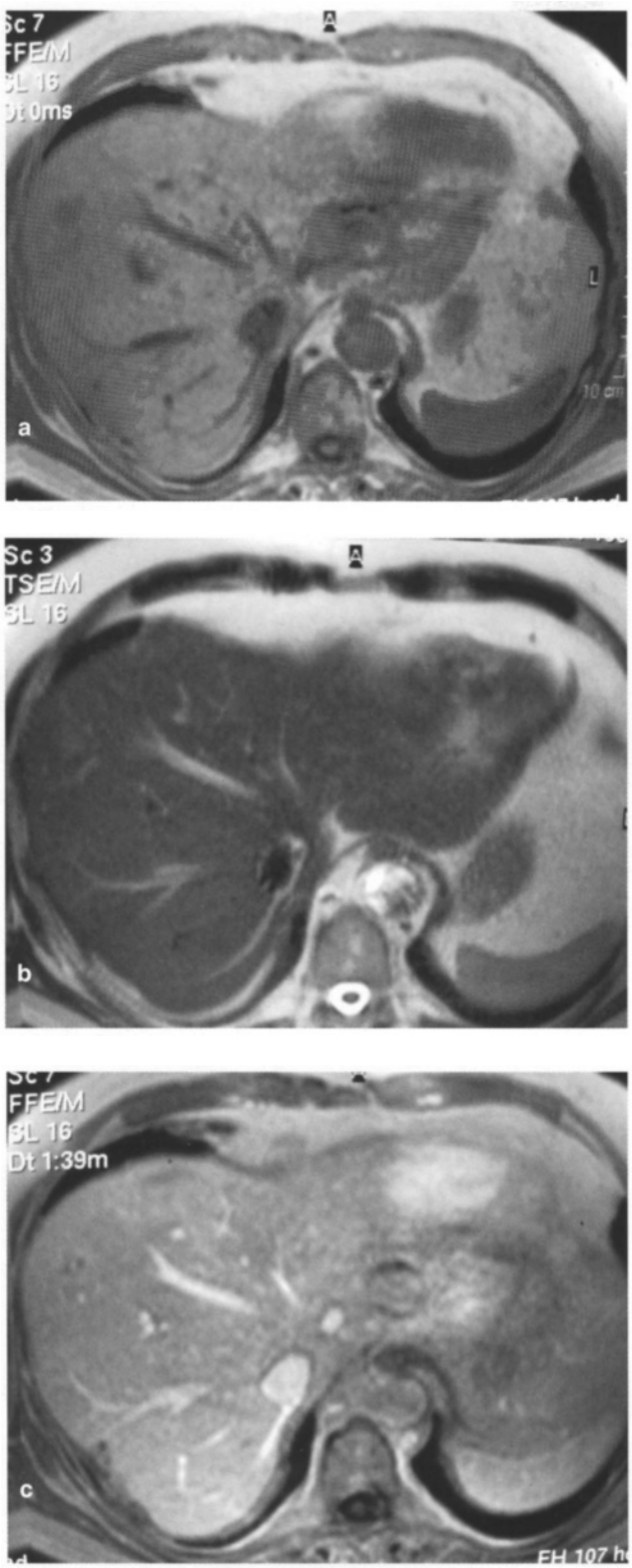

Fig. 23.8. a) T1WI b) T2WI c) T1WI after IV contrast material administration: Two lesions are visualized with enhancement in VII and VIII liver segments.

weighted images decrease the motion artifacts from subcutaneous and intra-abdominal fat, and increase the ability to distinguish subtle differences in soft tissue signal intensity. It can be used when performing a dynamic contrast-enhanced study to increase tumor-to-liver contrast [33].

Most imaging of the liver is performed to evaluate focal disease. Liver-directed contrast agents were developed for better liver tumor characterization [34]. Superparamagnetic iron oxide (SPIO) is a liver specific contrast agent, which is cleared from blood by the reticuloendothelial system. It concentrates on functioning Kupffer's cells of the hepatic parenchyma and within the intracellular space over time. Most liver tumors do not possess Kupffer's cell or the ability to uptake this agent. Iron oxide results in paramagnetic effects that decreases signal in normal liver parenchyma on T2-weighted images, facilitating tumor detection. Tumors with intermediate to high signal on T2-weighted sequences do not take up contrast and become more conspicuous as the background of normal liver develops progressively to lower signal due to uptake of iron oxide [36].

The hepatobiliary contrast agents (HBCA), a T1-shortening agent, is taken up by normal hepatocytes through the same transport mechanism used by circulating bile salts, and secreted into the bile duct canaliculi without being metabolized. Adequate liver uptake requires at least 20 minutes delay after intravenous administration and results in elevated signal on T1-weighted spoiled gradient echo (SGE) images in normal liver and bile ducts, rendering focal liver masses, which lack functional hepatocytes, as relatively lower signal foci [36]. As with SPIO, HBCA lack critical dynamic enhancement characteristics. Furthermore, certain benign and malignant tumors have been shown to take up the HBCA, becoming relatively less conspicuous [37].

The depiction of the biliary tree is based on high signal techniques, in which the bile appears bright. Such techniques include the contrast enhanced Fourier acquired steady state (CE FAST) and fast spin echo (FSE) pulse sequences without contrast media administration. Preliminary data suggest that CE-FAST technique is more effective in revealing the cause of obstruction in malignant biliary or pancreatic disease, whereas the FSE technique is more accurate in demonstrating choledocholithiasis [38].

Finally MR angiography is a virtual non operative technique that can be used as CT angiography for assessment of hepatic (arterial and venous) vessels.

23.5. Scintigrams – PET Scanning

The liver scan is essentially obsolete in standard clinical practice. It can be used in certain niche areas with excellent results, yet it has no presence in daily practice [39]. Hepatic scintigraphy is performed to help determine how well the liver is functioning. It is also used to help confirm other test results.

The liver parenchyma contains two main cell types, the hepatocytes (effecting metabolic function such as bile production) and the Kupffer cells (histiocytic cells of the rericuloendothelial system). The radiopharmaceutical is tailored to the clinical indication [40]. Table 23.1.

Table 23.1. Liver radiopharmaceuticals and clinical indications.

Radiopharmaceutical	Mechanism of uptake	Most common indication
^{99m}Tc-sulfur colloid	RES (Kupffer cell) extraction	Focal nodular hyperplasia
^{99m}Tc-hepatobiliary iminodiacetic acid analogue (HIDA)	Hepatocyte uptake	Acute cholecystitis
^{99m}Tc-red blood cells (RBC)	Blood pool agent	Cavernous hemangioma
^{99m}Tc-macroaggregated albumin (MAA)	Blood flow, capillary blockage	Intraarterial hemotherapy
^{133}Xe	Lipid soluble	Focal fatty tumor uptake
^{67}Ga	Iron binding, lactoferrin binding	Tumor/abscess imaging
^{18}F-FDG	Glucose metabolism	Tumor imaging

The liver maximum agent uptake is about 15 min after the injection. Views in anterior and oblique position are taken at 5min, 15min, 30min and 60min. A normal liver appears with homogenous parenchymal radioactivity which should decrease to less than one-third of its peak intensity within 1 hour. Tracer should be seen in either the gallbladder or intestine within 15 minutes or earlier. As mentioned above, most liver tumors, especially malignant, do not possess Kupffer's cell or the ability to uptake this agent. Abnormal results are detected as hepatomegaly (e.g., hepatitis, heart failure, tumors), innomogeneity (eg., metastases, hepatitis, fatty metamorphosis), focal defect (e.g., cyst, tumor, abscess), and increased focal uptake (e.g., inferior vena cava obstruction, focal nodular hyperplasia, regenerative nodule). In cases of suspected hepatic hemangioma a ^{99m}Tc-labeled red blood cells test is used which has a 100% positive predictive value [41].

Briefly, the liver scan can be of great help in distinguishing focal fatty infiltration from a more significant mass; in confirming the presence of a macroregenerative nodule (and distinguishing this mass from a HCC); and in characterizing primary liver tumors and tumor-like conditions, particularly focal nodular hyperplasia [39].

For the study of the billiary tract, a gamma emitting tracer (^{99m}Tc-HIDA) is used to assess gallbladder function, and/or look for an infected gallbladder or obstructed bile ducts [42]. Morphine sulphate or cholecystokinin may be used, when necessary. This test is very effective in detecting acute infection of the gallbladder or blockage of a bile duct. It is also helpful in determining whether there is rejection of a transplanted liver. Furthermore, it is the procedure of choice in evaluating surgical biliary-enteric anastomoses [43], and is the only non-invasive procedure for direct documentation of biliary leakage (fig. 23.9).

The radionuclide is administered intravenously after 2 hours fasting and is taken up by functioning hepa-

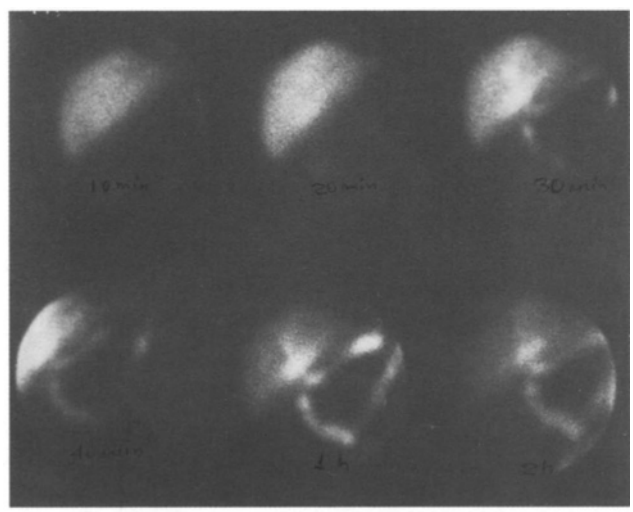

Fig. 23.9. Normal cholescintigraphy, en-series.

tocytes and excreted into the bile. The functioning liver parenchyma is delineated homogenous at 15 to 30 min, the extrahepatic biliary tract at about the same time. The gallbladder finally becomes visible 10 min onwards. The radionuclide is excreted into the bowel at 1 hour, providing morphologic and functional information (e.g., cholecystitis, bile duct obstruction, hepatobiliary system cancer).

FDG-PET provides a functional metabolic map of glucose uptake in the whole body. FDG is a glucose analogue that is labeled with a positron emitting radioisotope. The resulting radiopharmaceutical 18-fluorodeoxy-glucose (F-18 FDG) is taken up by metabolically active tumor cells using facilitated transport similar to that used by glucose [40]. Malignant cells have an elevated glucose utilisation compared with that in healthy tissue [44]. Increased metabolic activity in malignant tissue is accompanied by increased glucose uptake relative to that of surrounding normal tissue. This focal increase in glucose uptake can be detected with FDG PET, which allows identification of malignant tumor foci.

The rate of uptake of FDG by tumor cells is proportional to their metabolic activity. Since FDG is a radiopharmaceutical analogue of glucose, it also undergoes phosphorylation to form FDG-6-phosphate like glucose; however, unlike glucose, it does not undergo further metabolism because expression of glucose-6-phosphatase is often significantly decreased, thereby becoming "trapped" in metabolically active cells allowing visualisation by PET [45].

In normal liver parenchyma, the concentration of glucose-6-phosphatase is high, causing rapid clearance of FDG from the liver. This may account for the mild intensity of the normal liver on whole-body PET, especially at later imaging times post tracer injection [46] (fig. 23.10).

Liver malignant tumors (primary and metastatic) avidly accumulate FDG [40]. Liver metastases account for the most malignant hepatic tumors. FDG-PET holds great sensitivity (90%) in detecting liver metastases and differentiates them from primary tumors. It has been used in patients scheduled for primary tumor surgery or for solitary metastatic lesion in the liver. Frequently disease is show to be more extended by FDG-PET than that shown by CT and MRI, changing the whole concept in management [47].

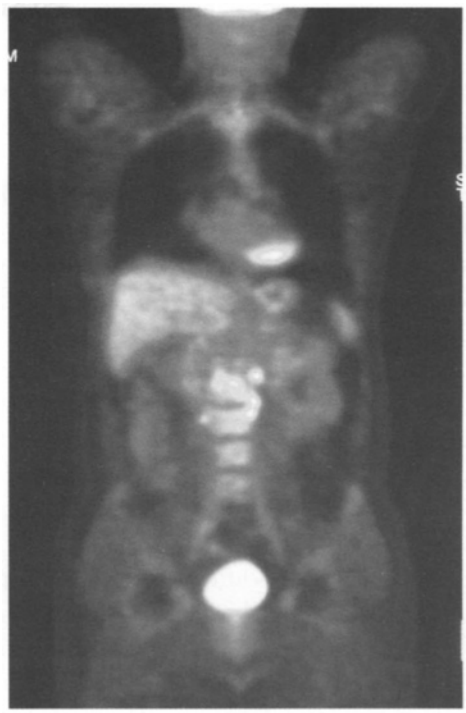

Fig. 23.10. Normal whole body PET-scan.

FDG-PET can detect cholangiocarcinoma of considerable size, but can also visualise unsuspected extrahepatic metastatic disease. Gallbladder carcinoma in most cases is presented as incidental finding at cholecystectomy. PET can differentiate benign from malignant tumors with sensitivity 75% and specificity 87.5%. Metastatic disease and local recurrence can equally be detected [48].

23.6. Angiography

With the development of new non invasive imaging techniques the indications for hepatic angiography have narrowed and are strictly defined. Today, angiography is mostly performed as part of interventional procedures, as in embolization of tumors and vascular lesions (traumatic hemorrhage, arteriovenous malformation), balloon dilatation of occluded hepatic veins, thrombolysis of portal vein and transjugular intrahepatic portosystemic shunt (TIPS).

Arteriography is used to evaluate hepatic neoplasms when other diagnostic tools and needle biopsy

fail to produce a satisfactory diagnosis (fig. 23.11). Such is the case of a large regenerating nodule which needs to be differentiated from a possible hepatocellular carcinoma and the case of pathologic uncertainty of tumor malignancy that may have angiographic features that avouch diagnosis. Another role of hepatic angiography is the preoperative surgical mapping in case of hepatectomy or transplantation. Arteriography remains a prime diagnostic tool in this situation till now, although MR- and CT-angiography with modern equipment tend to replace it in many centers [17]. Other current indications include preoperative evaluation of portal hypertension, vascular malformations, trauma and Budd-Chiari syndromes.

In unresectable tumors, transcatheter chemoembolization may be chosen for treatment.

The anatomy of liver differs from other organs by its dual, arterial and venous supply. The branches run parallel to one another and terminate in the acinus. Blood flows through the hepatic sinusoids into the periphery of each acinus. These small vessels drain into the three major hepatic veins which enter the inferior vena cava and define surgical lines of cleavage.

The arterial supply of liver is variable. Michels [49] has described 10 anatomic categories. He found that only 55% of the cadavers studied had complete arterial supply from a common hepatic artery arising from celiac axis. A branch of the superior mesenteric artery (SMA) provided a complete blood supply (replaced right hepatic artery) or incomplete supply (accessory right hepatic artery) to the right lobe in 17%. Replaced or accessory left hepatic arteries arose from the left gastric artery in 25%. Rarely one may find the hepatic artery originating from the SMA or left hepatic artery. The middle hepatic artery is as likely to come from the right hepatic artery as from the left.

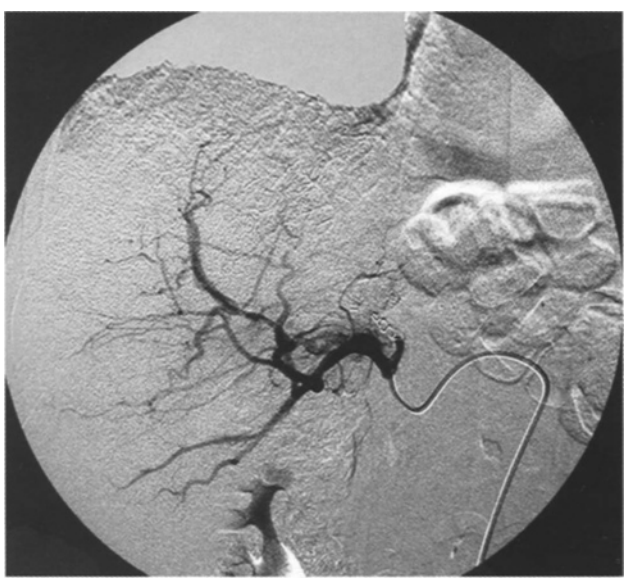

Fig. 23.11. Digital subtraction arteriography of the liver after selective catheterization of the hepatic artery.

The diagnostic accuracy of hepatic angiography has been reported between 74% and 96%. Presence of cirrhosis or obstructive jaundice can make diagnostic interpretation considerably difficult. Certain lesions can have non specific angiographic characteristics but nevertheless many of them have a sufficiently characteristic appearance to make angiography worthwhile. Angiography is reserved for those in whom surgical resection is required determining the vascular anatomy, or in preoperative embolization. Arteriovenous malformations and arteriovenous fistulae can easily be detected and embolized. Arteriography is of limited value in diffuse liver disease.

Angiography is used in prospective liver transplant recipients for determination of arterial anatomy, IVC patency and portal vein patency. It is also useful in post transplantation individuals to evaluate arterial stenosis or thrombosis, and diffuse intrahepatic arterial narrowing and arterioportal shunting indicating rejection [50].

The Budd-Chiari syndrome is caused by obstruction of hepatic venous outflow resulting in congestion, portal hypertension and progressive liver failure. Obstruction can be due to thrombosis of hepatic veins or IVC, tumoral invasion of the vessels or vascular webs and can be partial or complete. The treatment of complete obstruction is surgical placement of a portocaval shunt and the less invasive procedure of transjugular intrahepatic portosystemic shunt placement (TIPS) [51].

Conclusively the most direct evidence for Budd-Chiari syndrome is provided by IVC cavography and hepatic venography with pressure measurements in all vessels studied. Failure to opacify any veins gives the presumptive diagnosis of hepatic vein occlusion. Multiple veins should be entered, if possible, to exclude the eventuality of partial Budd-Chiari syndrome.

Portal venography (fig. 23.12) which is primarily

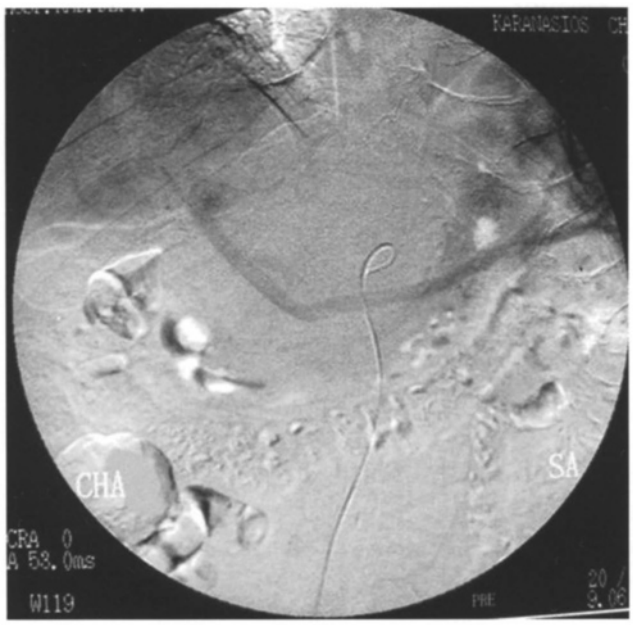

Fig. 23.12. Digital subtraction portography.

used for evaluation of patients with portal hyperpension prior to portosystemic shunt surgery or TIPS, assesses the patency and size of portal, splenic and mesenteric veins as well as the direction of flow and presence of portosystemic collaterals [52].

Other indications for portal venography include problems following placement of a portosystemic shunt, suspected mesenteric venous thrombosis, colonic or small bowel varices, and preoperative localization of functioning pancreatic islet cell tumors.

Hepatic transplantation is dependent on the patency and the size of portal vein.

Large portosystemic collateral vessels may jeopardize portal perfusion in patients with liver transplants; preoperative recognition and intraoperative ligation improve graft and patient survival [53].

Portography is occasionally useful for determining if hepatic, pancreatic or other intrabdominal tumors are surgically resectable.

The portal venous system drains blood from the small bowel, stomach, spleen, pancreas and colon. The confluence of the superior mesenteric vein at the pancreatic head forms the portal vein. The inferior mesenteric vein usually enters the splenic vein several centimeters from the origin of the portal vein.

If normal portal flow is obstructed, blood flow may pursue various collaterals to rejoin the systemic circulation. Potential portosystemic communications include left portal vein to paraumbilical veins, superior rectal veins, spontaneous splenorenal or other retroperitoneal shunts, left gastric or short gastric branches to the azygos system by way of eosophageal veins. Obstruction of main portal or splenic veins can result in the emergence of gastroepiploic, pancreatic or biliary/gallbladder venous collaterals.

Hepatic venography transjugular venous biopsy may be performed in patients with coagulopathy and diffuse liver disease for whom percutaneous transhepatic biopsy would be a high risk procedure.

23.7. Needle Biopsy of the Liver

The liver is frequently involved in a variety of diseases, focal or diffuse, benign or malignant, whose detection has been facilitated by the stride in cross-sectional imaging techniques. Nevertheless the characterization of a hepatic lesion seems unequivocal. Even in the presence of known primary tumor, liver lesions cannot always be assumed to be caused by metastasis [54]. On the other hand the new sophisticated therapeutic protocols demand a specific diagnosis. Biopsy provides the solution bearing sensitivity greater than 90% in liver than in most study series, even in cases of lesions as small as 0.5 mm [55, 56]. It is a safe and accurate diagnostic procedure for the evaluation of focal or diffuse hepatic disease that has been well established in recent years. The success rate has increased following new innovations in biopsy needles (larger calibre cutting needle that provide a tissue core), and improvement in image quality and cytologic and histopathologic techniques [57, 58].

The modalities of choice for imaging guidance are fluoroscopy, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) or a combination of these. The selection depends on the availability of equipment and personal preference, the experience of the radiologist performing the biopsy, the patient's somatotype, the lesion's location, and the relative cost.

Fluoroscopy is usually used for interventional procedures in biliary tract and not for biopsy of liver tumors. Ultrasound is the modality of choice since, com-

pared to CT-guided biopsy, it is more readily available, easier to perform, less expensive, and does not expose the patient to radiation. There are attached guides that can be fitted to transducers to facilitate the biopsy. Although these guides are widely available, many radiologists prefer the hand-free approach. It is optimal for biopsy of superficial or of moderate depth lesions in slim or average-sized individuals. In patients with anatomic variations (e.g., Kilaiditi syndrome), in lesions in difficult locations (close to the dome of the hemidiaphragm) and in obese individuals, guidance under CT is preferable [57] (fig. 23.13). Also CT- guided biopsy is universally favoured because of better visualization of the needle inside the parenchyma, and better spatial resolution. The only disadvantages are that there is no real time imaging of the needle during the insertion, the modality is not always available, and it has a relatively higher cost [59]. MRI is rarely used as a guided modality in liver lesions that are non-visible with CT or US images. This modality requires the use of special compatible needles which create a small artifact [60].

Whilst there are no absolute contraindications to liver needle biopsy, there are three relative. The first is an uncorrectable bleeding diathesis with an international normalized ratio [INR] >1.5 or a platelet count less than 50-109/L. Plugged biopsy is proposed from some authors in such cases to decrease the risk of hemorrhage [61]. The second is, an unsafe access route to the lesion (large vessels), and the third is an uncooperative patient. In ascites, considered a contraindication for percutaneous liver biopsy in the past, no statistically significant difference in rates of major complications has been proved irrespective of the needle types used, the number of biopsy passes made, or the type of imaging modality employed [62].

Most biopsies are performed with local anaesthesia under sterilized conditions on an outpatient basis. The whole procedure with its rare but possible complications explained to the patient. Knowledge of the procedure leads to a better patient collaboration.

The patient lies in a comfortable supine position. The optimal (shortest and safest path, avoiding large vessels [e.g., IVC,, hepatic arteries] and adjacent structures [lung, intestine, gallbladder] [57] inlet is selected from the available images. The needle is advanced into the lesion under guidance from the chosen inlet. There are two different techniques that are used for multiple tissue sampling. The single-needle technique, where one needle is used to make one or more insertions into the tumor, (fig. 23.14) and the coaxial technique, through a large calibre needle which enters first into the lesion and serves as a guide followed by a second longer and finer needle. This last technique has the advantage of allowing more than one sample to be taken with one puncture of the organ. Multiple core specimens must be obtained in order to confirm specific diagnosis.

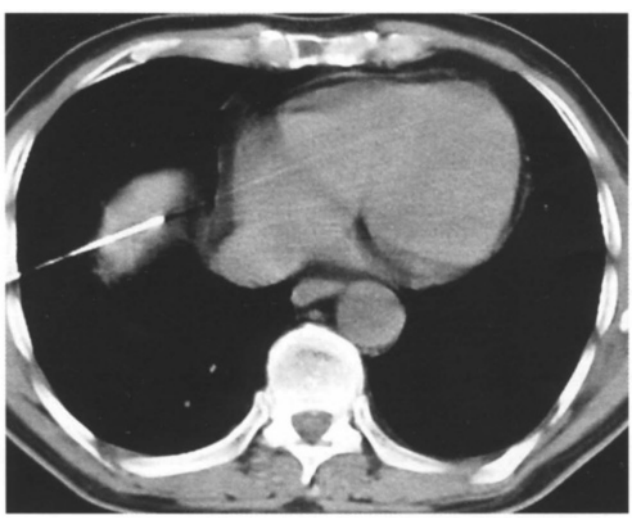

Fig. 23.13. Transthoracic liver biopsy under Ct-guidance in a subdiaphragmatic lesion in VIII segment.

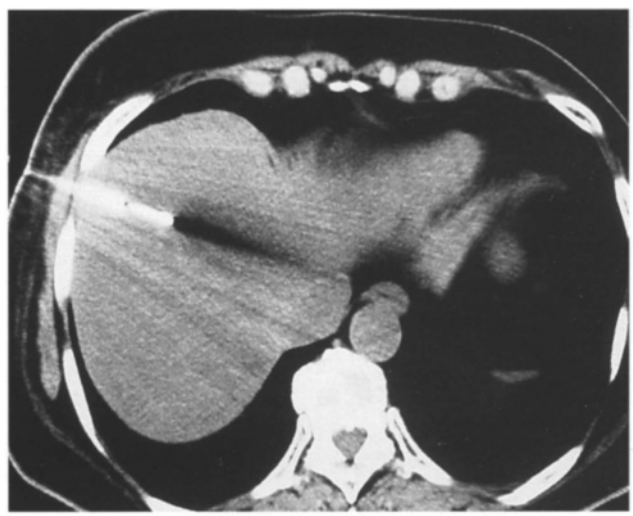

Fig. 23.14. Insertion of the needle in to the liver tumor.

The specimens handling techniques differs among institutions, so the radiologist performing the biopsy must have a prior discussion with the pathologist of the laboratory elaborating the tissue. Whatever the laboratory techniques, specimens must be handled with care. If an electron microscope is available, specimens are dipped in formaldehyde or in gloutaraldehyde. If microbiologic, PCR and culture studies are required they are placed neat in sterile boxes. A post-procedural control is performed to detect early complications. If an outpatient, the patient remains on a stretcher in the radiology department for observation 1 to 5 hours after which they are discharged. The inpatients remain in bed.

The most serious complication and the major cause of death associated with the procedure is liver hemorrhage. Other complications referred to in the literature include pneumothorax, biliary peritonitis, subcapsular hematoma, intrahepatic arteriovenous fistula. A large needle size will result in greater diagnostic accuracy but will also result in an increased complication rate [63]. Correction of abnormal coagulation indices before the procedure, patient collaboration and prudent performance of the procedure with the immediate post-biopsy follow up reduces the incidence rate of complications.

In regard to coagulopathy there are two methods of performing a liver biopsy: the plugged biopsy, mentioned earlier, and the transjugular biopsy [64]. Liver capsule transgression is avoided with the second technique. The right internal jugular vein is catheterized under fluoroscopic control, and the catheter is advanced through the inferior vena cava into a hepatic vein. A long biopsy cutting needle is advanced through the hepatic vein wall into the liver parenchyma and a specimen is taken. This method can be used only to diagnose diffuse hepatic disease.

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CHAPTER 24

THREE DIMENSIONAL (3D) COMPUTED TOMOGRAPHY IMAGES RECONSTRUCTION IN LIVER SURGERY

O. Damrah, R. Canelo, D. Zacharoulis, P. Tait, L.R. Jiao, N. Habib

24.1. Introduction

Advancement in radiological imaging technique has been crucial in the development of most of the surgical fields. Planning for operations needs good visualization of the organ and localization of the lesion within it, which was possible by Computed Tomography (CT) & Magnetic Resonance Imaging (MRI). However, without knowledge of major blood vessels or other important structures related to the lesion, surgery cannot be performed curatively and safely at the same time. In neurosurgery, this fact has been early recognized and three-dimensional (3D) imaging technique widely adopted to increase accuracy of the procedures. Similarly, reconstructed 3D images have been very useful in orthopaedic and maxillofacial surgery as well [1]. And recently, it has been widely implicated in liver surgery; liver transplantation and oncologic liver resection

24.2. Liver Anatomy

Surgeons have to know the anatomical and clinical peculiarities of the liver in order to be able to determine the site and extent of liver damage, its relationship with blood vessels and determine exactly which part of the liver should be resected.

Many anatomical classifications of the liver were proposed, in this chapter we will refer to Couinaud's classification on which liver resection planning has been based.

C. Couinaud in 1957, suggested dividing the liver based on portal and hepatic veins. He proposed a division into eight segments by the third order branch of portal vein (fig. 24.1).

C. Couinaud divided the liver into functional parts: left and right liver by a main portal scissurae containing the middle hepatic vein which is known as Cantlie's line. The surface markings of Cantle's line correspond to a plane passing from the middle of the gallbladder fossa anteriorly to the left side of the inferior vena cava posteriorly. Each right and left liver is subdivided by the left and right hepatic veins, lying in the left and right portal scissurae, respectively [2].

The right portal scissura passes at from a point at the right gallbladder fossa border back to the confluence of right hepatic vein with the inferior vena cava posteriorly. The right liver is hence divided into two sectors: right lateral sector, lying posterolateral and another right paramedian sector, lying anteromedially. Each sector consists of two segments: the right lateral sector consists of segments VI and VII and right paramedian sector of segments V and VIII. The left portal scissura or umbilical scissura lies posterior to the ligamentum teres within the liver parenchyma and corresponds to a plane passing from the confluence of the left hepatic vein with the inferior vena cava towards the most lateral left lobe tip, dividing it into left paramedian and left lateral sectors. The left paramedian sector consists of segments III and IV. The left lateral

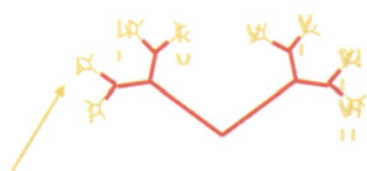


Fig. 24.1. The essence of Couinaud's idea.

sector is comprised of only one segment II, which is the posterior part of the left lobe [2].

The caudate lobe (or segment I) is functionally considered an autonomous segment, for its vascularisation independent of the portal division and three main hepatic veins.

However, in more recent studies C. Couinaud suggested that the caudate lobe could be divided into a left part or Spiegel's lobe or segment I and the right part or segment IX or paracaval portion [3].

In summary C. Couinaud described eight segments: one for the caudate lobe (segment I), three on the left (segments II, III and IV) and four on the right (segments V, VI, VII and VIII). All segments are numbered clockwise on the diaphragmatic surface and Counter clockwise on a visceral view (fig. 24.2).

24.3. Clinical Application of 3-D Reconstruction of the Liver: 3-D Imaging and Liver Transplantation

The appropriate recipient/donor match is a prerequisite for successful living donor liver transplantation (LDLT). Thus an accurate knowledge of the liver anatomy and liver volume is the most important factor in determining live liver donor candidates. A 3D visualization system that improves anatomic assessment, allows interactive surgery planning, and acts as an intraoperative guide with enhanced precision is required [4].

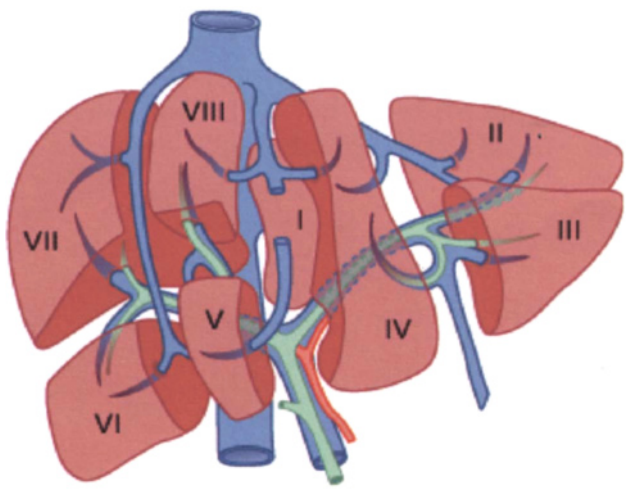


Fig. 24.2. C. Couinaud, Liver Division.

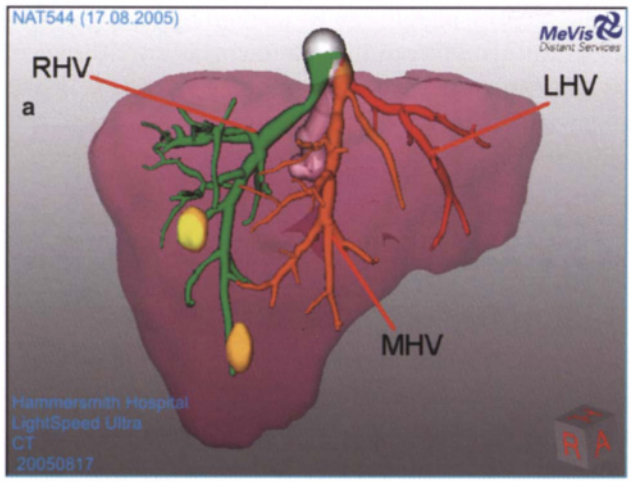
In a study conducted to assess the accuracy and efficacy of 3D CT-based visualization in LDLT, sixteen LDLT candidates and three LDLT recipients were assessed by multislice CT examination. Image processing of the digital raw data for 3D visualization included segmentation and calculation of center lines and hierarchical mathematical model representing the vascular and biliary tree was created. It was found that 3D CT-based visualization in LDLT facilitates diagnostic workup with high accuracy for analyses of vascular and bile duct variants, volumetry, and assessment of the optimal surgical splitting line of the living donor liver. Thus, the diagnostic method is of major impact on patient selection and directly influences intraoperative surgical guidance [4].

24.4. Oncologic Resections

Resection of liver tumors increases survival but success greatly depends on removal of all tumor tissue. Thus, understanding the spatial relationships between the tumor and the liver with all its architecture, stroma, blood vessels and capsule is essential. This can be achieved by using the 3-D reconstruction techniques (fig. 24.3), which allows accurate determination of the required parenchymal resection line (fig. 24.4), with an appropriate safety margin.

In addition to the determination of spatial relationships of the liver tumor, 3-D reconstruction is used for volumetry to estimate liver resection volume and the volume of the residual liver, which is the most important factor in predicting postoperative liver failure.

3-D CT volumetric measurements are acquired by outlining the hepatic segmental contours and calculating the volumes from the surface measurements from each slice. In order to identify the vascular landmarks of the liver, IV contrast administration is essential in different phases. With this technique, the total liver volume and FLR volume can be calculated immediately after scanning [5]. Two techniques of CT volumetry are used. The first method measures the volume of the entire liver plus tumors and then the volumes of each measurable tumor. Total "normal liver" volume is then estimated by subtracting tumor volume from total volume and calculated as follows [6, 7]:



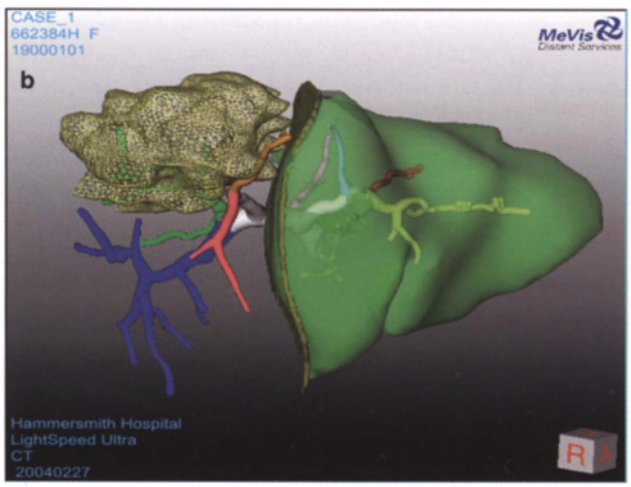


Fig. 24.3. a-b: 3-D reconstruction techniques.

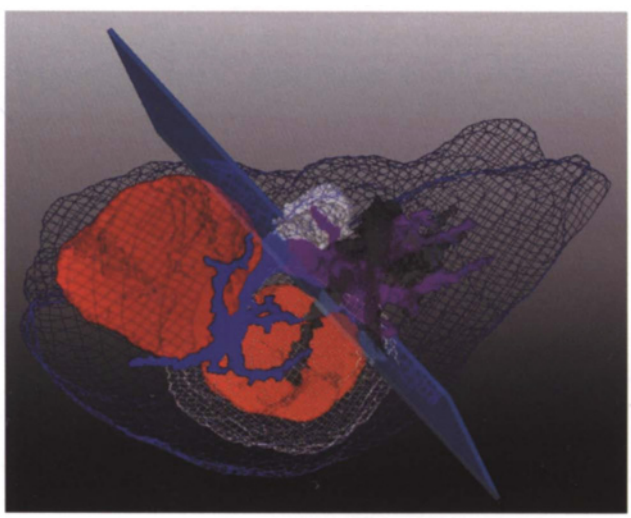


Fig. 24.4. Accurate determination of the required parenchymal resection line.

(resected volume - tumor volume)
/ (total liver volume - tumor volume)

This method can be difficult with multiple tumors. And also this approach does not account for the actual functional liver volume when there is vascular obstruction, chronic liver disease, or biliary dilation in the liver to be resected [8]. A more accurate method standardizes liver remnant size to individual patient size to account for the reality that large patients need a larger liver remnant than smaller patients need. CT is used to directly measure the FLR. The total liver volume is then estimated (total estimated liver volume; TELV) by a formula {TELV = -794.41 + 1,267 (54, 62, 63) body surface area [BSA]; $r2 = 0.454$; $P < .001$} derived from the close association between liver size and patient size based on body weight and BSA [9, 10].

The FLR/TELV ratio is then calculated to provide a volumetric estimate of function of the FLR. From this method of calculation, called standardized FLR measurement, a correlation between the anticipated liver remnant and operative outcome has been established [9].

Wigmore [11], conducted a study to establish the accuracy of virtual hepatic resection using three-dimensional (3D) models constructed from computed tomography angioportography (CTAP) images in determining the liver volume (LV) resected during liver surgery. And he found that a significant correlation was found between body weight and functional LV but not total LV. The computer prediction of resected LV after virtual hepatectomy of 3D models compared well with resected liver weight.

Another use of 3-D CT in liver oncology is its use in tumor ablation, as the success of RF ablation is dependent on an accurate positioning of the ablation probe [12].

24.5. 3-D and Training

Recent developments in 3-D CT have enabled surgeons to visualize the structures of the liver from desired viewpoints. In a study conducted by Herfarth [13], data of 7 virtual patients were presented to a total of 81 surgeons in different levels of training; surgeons were stratified concerning 2D and different types of 3D presentations. It was found that the impact of individual 3D-reconstruction on surgical planning has been pro-

ven to be significant and increases precision quantitatively.

24.6. Technique

3D models are reconstructed from multidetector-row CT-MDCT slices. They can also be reconstructed from MRI data. Triphasic contrast enhanced MDCT study with a four-channel scanner is performed. 120-140 kV tube voltage and 300-380 mAs current are used. After contrast agent injection with a flow of 5 ml/s 150 ml, 370 mgI/ml), bolus triggered scans at the early arterial, late arterial and portal venous phases are acquired (approximately 20, 40 and 65 s after injection). A collimation of 5mm is used at the arterial phases of imaging and a collimation of 2.5mm at the portal venous phase scanning [14].

24.7. Segmentation

Segmentation of the data, which is the assignment of image elements (called pixels or voxels) to different anatomical structures, is the next step in the process. Segmentation is of crucial importance for both quantification and visualization of the image material. The segmentation of the vessels can be done automatically by using a standard threshold technique because of the use of a contrast agent. This segmentation step is based on the preceding basic segmentation. Only the voxels assigned to the area of the liver are used as data input.

24.8. Data Processing

Data processing is the calculation of the safety margins belonging to each area assigned to the tumor. This means to calculate the distance between every voxel belonging to sound liver tissue and the areas marked as tumor. This is done by a distance transformation. The binary image of the tumor is used as the input image.

The different resolutions (pixel resolution and slice distance) are stored in the image header and have to be considered during the transformation. We calculate the distances in an interpolated data set where the pixel resolution equals the distance between slices.

The distance transformation results in an image where the security margin can be marked by setting a threshold calculated from the minimum-security distance. By combining this information with the image of the segmented vessels, the vessels located in the safety margin is detected [14] (fig. 24.5).

24.9. Visualization

A visualization of all interesting regions provides important information about the three-dimensional intrahepatic relations. By assigning labels to segmented regions it is possible to visualize these structures in different colors. The color visualizations are produced in batch mode and the results are presented as a digital movie or a video tape. The regions belonging to anatomical structures are assigned to "natural colors" like the liver (brownish), the vessel trees (red), or the tumor areas (gray). Information gained from the analysis is presented in colors like green for the safety margin, yellow for the vessels in the safety margin and blue for the resection proposals.

24.10. Analysis

A quantitative analysis of the image data is an important component in an operation planning system. For example, in the case of liver resection planning the resection index is a meaningful parameter. This value describes the ratio of pre- and post-operative volumes of sound liver tissue [15].

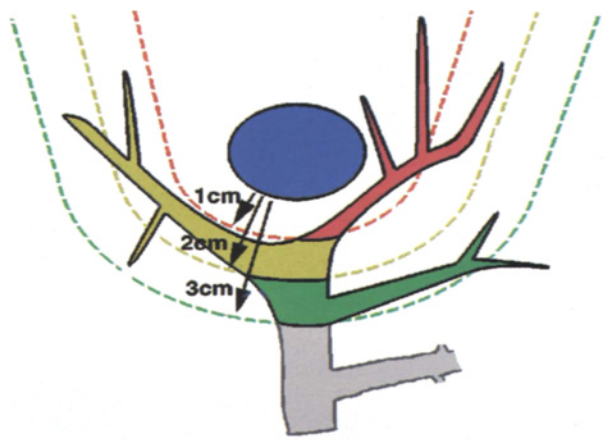


Fig. 24.5. Schematic representation of an image where security margin is marked.

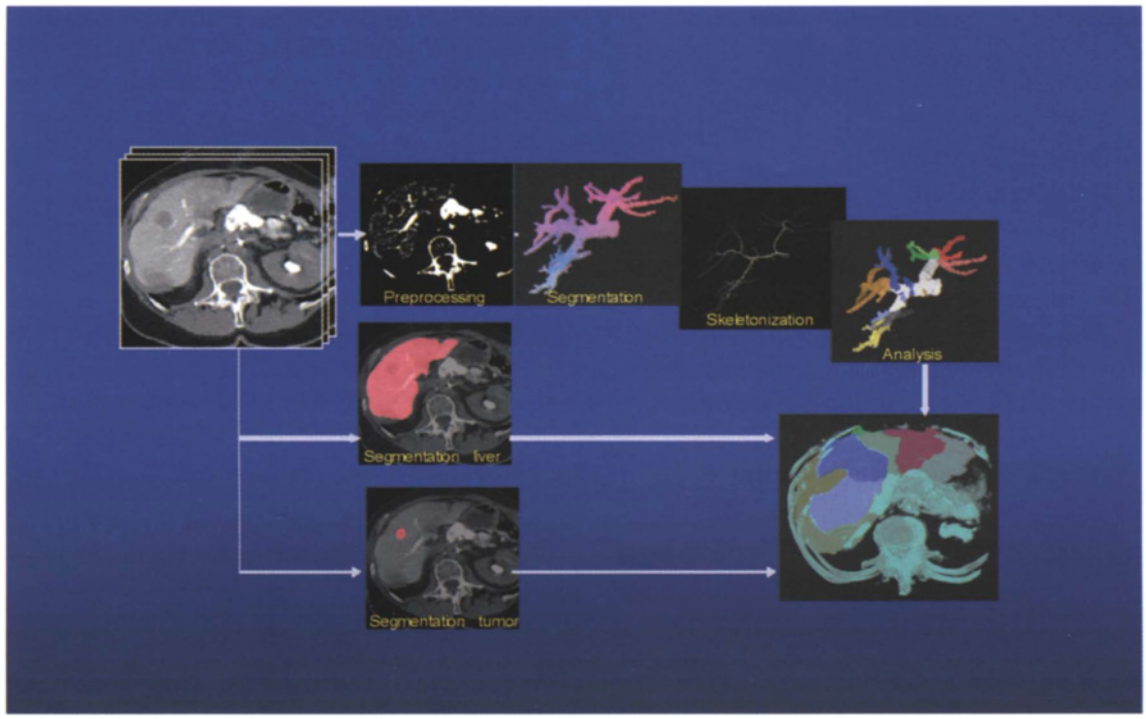


Fig. 24.6. Computer assisted surgical planning

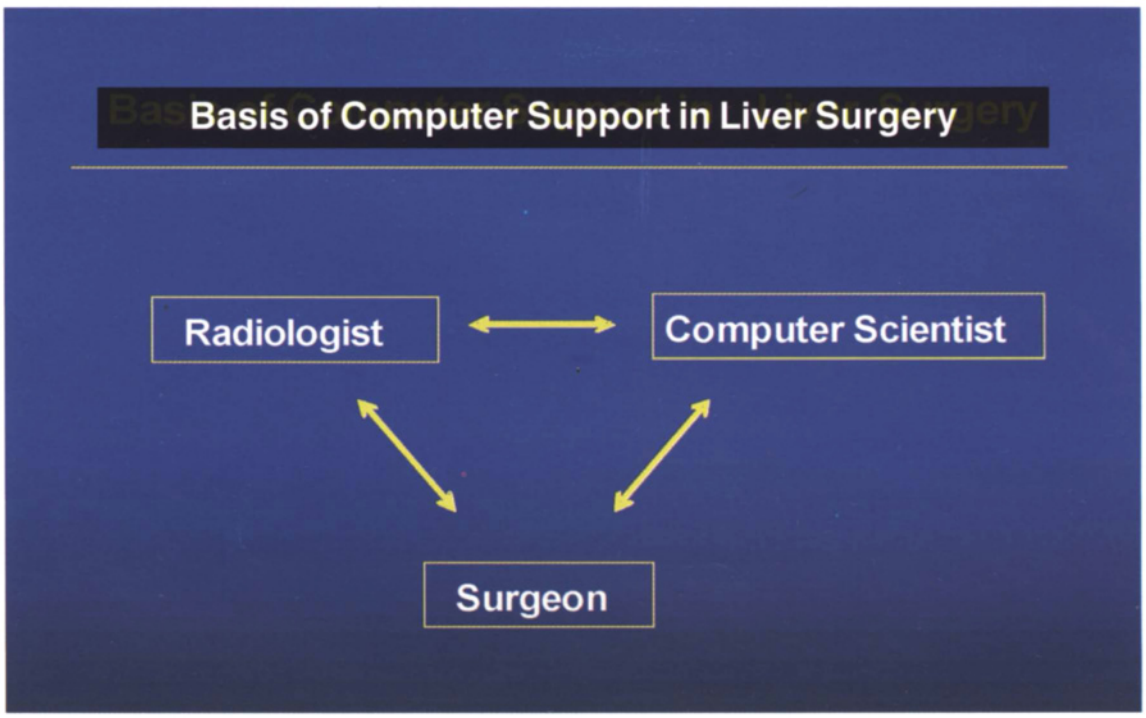


Fig. 24.7.

24.11. Softwares for 3-D CT Reconstruction

For the interactive planning of liver surgery, three systems exist: HepaVision2 (MeVis GmbH, Bremen), LiverLive (Navidez Ltd, Slovenia) and OrgaNicer (German Cancer Research Center, Heidelberg). All these systems have identified an automatic liver-segmentation procedure to visualize liver segments, vessel

trees, resected volumes or critical residual organ volumes, either for preoperative planning or intraoperative visualization (fig. 24.6, 24.7) [16].

24.12. 3-D CT and Navigation

Navigation is the art of finding the way from one place to another [17]. In surgery, computer-assisted navigation systems are highly advanced and used in clinical routine, mainly in neurosurgery and orthopedic surgery. Real-time movies of the surgical field can be matched with the virtual object that results from CT and MR images. In liver surgery, navigation is much more complex.

Critical assessment of tumor resectability of liver tumors is usually determined preoperatively, using tomographic imaging. However, this preoperative information, at present, cannot be actively used during surgery to guide resections and probe placements for ablative therapies (e.g., cryoablation or radiofrequency ablation). Intraoperative ultrasonography (IOUS) can provide intraoperative imaging information regarding tumor location and surrounding vascular anatomy, but it requires special expertise to perform and to interpret properly. A promising step towards a navigated liver operation is intraoperative computer projections of preoperatively computed visualizations in the operation theatre which demonstrated their benefit for better visualisation and improved orientation [17].

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CHAPTER 25

PREOPERATIVE ASSESSMENT OF LIVER FUNCTION

G. Sgourakis, Th. Christofides, Ch. Con. Karaliotas, Con. Ch. Karaliotas

25.1. Introduction

Hepatic failure following hepatectomy carries a dismal prognosis. Inadequate reserve compromises liver function, the ability of the liver to regenerate and results in liver failure. Jarnagin et al defined postoperative hepatic insufficiency and failure as "prolonged hyper-bilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring fresh frozen plasma and/or hepatic encephalopathy" [1].

From the oncologic perspective a R0 liver resection is ideal, but the surgeon has to balance between this concept and achievement of a sufficient functioning liver remnant to sustain life. In an effort to stratify patients in regard to the liver reserve and tailor surgical intervention, several investigators developed a spectrum of methods that range from clinical scores, to the assessment of metabolic liver pathways and radiological imaging.

Factors influencing the postoperative outcome are:

1. Larger resections [2],
2. Presence of ≥ 1 comorbid conditions [1] (diabetes is associated with increased postresectomy mortality but not all authors share this aspect) [3, 4],
3. Clinically significant portal hypertention in cirrhotics [5] and
4. Ongoing active hepatitis.

Although in theory quantitative liver function tests are superior to conventional liver function tests because they enable evaluation of specific liver functions in a quantitative manner, each dynamic test probes only to a partial aspect of liver integrity and its derangement in disease. The predictive value of standard liver function tests is equivocal but not all investigators share this skepticism [6, 7].

Peroperative predictors of liver failure include cirrhosis, ongoing hepatitis, preoperative chemotherapy, ASA classification, Child-Pugh class B and C patients, age, extent of resection, need for reoperation, peroperative blood loss > 2000 ml, transfusion with more than four units of blood, bilirubin and the development of postoperative complications [8, 9, 10].

A large proportion of patients with hepatocellular carcinoma are found to have a concurrent chronic hepatitis or cirrhosis and are considered at most risk of developing liver failure after resection than those patients with metastatic liver disease with seemingly normal livers.

Significant fatty infiltration in cadaveric donor liver enhances the possibility of graft primary nonfunction, macrovascular steatosis and also increases the severity of ischemia – reperfusion injuries [11]. There are conflicting data on literature regarding the role of steatosis as an independent predictor of a poor outcome [1, 11, 12].

There is a distinct percentage 5-25% versus 3-8% in operative mortality in cirrhotic compared to non cirrhotic patients according to several authors [1, 7, 13, 14].

Hepatectomy of up to 75% of the total liver volume (TLV) has been regarded as safe if the liver is normal. This concept of the permissible extent of liver resection has been challenged since the introduction of living-donor liver transplantation (LDLT) using a right lobe graft. Most LDLT centers have set the upper limit of safe donor hepatectomy as 65% or 70% of TLV. Unfortunately, a few living donors themselves had to undergo liver transplantation, or died due to post-hepatectomy liver failure (PHLF) [15]. On the other hand, a

considerable proportion of recipients whose partial liver graft was equivalent to near 30% of the standard liver volume (SLV) have survived uneventfully [16]. Furthermore, Preoperative Transhepatic Portal Embolization (PTPE) is now more commonly used than before, by which interlobar shifting of some liver volume and a tolerance to the elevated portal pressure can be expected [17, 18]. The development of postoperative complications may be crucial in those with borderline liver reserves [19].

Many institutions apply the Child-Pugh classification for evaluation of the liver functional reserve of patients with chronic liver disease when they undergo hepatectomy. The Child-Pugh classification (table 25.1) was originally proposed for deciding operative indications for portal hypertension [9, 10]. This classification has proven its prognostic significance in many prospective [11] and randomized [12, 13] trials, not only in patients scheduled for portosystemic shunt surgery but in conservatively treated cirrhotic patients as well [14]. However, this classification does not indicate how much liver parenchyma can be removed from patients with associated chronic liver disease. Nagao et al and Nagasue et al were not able to demonstrate any differences in mortality amongst patients stratified by Child-Pugh classes [20, 21]. Bismuth et al reported some success. They noted five deaths in their series, who by preoperative prediction should have survived [22].

Table 25.1. Child-Pugh scoring system.

Points	1	2	3
Ascites	None	Small or diuretic ontrolled	Tense
Encephalopathy	Absent	State I-II	State III-IV
Albumin (g/L),	> 3.5	2.8-3.5	< 2.8
Bilirubin (mg/dL)	< 2	2-3	> 3
INR	< 1.7	1.7-2.3	> 2.3

Child-Pugh Class A, 5-6 total points; Child-Pugh Class B, 7-9 total points; Child-Pugh Class C, 10-15 total points.

Several laboratory and imaging studies that are mentioned below have been developed to augment the preoperative Child-Pugh liver function assessment.

25.2. Indocyanine Green Retention

Indocyanine green (ICG) is a tricarbocyanine dye that binds to albumin and alpha-1 lipoproteins. Once given intravenously, it binds almost completely to plasma protein and is distributed exclusively in the serum presenting no extravascular distribution. The dye is entirely removed by the liver via a carrier-mediated mechanism, and excreted unaffected to the bile without becoming involved in the enterohepatic circulation. Biliary ICG excretion correlates with decreased hepatic adenosine triphosphate (ATP) concentration, and a decrease in hepatic energy status may reflect a compromised ability for regeneration after surgery [23] ATP-independent transporters located on the basolateral membrane of the liver embark on uptake of ICG into hepatocytes, whereas the excretion of bile into the canalicular space is initiated by an ATP-dependent mechanism. Decreased hepatic ATP level has been proposed as an important factor in liver regeneration, liver failure, and postoperative death [24]. A single intravenous bolus injection produces a typical biexponential decay plasma disappearance curve that yields two distinct linear components. This type of disappearance curve is best explained by the two-compartment model [25]. Quite the reverse to the usual two-compartment model, ICG is excreted from the liver (peripheral compartment) and not from plasma (the central compartment). In accordance with this, the initial rapid concentration fall (distribution phase), represents the uptake of ICG from the plasma into the liver, and the consequent relatively slow fall (elimination phase), represents elimination of ICG from the liver into the bile.

After the administration of ICG, the shift from the distribution phase to the elimination phase lasts approximately 20 to 30 min. Several serum values are used to obtain a number of time points to generate a rate-constant. ICG K (min-1) (elimination constant in the distribution phase from the plasma to the liver) is usually determined from the first 15-min component of the ICG disappearance curve. Hepatobiliary surgeons, generally ranged themselves with the retention time at 15 minutes as a single test. Making the assumption of a plasma volume of 50 ml/kg body weight, a single bolus intravenous administration of ICG in a dose of 0.5 mg/kg body weight results in an initial concentration of

100 mg/ml and based on this assumption, ICG R-15 can be calculated from one-point (as the ratio of the ICG plasma concentration at 15 min to its initial concentration) blood sampling data and expressed as a percentage (%). Provided that the assumption of the initial concentration of ICG is acceptable, ICG R-15 is pharmacologically comparable to ICG K, and has been commonly used as an alternative to ICG K for its convenience [26].

There is a wide-ranging concordance on the retention values that support major liver resection. Elimination is considered to be impaired when 15% or more of the dye remains within the plasma 15 minutes following administration of the dye.

The invasive ICG measurement is accomplished as follows: An intravenous bolus of 0.5 mg/kg ICG is injected rapidly through a central venous catheter or large peripheral venous line, and samples are obtained from peripheral venous line at 0, 5, 10, 15, 20 min thereafter and kept in an EDTA tube at room temperature until centrifuged at 3000 r/min for 10 min. Absorbance is measured by a Perkin Elmer spectrophotometer at 805 nm. Direct ICG retention rate at 15 min (ICG_{15D}) and the elimination rate constant ($ICG(K)_D$) values are calculated using a commercial computer program. [27]. There is also a non invasive liver function monitoring apparatus the ICG pulse spectrophotometry. Pulse-dye densitometry (LiMON, Stahigruburring, Munich, Germany) is used to measure the blood ICG concentration non-invasively in real time. This appliance makes such measurements possible by constantly monitoring the optical absorption at 805 nm and 890 nm, via an optical probe attached to the patient's finger. During the first 5-10 min after ICG is injected, blood ICG concentrations are monitored at every pulse interval via pulse spectrophotometry. The elimination rate constant $ICG(K)_E$ is calculated automatically by the time course of blood ICG concentration. The estimated ICG15 retention rate (ICG_{15E}) is obtained via pulse spectrophotometry computer analysis during the first 5-10 min. As the usual measurement time of the Limon is between 5 and 10 min, the (ICG_{15E}) is simply calculated from the ICG plasma disappearance rate.

The correlation between ICG-15_D, ICG-15_E, ICG $(K)_D$, $ICG(K)_E$ values for ICG-15 and ICG(K) by these two methods is excellent (r^2 = 0.977, 0.855) [27].

The conventional ICG clearance test is invasive and procedure-dependent. The whole process requires more than 40 min bedside for central venous catheterization and loading dosage. The two major drawbacks that may result in failure are: patient's underlying disease and medications such as for gout, arthritis, and anti-TB drugs. Technical failure may be due to blood hemolysis or laboratory errors. The real-time pulse spectrophotometry ICG clearance test is non-invasive and machine-dependent. Failure may be due to malpositioning of the detecting probe, and patient's movement. The correlation between conventional and pulse spectrophotometry ICG clearance tests is excellent in transplanted patients. ICG pulse spectrophotometry appears to be a sensitive and specific test to predict graft function in ischemia/reperfusion and patients potentially candidates for acute rejection [28]. The correlations between ICG(K) and ICG_{15} using these two methods in transplanted patients are exceptional [29].

Concomitant use of certain drugs and injectables can alter the absorbance of ICG. Injectables containing sodium disulphite particularly in combination with heparin reduce the absorption. The following drugs reduce the absorption - anticonvulsants, disulphite compounds, haloperidol, heroin, meperidine, metamizol, methadone, morphium, nitrofurantoin, opium alkaloids, phenobarbital, phenylbutazone. Drugs like cyclopropane, probenicid and rifamycin increase the absorption.

An experimental study by El-Desoky et al [30] showed the sensitivity of measurement of ICG uptake and excretion rates in hepatic artery occlusion (significant decrease in ICG uptake rate), portal vein occlusion (significant decrease in ICG uptake rate), ischemia-reperfusion injury (significant reduction in ICG uptake rate), hepatic microcirculation (positive correlation), colchicine treatment (significant decrease in ICG uptake rate), and bile duct ligation (significant decrease in ICG uptake rate).

It is postulated that, rather than considering this a true index of parenchymal function, there is a substantial influence of hepatic blood flow on the retention of the dye [31]. Hepatic artery vasodilatation may markedly influence the value in the same patient, even on the same day.

Wide variations of ICG R-15 rates among patients with CP grade A are noted. This may highlite the restrictions of using this system alone because postoperative

mortality occurs even in those patients with Child-Pugh (CP) grade A. Fan et al proposed that patients with an ICG retention >14% at 15 minutes have a greater postoperative risk [32], and this should prompt amendment of the extent of liver resection. Subsequent work coming across further at a preoperative ICG R-15 >14% in patients undergoing hepatectomy for HCC demonstrated no statistically significant difference in outcome. This study carefully enrolled patients with high ICG R-15 so that the volume of non-tumour bearing parenchyma was small (i.e., larger diameter tumours), and no difference in blood loss, morbidity, or mortality postoperatively, including major lobectomy, was noticed [33]. Authors acclaim the importance of a meticulous operative technique and postoperative intensive care.

ICG retention rate correlates sturdily with the rate of disappearance of tagged asialoglycoproteins [34]. Assessing the technique of portal vein embolization-recuperating hepatic functional reserve, in their great magnitude papers Wakabayashi et al and Nakano et al associated ICG values with hepatic hypertrophy of the contralateral lobe after portal vein embolization [35, 36]. The ICG disappearance rate generally worsened (in 16 of 19 patients) at two weeks postprocedural. ICG retention was prolonged in a number of patients who subsequently died, but other numerous patients underwent resection uneventfully, yet in the feature of elevated or prolonged ICG clearance. Captivatingly, the ICG retention rate deteriorated in virtually all patients following portal vein embolization at two weeks, increasing from a mean of 15.9 ± 6.27% to 20.8 ± 5.6% at two weeks. Possibly a two weeks time limit is too small to see ICG return to baseline clearance, or the altered blood flow due to portal vein embolization results in ICG 15 retention rates that do not allow an estimate of the hepatocyte function [37]. Uesaka et al [38] studied patients with complete obstruction of the hepatic hilus who had undergone multiple percutaneous transhepatic biliary drainage catheterizations. Biliary ICG excretion in each hepatic lobe was estimated and compared with hepatic lobar volume measured by computed tomographic volumetry before and an average of 11 days after right portal vein embolization. The percentage of ICG excretion in the left lobe to the whole-liver excretion showed a mean increase of 20.1%, which was statistically significant. In contrast, the percentage of left lobar volume to the total liver volume increased by only 8.3%.

Kawasaki et al have evaluated the plasma disappearance curves of ICG in both healthy subjects and cirrhosis patients. [25]. Plasma clearance of ICG in the cirrhosis patients was significantly lower than in the healthy subjects. Further analyses by the two compartment model (plasma compartment – liver compartment) revealed that it was the uptake constant of ICG from the plasma into the liver that decreased significantly in the cirrhosis patients; whereas the elimination constant from the liver into the bile remained relatively unchanged. Judgment is made that the decreased ICG clearance in cirrhotic patients is attributed to the decreased ICG uptake by the liver from the plasma, and the ICG excretion by the liver into the bile is upholded relatively intact. On account of this, ICG K and ICG R-15, which are estimated from the distribution phase of disappearance curve up to 15 min, are considered to be adequate as indices of Liver Functional Reserve in chronic liver disease, including cirrhosis. The core mechanism of the decreased ICG uptake (elevated ICG R-15 value) in cirrhosis patients can be explicated by decreased ICG delivery from the systemic circulation to the liver and/or by decreased uptake from the sinusoids into the hepatocytes. Several pharmacological studies have been accomplished in this regard [39, 40] and they have made known that the extraction ratio of ICG in cirrhosis patients is only 20%-30%, weighed against 70%-80% in healthy subjects. Similarly, decline in the intrinsic ability to remove ICG (internal clearance of ICG) is far more noticeable than that in liver blood flow in patients with cirrhosis [18, 40]. Intrahepatic portovenous shunt [31, 41] and the sinusoidal capillarization [34-36] are pathological changes that would explain the decreased ICG extraction ratio and intrinsic clearance that occur in cirrhosis. Unlike the capillary vessels of other organs, liver sinusoids are unique in that, substances including proteins diffuse freely between them and hepatocytes. As the capillarization of the sinusoid advances, diffusion of these substances becomes impaired and barrier-limited [34]. Diffusion of proteins such as albumin that have high molecular weights is greatly influenced by sinusoidal capillarization. ICG is almost utterly bound to plasma protein, and thus is susceptible to this adjustment. Considered together, ICG K and ICGR-15 in pa-

tients with chronic liver disease, including cirrhosis, are thought to reflect the degree of sinusoidal capillarization, intrahepatic portovenous shunt, and, to some extent, the alteration in liver blood flow.

As the ICG R15 is directly influenced by the degree of bilirubinemia, due to excretory antagonism with bilirubin, the result is not consistent until the total bilirubin level falls below 2-5 mg/dl. Prolonged obstructive jaundice and repeated cholangitis may induce diffuse shrinkage of the hepatic parenchyma, which is accompanied by prominent ductal dilatation. In such patients, Sung-Gyu Lee et al occasionally found a significant rise of ICG R15. They compared the regeneration rates of the remnant livers after right lobectomy in 30 patients with normal livers and resolved icteric livers, and did not notice any significant differences in the remnant liver regeneration during the first 7 days. They concluded that completely decompressed liver may have the same, or at least not significantly different Functional Hepatic Reserve compared with the normal liver. They also think that, the same extent of volume alteration can be expected in resolved icteric livers and normal livers after Preoperative Portal Vein Embolization. [42].

Etiological complexity makes assessment of liver function difficult in transplanted patients. The differential diagnosis comprises primary non-function of the graft, rejection, virus re-infection, drug intoxication, and thrombosis of hepatic blood vessels. Liver function tests are often difficult to interpret and are non-specific after liver transplantation. The diagnosis at present relies on a combination of biochemical, hemodynamic, clinical markers, and occasionally liver biopsy while serial observations up to 72 h are required. ICG clearance appears to be a simple and safe test to evaluate early liver graft function. The emergence of non-invasive pulse spectrophotometry has enabled bedside assessment of the elimination of ICG, hence increasing its clinical usefulness [27].

A study by Jalan et al [28] showed that the ICG measured at 24 h after liver transplantation accurately reflected graft function and predicted graft survival and outcome. In other studies, ICG excretion was a sensitive index of ischemia/reperfusion injury during the early stages post-liver transplantation [29].

25.3. 99m-Tc-Galactosyl-Human Serum Albumin Scintigraphy

Hepatocyte membrane receptors via an active transport process elaborate the metabolism of senescent proteins. Several investigators proposed the use of a liver scanning agent. EcKelman [43], Pimstone [44], Stadalnik [45], Vera [46] suggested a synthetic asialoylycoprotein, galactosyl - neoglycoalbum (NGA) complexed to ^{99m}-Tc to study binding to the hepatocytes via the asialoglycoprotein receptor. In conjunction, images that provided volumetric and anatomic data and functional assessment of the liver to clear synthetic asialoglycoproteines were processed. Kudo et al [47] adopted another synthetic asialoglycoprotein galactogyl human serum albumin (GSA) which gained a widespread use. A bolus injection of 185 MBq 99m-Tc-GSA is administered and a dynamic scintigraphy (GSA time-activity curves) with gamma camera over the heart and liver is obtained. Data acquisition is conveyed as planar or single photon emission computed tomopraphy (SPECT) images. Impaired liver function generates abnormal time - activity curves. The whole process indicates both the rate of liver uptake (elimination from blood) and the total number of asialoglycoprotein receptors.

With regard to surgical practice there is a general agreement for the use of L15 value as an overall estimate of hepatocyte asialoglycoprotein number of receptors. Postoperative receptor volume, in cases of hepatectomy, is predicted through either SPECT images or CT volumetry. Verification of the acquired data from clinical use of NGA or GSA followed the correlation of these tests with CP score, aminopyrine breath test, ICG retention and the index of cirrhosis [45, 48]. Hwang et al [49] predicted the postoperative Residual Liver Function, by 99mTc-GSA clearance estimated by dynamic SPECT analysis. Good correlation was observed between the total hepatic 99mTc-GSA clearance and conventional hepatic function tests: plasma retention rate of iodocyanine green (ICG) at 15 min (ICG R15), plasma disappearance rate of ICG (k ICG), cholinesterase, serum albumin, and hepaplastin test. There was good correlation between the predicted residual 99mTc-GSA clearance and the postoperative total hepatic 99mTc-GSA clearance in patients who underwent segmentectomy or lobectomy ($r = 0.84$, $p < 0.0001$, $n =$

28) and between the pre- and postoperative total hepatic 99mTc-GSA clearance in patients who underwent subsegmentectomy ($r = 0.91$, $p < 0.0001$, $n = 25$). Five patients who had postoperative complications due to hepatic insufficiency showed significantly lower predicted residual 99mTc-GSA clearance compared with the patients without complications (90.3 +/- 37.2 versus 320.9 +/- 158.8 mL/min; $p < 0.005$).

Kawamura et al [50] studied the natural course of changes in hepatic functional reserve in patients (12 healthy subjects, 86 patients with chronic hepatitis, and 226 patients with cirrhosis) with chronic liver diseases evaluated by scintigraphy with GSA. The receptor index was lower for more severe disorders, decreasing in the order of chronic hepatitis and cirrhosis in stages A, B, and C. The index of blood clearance was higher for more severe disorders, increasing in the order of chronic hepatitis and cirrhosis in stages A, B, and C. The mean annual change in the receptor index with chronic hepatitis was -0.0007, that with cirrhosis in stage A was -0.0023, and that with cirrhosis in stage B or C was -0.0117. The difference between the median annual change with cirrhosis in stage B or C and that with chronic hepatitis or cirrhosis in stage A was not significant ($p = 0.064$ and 0.251, respectively). The mean annual change in the index of blood clearance with chronic hepatitis was 0.0018, that with cirrhosis in stage A was 0.0060, and that with cirrhosis in stage B or C was 0.0330. The difference between the median annual change in the index of blood clearance with cirrhosis in stage B or C and that with chronic hepatitis or cirrhosis in stage A was significant ($p = 0.004$ and 0.007, respectively). Kwon et al [47, 51] suggested that there is an absolute threshold in receptor number below which extended hepatectomy is refractory. It is also postulated that in patients with chronic hepatitis a discrepancy between ICG and GSA data may be important, since patients who have the potential to regenerate may also have active cirrhosis that may confuse outcome. The spectrum of time – activity curves for cirrhosis was depicted by Ha-Kawa et al [52] and their data was reproducible in a number of settings.

As stated by Kokudo et al there is a receptor concentration reduction after liver resection and a following receptor recovery over time (possibly due to an impaired asialoglycoprotein endocytosis and hepatic blood flow) even after 150 days postresection [53].

Portal vein embolization resulted in receptor number reduction on the affected segment according to Akaki et al [54] in cases of cholagiocarcinomas of the liver hilum. They also postulated that in cases of hilar cholangiocarcinoma that involves the portal veins and decreases portal venous flow, lobar decrease in 99mTc-GSA accumulation correlated well with decrease in ipsilateral portal venous flow ($p < 0.0005$). The count ratio was significantly reduced when unilateral portal venous flow decreased ($p < 0.05$) [55]. Nakano et al [56] formed an increase in receptor numbers of the entire liver after the resection, in patients received preoperative portal vein embolization. Another noteworthy conclusion in this study was the reduction in receptor numbers in patients (potentially resection candidates) who underwent preoperative transarterial chemoembolization.

In fact there is a trend towards an increase in receptor numbers after homeostasis but not on a predefined timely course. Alterations in hepatic blood flow, such as in the case of portal vein occlusion, may intervene with GSA or ICG retention results. Tanaka et al [57] demonstrated changes upon GSA time activity curves and questions have been answered [58] regarding the relationship of receptor numbers and hepatocyte mass in cases of portal vein embolization and specific surgical procedures. Using GSA data several authors [59] and an accurate assessment of postoperative receptor numbers tried to select patients for specific surgical procedures based on calculations of functional remnant receptor volume but Wakabaashi et al [60] disclosed that these estimates markedly changed after alterations of blood flow, making these assumptions inapplicable for the extent of liver disease or postoperative recovery. In due course there was a shift in receptor numbers towards the hyperplastic liver lobe after contralateral portal vein embolization as stated by Kubo et al [61]. Besides the predictable volume increase in liver parenchyma there was also a functional improvement (even in cirrhotics) detected on GSA time activity curves. The predictive value of the test to identify patients with likely complications is limited by concomitant careful patient selection and the exclusive reduction of deaths from liver failure in recent years [57]. GSA results correlate well with (ICG, Child-Pugh and other indices of liver function and recent studies try to more appropriately link the acquired data with outcomes.

Xiao-Feng Li [62] investigated asialoglycoprotein receptor concentration in tumor - bearing livers and potential changes after sectorial resection in 10 normal liver controls and 44 liver tumor patients who underwent segmental hepatectomies. Receptor concentration was reduced in tumor bearing liver. Receptor concentration early after hepatectomy showed great variability and was negatively correlated with the percentage of resection of hepatic functional volume. In small resections postoperative receptor concentration exceeded preoperative levels or remained unchanged. In large resections portoperative receptor concentration decreased. Postoperative change in receptor concentration had a negative correlation with change in functional volume.

Ohno et al [63] in their preliminary report recorded a quantitative evaluation of the regional dynamic function of hepatocytes after living donor liver transplantation using 99m-Tc-GSA. Distinctive features in their modality were that the influence of the blood flow and the thickness of the hepatic parenchyma was completely excluded and no attenuation correction was required and they also could set arbitrary regions of interest in the liver so that it was easy to compare the dynamic function between various regions inside the liver. Authors consider that this modality is a valuable adjunct to evaluate the regional deterioration of the dynamic function of the liver following liver transplantation or auxiliary partial orthotopic liver transplantation. Kwon et al [64] evaluated the preoperative assessment of the safety of an elective hepatectomy for living donors using GSA liver scintigraphy in 152 patients. The maximal removal rate of GSA (GSA - Rmax) was calculated using a radiopharmakoninetic model. They determined the areas for resection preoperatively depending on the operative procedure and calculated the local GSA - Rmax in the predicted residual liver (GSA - RL). A significant correlation was found between the GSA - Rmax and the 15 minute retention rate of ICG. GSA - RL should be > 0.15 (mg/min/50 kg body weight) to avoid postoperative hepatic failure.

Onodera et al [65] studied 20 healthy volunteers and 137 patients with hepatic diseases (102 patients were diagnosed with hepatocellular carcinoma, 28 chronic hepatitis and 109 cirrhosis). They defined the new indicator "LUR" (Liver Uptake Ratio) dividing the liver SPECT of 99m-Tc-GSA by a syringe SPECT of 99m-Tc-GSA. According to this study, assessment of liver function was more accurate with the SPECT method than the planar method. The border value of LUR was 30%, so a LUR of 30% was the 25th percentile of the Child-Pugh A group, for which the prognosis was comparatively good. The mean - standard deviation of ICG R15 was 32% in the same way. Patients having LUR > 30% had a 5 years survival rate 65% and for those having LUR < 30% the corresponding number was 32%.

Bennink et al [66] investigating the role of liver scintigraphy in hepatic resection for malignant and symptomatic benign hepatobiliary tumors found a strong positive association between liver function reserve determined with scintigraphy and ICG clearance. A strong positive association was found between the remnant liver function determined preoperatively and the actual measured value postoperatively. They stated that determination of the Remnant Liver Function rather than Remnant Liver Value might clarify some of the discrepancies observed in the literature between Remnant liver volume and clinical outcome in patients with an inhomogeneous liver function. Liver function regeneration could also be well monitored.

Nishigama et al [67] devised an original Predictive Residual Index (PRI) by combining the k-value (rate of disappearance of circulating radiotracer) with Functional Liver Volume which were measured by dynamic liver SPECT immediately before and 2 weeks after percutaneous transhepatic portal embolization on 22 patients. They concluded that when PRI value was above 0.400 (20 patients) there was a low probability of hepatic failure postoperatively.

Satoh et al [68] devised the same Predictive Residual Index in 55 patients. The cut off PRI value was 0.370, above which there was a low probability of postoperative hepatic failure. Hirai et al [69] performed Right Portal Embolization (PTPE) in 30 patients. Morphologic and functional hypertrophy in the left lobe after PTPE was determined and related to the presence or absence of cholestasis, biliary drainage of the embolized lobe, and postoperative liver failure. The volume of the left lobe and (99m)Tc-GSA uptake increased rapidly for the first week after PTPE, but no significant increase was observed during the second week. Morphologic hypertrophy was less pronounced in patients with jaundice ($p = .03$). When PTPE was

performed at a total bilirubin level above 2 mg/dL, the interval between PTPE and surgery was prolonged due to cholangitis and liver abscess formation. The net morphologic hypertrophy ratio was significantly higher in livers that had undergone left lobe drainage only (9.1% +/- 0.9%) compared with those in which there was drainage of the embolized lobes (5.7% +/- 0.9%; p = .03). The volume and (99m)Tc-GSA uptake of the left lobe in the second week after PE was significantly smaller in patients with postoperative liver failure (33.7% +/- 2.4% and 18.0% +/- 2.1%, respectively) than in patients without liver failure (46.2% +/- 1.4% and 38.4% +/- 2.3%; p = .003 and p = .01, respectively). Sugai et al [70] devised LUD (Liver Uptake Density) to Preoperative Transhepatic Portal Embolization (PTPE) in 11 patients. Responses of LUD to PTPE before hepatic resection in the future remnant lobe represent changes in asialoglycoprotein receptor activity per hepatocyte and predict responses to subsequent hepatic resection. LUD increased significantly after PTPE in the group showing a good outcome after hepatic resection but decreased after PTPE in the group showing a poor outcome (post-PTPE LUD, 0.064+/-0.017%/cm^3 versus 0.035+/- 0.006%/cm^3, P < 0.05; response rate, 22.2%+/-11.9% versus -8.9%+/-17.6%, p < 0.01). Fukui et al [71] assessed liver function in chronic liver disease and regional function of irradiatead liver with (99m)Tc-GSA. The Hepatic Extraction Fraction (HEF), the rate constant for liver uptake of the tracer from the blood and Hepatic Blood Flow Index (HBFI) values for the irradiated portion of 20 patients before and after irradiation were compared. The HEF value in patients with a cirrhotic liver significantly (p < 0.002) decreased compared with that in patients with a normal liver at a dose of less than 40 Gy, whereas the HBFI value in patients with a normal liver significantly (p < 0.05) decreased compared with that in patients with a cirrhotic liver at a dose of 40 Gy or greater. Akaki et al [72] found non-tumorous decreases in 99mTc-GSA accumulation in 32 of 269 patients (12%). In 16 of the 32 patients (6%), non-tumorous decreases in 99mTc-GSA accumulation corresponded to regional decrease in portal venous flow. The causes of such decrease in portal venous flow were portal thrombus of hepatocellular carcinomas in eight patients, portal venous stenosis or occlusion by hilar cholangiocarcinomas in five patients. In eight patients (3%), the regions with decreased 99mTc-GSA accumulation correlated with massive hepatic necrosis in fulminant hepatitis, scar in hepatitis, or confluent in portal venous flow, lobar biliary stasis, or both. In four patients (1.5%), the exact causes of non-tumorous decrease in 99mTc-GSA accumulation could not be determined. Fukunaga et al [73] correlated Hepatic functional reserve in patients with biliary malignancies and showed that LHL15 (the count ratio of the liver to the sum of the heart and liver 15 min after injection of 99mTc-GSA) was significantly associated with bilirubin half-life in patients treated preoperatively with percutaneous transhepatic biliary drainage (p = .007). After surgery, 4 of 18 patients with LHL15 < 0.925 died within 30 days. The postoperative mortality was significantly greater in patients with LHL15 < 0.925 than in patients with LHL15 > or = 0.925 (p = .033). Sasaki et al [48] in their study for clinical usefulness of scintigraphy with 99mTc-galactosyl-human serum albumin (performed in 10 healthy subjects, 42 patients with chronic hepatitis and 158 patients with cirrhosis) for prognosis of cirrhosis of the liver found that the median receptor index was lower in patients with cirrhosis than in patients with chronic hepatitis or in healthy subjects, and the median index of blood clearance was higher. The receptor index was significantly lower when a complication (varices, ascites) was present. The index of blood clearance was significantly higher when a complication (varices and ascites) was present. Correlation of the two indices with classic indicators for functional reserve was significant. On the basis of the receptor index, the patients with cirrhosis were divided into two groups of roughly equal size: group A, receptor index over 0.85, and group B, receptor index 0.85 or less. On the basis of the index of blood clearance, the patients with cirrhosis were divided into two groups of roughly equal size: group A, index of blood clearance < 0.70, and group B, index of blood clearance > or = 0.70. The cumulative survival rates were lower in group B than in group A.

Kira et al [74] performed 99mTc-GSA in 32 patients with hepatocellular carcinoma before and after chemolipiodolization, which was performed from the right hepatic artery (RHA) in 15 patients and the proper hepatic artery (PHA) in 17 patients. The regional hepatic accumulation index (LHL15) and the regional uptake constant index (KU) were also calculated from the time-activity curves. In the RHA group, regional LHL15

and KU of the left lobe significantly increased, but they did not significantly increase in the PHA group. In the right lobe, no significant change in regional KU or LHL15 was observed. In the poor prognosis group, all indices in both regions decreased after chemolipiodolization, especially the value for regional KU which had a poor score before chemolipiodolization.

25.4. Hippurate Ratio

The hippurate ratio is estimated by comparing PABA levels and hippurated metabolites levels (30 minutes after per os PABA administration of 5 mg/kg) in relation to the baseline values. The total amount of glycine conjugates of PABA is reflected by the hippurate ratio and there is a well established correlation with the severity of liver disease [75].

According to the study of Furuya et al [76] individuals with Child's C chronic hepatic failure had a hippurate ratio of 1.9 ± 5 % while the respective value for healthy controls was 59 ± 10,5%. With the exception to child class A patients where clear cut values were not observed between controls and patients with chronic liver failure, there was a clear distinction between values across all other Child's classes.

The measured levels of para-aminohippuric acid may be useful in the prognosis of acute liver failure. Lebel et al [77] have investigated the role of para-aminohippuric acid in predicting children with fulminant hepatic failure and found a greater sensitivity than King's College Criteria in anticipating poor outcome.

The hippurate ratio was used in a recent prospective study of 61 cirrhotic patients being considered for resection of HCC [78]. The hippurate ratio compared to ICG clearance in the same patient population was found to be an accurate predictor of liver failure in distinction to ICG clearance rates. However, although an interesting study, its results will need to be confirmed in a larger group of patients, as only 35 of the 61 cirrhotic patients actually underwent liver resection.

In relation to MEGX (a test with comparable results) clear advantages were noticed by Duffy et al: oral administration, independency of cytochrome p450 and fewer adverse effects [79].

25.5. Amino Acid Clearance Test

The uptake of amino acids by the liver in protein synthesis is measured by the amino acid clearance test [75]. Clowes et al [80] found significant differences between survivors and non survivors after portocaval shunt. On the contrary Lau et al [81] were not able to demonstrate significant differences in those patients dying from postoperative liver failure, but this conflicting evidence was attributed to the relatively early grade of cirrhosis in the study population.

25.6. Aminopyrine and Phenylalanine Breath Test

The demetlylation and metabolism of intravenously administered radioactive carbon-labeled aminopyrine is measured by the Aminopyrine Breath test [75]. N-demethylation of aminopyrine takes place in liver microsomes and amino-antipyrine and formaldehyde are produced. Oxidation of formaldehyde into bicarbonate follows and part of it is exhaled as carbon dioxide [82]. The phenylalanine breath test is non-invasive and relativelly simple to perform. The patient ingests an oral dose of L-[^{13}C] phenylalanine and then the individual breathes into a device that collects expired CO2 at intervals for up to 2 hours after the radiolabeled complex is ingested. The amount of exhaled ^{13}CO2 is then used to compute the percentage of the original phenylalanine dose undergoing hepatic demethylation or oxidation. The exhaled radioactive carbon dioxide represents a quantitative measurement of microsomal function through pathways dependent to cytochrome P450 (thus affected by numerous factors).

Merkel et al [83] concludes that there is no superior advantage over Child-Pugh classification in assessing prognosis. The test reliably predicts mortality in patients with chronic liver disease undergoing non hepatic surgery [84]. Horsmans et al found decreased values to be associated with poor outcome, one year after portocaval shunt [85]. However, Lau et al doubts its prognostic value in patients undergoing hepatectomy for HCC [6] and Fun et al did not find it to be superior to ICG in predicting postoperative mortality [32].

25.7. Monoethylglycinexylidide Test

A measurement of the levels of monoethylglycinexylidide (MEGX) a hepatic microsomal metabolite of lidocaine, in the serum 15 minutes after an intravenous injection of lidocaine (1 mg/kg) is useful in distinguishing patients with mild liver dysfunction from those with cirrhosis [86]. MEGX has been used to determine risks of developing liver failure after transcatheter arterial chemoembolization in patients with HCC [87] and in the field of liver transplantation because patients with chronic liver disease and decreased MEGX formation (< 10 ng/mL) have been shown to have a poor 1 year survival [88].

There is some overlap of the levels of MEGX between Child's classes [89]. Nonetheless, using this test in addition to ICG clearance can be useful in selecting patients to undergo partial hepatectomy who are at low risk of developing postoperative liver failure, despite the presence of a fatty or cirrhotic liver.

25.8. Measurement of Liver Volume

Preoperative measuremens of liver volume are obtained by contrast enhanced computed tomography (triphasic whole liver spiral CT). Blood vessels are considered as anatomical landmarks for hepatectomy simulation and conclusively the second (portal venous) phase is used in the majority of the protocols [90]. For hepatectomy simulation, scheduled resection lines and liver surfaces are traced on all sections referring to various anatomical landmarks (e.g. hepatic veins, gallbladder fossa). Whole liver, resection and tumor areas are added in all CT sections and each volume is calculated [91].

The following equation computes the anatomical resection ratio: Anatomical resection ratio (%) = resection volume - tumor volume/total liver volume - tumor volume × 100. Radionuclide scanning nevertheless shows different results from CT volumetry evaluating the Functional Resection Ratio [91].Computed tomography volumetry may overestimate the resection volume in patients with unilateral portal venous flow decrease or stenosis/occlusion because it calculates values for hypofunctioning lobes. This ascertainment poses the dilemma between avoidance of post resection failure and the reduction in the number of the potential surgical candidates. There is a large body of skepticism with large tumors replacing a large volume of the liver because these may artificially augment the percentage of postresectional liver parenchyma due to compression and destruction of normal tissue. [75].

Azoulay et al limited resection (no more than 2 segments) to those patients who were <70 years of age with ICGR-15 <10%, albumin >30 g/L, bilirubin <20 mmol/L, prothrombin time >80% of normal, and an estimated rate of remnant functional liver parenchyma >40% as measured by spiral CT [92].

Zhu Ji-Ye et al [93] found that the average liver volume of portal hypertensive patients was 797.02 cm^3 ± 227.52 cm^3. All portal hypertensive patients were HbsAg or HCV - antigen positive with neither existing cardiac disease nor space-occupying hepatic lesion. Among 24 cirrhotic portal hypertensive patients who received H-graft portocaval shunt (8 mm), the morbidity of postoperative encephalopathy and the one year mortality were found to be higher in those patients in whom liver volume was lower than 750 cm^3.

Shirabe et at [94] documented that in hepatitis B or C positive patients who undergo right hepatectomy, a postoperative liver volume <250 ml/m^2 is predictive of postoperative liver failure. Based on the results of computed tomography volumetry several authors [95] selected patients as candidates for liver resection for preoperative portal vein embolization.

25.9. D-Sorbitol

Blood and urine samples are collected four times before and after intravenous D-sorbitol infusion. The hepatic clearance of D-sorbitol is then calculated according to enzymatic spectrophotometric method [96].

In a study Zheng Pan et al aiming to evaluate hepatic reserve function by investigating the change of functional hepatic flow and total hepatic flow in cirrhotic patients with portal hypertension combined modified hepatic clearance of D-sorbitol with duplex doppler color sonography. They found the method to be effective in the measurement of Functional Hepatic Flow (FHF) and Total Hepatic Flow (THF) and that FHF can be used to estimate hepatic reserve function [97].

25.10. Clearance of Galactose

Another test of hepatocyte microsomal capacity involves an intravenous injection of galactose followed by serial measurement of serum galactose levels to determine hepatic clearance of galactose. This test is not affected by altered hepatic blood flow rates that may occur with cirrhosis. Both of the radiolabeled tracer studies and galactose elimination rate have been shown to increase the predictive accuracy of postoperative liver failure in cirrhotic patients with borderline abnormal ICG clearance rates. It is also prognostic in chronic active hepatitis and primary biliary cirrhosis [98].

25.11. Other Tests

Carbon-13-caffeine is principally metabolized to theophylline, paraxanthine, and theobromine with release of radiolabeled carbon dioxide. Measures by means of blood, saliva, and breath tests can be done to count its metabolites [99]. Few data exist in the assessment of preoperative functional reserve.

The arterial ketone body ratio is a measure of the ratio of ketone bodies, acetoacetic acid and beta-hydroxybutyric acid, after a period of fasting. There is a statistically significant difference between the ratio of patients with cirrhosis and that of normal livers, and a ratio < 0.5 discriminates those with a higher rate of postoperative mortality and morbidity [100]. It has also been used to predict graft survival in the early postoperative period [101].

Trimethadione (TMO) is N-demethylated in liver microsomes by a P450-dependent procedure to dimethadione (DMO). The ratio of TMO to DMO calculated 4 hours after oral administration of TMO is associated with the severity of liver disease [102]. Ishikawa et al, found 5 out 45 patients with HCC to have DMO-to-TMO ratios <0.15 with a poor postoperative outcome [103].

25.12. Patient Selection, Scoring Systems and Resection Outcomes

Some recent studies address the question of whether there is a formula that provides a substantial benefit in the selection of patients for resection, beyond clinical experience and the CP score. As stated by Sneider [37], the awesome note is that there is a sizeable amount of experience-based patient selection among authors. Discerning which patients are the poor risk Child Class A patients is the required objective. Avoiding resection of more than four-segment in "poor-risk" Child-Pugh Class A patients is a straightforward target, unless Preoperative portal vein embolization is to be pursued.

Performing more than 3000 liver resections since 1989, Lee and Hwang [42], included liver function tests, ICG R15, doppler untrasonography, and CT, in their protocol to assess Functional Hepatic Reserve (FHR) for non-transplant hepatectomy. Risk factors such as degree of hepatic steatosis, age, diabetes, cardiopulmonary diseases, and general performance were moreover taken into account. The Parencymal Hepatic Resection Rate (PHRR) was utilized for livers with a mass and was computed as follows: PHRR (%) = (resected liver volume - tumor volume)/(Total Liver Volume - tumor volume) × 100. The Standard Liver Volume (SLV) was also employed for large hepatic tumors, as a replacement for the Total Liver Volume (TLV). SLV was calculated according to their own modus operandi as follows: SLV (ml) = 691 × body surface area (m^2) + 95. In the absence of significant risk factors, the maximal extent of liver resection was settled on leaving a Remnant Liver Volume (RLV) of at least up to 35% of the TLV or SLV. In cases of small tumor size, the PHRR could reach 65%. On the contrary, SLV was used in huge infiltrating tumors (the PHRR is not accurate) in a way comparable to the Living Donor Liver Tranplantation. If RLV was less than 35% of TLV, or in cases of coexisting risk factors, they usually performed Percutaneous Transhepatic Portal Embolization (PTPE). They stated that almost all liver resections leaving an RLV equivalent to 35% of TLV or SLV will avoid post-hepatectomy liver failure (PHLF), given a normal liver parenchyma, a mild degree of steatosis and a patient age of less than 70 years. The results of this guiding principle were justified in their review of 400 consecutive cases of living-donor hepatectomies, in which the only significant risk factor was the extent of parencymal resection over or in the vicinity of 65% of TLV.

In the same study [42] the authors addressed the predicament of assessment of FHR for patients with icteric livers. Completely decompressed cholestatic li-

ver had the same, or at least not significantly different, FHR compared with the normal liver. They also thought that the same extent of volume shifting could be expected in resolved icteric livers (PTPE and liver resection after biliary decompression was accomplished when serum total bilirubin levels were 5mg/dl and 2mg/dl, respectively) and normal livers after PTPE. If ICG R15 was 15%-20%, they opted for PHRR to less than 50% of TLV. Constrained parenchymal resection should be considered for patients with ICG R15 beyond 20%. They adjusted the minimal RLV to the value of more than 35% of TLV to prevent PHLF, when performing hepatopancreatoduodenectomy.

In dealing with cirrhotic livers authors [42] weigh up functional hepatic reserve as follows: If ICG R15 values are between 15% and 20%, they try to make PHRR less than 50% and PLV certainly over 40% of the SLV or over 50% of the TLV. If the ICG R15 exceeds 20%, hepatectomy should be contemplated cautiously, on an individual basis, and the tolerable extent of liver resection should be lessened to segmentectomy or nonanatomical hepatectomy. PTPE reduced PHRR to less than 60% in livers with small HCC. If the ICG R15 is over 30%, they do not attempt any type of resection, but resort to radiofrequency (RF) ablation.

Jarnagin et al [104] reported 1803 hepatectomies for primary and metastatic liver disease. The selection of CP Class A patients, with an in depth radiologic workup and a comprehensive intraoperative evaluation yielded a mortality of 3.1%, with only 10.9% of deaths associated unequivocally to hepatic failure. In their series factors that consistently predicted postoperative mortality were the projected number of hepatic segments involved and the perioperative blood loss.

Imamura et al [26] developed a decision tree to stratify patients with hepatocellular carcinoma (HCC), based on three variables: the presence or absence of ascites, the serum total bilirubin level, and ICG R-15 value. In patients with signs of decompensated cirrhosis as reflected by an elevated bilirubin level or uncontrollable ascites, hepatectomy was not performed. In patients without ascites and with normal bilirubin level, ICGR-15 value became the main determinant for resectability. For patients with ICGR-15 value in the range of 10%-19%, one-third of the liver parenchyma, which corresponded to left hepatectomy and right paramedian or lateral segmentectomy, was resected. When the ICGR-15 value range was between 20%-29%, approximately one-sixth of the liver parenchyma was resected. Also, limited resection was indicated in patients with ICGR-15 values of 30% or more. This decision tree was also applied to non-HCC patients whose liver function as evaluated by the ICG test was mildly impaired. If the scheduled operation corresponded to the removal of more than 60% of entire hepatic volume in patients with normal liver, e.g., right hemihepatectomy or left trisectorectomy, or removal of 40%-60% of the entire liver in patients who had a slightly impaired liver function (ICGR-15 between 10% and 20%), preoperative portal vein embolization was performed to induce compensatory hypertrophy of the liver part to remain after hepatectomy in order to prevent postoperative hepatic insufficiency. Only a single death ensued by applying this algorithm to 1429 consecutive cases of hepatectomies (685 HCC). Since posthepatectomy mortality happens to be exceedingly low, mortality cannot be used as the primary outcome. The results of more than 100 hepatectomies performed by the author, with zero mortality under the strict application of the above patient selection criterion, instead considered, satisfactory verification of its strength [105].

Torzilli et al reported 107 patients who underwent resection for hepatocellular carcinoma without mortality [106]. Preoperative selection parameters were: the presence of ascites, the serum bilirubin level, the value of ICG 15 and the anticipated remaining liver volume. Preoperative portal venous embolization was carried out to increase the remnant volume, for patients with anticipated remnant volumes under 40% or ICG 15 values of 10% to 20%. A scrutiny upon their selection parameters designates that only CP Class A patients underwent surgery. ICG 15 value was employed for optimum patient selection (ICG 15<10%), aiming for extended resection (four or more segments). All other CP Class A stratified patients underwent minor resections as conducted by the ICG 15 value.

Poon et al [107] applied their selection algorithm based on: CP Class, ICG 15 value and a combination of anticipated remnant volume with laparoscopy and laparoscopic ultrasound (in order to notice moderate to severe cirrhosis at the time of intended resection). Forty five patients, who underwent extended resections (greater than four segments) for hepatocellular carcinoma, were compared with a group of 161 pa-

tients with four or fewer segment resections. Liver failure instigated death in one patient in each group. The authors speculated that satisfactory outcome after major resection could be anticipated among patients of CP Class A, presenting with ICG R15 <14%, or patients with a predicted large liver remnant volume with an ICG R15 value between 14% and 20%. CP Class B patients were not recommended for extended resection.

Redaelli et al [108] employed GSA time-activity curves along with the aminopyrine breath test, to select 167 patients who underwent curative resections (77 classical hemihepatectomies and 90 tissue-preserving resections). Total mortality and morbidity for the series was 3.6% and 29.9%, respectively. Morbidity but not mortality was significantly lower after tissue-preserving resections than after classical hemihepatectomy. Only 2 patients died of acute liver failure.

In selected cases with small liver remnants, operation planning may be improved substantially by preoperative computer-assisted risk analysis. Image-based computer assistance allows for areas at risk of devascularization or venous congestion to be identified and precisely calculated before resection. Lang et al [109] evaluated 25 consecutive patients admitted to hospital for major hepatectomy. The deviation between liver volumes determined by 2-dimensional computed tomography and by computer-assisted risk analysis was less than 20% in 14 of 21 patients, between 20% and 30% in 3, between 30% and 40% in 2, and 41% and 43% in 1 patient each. The most extensive deviations were found in extended left hepatectomy or when left hepatectomy was combined with additional wedge resection in the right lobe. In 7 cases, all with a deviation greater than 20%, the results of computer-assisted risk analysis led to a change of operation planning with regard to the extent of resection (n = 3) or the need for vascular reconstruction (n = 4), although in 1 of these cases resection was not performed because of peritoneal carcinomatosis.

On a multiple regression analysis Yamanaka et al [110] evaluated initially 17 preoperative parameters. In their regression equation (predicting postoperative liver failure if score > 50) parameters ultimately included were: Parencymal Hepatic Resection Rate as estimated by CT, the ICG retention rate and patient's age. Implementation of these scores preoperatively modified their policy of patient selection and mortality was reduced from 17% to 6%. A further refinement of this scoring system based on 10 years of use, classified patients in several categories. A score > 55 showed patients at risk, borderline values were regarded between 45 and 55 and a score < 45 was considered as safe [111]. From those patients considered to be in the safe zone suffering from HCC, 7.3% died due to hepatic failure but none undergoing resection for metastases [112].

Gazzaniga et al [90] use CT and US portal Doppler analysis and liver biopsy in non cirrhotics to select patients for major hepatic resection based on the activity index (scoring system adopted by the "Gruppo Italiano Patologia Apparato Digerente" [113]. Patients who indicate a mild or moderate activity index on liver biopsy are considered for major resection. In cirrhotics only patients of Child class A with the absence of F2-F3 varices, normal renal function, age < 65 years, aminopyrine breath test > 8% dose/hour and activity index mild or moderate are considered as candidates for major hepatic resection.

Combining CT volumentry and ICG-RI5 Kubota et al [114] proposed that resection ≤ 60% of nontumorous parenchyma was acceptable in patients with normal livers and that resections ≤ 50% of nontumorous parenchyma was acceptable in patients with an ICG-RI5 between 10 and 20%. They recommend that when the nontumorours parenchyma volume in noncirrhotic patients is > 60% with IGC-RI5 value between 10 and 20%, then preoperative portal vein embolization is indicated to increase the volume of the residual liver.

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CHAPTER 26

INDICATIONS FOR LIVER RESECTION

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26.1. Introduction

Over the past twenty-five years, hepatic resection has evolved from a high risk, resource intensive procedure with limited application to a safe and commonly performed operation, with broad indications. This period has seen dramatic improvement in perioperative outcome, including reductions in mortality, blood loss, transfusion rates, and hospital stay [1-2]. These improved perioperative results are largely responsible for the emergence of hepatic resection as a viable and effective treatment option for selected patients with 1 and 2 hepatobiliary malignancy. Continued advances in imaging technology, along with a heightened awareness of the clinical and tumour-related variables that dictate outcome, have allowed better preoperative assessment of disease extent and improved patient selection. Advances in other areas, such as minimally invasive and ablative techniques, have increased the treatment options and have had some impact on the approach to patients with malignant hepatobiliary disease. However, resection remains the most effective therapy. The current status of partial hepatectomy is not the result of any randomised trial, demonstrating greater efficacy over other therapy. On the contrary, no such studies has ever been performed, nor is one likely to be, as the long-term results of resection are far superior to any other existing therapy [3]. Despite this, recurrence rates remain high, and further improvements in survival will require more effective systemic agents. As better adjuvant and neo-adjuvant therapies emerge, the results of resection are likely to improve and the indications for its application perhaps will extend to patients currently considered to have unresectable disease.

26.2. Indications

26.2.1.Colorectal Liver Metastasis (CLM)

Stage IV colorectal carcinoma is by far the most common indication for hepatic resection in Western countries [3]. However, no single concensus exists on the indications for surgical resection. Colorectal cancer is the third most common cause of cancer death in the UK. Surgery is the treatment of choice in patients with localised disease but more than the half of all patients will develop metastases. The liver is the first site of metastatic disease and may be the only site of spread in as many as 30-40% of patients with advanced disease. It has been postulated that, because haematogenous spread usually occurs in a stepwise fashion, initially to the liver, with subsequent intrahepatic spread via the portal vein and further spread to the systemic circulation, surgical resection of isolated hepatic metastases from colorectal cancer may be curative. The natural history of colorectal cancer is variable, with a median without treatment survival of only 8 months. Patients with isolated metastases have a better prognosis than those with more extensive metastatic disease. However, few patients with only liver metastases survive for 5 years. Around 20-30% of these are potentially resectable. Selection criteria for surgery are usually controlled primary tumour, no extrahepatic metastases and the presupposition that resection is technically feasible leaving tumour free margins. Chemotherapy is palliative when used alone, but can prolong survival in inoperable disease. Used in combination with surgery it may prolong time to recurrence after resection or downsize to resectability patients previously judged inoperable.

Indications for surgery are based purely on pro- and retrospective series, detailing the results of surgery with curative intent. The nature of these published stu-

dies does not allow quantitative analysis of the effectiveness of surgical intervention but qualitative analysis is as follows:

Surgical resection of hepatic metastases can be undertaken safely in a majority of patients (median postoperative 30 day mortality 2.8%). The most common reported causes of postoperative death include hepatic failure, postoperative haemorrhage and sepsis. Five-year disease free survival rates range average 18% in radically resected patients [4-5].

26.2.2. Hepatocellular Carcinoma (HCC)

Worldwide, primary hepatocellular carcinoma (HCC) is among the most frequently encountered solid organ tumours in the world, responsible for approximately 250,000 new cases annually. Previously considered uncommon in western countries, the incidence and mortality related to HCC is increasing, due mostly to the increasing incidence of hepatitis C virus infection. The treatment of HCC, unlike other hepatic malignancies, is often complicated by the coexistence of chronic liver disease and cirrhosis, the presence of which frequently limit treatment options. Untreated, the prognosis is grim and the only curative treatment is resection. Improvements in operative technique and postoperative care now mean that 10% mortality for the resection of cirrhotic livers with up to 50% 5 year survival rates are to be expected [5].

When HCC arises in non-cirrhotic liver, it is often diagnosed when the tumour becomes large and symptomatic. In the absence of diffuse disease involving lobes or metastases, aggressive surgical management is indicated. In these patients resection of the tumour can be considered, regardless of the tumour size, since they usually are in good general condition and surgical resection tends to involve only tumour mass rather than functional hepatic parenchyma.

Most HCCs however, occur in patients with chronic liver disease or cirrhosis. This often results in important changes in portal haemodynamics and a reduction in the functional liver parenchyma. The Child-Pugh classification is the most useful tool in evaluating cirrhotic patients with impaired liver function. Other sophisticated techniques for determining hepatic reserve, for example the plasma retention rate of indocyanine green at 15mins, preoperative portal pressure assessment and 3D-CT reconstruction of the liver can be used in deciding whether to proceed with surgery.

Resection of HCC is only considered in Child-Pugh A patients. However Child-Pugh is only used in cirrhosis and liver damage at resection can vary widely from periportal fibrosis to extensive fibrosis/cirrhosis. Therefore the operating surgeon must modify his technique, using as many preoperative investigation results as possible, before proceeding. A decision algorithm combining the presence or absence of ascites, total serum bilirubin level and ICG retention at 15 min has been proposed by Makuuchi et al. Limited resections are performed in those patients with increased ICG15.

Other modalities, for example hepatic venous pressure gradient (HVPG) have been proposed, with 10 mmHg, a threshold below of which patients are eligible for resection and above of which they are referred for nonoperative management. Factors such as the tumour size, the depth and distance of the tumour from the major vessels or the presence of intrahepatic metastases should be taken into consideration. Surgical resection is suitable for those patients with small sized solitary tumours with no portal invasion. Patients with larger tumours require careful selection. In clinical practice, these patients benefit most from multidisciplinary discussion.

Liver resection for HCC in a cirrhotic liver is contraindicated in the presence of severe liver functional impairment (such as ascites, jaundice, Child-Pugh B and C, and liver atrophy). In these cases there is increased risk of liver decompensation or failure during the postoperative period. Other situations that preclude resection are the presence of portal vein thrombosis reflecting extensive disease, lymph node metastases, extrahepatic localisations and intrahepatic multiple, diffuse disease. All these situations render any treatment palliative. The use of laparoscopic ultrasound, as a preoperative assessment tool, has further reduced liver resection rates by as much as 60%.

26.2.3. Neuroendocrine Tumours

Cytoreductive therapy is effective in the management of metastatic neuroendocrine tumours to the liver, independently of their functioning status [6]. In functioning tumours, clinical endocrinopathies are relieved in most patients and this response usually lasts for several

months. At major centres, major morbidity and mortality are within the average complication rate for resection for nonneuroendocrine metastatic tumours; therefore, surgical outcomes appear to justify operative intervention. Patients whose primary tumour can be controlled, whose metastases outside the liver are limited and who have a reasonable performance status are candidates for resection. The current mortality rate of 1.2% and major morbidity rate of 15% clearly represent the success of the operative approach in such complex cases (more than the half of the patients receive a resection of at least one lobe). A symptomatic response in up to 95% patients with median response duration of 45 months adds many months of symptom-free survival to the lives of most of them. In many patients undergoing a major hepatic resection, concurrent resection of the primary tumour is performed. These data confirm that resection in selected patients is not more complicated or risky than resection for other metastatic tumours. Endocrinopathies do not increase anaesthetic or operative risk in selected populations. However, the best results are the product of managing these patients over time, becoming familiar with their clinical syndromes and actively optimising prevention of life-threatening endocrine complications (i.e. carcinoid crisis).

Patients with cardiac-valvular disease are not good candidates for surgery. These patients develop right-sided heart failure with an increase in the central venous pressure. This condition can result in massive hemorrhage, during the liver resection, because of the difficulty in controlling backbleeding from the hepatic veins. It should, therefore, be a common preoperative policy to rule out valvular disease in every patient with carcinoid tumours and repair the valves prior to hepatic resection, when indicated.

Liver transplantation seems to be very attractive as a means of eradicating the disease. Unfortunately, it is not common in clinical practice because the shortage of allografts and the overall costs and complications of the procedure override its benefits, especially when compared with partial hepatectomy. Current methods, that were not readily available in the past, for detecting the spread of disease such as MRI and indium-111 pentetreotide (Octreoscan), may expand the applications of transplantation and allow a better selection of candidates. The option of transplantation is still open to improvement and is dependent on organ availability and better staging of the disease. Metastases from neuroendocrine tumours are hypervascular, favouring the application of MRI as the single imaging method. MRI not only evaluates the location and characteristics of the lesions but also determines the relationship with major vessels and bile ducts. Spiral CT scan has been used extensively in the past with acceptable results. Indium-111 pentetreotide functions on the base of somatostatin receptors present in these tumours, but its use has not been established definitely in the work-up of these patients. The best use of indium-111 pentetreotide is in the evaluation of disease beyond the primary and liver locations, for example to exclude bone metastases; its use, therefore, will likely affect the preoperative work-up of candidates for operative management.

Once the patient has been deemed to have resectable disease by the preoperative work-up, several steps need to be completed prior to surgery for decreasing the effect of specific endocrinopathies. For patients with symptoms related to carcinoid tumours, preoperative preparation with 150 to 500 micrograms of somatostatin decreases the chances of carcinoid crisis, which is manifested by haemodynamic instability. The use of this medication intraoperatively should be kept in mind because a carcinoid crisis can occur despite anesthetic premedication. In most patients with islet cell tumours, treatment of underlying endocrinopathy has been initiated before referral for surgical treatment.

Surgery is appropriate for patients with metastatic neuroendocrine tumours for the following two reasons:

(a) many of them still have the primary tumour in place and resection should be undertaken to avoid acute complications and
(b) the addition of adjunctive ablative therapies to surgical resection accomplishes the control of greater than or equal to 90% of the bulk of the tumour. If preoperative evaluation indicates that less than 90% of the tumour is treatable, surgical therapy is contraindicated. Last, even when complete resections are performed, the recurrence rate for these tumours is extremely high. In practical terms, patients with metastatic neuroendocrine tumours are

seldom cured. The best hope physicians can offer to these patients is an extended survival period with minimal endocrine symptoms and decreased requirements of somatostatin analogues.

26.2.4. Non-Neuroendocrine, Non-Colorectal Liver Metastases (NCNN) [9]

The role of metastatectomy for colorectal and neuroendocrine liver secondaries is well established [7-8]. Significant palliation and survival have been reported after aggressive surgical resection. Surgical resection of liver secondaries for NCNN tumours is less well defined. In the past, patients with metastatic liver disease were not considered curable and life expectancy was limited. However, progress in liver surgery has spurred the development of surgical strategies to cope with patients presenting with liver secondaries from other primary tumours. Diversity of tumour types and wide variation in adjuvant treatment schedules make it difficult to draw conclusion from the published data, but liver resections have been performed for metastatic spread from stromal (GIST), renal, lung, thyroid, parotid haemangiopericytoma, ovarian, cervical, ampulla of Vater, pancreatic and melanoma primaries to name a few. Survival is related to the nature of the primary tumour. Reports to date suggest no survival advantage in resection of liver metastases from oesophageal, stomach, small intestine or pancreas. However, survival advantages can be shown in renal cell carcinoma for example (median survival 26 months for resection vs. 6 months only for conservative treatment). Indeed, 3- and 5-year survival rates for resected metastatic breast tumours are 53.9% and 24.6%, genitourinary tumours 50.4% and 37.8%, and leiomyosarcoma 63% and 36% respectively.

Selection criteria in cases with intention to cure include; (i) absence of extrahepatic disease at the time of detection, (ii) adequate functional status of the liver and volume of remnant liver after hepatectomy, (iii) ability to obtain a clear margin of tumour clearance, and (iv) fitness for major hepatic resection. Importantly, the decision for all these patients should be agreed at a multidisciplinary tumour board before surgery, in which the expected life expectancy of an individual, the general level of fitness, comorbidities and feasibility of the surgery in such a patient need to be carried out. Furthermore, surgery can be considered to palliate symptoms of crippling pain in thyroid and ovarian metastases, with no significant difference in operative morbidity or mortality, when compared to patients undergoing curative resections for NCNN metastases.

26.3. Preoperative Management

26.3.1. Preoperative Evaluation

Medical evaluation for liver resection is the same for any other major operation. Active healthy patients under 65 can generally tolerate liver resection. Patients over 65 and those with significant comorbidity are routinely sent for formal cardiopulmonary evaluation. Those patients with lung disease are at particular risk for postoperative complications, because pain associated with the high abdominal incision, required for access to the liver, and the development of symptomatic pleural effusions, combine to limit respiratory effort.

26.3.2. Liver Failure

Major hepatic resection is possible only because of the liver's remarkable capacity to regenerate. It is generally accepted that up to 80% of a healthy liver can be resected with the expectation that complete regeneration will occur. However the presence of underlying hepatic parenchymal disease is an impediment to normal regeneration. This is particularly important in the consideration of patients with HCC, as over the half of them have some degree of cirrhosis. Even in those without cirrhosis, preoperative chemotherapy and subsequent fibrosis can have a similar effect on regenerative capacity. In the cases where regeneration is severely impaired or even prevented, the patient will go into postoperative hepatic failure.

26.3.3. Preoperative Evaluation of Patients with HCC

Stigmata of chronic liver disease may be appreciated on physical examination (ascites, telangiectasia, palmar erythema, gynaecomastia, splenomegaly, testicular atrophy, etc.), or on imaging studies. As previously discussed the Child-Pugh classification, although not perfect, is a reliable means for assessing hepatic functional reserve in patients with cirrhosis. Resection is only

considered in those in Child's A. Even in these patients, the suggestion of portal hypertension (for example the presence of thrombocytopaenia), can often imply that major resection carries too great an operative risk. Hepatic vein wedge pressure, although an invasive investigation is more discriminatory. A test commonly used to assess hepatocellular function is the clearance of indocyanine green dye 15 minutes post intravenous administration. An ICG hepatic retention value of 14% or less is considered a safe limit for identifying patients likely to tolerate resection with low risk of postoperative liver failure.

There are several staging schemes for HCC. The two most used are the Okuda and American Joint Commission on Cancer systems (diagx2). Of the two, only the Okuda provides some assessment of hepatic reserve. Patients are stratified for risk and outcome based on tumour size, presence of ascites and serum levels of albumin and total bilirubin. Patients are given a stage I-III, based on number of criteria, with increasing risk-to-benefit ratio.

26.3.4. Preventing Liver Failure

Selective portal vein embolisation (PVE) is a technique designed to increase the safety of hepatic resection and, furthermore, induces compensatory hypertrophy of the future liver remnant. In theory, by inducing atrophy of the liver to be resected prior to operation, less functional parenchyma is removed, and perioperative risk is reduced. In carefully selected patients, the portal vein branch is cannulated through percutaneous and transhepatic route and embolised with cyanoacrylate glue mixed with lipidiol, polyvinyl alcohol, or particle administration. One month after embolisation the liver is reimaged with CT, prior to consideration for resection. The degree of hypertrophy varies. The group most likely to benefit are those with underlying disease. Furthermore, some patients in this group develop hepatic dysfunction post embolisation which may predict post resection complications. To date, clear guidelines are not established.

26.4. Standard Resections-Segmentectomies

26.4.1. General Principles

The objectives of hepatic resection for malignant disease are removal of all tumour-involved liver, with a clear margin, while leaving behind an adequate, well-perfused liver remnant with intact biliary drainage [7]. Intaoperatively, the key steps involve the following: a full exploration of the peritoneal cavity, pelvis, retroperitoneum, and porta hepatis, for excluding extrahepatic disease (usually a contradiction to resection), examination of the liver with bimanual palpation and intraoperative ultrasonography, for assessing the extent of hepatic disease, control of the vascular supply to and from the portion of the liver to be resected, and parenchymal transection [4]. For cancers of the gallbladder and proximal bile ducts, the operation also includes removal of the extrahepatic biliary tree, subhilar lymphadenectomy and biliary reconstruction. In selected cases open exploration may be preceded by diagnostic laparoscopy.

The most common types of resection performed include nonanatomic wedge resection, sublobar segmental resection (single or multiple), right or left hepatectomy (lobectomy) and extended right or left hepatectomy (trisegmentectomy). More extensive resections (hepatectomy and extended hepatectomy), may be combined with wedge or segmental resections of the contralateral liver, if clinically indicated. For less extensive resections (less than one lobe), anatomically based segment-orientated resections are superior to nonantomical wedge excisions. Segmental resections involve intra- or extra hepatic control of segmental blood flow and are associated with less blood loss and lower tumour positive margin rates. Wedge resections may be safely used for small, peripheral lesions but are inappropriate for larger, deeper tumours.

26.4.2. Liver Resection: Operation [10]

Once the decision has been made to resect, the liver is fully mobilised and vascular control obtained. For major resections, the inflow vasculature can be secured by dissection in the porta hepatis and division of the arterial and portal venous trunks individually. Alternatively, the entire pedicle may be identified and divided from within the parenchyma. This technique is based on the work of Couinaud, Launois and Jamieson, which demonstrated the presence of a fibrous sheath that envelops the portal triad as it enters the liver.

Pedicle ligation is rapid, minimises the risk of injury to the other hilar structures and is particularly useful

in patients who have previous right upper quadrant surgery, which precludes further safe hilar dissection. It must be emphasised that pedicle ligation may not be performed when there is tumour near the hilus, as it may compromise tumour clearance.

Division of inflow blood supply demarcates the portion of the liver to be excised, guiding the plane of transaction. A number of different approaches exist for transection of the liver and are described in the next chapter. The most common used is the clamp crushing technique.

During hepatic resection, significant intraoperative haemorrhage typically arises from the hepatic veins, which inflow occlusion alone cannot prevent. One technique that addresses this is hepatic vascular exclusion (HVE). HVE involves inflow control (Pringle) and venous outflow control by occluding the infra-and suprahepatic vena cava. This allows parenchymal transaction in a bloodless field but results in significant haemodynamic changes due to interruption of venous return. As a result, maintenance of a high central venous pressure is required to maintain cardiac output, which can cause brisk haemorrhage on release of the clamps. A different approach reduces back bleeding from hepatic veins by maintaining low central venous pressure through anaesthetic and pharmacological means coupled with outflow exclusion. This has been shown to be associated with shorter operative time, fewer postoperative complications and shorter inpatient stay, when compared to HVE.

26.4.3. Segmental Liver Resections

The techniques of segmental liver resection have evolved from a better understanding of the intrahepatic organisation of the liver. Segmental resections have become common and account for up to 20% of specialist centre workload. Segmental hepatectomy is based on the anatomical segments of Couinaud and has several advantages. Firstly, blood loss is reduced, since the vascular inflow and outflow are controlled prior to parenchymal transaction. Secondly, segmentectomy preserves hepatic parenchyma better than lobar resection. Consequently, it is a very valuable technique in patients with cirrhosis, in whom the sacrifice of parenchyma must be minimised. Finally, and most importantly, segmental achieves better tumour clearance than wedge resection, resulting in better survival rates. It has been shown that wedge resection of CLM can result in a 30% rate of tumour positive margins, compared to 2% in segmental resectons. It is thought that wedge resections offer a poorer oncological outcome because (a) the traction on the specimen during parenchymal transaction often fractures the tumour-liver interface and (b) bleeding occurs because there is limited exposure and no inflow/outflow control.

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CHAPTER 27

LIVER RESECTION AND STAPLING DEVICES – LAPAROSCOPIC RESECTION

A. Healy, J. Tracey, N.A. Habib, L.R. Jiao

27.1. Introduction

The role of liver resection for benign and malignant hepatobiliary diseases is expanding, because of the markedly reduced operative mortality in recent years, as the result of better patient selection, improved surgical techniques and better perioperative management. The major technical challenge of liver resection is control of bleeding during transection of the parenchyma. Liver resection can be performed by different transection devices with or without inflow occlusion (Pringle manoeuvre). Only limited data is available on the best transection technique. The most popular devices facilitating bloodless transection include the ultrasonic dessicator (e.g: Cavitron Ultarsonic Surgical Aspirator (CUSA), Tyco Healthcare, Mansfield, MA), water jet dissector [1] (e.g: Hydro-jet, Erbe, Tubingen, Germany), harmonic scalpel, mono and bipolar cautery devices, and the dissecting sealer (e.g: Tissuelink, Dover, NH0) [2]. Parenchymal dissection has been performed under routine inflow occlusion with finger fracture technique (digitoclasy), where liver parenchyma is crushed between finger and thumb, isolating vessels and bile ducts, which then can be ligated and divided. This particular technique has been subsequently been improved using surgical instruments, such as small Kelly or Pean clamps (clamp crushing) for blunt transection. These devices have gained wide acceptance for hepatectomy, although only three randomised control trials comparing them exist to date. Other important advances in liver surgery, that have contributed to improved perioperative outcomes include intraoperative ultrasound, use of vascular staplers, and the reduction of bleeding by the development of low central venous pressure anaesthesia. Laparoscopy is useful for staging purposes and laparoscopic resection is also gaining popularity. The development of local ablative therapies for liver tumours, such as radiofrequency ablation, is posing competition to the more established resection techniques.

27.2. Techniques for Liver Parenchymal Transection

The techniques and tools listed below do not require intermittent clamping nor ischaemic preconditioning [3].

27.2.1. Clamp Crushing

Pringle's manoeuvre is routinely employed with this technique, typically for no longer than one hour at a time. One method includes the use of 4mm mersilene tape as a tourniquet around the portal triad, to achieve total inflow occlusion. The result is reduced operative blood loss but there is no impact on postoperative survival or complication rate. The parenchyma is crushed using small Kelly clamps (3 mm diameter tips for example). Small identified vessels (< 2mm) are coagulated with irrigated bipolar forceps (120W). All other structures, including major intrahepatic bile ducts, are ligated or clipped. This technique is widely used and objectively it may represent one of the more cost-effective techniques, due to its simplicity [4].

27.2.2. Ultrasonic Desiccator [2]

This technique uses ultrasonic energy (typically 23,000 Hz, 70W) with a water flush (4 ml/min) to clean the tip of the device as it transects the parenchyma.

27.2.3. Water-Jet Dissectors [2]

This technique employs a high pressure (30-40 Bar) water jet fired through a nozzle (Helix Hydro-Jet) to 'wash' soft parenchymal liver tissue from the more resistant vessels and bile ducts. These were ligated or clipped as described above.

The CUSA and Hydrojet tools divide the liver by fracture aspiration of the liver parenchyma, but they cannot be used for coagulation of cutting. Moreover, adjustment of the vibration setting is required during the dissection of diseased liver parenchyma, causing longer transection times. However, the addition of an electrocautery function to an ultrasonic dessicator does not significantly improve the outcome of hepatectomy.

27.2.4. Harmonic Scalpel

This tool is composed of two handpieces; a coagulation shear (CS) and a ball coagulator. As the names suggest, in contrast to the CUSA and hydrojet dissector, the harmonic scalpel can be used for both coagulation and cutting. The coagulation temperature with the harmonic scalpel is less than 100 degrees and, when compared with electrocautery for example, this minimises tissue damage and allows successful resection regardless of the condition of the liver [4].

Nevertheless, the harmonic scalpel is really only of use in the superficial layers of the liver because, as the deep areas of the liver are divided, the tip of the CS creates a 'blind spot', increasing the risk of massive bleeding when the lateral wall of a large vessel is cut, and under these conditions it is hard to control bleeding using a harmonic scalpel alone.

27.2.5. Dissecting/Radiofrequency Sealers [2]

This device (Tissuelink) couples radiofrequency with a conductive fluid to seal liver tissue to precoagulate parenchyma and isolate intrahepatic structrures. Another approach incorporating radiofrequency energy to transect the liver employs monopolar cooled tip probe, (Radionics) for developing a plane of coagulative necrosis around the resected lesion. This promising technique is associated with low postoperative biliary leak and blood loss rates.

One randomised control trial has compared the above techniques, using the endpoints: blood loss during parenchymal transection, resection time and postoperative hepatocyte injury, in noncirrhotic, noncholestatic patients. Results suggest that the clamp crushing technique has the highest transection velocity (3.9 cm^2 per min) and lowest blood loss. The three other techniques showed little difference in transection velocity. There was no difference in postoperative complications or reperfusion injury between the four techniques. A randomised trial comparing CUSA and clamp crushing further supports routine use of the latter as CUSA resulted in a higher rate of tumour positive resection margins [5].

27.2.6. Vascular Stapler [6-7]

Today, staplers have become a vital instrument in a high number of surgical specialties. Vascular staplers have greatly facilitated the speed and safety of lobar resections, of the lung for example. Since the nineties, vascular staplers used to divide hepatic veins and portal branches, during hemihepatectomy, are considered an achievement that helps minimise blood loss and thereby reduces the need for hepatic inflow occlusion. Furthermore, vascular staplers seem to be advantageous in the deroofing of hepatic cysts, since any inadvertently injured bile duct or blood vessel is sealed. Indeed, vascular staplers under ultrasound guidance have been used in selective division of major hepatic blood vessels, before parenchymal transection, with the more established CUSA or clamp crushing techniques. The success of staplers in nonselective tranparenchymal application in deroofing hepatic cysts has led to the wider use of staplers, as a new tool in parenchymal transection [8]. Initially, they were used in only minor resections; left lateral segmentectomies and wedge resections but more recently endo-GIA vascular staplers have been used in major hepatectomies with comparable operative morbidity and mortality rates to conventional high volume centres, (33% and 4%, respectively).

27.3. Laparoscopic Liver Resection

27.3.1. Introduction

The first reported laparoscopic liver resection was by Gagner et al. in 1992. Since then, over 700 laparosco-

pic liver procedures have been reported. A vast majority (70%) of procedures performed are for benign lesions; cyst fenestration and deroofing is the most frequently performed. The remaining 30% are malignant tumour resections, though the precise role of laparoscopy in resection of liver malignancies (hepatocellular carcinoma (HCC) and liver metastases) remains controversial. Indeed, the usual benefits of laparoscopic surgery (cosmetic aspect, rapid recovery, short postoperative stay) are challenged by the paramount oncological objective, overall disease-free survival. There are also concerns over possible tumour cell exfoliation and port site metastases.

27.3.2. Technique

Indications for surgery are identical to open surgery. For resection of benign lesions, indications include the presence of symptoms, diagnosis of adenoma or cystadenoma and an uncertain diagnosis on biopsy. Surgery is contraindicated if there is; disease in more than three segments, biliary or venous reconstruction is required, suspicion of gallbladder carcinoma, previous abdominal surgery, decompensated cirrhosis and cardiac or respiratory failure. Indications for those with HCC are Child class A with superficial tumours.

For resections of segments II through V, the patient is placed in the supine position. For lesions in segment VI, the patient is placed in the left lateral decubitus position, to expose the lateral and posterior aspects of the right lobe, as described for adrenal resection. Pneumoperitoneum is established with CO2 and intrabdominal pressure maintained under 15mmHg. A method incorporating abdominal wall lifting, without pneumoperitoneum, has been used but is generally regarded as providing insufficient visualisation for complex hepatic resection. The number of required trochars varies, but most often totals five, (port site diag Vibert/Cherqui). The lesion location is explored visually in all patients using a 30 laparoscope, often supplemented by laparoscopic ultrasound. The liver is then mobilised. In left sided resections, (left hepatectomy, left lateral hepatectomy or single left segmentectomies), the round, falciform and left triangular ligaments and the lesser omentum are divided. In right resections, the right triangular ligament is divided. Assuming no contraindications, liver parenchymal dissection is then performed. The tools to dissect the liver are adapted from the same range used in open liver resection. They include; crushing forceps, hook coagulator, harmonic shears, staplers, ultrasonic desiccator and radiofrequency ablation probes. Intraparenchymal vascular control can be obtained by monopolar cautery, intraperitoneal ligation, harmonic shears, endostaplers, etc. There have been cases incorporating Pringle's manoeuvre and intermittent clamping, (for example 15min on, 5 min off) in reported series but these are usually limited to the major resections. Transection line haemostasis can be achieved by monopolar cautery, harmonic shears, argon beam coagulator or other procoagulants e.g: haemostatic swabs or fibrin glue. The use of the argon beam coagulator is generally avoided for parenchymal resection as it has been associated with elevated rates of gas embolism. Control of biliary leak at the liver surface is assessed by eye or, in difficult cases, intraoperative cholangiography. Extraction of the surgical specimen is through extraction in an endobag through an enlarged trochar site, minilaparotomy (old appendicectomy scars or suprapubic incisions for example) or conversion to open technique in complicated cases.

27.3.3. Results

As with open resection, bleeding is the most common perioperative complication. This most commonly arises from the liver parenchyma, but has also been described as a result of portal vein injury and splenic laceration. The length of postoperative hospital stay, following laparoscopic resection, varies. Some series show no difference when compared to open, but on balance there are more suggesting of a quicker recovery time. The inpatient stay has been shown to be affected by the type of lesion and extent of resection. For example, patients undergoing resection of HCC [9] tend to have a longer inpatient stay than those of colorectal liver metastases, (10 vs 6 days). Similarly, those patients with greater than 2 segments resected remained in hospital longer than those with one or fewer, (8 vs 6 days). The longer stay in those patients with HCC with underlying cirrhosis, is at least partly offset by an improved postoperative course, because the abdominal wall is preserved, the kinetics of the diaphragm are improved, collateral venous drainage is better and there is less postoperative ascites.

In benign lesions, the main objectives are the absence of postoperative mortality, low morbidity rate, the absence of heterologous blood transfusions and a satisfactory late outcome. In resections of malignancies, the short term survival rates compare favourably with the open technique, for both overall and disease-free survival. However, there are currently no randomised control trials comparing the two approaches, nor long term oncological follow up in those series to date. Indeed, despite the early favourable survival data, resection margins have been shown to be < 1 cm in up to 30% of patients resected laparoscopically and port site metastases have been described, lending further weight to the need for a multicentre randomised control trial.

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CHAPTER 28

LIVER RESECTION ASSISTED WITH THE RADIOFREQUENCY TECHNIQUE

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28.1. Introduction

Liver surgery remains the gold standard for the treatment of liver tumours. To aid with hepatic resection, several devices have been developed in an attempt to stem significant blood loss and reduce the necessity for vascular exclusion. Of note are the Harmonic scalpel, bipolar scissors, hydrodissectors, Ligasure diathermy, Cavitron ultrasonic aspirator (CUSA) and Monopolar floating ball. However, most of these devices still require some degree of vascular inflow occlusion or are time consuming and none, except radiofrequency, can also be used to successfully ablate tumours. Furthermore, vascular occlusion– whether it is intermittent, continuous, partial or total- affects postoperative function of the hepatic remnant, especially in those patients treated with neo-adjuvant chemotherapy or in those patients with underlying chronic liver disease. Of all the new techniques now being applied to liver surgery the most successful and versatile is radiofrequency, which, until recently, was used only for *in situ* ablation of unresectable tumours.

28.2. Background

Radiofrequency has been extensively applied to unresectable liver tumours for *in situ* tumour ablation, with much success. Radiofrequency (RF) energy works by ionic agitation from an alternating current source, causing tissue coagulative desiccation through frictional heating. In 2002 the principle of RF was applied to hepatic resection, using the cool tip single probe device. The single probe was applied to the liver parenchyma where it developed a zone of coagulative necrosis, allowing a right hepatectomy to be performed in 80 min, without inflow occlusion and with only 30 cc of blood loss. The technique while dramatically decreasing blood loss [1] and postoperative related morbidity was still relatively time consuming and used monopolar energy with all its inherent drawbacks.

28.3. Monopolar Electrodes

The first clinical use of RF technology was for the management of cardiac arrhythmias and hyperactive neurological foci. All of these early applications used monopolar electrodes to generate small focal areas of ablation. Monopolar energy devices rely on a grounding pad, whereby current goes from the active electrode to the neutral, grounded electrode on the skin surface. This electrical current travelling through the body may lead to grounding pad burns, cardiac arrhythmias and myoglobinuria. In order to avoid untoward injury, the current is lessened and operative time lengthened. Soon after the introduction of RF studies began using modifications of electrode size, treatment durations and tip temperatures on the area and amount of coagulative necrosis.

28.4. Bipolar Electrodes

To eliminate the complications associated with monopolar RF, bipolar systems were developed. In these systems, the applied RF current runs from an active electrode to a second grounding electrode, in place of a grounding pad. Heat is generated around both electrodes, creating elliptical lesions. The main advantage is

the elimination of grounding pads and the conduction of electrical current throughout the body, both of which have inherent disadvantages.

28.5. General Considerations

As previously mentioned, when the single tip RF design was applied to liver resection, blood loss was reduced but there was no reduction in operative time. The single tip requires multiple sequential entries, as only an area of 1cm is coagulated at a time. The first step consists of marking the border as of the tumour discerned by palpation or US by scoring with electrocautery or diathermy the liver surface. This is important since, with the application of RF, the parenchyma hardens and palpation and/or US visualization of the tumour edge becomes difficult. In the next step, a 2cm scored boundary, away from the first inner marking, is made.

The third step is the application of the probe and RF, to achieve the coagulative necrosis along the transection line. The number of probe applications step 4, is dependent on the depth of the deep margin of the tumour. And the final step is the division of the parenchyma by a scalpel, with attention paid to leaving a 1 cm coagulation zone edge *in situ*.

For RF to be effectively used for timely hepatic parenchymal resection, the design had to be altered from a single probe to a multi probe one. The multi probe design allows for a greater area to be coagulated faster, leading to a reduction in operative time. There are presently two devices on the market which fulfil these requirements. The first is the Habib® 4X available in a hand held short and long model, for open surgery and a smaller device for laparoscopic surgery. The second is the newer InLine™ (ILRFA/ILRFC) system (Resect Medical, Fremont, CA), which is available in a linear depth adjustable model that can be used in hand assisted laparoscopic or open surgery [2].

28.6. Design of the Habib® 4X

The new generation Habib® 4X is a bipolar device, which eliminates complications from electrical conduction. Since there is no possibility of a conduction injury and the current need not be lessened, there is a marked decrease in operative time. Two versions are currently available, the hand held sealer available for open surgery and a smaller laparoscopic device. Both the open and laparoscopic sealer consists of an array of four electrodes in a square arrangement (fig. 28.1). There is a long version with corresponding long electrodes (120 mm) to access deeper tissue planes and a short version with short electrodes (60 mm) for more superficial tissue coagulation. The electrodes are made of stainless steel, covered with a non-stick coating (Tomlinson Tube & Instrument Ltd., Warwickshire, UK), with a polished titanium nitride non-stick coating (Tecvac Ltd., Cambridgeshire, UK; Integrated Surgical Sciences Corporation, Colorado, USA), to facilitate insertion and removal from the hepatic tissue. The long electrodes are sufficient to reach distal regions of the parenchyma; however the active portion is restricted to the distal 40 mm of the probe in order to allow rapid heating. The entire length is not heated as the energy required would be too great and would compromise the time to coagulate the tissue. The proximal portion of the probe is insulated with a PTFE coating. The short probe device is designed to coagulate superficial vessels and ducts and for more superficial tumourectomies. In both devices the four needles are arranged in a 2 × 2 array with the two pairs of needles connected together and each pair is connected to a single terminal of a bipolar RF generator (Generator 1500X, RITA Medical Systems Inc., California, USA) (fig. 28.2).

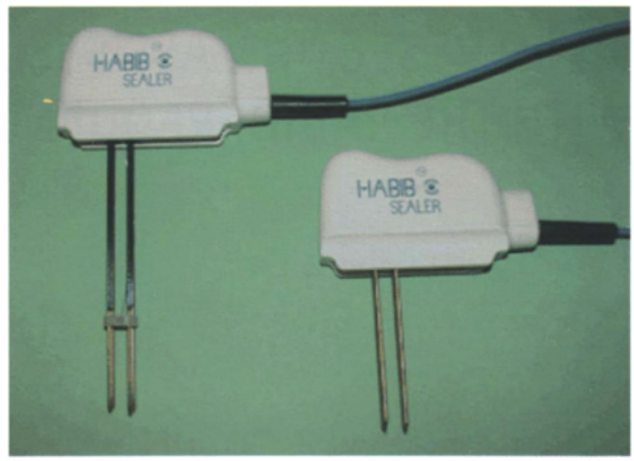
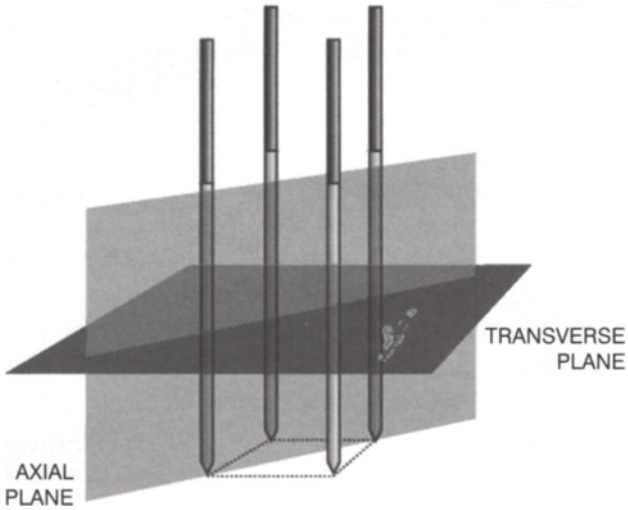


Fig. 28.1. Habib® 4X.



28.7. Application

The probe is placed perpendicularly to the transection surface and the power applied [3]. The power can be set to variable settings but is recommended at 100W –the lower the power the longer the coagulation time– during application the impedance is monitored, the ablation is completed, when the impedance is increased to 5 OHMS above the quiescent value. During activation the impedance shows three phases: first, a decrease due to improved electrical conductivity as the tissue becomes heated; second, a plateau phase and third, a slow then rapid increase, due to dehydration and carbonization of the tissues. Once the tumour is localized, by manual palpation and intraoperative liver ultrasound, the resection line is scored on the liver surface 1 cm from the tumour's edge with argon diathermy. The marking of the transection line is very important, as RF application renders the tumour edge uninterruptible by intraoperative ultrasound or palpation. Then, the sealer is then introduced perpendicularly into the liver, abutting the transection line. This allows a small, less than 10mm, margin of coagulated liver parenchyma to remain behind ensuring sealed vessels and bile ducts. Less than 1cm of tissue is left behind, just enough to ensure vascular and biliary duct sealing, yet not so much as to increase the rate of postoperative collections and/or abscess formation. During the removal of the probe, the coagulated parenchyma must be supported by the surgeon's fingers from both sides, in order to avoid fracturing the parenchyma leading to unnecessary blood loss and damage. The probe is introduced again adjacent to the last coagulated area, in a serial fashion, until the area to be transected is ablated. Next, a scalpel is applied perpendicularly to divide the parenchyma near to the coagulated edge next to the tumour, leaving < 10 mm of the coagulated edge (fig. 28.3a and 28.3b). Care must be taken to avoid application of the device near the hepatic veins and liver hilum with their associated structures. For deep tumours, the Habib® 4X is first applied to the li-

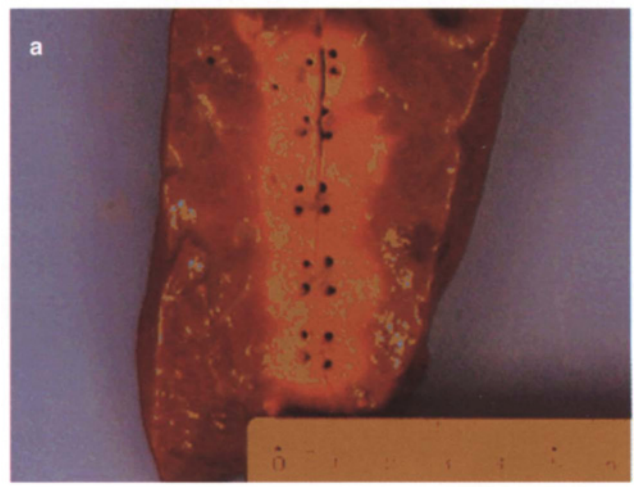


Fig. 28.3. a. Result of in-line ablation with Habib® 4X in a porcine liver.

Fig. 28.3. b. Result of multiple in-line application to induce necrosis with Habib® 4X in a porcine liver.

ver surface, the surface is cut with a scalpel to a depth of 3-4 cm and the probe can then be subsequently reapplied to the deeper tissue.

28.8. Results

Outcome data for hepatic resections without vascular clamping has recently been reported. In brief, dissection of the hepatic pedicle is not performed, except in those cases where the tumour is located close to the hilum and where separation of the tumour from the hilar structures is necessary. In such cases, ligations of the arterial and portal vessels are completed prior to application of the probe. Likewise, dissection of the hepatic veins need not to be routinely performed, unless the tumour is located close to these major vessels, in which case dissection and ligation of the vessels is conducted first. Thus far, 156 patients have been treated with the device. Of these, 106 underwent a tumourectomy (fig. 28.4) and 30 underwent a major hepatectomy. In this experience, the rate of major hepatectomies dropped from 64% (before RF) to 20% with RF, allowing the completion of more minor hepatectomies vs. major hepatectomies. Actual resection time was 75 +/- 51 minutes in minor resections and 110 =/- 86 minutes in major resections. Intraoperative blood loss was 139 +/- 222ml. Only 5% of patients received a blood transfusion intraoperatively, no patient required fresh frozen plasma or a blood transfusion postoperatively. The mortality rate was 3.2% and mean hospital stay 12 +/- 12 days. Only 5 patients were admitted to the intensive care unit postoperatively, of these three were planned due to known cardiac and respiratory comorbidities. Four patients developed a bile leak; all were treated with percutaneous drainage.

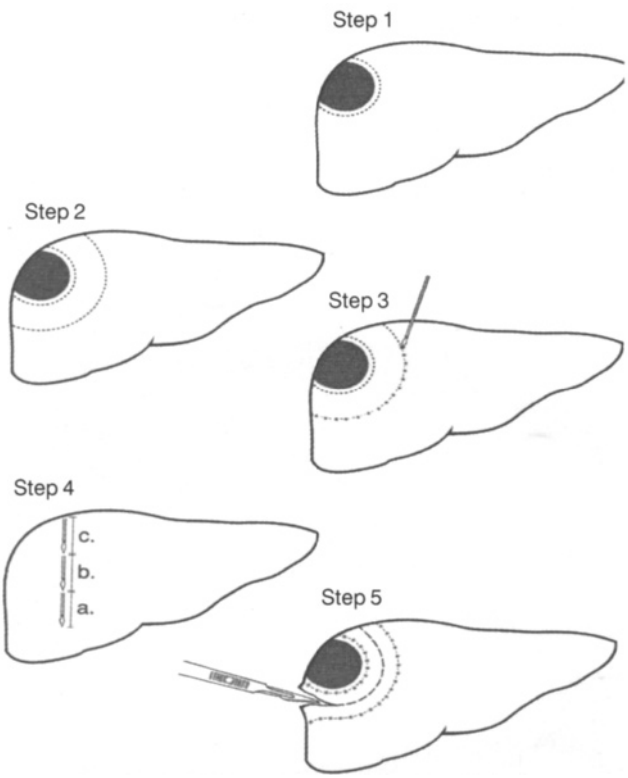


Fig. 28.4. The five steps to achieve liver resection using radiofrequency energy probe.

Hepatic recurrence occurred in 36 patients with a mean time of 10 months. Recurrence was distant from the resection margin in all but 2 of the 36 patients. On re-examination, the resection margin was histologically negative in these 2 patients, so these were thought to be new tumours and not resection zone recurrences. The elimination of inflow occlusion avoids ischemic reperfusion hepatocyte injury, well known to predispose to postoperative liver failure. The elimination of pedicle dissection is a further benefit of this technique, decreasing operative time and allowing the relative ease of re-operation. Re-resection of recurrent hepatic tumour increases the likelihood of survival, since extensive mobilization and pedicle dissection is avoided with this technique and the adhesions encountered at re-exploration tend to be limited to the area of previous resection.

28.9. The InLine™ (ILRFA/ILRFC)

This system has been more recently developed and there is scant data on human resections. The system has a single row of six variable depth RFA electrodes, spaced approximately 1 cm apart which can be deployed simultaneously into the parenchyma to rapidly coagulate a resection plane (fig. 28.5). The insertion is guided by ultrasound or palpation. Ablation sizes are 1 cm wide × 5 cm long × 1-6 cm deep. In a controlled animal study, the bleeding was significantly reduced and coagulation occurred in 3 min, making it a very effective and fast instrument. Incremental movement of the

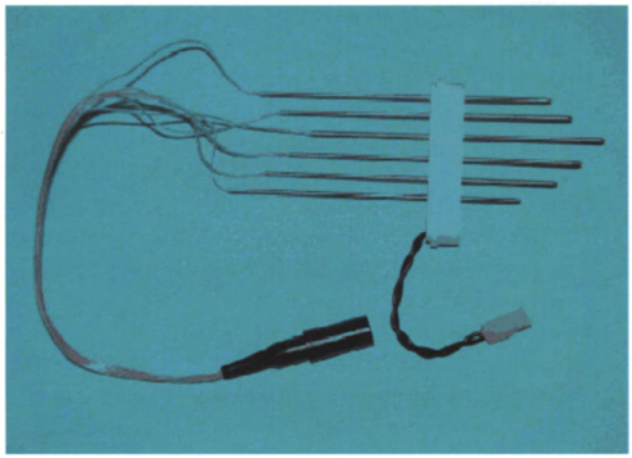


Fig. 28.5. InLine™ ILRFA instrument.

device allows coagulation along the entire 1 cm plane of transection. With this method large vascular structures may be visualized or detected by US and ligated or clipped at one's discretion. There is no need for inflow occlusion. At the time of writing, there was no data on recurrence at the transection line, nor postoperative complications and hospital stay.

28.10. Laparoscopic Hepatic Resection with RF

Laparoscopic hepatic surgery has not yet been widely accepted, mainly due to the difficulties encountered with control of possible intraoperative bleeding. It has also been mainly employed for non-malignant tumours, wedge resections and for left lateral segmentectomies. Recently, there is data suggesting laparoscopic resection is safe for patients with small malignant tumours as well, although patients with hepatocellular carcinoma or cirrhosis might suffer more complications. Laparoscopic liver resection has been suggested to be feasible in cirrhotic patients who, otherwise, might not tolerate hepatectomy. Combining RF coagulation at the line of transection has been shown to minimize blood loss, operative time and obviate the need for inflow occlusion all of which may mean that RF assisted resection may play more than one role in patients with underlying liver disease. In addition, the zone of coagulation can be controlled and helps minimize unnecessary damage to liver parenchyma. Both the Habib® 4X and the InLine™ (ILRFA/ILRFC) [4] are available in laparoscopic or laparoscopic assisted models [7].

28.11. Trans-metastasis Hepatectomy Using RF

This is another novel approach, which has to be evaluated with time. Long term data are still pending. The idea is that multiple metastases will be ablated in the remnant liver and that a formal hepatectomy along a clear resection line would result in too small of a remnant liver, especially in light of the numerous ablations (fig. 28.6). Therefore, the tumour falling along the resection line will be ablated and then transected leaving some of the ablated tumour on the resection line. According to the authors, 13 patients with colorectal metastasis were treated in this manner with a mortality of 7.6% and a grade 3-4 morbidity of 30%. After a mean follow up of 19.4 months there was no recurrence along the transection line. Since 77% of recurrences occur within 6 months and 96% within a year, this novel technique adds another tool in the armamentarium in the aggressive treatment of otherwise unresectable liver metastases. Although combining partial resection with multiple RFA increases the number of patients that can be treated surgically, caution must be employed as calculation of the remaining parenchyma after combining multiple ablations and resection is not easily achieved [5, 6, 7, 8, 9]. Further studies will be necessary before this technique can be widely adopted.

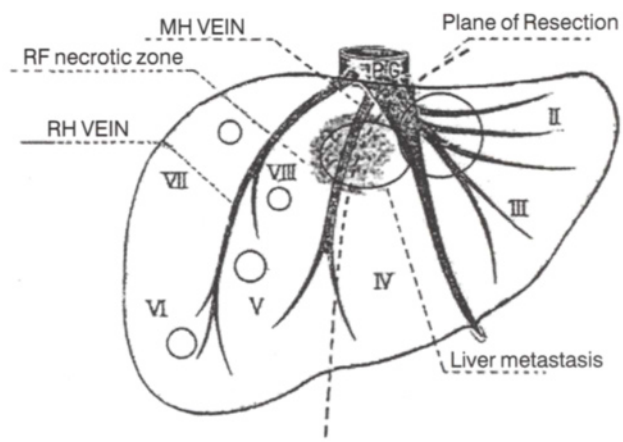


Fig. 28.6. Trans-Metastasis Hepatectomy.

28.12. Conclusion

In summary, RF assisted surgery allows more rapid nonanatomical liver resections to be performed without pedicle clamping which helps to preserve liver parenchyma and reduces the likelihood of hepatic failure. In addition, it minimizes blood loss, reduces operative time and allows easier repeat liver surgery to be performed. The use of bipolar devices has the added benefit of eliminating conduction dysrhythmias associated with monopolar devices. Moreover, most patients can avoid an ICU stay, which results in a substantial cost savings. Unlike the Habib® 4X, which gives a wider area of coagulative necrosis, the InLine™ is a single line of probes with a more narrow area of coagulation. It will be interesting to see if this has an impact on postoperative bile leaks and bleeding. Of note a word of caution, major hepatic surgery should continue to be performed by experienced hepatobiliary surgeons in specialized centres.

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CHAPTER 29

LIVER RESECTION FOR CHOLANGIOCARCINOMA

G.C. Sotiropoulos, H. Lang, Ch. E. Broelsch

29.1. Resection of Hilar Bifurcation and Biliary Reconstructions (Fig. 29.1-29.6)

In case of tumor infiltration the hilar bifurcation is removed en-bloc with the liver and the biliary tree is reconstructed by means of a hepatico-jejunostomy. For operative technical reasons, a resection of the hilar bifurcation may be necessary, even without tumor infiltration, i.e. in liver tumors of the right lobe, close to the left umbilical sulcus, with corresponding involvement of the blood circulation of the left hepatic duct. In these cases a resection of the hilar bifurcation is inevitable to avoid ischemia of the hilar bifurcation. In extended hepatectomies even the resection of biliary trees of the second order could be necessary [1-5].

The required hepatico-jejunostomy is to be performed with a direct and accurate suture between bile duct and jejunal wall under respective inclusion of the edge of mucous membrane. The anastomosis is performed end-to-side with a 40-60 cm switched off jejunal-loop, which is conducted far on the right of the retrocolic area. In difficult anastomoses (for example re-operation in the presence of a bile leakage) endoluminal transcutaneous conducted drains could be placed, remaining for approximately 3-6 weeks. The drains can be applied for continuous blind drainage or entrained transhepatically. Thus, in swelling of mucous membrane, it is prevented from occluding the anastomosis. Also a small anastomotic insufficiency can heal completely with lying intraluminal drainage. However, even with longer staying of endoluminary drainage, a protection against potential contraction of the anastomosis with subsequent stenosis can hardly be achieved. Only in case of severe technical difficulties of the anastomosis the drainage will be left for a longer period of time.

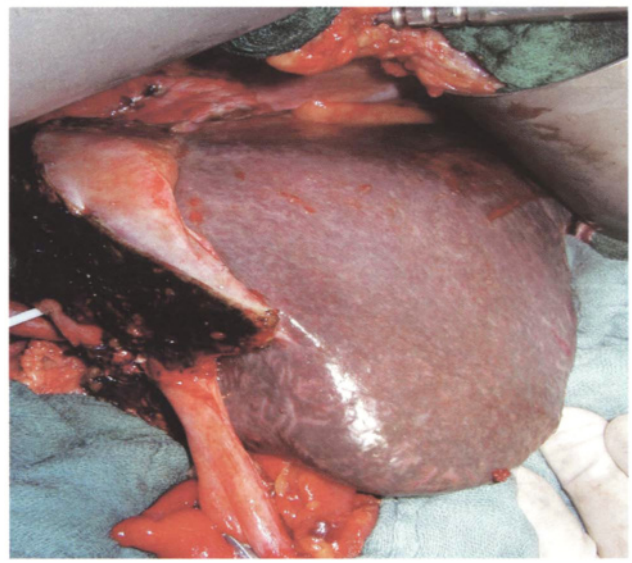

Fig. 29.1. a. Liver remnant after extended right hepatectomy.

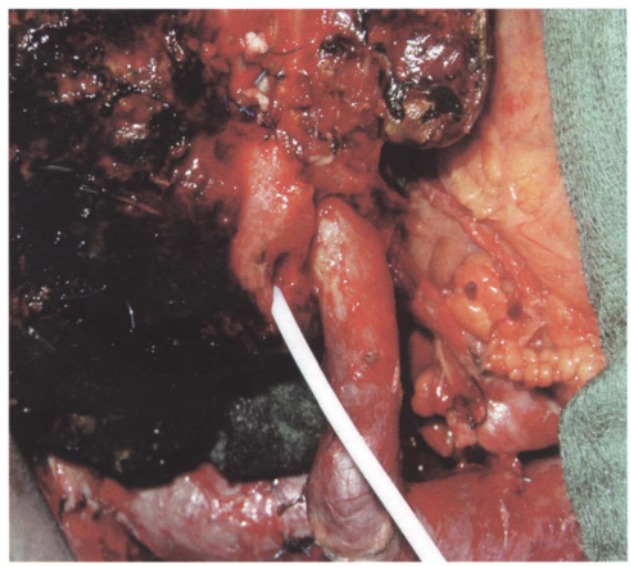

Fig. 29.1. b. Portal vein, caval vein and transected bile duct at the left umbilical fissure.

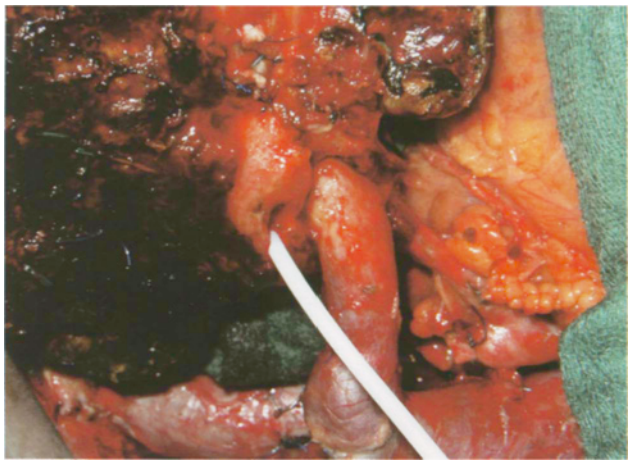

Fig. 29.1. c. Specimen after extended right hepatectomy (right trisectionectomy)-Seg. I, IV-VIII including hilar bifurcation in Klatskin tumors.

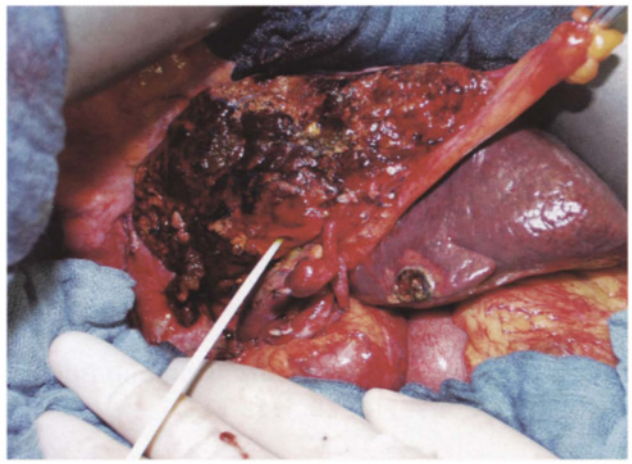

Fig. 29.4. Situs after extended right hepatectomy and resection of hilar bifurcation with transection of left hepatic duct at the umbilical fissure.

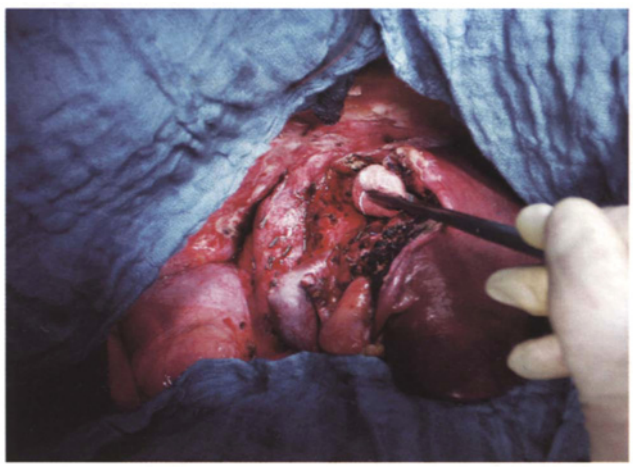

Fig. 29.2. Situs after extended right hepatectomy and resection of hilar bifurcation.

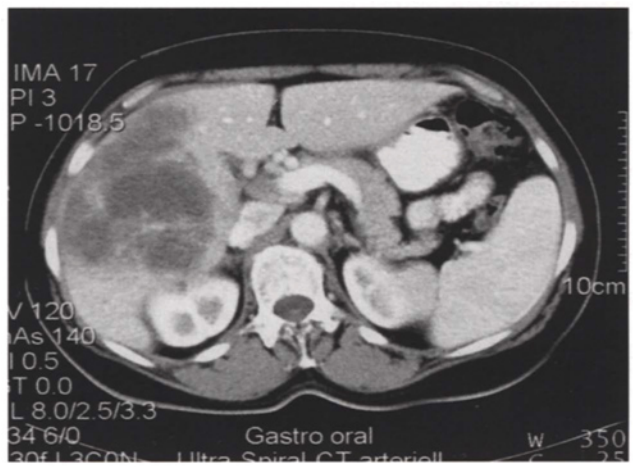

Fig. 29.5. a. CT-scan of large intrahepatic cholangiocarcinoma.

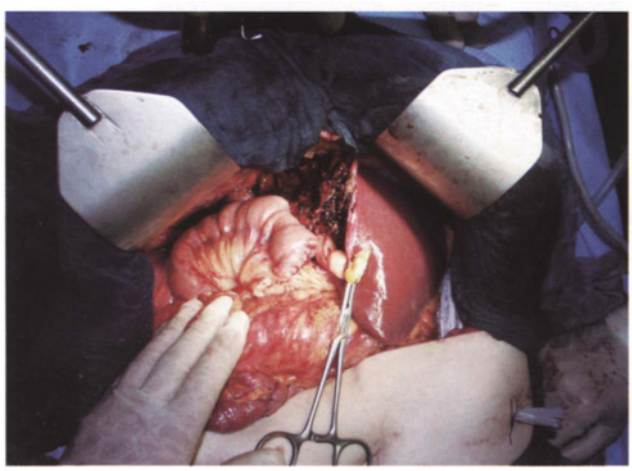

Fig. 29.3. Situs after reconstruction with a Roux-Y loop.

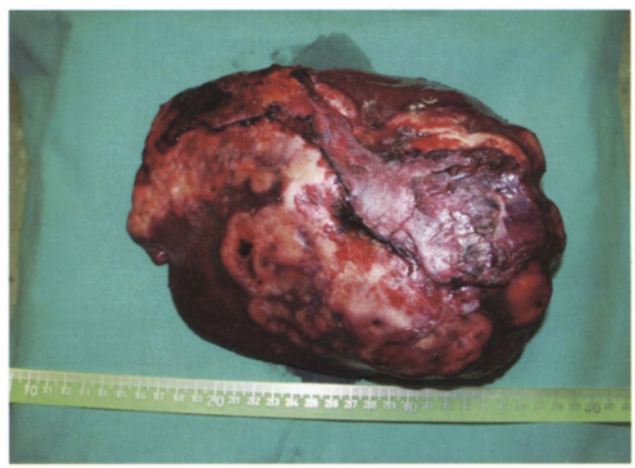

Fig. 29.5. b. Resection specimen after extended right hepatectomy.

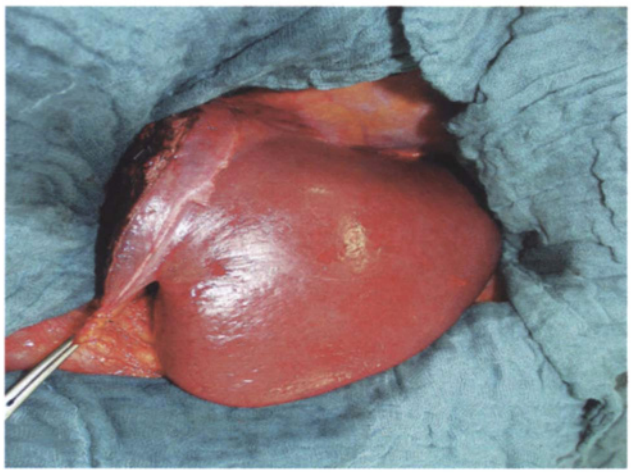

Fig. 29.5. c. Liver remnant

29.2. Vascular Reconstructions (Fig. 29.7-29.9)

After partial resection of the portal vein, usually of the portal vein bifurcation, a direct reconstruction is ordinarily possible without additional interposition, for example between the main trunk of the portal vein and the right or left-sided portal branch. If a vascular replacement is necessary, an allogenic vein interposition is preferred.

More rarely than portal vein resection, resection of the hepatic artery is required. In these cases a direct anastomosis is generally not possible. An autologous

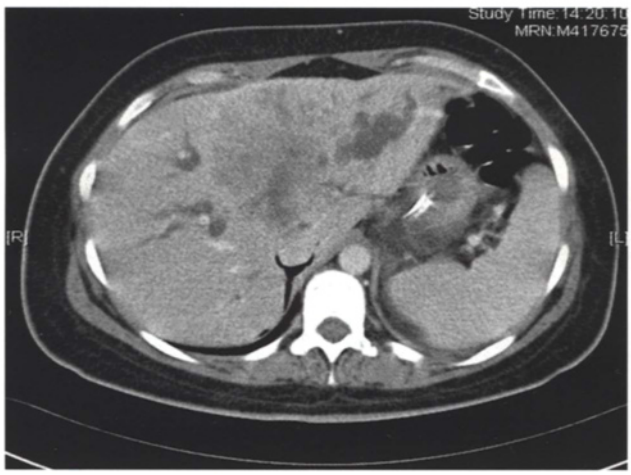

Fig. 29.6. a. Intrahepatic cholangiocellular carcinoma with dilatation of bilateral intrahepatic ducts.

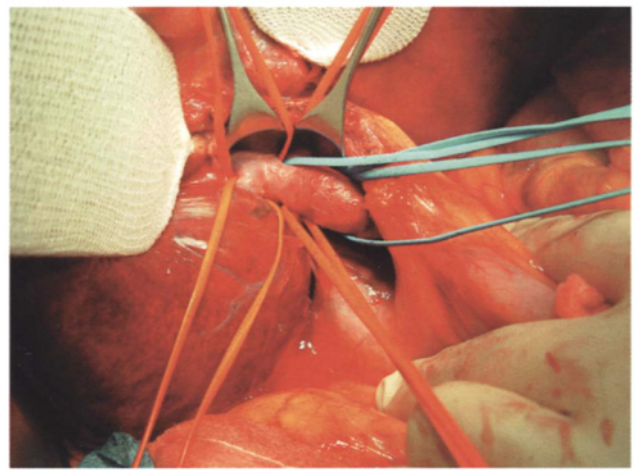

Fig. 29.7. Dissection of portal vein and intra-glissonic approach to portal pedicles.

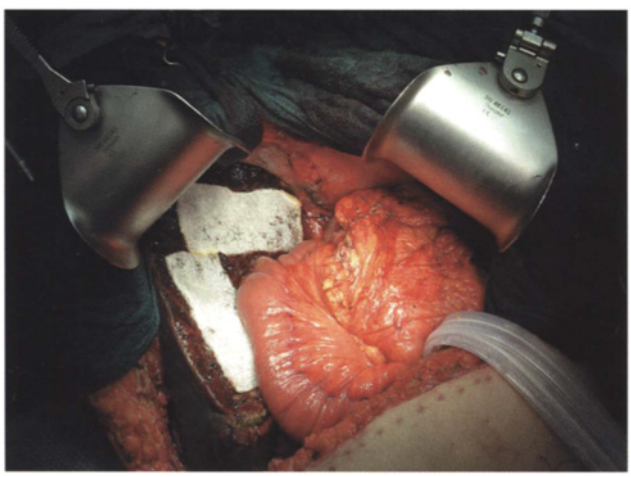

Fig. 29.6. b. Situs after extended left hepatectomy and resection of hilar bifurcation and reconstruction by hepatico-jejunostomy with a Roux-Y loop.

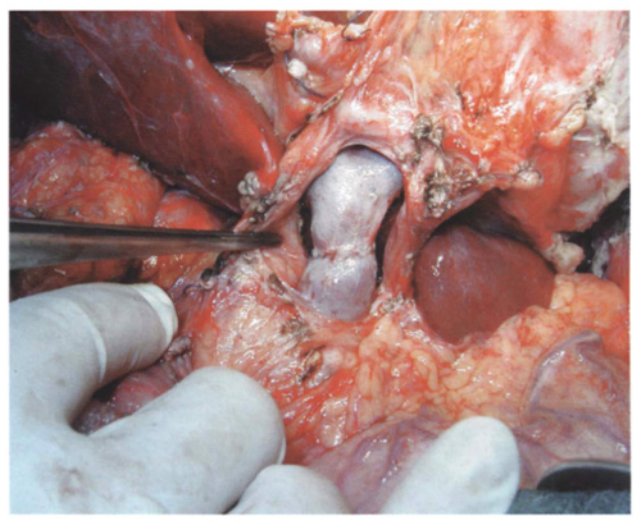

Fig. 29.8. Situs in liver hilum after portal vein reconstruction.

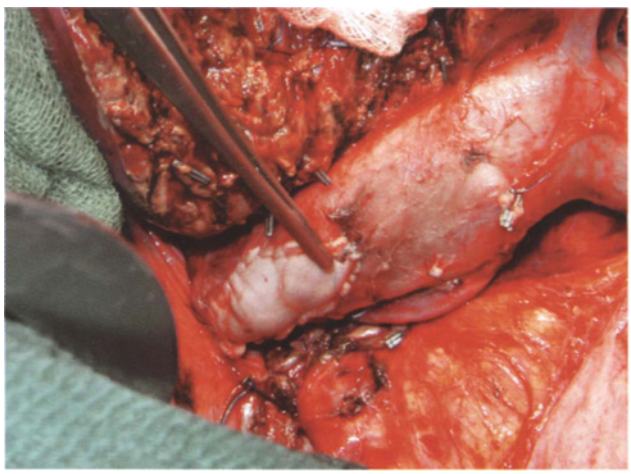

Fig. 29.9. Situs after right hepatectomy with partial resection of the caval vein and reconstruction by allogenic venous patch.

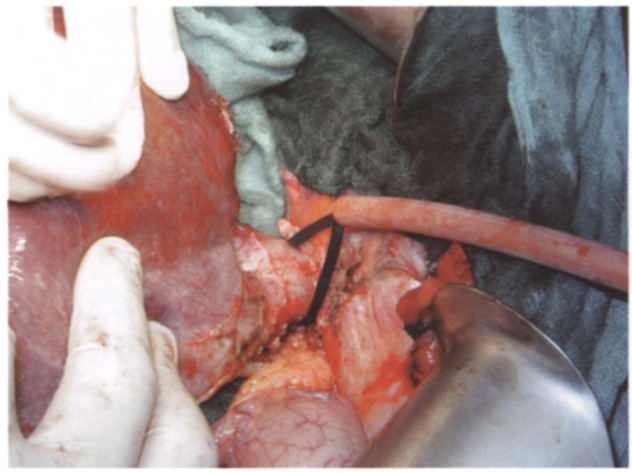

Fig. 29.10. Preparation of the suprahepatic caval vein prior to total vascular occlusion.

vein interposition (for example great saphenous vein) is suitable as an interposition graft.

A reconstruction of the caval vein is possible with both autologous venous material (for example several times doubled saphenous vein or in addition, liver veins from the removed specimen) and the allogenic vein (vessel-bank). With smaller defects a direct vein suture can also be applied, taking into account that in so doing, it could result in a smaller lumen.

For the caval vein replacement gore-tex prostheses are suitable. With regard to the antithrombosis prophylaxis, anti-coagulation is recommended for at least 6 months (if necessary also with placement of an arterio-venous-fistula at the thigh).

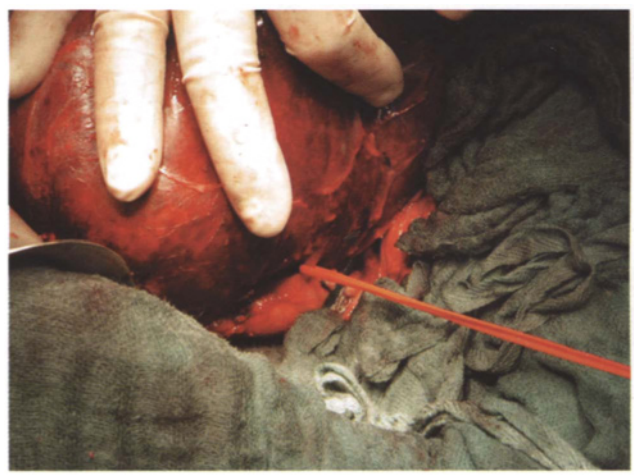

Fig. 29.11. Preparation of inferior hepatic vein.

29.3. Vascular Occlusion (Fig. 29.10-29.11)

The restriction of the blood loss during the liver resection is of crucial importance. The Pringle manoeuvre, which involves clamping of the entire liver hilum by means of a tourniquet, is common practice. Generally, up to 45-60 min is tolerated without serious consequences to the liver function. If necessary, it can also be used intermittently, in order to extend the total occlusion time.

The ischemic tolerance of the liver can usually be increased by ischemic pre-conditioning prior to hilar occlusion (arterial and portal-venous occlusion for 10 minutes, followed by reperfusion).

In total vascular occlusion of the liver (TVO), the sub- and suprahepatic caval vein will be clamped in addition to the Pringle manoeuvre. Thereby venous bleeding is avoided during parenchymal transection (if the liver is perfectly free). Compaired to the Pringle manoeuvre, the ischemic damage for the liver is clearly larger with TVO (no retrograde liver-venous perfusion). Furthermore, total vascular occlusion may lead to severe hemodynamic changes (confine arrangement with the anaesthesia necessary).

With extended right or left resections including the caudal lobe, a total vascular occlusion is also possible by hilar occlusion and clamping of the only remaining

liver vein. Thus, the blood flow in the caval vein is not impaired and the hemodynamic changes are comparable to those of a Pringle manoeuvre.

29.4. Non-conventional Liver Resections (In Situ-Ante Situm and Ex-Situ)

In extremely difficult resections, i.e. in extended reconstruction of the liver vein confluence (if necessary in combination with a portal reconstruction), it can be favourable to perform a total vascular occlusion of the liver exceeding one hour. In order to extend the ischemic tolerance a hypothermic perfusion of the liver is necessary, based on the experiences from the liver transplantation. Besides, a portal-femoro-axilliary veno-venous bypass must be implemented with these forms of liver resection to ensure venous blood return and to achieve hemodynamic stabilization.

Three different proceedings are possible:

- **In-situ resection**

The in-situ resection requires a total vascular occlusion and hypothermic perfusion of the liver follows in regular intervals (about every 10-15 minutes) via the portal vein (if necessary. also via the hepatic artery or via a catheter placed into the gastroduodenal artery) with cold preservation solution (HTK). The resection takes place at the blood-empty and cooled liver.

- **Ante-situm resection**

The ante-situm resection corresponds in principle the in-situ-resection; however, the suprahepatic caval vein is additionally cut just under the diaphragm. Thereby the liver can be resected folded forward, which facilitates the technical approach to the liver vein confluence. In the case of an additional disconnection of the infrahepatic caval vein the liver can be rotated laterally.

- **Ex-situ resection**

In ex-situ-resection, the liver is taken completely out of the body, followed by hypothermic perfusion. The liver resection takes place on the cooled liver outside of the body on a providing table (bench procedure). After resection, the liver is auto-transplanted with the appropriate vascular and bile duct anastomosis.

Due to the inevitable and necessary arterial reconstruction and bile duct anastomosis, the ex-situ resection is accompanied by a very much higher morbidity compared with the two other procedures. Since even the most complex reconstructions of the liver vein confluence or the caval vein as well as the portal vein can usually be performed in situ, in our own procedure, the in-situ technique is preferred nearly without exception, and more rarely the ante-situm technique [6-7]. In our opinion, the need or indication for a ex-situ resection arises rarely.

29.5. Lymphadenectomy by Liver Resection (fig. 29.12-29.13)

The value of lymph nodes dissection in the context of a liver resection has not, yet, definitely been clarified for either primary or secondary liver tumors [1, 8-12]. A systematic lymphadenectomy along the hepatic ligament appears particularly meaningful for primary liver tumors for oncological reasons, although it probably has a different meaning for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. While in resectable hepatocellular carcinoma, the regional lymph nodes are only extremely rarely invaded, tumor infiltration of the regional lymph nodes must be accounted in some of the instances in the case of intrahepatic cholangiocarcinoma. Apart from an at least theoretical

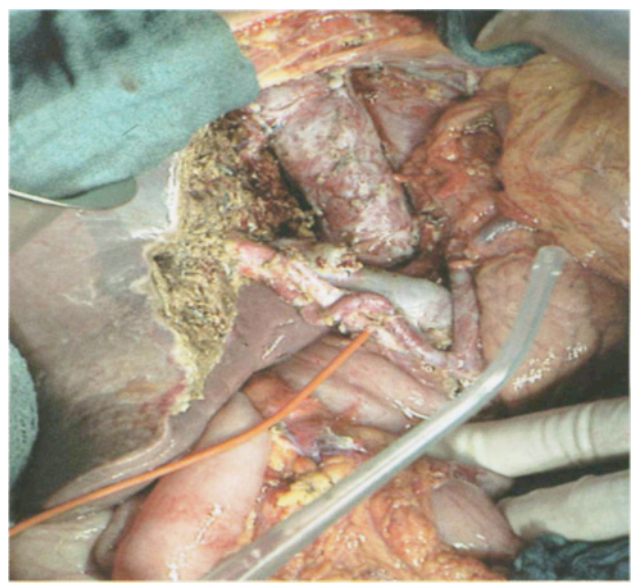

Fig. 29.12. Operative situs after left hepatectomy with lymphadenectomy in the hepatic hilum and along the common hepatic artery.

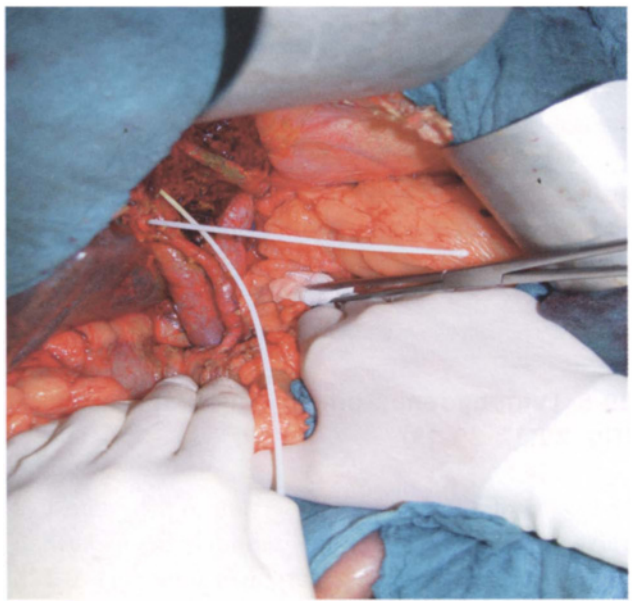

Fig. 29.13. Left hepatectomy in hilar cholangiocarcinoma with complete lymphadenectomy in the hepatic hilum. There are two bile ducts to the right (white probes).

chance of complete tumor removal (with a probable improved prognosis) the systematic lymph node dissection permits a better tumor staging.

The prognostic meaning of hilary lymph node invasion and the meaning of the corresponding lymphadenectomy in the context of secondary liver tumors are differently discussed. In our own procedure, a local lymph nodes resection is usually performed, because of the possible improved oncological radicality.

29.6. Intraoperative Management During Liver Resection

The main danger of liver resection is the venous hemorrhage during the parenchyma dissection. In order to reduce venous blood loss, the central venous pressure should lie as low as possible (not over 5 mmHg). Depending on the liver function, on the extent of the parenchyma removed as well as the blood loss, disturbances of the coagulation and the fibrinolysis must also be considered in the context of extended liver resections. This requires close intraoperative control of the coagulation status as well as an early substitution of coagulating factors. In these cases, the protease-inhibitor Aprotinin (100,000 IE/h) can lead to a clear improvement of the coagulating procedure, in particular if supported by a parallel analysis of the hyperfibrinolysis by means of a thrombelastogramm.

29.7. Repeated Hepatectomy for Reccurent Malignant Tumor

From the technical point of view, repeated liver resections differ in various aspects from the primary liver operation. The mobilisation of the liver from the retroperitoneal cavity can already be very difficult, particularly after extended previous operations. In the event that the hepatic round ligament and the falciform ligament were refixed to the diaphragm and the ventral abdominal wall at the primary resection, severe bleedings can occur as a result of opening diaphragmatic fascia, parenchymal lesions or defects of the liver capsule. After right and left resections, the diaphragm and the right colon's flexure or the stomach and the transverse colon respectively, can be best bound to the former liver resection surface.

Frequently liver tissue can possess acertain brittleness due to the prior operation or as a consequence of chemotherapy, resulting in an increased bleeding inclination during the parenchymal transection. Recently, hepatic surgeons in Europe and the United States have reported an increased incidence of vascular changes and steatohepatitis in livers of patients treated with chemotherapy [13-15]. Most of the reports involve oxaliplatin; however, this may simply reflect the wide use of this agent in this setting. Steatohepatitis also seems to occur in patients treated with irinotecan [13]. The changes seen with chemotherapy can have a profound effect on the safe performance of standard liver resection. Thereby the ischemic tolerance of the liver tissue can decrease, urging special caution during the resections phase with the hilar occlusion. Using a very gentle preparation technique and a performing parenchymal transection –if necessary, by means of ultrasonic or water jet dissector– blood consumption can be kept mostly very small even without hilar occlusion.

The risk for bile leakage is not substantially increased in the second operation, if this can be accomplished as an anatomical resection. On the other hand, the insertion of T-drainage can be considered during

atypical resections or impaired blood circulation of the resection boundaries, in order to reach a discharge of the biliary tree and prevent possible leakages.

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CHAPTER 30

PORTAL VEIN EMBOLISATION

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30.1. Introduction

Despite improvements in the management of liver tumours, both primary and metastatic, these tumours are still considered one of the most common malignancies worldwide with a high mortality rate and disappointing long-term survival rates. Hepatic resection has become the standard modality of treatment for patients with liver tumours, and currently remains the only potentially curative therapy. Many factors can affect hepatectomy, such as tumour size, location, multifocality, patients' status, and hepatic function. But in order to attain a tumour free margin extensive hepatectomy is often necessary, which has led to an increased survival and improved outcome after hepatic resection for liver tumours: colorectal metastases [1-2], hilar cholangiocarcinoma [3-4] and hepatocellular carcinoma [5-7]. However, it involves considerable reduction of the hepatic mass that may lead to hepatic insufficiency, manifested by cholestasis, impaired synthetic function, bleeding and fluid retention which in turn contributes to prolonged recovery times and extended hospital stays [8, 9], and the insufficient remnant volume is considered the principal cause of postoperative death after major hepatectomy.

In a study conducted by Shirabe on 80 patients who underwent major hepatic resection for hepatocellular carcinoma, it was found that all major hepatectomy patients who died of liver failure had undergone a right lobectomy of the liver. The most important risk factor for liver failure following right lobectomy was remnant liver volume. In the patients who underwent right lobectomy of the liver and thereafter died of liver failure, remnant liver volume was never more than 250 mL/m^2. In the central bisegmentectomy and left lobectomy group, no patients died of postoperative liver failure and remnant liver volume was over 250 mL/m^2 in all patients [9]. Patients with a background of cirrhotic or diseased liver in addition to liver tumours who undergo resection of more than 60% of the liver's functional mass and patients with an otherwise normal liver who have more than 75%-80% of the functional liver mass resected are considered at higher risk for postoperative liver complications [9-13]. In order to decrease the complications and improve the safety of extensive liver surgery in patients with insufficient anticipated liver remnants preoperative percutaneous transhepatic one-sided portal vein (PV) embolisation (PVE) has been used in patients with or without chronic liver disease who have primary and secondary liver tumours [13-22]. In fact, preoperative PVE is now considered the standard of care before major hepatectomy for this subset of patients. PVE redirects portal flow to the intended future liver remnant (FLR) to initiate hypertrophy of the nonembolised segments before surgery, with an even more rapid functional gain.

In appropriately selected patients, PVE can reduce postoperative morbidity and enable safe, potentially curative hepatectomy for patients not previously considered candidates for resection based on anticipated marginal FLRs, and with minor and transient complications [13-22, 91].

30.2. Background

Experiments on the use of PVE date back to 1920 when Rous and Larimore [23] found that ligation of PV branches in a rabbit model leads to progressive atrophy of hepatic segments with occluded PVs and hypertrophy of hepatic segments with patent PVs. After that studies found that bile duct or PV occlusion by tumour or ligation leads to atrophy of the supplied liver and hypertrophy of the unoccluded portion [25]. In 1975, Honjo

et al [24] tried portal vein ligation in liver cancer patients not fit for hepatic resection, which resulted in atrophy of the ligated lobe of portal vein and its tumour and hyperplasia of non ligated lobe. Things remained experimental and unclear until 1986 when Kinoshita et al [27] first reported the use of PVE to limit extension of portal tumour thrombi, and he observed hypertrophy of the unembolised liver, demonstrating by this the efficacy of PV occlusion before resection of hepatocellular carcinoma. Transarterial embolisation, at that time, was the only method used, and it was ineffective. That led Makuuchi et al in 1990 [18], to report the first use of preoperative PVE performed to induce left liver hypertrophy before major hepatic resection in patients with hilar cholangiocarcinoma. These findings have led to the exploration of preoperative PVE prior to extensive liver hepatic resection for HCC, cholangiocarcinoma, and liver metastases. And since then it has been used successfully to increase candidates for liver resection and decrease postoperative complications related to liver remnant insufficiency.

In this chapter we will discuss the mechanism of liver regeneration, some anatomical considerations, indications, contraindications, rationale, techniques, outcome and complications of PVE with a prospective view to the future of PVE.

30.3. Liver Regeneration

Although PVE has been used in clinical practice for more than 10 years, its underlying mechanism of atrophy-hypertrophy complex is poorly understood. PVE causes a rapid change in hepatic haemodynamics and a significant increase in portal pressure, similar to that observed after major hepatic resection [28]. Cessation of portal flow, which is presumed to have a hepatotrophic effect [29], induces apoptosis with occasional minimal necrosis in the embolised lobe [30]. Hepatocyte deletion is thought to lead to atrophy of the embolised liver, which in turn is followed by cellular hyperplasia and hypertrophy of the other side, as hepatocytes enter a highly active phase of proliferation after PVE. This ability of the liver to regenerate after PVE is the basis for preparation for major hepatectomy in a patient with an anticipated small liver remnant. Despite its considerable metabolic load, the liver is essentially a quiescent organ in terms of hepatocyte replication, with only 0.0012%-0.01% of hepatocytes undergoing mitosis at any time [31-33]. However, this low cell turnover in the healthy liver can be altered by toxic injury or surgical resection, or PVE which stimulates sudden, massive hepatocyte proliferation resulting in recovery of the functional liver mass within 2 weeks after the loss of as much as two thirds of the liver. The regenerative response is typically mediated by the proliferation of surviving hepatocytes within the acinar architecture of the remnant liver.

The molecular and cellular events during liver regeneration result from growth-factor stimulation in response to injury. In the regenerating liver, hepatocyte growth factor, transforming growth factor-a (TGF-a), and epidermal growth factor are important stimuli for hepatocyte replication. Hepatocyte growth factor is the most potent mitogen for hepatocyte replication, and in combination with the other mitogenic growth factors (ie, transforming growth factor-a (TGF-a) and epidermal growth factor), can induce the production of cytokines, including tumour necrosis factor TNF and interleukin-6, and activate immediate response genes that ready the hepatocytes for cell-cycle progression and regeneration [91]. Co-mitogenic factors have also been identified, like insulin which explains the slower regeneration rates seen in patients with diabetes compared with those without diabetes [34]. Other comitogenic factors include noradrenaline [36], triiodothyronine and retinoic acid, although the precise role of some of these has not been clearly defined [32]. Their synergistic action lead to gene induction and DNA synthesis with subsequent expansion of the hepatocytes clones [37]. Importantly, extrahepatic factors are transported primarily from the gut via the PV and not by the hepatic artery [17, 38-40].

The negative regulators are even less well understood. TGF-Beta is one of several candidates for signals that lead to the arrest of cellular expansion when appropriate liver mass for the patient is regained [41, 42]. Anatomically the process begins near portal triads and spreads to the pericentral areas [30]. The degree of hepatocyte proliferation is directly proportional to the degree of stimulus, i.e., a minor liver stimulus will result in only a localised mitotic reaction, but any injury greater than 10% will result in proliferation of cells throughout the liver [91, 43]. When more than 50% of

the liver is resected, a second, less distinct wave of hepatocyte mitoses is observed. Compared with replication after resection, the peak replication after PVE is delayed approximately 3 - 4 days, suggesting that the hypertrophy stimulus generated by hepatocyte removal is stronger than the stimulus produced by apoptosis seen after PVE [91, 44]. The distinction between healthy and injured livers is important as chronically damaged livers are less able to regenerate [28, 45]. This may be the result of the diminished capacity of hepatocytes to respond to hepatotropic factors or because parenchymal damage such as fibrosis leads to slower portal blood flow rates [91, 46]. Non-cirrhotic livers in humans regenerate fastest, at rates of 12 - 21 cm^3/d at 2 weeks, 11 cm^3/d at 4 weeks, and 6 cm^3/d at 32 days after PVE [91, 35, 47]. The rates of regeneration are slower (9 cm^3/d at 2 weeks) in patients with cirrhosis, with comparable rates found in patients with diabetes [91, 35, 48]. As hypertrophy is also associated with a functional gain in the non-embolised lobe [49, 50], radiological, biochemical and haemodynamic parameters have been studied to predict the extent of regeneration. In 1998, Goto et al. [46], reported that the hypertrophy rate after embolisation is predictable from the increase in the portal blood flow velocity, as measured by Doppler ultrasound the day after the procedure. In a recent report from Wakabayashi et al., [28], multiple regression analysis revealed that the prothrombin time and FRLV/TLV ratio in normal liver were independent parameters predicting hypertrophy after PVE. In series of 84 PVEs, multivariate analysis indicated that diabetes mellitus, a high bilirubin level and male gender were important cofactors associated with a reduced hypertrophy [51].

30.4. Clinical Rationale for PVE Before Major Liver Resection

The rationale for the use of PVE is to (i) minimise the abrupt increase in portal pressure at resection that can lead to hepatocellular damage to the FLR; (ii) dissociate portal pressure-induced hepatocellular damage from direct trauma to the FLR during physical manipulation of the liver at the time of surgery (together these forms of damage might result in hepatic congestion and post resection dysfunction); and (iii) improve overall tolerance to major resection by increasing hepatic mass before resection to reduce the risk of post resection metabolic changes [91]. Minor and transient changes in liver function test results are seen after PVE. When aminotransferase levels do increase, they generally peak at levels less than three times baseline levels 1 - 3 days after PVE and return to baseline levels within 7 - 10 days regardless of the embolic agent used [18, 19, 35, 48, 52-54]. Slight changes in white blood cell count and total serum bilirubin level may be seen. Synthetic functions are almost never affected by PVE [91]. Portal blood flow to the nonembolised hepatic segments measured by Doppler ultrasound (US) increases significantly and then decreases towards, but does not reach, the baseline value after 11 days. The resultant hypertrophy rate correlates with the portal flow rate [17, 46]. Signs and symptoms of postembolisation syndrome are infrequent and include nausea, vomiting, fever and pain. This is because PVE is less toxic than arterial embolisation [17] and causes less inflammation and necrosis to the liver parenchyma [18, 55].

30.5. Measurement of FLR Volume and Predicting Function after PVE

Remnant liver volume after hepatic resection directly correlates with surgical outcome. Thus accurate measurement of liver volume is crucial and is commonly performed by computed tomography (CT) with volumetry. Volumetric assessment is necessary prior to and after PVE, and CT estimations of the liver volume correlate well with real intraoperative volumes, despite potential sources of error (partial volume effect, respiratory phase) [15, 51, 52]. The role of CT has extended beyond its use for liver imaging to include three-dimensional volumetric measurement before liver transplantation or major hepatic resection [9, 11, 57, 58]. This has been possible because of a close correlation between the volume obtained by three- dimensional reconstruction of computed tomographic images and actual liver volume [59]. Three dimensional CT volumetric measurements are acquired by outlining the hepatic segmental contours and calculating the volumes from the surface measurements from each slice (fig. 30.1).

In order to identify the vascular landmarks of the li-

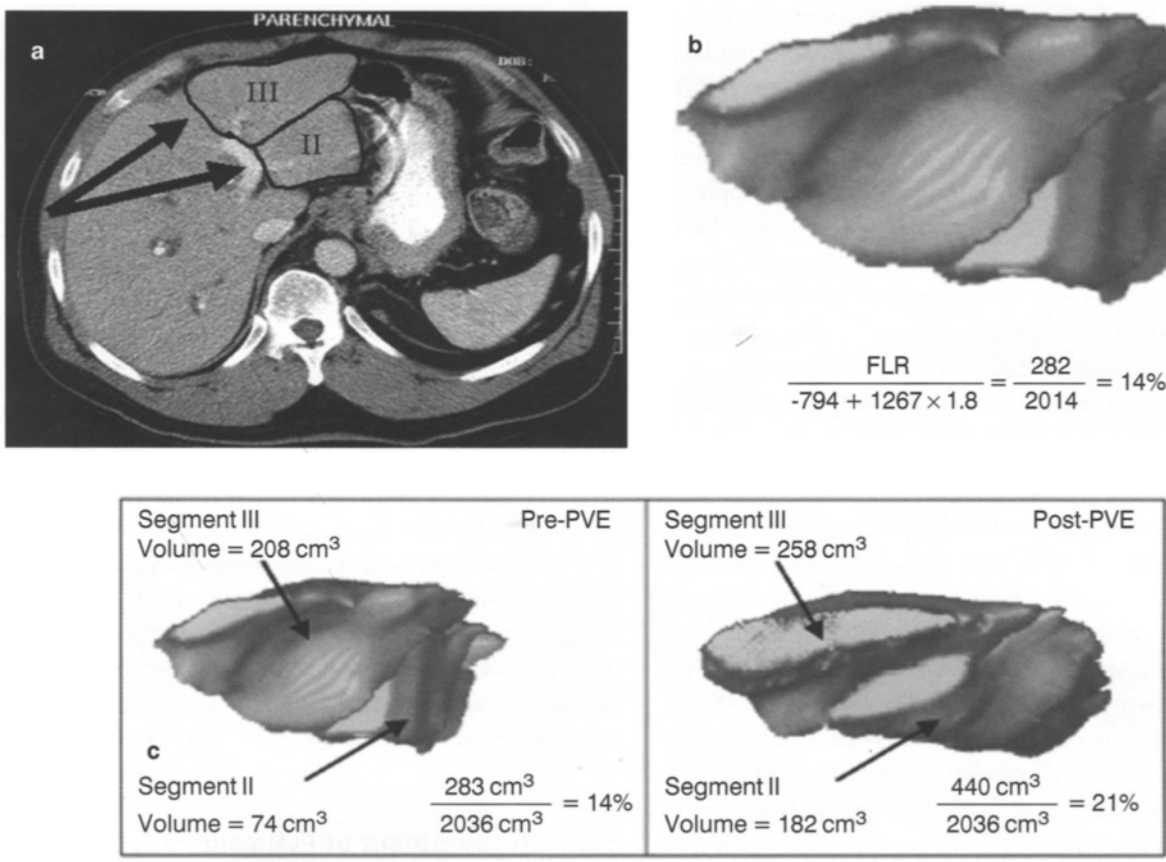


Fig. 30.1. Hypertrophy of the FLR after PVE as determined by three-dimensional reconstruction of CT images. (a) Three dimensional volumetric measurements are determined by outlining the hepatic segmental contours and then calculating the volumes from the surface measurements of each slice. (b) Formula for calculating total liver volume is based on patient's BSA. (Modified with permission from Reference 14). (c) Before embolisation, the volume of segments II/III is 283 cm^3, or 14% of the total liver volume (2,036 cm^3). After embolisation, the volume of segments II/III is 440 cm^3, or 21% of the total liver volume (an increase of 7%).

ver, intravenous (IV) contrast administration is essential in different phases. With this technique, the total liver volume and FLR volume can be calculated immediately after scanning [60]. Two techniques of CT volumetry are used. The first method measures the volume of the entire liver plus tumours and then the volumes of each measurable tumour. Total "normal liver" volume is then estimated by subtracting tumour volume from total volume and calculated as follows [15, 61]:

(resected volume - tumour volume)
/ (total liver volume - tumour volume)

This method can be difficult with multiple tumours. And also this approach does not account for the actual functional liver volume when there is vascular obstruction, chronic liver disease, or biliary dilation in the liver to be resected [91].

A more accurate method (fig. 30.1) standardises liver remnant size to individual patient size to account for the reality that large patients need a larger liver remnant than smaller patients need. CT is used to directly measure the FLR. The total liver volume is then estimated total estimated liver volume (TELV) by a formula:

(TELV = -794.41 + 1,267 body surface area [54, 62, 63] [BSA]; $r2 = 0.454$; $P < .001$)

derived from the close association between liver size and patient size based on body weight and BSA [11, 25]. The FLR/TELV ratio is then calculated to provide a

volumetric estimate of function of the FLR. From this method of calculation, called standardised FLR measurement, a correlation between the anticipated liver remnant and operative outcome has been established [11]. CT images are obtained immediately before PVE and approximately 4 weeks after PVE to assess the degree of FLR hypertrophy. In cases of cirrhotic livers, functional tests are sometimes used to assess liver function, with the most common test being indocyanine green retention. Makuuchi et al [64] use a clinical algorithm to determine the extent of safe resection in a patient with cirrhosis based on indocyanine green (ICG) retention and extent of planned resection. Its clearance can be used as an indicator for hepatocyte function. Retention rate 15 min after intravenous injection of ICG (0.5 mg/kg) correlates with outcome in some series [54, 62, 63]. ICG excretion and bile volume from the unembolised lobe increase after PVE and correlates with volume increase of that lobe [49]. Others found that 99mTc GSA liver scintigraphy is more useful than CT for accurately predicting remnant liver function before hepatectomy based on ICG and for evaluating changes in regional liver function after unilateral occlusion of the portal vein [65]. However, the only consistently used test is CT volume estimation. Current developments in nuclear imaging technology designed to measure anatomic and functional differences in liver volume are being evaluated. Technetium 99m –labeled diethylenetriamine pentaacetic acid– galactosyl human serum albumin specifically binds to asialoglycoprotein receptors on the cell membranes of hepatocytes. Distribution of this agent can be monitored in real time with use of single-photon emission scintigraphy and has been shown to correlate with indocyanine green retention [65]. Another technique, axial image reconstruction, can be used to estimate the differential functions of the right and left liver. However, neither technique has been established as sufficiently accurate for use in assessing segmental or bisegmental function during planning for extended hepatectomy [91].

30.6. Anatomic Considerations

A comprehensive understanding and application of surgical anatomy of the liver is essential in performing PVE. The liver is divided into two lobes (left and right, separated by the main portal fissure) and eight segments. Hepatic segmentation is based on the distribution of the portal pedicles and the location of the hepatic veins (fig. 30.2).

30.7. Portal Venous Anatomy

The portal vein is formed by the union of the superior mesenteric and splenic veins behind the neck of the pancreas at the level of the L1/L2 lumbar vertebra. It then runs to the right behind the neck of pancreas and behind the first part of the duodenum and behind the common bile duct and hepatic artery to reach the porta hepatic where it divides into right and left branches. The bifurcation may be extrahepatic, intrahepatic or just at the entrance of the liver.

On the right there are usually two sectoral portal branches (anterior and posterior); on the left, there are two parts to the (main) left portal vein: the extrahepatic portion and the intrahepatic portion. The sectoral branch divides into several segmental portal branches, which in turn supply the various segments. One segmental branch usually supplies segments II, VI, and VII and, more rarely, segment III. Segments IV, V, and VIII

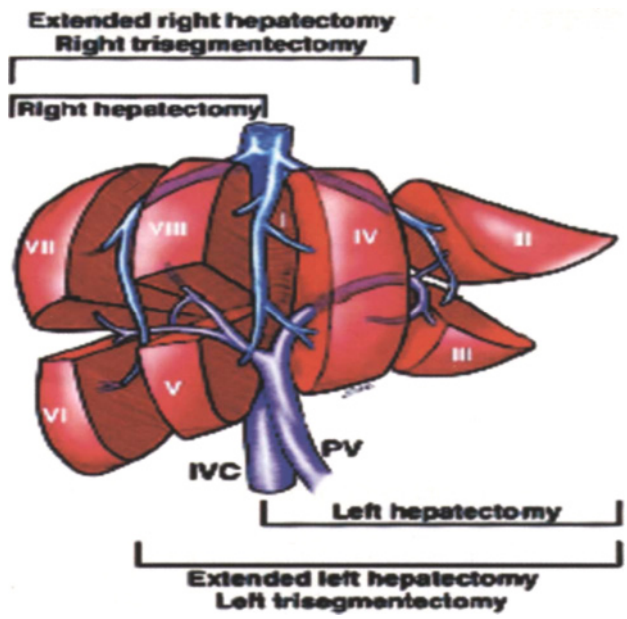
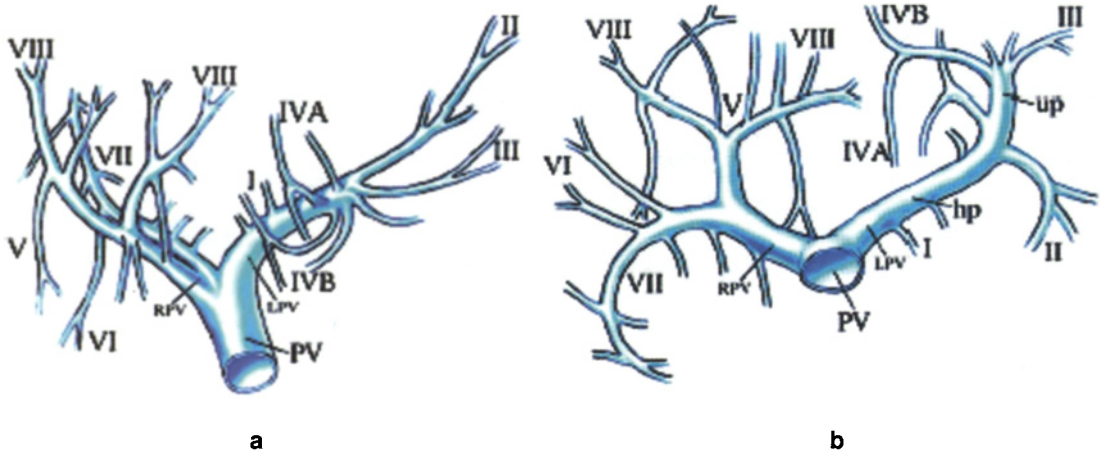


Fig. 30.2. Schematic illustrates Couinaud segmental liver anatomy and the normal portal venous structures. The possible hepatic resection procedures are also shown. IVC – inferior vena cava, PV – portal vein.



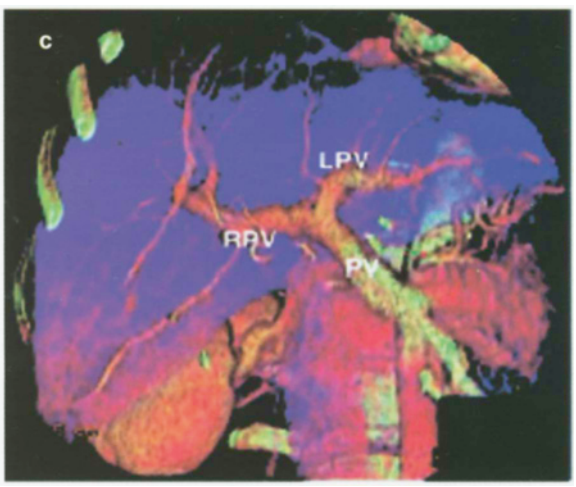


Fig. 30.3. (a, b) Schematics illustrate the normal portal vein (PV) branches from anterior (a) and inferior (b) perspectives. hp – horizontal part, LPV – left portal vein, RPV – right portal vein, up – umbilical (vertical) part. (c) Three-dimensional computed tomographic (CT) reformatted image (anterior view) demonstrates normal portal venous anatomy. LPV – left portal vein, PV – portal vein, RPV – right portal vein.

are commonly supplied by more than one segmental branch. Segmental veins then divide into subsegmental branches, which further divide into small veins leading to the portal venule of the liver acinus.

30.8. Portal Venous Variants

Anatomic variants of the portal vein, though uncommon can have serious implications on performing a successful PVE. The PV may have one left and two right (anterior and posterior) portal branches. This is known as portal trifurcation. The right anterior segment portal vein may branch from the left main portal vein, or the left main portal vein may branch from the right anterior portal vein. Alternatively, the right posterior branch may stem from the main portal trunk, with the anterior branch forming a bifurcation with the left portal vein. Quadrifurcation of the portal vein is another possible variant, consisting of a branch for segment VII, a branch for segment VI, an anterior branch, and a left main portal branch (left portal vein). Rarely bifurcation of the portal vein is completely absent (ie, no right portal vein) [67]. In this case, the solitary portal vein in the hilum passes through the entire liver, either from right to left or from left to right. It is essential to be aware of these variants and others, though rare, in order to perform a safe well targeted PVE and prevent injury to the FLR.

30.9. Mechanism of PVE

PV occlusion can be achieved either by PV ligation (PVL) or by PVE. Broering et al. conducted a study on 34 patients with primary or secondary liver tumours to assess the efficacy of right PVE vs. right PVL for induction of hypertrophy of the left lateral liver lobe before extended right hepatectomy. The study found PVE to be superior to PVL in terms of volume gain in a shorter time, shorter hospital stay, and fewer adhesions during major hepatectomy [10]. PVE can be performed by any of three standard approaches: the transhepatic contralateral (ie, portal access via the FLR), transhepatic ipsilateral (ie, portal access via the liver to be resected), and intraoperative transileocolic venous approaches. These approaches are chosen on the basis of operator preference, type of hepatic resection planned, extent of embolisation (eg, right PVE with or without extension to segment IV), and type of embolic agent used [91].

PVE is performed to redirect portal blood flow toward the hepatic segments that will remain after surgery (ie, the FLR). To ensure adequate hypertrophy, embolisation of portal branches must be as complete as possible so that recanalisation of the occluded portal system is minimised [91]. The entire portal tree to be resected must be occluded to avoid the development of intrahepatic portoportal collaterals that may limit regeneration [68].

Necessary laboratory studies are done prior to the procedure including complete blood count, prothrombin time, total bilirubin value, liver function tests, blood urea nitrogen/creatinine levels prior to PVE. If the patient has an elevated total bilirubin value (>3.0 mg/dL), percutaneous or endoscopic biliary drainage is performed. Cross-sectional imaging for procedural planning is performed immediately prior to PVE to document the extent of disease (ie, extrahepatic disease or involvement of the planned FLR), FLR size, and portal venous anatomy [91, 69]. On the day of the procedure, prophylactic broad-spectrum antibiotics (e.g., cefazolin, ceftriaxone sodium) are administered intravenously for prevention of biliary sepsis [70]. Although general anaesthetic may be requested, the procedure is most often performed with local anaesthetic (1% lidocaine hydrochloride) and intravenously administered sedatives that allow the patient to remain conscious. Ultrasonography of the liver is performed to determine the best access route into the portal venous system. Under sterile conditions, access into the portal venous system is gained under ultrasonic or fluoroscopic guidance or both. The percutaneous transhepatic method is an application of Lunderquist's technique for sclerosis of esophageal varieces via the coronary vein [71].

The transhepatic contralateral approach, developed by Kinoshita et al [27], is the most commonly used technique. With this approach, a branch of the left portal system is accessed and a 6-F balloon occlusion catheter is advanced through an introducer into branches of the right portal tree for embolisation. Modifications of this technique have been made since the initial report [52]. This makes the procedure technically easier since the catheterisation of the desired right PV branch is more direct via the left system than via the right system. However, the disadvantage of this technique is the risk of injury to the FLR parenchyma and the left PV [60]. The transhepatic ipsilateral approach was first described by Nagino et al [73] in the mid 1990s. For this approach, a peripheral PV branch in the liver to be resected is accessed and a 6-F sheath is advanced through it. Nagino and colleagues [73] designed two types of balloon occlusion catheters, "type 1" and "type 2," that facilitate "trisegment" PVE from the right or the left, depending on the type of resection to be performed (eg, extended right or extended left hepatectomy). Both catheters are 5.5-F and have three lumens, one to the balloon and the other two at the catheter tip (type 1) or just proximal to the balloon (type 2). These catheters serve distinct functions of targeting embolisation with adhesive or sclerosing agents proximal or distal to the balloon. Because the ipsilateral approach requires the use of catheters unavailable outside of Japan, modifications of the ipsilateral technique have been developed. At the M. D. Anderson Cancer Center standard angiographic catheters are used for combined particulate and coil embolisation [91, 69, 74, 75] (fig. 30.4).

Increasing attention is paid to embolising not only the right portal vein but also the branches to segment IV [20, 21] if an extended right lobectomy is needed. Systematic embolisation of segment IV branches is important for 2 reasons. First, all tumour bearing liver is embolised because accelerated tumour growth has been reported after incomplete embolisation [76]. Second,

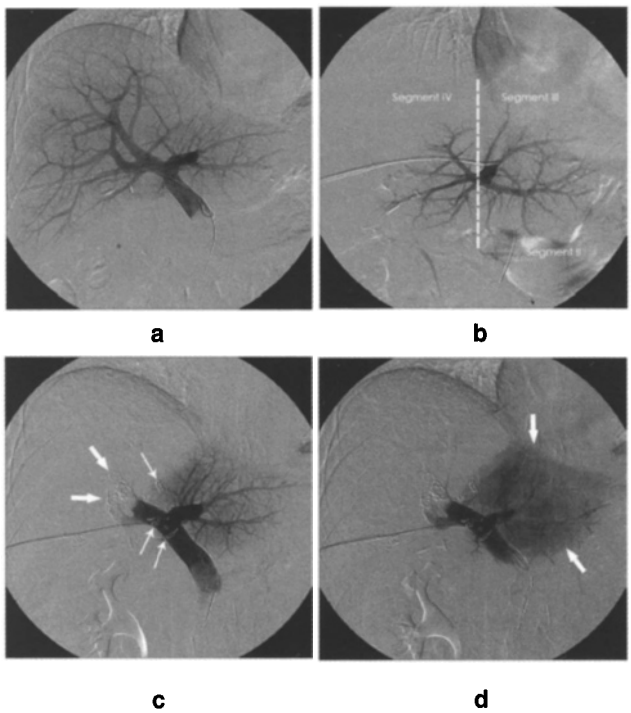


Fig. 30.4. (a-d) Technique of transhepatic ipsilateral right PVE extended to segment IV with tris-acryl microspheres and coils. (a) Anteroposterior flush portogram shows a 6-F vascular sheath in a right PV branch and a 5-F flush catheter in the main PV. (b) Selective left portogram shows the veins that supply segments II, III, and IV. (c) Post procedural portogram shows occlusion of the PV branches to segments IV-VIII (small white arrows point to coils within segment IV PV branches; large white arrows point to coils within the proximal anterior and posterior sector right PV branches) with continued patency of the veins supplying the left lateral lobe (segments II/III). (d) Later phase of post procedural portogram demonstrates normal parenchymal flow to the left lateral lobe (white arrows) with complete absence of flow to segments IV-VIII.

systematic embolisation of segment IV may contribute to better hypertrophy of segments I, II and III before extended right lobectomy. Avoiding reflux of embolising material into contralateral lobar veins is essential when occluding segment IV veins with any substance; bilateral or main portal vein occlusion, although never reported remains a definite risk. Nagino et al [20] recommended particulate embolisation of segment IV before embolisation of the right system to minimise the risk of such complications. A 3-F microcatheter is advanced coaxially through a 5-F angled catheter into the PV branches in segment IV so that particles (eg, polyvinyl alcohol [PVA] particles or tris-acryl gelatin microspheres) and coils can be delivered. When segment IV embolisation is completed, a reverse-curved 5-F catheter is used for right PVE [91]. Embolisation of the access tract is performed with coils to reduce the risk of perihepatic haemorrhage at the puncture site [91].

One advantage of the ipsilateral approach is that the contralateral liver is not instrumented and thus avoiding vascular injury to the anticipated liver remnant. However, catheterisation of the right PV branches may be more difficult because of severe angulations between right portal branches, and the technique usually requires the use of reverse-curved catheters. Another potential disadvantage of this approach is that some embolic material could be displaced on catheter removal, leading to non target embolisation; however, this has not occurred in more than 50 ipsilateral PVE procedures with or without extension to segment IV portal branches with particles and coils [91, 74, 75]. The transileocolic venous approach is performed during laparotomy by direct cannulation of the ileocolic vein and advancement of a balloon catheter into the PV for subsequent embolisation [18]. Tumour extent can be assessed at the time of PVE by this method.

This approach is often performed when an interventional radiology suite is not available, when a percutaneous approach is not feasible, or when additional treatment is needed during the same surgical exploration [77]. A pilot study of PVE via a transjugular approach in 15 patients was reported [78]. Under US guidance, a right or left PV branch is punctured from the right, median, or left hepatic vein. A catheter is then placed near the portal bifurcation and used to perform right portal branch embolisation with a mixture of n-butyl-2-cyanoacrylate (NBCA) and iodised oil. All 15 cases were successful. FLR hypertrophy was adequate with this approach, and right hepatectomy was performed in 12 patients. Although this approach appears safe and effective, the series is small, and additional studies will be necessary before this technique becomes widespread. For right PVE in patients with cirrhosis, this may be an attractive approach; however, the technical feasibility of right PVE extended to segment IV has not been explored [91].

30.10. Embolic Material

Many embolic materials have been used for PVE. These agents include, fibrin glue, NBCA and ethiodised oil, gelatin sponge and thrombin, coils, microparticles (microspheres), and absolute alcohol. Both gelfoam and coil are always used along with other substances for the embolisation of large branches of portal vein [70, 88]. Gelatin sponge and Fibrin glue are commonly used as embolic material but found to have high rates of early recanalisation, as early as 2 weeks. Kaneko et al [79] proposed a combination of gelatin sponge with the sclerosing agent polidocanol. Used in a canine model, this emulsion produced occlusion of the desired PV branches for as long as 8 weeks after PVE [91]. NBCA mixed with ethiodised oil leads to fast, reliable hypertrophy and minimizes the delay between PVE and definitive resection [52]. Different embolic materials differ also in the rate and degree of regeneration. NBCA embolisation leads to a 90% increase in liver volume after 30 days whereas the combination of gelatin sponge and thrombin resulted in only a 53% volume increase after 43 days [19]. But massive peribiliary fibrosis results with the use of NBCA, and this in turn increases operative difficulty. PVE with absolute alcohol has been found to be particularly useful in the treatment of HCC as a result of its strong coagulation effect, although obvious alteration was found in measured liver function following the embolisation [70].

Another commonly used agent for PVE is a mixture of fibrin glue with ethiodised oil. This mixture usually induces less than 75% portal occlusion at 2 weeks and less than 25% portal occlusion at 4 weeks [80]. However, fibrin glue with ethiodised oil was found to increases FLR volume by 10%-20% after a mean of 18 days after PVE [20, 35, 83]. Recently, the use of particles such as PVA particles for PVE has been proposed [30, 69, 74, 84]. PVA particles are safe, cause little periportal reaction, and generate durable PV occlusion when used in combination with coils [30].

30.11. Postembolisation Course

Evaluation for signs of postembolisation syndrome or liver insufficiency includes review of patient symptoms, clinical signs, and laboratory data (such as elevated white blood cell count, increasing transaminase levels, or prothrombin time). Patients are discharged when they are clinically stable and without complications, usually the next day [69]. CT is repeated after 2-4 weeks to assess FLR hypertrophy and disease changes. If liver regeneration occurs, resection is performed. Otherwise, follow-up CT is performed after 4 weeks. Although studies in animals show that most regeneration occurs within the first 2 weeks, this has not yet been proved in humans [69].

30.12. Indications for PVE

A number of factors must be taken into consideration for selection of patients who will benefit from PVE. The most important factor is the status of the liver to be operated upon, whether healthy or cirrhotic, because that will affect the FLR volume needed for adequate function. And correlating that with the patient's size is another important factor. Large patients will need more remnant volume. Another factor is the extent of the planned resection. All of these factors along with patient's age, status, and any underlying disease must be taken into consideration when deciding whether to perform PVE or not. The first factor to be considered in determining whether PVE is indicated is the presence or absence of underlying liver disease. A normal liver has a greater regenerative capacity than a cirrhotic liver, functions more efficiently, and tolerates injury better [91]. Post resection hepatic failure and complications were found to occur more frequently in patients with liver cirrhosis. Standardising the FLR size to patient size is critical to appropriate determination of the need for PVE [91]. A recent prospective randomised study [88] confirmed the benefit of PVE in patients with cirrhosis before right hepatectomy, and Kubota et al [15] suggested an FLR less than 40% should prompt PVE before major hepatectomy. This guideline has been extended to patients in whom the liver is compromised by chronic liver disease, high-dose chemotherapy, or severe fibrosis [11, 17, 44, 48].

In patients with an otherwise normal liver, the indications for PVE have evolved with greater accuracy of liver volume measurement and the use of standardized liver volumes [91]. An FLR/TELV ratio greater than 20% is associated with fewer complications than an

FLR/TELV ratio of 20% or more [13]. It is important to recognize and individualize the indication for PVE with use of a standardized 20% cutoff for liver volume because of intrahepatic segmental variability. Liver volume analysis has revealed that the lateral left liver (segments II/III) contributes less than 20% of the total liver volume in more than 75% of patients in the absence of compensatory hypertrophy [91]. In addition, the left liver (segments II, III, and IV) contributes 20% or less of the total liver volume in more than 10% of patients [89]. Therefore, an FLR/TELV ratio less than 20% can be expected in most patients who do not develop compensatory hypertrophy from tumour growth and require an extended right hepatectomy. In this subset of patients, the use of right PVE with extension to segment IV is indicated [91]. One novel indication for PVE other than what was mentioned, is to induce hepatocyte replication to enable hepatic gene therapy. Hepatic gene therapy is being investigated for treatment of serum protein deficiencies including haemophilia and metabolic defects. Gene therapy delivery vehicles under investigation provide only transient transgene expression in the liver. Retroviral delivery systems have the advantage of providing more durable transgene expression but require cell replication to enable transfection. Thus, limited PVE may play a role in future hepatic gene therapy with retroviral delivery systems [30].

30.13. Contraindications

So far, there has been no absolute contraindication to PVE. However there are some relative contraindications which include: i) Patients with metastatic disease, such as distant metastases or periportal lymphadenopathy, cannot undergo resection and therefore are not candidates for PVE; ii) patients with widespread intrahepatic disease involving the entire right lobe and segment I, II, or III or involving the entire left lobe and segment VI or VII are not candidates for right or left trisegmentectomy, respectively and would not benefit from PVE; iii) uncorrectable coagulopathy; iv) tumour invasion of the portal vein; v) tumour precluding safe transhepatic access; vi) biliary dilatation (in cases of biliary tree obstruction, drainage is recommended); vii) portal hypertension; viii) renal failure, which requires dialysis [69]. The presence of an ipsilateral tumour may preclude safe transhepatic access if the tumour burden is great, but this is also unlikely, as there is no evidence that tumour spread occurs during PVE. If access to an adequate PV branch for PVE is not possible, the contralateral approach can be considered [91]. However, this option must be weighed against the possibility of causing injury to the FLR or the portal veins that supply it.

30.14. Outcomes After PVE and Hepatectomy

PVE induces hypertrophy of the nonembolised lobe of both abnormal and normal liver parenchyma, with better results in the normal livers. And it was found to reduce postoperative morbidity and enable safe, potentially curative hepatectomy for patients not previously considered candidates for resection based on anticipated marginal FLRs, and with minor and transient complications [13-22].

However, successful PVE does not necessarily lead to surgical resection, Azoulay [16] conducted a study in which thirty patients underwent preoperative PVE before resection of unresectable liver metastases from colorectal cancer. Liver resection was performed after PVE in 19 patients (63%) only. Reasons for unresectability after PVE were related to contralateral tumoural progression and extrahepatic tumour spread precluding curative resection. Other factors leading to cancellation of resection post PVE are: insufficient hypertrophy of the nonembolised liver, and complete portal thrombosis [72]. But when followed by resection PVE and PVL are considered both feasible and safe methods of increasing the remnant functional liver volume and achieving resectability of extended liver tumours without increasing mortality and morbidity [10]. The following table summarises the outcome of PVE in a number of studies conducted on patients with liver metastases (table 30.1).

Table 30.1. Summary of the outcome of PVE in a number of studies.

Study		n	PVE to surgery	% FRLV	Increase (mean) % resected
De Baere et al. [52]	1996	22	32	13	77
Azoulay et al. [86]	2000	30	63	11	63
Kokudo et al. [90]	2001	18	24	8	100
Elias et al. [45]	2002	68	30	13	8

Knowing that chronically damaged livers are less able to regenerate, evaluating the outcome of PVE in normal and abnormal liver parenchyma separately is more convenient.

30.15. PVE in Patients with Chronic Liver Disease

PVE is less effective in patients with chronic liver disease. Because liver growth is triggered by hepatic function loss, the more normal and functional liver parenchyma is embolised, the more likely adequate liver growth will be observed [28, 45]. In patients with chronic liver disease (chronic hepatitis, fibrosis, or cirrhosis), the increase in nonembolised liver volumes after PVE varies (range, 28%-46%), and hypertrophy after PVE may take more than 4 weeks because of slower regeneration rates [91, 35, 48]. The complication rates after PVE are higher in patients with chronic liver disease than in those with an otherwise normal liver because of the increased risk of secondary PV thrombosis, presumably from slow flow in the PV trunk after PVE [91, 72].

In patients with underlying liver disease, number and severity of complications and incidence of postoperative liver failure and death after major hepatectomy are decreased by PVE. Compared with patients treated with major hepatectomy without PVE [91, 44, 48, 86, 96, 97]. Tanaka et al [97] reported several benefits of PVE in a larger study of patients with cirrhosis and HCC. Disease-free survival rates were similar, but cumulative survival rates were significantly higher in the PVE group than in the non-PVE group. In addition, patients with recurrence after PVE plus resection were more often candidates for further treatment, an additional benefit of PVE in the long term [91].

30.16. PVE in the Absence of Chronic Liver Disease

The outcome of embolisation and subsequent resection may be even more closely linked to the PVE technique in patients with otherwise normal livers than in patients with cirrhotic livers [91]. Several studies have validated residual volume as the key to prediction of postoperative liver function and posthepatectomy course. Vauthey et al [14] recently reported 127 consecutive extended hepatectomies with standardised liver volume calculations used to select patients for PVE and extended hepatectomy. In that series, 24% of patients underwent PVE before extended hepatectomy. Of 127 patients, only six (5%) experienced significant postoperative liver insufficiency; the postoperative complication rate was 31%, and only one patient (0.7%) died after hepatectomy. The median survival was 41.9 months, and the overall 5-year survival rate was 26% for the entire group.

PVE has clearly been shown to enable safer resection with acceptable oncologic outcomes in correctly selected patients with otherwise normal livers. Technical aspects of the embolisation can impact the degree and rate of hypertrophy of the liver remnant, and although changes in tumour size related to PVE appear not to have clinical significance, increases in tumour size can be avoided and FLR hypertrophy can be maximised if the entire tumour-bearing liver is systematically embolised, including the right liver and segment IV, before extended right hepatectomy [91]. It was observed that in patients with a normal liver the growth rate of tumour appeared to be more rapid than that of the parenchyma during liver regeneration following right PVE [76].

Apparently, tumour growth after PVE is not controlled by the same mechanisms as hypertrophy of the preserved portion of the liver. Tumour growth after PVE may be controlled by 3 factors: malignant potential of the tumours, changes in cytokines or growth factors induced by PVE, and changes in blood supply after PVE [92]. The approach to these multiple bilobar liver tumour cases is through a two-stage hepatectomy procedure (TSHP) combined with portal vein embolisation. In which metastases located in the FRL should be ideally resected before PVE in a first-stage hepatectomy; a major hepatic resection can then be performed, after PVE, in a second-stage hepatectomy. In a study conducted on 33 patients with unresectable MBCLM, Jaeck [93] found that in selected patients with initially unresectable MBCLM, a TSHP combined with PVE can be achieved safely with long-term survival similar to that observed in patients with initially resectable liver metastases. In summary, no current evidence exists that PVE-induced tumour growth is of clinical significance, whereas the clinical utility of PVE has been clearly established.

30.17. Complications

PVE is considered a relatively safe adjuvant method to liver resection, less toxic than arterial embolisation, and with minimal side effects. In a study conducted by Di Stefano evaluating adverse effects in 188 patients who underwent preoperative PVE (PPVE) for primary or secondary liver tumours, he found that 6.4% of complications necessitated treatment or prolonged hospitalisation, including 0.5% that precluded the scheduled liver resection. These complications included thrombosis of the portal vein feeding the FLR (one patient), embolic material migration in portal vein feeding the FLR (two patients), haemoperitoneum (one patient), transitory haemobilia (one patient), rupture of a metastasis into the gallbladder (one patient), migration of small emboli in non targeted portal branches (ten patients), subcapsular haematoma (two patients), and transient liver failure (six patients). Post-PPVE transient liver failure was more common in patients with cirrhosis than in those without cirrhosis. So, PPVE was found to be a safe procedure in more than 93.6% of cases [72]. Signs and symptoms of postembolisation syndrome, such as nausea and vomiting, are rare. Fever and pain are infrequent. Changes in liver function following PVE are usually minor and transient (50% of patients have no appreciable change). When transaminase levels rise, they usually peak at a level less than three times baseline 1 - 3 days after embolisation and return to baseline in 7-10 days, regardless of the embolic materials used. Slight changes in total bilirubin value and white blood cell count may be seen. Synthetic function (e.g., prothrombin time) was almost never affected [70]. Other complications include, pseudoaneurysm which is considered to be a severe complication and may result in death, it is treated by transcatheter arterial embolisation (TAE). Arteriovenous, fistula, arterioportal shunts, pneumothorax and sepsis [72, 101]. As most technical complications occurred in the punctured lobe, Kodama and colleagues [101] recommended that the transhepatic ipsilateral approach be tried first. Of interest, complication rates differed depending on the segments punctured in their study. When the anterior segment was punctured, the complication rate was lower than when the posterior segment was punctured. A possible explanation for this finding is that the posterior branch of the PV is more difficult to visualize clearly than the anterior branch, making it more difficult to set up an adequate puncture line [91].

30.18. Future

Although PVE is considered a big leap in the history of liver surgery, much is still yet to be understood about how PVE actually works, and how we can apply it in a way to improve the outcome of liver resection. Since liver regeneration after hepatic tissue loss is the principle by which PVE works, further analysis is needed to fully understand the mechanism. The role of stem or progenitor cells in liver regeneration has long been controversial, liver is unlike skin and GI tract which have a specific stem cell population responsible for the continuous rapid turn over. This population isn't implicated in a clear straight forward sense in the hepatic regenerative process. Many factors are being implicated in the initiation, progression and cessation of this growth response, those factors are either intrinsic secreted by hepatocytes itself or secreted by other organs. However it works differently on different livers. Why do cirrhotic livers respond in a different way to PVE in comparison to normal livers? And even normal livers differ in degree and rate of hypertrophy after PVE. All are issues which need to be better understood. Another controversial issue is tumour growth after PVE. Not much data is available to make a clear idea whether PVE induces tumour growth and how would this adversely affect the outcome of it, however this represents a point to be thoroughly investigated in order to keep claiming the safety and justification for PVE. I believe that a multidisciplinary approach, including a better understanding of how our bodies function and regenerate, a thorough knowledge of liver pathobiology, this fascinating organ, an improvement in surgical techniques and post operative care, a large pool of patients, and long term follow up results, will definitely improve our understanding of PVE and how to implicate it in a way that will maximally benefit patients with liver tumours and have significant effect on the surgical outcome and long term survival.

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CHAPTER 31

HEPATIC CHEMOEMBOLIZATION

Paul Tait

31.1. Introduction

End stage liver disease accounts for approximately 1 in 40 deaths world wide. Hepatitis B (HBV) and hepatitis C (HBC) viruses are recognised risk factors for cirrhosis and liver cancer. It has been estimated that, globally, 57% of cases of cirrhosis can be attributable to HBV (30%) or HCV (27%) and that 78% of hepatocellular carcinoma (HCC) is attributable to HBV (53%) or HCV (25%). Applied to 2002 mortality figures these fractions would represent estimates of 929,000 deaths due to chronic HBV and HCV infections, including 446,000 cirrhosis and 483,000 liver cancer deaths [1].

Early stage HCC is clinically silent and the disease is often advanced at presentation. Without treatment the 5 year survival is less than 5% [2]. The World Health Organisation (WHO) has estimated that by 2010 HCC will have surpassed lung cancer as the foremost cause of cancer mortality worldwide [3].

In the United States the incidence of histologically proven HCC has increased from 1.4 per 100,000 in the 1976-1980 population to 2.4 per 100,000 in the 1981-95 population [4]. The increasing incidence in the latter cohort is related to the spread of viral hepatitis (B and C) in the 60's and 70's secondary to blood and sexual transmission [4]. However, hepatocellular carcinoma can develop in any patient with underlying cirrhosis, whatever the aetiology of that cirrhosis.

Only 20% of cases of HCC are surgical candidates at presentation [5]. Even though patients may present with lesions that are resectable, co-existing medical morbidities or the status of the underlying liver may make them unsuitable surgical candidates.

It has been postulated that patients with established cirrhosis should be monitored with ultrasound every 6 months to detect early tumours. Such lesions can then be treated by resection, liver transplantation or percutaneous treatment (chemical ablation or radiofrequency ablation). This would prove suitable for 30% of patients and could achieve survival rates greater than 50%. Resection can be considered in those cases with one tumour and well preserved liver function. The only absolute contraindication to surgery is the presence of extrahepatic disease. However, many clinical and morphological factors may affect the success of surgery and may lead to a different form of therapy. The most notable of these is the association of HCC with underlying cirrhosis [6]. In general, surgical resection is limited to those cases with Child-Pugh class A or B liver disease [7]. Liver transplantation can be considered for patients with decompensated cirrhosis and one tumour less than 5cm diameter or up to 3 nodules less than 3cm diameter. There is always the problem of suitable donors [8]. Most patients present with advanced disease and hence palliation is the only possibility.

Possible non surgical therapies for HCC include systemic chemotherapy, chemical ablation (ethanol or acetic acid), other percutaneous ablative measures (radiofrequency ablation, microwave ablation and cryotherapy), transarterial chemoembolisation (TACE) and Selective Internal Radiation Therapy (SIRT). Chemical ablation and Radiofrequency ablation can be used in the management of small unresectable HCC's that are few in number. These treatments can also be of benefit as a bridge or controlling the malignant disease process prior to transplantation. More widespread disease is treated with either TACE or SIRT [7]. Systemic chemotherapy is relatively ineffective with a low response rate (<20%) and a mortality rate up to 25% [9].

TACE has been utilised in Japan and the Far East for numerous years but the benefits have been disputed [10, 11].

However, in 2002 were published the results of two landmarks, well designed, randomized controlled trials

that clearly demonstrated a survival benefit for those patients with unresectable HCC treated with TACE compared with best medical care. The Barcelona Liver Cancer Group utilising Doxorubicin as the chemotherapeutic agent demonstrated a survival benefit with TACE of 82% at one year compared with 63% for best medical care. There was also a benefit of TACE over simple embolisation without the chemotherapy but the results did not reach statistical significance [12]. A group from Hong Kong used Cisplatin as the chemotherapeutic agent and demonstrated a survival benefit of 57% versus 32% for TACE compared with best medical care [13]. Patients enrolled in these studies were of relatively good performance status, being limited to Child-Pugh groups A and B. Child-Pugh score is determined on the basis of serum albumin, total serum bilirubin, prothrombin time and the presence and degree of ascites and hepatic encephalopathy. Thus only patients in a relatively good clinical condition are likely to benefit from any invasive procedure.

31.2. Theoretical Aspects

It is the dual blood supply to the liver that provides the advantage to allow direct therapeutic interventional procedures. Liver neoplastic disease primarily obtains its blood supply from the hepatic arterial circulation whilst the converse is true for the hepatic parenchyma. Liver tumours receive as much as 95% of their blood supply from the hepatic artery whereas the normal liver parenchyma obtains 70% of its blood supply from the portal vein [14]. This differential blood supply has been demonstrated by a variety of means, including CT, CO2 microbubble ultrasound and study of explanted livers [15-17]. Injection of the chemotherapeutic agent into the hepatic arterial circulation will achieve high doses of that agent in the tumour vasculature compared with normal liver or the systemic circulation. The chemotherapeutic agent is mixed with an oily contrast medium, lipiodol which helps to achieve concentration of the drugs in the tumour circulation [18]. In addition, there is a lack of Kupfer cells within liver neoplasms which results in a reduced clearance of the chemotherapy/lipiodol suspension. Following injection of the chemotherapy/lipiodol suspension the artery or arteries supplying the area of treatment are occluded with particulate matter. This will result in increased tissue ischaemia (the lipiodol itself has an embolic effect) which leads to hypoxia and cell death in the tumour. Moreover, anoxia causes an increase in tissue permeability and in the local concentration of chemotherapy agents [7]. Arterial occlusion is also a further inhibitor of chemotherapy washout [19]. The contra-argument to arterial embolisation is that it acts as a stimulus to new vessel formation in HCC by stimulating the expression of various angiogenic factors [20]. Permanent occlusion of major vessels may also prevent subsequent treatments. The use of relatively small particles in the embolisation procedure may achieve a more distal embolisation, a better ischaemic insult and a lesser "drive" for the angiogenic process. Peroxidase free radical formation and retention in chemoembolisation is potentiated by an ischaemic insult with relatively higher local doses of chemotherapeutic agents and peroxidase free radicals after embolisation. Thus there is a greater benefit in having a static blood flow [21, 22]. The converse is true with SIRT where optimal perfusion is required to generate oxygen free radicals as the generation of the same is known to be a triggering point for apoptosis response [23]. Cancer cells are thought to have difficulty in compensating to an environment rich in free radicals due to their relative lack of superoxide desmutase compared with normal cells [24]. Thus, arterial embolisation is likely to result in a greater therapeutic response in TACE but not in SIRT.

31.3. Patient Selection

Most of the literature applies to the treatment of HCC with TACE though the technique has been used to treat certain metastatic disease, including colorectal metastases. The requirements are such that the lesions within the liver should be hypervascular and a chemotherapeutic agent is utilised to which the neoplasm is sensitive.

All patients must have unresectable liver tumours which may involve both lobes of the liver or there are complicating factors that make surgery untenable. HCC lesions to be treated by TACE tend to be large, infiltrative or multifocal. Severe liver dysfunction is as much a contraindication to TACE as it is to surgery. Patients with Child-Pugh C disease should be referred for me-

dical or supportive treatment only. Other factors which increase the risks of TACE include severe thrombocytopaenia or leukopenia, cardiac and/or renal insufficiency, uncorrectable coagulopathy, ascites, portal vein occlusion with hepatofugal flow and anomalous or abnormal vasculature that increases the risk of non-target embolisation [7].

Patients referred for TACE have usually undergone some form of cross-sectional imaging as part of the staging process: either a contrast enhanced helical computed tomography (CT) or Magnetic Resonance (MR) scan. Disease should be limited to the liver though treatment of slow growing lesions such as the fibrolamellar variant of HCC can be considered if the extrahepatic disease is stable or can be subsequently treated by some other means. Liver rupture is a contraindication for TACE as there is the increased risk of worsening liver rupture with the potential for extravasation [25].

An adequate amount of residual uninvolved liver must be present. What constitutes an adequate amount of uninvolved liver is open to question. Replacement of more than 75% of the liver by tumour is considered a contraindication [26]. The functional status of the uninvolved liver is probably of greater significance [25]. What constitutes a safe bilirubin level to allow a safe TACE procedure varies in the literature between 34 moles/l (2 mg/dl) [26] to 50 moles/l (3 mg/dl) [25]. Serum markers, α-fetoprotein have often been performed as part of the diagnostic process and are of use in monitoring the therapeutic response.

Knowledge of any previous therapy is important including any previous or regional therapies, total doses and lifetime limits of drugs such as doxorubicin and any complications or side effects the patient may have experienced. For example, dose-dependent cardiomyopathy is seen is as many as 30% of patients who have received a total dosage of doxorubicin of 550 mg/m^2 [27].

Any decision to treat HCC with TACE should be taken in the context of a Multidisciplinary Team Meeting, where input by surgeons, physicians, oncologists, radiologists, histopathologists and nurse specialists can occur into the management of the patient such that the most appropriate treatment plan is instigated.

31.4. Technique

31.4.1. Patient Preparation

Patients undergoing a TACE procedure should be well hydrated with intravenous fluids if necessary – one regimen being 500 ml of dextrose saline pre-procedure followed by 100 ml/hr for 24 hours or longer, if there is delay in resuming full oral intake [25]. Pre-procedure, broad-spectrum antibiotics are administered intravenously. Infection is one of the potential complications of a TACE procedure and there is a greatly increased risk of infective complications if there has been previous intervention on the biliary tree (endoscopic sphincterotomy, stent insertion or biliary bypass surgery) where there is likely to be bacterial colonisation. A more prolonged course of antibiotics should be considered in these instances.

The procedure is performed under conscious sedation and intravenous pain relief.

31.4.2. Chemotherapeutic Mixture

There is no consensus on the best chemoembolisation protocol. Doxorubicin was the chemotherapeutic agent used by the Barcelona Liver Group whereas the Lo et al used Cisplatin [13]. In the United States combinations of Doxorubicin with Cisplatin and Mitomycin have been used [7].

The chemotherapy used is mixed with lipiodol 10-20 ml and 10 ml of water-soluble contrast material. As the materials are of different densities and consistencies they have to be vigorously mixed to produce an emulsion. The mixture is quite viscous and can be difficult to inject through micro-catheters.

31.4.3. Angiographic Procedure

An indication of the angiographic anatomy, particularly portal vein patency (fig. 31.4, 31.7, 31.8), can be obtained from previous cross-sectional imaging. However, full angiographic assessment is required with selective injections of contrast into the celiac axis, splenic, hepatic and superior mesenteric arteries. With peripheral or very large lesions there is the possibility of parasitization of supply from other vessels such as the internal mammary artery, intercostal, renal and phrenic arteries. The arterial anatomy needs to be stringently assessed. There is the potential for significant varia-

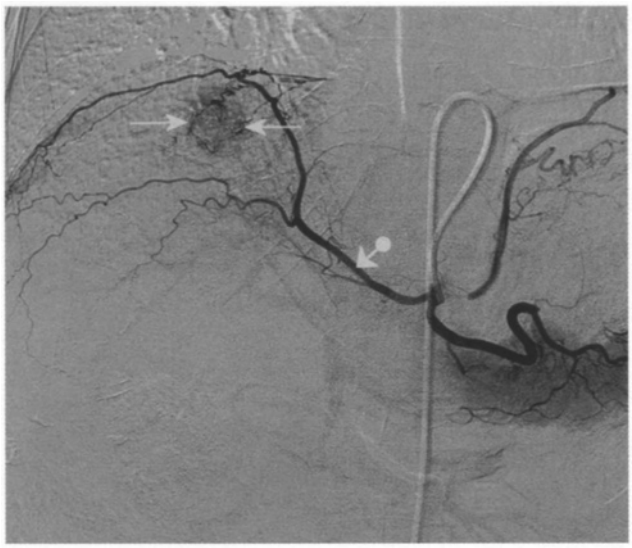
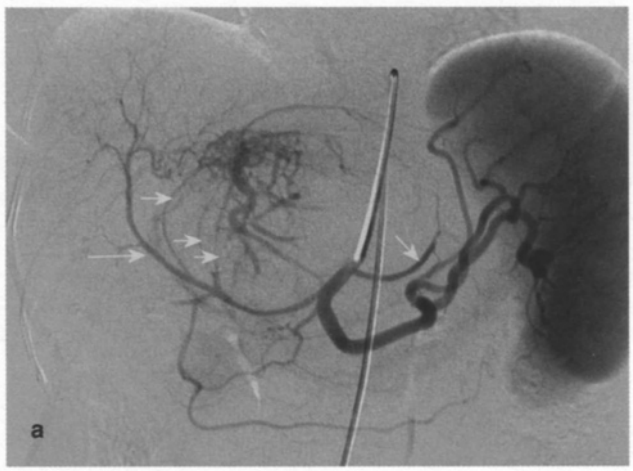


Fig. 31.1. Subdiaphragmatic lesion supplied by the phrenic artery.



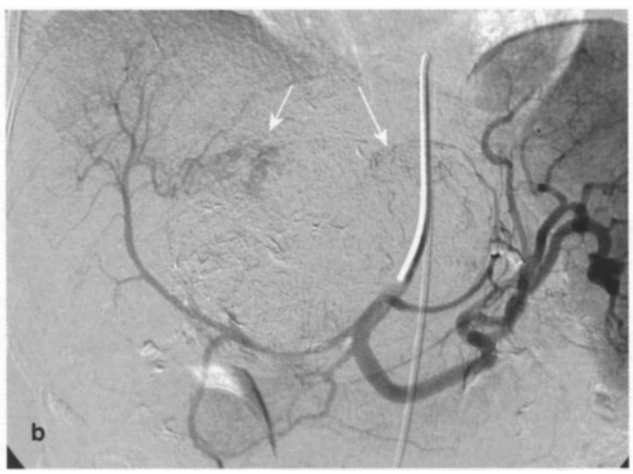
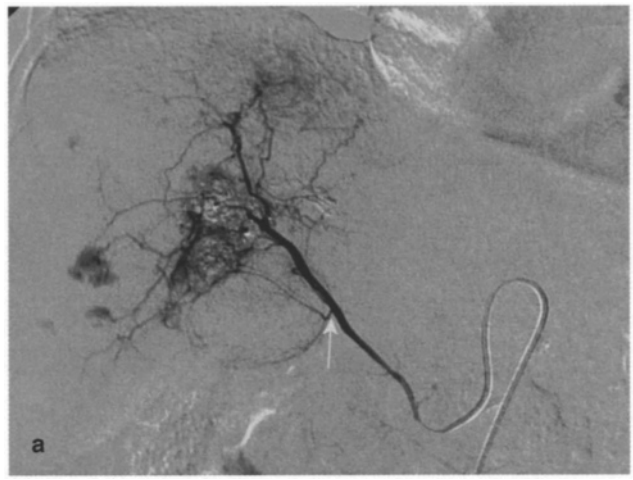


Fig. 31.2. a-b: Embolization of Hepatocellular carcinoma supplied by the left hepatic and left gastric arteries.



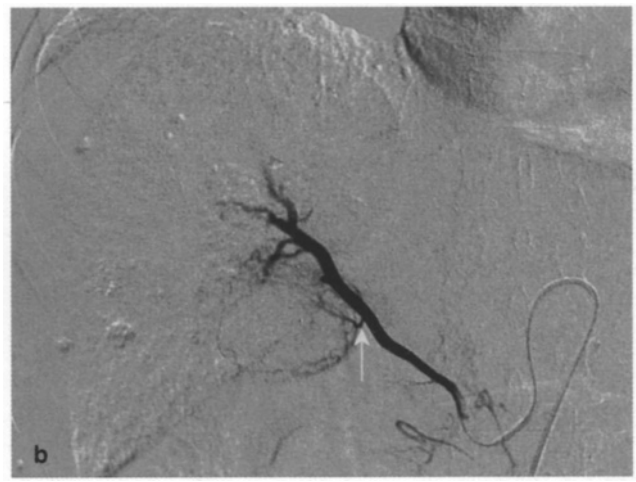


Fig. 31.3. a-b: Multiple right liver lobe lesions. Catheterization of the right hepatic artery form the superior mesenteric artery and chemoembolization.

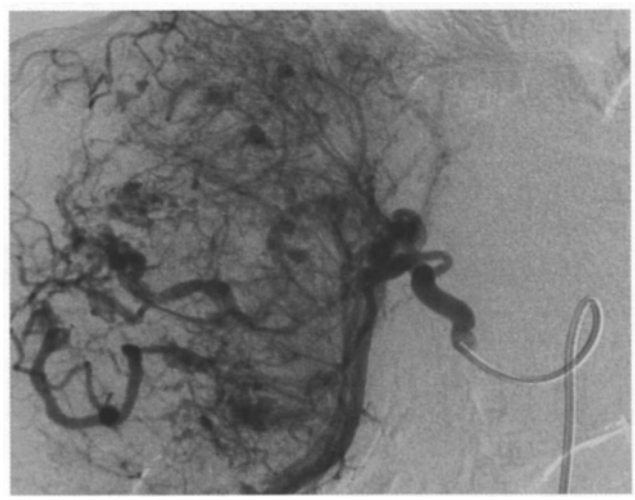


Fig. 31.4. A-V shunt in a HCC patient with visualization of the right hepatic vein.

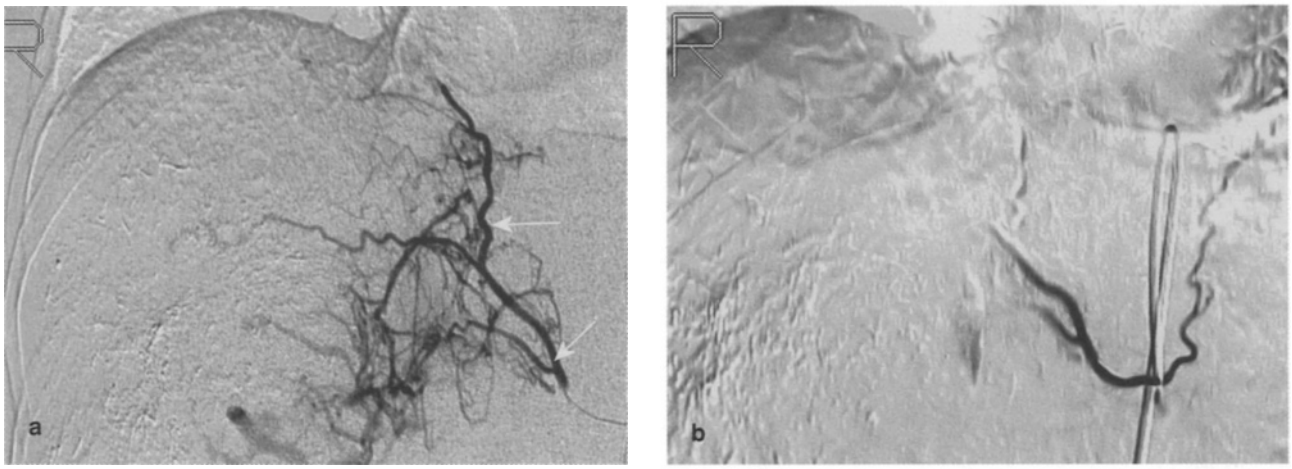


Fig. 31.5. a-b: Pre and post-chemoembolization angiography.

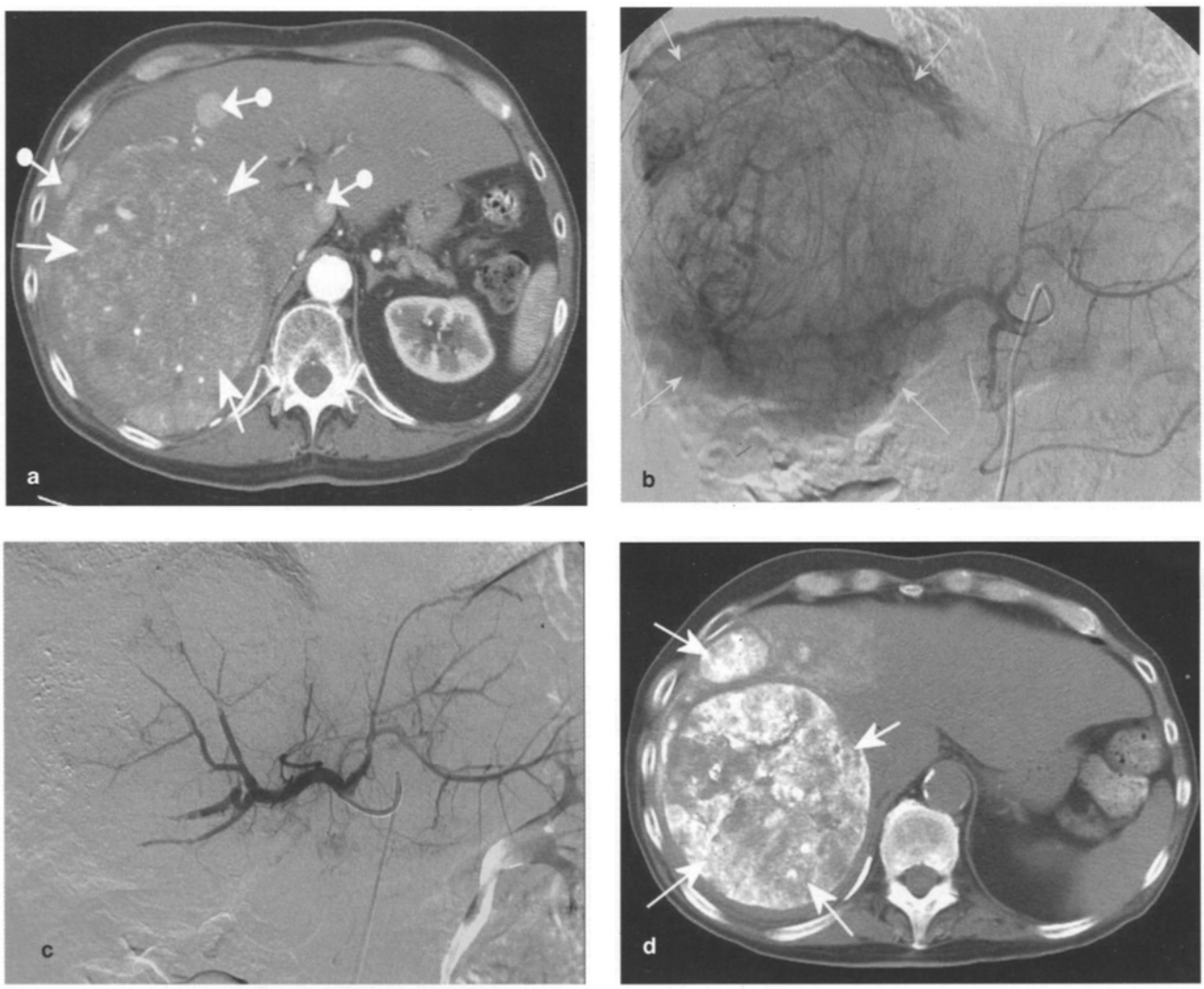


Fig. 31.6. a-d: Huge multifocal HCC with neoangiosis and A-V shunts. Selective catheterization and embolization. Postoperative CT scan.

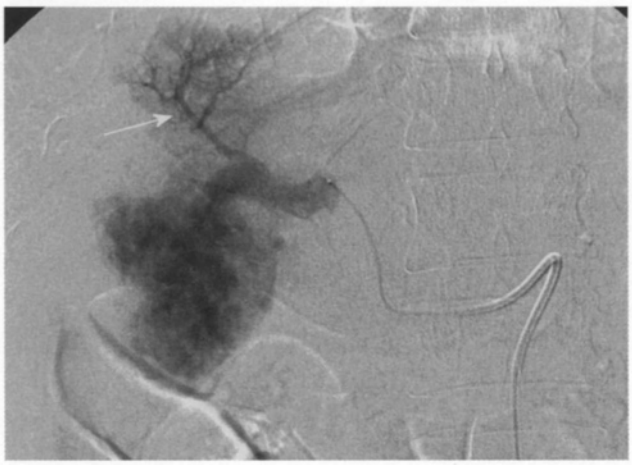


Fig. 31.7. Liver lesion with A-V shunt between the right hepatic artery and portal vein.

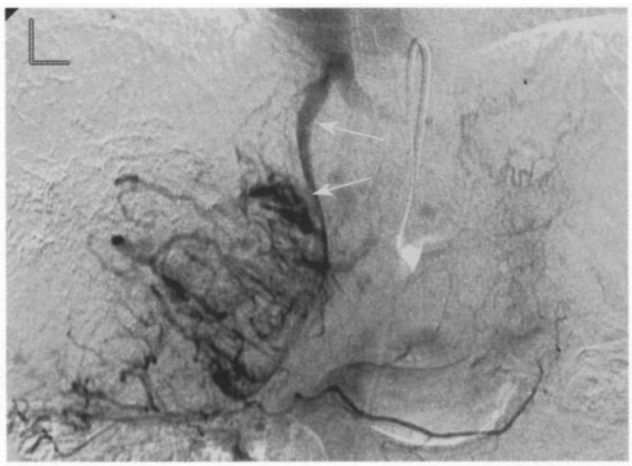


Fig. 31.8. A-V shunt in a HCC patient with visualization of the middle hepatic vein.

tions and anomalies in the upper abdominal vasculature which may require alterations in technique and potentially multiple sites of injection. Failure to identify variations in the arterial anatomy can have significant consequences with delivery of chemotherapeutic material to non-target areas such as the cystic artery, gastroduodenal, cutaneous and phrenic capillary beds [28-34]. Failure to identify significant arterial variations will result in inadequate delivery of chemotherapeutic agent to the whole tumour vasculature and thus suboptimal treatment. Two separate injections are required for full treatment. Use of selective catheter techniques and co-axial catheters are necessary for the safe delivery of chemotherapeutic materials. Injection of the chemotherapeutic emulsion is usually made into left or right hepatic arteries or the segmental divisions thereof. Usually only one lobe is treated at a time. Following the injection of the chemotherapy the arterial supply to the tumour is occluded with particulate matter such as polyvinyl alcohol particles or spheres, embolospheres or gelfoam slurry [fig. 31.3 (a-b), 31.5 (a, b), 31.6. (a-d)]. A combination of different size particles or agents may be required to obtain a satisfactory result. The importance and relevance of various vacular anomalies and arterial arrangements to liver targeted therapies has been well documented [35].

If the cystic artery is identified then if at all possible TACE is performed beyond its origin to lessen the chance of chemical cholecystitis. Sometimes the cystic artery may in fact be supplying a particular lesion that requires treatment. If a co-axial catheter can be manipulated to the small vessels supplying the lesion beyond those branches supplying normal gallbladder tissue, all well and good, if not TACE should be performed proximal to the cystic artery and vigorous antibiotic treatment considered to lessen the chances of significant chemical cholecystitis. Sometimes the neoplastic circulation is so profound it is impossible to identify the cystic artery. Coil embolisation of the cystic artery can be performed but increases the complexity of the procedure. Lipiodol may be seen in the gallbladder wall in up to 14% of cases post TACE but the incidence of chemical cholecystitis is less than 1% [25]. Coil embolisation of the origin of the gastroduadenal artery (GDA) can also be performed to prevent material entering this arterial territory if injection of chemotherapy is to be performed in the common hepatic artery. However, the use of co-axial catheter systems means that the TACE procedure can usually be safely performed beyond the origin of the GDA.

The right gastric artery can arise from the proper hepatic artery, left, right or middle hepatic artery or the gastrodudenal artery. Identification with avoidance or coil occlusion of the origin of this vessel is required as gastric necrosis; ulceration and perforation have all been documented following inadvertent delivery of chemotherapeutic agent into the right gastric artery [36, 37].

The superior portion of the posterior pancreaticoduodenal arcade most commonly arises from the GDA

(78%) but can arise from branches of the hepatic artery (15%). Again identification and avoidance of these vessels may prevent therapy induced pancreatitis [38] and duodenal damage [39].

The falciform artery may arise from one of the hepatic arteries and course in the falciform ligament towards the umbilicus. Delivery of embolic agent into the terminal branches of the falciform artery has been correlated with the development of supraumbilical skin rash, epigastric pain and skin necrosis [33, 40, 41].

Peripheral tumours or extracapsular spread of tumour may parasitize blood supply from other vessels [fig. 31.1, 31.2 (a-b)]. The right inferior phrenic artery is the most common source of extra hepatic parasitization in those cases of HCC that have undergone previous TACE [35]. Chemoembolisation of this vessel is possible but it is noteworthy that the inferior phrenic artery will also supply the diaphragm, oesophagus, inferior vena cava and retroperitoneum. If at all possible as selective an injection into the tumour vasculature should be performed. The same applies for angiographic treatment of the internal mammary and intercostal arteries to avoid collateral tissue damage.

It is noteworthy that many of the documented instances of complications have followed intrarterial infusional chemotherapy through a surgically implanted port/catheter system rather than following TACE. It is possible that this is due to inadvertent migration of the delivery catheter tip with subsequent non-target delivery of the chemotherapy. In addition, chemotherapy delivery is monitored with fluoroscopy during TACE when any changes in flow dynamics can be swiftly identified. This is not the case with intrarterial infusional chemotherapy.

Flow dynamics during TACE is important and needs to be constantly monitored. At the start of the TACE procedure there should be rapid forward flow of material. If flow is poor, this may be an indication of arterial spasm. This is less likely with the use of small diameter co-axial catheters. The possibility of arterial blood flow slowing during the course of the TACE procedure with potential reflux of material into non-target arterial territories always needs to be given due consideration. MAA (macro-aggregated-albumin) arteriography has demonstrated reversal of flow in the main hepatic artery 4 hours post liver embolisation with normalisation in 24hrs [42]. Thus, there is a theoretical possibility of reflux of material into non target areas and that the angiographic end point may not be an absolutely true reflection of the final distribution of the chemotherapeutic material. A prolonged or severe post-embolisation syndrome may indeed reflect non-target distribution of chemotherapeutic material [35]. This situation is only likely to occur where there has been a vigorous chemoembolisation procedure performed with complete obliteration and occlusion of the hepatic artery branches. Embolisation should not be performed to complete stasis. Some forward flow should be preserved in the embolised arteries [25].

If the Portal vein is occluded, TACE can still be performed but there should be a modification of technique with reduction in the dosage of the chemotherapeutic agent by up to 50% and consideration given as to whether to forego the embolic occlusion of the supplying arteries. If the patient tolerates this less aggressive procedure with no ill effects then a more substantial TACE procedure can be performed at a subsequent treatment session.

It is not absolutely certain how many TACE sessions should be performed in the same patient. Multiple sessions appear to be associated with better survival [43-46]. At least 3 sessions at 6 weekly intervals should be considered in each patient as different liver areas and arterial territories may require treatment at each individual session. However, there is no definitive evidence as to what constitutes the optimum number of treatment sessions.

31.5. Post Procedure

Patients will invariably have a "post-embolisation" syndrome constituting right upper quadrant pain and tenderness, fever, influenza-like symptoms and mild temperature. Pain relief and anti-emetics are mandatory. These symptoms usually abate in 2-3 days.

There may be some worsening of hepatic function post TACE, with increases in serum bilirubin and transaminases, ascites or development of hepatic encephalopathy [31, 47]. Some of these phenomena may be due to tumour lysis or the effects of the chemotherapy on the non-tumour containing liver. These effects are usually transient and disappear within 2-3 weeks, the liver function returning to its pre-treatment status [47,

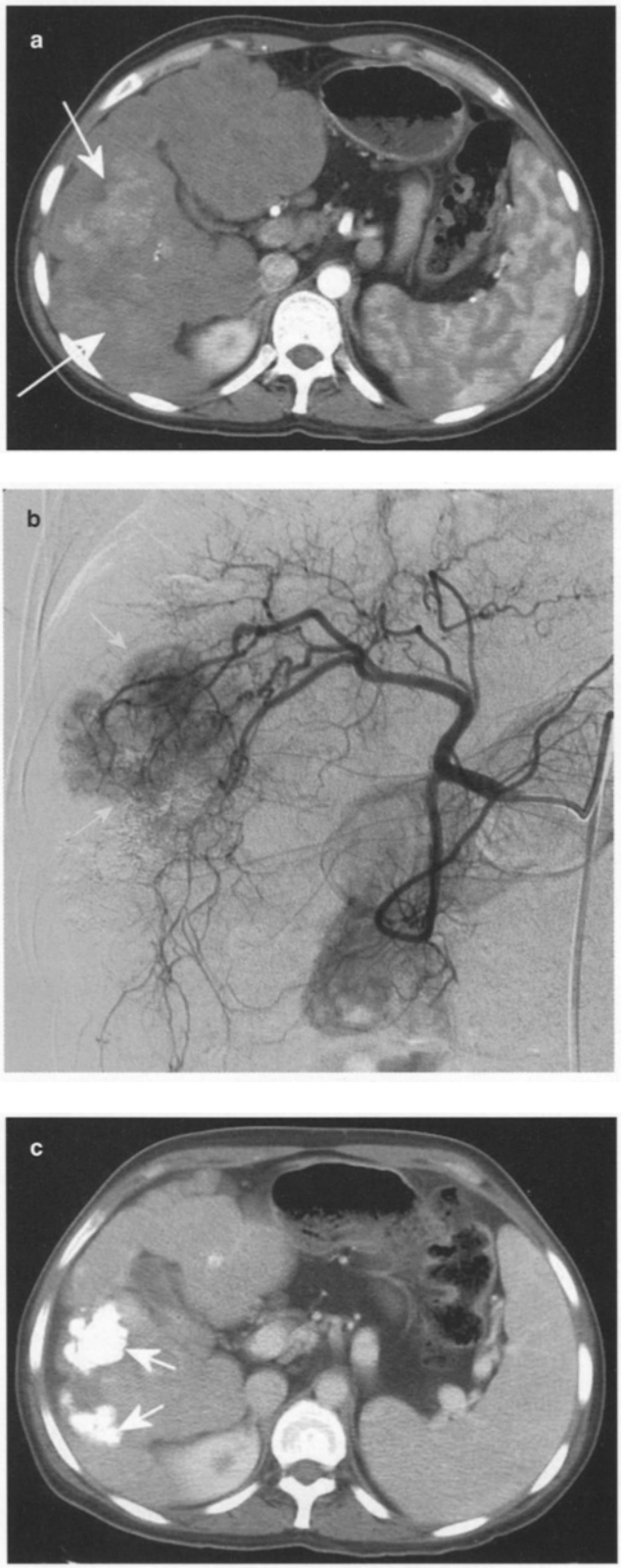


Fig. 31.9. a-c: The Patient underwent consecutive sessions of chemmoembolization.

48, 49]. These side effects of TACE are less pronounced following repeat procedures [50].

Urine output and renal function are monitored as hepatorenal syndrome can occur post TACE.

Patients are discharged once the post-embolisation syndrome has settled or controlled on simple analgesics.

Follow-up imaging constitutes non-enhanced CT scan at 1 day to assess the distribution of lipiodol, including any possible extra-hepatic deposition. Further scans are obtained at 1 month, 3 months, 6 months and 1 year [25] [fig. 31.9 (a-c)]. The purpose of these scans is to assess the size and appearance of treated lesions, presence of untreated areas, the identification of new lesions or spread and the overall appearance of the liver. The pattern of follow-up scanning may vary in timing depending on clinical factors or subsequent treatment sessions.

The tumour marker a-fetoprotein, if elevated pre TACE, provides a non invasive method of assessing tumour response. Falling serum levels would indicate a good therapeutic response whereas subsequent rising levels would be a sign of tumour recurrence, development of new lesions or metastatic spread.

31.6. Complications

31.6.1. Liver/Cardiac/Renal Failure

Severe liver failure can lead to a hepatorenal syndrome, which can be a consequence of the severity of the underlying liver disease and the contrast load. Severe liver dysfunction (Child-Pugh C) and renal impairment are relative contraindications to TACE. Maintenance of good hydration throughout the procedure lessens the risk of such an event. The mortality from TACE can vary between 1-3%, many of these deaths being related more to the underlying liver disease rather than the liver tumour itself.

31.6.2. Liver Infarction

It is to be hoped that the procedure will result in significant ischaemia of treated lesions. Severe liver ischaemia or infarction is only likely to occur with over vigorous TACE in the presence of portal venous occlusion.

31.6.3. Infection

Imaging of the liver post TACE may well demonstrate gas in a treated, necrotic lesion but this is not necessarily a sign of infection. It can be a normal finding. Clinical signs of sepsis should be a pointer to further evaluation.

31.6.4. Biliary Necrosis/Biloma

The blood supply to the biliary tree is via a microscopic peribiliary network of vessels that is never visualised. However, it can be damaged in the course of a vigorous TACE procedure. Predisposing factors for this and other intrahepatic infective complications is the presence of biliary dilatation and previous biliary intervention or surgery [51, 52, 53]. Biliary complications remain a relatively rare event following TACE due to the diversity of supply to the biliary tree which includes supply from arteries other than the hepatic artery.

31.6.5. Extrahepatic Deposition of Chemotherapeutic Material

Lipiodol may be demonstrated at CT in sites other than the liver, including the lungs, gallbladder and stomach.

Hepatocellular carcinomas may be highly vascular with significant arteriovenous shunting, both into the portal venous system and hepatic venous system.

Chemoembolic material may be deposited in the portal vein, particularly if there is tumour ingrowth into a portal venous branch. Lipiodol entering the systemic circulation may be deposited in the lungs. This rarely causes problems but the deposition of large amounts has been associated with pulmonary infarction [54]. It is more likely that atelectasis at the lung bases post-procedure is due to splinting of the diaphragm and poor lung expansion as a result of pain post procedure.

Gastric uptake is demonstrated as lipiodol following the line of the gastric mucosa. This is uncommon (1% of cases) and usually of no significance [55]. However, it has been associated with peptic ulceration [39, 56]. Deposition of material in the arterial supply to the pancreas may result in post procedure pancreatitis [38]. Even though the deposition of material in the stomach post TACE may not be of significance, this is certainly not the case with SIRT where even small quantities of the radioactive microspheres in an extra-hepatic location may be associated with symptomatology. Prophylatic proton pump inhibitors should be considered to lessen the risks of gastric complications in any liver directed therapeutic procedure. As previously mentioned, gallbladder infarction may occur as a result of TACE.

As there is the potential for extra hepatic deposition of chemotherapeutic material, there is therefore the potential for systemic effects of chemotherapy. Patients should be made aware that though TACE is a liver-directed therapy there is the potential for systemic side-effects such as hair loss and effects of chemotherapy on the haemopoietic system.

These effects are likely to be much less severe when compared to systemic chemotherapy.

31.7. Conclusion

Transarterial chemoembolisation is now an established technique for the treatment of non-resectable liver tumours, particularly hepatocellular carcinoma. It is not only associated with a definite increase in survival but also an increase in the quality of life. Sometimes a very gratifying response can be obtained allowing a more definitive treatment option to be instigated [56]. Though TACE can be used to treat HCC in the presence of portal vein thrombosis using a modified technique, there is no data to show whether there is an increased survival in these circumstances.

There are still some unanswered questions to this procedure, such as what constitutes the best chemotherapy regimen and the best means of its delivery. New concepts in delivery are being developed such as drug eluting beads that are based on polymer technology to provide a means of localized delivery with controlled and sustained release of the chemotherapeutic material in the tumour bed and increased killing efficiency. There is reduced plasma concentrations and thus reduced systemic toxicity. Other potential means of delivery include microspheres and nanoparticles. New drugs are also being developed that target tumours more specifically at molecular level rather than any rapidly dividing cell, leading to increased specificity and less systemic effects. Targets being evaluated include genes (aberrant p53, c-myc, BH4), receptors (glut, EGFR), antibodies (VEGF) and enzymes (GTP inhibitors and

ATP inhibitors). There is a potential for a very interesting future in the field of interventional oncology.

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CHAPTER 32

SELECTIVE INTERNAL RADIATION THERAPY (SIRT) IN THE MANAGEMENT OF LIVER TUMOURS

32a. Selective Internal Radiation therapy

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32a.1. Introduction

Primary and secondary liver tumours are common malignancies associated with unsatisfactory treatment and bad prognosis. Hepatocellular carcinoma (HCC) ranks among the 10 most common cancers worldwide and is the most common primary malignancy of the liver. The geographic distribution of HCC is clearly related to the incidence of hepatitis B virus (HBV) infection with the highest incidence in Southeast Asia and tropical Africa.

However, the most common malignant tumours of the liver are metastatic. The liver is a common site of metastases from gastrointestinal tumours, due to dissemination via the portal venous system. The most relevant metastatic tumour of the liver is colorectal cancer, but other metastases from organs such as lung, prostate, breast, pancreas, stomach, kidney, cervix, and ovary can also end up in the liver.

There are a number of treatment options for patients with primary or secondary liver tumours. Surgical resection is considered the treatment of choice if liver functional reserve is adequate. The post resection 5-year survival in HCC is around 50% but the majority of patients are not candidates for resection because of advanced tumours and efforts have been directed toward the development of non-surgical therapeutic options [1]. Indeed only 5-10% of patients with metastatic deposits are candidates for potentially curative liver resection.

External beam radiation therapy (EBRT) has a limited role in the treatment of HCC, although occasional dramatic responses are seen. EBRT is limited by damage to normal liver parenchyma and to surrounding organs.

Systemic chemotherapy with a variety of agents has been ineffective for the treatment of HCC. Response rates are generally under 20% and of short duration. Systemic chemotherapy is also ineffective as a sole therapy for hepatic colorectal metastases, with median survivals of around 12 months and partial response rates of 20% to 30% [2]. Adjuvant systemic chemotherapy after liver resection for metastatic colorectal cancer is often given but is not supported by prospective trials.

Percutaneous ethanol injection (PEI) induces tumour necrosis by cellular dehydration, protein denaturation, and thrombosis of small vessels and can be done as an outpatient procedure under local anaesthesia but is associated with high incidence of recurrence. Cryotherapy has been used for the treatment of liver tumours since the 1980s, with the initial experience mainly in patients with metastatic disease [3]. Rapid freezing to sub-zero temperature leads to ice formation in the extracellular space and drawing of water from the cells, causing cellular damage by dehydration and destruction of the normal cellular structures. Cryotherapy is most effective for tumours smaller than 5 cm, although larger tumours can be treated by multiple probes inserted simultaneously [4].

Microwave coagulation therapy (MCT) is a form of thermo-ablative treatment in which tissue necrosis is induced by the heating effect of microwaves and creates a more predictable and reproducible area of tissue necrosis and can ablate the tumour capsule as well as surrounding extracapsular invasion. Laser is another method of interstitial therapy for liver tumours that causes tissue destruction by hyperthermic coagulative necrosis. Similar effect can be achieved with radiofrequency ablation (RFA) using high-frequency alternating current.

Hepatic arterial infusion chemotherapy utilizing 5-

fluorouracil-based compounds, cisplatin and doxorubicin has been studied in limited numbers. Response rates of 25% to 60% have been reported, but the requirement of a laparotomy to place the pump and associated hepatic toxicity limits the applicability of this approach. Percutaneous transarterial embolization can induce ischemic necrosis in liver tumours, resulting in response rates as high as 50%. Attempts to improve the efficacy of arterial embolization have included adding chemotherapeutic agents (chemoembolization) to the embolization particles and oils such as Lipiodol that are selectively taken up by HCC (TACE procedure).

The role of orthotopic liver transplantation is controversial and is limited by the need for chronic immunosuppression as well as the lack of organ donors.

32a.2. Selective Internal Radiation Therapy

The concept of selective internal radiation therapy (SIRT) is based on delivering a high dose of localized radiation to tumour cells with minimal effect on adjacent healthy tissue. This can be achieved by the use of radiolabelled microspheres that are trapped in the microvasculature of tumours to deliver long-term radiation effect. Unlike other cancer treatment modalities (radiotherapy and chemotherapy), the undesirable effect on surrounding healthy tissue and other body organs and systems would be reduced to a minimum.

There are two types of microspheres: glass beads (e.g. TheraSphere) and resin beads (SIR-Sphere). Glass microspheres have a mean diameter of 20-30 m, while resin microspheres have diameters of 20-40 m [5]. These microspheres are not metabolised or excreted but merely remain in the liver as a permanent implant delivering a target dose in excess of 100 Gy. After 10-14 days, they are no longer radioactive.

Our experience is based on the use of SIR-Spheres (Sirtex, Sydney, Australia), a radiopharmaceutical combining Yttrium-90 (^{90}Y) to resin biocompatible microspheres. ^{90}Y is a high-energy pure beta-emitting isotope with no primary gamma emission. It emits beta particles with a maximum energy of 2.27 million electron volt (MeV) and a mean energy of 0.93 MeV. The beta particles will travel with a maximum range in tissue of 11 mm (mean range 2.5 mm). The half-life of ^{90}Y is 64.2 hours with an effective treatment time of 92.3 hours. In therapeutic use, 94% of the radiation is delivered in 11 days. In addition, the secondary Bremsstrahlung radiation of ^{90}Y can be used advantageously after the delivery of SIR-Spheres to map their distribution in the body by imaging the patient with a gamma camera.

Therapy with SIR-Spheres has so far been exclusively used to treat primary and secondary liver tumours. It has been demonstrated that malignant liver tumours derive 95% of their blood supply from the hepatic artery, whereas only 25-30% of the blood supply of normal parenchyma is from the hepatic artery [6], the rest coming from the portal vein. This has been demonstrated using CT and carbon dioxide microbubble ultrasound [7-8]. It has also been shown that the distribution of many therapeutic agents introduced through the hepatic artery concentrates around the tumour sites [9].

The delivery of SIR-Spheres requires catheterization of the hepatic artery either via a trans-femoral catheter or a surgically implanted hepatic artery port with catheter. Once delivered, the microspheres are trapped (and remain so permanently) in the microvasculature of tumours. As the penetration distance of the beta radiation emanating from SIR-Spheres is short, there is little radiation effect on the normal liver. The permanent residence of the spheres in the vascular network of the tumours (following the decay of ^{90}Y) has been shown to exert no adverse reactions or mutagenic effect as resected liver tissue adjacent to SIR-Spheres have been shown to remain healthy. The longest survival time following SIR-Spheres has been 14.5 years in a patient with a single liver metastasis from colorectal cancer (personal communication with SIRTEX).

32a.3. Indications for SIR-Spheres Therapy

SIR-Spheres are indicated for use in the treatment of malignant liver tumours of primary or secondary origin that are not suitable for resection with curative intent. If all macroscopic evidence of tumour can be resected while maintaining sufficient normal parenchyma to sustain life, then surgery is adopted. However, a proportion of patients will be considered unsuitable for surgery and more likely to benefit from SIRT, for a variety of reasons including:

A. Multiple liver metastases with involvement of both lobes such that resection would require removal of more liver tissue than is necessary to sustain life.
B. Tumour invasion of the hepatic confluence when surgery could compromise the three hepatic veins entering the inferior vena cava.
C. Tumour invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken.

32a.4. Contraindications

SIR-Spheres therapy is contraindicated in the following conditions:

A. History of external beam radiotherapy.
B. Ascites or severely abnormal liver function tests suggesting clinical liver failure.
C. Hepatopulmonary shunt greater than 20%.
D. Pre-assessment angiogram demonstrating significant reflux of hepatic arterial blood to the stomach, pancreas or bowel.
E. Disseminated extrahepatic disease.

32a.5. Patient Selection

The selection of patients for SIR-Spheres is best made within a multidisciplinary team (MDT) discussion where clinical details, laboratory and imaging data along with histopathological analysis are reviewed by hepatobiliary surgeons, oncologists, histopathologists, radiologists, and nuclear medicine physicians. SIR-Spheres can be used alone but has also been used in combination with both systemic and hepatic perfusion chemotherapy [10-12]. Patient selection is critical in achieving a benefit from the use of SIR-Spheres and since there are no data to suggest they are curative, efforts should be made to ascertain that the tumour(s) are not amenable to resection with curative intent as demonstrated with a triple phase contrast enhanced CT scan or MRI.

Therapy with SIR-Spheres is not specific to any particular cell type and has been used primarily in metastatic disease from adenocarcinoma arising from the bowel. However, its mode of action allows for use in patients with liver metastases from primary tumours at other sites. In our own experience, SIR-Spheres can be used in the treatment of a wide range of metastatic liver disease including metastasis from unknown primary. Likewise, it can be used in primary hepatobiliary tumours such as HCC and cholangiocarcinoma (CC).

Renal and hepatic function as well as tumour markers should be assessed to establish baseline values for follow-up. Seriously ill patients, or those with compromised liver function, may not tolerate radiation therapy or handle concurrent chemotherapy and should be ruled out.

Since SIR-Spheres are a form of loco-regional treatment only and have no beneficial effect on extrahepatic metastases, assessment of the presence or absence of such metastases is mandatory with CT and positron emission tomography (PET) before administration. On rare occasions, and particularly when the liver tumours are considered the immediate life threatening event, treatment with SIR-Spheres may still be indicated in the presence of minimal extrahepatic disease.

SIRT is generally administered only once, either alone or in combination with reduced dose chemotherapy, originally with 5-fluorouracil (5FU) and more recently in combination with oxaliplatin as "FOLFOX" [12]. Occasional patients may benefit from repeated SIRT treatment as in cases where the tumour progresses again, but is still largely confined to the liver.

32a.6. Diagnostic Angiography

Once a patient is selected for SIR-Spheres therapy, a diagnostic visceral angiogram is performed for the following purposes:

A. To assess the visceral arterial anatomy and identify any vessels that may potentially result in microspheres being diverted to non-target organs. These vessels may require embolisation to prevent microspheres reaching those non-target organs.
B. To assess the vascular supply to the liver. There may be discrete, separate vessels supplying the liver, which would mean multiple injections to achieve uniform distribution of microspheres throughout the liver parenchyma. With embolisation of carefully selected vessels, the blood supply to the liver can be

altered with intrahepatic collaterals developing to supply the territory of previously occluded vessels. The vascular supply is thus modified to allow a simpler injection technique with regard to the radiolabelled microspheres. The strategies A and B can be construed as preparing the field for the injection of radiolabelled microspheres.

C. To inject radiolabelled 99mTc-MAA (Macroaggregated albumin) as a means to assess the presence and degree of hepatopulmonary shunt into the systemic circulation.

The right gastric artery and the accessory left gastric artery may arise from the hepatic artery. Microspheres entering these angiographic territories can result in gastric and duodenal ulceration. The hepatic falciform artery has been reported as arising from the hepatic artery. Material entering this artery may cause damage to the periumbilical tissues [13]. Rigorous assessment of these and other vessels such as the gastroduodenal and peripancreatic arteries must be performed and coil embolisation/occlusion of vessel origins undertaken to increase the safety of microspheres injection [14]. However, despite all these methods to improve the safety of the procedure, there is still the requirement, on the part of the operator, for experience in angiographic techniques particularly in co-axial catheter utilization as usage of these particular catheters may be the only means by which a satisfactory point can be reached to safely inject the microspheres.

As a result of the complex embryological origins of the liver and biliary tree, there may be multiple arteries contributing to the supply of the liver, arising from the aorta, celiac axis and superior mesenteric artery. The classic arterial pattern is demonstrated in 57-61% of the population [15]. Consequently, there may be a necessity to inject microspheres into multiple vessels to treat the full tumour load. However, by selective embolisation of some of these variant vessels the development of intrahepatic collaterals can allow simpler injection techniques and yet uniform distribution of microspheres throughout the liver parenchyma. In addition to the anatomy, the flow characteristics of various vessels require attention both before and during the procedure. Occasionally flow characteristics can be of benefit, such as reversal of flow in the gastroduodenal artery as this can act as protection for the tissues in that arterial territory. However, as the microspheres exert an embolic effect the flow must be continually assessed during the procedure as flow characteristics may alter with subsequent risk of inadvertent embolisation of microspheres to non-target tissues [14].

32a.7. Assessment of Hepatopulmonary Shunt

In about 3% of patients with liver tumours, there will be significant hepatopulmonary shunting resulting in more than 10% of the SIR-Spheres delivered into the hepatic artery passing through the liver and lodging in the lungs. Measurement of this hepatopulmonary shunt is essential for ensuring the suitability of the procedure and calculating the administered dose. This is done, at the same time as the diagnostic angiogram by injecting 100 MBq Technetium-99m-macroaggregated albumin (99mTc-MAA) through the hepatic artery catheter. This radiopharmaceutical is used routinely in the detection of pulmonary embolic disease and is made of biodegradable particles that would normally be caught in the microvasculature mesh. In the presence of detectable hepatopulmonary shunts, a proportion of the microspheres would bypass the hepatic capillaries and end up in the pulmonary capillary mesh. Using a gamma camera, the amount of 99mTc-MAA in the lung can be quantitated and compared to the injected dose, allowing for calculation of the hepatopulmonary shunt.

Administering SIR-Spheres in the presence of a sizable shunt will have the adverse effects of causing a heparin-resistant thromboembolic incident coupled with severe radiation pneumonitis. A shunt greater than 20% is a strong contraindication to SIR-Spheres therapy.

32a.8. Dose Calculation and Delivery

Several factors contribute to the calculation of the administered dose of SIR-Spheres, including the tolerance of the liver to ionizing radiation, the magnitude of liver involvement and the degree of hepatopulmonary shunt. The relative proportions of SIR-Spheres that lodge in the tumour and normal liver may vary widely between patients but generally the greater the bulk of tumour within the liver then the greater the relative

Table 32a.1. Empiric method of dose calculation of SIR-Spheres based on liver involvement.

Estimated Degree of Tumour Involvement of the Liver	Recommended ^{90}Y dose
• >50%	3 GBq
• 25-50%	2.5 GBq
• <25%	2 GBq

Table 32a.2. Dose calculation of SIR-Spheres based on hepatopulmonary shunt.

Percent Lung Shunting	Recommended SIR-Spheres dose
• < 10%	Deliver full dose of SIR Spheres from Table 32.1
• 10% to 15%	Reduce amount of SIR Spheres by 20%
• 15% to 20%	Reduce amount of SIR Spheres by 40%
• > 20 %	Do not give SIR Spheres

proportion of hepatic arterial blood flow, and consequently a greater proportion of SIR-Spheres that will flow to the tumour as opposed to the normal liver parenchyma. The administration of vasoactive agents has been shown to shunt arterial blood away from the normal liver parenchyma and into the tumour [16-17].

The practical method of dose calculation uses a standard amount of activity that is varied only according to the size of the tumour within the liver (table 32a.1). This is further modified according to the severity of hepatopulmonary shunt. Normally the latter is less than 10%, but when higher shunts are encountered, the administered dose of SIR-Spheres is reduced as shown in table 32a.2.

Once a dose has been calculated, the patient is taken to the angiography suite and injection of radiolabelled microspheres is performed under strict radiation protection measures. The input of Medical Physics personnel is essential. The injection of the microspheres is from a closed vessel, driven through the delivery catheter by water for injection. The microspheres are not radiopaque; hence there is a requirement to check the status of the arterial tree by intermittent injections of contrast. A valve system in the injection vessel and connecting tubing allows the switching from injection of microspheres to that of contrast without disconnecting the system from the delivery catheter.

Once delivery is completed, the patient is transferred to the nuclear medicine department and imaged with a gamma camera to document the distribution of the SIR-Spheres using the Bremsstrahlung emissions from ^{90}Y.

32a.9. Adverse Reactions

Abdominal pain and fever are generally experienced after administration of SIR-Spheres and may last from a few days to a week. The fever may be related to the embolic and toxic effect of the microspheres on the tumour. Many patients will experience nausea that may last up to several weeks and this may require anti-emetic medication.

Pain that does not remit may suggest that the microspheres have lodged in an organ other than the liver such as the pancreas, gallbladder or stomach causing pancreatitis, acute cholecystitis and peptic ulceration respectively [18]. The risk is minimised with careful embolisation of the visceral arteries before administration of microspheres to the liver. However, there is also documented evidence of reversible gastritis and duodenitis without imaging or biopsy evidence of extrahepatic deposition of microspheres [19]. Prompt investigations, including review of the ^{90}Y Bremsstrahlung images, should facilitate the diagnosis.

High levels of radiation to the lungs due to excessive shunting may lead to radiation pneumonitis that may require systemic corticosteroids. This should be avoided by not using ^{90}Y-microspheres in patients with marked hepatopulmonary shunts and indeed there are no recent documented cases.

Similarly, excessive radiation to the normal liver parenchyma may result in radiation hepatitis that can be difficult to diagnose, and may appear many weeks after the implantation of SIR-Spheres. The risk increases with increased pre-treatment total bilirubin level and is more likely to occur where the radiation dose for a single administration is around 150Gy [20].

In our own experience, treatment with SIR-Spheres is well tolerated with very few complications. Over the last 2 years, we carried out 22 procedures in 21 patients with advanced hepatic primary and secondary tumours. We encountered four cases of complications, including one cholecystitis and portal hypertension, one peptic ulcer and two cases of radiation hepatitis. All complications resolved with appropriate measures. Of the six patients who received SIR-Spheres therapy

18-24 months ago, three are still alive. The safety of SIR-Spheres in pregnancy or children has not been established.

32a.10. Clinical Experience with SIRT

Initial trials of glass microspheres demonstrated that doses of up to 100 Gy were well tolerated and that tumour response was only seen at higher absorbed doses [21-22] and even at doses greater than 100 Gy [23]. Patients who received absorbed doses of 47-270 Gy showed survival times similar to those of chemoembolisation [24]. Lau and colleagues showed that the non-tumourous liver appeared more tolerant to internal radiation than external beam radiation and downstaging of tumours allowed lesions in 4/71 patients to become amenable to surgery [25].

The distribution of the SIR-Spheres has been studied in four explanted whole livers [26] demonstrating preferential and heterogenous deposition of microspheres at the edge of tumour nodules compared to the central portion and normal liver parenchyma. The same study confirmed a radiation dose delivery to the tumour ranging from 100-3000 Gy.

Clinical studies have shown therapy with ^{90}Y-microspheres to be well tolerated and effective. One large series [27] reported on the outcome over 4 years of 43 patients with hepatocellular carcinoma treated with ^{90}Y-microspheres and showed a tumour response in 79% in terms of reduction of size and/or necrosis with a median survival time of 24.4 months and 12.5 months by Okuda scores of I and II respectively. Quality of life in patients with hepatocellular carcinoma showed modest improvement following treatment with ^{90}Y-microspheres at 6-month follow-up with better functional well-being when compared to patients treated with hepatic arterial infusion of Cisplatin [28]. A good response has also been shown in cholangiocarcinoma. In a study of 23 patients with unresectable nodular cholangiocarcinoma, a response rate of 90% was demonstrated by PET and localized recurrence was treated successfully with radiofrequency ablation [29].

In trials of patients with colorectal metastases receiving ^{90}Y-microspheres, 10 of 14 patients receiving doses of up to 100 Gy experienced no progression over 7 months [30]. The same authors looked at a larger cohort of 37 patients with colorectal metastases; of whom 22 had beneficial effects at 4 months and 15 with diffuse liver involvement on CT had unchanged scans [31]. At doses of 150 Gy, more than 50% patients experienced no progression including patients who did not respond to chemotherapy [32].

Survival times have been shown to increase following treatment with SIR-Spheres. Lau and colleagues investigated 18 patients with inoperable hepatocellular carcinoma who received variable doses of SIR-Spheres [33]. All patients showed reduction of tumour marker of 41% to 0.2% of the pretreatment level. However, tumour regression was found to be dose related with progressive or static disease occurring in a higher proportion in patients whose tumours received < 120 Gy. Survival was better in those whose tumours received >120 Gy (median survival = 55.9 weeks) than those whose tumours received lower doses (median survival = 26.2 weeks). The same group looked at outcomes in 82 patients treated with SIR-Spheres and found that a lower pre-treatment level of alpha fetoprotein and higher tumour-to-normal uptake ratios of yttrium-90 favoured longer survival, with 38% of those patients survived in excess of 1 year [34].

Clinical trials in patients with unresectable colorectal metastases treated with SIR-Spheres showed a fall in CEA in all 26 patients in whom serial CEA measurements were undertaken and a decrease in tumour volume on CT in18 of 22 patients. In 48% of patients, the decrease in tumour volume was more than 50% and the authors concluded that SIR-Spheres therapy resulted in a high rate of tumour regression in patients with colorectal liver metastases [35]. Similar results where found in 38 patients showing that ^{90}Y-microspheres was well tolerated and achieved good liver responses with survival being determined by the development of extra hepatic disease [36-37] and that survival at one year in patients with colorectal metastases receiving SIR-Spheres was 67% with a median survival of 17.5 months [38].

SIR-Spheres also produce a favourable outcome when used in combination with chemotherapy [10-12, 39]. Combination therapy with fluorouracil/leucovorin increased time to disease progression in patients with colorectal liver metastasis from 3.6 to 18.6 months and increased survival from 12.8 to 29.4 months [11]. Another study of 74 patients with inoperable liver metasta-

ses concluded that the partial and complete response rate for patients receiving SIR-Spheres plus chemotherapy was significantly greater than for chemotherapy alone. The survival rate at one, two, three and five years was 72%, 39% 17% and 3.5% compared to 68%, 29% 6.5% and 0% for combination therapy and chemotherapy alone respectively [10]. Even after multiple chemotherapy regimes for advanced unresectable colorectal metastases, treatment with SIR-Sphere has induced a favourable response [39].

32a.11. Follow up after ^{90}Y-microsphere Therapy

Assessment of response to SIRT is commonly performed by clinical examination supplemented with tumour markers and various imaging procedures. Lau and colleagues have shown a reduction of tumour markers in all patients receiving SIR-Spheres of up to 41% of pre-treatment levels [33]. However, reduction in tumour markers may not reflect the true response in the treated area, since untreated liver metastasis and extrahepatic deposits may contribute to a stable or rising tumour marker levels.

Imaging plays a major role in following up the response to therapy. CT is the standard tool demonstrating changes in anatomical details of the metastatic lesions, with the earliest being a reduction in attenuation of lesions that can be diffuse or heterogenous depending on the delivered dose, and can be seen at 8 weeks following treatment but were noted to diminish after 16 weeks [40]. Later changes include reduction in the size and number of metastases, though simple measurement of orthogonal diameters is insensitive because of the presence of necrosis, edema, hemorrhage, and cystic changes [41]. The RECIST criteria have been established to monitor response to chemotherapy and are based on changes in the size of tumour. However, it may fail to provide an accurate assessment in relation to certain types of treatment such as laser and radiofrequency ablation as well as chemoembolisation. Completely necrotic lesions may not demonstrate a significant reduction in size [42], while discrepancy was demonstrated between the reduction in tumour size seen on CT and histopathology [43]. It is therefore thought that RECIST criteria might not be valid for assessment of response to SIR-Spheres therapy [29, 44].

Metabolic imaging with PET is more effective in demonstrating response to SIRT therapy at an early stage [8, 29, 44, 45]. Wong and colleagues found a significant difference between the metabolic and the anatomical response in eight patients when comparing FDG-PET with CT and MRI obtained at baseline and approximately 3 months after treatment. The metabolic response was significantly greater than the response on CT or MRI, and the reduction in the serum CEA level was significantly correlated with the PET response but not with the CT or MRI response. The same group confirmed their results in 19 patients showing significant reduction of hepatic metastatic load evaluated objectively by PET [45]. Bienert and colleagues used FDG-PET/CT to follow up 30 liver lesions in 5 patients following SIR-Spheres therapy. The standard uptake values (SUVs) in the 30 treated liver metastases decreased from 6.5±2.3 at baseline to 4.2±1.8 after the first follow-up PET/CT scan (p=0.001). In contrast, the SUVs of untreated metastases increased slightly from 7.2±2.3 to 8.0±0.8, while there was no difference in FDG uptake in normal liver tissue [44]. Other groups have shown FDG uptake to regress to normal appearance in three of 10 patients treated with SIR-Spheres, corresponding to return of tumour markers to normality while CT showed only a slight decrease or stable findings of hepatic tumor load [18]. Along similar lines, a recent study involving 23 patients with nodular cholangiocarcinoma treated with SIR-Spheres has shown a response rate of 90% with PET but only 45% with CT. The study concluded that the use of RECIST was not an adequate indicator of the effectiveness of this therapy, and PET should be the method of choice in the assessment of response to therapy with SIR-Spheres [29].

Our own unpublished data of follow up after therapy with SIR-Spheres in 21 patients with liver metastases from various primary tumours confirm the above. SUV measurements on PET studies before treatment and 6 weeks after treatment showed a reduction from a mean of 12.2 +/–3.7 to 9.3 +/– 3.6 (p = 0.01) while CT follow-up has been less reliable with the majority of scans being unchanged at 6 weeks. In one patient with liver metastasis from an unknown primary, the uptake in the lesions disappeared after two doses SIR-Spheres with SUV falling to levels similar to that of the surrounding normal liver (fig. 32a.1).

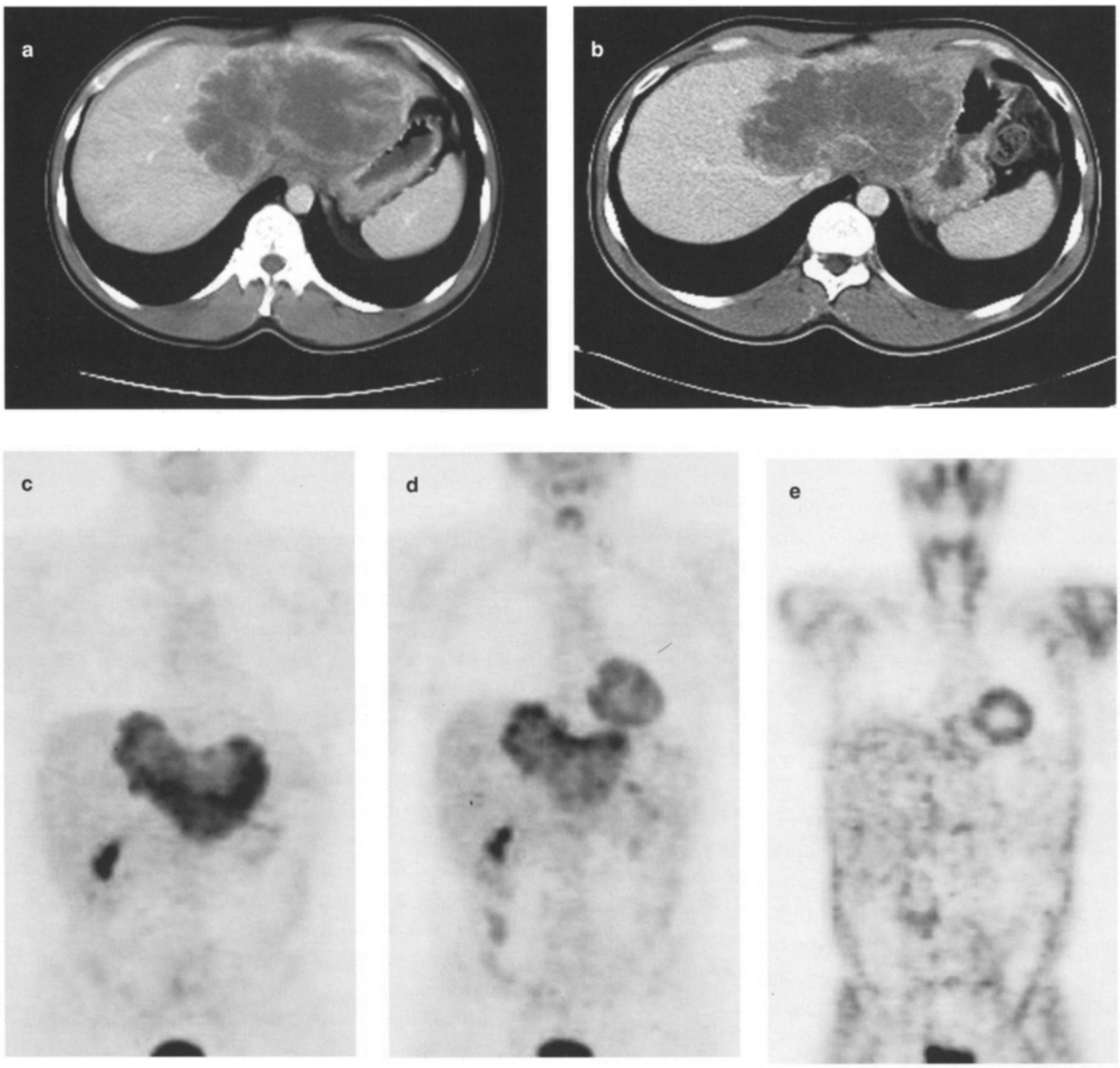

Fig. 32a.1. Response to therapy assessed with FDG-PET following two therapy doses with SIR-Spheres in a patient with liver metastasis from a primary of unknown origin.
a: Pre-therapy CT scan showing involvement of segments II, IV and VIII.
b: CT obtained 6 weeks after first dose showing no change in size and attenuation of tumour.
c: Pre-therapy coronal section of FDG-PET scan showing increased metabolic activity in the metastatic lesions.
d: Coronal section of FDG-PET, 6 weeks after first dose of SIR-Spheres, showing clear reduction in tumour uptake.
e: Coronal section of FDG-PET scan, 6 weeks after second dose of SIR-Spheres showing no metabolic activity in tumour with uptake that resembles normal surrounding liver tissue.

32a.12. Conclusion

The introduction of selective internal radiation therapy has added another effective method for treatment of primary and secondary liver tumours. The procedure requires prompt patient selection, best done through a multidisciplinary discussion, and has been used successfully in a large number of patients worldwide. It is well tolerated and has minimal adverse effects that can be effectively minimized by proper patient selection and preparation, dose adjustment and delivery. Despite being regarded as non-curative, it has been associated with improved survival, reduction in tumour marker, and regression in the number and size of lesions. Follow up with imaging is essential to assess the response to therapy, and in this respect FDG PET has been shown to be more sensitive than CT, particularly in the early stages.

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32b. The Use of Sirtex in Inoperable Liver Tumours. A Surgeon's View

D. Zacharoulis, N.A. Habib, R. Jiao

32b.1. Introduction

Over the past few years, selective internal radiation therapy (SIRT) has been used clinically for the treatment of non-resectable hepatic metastases in the absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy. The procedure involves using Yttrium-90 microspheres (25-35 u in diameter (fig. 32b.1), that are injected using a syringe into the hepatic artery via an access route: either a trans-femoral catheter or a permanently implanted hepatic artery port with catheter (fig. 32b.2). Once injected, the spheres travel through the blood stream and target the tumour within the liver, delivering high doses of beta radiation of 0.93 MeV energy, with a maximum 11 mm and mean 2.5 mm penetration distance [1, 2]. Treatment takes around 20-30 minutes and is delivered under mild sedation. In a randomised controlled trial of selective internal radiation therapy in combination with chemotherapy, patients receiving SIRT had improved response rates as measured by tumour area, volume and CEA in comparison to those patients receiving chemotherapy alone. However, evidence on survival indicated no statistically significant difference in the outcomes of patients receiving SIRT, compared with those treated with chemotherapy alone. More or less, this treatment modality has been increasingly adopted in recent years with a great enthusiasm for management of patients with liver cancer as an established treatment option without a clear evidence of survival benefit and its cost implications [3].

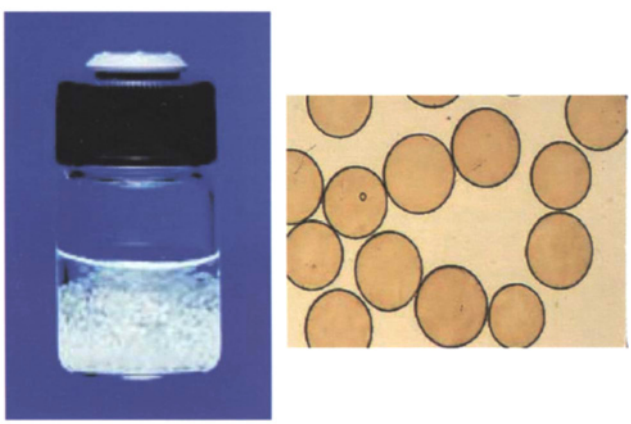
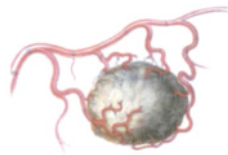


Fig. 32b.1. Microspheres: spherical, hydrophilic, micro-porous beads made of an acrylic copolymer (trisacryl) which is then cross-linked with gelatin ranging from 40 to1200 um in diameter.



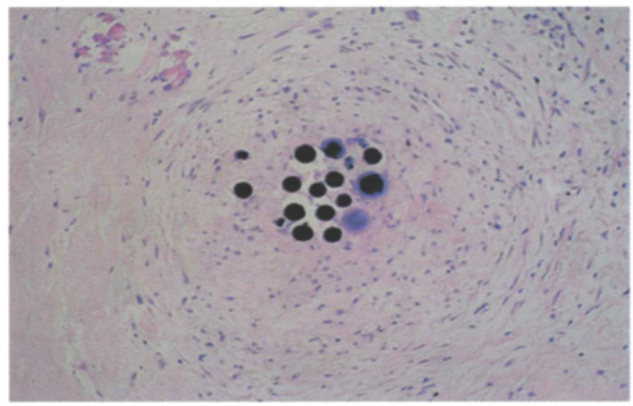


Fig. 32b.2. Histological appearance following SIRT showing beads within artery, with perivascular fibrosis and necrosis.

32b.1.1. Indications

a) Non-resectable colorectal liver metastases not suitable for any further systemic, regional or local therapy.
b) Non-resectable HCC not suitable for any further systemic, regional or local therapy.

32b.1.2. Contra-Indications

a) Any patient with uncontrolled extrahepatic disease.
b) Extrahepatic shunt of more than 20%.
c) Any patient with poor liver function tests.

32b.1.3. Procedure

Radioactive spheres are injected using a syringe into the hepatic artery via a transfemoral catheter or a permanently implanted port with a catheter to the hepatic artery. For the placement of this access port, patients may need to undergo a laparotomy.

32b.2. Results

In a randomised controlled trial (RCT) of SIRT, in combination with hepatic artery chemotherapy, patients receiving SIRT had improved response rates, compared with patients receiving chemotherapy alone. Response rates were measured by tumour area and volume, and carcinoembryonic antigen levels. Evidence on survival indicated no statistically significant difference in the outcomes of patients receiving SIRT compared with those treated with chemotherapy alone. The RCT, however, was stopped early and was therefore insufficiently powered to detect the level of increase in overall survival, which was the original aim of the study. Reported survival from time of treatment in the uncontrolled studies ranged from 9.8 to 12 months. In many of these studies, it was not possible to determine whether survival was measured from time of diagnosis or of treatment [4, 5, 6, 7].

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CHAPTER 33

RADIOFREQUENCY ABLATION (RFA) OF LIVER TUMOURS

33a. Basics of Radiofrequency Tissue Ablation

L.R. Jiao, D. Zacharoulis, N.A. Habib

33a.1. Introduction

Surgical advances generally follow either a scientific discovery or a technological breakthrough, for example magnetic resonance imaging or joint replacement. Over the past few years, the advent of new energy sources, such as radiofrequency, has had an increasing impact on surgical practice, especially in the field of liver tumours. Liver resection presently offers the only opportunity for cure in patients with liver cancer, either primary or secondary. Unfortunately, most hepatic cancers are unsuitable for curative resection at the time of diagnosis. Limitations for surgical resection can broadly be classified as either:

1) tumour-related, i.e. lesions that are extremely large, awkwardly sited, multiple, involving major vascular structures, associated with extrahepatic disease or
2) patient-related, i.e. intercurrent medical conditions, old age and poor liver function, especially in those with underlying cirrhosis. Therefore, there is a clear need, for the development of a simple and effective technique to control unresectable tumours within the liver and, preferably, one that avoids a lengthy hospital stay in patients with limited duration of survival. In the past few years, minimal access has become available for the destruction of hepatic carcinomas by methods such as ethanol injection and thermoablation, with cryoprobes, laser or radiofrequency.

Radiofrequency ablation (RFA) has now been widely accepted as an effective modality for treating liver tumours that are unsuitable for resection. It is based on the conversion of radiofrequency waves into heat, leading to coagulative necrosis, and it can be delivered either percutaneously or at open operation.

33a.1.1. Principle

Radiofrequency ablation (RFA) is a thermoablative technique, that destroys tissue by heating cancer cells to temperatures exceeding 60°C. In RFA, temperature changes are induced using a high-frequency alternating current applied via an electrode or electrodes placed within the tissue to generate ionic agitation.

The diameter of the lesions generated by monopolar radiofrequecy is largely depended on the tip temperature and the power created in the tissue. By maintaining the tip temperature of the probe between 25-35°C with perfusion of chilled saline, Goldberg and colleagues [1] have obtained maximal tissue destruction in porcine liver in vivo [1]. Since this technique is creating a 2.4 cm diameter zone of necrosis without inducing tissue charring, it should be able to treat large tumours with fewer insertions of the probe.

33a.2. Indications for Radiofrequency Ablation of Primary and Metastatic Liver Cancer

33a.2.1. Indications

33a.2.1.1. *Hepatocellular Carcinoma*

- Patients with unresectable tumours with normal clotting.
- Downstaging for patients suitable for staged liver resection.
- Bridging therapy for patients waiting for liver transplantation.

33a.2.1.2. *Metastases*

- An alternative for patients not suitable for resection.

- Previously resected patients, requiring further non-surgical treatment.
- Downstaging for patients suitable for staged liver resection.
- Patients with a low-volume disease who prefer a less invasive treatment.

33a.2.2. Results

Two small comparative series reported survival data on patients who had undergone radiofrequency ablation. In one study, a mean survival for patients not suitable for resection, who are treated with RFA, was 37 months (range 9-67 months) after treatment, with a 3-year survival rate of 52.5%. In the other study, patients had a mean survival of 44 months from diagnosis of liver metastases, with a reported 5-year survival rate of 40%. Furthermore, in uncontrolled studies, survival after treatment ranged from 88% (7/8) at 2-6 months to 17% at 11 months. However, comparisons between RFA studies and with other procedures are difficult, because of the different clinical scenarios in which RFA is used. There is also a lack of data on long-term outcomes [2, 3].

A systematic review reported complication rates after RFA that ranged from 0% to 33% [3-9]. Complications included bile duct stricture, bowel perforation, wound infection, peritoneal seeding and postoperative bleeding.

A high incidence of needle track seeding in patients treated with percutaneous RFA raises a great deal of concern [3]. There are several possible explanations for this phenomenon: dissemination of tumour cells on retraction of a radiofreqency probe, tumour cell spread from needle track haemorrhage and cells extruded by an increased intra-tumoural pressure during RFA. To prevent needle track seeding, when cauterisation of the intrahepatic track cannot be safely achieved without the risk of burning the abdominal wall, the use of percutaneous RFA for subcapsular liver tumour should be discouraged. Furthermore, the result of percutaneous RFA for colorectal liver metastases is far less effective than open or laparoscopic approach (table 32a.1) [4].

Although intraoperative RFA cannot be repeated more than once or twice, it is particularly indicated for multiple, peripheral, vascular or potentially resectable tumours. Laparoscopic RFA offers an intermediate approach, with certain advantages over both percutaneous and open RFA. In our own unit, patients have been treated with laparoscopic RFA with good results [2, 3]. However, the technique requires both a skilled laparoscopic surgeon and laparoscopic ultrasound and it is more expensive than either the percutaneous or the open technique [2, 5].

Although RFA is effective in management of liver tumours, is merely one of many palliative modalities available to clinicians. By this technique, foci of intact tumour cells are present on histological evaluation of previously ablated liver tumours, indicating incomplete destruction of the cancer. Today, surgical resection remains the method of choice for the cure of liver tumours.

Table 33a.1. Recurrence rate following RFA with different approaches.

	Local Recurrence Rate According to Size and Approach	
	Percutaneous(%)	Laparoscopy/Laparotomy (%)
• ≤ 3 cm	16.0	3.6
• 3-5 cm	25.9	21.7
• > 5 cm	60.0	50.0

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33b. Radiofrequency Ablation of Liver Colorectal Metastases

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Those diseases which medicines do not cure, iron (the knife?) cures; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable.

33b.3. Background

Taken from the book of Aphorisms –a collection of pithy statements attributed to Hippocrates around 400 B.C.– from antiquity to medieval times, the afore mentioned maxim had an enormous influence on the development of surgical practice. However, with the introduction of gunshot wounds during the Renaissance this principle was questioned, leading to the subsequent discarding of cautery as a treatment option for injuries. Although direct application of heat generated from an electrical current is rarely used today, modern electro surgery is based on heat generation via the passage of current through body tissues.

In recent years, direct application of temperature extremes has been introduced in oncological surgery, in an attempt to accurately target tumours without affecting surrounding tissue and structures. The focus of this chapter will be on the use of localised hyperthermia as a product of radiofrequency (RF) to achieve targeted tissue ablation. The operative, endoscopic and percutaneous routes may all be used to facilitate the application of RF ablation under appropriate image guidance. RF ablation is minimally invasive and has excellent tissue-sparing features, thus becoming a favourable technique in the treatment of tumors residing within the hepatic and pulmonary parenchyma. As with all surgical endeavors, limitations do exist. In order to avoid any baneful effect, careful patient selection with specific disease stage is warranted.

33b.4. Introduction

Hepatocellular carcinoma (HCC) and colorectal liver metastases (CLM) are the 2 most common malignant liver tumours. While surgical resection remains the gold standard of therapy, only a few patients are suitable candidates for curative surgical resection because of the presence of liver malignancy in unresectable locations, the number and anatomic distribution of tumor lesions or the presence of extrahepatic disease or poor liver function [1, 2]. Several alternative treatments to control and potentially cure liver disease have been developed for use in patients with malignant liver tumours, whether primary or metastatic, who are not candidates for surgical resection such as hepatic arterial infusion chemotherapy, percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) also known as "percutaneous microwave coagulation". Coagulation necrosis and hemostasis result, destroying tissue in the treated area. Laser-induced thermotherapy (LITT), also referred to as "interstitial laser thermal ablative therapy".

Radiofrequency ablation (RFA), also known as "radio-frequency thermal ablation", is a recently developed thermoablative technique. It induces temperature changes by using high-frequency alternating current, applied via electrodes placed within the tissue to generate areas of coagulative necrosis and tissue desiccation [3, 4]. Radiofrequency ablation can be applied percutaneously, laparoscopically or at open surgery.

Various studies have shown that RFA generally resulted in larger and more complete areas of ablation, and RFA may also be associated with higher survival rates compaired to the other ablative techniques.

33b.5. Basic Science of Radiofrequency Ablation

In order to perform oncological procedures using radiofrequency ablation (RFA), an understanding of the underlying basic science is essential. This applies not only to the operational principles but also to the mechanics of RFA and tissue interaction.

33b.5.1. Hyperthermia Effect on Tissue

The principal goal of thermal tumour ablation is the

destruction of all malignant cells, constituting the primary or metastatic deposit, and a surrounding zone (0.5-1 cm) of healthy tissue, in order to achieve a negative surgical margin. The effect of rising temperatures on tissue is summarized in the following table 33b.2.

Table 33b.2.

Temperature	Cellular Effect
• 40°C	Maintenance of cellular homeostasis.
• 42-45°C	Cells are more susceptible to damage by other agents like radiation; even prolonged heating though will not destroy all cells.
• 46-49°C	Irreversible cellular damage occurs, depending on duration of exposure; 60 minutes required at 46° C.
• 50-52°C	Cytotoxicity achieved in 4-6 minutes only.
• 60-100°C	Almost instantaneous cellular protein denaturation, melting of lipid bilayers and destruction of DNA, RNA and key cellular enzymes.
• >105°C	Boiling, vaporization and carbonization may be observed.

In a temperature of about 46°C the predominant mode of cellular death appears to change from apoptosis to necrosis [2]. Heat shock proteins, which provide cells with an immediate repair mechanism following thermal injury and an increased threshold against subsequent insults, are key modulators in this process. Induction of these proteins was not demonstrated above 42°C, although the exact mechanism is unknown, the authors suggest it is an inherent cellular protective mechanism to avoid repair and replication of thermally injured cells. Cells exposed to temperatures between 60-100°C undergo progressive coagulative necrosis, culminating in fibrosis in 28 days time [3]. In order to achieve tumour ablation, a temperature between 60-100°C must be achieved and maintained throughout the tumour volume. In order to assess the effect of RFA, ablated tissue may be excised and examined immediately, since special stains are required to assess cellular death [4].

33b.5.2. Principles of Radiofrequency Ablation Energy Deposition

A complete RF circuit consists of a programmable radiofrequency generator, a disposable surgical hand piece incorporating a needle electrode and finally a grounding pad. From the clinical perspective, it is important to delineate the physical parameters of the electrical circuit controlling the size of the created lesion. Tumors are variable three dimensional structures, even though in most experimental designs are considered spherical. Destruction via thermal necrosis denotes reaching a predetermined temperature throughout the tumor mass. The electrical generator produces a high frequency alternating current which is delivered by the needle electrode. In an attempt to follow the continuous directional change of the current, surrounding tissue particles are prompted into ionic vibration that, subsequently, leads to electrical heat production. Tumor destruction via electrical heating accounts only for the tissue adjacent to the probe; peripheral to this "core", necrosis is completed by conducted heat.

The transfer of thermal energy through living tissue remains an area of ongoing research, especially in the context of newly introduced energy sources in surgery. Based on the inverse square relationship between electric field strength and distance, it may easily be understood that electrical heating is inversely related to the fourth power of the distance from the probe. As with thermal conductivity, electrical conductivity is also temperature dependent [5, 6]. Electrolyte properties and distribution in both the intracellular and extra cellular compartments, as well as overall fluid volume shifts in tissue appear to be the two main reasons for this [7]. As water and sodium concentrations have been shown to differ between tumor and normal tissue [8], and fluid change in tumors follow an irregular pattern [7]. One may easily realize the difficulty in predicting tumors' electrical behavior under dynamic RF ablation conditions. Taking this concept a step further saline infusion has been utilized in conjunction with RF ablation to maximize therapeutic efficiency [9-14]. By increasing tissue tonicity, saline infusion (prior to, as well as during RF ablation) decreases tissue resistance, permitting greater current density application for longer periods of time.

In the attempt to reach thermal equilibrium, the blood flowing through tissue that is being ablated, as well as the surrounding tissue, are subjected to temperature changes. Goldberg et al [15] documented an 8.5°C increase in temperature requirements to achieve the threshold for coagulation necrosis in vivo, compared to ex vivo. This phenomenon has been suggested to

be secondary to perfusion-mediated connective tissue cooling. As blood flow transverses actively heated areas, convective heat loss occurs, leading to "indentation" of the ablation zone near large vessels. Although this mechanism of heat transfer does not aid tissue ablation, it does offer protection to vascular structures. In contrast to large diameter vessels that maintain their vascular flow, direct thermal injury with subsequent thrombosis takes place in smaller vessels within the ablation zone [16]. In an experimental porcine model, vascular inflow occlusion resulted in significantly larger lesions compared to control animals [17]. Applying this concept to human subjects, Goldberg et al demonstrated that, when compared to conventionally treated tumors, RFA and portal inflow occlusion lead to a larger coagulation area [18]. The authors also noted a further 10°C increase in hepatic parenchymal temperature at 1 cm and 2 cm from the electrode after 5 minutes of portal inflow occlusion.

As electrical field intensity is a vector quantity, the configuration of the field lines created by the RF probe within the targeted tissue volume is of extreme importance. Physical aspects of the active electrode that may influence the size of the created thermal lesion include positioning, shape, length of probe tip exposure, gauge, duration of treatment, as well as applied temperature. A positive correlation has been noted between increases in length of exposed probe tip as well as gauge and observed volumetric necrosis [19]. In a canine model, the obtained volume of resistive heating and lesion depth were shown to be associated with larger electrodes. The authors concluded that added electrode cooling and increased electrode-tissue interface were responsible for this [20]. When saline irrigation was used for active cooling by the same group, the previous relationship was reversed as smaller electrodes were demonstrated to transmit a greater fraction of the radiofrequency power to the tissue, thus resulting in higher tissue temperature and larger lesions [21]. It has been shown by Goldberg et al [19] that another important factor to be considered is overall time exposure. In conclusion, two interfaces are theoretically important for achievement of thermal necrosis in the RF ablation zone a-c (fig. 33b.1). The first interface a represents the zone between the electrode and tissue in direct contact; to facilitate electrical heating, electrical resistance should be kept at levels that allow maximal

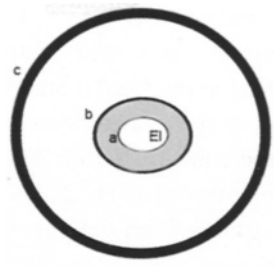

Fig. 33b.1. RF ablation active electrode EI creates an electrical heating zone a-b. Low resistance in this zone leads to large energy transfer, while good thermal conductivity is required to attain thermal necrosis in zone b-c. If thermal conductivity decreases beyond interface c, this allows for more efficient "cooking" of the ablations zone.

current flow. Saline infusion at this interface may lower resistance. On the other hand, if probe temperature exceeds 105°C, local carbonization leads to an opposite effect [15]. The second interface c represents the transition zone between the desired ablation zone (tumour with safety margins) and surrounding tissue. As beyond the electrical heating zone a-b convection is the main heat transfer method, thermal conductivity of the surrounding tissue only partly determines how effective heating will be in zone b-c. In cases of surrounding tissue (beyond zone c), being poor thermal conductors, effective thermal insulation may be observed, a phenomenon termed as the "oven-effect" by Livraghi et al [22]. Clinical examples include cirrhotic hepatic parenchyma surrounding hepatic tumors [22], pulmonary parenchyma as air acts as a thermal insulator [23] and cortical bone in vertebral body lesions [24].

It would be extremely useful to be able to predict the effect of RF ablation under given conditions. Due to the complexity of the equations governing this process, extensive mathematical modelling and computer simulation methods, such as finite element analysis, must be employed [25-27]. Incorporation of a convective heat transfer coefficient in the thermoelectric differential system transforms it into an electric-thermal-hydrodynamic three-field coupling system, the solving of which is even more complex [28].

33b.6. Colorectal Carcinoma

33b.6.1. Introduction

Colorectal cancer is one of the commonest malignancies afflicting the Western world, despite screening programs and increased public awareness. The overall prognosis for colorectal carcinoma remains poor, espe-

cially when distant metastatic disease is present. On average 500,000 new cases present each year, with roughly 140,000 of these occurring in the United States alone, a little over a quarter of all new cases present with synchronous liver metastases; in time, over 70% of all patients will develop liver metastasis [1, 2, 29]. The most frequent sites of metastases from colorectal cancer are the liver (20% to 70%) and lung (10 to 20%) [30-32].

Although surgical resection remains the gold standard and provides the only chance for cure, only 10-30% of patients are eligible for liver resection [30]. To help increase the number of surgical candidates, several new adjuvant treatment modalities are being used. These include portal vein embolization, downstaging chemotherapy regimens, two stage hepatectomy and radiofrequency ablation (RFA) [33-35]. A substantial group of patients develop lesions which are amenable to RFA as a minimally invasive method of tissue destruction.

Radiofrequency ablation of colorectal liver metastases is widely accepted and well described and dates back to 1989 when the first ultrasound guided interstitial laser treatments were performed [36].

33b.6.2. Natural History of Colorectal Carcinoma

On average, patients with a solitary untreated colorectal liver metastasis may live 25 months. In unilobar multicentric disease the median survival is 17 months; in bilobar diffuse disease the median survival is reduced to 3 to 6 months. Seldom will an untreated patient with liver metastases survive 5 years [37-40]. If colon cancer is treated with chemotherapy alone, (presently the standard of care is FOLFOX or FOLFIRI with or without Avastin), the median survival exceeds 20 months [41]. These results are encouraging and modern chemotherapy is well tolerated but in the presence of metastatic disease it is less effective, though long term studies are pending at this time. Regional chemotherapy using hepatic artery infusion of 5-fluorodeoxyuridine (FUDR), was popular in the 1980s but overall results are inconclusive though there does appear to be some short term benefit [42]. Long term data regarding local and regional chemotherapy is currently being evaluated [43].

For the patients who undergo hepatic resection, 25%-37% can be expected to survive for 5 years, with a median survival between 28 to 40 months [37]. In general, resection with clear surgical margins for metastatic disease confined to the liver has an overall survival at 3, 5 and 10 years of approximately 40%, 30% and 20% respectively with postoperative adjuvant chemotherapy being generally indicated [44].

Thus, hepatic resection remains the most effective treatment for metastatic colon cancer to the liver. In fact, hepatic surgery continues to improve with decreased operative mortality and morbidity. The best data comes from specialized centers reporting a mortality under 3% and a morbidity in the range of 10-15% [45, 46].

Factors affecting long term survival in patients undergoing hepatic resection have been shown to include the number and distribution of lesions, resection margins, size of the metastases, synchronous versus metachronous development, the presence or absence of extrahepatic disease, the type of resection, age, gender, blood loss, blood transfusion requirement, primary tumour characteristics and carcinoembryonic antigen (CEA) level [47].

Even after resection, some 60%-70% of patients develop recurrent disease within 5 years. The liver is the preferred site involving 45-75% of cases and the liver as the sole site is seen 40% of the time. Only one third of patients with recurrent metastases confined to the liver are candidates for re-resection [40, 48]. Re-resection can yield a median survival of more than 30 months, with a 5-year survival of 16%-32% [49]. This demonstrates that selected patients will benefit from repeat hepatic resection but, many may not be surgical candidates due to multicentric disease, bilobar disease, local anatomic invasion, juxtaposition to major pedicles or structures and the presence of other comorbid conditions [45].

So, the indication to undergo hepatic RFA includes unresectable tumours, recurrent hepatic tumours and the inability to tolerate major surgery. RFA can be performed percutaneously, laparoscopically or via open surgery and may be combined with partial resection, resection or extra hepatic resection [36].

33b.6.3. Background

The first ultrasound (US) guided interstitial laser treat-

ment dates back to 1989, applied for the treatment of hepatocellular carcinoma (HCC) [36]. Over the last decade and a half rapid technological developments have led to the employment of numerous ablative techniques, different electrode designs and higher power generators. Currently, much larger tissue volumes can be ablated. Today, inoperable metastatic colorectal lesions in the liver are the most frequent indication for application of RFA in the UK [36].

Although US is the preferred technique for needle placement, in both lung and occult liver tumours Computed Tomography (CT) or Magnetic Resonance (MR) are used.

Thermal techniques result in coagulation necrosis and thermal fixation, preserving tissue architecture, routine histological stains are misleading and enzymatic assays are required to establish cellular nonviability [50, 36].

Determination of efficacy of ablation is achieved with contrast enhanced CT or MR images. Absent enhancement denotes the area of necrosis non-viability [50].

33b.6.4. Colorectal Liver Metastases

In the UK colorectal liver metastases is the most common indication for RFA, since many patients are not surgical candidates either due to co-morbid conditions, tumour location and/or number of lesions, inadequate hepatic reserve from a previous resection or underlying liver disease [36]. These patients may benefit from RFA with or without chemotherapy. Most centers will accept patients with as many as five tumours with a maximum diameter of 5 cm. Median survival time of 38 months is a reasonable expectation with a potentially longer survival time if fewer and smaller lesions are treated [51].

Survival analysis of those non-surgical patients with small, 2.5 cm, solitary lesions is even greater with achievable mean survival times of 67 months and 66% 3 years survival [36]. Two retrospective studies suggest that survival after surgery and RFA are comparable for small solitary lesions [52, 53]. To date there are no prospective studies underway.

Another approach to liver metastasis is "the test of time", where potential surgical candidates are given RFA [54]. These patients that do not develop additional disease are spared a resection, these who develop more extensive disease in a short follow up are spared an unnecessary and ineffective resection and these that recur can undergo a resection. In one study 60% achieved complete ablation and did not require resection [54]. Theoretical projection models, based on the phase III European trial of chemotherapy alone vs. chemotherapy plus RFA suggests that, in multiple metastases, chemotherapy plus RFA provides a discernable advantage over chemotherapy alone [55]. However, these are projection models and only the results from prospective studies will provide the required level of evidence.

33b.7. Lung Metastasis

Although resection of pulmonary metastases is less common than resection for liver metastases long term survival has improved [56]. During the past decade, the indications for surgery have increased and resection is now proposed for solitary and multiple metastases or in patients in whom liver metastases have been previously resected. The typical pattern of lung metastases from colorectal cancer is single or multiple nodules rather than miliary tumours or lymphangitis carcinomatosa.

Due to the frequency of screening CT scans and closer patient follow up after resected colorectal cancer, the number of operable cases with lung metastases has increased [57]. In a recent study, no difference in prognosis was found in patients undergoing hepatectomy for colorectal metastatic disease simultaneously or with a later staged metastatic lung resection [58].

33b.8. Liver and Lung Metastases

The lack of difference, that is registered in finding, between wedge or lobar pulmonary resection and pneumonectomy, laid the foundation for using RFA for pulmonary metastases [59, 60]. In general, surgery should be considered only when complete removal of all pulmonary metastases is possible. In most cases, the primary tumour should be completely excised with no evidence of local recurrence or extra pulmonary disease. However, in some other cases, a combined resection of liver and lung metastases can be considered. In two published studies median survival was 19 months

and three, five and eight-year survival were 36%, 31% and 23% respectively [2, 3]. Pulmonary resection for colorectal carcinoma metastases is associated with 5-year survival rates of 35-41% [61, 62].

Once again, RFA plays a role in addressing bilobar disease and is useful in those patients who are not surgical candidates.

33b.9. Improving Local Ablation Efficacy

Tissue perfusion-mediated cooling, the so called "heat-sink effect", restricts the volume of tissue ablated. This relationship has been demonstrated using pharmacologic Halothane manipulation which resulted in a 46% reduction in blood flow and doubled the diameter of coagulative necrosis [63].

This relationship has also been demonstrated in animal models whereby arterial occlusion resulted in a 1.8-2.5 fold increase in the area of necrosis, portal vein occlusion showed a 1.5-2.0 increase and occlusion of both resulted in a 2.9-5.7 fold increase, depending on the RFA system used [64, 65]. Percutaneous balloon occlusion is practiced by some and during surgery the pedicle can be clamped. But, there is an increased incidence of bile duct injuries, since the cooling/protective effect of the blood flow is removed [65]. Another option, to increase the ablative field, is hypotensive anesthesia (lowering the CVP to 5 mmHg or less). However, this should only be practiced by an experienced team [66].

33b.10. Complications

Using RF coagulation, the overall mortality rates, for all liver tumours, is about 0.1-0.8% and complications range from 1.5-10% and include abdominal bleeding, infection, biliary tract damage, hepatic vascular damage, coagulopathy, tumour seeding, myoglobinuria, pulmonary complications and renal failure [36, 67, 68]. Mortality rates for pulmonary metastasectomy are probably less than liver metastasectomy but exact data do not exist [69, 70].

Intraperitoneal bleeding can be controlled by careful cauterization of the electrode track to prevent back bleeding and persistent oozing [67]. Cauterization is accomplished by continuing power upon slow deliberate withdrawal of the electrode, after stopping the cooling for cooled electrodes and after retraction of the prongs for expandable electrode probes [71].

Secondary infection does occur, usually as a late complication, and is more frequent in those patients with bilio-enteric anastomoses or biliary stents. This is presumably due to reflux of enteric organisms into the biliary tree and these patients are predisposed to increased septic complications. The usual perpetrators include Clostridium perfringens, streptococcus D and enterococcus [72]. Patients with bilio-enteric anastomoses or biliary stents should be empirically treated with post procedural antibiotics for at least 2 months.

The occurrence of electrode tract seeding is a real concern, with rates ranging from 0.2 to 12.5% [67, 73]. Several mechanisms may contribute to seeding. The needle itself may contain viable adherent cells on the surface during withdrawal which may lead to seeding along the track [67]. Back bleeding into the track may also seed viable cells [73]. During RFA heating and expansion, the increased intratumoural pressure may force some viable cells well into the tract [67]. Pre-procedural biopsies may seed even before ablation [74]. In addition, no cauterization of the tract, inadequate heating and ablation and perpendicular approach to subcapsular tumours, all the above may contribute to seeding [75].

Tumours closer than 1 cm to the gallbladder is a contraindication for the percutaneous approach [67]. Thermal cholecystitis or gallbladder perforation can be avoided by performing a laparoscopic or open cholecystectomy while performing RFA.

Likewise, lesions less than 1 cm from the liver surface should be ablated laparoscopically or by the open method to avoid burns to adjacent viscera [76].

Major bile ducts stenosis caused by RFA has been noted in cases when, at the same time, a Pringle manoeuvre had been carried out [71]. A Pringle manoeuvre allows vessels greater than 6 mm to become thrombosed whereas, without the manoeuvre, vessels greater than 4 mm generally remain patent [76]. Some authors propose the use of cooled saline within the bilary system for the ablation of large central tumours and some have proposed prophylactic placement of biliary stents. However, it is too early to be sure and caution is advised while ablating central liver tumours.

If hepatic arterial damage occurs, it usually results in an arterioportal shunt. Most of these resolve over a month or two. Arterial pseudo-aneurysms however, should be promptly embolized to minimize the chance of rupture [67].

33b.11. Local Recurrence

Local recurrence rate of liver tumours after RFA varies widely between 2% and 60% [77-79]. In a recent multivariate meta analysis, significantly fewer local recurrences were observed for small tumours (< 3 cm) versus large tumours (> 5 cm). A surgical approach was associated with few recurrences as well [80, 77]. Recurrence rates for tumours > 5 cm have been shown to be 58.1%, versus 14.1% for tumours < 3 cm [80]. In addition, a subcapsular location is associated with a significant increase in local recurrence rates [81, 82].

It must be stressed that the aim of treatment is cure and a resectable liver tumour must be resected and not simply ablated, regardless of the pressure for a minimally invasive approach.

33b.12. Technical Recommendations

Although many groups use local anesthesia with sedation for percutaneous RFA, general anesthesia is often recommended, as the final 2-3 cm underneath the hepatic capsule is painful. In an attempt to limit injury to major hepatic vessels, the use of a single probe may be safer when operating in the vicinity of several blood vessels.

With the addition of the Pringle manoeuvre, if the vein is already partially compressed by a tumour, the tendency for portal vein thrombosis is increased,. In general, if a Pringle manoeuvre is to be employed, a short duration is advocated versus a full long Pringle.

33b.13. Poor Prognostic Indicators

In cases of liver and lung metastases resection, patient selection is crucial. There are several predictors of poor outcome: a disease free interval, of less than one year between the first and second metastases, synchronous disease, lung metastases before hepatic, multiple lung metastases, elevated CEA, multiple lung resections and bilateral lung involvement. With the exception of synchronous disease, a second recurrence, particularly if pulmonary, has a major impact on survival [57, 83].

33b.14. Conclusion

Resection of isolated hepatic or pulmonary metastases from colorectal cancer has been shown to be safe and likely beneficial. Surgical resection continues to be the gold standard for survival. Unfortunately, most patients are not surgical candidates and RFA appears to be the most effective second line treatment. Further advances in RFA device technology and imaging modalities promise to make it even more efficient in the future. It will likely continue to compliment new developments in regional and systemic chemotherapy along with resection. Large-scale trials and long term data are needed to establish its place in the future.

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CHAPTER 34

STEM CELL THERAPY IN LIVER DISEASE

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34.1. Introduction - Incidence

Cirrhosis, the end result of long term liver damage, has long been an important cause of death in UK. The data from Chief Medical Officer in 2001 showed following trends [1]. Over 4,000 people died from the disease in the last year of the 20th Century, two thirds of them before their 65th birthday. Cirrhosis of the liver is an important cause of illness and death. In 2000 it killed more men than Parkinson's disease and more women than cancer of the cervix. Large rises in death rates from chronic liver disease and cirrhosis have occurred in most age groups. The rise in deaths from cirrhosis amongst younger people is of particular concern where binge-drinking patterns appear to be common. In 2000 cirrhosis accounted for nearly 500 deaths in men aged 25-44 years and nearly 300 deaths in women of this age group [1].

Trends in deaths certified as due to "chronic liver disease and cirrhosis" shows a striking pattern. In the last 30 years of the 20th Century deaths from liver cirrhosis steadily increased. The largest increases were in people aged 35 to 44 years where the death rate went up 8-fold in men and almost 7-fold in women. By 1999, there were about 9,000 admissions with a main diagnosis of alcoholic liver disease and about 3,000 admissions with cirrhosis of the liver [2].

34.2. Causes

There are many possible causes of liver cirrhosis – it can be present at birth as an inherited disease, it can be a rare side effect of certain medications, it can be caused by parasitic infections. However, the most common causes are sustained alcohol misuse or the late effects of infection with one of the hepatitis viruses (hepatitis B and C).

In the UK hepatitis C affects 0.6% of blood donors [3] and has been estimated to affect around 1% of the population. Infection frequency is much higher in other countries such as Italy (up to 3%) [4] and Egypt (up to 40%) [5]. Altogether 75% of patients exposed to hepatitis C fail to clear the virus spontaneously and become chronically infected. After 20 years of chronic infection, approximately 20% of patients develop cirrhosis, where after there is a 3% annual risk of hepatocellular carcinoma. Although in the future combination antiviral therapy may substantially reduce the number of patients with hepatitis C related cirrhosis and hepatocellular carcinoma, this is currently the commonest indication for liver transplantation in Europe and the USA [6].

Alcoholic liver disease (ALD) is one of the major medical complications of alcohol abuse. Alcohol is the major cause of liver cirrhosis in the Western world. ALD is the commonest cause of chronic liver failure in Europe and North America and is one of the most controversial indications for transplantation. Alcohol accounts for 80% of all liver cirrhosis cases seen in district general hospitals in the UK [7]. However, the sheer burden of alcoholic cirrhosis means that ALD accounts for a substantial and increasing proportion of all liver transplantation. ALD has accounted for 5716 transplants in Europe between January 1988 and June 2000 [6].

34.3. Current Treatment and Recent Advances

Liver transplantation is now a standard therapy for many end stage liver disorders. The success of liver transplantation has led to increasing numbers of referrals. However, at the same time the availability of cadaveric organs has diminished (partially due to improvements in road safety), resulting in the number of potential re-

cipients for liver transplantation exceeding organ supply with attendant deaths of patients on waiting lists.

In the past few years, multiple studies have demonstrated that adult stem cell plasticity is far greater and complex than previously thought, raising expectations that it could lay the foundations for new cellular therapies in regenerative medicine. The most widely studied example of adult stem cells is haematopoietic stem cells (HSCs), which sustain formation of the blood and immune systems throughout life.

34.4. General Concepts about Stem Cells

34.4.1. Stem Cells

A stem cell is a cell from the embryo, foetus, or adult that has, under certain conditions, the ability to reproduce itself for long periods or, in the case of adult stem cells, throughout the life of the organism [8]. It also can give rise to specialized cells that make up the tissues and organs of the body. Much basic understanding about embryonic stem cells has come from animal research. In the laboratory, this type of stem cell can proliferate indefinitely, a property that is not shared by adult stem cells [9].

Stem cells are unspecialized. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell); it cannot carry molecules of oxygen through the bloodstream (like a red blood cell); and it cannot fire electrochemical signals to other cells that allow the body to move or speak (like a nerve cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells [10, 11].

Stem cells are capable of dividing and renewing themselves for long periods. Unlike muscle cells, blood cells, or nerve cells -which do not normally replicate themselves- stem cells may replicate many times. When cells replicate themselves many times over it is called proliferation. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal [12].

34.4.2. Pluripotent Stem Cells

A single pluripotent stem cell has the ability to give rise to types of cells that develop from the three germ layers (mesoderm, endoderm, and ectoderm) from which all the cells of the body arise. The only known sources of human pluripotent stem cells are those isolated and cultured from early human embryos and from fetal tissue that was destined to be part of the gonads.

In 1998, James Thomson and his colleagues reported methods for deriving and maintaining human embryonic stem (ES) cells from the inner cell mass of human blastocysts that were produced through in vitro fertilization (IVF) and donated for research purposes [13]. At the same time, another group, led by John Gearhart, reported the derivation of cells that they identified as embryonic germ (EG) cells. The cells were cultured from primordial germ cells obtained from the gonadal ridge and mesenchyma of 5 to 9 week foetal tissue that resulted from elective abortions [14].

34.4.3. Stem Cell Differentiation

Differentiation is the process by which an unspecialized cell (such as a stem cell) becomes specialized into one of the many cells that make up the body. During differentiation, certain genes become activated and other genes become inactivated in an intricately regulated fashion [15]. As a result, a differentiated cell develops specific structures and performs certain functions. For example, a mature, differentiated nerve cell has thin, fiber-like projections that send and receive the electrochemical signals that permit the nerve cell to communicate with other nerve cells. In the laboratory, a stem cell can be manipulated to become specialized or partially specialized cell types (e.g., heart muscle, nerve, or pancreatic cells) and this is known as directed differentiation [10, 11, 16].

34.4.4. Adult Stem Cells

An adult stem cell is an undifferentiated (unspecialized) cell that occurs in a differentiated (specialized) tissue, renews itself, and becomes specialized to yield all of the specialized cell types of the tissue from which it originated. Adult stem cells are capable of making identical copies of themselves for the lifetime of the organisms. This property is referred to as "self-renewal". Adult stem cells usually divide to generate progenitor

or precursor cells, which then differentiate or develop into "mature" cell types that have characteristic shapes and specialized functions, e.g., muscle cell contraction or nerve cell signaling [17]. Sources of adult stem cells include bone marrow, blood, the cornea and the retina of the eye, brain, skeletal muscle, dental pulp, liver, skin, the lining of the gastrointestinal tract, and pancreas [18]. They are multipotent, differentiating into a restricted number of cell types based on the tissue they reside in. They usually form only 1-2% of the cell population, their main role being the replenishment of the tissue's cells in appropriate proportions and numbers in response to "wear and tear" loss or direct organ damage [19].

The most abundant information about adult human stem cells comes from studies of haematopoietic (blood-forming) stem cells isolated from the bone marrow and blood. These adult stem cells have been extensively studied and applied therapeutically for various diseases [18].

As indicated above, scientists have reported that adult stem cells occur in many tissues and that they enter normal differentiation pathways to form the specialized cell types of the tissue in which they reside. Adult stem cells may also exhibit the ability to form specialized cell types of other tissues, which is known as transdifferentiation or plasticity. Their primary functions are to maintain the steady state functioning of a cell called homeostasis and, with limitations, to replace cells that die because of injury or disease [20]. Adult stem cells are rare. For example, only an estimated 1 in 10,000 to 15,000 cells in the bone marrow is a haematopoietic (blood forming) stem cell (HSC) [21]. HSCs are constantly being generated in the bone marrow where they differentiate into mature types of blood cells.

34.4.5. Haematopoietic Stem Cells (HSCs)

HSC, first identified in 1961 [22] are multipotent cells derived from the bone marrow that self-renew and generate all oligolineage progenitors and differentiated progeny of the blood system [23]. However, the isolation of these cells proved to be difficult initially as they do not express unique characteristics and is also very rare, comprising only between 1 in 10,000 to 1 in 100,000 blood cells. Therefore an important breakthrough in stem cell research was the discovery of the sialomucin CD34 as a haematopoietic cell surface antigen. Furthermore, its expression was found to be down regulated as the cell matures and differentiates, making CD34 a distinguishing feature in the isolation, enumeration and manipulation of HSC [24, 25].

Other surface markers are important in the homing of haematopoietic stem cells to the bone marrow. These include the integrin very late activation antigen-4 (VLA-4) and adhesion receptors such as CD44. In addition, chemokine C-X-C motif receptor 4 (CXCR4) on the HSC surface binds to stromal derived factor-1 (SDF-1) in the bone marrow microenvironment and activates other cell adhesion receptors through intracellular signalling [26].

While the bone marrow is the classic source of HSC, their retrieval directly from bone is rapidly decreasing as they can be obtained simply from peripheral blood [27]. Most recent medical treatments using HSC including "bone marrow" transplants in fact use peripheral blood as a source rather than the bone marrow. It is preferred as it is less taxing on the donor with minimal pain, no anaesthesia and no hospital stay, and also generates better cells for transplantation [28]. Other sources of HSC include umbilical cord blood [29], and the foetal liver, as during this stage it functions simultaneously as a haematopoietic and hepatic organ [30].

Genes commonly used as liver markers for analyses of transdifferentiation are albumin, alpha-fetoprotein (AFP), alpha-1-antitrypsin (A1AT), c-met, hepatocyte growth factor (HGF), transferrin and vimentin. Albumin and AFP are both important blood plasma proteins synthesised in the liver [31]. AFP secretion is most prominent during embryonic development becoming down regulated in the adult, yet its role remains unknown in the foetus [32]. The protease inhibitor A1AT is found in hepatocytes and its deficiency is associated with liver disease [33]. HGF, along with its receptor c-met, is a potent mitogen for hepatocytes and a hepatotrophic factor for liver regeneration as its neutralisation impairs this process [34]. Other liver markers are the iron transporter transferrin, and the intermediate filament protein vimentin, which is expressed in mesenchymal cells such as Kupffer cells and sinusoidal endothelial cells of the liver [35].

34.5. Stem Cell Plasticity

Plasticity is the ability of an adult stem cell from one tissue to generate the specialized cell type(s) of another tissue. Adult stem cells such as HSC were until recently considered to be lineage restricted, but following recent research it has been proposed that they may have wider differentiation capabilities when they are removed from their usual niche [12]. HSC, for example, were first shown to be able to differentiate into muscle [16]. Subsequent research has demonstrated apparent transdifferentiation of these cells into liver [36], kidney [37], cardiac [38] and neural cell lineages [39]. Evidence suggests that, given the right environment, some adult stem cells are capable of being "genetically reprogrammed" to generate specialized cells that are characteristic of different tissues [40].

In reports that transplanted adult stem cells show plasticity in vivo, the stem cells typically are shown to have integrated into a mature host tissue and assumed at least some of its characteristics [10, 41-44]. Many plasticity experiments involve injury to a particular tissue, which is intended to model a particular human disease or injury [44-46]. Most of the studies that show the plasticity of adult stem cells involve cells that are derived from the bone marrow [11, 41-43, 46]. Collectively, studies on plasticity suggest that stem cell populations in adult mammals are not fixed entities, and that after exposure to a new environment, they may be able to populate other tissues and possibly differentiate into other cell types.

34.6. Liver and Stem Cells

The liver in an adult healthy body maintains a balance between cell gain and cell loss. Though normally proliferatively quiescent, hepatocyte loss such as that caused by partial hepatectomy, uncomplicated by virus infection or inflammation, invokes a rapid regenerative response to restore liver mass. This restoration of moderate cell loss and "wear and tear" renewal is largely achieved by hepatocyte self-replication. More severe liver injury can activate a potential stem cell compartment located within the intrahepatic biliary tree, giving rise to cords of bipotential, so-called, oval cells within the lobules that can differentiate into hepatocytes and biliary epithelial cells. A third population of stem cells with hepatic potential reside in the bone marrow; these haematopoietic stem cells can contribute to the albeit low renewal rate of hepatocytes, make a more significant contribution to regeneration and even completely restore normal function in a murine model of hereditary tyrosinaemia.

Perhaps born out of necessity from the plethora of potentially cell-damaging xenobiotics that assail the liver, plus a myriad of other cellular insults e.g. hepatotropic viruses, the liver can invoke not just one, but three apparently phenotypically distinct cell lineages to contribute to regenerative growth after damage. In response to routine parenchymal cell loss the hepatocytes are the cells that normally restore the liver mass, rapidly re-entering the cell cycle from the G0 phase. However, when either massive damage is inflicted upon the liver or regeneration after damage is compromised, a potential stem cell compartment located within the smallest branches of the intrahepatic biliary tree is activated. This so-called "oval cell" or "ductular reaction" amplifies the biliary population before these cells differentiate into hepatocytes.

One of the first demonstrations of using bone marrow to reconstitute liver was reported by Petersen et al (1999). Lethally irradiated female rats were rescued using bone marrow transplants from syngeneic males following induced hepatic injury and treatment with 2-aminoacetylfluorine to prevent hepatic proliferation. This cross-sex model allowed identification of male liver cells in the female rats' livers which indicated that bone marrow-derived HSC have the capacity to transdifferentiate into hepatocytes [47]. In similar sex-mismatched experiments in mice Theise et al (2000) demonstrated the presence of Y chromosome positive hepatocytes in lethally irradiated female mice following bone marrow transplants from males. In this case no liver injury was induced supporting the theory that marrow-derived HSC can differentiate into hepatocytes in the absence of acute liver injury [48].

Although evidence of transdifferentiation to hepatocytes is compelling from animal studies, few have examined this possibility in humans. Alison et al (2000) detected Y-chromosome positive cells in retrospective analysis of the livers of female recipients of bone marrow transplants from male donors. These cells were confirmed as being hepatocytes as they also expressed

cytokeratin-8 [36]. The authors also looked for the presence of Y-chromosome-positive cells in female livers transplanted to male recipients that were later removed due to recurrent disease. They found many Y chromosome-positive cells that expressed cytokeratin-8. This confirmed that circulating extra-hepatic stem cells may colonise the liver [36]. Thiese et al (2000) reported their analysis of archival autopsy and biopsy specimens from female recipients of male donor bone marrow transplants and male recipients of female livers. The marrow-derived cell engraftment in the liver ranged between 4 and 40%. The study showed that hepatocytes and cholangiocytes can be obtained from extrahepatic circulating stem cells, probably of marrow origin in humans [48]. A study by Korbling et al (2002) analysed biopsies from sex-mismatched bone marrow transplants in patients with no significant liver damage. Donor cells were detected in biopsies from the liver, skin and gastrointestinal tract, but the origin of these non-haematopoietic cells is uncertain [49].

Several possible mechanisms are postulated for HSC plasticity. Trans-differentiaion is one of the main mechanismsand refers to the ability of one committed cell type to change its gene expression pattern to that of a completely different cell type. An alternative mechanism for plasticity could be the fusion of a HSC with a nonhaematopoietic cell to form a heterokaryon, thereby converting the gene expression pattern of the original HSC to that of the fusion partner.

Clinical studies looking at the therapeutic application of bone marrow stem cells (BMSCs) has demonstrated that CD34+ cells transplanted into ischemic myocardium incorporate into foci of neovascularization and have a favourable impact on cardiac function [50]. Boyle et al. used granulocyte colony stimulating factor (G-CSF) for bone marrow mobilization of CD34+ cells, enabling intracoronary infusion of large numbers of CD34+ stem cells. Sustained reduction in anginal symptoms and improvement in quality of life scores was seen in all patients following infusion of cells. Mean collateral flow grade at 12-month follow-up angiography significantly improved, indicating sustained myocardial neovascularization [51]. Infusion of hepatocytes through the portal vein in a patient with Crigler-Najjar syndrome demonstrated in persistent reduction of serum bilirubin and increased bilirubin conjugates in the bile in a study by Fox et al [52]. Widespread application of hepatocyte transplantation is limited by organ availability, viability of isolated hepatocytes after cryopreservation and potential formation of hepatocyte aggregates during injection that can obstruct the liver sinusoids resulting in portal hypertension or lead to fatal emboli.

Our group published one of the first clinical trials on application of adult stem cells in hepatology [53]. In this study we have demonstrated the feasibility and safety of G-CSF administration and mobilization, leukapheresis and intrahepatic transfer of CD34+ stem cells in five patients with chronic liver disease. There were no problems of bleeding or precipitation of liver failure. The initial treatment protocol was well tolerated. Three of the five patients showed improvement in serum bilirubinand four of five in serum albumin. Recently, another clinical trial explored the benefits of intraportal administration of autologous CD133+ stem cells into the left branch of portal vein following embolization of right portal venous branch. Computerized tomography volumetry revealed 2.5-fold increased mean proliferation rates of left lobe compared with three patients treated without application of stem cells [54]. This early experience suggests that this novel therapeutic approach bear the potential of enhancing and accelerating hepatic regeneration in a clinical setting.

HSC may be advantageous for liver regeneration compared to hepatocytes since bone marrow can be obtained from living donors using a moderately invasive procedure, cord blood or mobilized HSC are other readily available sources of HSCs, and tissue banks of cord blood and bone marrow are established in many countries. Additionally, repopulation of both the hematopoietic and hepatic system from the same donor can induce a state of immunological tolerance in the transplant recipient that could reduce or eliminate lifelong immunosuppression for the prevention of allograft rejection.

In hepatology, the data presented here provide hope that somatic stem cells could eventually be used in tissue replacement protocols for the treatment of inherited and acquired end-stage liver diseases. Rather than relying on cadaveric organs from deceased donors who are often immunologically disparate, HSCs offer ready availability of liver-repopulating stem cells or progenitors obtained from living donors.

Use of adult stem cells overcomes many of the mo-

ral and ethical barriers of ES cell manipulation, and if somatic cells genuinely can switch lineage barriers, then HSCs are ideal sources. There is already considerable experience in their handling, and they are relatively accessible. The new findings in adult stem cell biology are transforming our understanding of tissue repair with promising hopes of regenerative hepatology.

The potential clinical applications of HSCs differentiating into nonhaematopoietic cell types are unlimited. These cells could be used to treat tissue injury and multiple diseases of nonhaematopoietic tissue in the following ways: transplantation of nomal autologous cells; enhancement or mobilization of endogenous marrow derived stem cells; transplantation of gene-modified autologous marrow cells; and transplantation of allogeneic bone marrow cells. For some applications cells could be administered directly into the non haematopoietic tissues.

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CHAPTER 35

LIVER GENE THERAPY: WILL GENE THERAPY DELIVER TO THE LIVER PATIENT?

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35.1. Introduction

The gene therapy dream started well over a decade ago. Despite its wide and successful application in research, it still has not reached the clinics in a meaningful way. No doubt that successful gene therapy has a lot to offer to patients with inherited, benign or malignant diseases.

Several challenges need to be addressed for gene therapy to succeed. The therapeutic gene has to go from the general circulation to the targeted diseased liver cell. It has to go through the cell membrane, escape the lysosome compartment in the cytoplasm and subsequently penetrate the nuclear membrane and reach the nucleosome. Finally, the gene should be expressed highly enough to produce significant level of protein that would change the behaviour of targeted cells and/or affect the function of neighbouring or distant cells.

Various imaginative ways were developed to overcome these difficulties, such as the use of liposome to surround the plasmid containing the therapeutic gene, the introduction of the cassette containing the gene in a viral vector such as adenovirus, adeno-associated virus, retrovirus, vaccinia virus and others. These were successful but not enough to have a clinical impact. They were not effective as in non-viral plasmid approach. They were toxic such as in the use of adenoviruses. They were also associated with malignant transformation such as in the use of retrovirus. The most potent viral vector available today is the lentivirus. However due to its inherent danger this vector has only been used today in HIV patients. It is difficult to speculate on its introduction to the clinic in the near future let alone in patients with benign disease.

Our group has been involved in several clinical trials with the use of plasmid DNA, adenovirus, retrovirus and vaccinia virus. It is unfortunate that these clinical trials failed. Despite our lack of success our research is still going strong.

Currently we believe clinical breakthrough success in the near future could be achieved via one of these three approaches:

(1) Hydrodynamic Gene Delivery (fig. 35.1, 35.2, 35.3): This technique was developed successfully in mice. We applied it successfully in pigs and subsequently to man. The principle is the percutaneous introduction of a Gene-Cath via the internal jugular vein or femoral vein to the hepatic vein. Then a large volume of fluid containing the therapeutic gene is injected rapidly. This creates a large pressure on the hepatocyte and produces holes in their

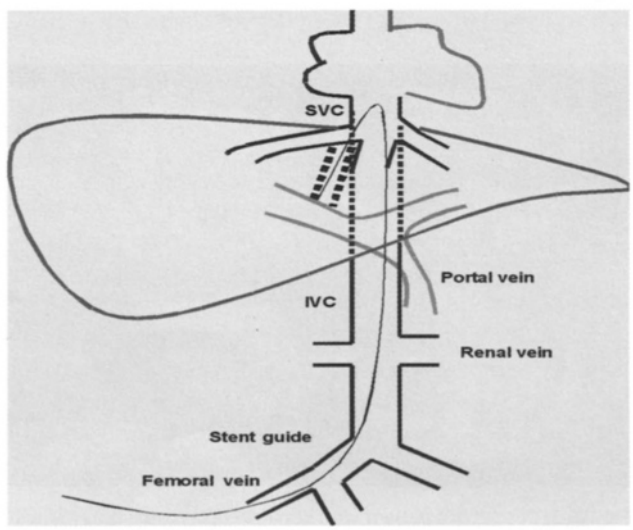

Fig. 35.1. Schematic guide of the stent routing via the right neck to obtain access to the hepatic veins feeding the left lobe the liver in the pig.

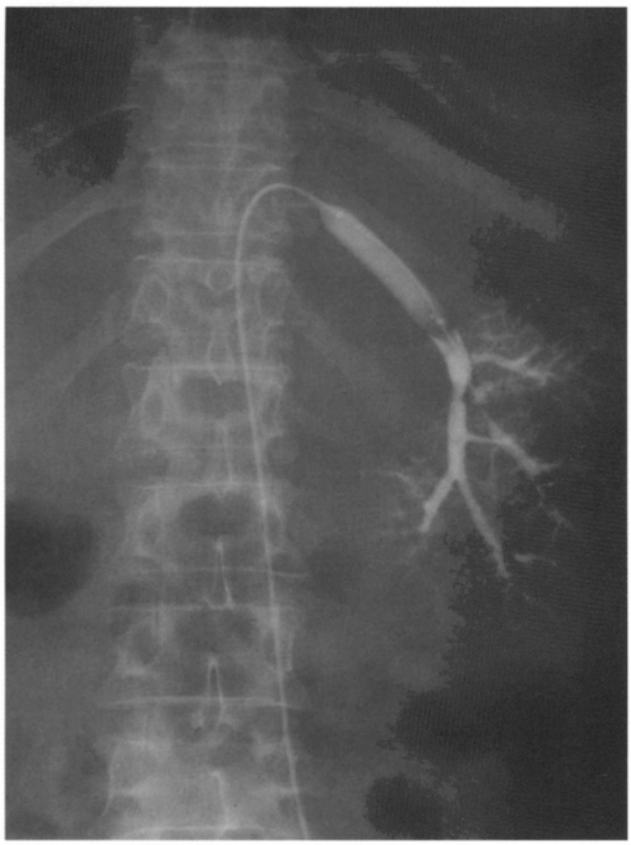

Fig. 35.2. Hydrodynamic gene delivery with thrombopoietic gene in a patient with thrombocytopenia due to liver cirrhosis complicating with hepatitis C. The Gene-Cath ascending is from the femoral vein to the left hepatic vein via inferior vena cava. The balloon is inflated and following contrast injection the venous drainage of the left lobe is opacified.

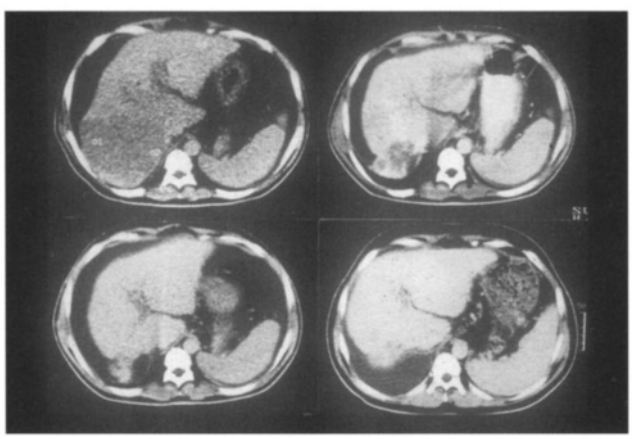

Fig. 35.3. CT scan of a patient with hepatocellular carcinoma complicating liver cirrhosis. The tumour is occupying most of the right liver. Following administration of p53 gene therapy, the tumour disappeared completely. Consecutive scan were performed after 3, 6 and 12 months.

cell membrane through which the plasmid gets entry into the hepatocytes.

(2) The cholesterol-DNA mixture that allows genes to be introduced into the hepatocytes via a systemic injection. This is a new technique and if successful will contribute greatly to the field.

(3) Combination of gene with cell therapy and in particular with adult bone-marrow derived stem cells progenitors. This approach allows the introduction of genes using viral vectors in an in-vitro ex-vivo approach where the cells are exposed to the vector and then the cells are washed. This would remove any virus that is still remaining outside the cells, therefore reducing the risks of potential toxicity and potential immune reactions.

Some of the clinical applications potentially could include the following:

- Introducing the genetically defective genes in adult bone marrow stem cell progenitors in diseases such as cystic fibrosis, glycogen storage diseases etc.
- Introducing siRNA in the stem cells in order to protect them from HBV and HCV infection.
- Introducing in the stem cells anti-cancer genes that would produce soluble tumour suppressor genes, cytokines or suicidal genes with by-stander effect.

We believe that the above three approaches will have their clinical début in the near future. If successful this will lead to the introduction of clinical gene therapy in conditions, where transient gene expression could be beneficial in patients with liver disease.

Long term gene expression will remain a problem with existing technologies. Currently the only technology that offers gene expression is with integrating viruses such as retrovirus, lentivirus or some non-viral approaches such as with the integrate system. These approaches succeed in long term expression as they lead to genetic integration in the host DNA. However, the integration is random and can occur at sensitive locus that may lead to activation of an oncogene or inactivation of a tumour suppressor gene leading to cell malignant transformation. At the time of writing long term gene expression remains a clinical challenge that still awaits further scientific breakthrough.

It is a reality that sometimes attractive scientific and biological concepts take long time for their clinical ex-

ploitation. Translational research can be a long lead way from the basic science discovery to the clinical application such as in the monoclonal field. Once considered as an area that never delivered monoclonal antibodies have provided recently important pharmaceuticals nearly three decades following their début in basic research. No doubt the same will happen in the gene therapy area. Its success will be both in its purest basic form with systemic and local delivery of genetic material as well as piggy-backed on the cell therapy application such as stem cell, adoptive T-cell or dendritic cell. When the gene therapy field will succeed it will have a major positive impact in the management of patients with liver diseases.

In this paper we summarised recent developments in gene therapy for malignant and non malignant liver diseases.

35.2. Gene Therapy Vectors

The liver is an attractive target for in vivo gene transfer because hepatocytes are readily accessible via blood stream. The endothelium of hepatic sinusoids displays 100 nm wide fenestrations and that allows macromolecules to cross the endothelium and reach the hepatocytes. However, in liver tumours, endothelium is no longer fenestrated due to the capillarisation of endothelium and thickness of basal membrane, thus preventing effective gene transfer [1]. The last decade has witnessed the blossoming of studies devoted to gene transfer to liver using different strategies, viral and non-viral vectors.

35.2.1. Non-Viral Vectors

Non-viral vectors have some advantages over viral vectors. The handling is easier, toxicity is low, the capacity for DNA sequences is high, they can be specific targeted to a tissue, they are not immunogenic and therefore permitting multiple administration [2]. However, the transduction efficiency is relatively low.

Naked DNA approach in which plasmid DNA is directly injected into tissues have been pioneered by Wolff et al [3] and has shown DNA incorporation in liver cells. A major advance in this approach was developed recently using tail vein delivery procedure, which allows efficient transduction of hepatocytes (up to 40%) [4]. However, the clinical relevance of this technique is questionable.

Another non-viral system is DNA-protein complexes system, developed in 1980s. Hepatocytes were specifically targeted via asialglycoprotein or transferring receptor [5], however, low transgene expression and the absence of sustained expression limited the development of this system.

35.2.2. Viral Vectors

Viral vectors are the most efficient vehicles for gene transfer to the liver in vivo. Different viruses have been used to construct gene therapy vectors including adenovirus, retrovirus, adeno associated virus, lentivirus, herpesvirus, baculovirus, SV40 virus and others.

35.2.2.1. *Retroviruses*

Retroviruses contain RNA genome that is reverse-transcribed into cDNA after entering the cell and have the ability to integrate into the host genome of a dividing cell [6]. Although the integration does not guarantee stable expression of transferred gene, it is an effective way to maintain genetic information in self renewing tissue. Liver tissue is difficult to transduce, because hepatocytes do not proliferate under physiological conditions. Also, it has been shown that when using high-titer retroviral vectors, an immune response directed against the transgene product hampered its long-term expression [7, 8].

More recently, another group of retroviruses, termed lentiviruses have been engineered. Lentiviral vectors, mainly derived from human immunodeficiency virus (HIV) can transduce cells that are not undergoing cell division. Gene transfer into the intact liver has been shown, however, studies indicate that efficient in vivo lentiviral transduction of the hepatocytes requires cell cycling [9, 10]. There are some concerns regarding the use of lentiviruses in clinical applications, mainly because of their integration at the sites of active transcription [11].

35.2.2.2. *Adenoviral Vectors*

Recombinant adenoviruses can efficiently deliver genes to the liver. When administered systemically they localise predominantly in the liver [12] and can trans-

duce both dividing and non-dividing cells. First generation adenoviral vectors are double stranded DNA virions that have a deleted E1 gene. They have been used in animal models and clinical applications [13]. Although their ability to efficiently infect quiescent hepatocytes, it has been shown that the gene expression was transient due to the cytotoxic immune elimination of transduced hepatocytes [14]. Several strategies have been considered and developed to overcome immune rejection, including vector modification. This was obtained in second and third generation vectors, which contain additional deletions in E2 and/or E3 and E4 genes [15]. Pilot clinical study has shown very little expression of E1/E4-deleted adenovirus vector in human liver. Moreover, it was fatal in one case due to the massive inflammatory response and the trial was stopped [16].

Another strategy was the development of so called gutless vectors. These fully viral deleted vectors require helper adenoviral infection for provision of the viral proteins. They showed reduced toxicity and host immune response against vector and prolonged transgene expression [17] and are promising tool for liver gene therapy.

25.2.2.3. *Adeno Associated Virus (AAV)*

Adeno associated virus (AAV) are single stranded DNA virus. They can transduce dividing and non-dividing cells and allow long term expression either by incorporation into the genome or by persistence in the cells in episomal form [18]. When injected systemically, AAV mainly localise in liver. They are devoid of all genes and do not induce virus-directed immune response. Several animal studies have shown that they can transduce hepatocytes for prolonged period of time [19, 20] and they may be a promising tool for future liver gene therapy.

35.3. Gene Therapy for Liver Tumours

The main treatment strategy for liver tumours irrespectively of their origin (either primary hepatocellular carcinoma (HCC) or liver metastases) is surgical resection, which is associated with high risk of relapse. Liver transplantation, which is considered the most effective therapeutic strategy, is not applicable universally due to the shortage of organ donation. Moreover, conventional chemo- or radiotherapy is ineffective for HCC [21].

Therefore, several gene therapy strategies for liver tumours have been developed over the last decade. These strategies aimed at replacing function of tumour suppressor genes, sensitising tumour cells to prodrugs, stimulating the antitumoural immune response, antiangiogenic gene therapy [22]. Some of the developed gene therapy therapeutic strategies have been translated from bench to bedside with various successes.

35.3.1. p53 Suppressor Gene

The function of p53 tumour suppressor gene is lost in many cancers, including HCC. The altered p53 function leads to enhanced cell growth and tumour resistance to chemo- and radiotherapy [23, 24]. p53 gene therapy has been therefore proposed as possible anti tumour strategy. It has been shown that wt-p53 inhibits in vitro cell growth of HCC [25], induces cell apoptosis [26] and increases HCC sensitivity to chemotherapeutic agents [27]. Intra-tumoral [28] and repeated intra-arterial injections [29] of adenoviral vector expressing p53 inhibited tumour growth in experimental animal models of HCC.

A decade ago we performed the first pilot study assessing the therapeutic potential of percutaneous intratumoral injection of wt-p53 in five patients with primary HCC [30]. The protocol consisted of single intratumoral injection of p53 naked DNA under computed tomography (CT) scan control. The study showed that three out of five patients responded to wt-p53, with the reduction of the tumour volume and significant fall in alpha-fetoprotein. In contrast, when patients with colorectal liver metastases were treated with naked wt-p53 no objective response was observed [31, 32]. In order to completely eliminate the tumour and trigger apoptosis, the tumour suppressor gene should be expressed in every single tumour cell. Unfortunately, such an approach is currently beyond the capabilities of current vectors and significantly better gene therapy vectors must be designed to overcome the problem.

On the other hand, Guan et al [33] treated a patient with the multiple hepatic nodules which precluded reoperation with p53 gene therapy combined with trans-

catheter arterial chemoembolisation (TACE). They have injected p53 gene therapy (Gendicine) intratumorally in the largest nodule, followed by the infusion of p53 gene via the hepatic artery. Four days later they super-selectively embolised the patient's hepatic arteries with 5-fluorouracil, vinorelbine, and iodised oil. Seven months later, the patient had normal liver function and was in good clinical health with alpha-fetoprotein levels falling to normal. No further recurrence has been identified.

35.3.2. Oncolytic Viruses

Oncolytic viruses are designed to replicate selectively in cancer cells and destroy them by lysis. The most developed oncolytic viruses are E1B-deleted adenoviruses that replicate in p53 deficient tumour cells [34]. dl1520 (ONYX-015) is a replication-selective adenovirus type 2/5 chimera with a deletion in the E1B-55kD gene. Because E1b-55kD binds to and inactivates the p53 gene product, this mutant is unable to overcome the p53 mediated blockade of viral application in a normal cell [35]. In a tumour cell devoid of endogenous wt-p53 gene, E1B-55kD is expendable for p53 inhibition and is able to replicate [34]. HCC cells are susceptible to cell death induced by E1B-deleted viruses, which also had in vivo anti-tumour effect [36-38]. We reported the results of phase I and II studies, in which patients with advanced primary and secondary liver tumours were treated with dl1520 adenovirus [39]. The adenovirus was given via three different routes: intratumoral, intraarterial and intravenous. It was well tolerated as either montherapy or in combination with chemotherapy (5-flurouracil). However, there was no significant reduction in tumour size as measured by CT scan. Similar was observed in randomised prospective study, which included patients with HCC [40]. Patients were treated with dl1520 adenovirus and analysis showed that only one patient partially responded to gene therapy treatment, while four others showed disease progression. Another group performed phase I clinical study using dl1520 adenovirus. Reid et al [41] administered dl1520 into hepatic artery in dose escalating manner for two cycles (days 1 and 8). Subsequent cycles of dl1520 were administered in combination with intravenous 5-flurouracil and leucovorin. The treatment was well tolerated; however the objective response was only demonstrated in one patient, who received both dl1520 and 5-flurouracil, suggesting chemotherapy associated antitumoral effect.

35.3.3. Genetic Prodrug Activation

Molecular chemotherapy selectively transducing tumour cells with any genes (i.e. suicide genes) that render them sensitive to prodrugs that are innocuous for non-transduced cells. Such genes encode enzymes that convert the prodrug into a toxic metabolite. The destruction of non-transduced cells, so called "by-stander" effect is probably caused by the diffusion of the toxic metabolites to non-transduced neighbouring cells [42] and possibly stimulating anti-tumoral immune response [43]. The most common molecular chemotherapy system developed is the herpes simplex virus thymidin kinase (HSV-tk) given in combination with ganciclovir (GVC) [44]. HSV-tk phosphorylates GVC, triphosphorylated GVC incorporates into cellular DNA and inhibits DNA polymerase, what is leading to cell death [45]. HSV-tk transduced HCC cells are highly sensitive to GSV both in vitro [46] and in vivo [47, 48]. However, to completely eradicate tumours, repeated injections of the viral vector was required [47]. Systemic administration of adenoviruses resulted in severe liver dysfunction and high mortality [48, 49]. Intatumoral vector injection and the use of tumour-specific promoters such as alpha-fetoprotein have been shown to be safer [47, 50].

Sung et al [51] conducted a clinical phase I trial in patients with metastatic colorectal adenocarcinoma in the liver and demonstrated safety of intratumoral adenovirus RSV-tk injection followed by intravenous GVC. Again, the major obstacle preventing further development of genetic prodrug activation strategies is the inefficiency of gene delivery, systemic administration of the current vectors does not allows significant tumour cell transduction in vivo.

35.3.4. Genetic Immunotherapy

Immunotherapeutic strategies can be used to manipulate patient's immune system to stimulate anti-tumour immunity. Many gene therapy approaches have been developed for the therapeutic vaccination, including DNA vaccine, dendritic cells and allogenic tumour cells. Most of the strategies involve transfering genes of

immunostimulating molecules such as interleukin-2 (IL-2), interleukin-12 (IL-12), interferon-α, interferon-β and tumour necrosis factor-α (TNF-α) [22]. Interleukin-12 is a particularly potent anti-tumour cytokine which induces a TH1 type of response, activates cytotoxic T lymphocytes and natural killer cells and displays robust anti-angiogenic activities [52]. It has been reported that gene therapy with IL-12 induces tumour eradication without significant toxicity in experimental model of HCC [53]. Sangro et al [54] performed clinical trail in patiens with liver tumors, both primary or secondary tumours. Patinets received 1-3 intra-tumoral injections of a first-generation adenoviral vector encoding human IL-12 genes.The treatment was without any significant side effects, however, the anti-tumor effect was weak with only one partial response in a patient with HCC. Another clinical trial was performed in patients with primary or metastatic liver cancer using intra-tumoral injections of monocyte-derived DC transduced with adenoviral vectors encoding IL-12 [55]. The patients received up to three equal doses of cells at 21 days intervals. Although the procedure was well tolerated, the elicited anti-tumor effect was weak.

Administration of a vaccine combining Modified Vaccinia Ankara (MVA) vector with 5T4 elicits immune responses. Clinical trial to investigate the immunological effects of the vaccine, which has been administred before and after the surgical resection of colorectal cancer liver metastases showed that MVA-5T4 vaccine (Trovax) was safe, well tolerated and it induced immune response in the majority of the patients treated [56].

35.4. Gene Therapy for Hepatitis B and C

Hepatitis viruses which are leading causes for chronic liver disease worldwide, including cirrhosis and hepatocellular carcinoma [57, 58]. Therapeutic options for these viral infections are still limited by their short-lived effect, the emergence of escape mutants after prolonged treatment and their inability to totally eradicate the virus. Different strategies such as RNA interference (RNAi) and DNA vaccine have been considered for gene therapy for viral hepatitis.

RNAi is gaining favor as a potential therapeutic option for the treatment of virial hepatitis. RNAi, first discovered in plants, induces sequence specific degradation of messenger RNA following the introduction of short interference RNA (siRNA).

Several in vitro and in vivo experiments done so far conceivably demonstrated the effectiveness of RNAi in inhibition of hepatitis B and C [59]. However, much work have to be done before applying the RNAi in humans, developing efficient delivery methods improve delivery, maintain specificity and limit the development of virus resistance.

Another strategy is the use of DNA vaccine because of their ability to induce T-cell responses and stimulate antiviral immunity. Clinical trials have been already performed to test the safety, tolerability, and immunogenicity of a particle-mediated DNA vaccine against hepatitis B [60, 61]. The first trial demonstrated that particle-mediated administration of DNA encoding HBsAg was safe and well tolerated and in humans [60]. In the second trial, a DNA vaccine against the hepatitis-B virus was evaluated for safety and induction of immune responses in 12 healthy, hepatitis-naive human volunteers [61]. The second trial showed safety, tolerability, and immunogenicity of escalating doses of the DNA vaccine and a first demonstration of a DNA vaccine inducing protective antibody titers and both humoral and cell-mediated immune responses in humans.

35.5. Gene Therapy for Liver Cirrhosis

Gene therapy for liver cirrhosis is another option to repair chronic liver damage. Several different approaches have been considered as therapeutic strategies for cirrhosis. As summarised by Prieto et al [62] strategies include blockage of tumour necrosis factor β (TGF β) signalling, which resulted in reduced liver fibrosis in rats [63]. Introducing plasmid carrying hepatocyte growth factor (HGF) into livers of rats with lethal liver cirrhosis showed inhibited fibrogenesis and hepatocyte apotosis and improved survival [64]. Administration of adeno-mediated metalloproteinase 1 (MMP1), improved liver fibrosis, decreased the number of hepatic stellate cells and increased weight in rats with liver cirrhosis [65]. However, gene therapy for liver cirrhosis is still in developemental phase and no human clinical trial has been been performed yet.

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CHAPTER 36

LIVER TRAUMA

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36.1. Introduction

Trauma is the leading cause of death up to the age of 44, while in all age groups trauma related mortality is surpassed only by cancer and atherosclerosis. The liver is the second most commonly injured organ in blunt and the first in penetrating abdominal trauma [1]. Both blunt and penetrating liver injuries are more common in male adults who drive motor vehicles or engage in fighting. Although the prevalence of blunt liver injury has increased during the past three decades it is not certain whether this represents an actual increase in incidence or an artificial effect due to improvement in diagnostic modalities [2]. A definite decline in total mortality from complex hepatic injuries has been recorded, from almost 60% before 1990 to 10-15% nowadays [3]. However, damage to the liver remains the most common cause of death after abdominal injury, being responsible for more than 50% of all deaths after blunt abdominal trauma [4]. Liver injuries can be detected in up to 25% of patients with blunt trauma if whole-body computed tomography (CT) is performed on every severely injured patient [5].

36.2. Historical Evolution

The problem of liver injury was first addressed in a 1904 review by Tilton, who showed that, rupture of the liver was associated with mortality approaching 80% if the wound was caused by blunt forces, 40% if caused by gunshot wounds, and 38% if caused by stab wounds [6]. Historically, the first successful treatment of a liver injury is attributed to Hildanus in the early seventeenth century, who surgically treated a liver stab injury. Pringle in 1908 described direct compression of liver injuries with packs as well as digital compression of the portal triad to stop massive hemorrhage [7]. Hemorrhage control techniques used during the early 1900s included the use of the Pringle manoeuvre, cautery, packing with various materials such as gauze, muscle or omentum, and direct suture ligation carried out with a blunt, noncutting, supple needle [8].

In 1965 the diagnostic peritoneal lavage (DPL) was introduced [9] as an adjunct followed by the introduction of computed tomography (CT) in 1981 for the evaluation of the trauma patient [10]. Through the increased use of CT, it became evident that many liver injuries, particularly Grade I and II, did not require an operation, thus leading to the concept of nonoperative treatment [11]. During the same period damage control surgery was described for the first time [12]. Nonoperative management of abdominal trauma remaines the standard of care for most blunt trauma patients as well as for selected penetrating liver trauma cases [13, 14].

36.3. Anatomy of the Liver and Physiology of Liver Injury

The liver is the largest solid abdominal organ with a relatively fixed position which, despite its protection by the ribs, makes it prone to injury.

The anatomic descriptions of the liver are based on hepatic vasculature. Cantlie first described the main anatomic divisions along a main plane (Cantlie line) extending from the gallbladder fossa to the inferior vena cava, reaching the superior surface of the liver to

the right of the falciform ligament [15]. Couinaud refined the functional anatomy further and demonstrated that the liver was divided into 4 sectors and 8 segments [16]. The liver is divided by vertical and oblique planes, or scissurae, defined by the 3 main hepatic veins and a transverse plane or transverse scissura following a line drawn through the right and left portal branches. Hepatic veins lie between segments. The left hepatic vein divides the left side of the liver into medial and lateral segments. The middle hepatic vein divides the liver into left and right lobes. The right hepatic vein divides the right side of the liver into anterior and posterior segments. A further imaginary line (horizontal) drawn through the left and right main portal vein branches may be used to divide the hepatic lobes into superior and inferior segments. Determining the anatomy of the liver segments allows accurate localization of hepatic damage relative to the hepatic vasculature. The 8 liver segments (namely 1, 2, 3, 4a, 4b, 5, 6, 7, 8) are numbered clockwise on the frontal view (see figures in chapter "liver anatomy") [17].

Most liver injuries (> 85%) involve segments 6, 7, and 8 [18]. This type of injury is believed to result from simple compression against the fixed ribs, spine, or posterior abdominal wall. Pressure through the right hemithorax may propagate through the diaphragm, causing a contusion of the dome of the right lobe of the liver. This type of liver injury occurs more easily in children than in adults because the ribs are more flexible, allowing force to be transmitted to the liver. The liver's ligamentous attachment to the diaphragm and the posterior abdominal wall can act as sites of shear forces during deceleration injury. Liver injury can also result from transmission of excessively high venous pressure to remote body sites occurring at the time of impact. Deceleration injuries produce shearing forces that may tear hepatic lobes from each other and often involve the inferior vena cava and hepatic veins. Because the hepatic veins lie in rigid canals and contract poorly, the liver is incapable of achieving spontaneous hemostasis after injury. Gallbladder injuries are rare. Predisposing factors for gallbladder injuries include alcohol ingestion, which increases tone of the sphincter of Oddi, and a normal distended gallbladder. Paradoxically, chronic cholecystitis is less prone to rupture [19].

36.4. Classification

Through time, many schemes for the classification of liver trauma have been introduced in an effort to accurately and objectively describe liver trauma and probably predict patient's outcome [20].

36.4.1. Anatomical Classification

In 1990, Buechter suggested that the extent of parenchymal damage could be quantified by the number of liver segments involved and concluded that trauma involving two or more segments was associated with a significantly worse prognosis [21]. Furthermore, there appeared to be a direct correlation between morbidity and mortality rates and the volume of damaged hepatic tissue. This scheme provided a reproducible but rather simplistic way of reporting and comparing liver trauma, concentrating on the anatomical and operative aspects of the liver injury with minimal attention to the extent of vascular injuries. In addition, it was not very clear which injuries might benefit from a conservative approach to treatment, which began to be more widely adopted in the early 1990s.

36.4.2. Vascular Injury Classification

Early classification systems acknowledged that ultimately the extent of vascular injury, rather than the magnitude of the parenchymal damage, was the principal prognostic factor in patients with liver trauma. In 1994, Namieno proposed a three grade classification based on vessel injury: Grade I, subcapsular Glissonian vessel injuries; Grade II, transcapsular Glissonian vessel injuries; and grade III, in-/out-flow vessel injuries [22]. However, Namieno's classification did not have a significant impact as it concentrated mainly on the extent of the vascular injuries and failed to acknowledge that extensive parenchymal damage may well have a comparable outcome with some of the lesser vascular lesions.

36.4.3. Radiologic Classification

With the institution of CT for the evaluation of liver trauma, radiologic classifications were introduced. Several systems have been devised to classify liver injuries; however, the lack of consistency in scoring severity in organ injury presents a significant problem. To

rectify the problem, the American Association for the Surgery of Trauma (AAST) developed a system based on the amount of anatomic disruption of an individual organ [23]. The AAST injury grading scale's major drawback is that it includes some criteria that cannot be assessed by CT. Wide discrepancies have been found between the CT injury grade and the intraoperative findings, with CT findings generally leading to underestimation of injury severity [24].

36.4.4. Mirvis Revision

Using the AAST injury scale, Mirvis and co-workers developed a CT-based injury severity grading scale for blunt hepatic trauma. The Mirvis CT-based grading system is useful in predicting treatment needs and guiding management [25].

Table 36.1. Liver Injury Scaling (Revision by Mirvis).

I	Haematoma	Subcapsular, < 10% surface area.
	Laceration	Capsular tear, < 1 cm parenchymal depth.
II	Haematoma	Subcapsular, 10-50% surface area. Intraparenchymal, < 10 cm diameter.
	Laceration	1-3cm parenchymal depth, < 10 cm length.
III	Haematoma	Subcapsular, > 50% surface area or expanding. Ruptured subcapsular or parenchymal haematoma. Intraparencymal haematoma > 10 cm or expanding.
	Laceration	> 3 cm parenchymal depth.
IV	Laceration	Parenchymal disruption involving 25-75% of hepatic lobe or 1-3 Couinaud's segments in a single lobe.
V	Laceration	Parenchymal disruption involving > 75% of hepatic lobe or > 3 Couinaud's segments within a single lobe.
	Vascular	Juxtahepatic venous injuries ie. retrohepatic vena cava/central major hepatic veins.
VI	Vascular	Hepatic Avulsion.

36.5. Diagnosis

Although physical examination remains the cornerstone of investigation, modern technology plays a major role in the diagnosis and follow-up of abdominal trauma. Many modalities, such as diagnostic peritoneal aspiration or lavage, computed tomography (CT) scan, focused abdominal sonography for trauma (FAST), and laparoscopy have been extensively evaluated in both blunt and penetrating trauma.

36.5.1. Physical Examination

The presence of obvious peritonitis or hemodynamic instability is a strong indication for emergency laparotomy. The initial examination is often unreliable, mostly in children [26, 27]. Only 25.5% of patients with abdominal or pelvic tenderness were noted to suffer an intraabdominal injury confirmed by CT scan of the abdomen and pelvis [28]. Likewise, only 20% of those patients with a documented seat belt sign have intraabdominal injuries confirmed. The use of routine laboratory screening of hemoglobin, serum lactate levels, and arterial blood gas analysis fails to be predictive of patients sustaining intraabdominal injury secondary to trauma. Vital signs in the emergency department do correlate with the presence of intraabdominal injury, as 40% of patients admitted with hypotension had confirmed injury [29]. Since only a small percentage of trauma patients present with significant hemodynamic instability, trauma surgeons have been led to rely on additional diagnostic modalities to determine the presence or absence of intraabdominal injury [30].

36.5.2. Computed Tomography

Since the 1980s, CT has emerged as the imaging modality of choice for evaluating the hemodynamically stable patient with blunt trauma [10]. It can accurately help in identifying hepatic parenchymal injuries and their grade as well as quantifying the presence of hemoperitonneum and revealing associated injuries in other intra- and retroperitoneal structures [30]. The accuracy of CT in hemodynamically stable blunt trauma patients has been well established. Sensitivity ranges between 92% and 97.6% and specificity is reported as high as 98.7% in patients subjected to emergency CT [31]. The negative predictive value (99.63%) of CT is sufficiently high to permit safe discharge of Blunt Abdominal Trauma (BAT) patients following a negative CT scan. [13].

For an accurate diagnosis the examination should include the body from the diaphragms to pubic symphysis with slice thickness of 5 mm and pitch of 1.5. Scanning time has to be short to reduce artifact due to breathing and motion, especially in non-cooperative

critical patients. Contrast examinations are superior, if the haemodynamic condition of the patient is stable enough, and provide superior information about the densitometric characteristics of various organs and any eventual peritoneal or retroperitoneal fluid collections [32].

36.5.3. Important CT Findings

Major CT findings in hepatic trauma include contusion, laceration, subcapsular hematoma, active bleeding, and vascular lesions, such as pseudoaneurysms and traumatic arteriovenous fistulas, juxtahepatic venous injuries, and periportal low attenuation [33-36].

Hepatic contusion appears on contrast-enhanced CT as a poorly marginated low attenuation area compared with the normal enhancing hepatic parenchyma.

Hepatic lacerations (fig. 36.1) appear as well-defined, linear, or branching areas of low attenuation within the enhancing liver parenchyma. Perihepatic and intraperitoneal blood are common with liver lacerations and indicate tearing of the hepatic capsule.

Hepatic subcapsular hematomas (fig. 36.2) are seen on contrast-enhanced CT as a low-density crescentic collection of blood, typically around the right lateral hepatic margin. A subcapsular hematoma often compresses the underlying hepatic parenchyma, a characteristic that is useful in distinguishing this lesion from perihepatic blood.

Pseudoaneurysms and arteriovenous fistulas are hepatic vascular injuries that have a similar appearance

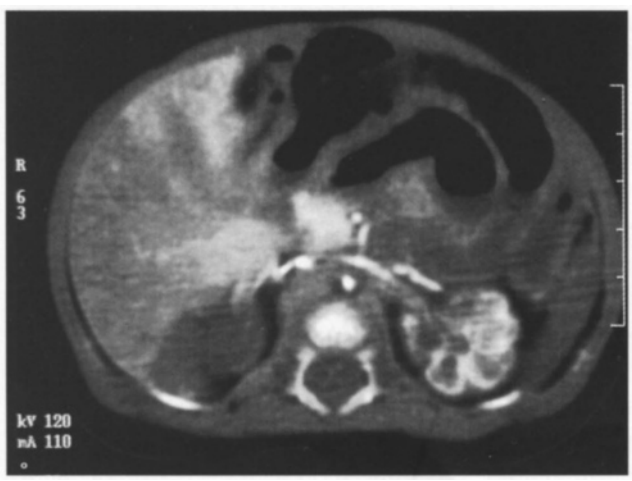

Fig. 36.1. Grade IV hepatic laceration in a paediatric patient.

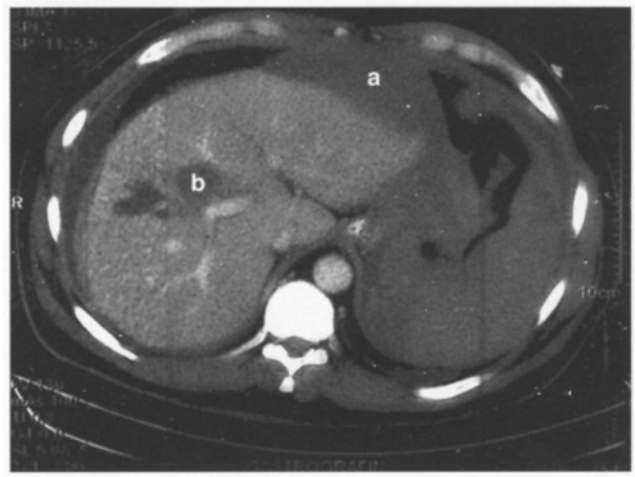

Fig. 36.2. Subcapsular (a) and parenchymal (b) haematoma.

on contrast-enhanced CT. Each of these lesions is seen as a well-circumscribed, rounded, high-density focus, usually surrounded by a low attenuation area.

Active bleeding within the liver (fig. 36.3) appears as an irregular or linear high-attenuation focus of extravasated intravenous contrast material that remains high in attenuation and typically increases in size on excretory phase images. Active extravasation in the liver may be seen in the hepatic parenchyma, subcapsular space, or peritoneum. Active contrast material extravasation at contrast-enhanced CT is a strong predictor of failure of nonsurgical management, recommending prompt surgical or angiographic intervention. The CT attenuation of free intraperitoneal blood measures between 20 and 40 HU, whereas clotted blood or hematoma measures between 40 and 70 HU. Active bleeding measures within 10 HU of the density of the vascular contrast material, seen within an adjacent major vessel. Helical CT has been shown to have 65% to 100% sensitivity and 76% to 85% specificity for detection of arterial vascular injury.

Major hepatic venous injuries are suspected if CT reveals hepatic lacerations or hematomas that extend into one or more major hepatic veins or the inferior vena cava (IVC). Such lesions can be life threatening and are an indication for surgical treatment.

Periportal low attenuation manifests as regions of low attenuation that parallel the portal vein and its branches on CT scans. Periportal low attenuation seen in proximity to a hepatic laceration may represent a

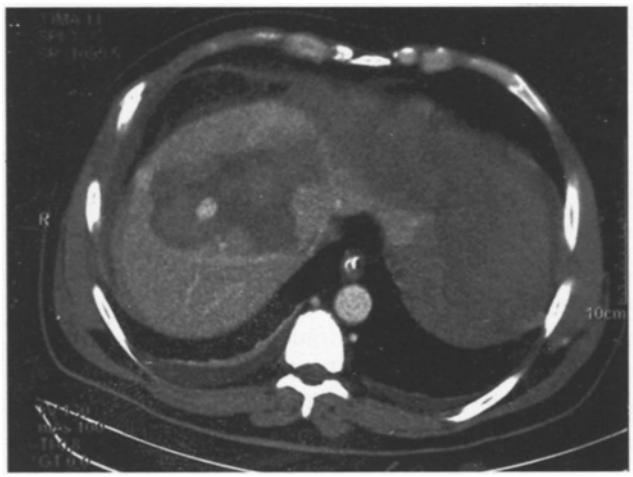

Fig. 36.3. On going liver hemorrhage surrounded by a large haematoma.

hemorrhage dissecting into the periportal connective tissue.

36.5.4. Diagnostic Peritoneal Lavage (DPL)

Diagnostic Peritoneal Lavage has become a well-accepted diagnostic technique in patients with either blunt or penetrating trauma since its introduction by Root in 1965 [9]. The overall accuracy is 97-99%; false-positive rate is 1.4%, false-negative rate is 1.3% and its accuracy is 98.1% [37]. A disadvantage of the method is its inability to help clinicians in determining the origin and extension of a traumatic lesion, often leading to non therapeutic laparotomies [38].

DPL is considered positive if one of the following criteria is met:

- aspiration of more than 5 cc of gross blood,
- red blood cell count of 100,000/mm^3,
- white blood cell count of 500/mm^3,
- Presence of bile, bacteria, food particles, or lavage fluid exited via a Foley catheter or chest tube [39].

The importance of interpreting DPL results in the context of the overall clinical condition of the patient is paramaount. This is especially true, since in the concept of non-operative management, the presence of blood in the peritoneum is no longer considered as indication for laparotomy in the haemodynamically stable patient [30].

The invasiveness of the method and its inability to identify specific organ injury are the main factors that contributed to the decreasing use of DPL. Its role has largely been replaced by the emergency room ultrasound for the hemodynamically unstable patients and the computed tomography scanning for the hemodynamically stable ones. However, DPL still has a definitive role in selected hypotensive patients, especially when ultrasound is either unavailable or nondiagnostic.

36.5.5. Ultrasonography

In 1968, Holm set up the framework for using ultrasonography in the trauma setting [40]. The initial focus of sonographic examination was a single view of the hepatorenal fossa (Morison's pouch). It was soon realized that a more comprehensive examination of the abdomen improved detection of free fluid.

The sensitivity of sonography depends on what is used as the "gold" standard to which US is compared. When sonographic results are compared with clinical outcome, the sensitivity rates of sonography are high, usually more than 95%, while only 63% when sonography is compared with CT or laparotomy and not using clinical observation as a gold standard. The probable reason for this discrepancy is that minor lacerations of the liver may be detected by CT but not by Focused Assessment with Sonography for Trauma (FAST). These patients do not require surgical intervention, and all improve clinically. In general, a positive sonogram proves the presence of intraperitoneal injury, whereas a negative sonogram fails to confidently exclude traumatic organ lesions [41].

There are three main variations on abdominal ultrasound for trauma. Focused Assessment with Sonography for Trauma, solid organ ultrasound, and contrast enhanced ultrasound.

36.5.6. FAST

This includes examinations of perihepatic, perisplenic, pelvic, and pericardial views for free fluid [42] (fig. 36.4). Free fluid typically appears as a hypoechoic region within the peritoneal cavity or pelvis and is usually linear or triangular in shape. Examination of Morison's pouch has the highest detection rate of free fluid in these patients (66%) [43] (fig. 36.5). In the hands of most operators, ultrasound will detect a minimum of

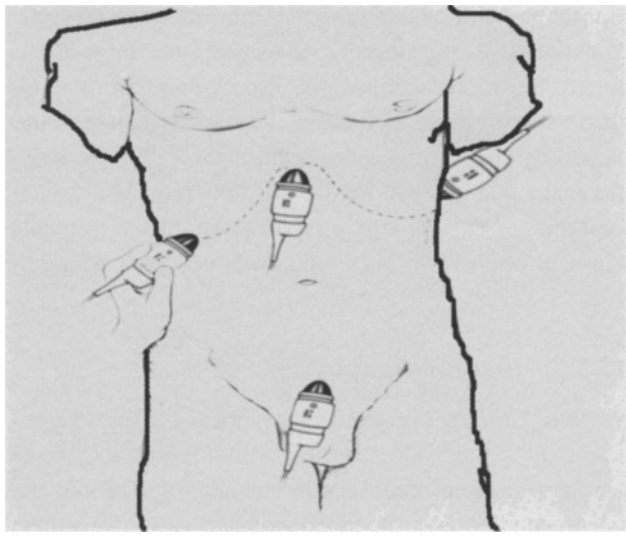

Fig. 36.4. FAST, examining perihepatic, perisplenic, pelvic, and pericardial space for free fluid.

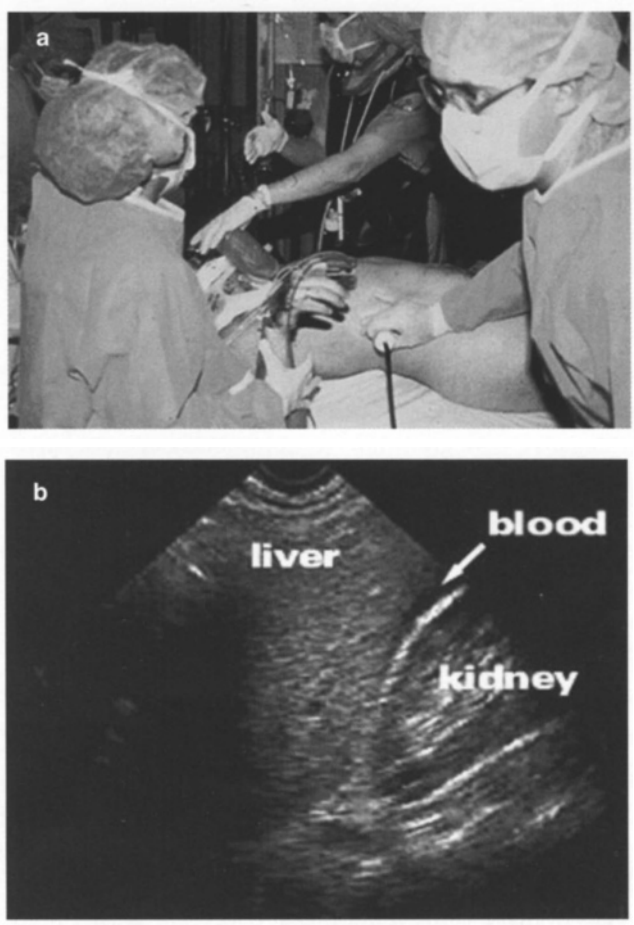

Fig. 36.5. Application of FAST in the Emergency Department (a). Blood is discovered around the liver (b).

200 mL of fluid. Injuries not associated with hemoperitoneum may not be detected by this modality [13].

FAST compares favorably with more traditionally utilized diagnostic tests. In the hemodynamically unstable patient with blunt abdominal injuries, FAST offers a viable alternative to DPL and reduces the mean time to completion of the diagnosis [41].

The main pitfall with locating "fluid" in the abdomen of an unstable patient is the identity and origin of that fluid. In an unstable trauma patient, when doubt exists about fluid identity or its presence, some would perform a DPL or alternatively sterile emergency diagnostic paracentesis under ultrasound guidance [44].

36.5.7. Solid Organ Ultrasound

Sonography is also able to detect parenchymal organ abnormalities but fails to exclude abdominal injuries as accurately, with reported specificity ranging up to 99% and sensitivity near 85%. When identified, acute solid organ injuries are often echogenic. A discrete hyperechoic or diffuse hyperechoic pattern is seen with hepatic injuries [45].

36.5.8. Contrast Enhanced Ultrasound

More recently, contrast-enhanced abdominal US has been used in the evaluation of solid organ injuries in trauma patients [46]. Initially used by cardiologists to improve visualization of the cardiac chambers and wall motion during transthoracic echocardiograms, ultrasound contrast is finding increasing utility in body ultrasound by using a sterile, nonpyrogenic suspension of microspheres of human serum albumin. An echogenic contrast effect is created, enhancing the image by producing contrasted images between the blood, organs, and soft tissue. In this manner, blood flow to and through specific organs can be seen [47]. The ultrasound contrast agent can greatly enhance ultrasound detection of blood flow in normal vessels as well as extravasated blood from damaged vessels. Intrahepatic hematomas are identified best on delayed scans during the latent phase of the contrast agent. The vasculature of each organ is easily seen. The entirety of the hepatic parenchyma is clearly visualized when enhanced with contrast [48]. The impact that this new technology will have on blunt abdominal trauma evaluation has yet to be determined.

36.6. Laparoscopy

Minimally invasive surgery has achieved pre-eminence for certain operations in general surgery over the last two decades, as the reduction in surgical insult has produced faster recovery with enhanced patient satisfaction and favourable health economics [49]. Minimally invasive techniques have been less enthusiastically adopted by the trauma surgical community, despite nearly 40 years of some evidence of efficacy [50]. The modern concept of diagnostic laparoscopy for trauma began in the 1960s, and as clearer indications emerge and technology improves, surgeons in the future will probably incorporate laparoscopy as a diagnostic and therapeutic tool in the traumatized patient [51].

Laparoscopy was found to have reduced the number of nontherapeutic laparotomies performed for hemoperitoneum by 25% [52]. It allows direct visualisation of intraperitoneal structures, but has the disadvantages of invasiveness, cost, a high incidence of false negative examinations for certain injuries and an inability to assess the retroperitoneum effectively [2]. Laparoscopic examination of injuries to the liver and spleen are limited to surface inspection of the damage. Additionally, establishment of a pneumoperitoneum in the presence of diaphragmatic injury may lead to tension pneumothorax [53].

The most effective use of laparoscopy is when it is performed to answer specific questions, such as assessing whether a tangential gunshot wound has breached the peritoneal cavity or not. Laparoscopy has excellent sensitivity (96.2%) and specificity (100%) for determining the need for therapeutic laparotomy [54].

36.7. Decision Making

After initial resuscitation and investigation the question that arises is whether the patient should be managed operatively or non-operatively.

Resuscitation follows standard ATLS principles: maintenance of a clear airway, urgent fluid resuscitation, ventilatory and circulatory support, and control of bleeding. Effective venous access should be obtained and volume replacement started immediately. The patient's blood is grouped and crossmatched and blood samples should be sent for urgent analysis of haemoglobin concentration, white cell count, blood gas pressures, and urea, creatinine, and electrolyte concentrations. Patients should also have a nasogastric tube and urinary catheter inserted.

36.7.1. Selection Criteria for Non-Operative Management

Those patients, who meet the critical criterion of haemodynamic stability and lack of signs that suggest peritonitis, can be managed nonoperatively [19]. The following signs are predictors of a more favourable outcome: absent peritoneal signs or signs localized only in the Right Upper Quartond (RUQ), timely and precise CT scan delineation of the injury (Haemoperitoneum < 500 ml on computed tomography), absence of associated intra abdominal or retroperitoneal injuries on CT that require operative intervention and no excessive hepatic related transfusions (usually limited to four). Most importantly, centres without intensive care facilities and 24-hour access to surgeon and operating theatres should not manage these types of injuries. In order to control bleeding and achieve permanent haemodynamic stability, arterial embolization can be used as an adjunct to initial resuscitation when active arterial bleeding from liver, spleen or pelvic vessels has been shown during contrast enhanced CT scan [13].

Non operative management can be safely applied even in neurologically impaired patients [55] and an initial period of observation in the ICU can be useful until ongoing haemorrhage is excluded. Routine follow-up CT scanning for low-grade injuries is generally considered unnecessary. The clinical picture should guide the need for repeating imaging. Routine follow-up scans for high-grade injuries are contentious and there is a lack of evidence-based guidelines to assist in this regard.

36.7.2. Selection Criteria for Operative Management

Emergency surgery can be necessary either for that subgroup of trauma patients arriving at the emergency department haemodynamically unstable or for patients that were initially treated non-operatively but have deteriorated along the way.

Those patients who remain in shock after 3 litres of intravenous fluid usually have continued bleeding and

require urgent laparotomy. Surgery should not be delayed to obtain the results of special investigations. Along with haemodynamic instability other major indications for urgent laparotomy are stab or gunshot wounds that have penetrated the abdomen, signs of peritonitis, unexplained shock, evisceration, uncontrolled haemorrhage, clinical deterioration during observation [19].

Although the decision of an urgent laparotomy is based almost exclusively on a clinical basis it has been shown that patients with an elevated injury severity score (ISS) present a significantly increased risk of failure of nonsurgical management.

Urgent surgery is recommended as the treatment of choice for patients with DPL findings consistant with bowel injury [56].

36.8. Non-Surgical Management

Non-surgical management was not widely performed until the mid-1990s. From 1995 to 1999, two thirds of all patients subjected to blunt injury, were treated nonoperatively, the percentage among them reaching 80% in the last 2 years. At the same time, patients with penetrating injuries continued, predominantly, to be treated surgically [57]. This shift took place gradually after observations that, by the time of surgical exploration, the injury was frequently found to have stopped bleeding in 50-80% of all patients. The rate of non therapeutic laparotomy in this group of patients was as high as 67% [58]. These two findings set the stage for an overall reassessment of the management of blunt hepatic trauma [59].

Nonoperative management of blunt hepatic injuries has since become the treatment of choice in hemodynamically stable patients. The most important criterion for nonoperative management is that the patient is hemodynamically stable at arrival or is stabilized with minimal resuscitation therapy [60]. Patient selection is the key to success and to present no single selection criterion can predict which patients will fail nonoperative treatment and eventually require celiotomy [61].

Several factors have promoted the use of conservative therapy including:

- The widespread use of new-generation CT scan that enables precise evaluation and grading of solid organs, reveales continuing arterial bleeding and reduces the risk of unrecognized hollow viscous injuries.
- The high success rate and clinical benefits of angiographic embolization as the primary therapeutic option for intra- or retroperitoneal bleeding.
- A better understanding of the natural history and pathophysiology of organ injuries and associated complications.
- A rate of up to 67% of non therapeutic exploratory celiotomies for the conventional management of hepatic and splenic injuries.
- The understanding that operative measures disturb the newly formed clot of a major liver laceration.

Monitoring guidelines include continous recording of systolic blood pressure, hematocrit level, urine output and an estimated amount of liver-related transfusion [4, 62]. Lesions of low or moderate grades (I-III), which represent 80% of all traumatic hepatic lesions, do not need intensive care monitoring [64]. However, there are no known parameters that can precisely reflect the ongoing hepatic hemorrhage occurring before hemodynamic deterioration [63].

Conservative management of liver injury was described initially for grades I-III. Currently, clinical experience has shown that haemodynamically stable patients, even those with complex hepatic injuries (grades IV and V), may be managed non-operativelly in specialized centers [65].

36.8.1. Adjuncts to Non-Surgical Management of Hepatic Trauma

36.8.1.1. *Computed Tomography*

The CT scan remains the first choice for imaging hemodynamically stable blunt abdominal trauma (fig. 36.6). It accurately depicts hepatic, splenic, and hollow viscus injury and can guide safe nonoperative treatment in 80% to 90% of all injured adults [60]. It may be useful for evaluating a change in clinical parameters or patients at high risk or it can be used to document healing. If vessel injury or active bleeding are suspected on the basis of CT scans of a stable patient, angiography should be carried out with the intent of embolizing the bleeding vessel [58].

Follow-up scans within 2 to 5 days can determine changes in the appearance of the injury. Follow up CT

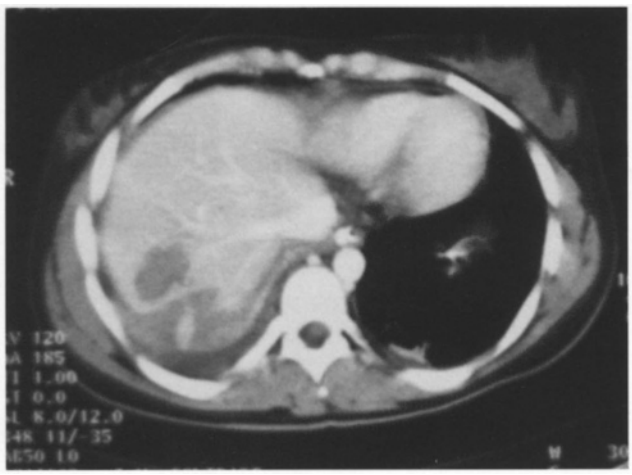

Fig. 36.6. Two patients treated non-operatively with a Grade II laceration and perihepatc free fluid (a) and with a Grade III laceration (b).

scans are not recommended for grade I to III injuries, while for more complex injuries (grade IV-V), they should only be applied on an individual basis [66].

36.8.1.2. *Angiography*

Hepatic angiography is performed to localize a bleeding site. It also allows embolization with Gelfoam pledgets, coils or other devices for bleeding control and it should be carried out in cases of pseudoaneurysms before further bleeding develops (fig. 36.7) [60]. It is also useful in selected patients after surgical hepatic packing, when there is evidence of ongoing arterial haemorrhage [67]. These indications have increased the use of angiography and embolization for hemorrhage control from less than 1% to 9% [57]. The absence of extravasation correlates well with successful nonsurgical management. The sensitivity and accuracy of angiography in the diagnosis of hepatic injuries is high. Hemobilia secondary to penetrating trauma may be localized with arteriography allowing selective hepatic arterial embolization to be performed for treatment [68]. Angiographic embolization is the first-line treatment of delayed vascular complications. The rate of success of embolization of post-traumatic hepatic vascular complications is very high, ranging from 88 to 94% [59]. A mortality of 30% has been reported in those patients suffering grade IV and V liver injuries who were subjected to angiographic embolization as an adjunct to surgery, which is a significant improvement when compared to the 65% mortality reported for those with a comparable grade of injury who had not been subjected to angioembolization [69]. Although gallbladder infarction has been reported to occur in up to 53% of patients undergoing selective right hepatic artery embolization for hepatocellular carcinoma, this complication has not been reported in the trauma literature [70].

36.8.1.3. *ERCP*

About 5% of liver trauma results in a major biliary tract injury [60]. In such cases, ERCP allows accurate localization of the fistula or tear and positioning a stent or nasobiliary drain. If a late biliary stricture is demon-

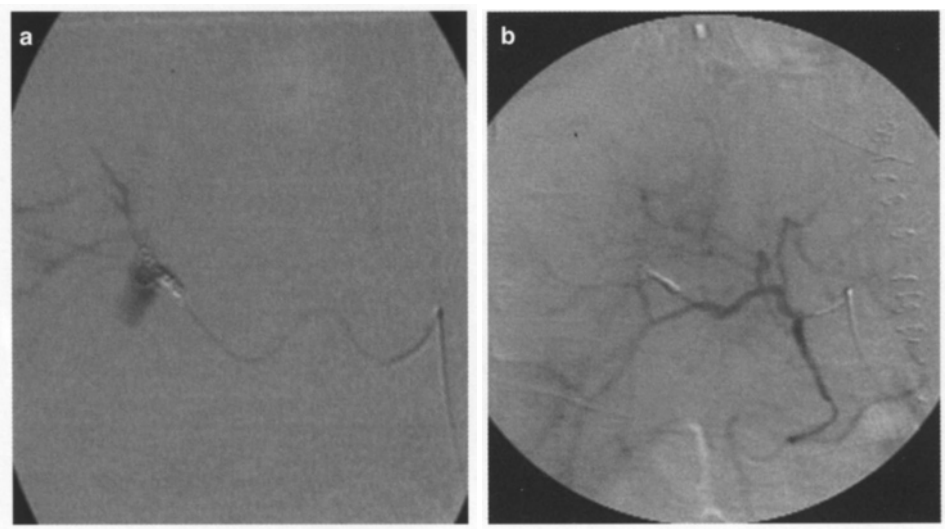

Fig. 36.7. Selective catheterization of a bleeding intraparenchymal artery (arrow) (a). Control of bleeding by coil embolization (b).

strated after hepatic trauma, percutaneous or ERCP-guided stenting can be successful [71].

36.8.1.4. *Laparoscopy*

Although laparoscopy is an operative technique, it is favored by some institutions as an adjunct to NOMLI, because of its minimal invasiveness [72]. It can be used to detect abdominal causes for deterioration of previously stable patients [73]. Nevertheless, owing to the required general anesthesia and the logistical and resource demand, it conflicts with the core principles of non-operative management (NOM) of Liver Injuries.

36.8.2. Outcome

Currently, in the adult population, the success rate of non-operative management of blunt hepatic injury ranges from 50 to 82 per cent [57]. Of those patients, who required an operation after failure of non-operative management, 67% were patients with grade IV or grade V injury. The success rate of non-operative treatment is high both for patients with low grade injuries as well for selected patients with high grade injuries [13]. Besides avoiding a non-therapeutic celiotomy and its inherent complications, it reduces transfusion requirements [4], shortens the length of stay in the ICU [74] and poses fewer intra-abdominal complications [59].

36.8.3. Complications

36.8.3.1. *Unrecognised Hollow Viscus Injury*

The true incidence of hollow viscus injury, associated with significant morbidity and mortality, is quite difficult to assess, with reports varying from 0.7% to 26.5% [75]. Direct surgical inspection and early repair of injuries to the gastrointestinal and bilary tract are the safest and best therapy known. However, routine laparotomy in all trauma patients at high risk of a ruptured bowel is probably not feasible or warranted. If there are no signs of peritoneal irritation, non-operative management should be applied, in conjuction with close for signs of peritonitis which could lead to therapeutic laparotomy [76].

36.8.3.2. *Biliary Injuries*

These are the second most common type of liver associated complications in patients undergoing NOM (bile leak, bile peritonitis, biloma, biliary-venous fistula, and bile duct injury) [77]. Blunt or penetrating hepatic trauma and damage to the intrahepatic biliary tree and bile extravacasion remain a challenging problem. The anatomical disruption to the biliary tree may well be repaired by endoscopic retrograde cholangiopancreatography (ERCP) and stenting [60]. Perihepatic bile collections are currently managed expectantly or by interventional radiologists using percutaneous techniques, with a success rate approaching 70% [78, 79].

36.8.3.3. *Delayed Haemorrhage*

Delayed hemorrhage is the most common complication of the non-operative management of hepatic injury and it is the usual indication for a delayed operation [80]. The incidence of delayed haemorrhage is less than 4% and blood transfusions are required in fewer than 20 per cent of those patients, with most of them requiring less than 4 units of blood [81]. Common treatment errors in patients with delayed haemorrhage include: (1) assuming that the haemorrhage is not related to the liver, (2) treating ongoing liver haemorrhage with multiple (more than four) blood transfusions in the hope that it will stop, (3) misreading the abdominal CT scan and underestimating the amount of haemoperitoneum or active hepatic haemorrhage (contrast "pooling"), and (4) overestimating the amount of blood loss from associated injuries [59].

36.8.3.4. *Intraabominal Abscess*

The rate of intra-abdominal abscesses does not increase with nonoperative management. CT-guided percutaneous drainage of liver abscess is widely accepted as the mainstay of treatment, being successful in 78-100% of cases. All patients with a well-organized intrahepatic abscess should primarily undergo a trial of medical treatment and percutaneous drainage [59].

A major concern is determining the appropriate time for a patient to return to normal activities. In experimental models there is complete liver restoration after 3-4 months but, after 3-6 weeks, the woundbreaking strength of a hepatic injury equals that of uninjured liver [82]. It is also known that a hepatic injury followed by serial CT shows healing within 3-4 months [83]. Currently, most institutes advise patients to avoid contact sports or heavy physical activity for just 8 weeks after liver injury grades III-V [64].

36.9. Operative Management

Although most hepatic injuries can be safely treated by non-operative methods, many patients present or become haemodynamically unstable, even with a low-grade hepatic trauma, necessitating a rapid laparotomy [84]. Most patients require minimal treatment to obtain haemostasis, allowing more aggressive techniques to be reserved for extensive involvement of the hepatic parenchyma [85].

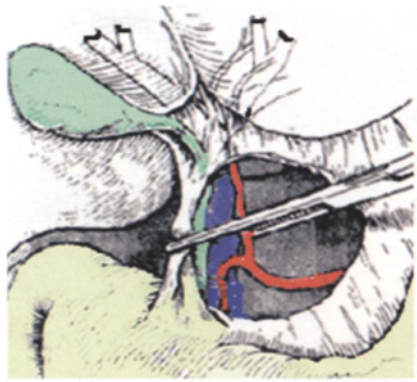

Fig. 36.8. The Pringle manoeuvre.

36.9.1. General Considerations

The principles of operative treatment of hepatic trauma are the same, regardless of the severity of injury. They involve control of bleeding, removal of devitalized tissue and establishment of adequate drainage [86]. Most liver injuries can be properly managed with simple procedures [87]. The aim of treatment when dealing with a bleeding liver wound is to stop the bleeding as quickly as possible, without further jeopardizing the viability of the injured organ [88]. The procedure of choice depends on the nature of the liver wound, the surgeon's experience and the patient's condition [89].

To deal with severe liver trauma, temporary control of hemorrhage and thorough exposure of the injured liver are the preconditions for success.

In surgery, skin preparation should allow the extension of a midline abdominal incision to a median sternotomy or thoracotomy, if necessary, for adequate exposure of posterior liver injuries. If the indication for surgery is a penetrating injury, a bilateral subcostal incision is a useful alternative [90]. Occlusion of the hepatic pedicle by the Pringle manoeuvre can provide a relatively avascular field if retrohepatic venus injury (RHVI) is not present. To expose the liver fully, the ligamentous attachments (falciform, right triangular, and coronary) should be divided to allow rotation of the liver [91].

36.9.2. Techniques

36.9.2.1. *Pringle Manoeuvre*

The occlusion of blood inflow to the liver, performed by clamping the hepatoduodenal ligament with a vascular clamp, is known as the Pringle manoeuvre (fig. 36.8) [7]. It is mostly utilized when active bleeding from a liver wound is encountered during exploratory laparotomy. If the bleeding ceases, the source of bleeding is either branches of the hepatic artery or tributaries of the portal vein. If the bleeding continues, it becomes obvious that we are dealing with laceration of the hepatic veins or retrohepatic vena cava [92]. Occlusion of the portal triad in normothermia is safe for up to 60 minutes without any temporary interruption; there are reports of the Pringle manoeuvre being maintained for up to 85 min without postoperative signs of liver dysfunction [93]. However, it is best to keep the time of occlusion as short as possible, because of the compromised tolerance of the liver to hypoxia in hemorrhagic shock [91]. Recent experimental data suggest the possibility of disruption of the gut barrier after the Pringle manoeuvre, followed by intestinal bacterial and endotoxin translocation, a phenomenon avoided by gut sterilization [94].

36.9.2.2. *Direct Ligation*

This is used for severe parenchymal liver injuries. It is feasible through extension of the liver wound, exposure of damaged vessels and hepatic ducts which can then be directly ligated. Direct suturing of vessels is recommended when the bleeding is from the branches of the hepatic artery or tributaries of the portal vein. Disrupted bile ducts can also be ligated [87].

36.9.2.3. *Resectional Debridement*

Debridement of the devitalized liver tissue down to normal hepatic parenchyma concomitant with suture ligation of the bleeding vessels (resectional debridement) is advocated when one lobe or segment of the liver is severely damaged (fig. 36.9) [95]. The portal

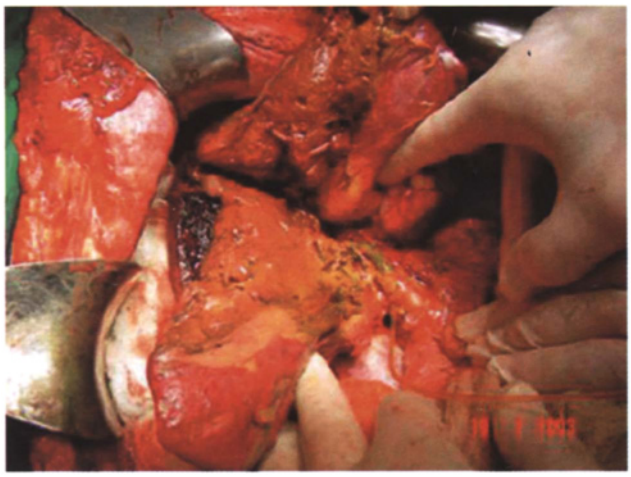

Fig. 36.9. Resectional debridement of damaged liver.

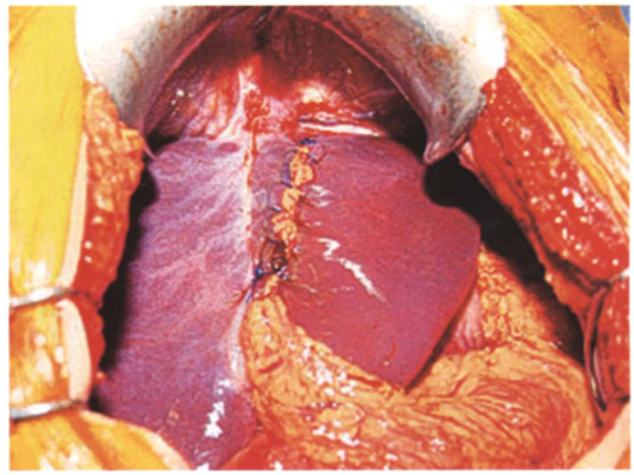

Fig. 36.10. Omental packing.

triad is usually clamped first and the finger fracture technique or an ultrasonic dissector is used to dissect outside the area of injury [96]. Resectional debridement of devitalised tissue is comparatively quick to perform and reduces the risk of postoperative sepsis, secondary haemorrhage and bile leakage [56]. To avoid the formation of a biliary fistula, all involved liver parenchyma with major bile duct disruption must be resected even if vascularization seems adequate [97].

36.9.2.4. *Omental Packing*

For deep liver lacerations with continuous venous bleeding, packing the wound with vascularized omentum and brinking the wound edges together with a few sutures is a useful procedure (fig. 36.10) [98]. The omentum is either partially removed from the left segment of the transverse colon or cut in a "Z" figure, providing its blood flow can be maintained, down to the diaphragm to evenly cover the damaged liver or resected surface [56]. It provides an excellent source of macrophages and fills a potentially dead space with viable tissue [99]. The authors have successfully treated 5 patients with grade IV hepatic injury by omental packing without any complication.

36.9.2.5. *Hepatic Artery Ligation*

In cases where control of arterial bleeding by direct suture ligation is not possible, Dr Aaron's group suggested selective ligation of the hepatic artery, a technique that obviated death in 59 of 60 patients treated [100]. No hepatic insufficiency was recorded among the survivors, as reconstruction of intrahepatic arterial flow is rapidly accomplished by collaterals. When the source of bleeding involves laceration to hepatic veins or and retrohepatic vena cava, ligation of hepatic artery is ineffective [101]. When bleeding cannot be controlled by arterial ligation, the presence of accessory hepatic arteries from the superior mesenteric or left gastric artery should also be suspected [102]. If blood flow to the right hepatic artery is occluded, the gallbladder shoud be removed to avoid necrosis, although this has not yet been completely documented.

The technique is not frequently used because of its association with a high rate of infection and, despite Aaron's report, hepatic insufficiency [103]. Nonetheless, it remains a useful alternative in desperate cases were the source of bleeding cannot be identified or if perihepatic packing fails to control massive arterial haemorrhage.

36.9.2.6. *Parenchymal Sutures*

Hepatorraphy, the placement of large mattress sutures to compress liver parenchyma and bleeding vessels, was one of the first reported successful techniques, but has become unpopular due to significant complications [1]. Most sources of venous hemorrhage within the liver can be managed with parenchymal sutures [104]. These sutures can successfully tamponade injuries, including those of the retrohepatic vena cava and the he-

patic veins, by closing the hepatic parenchyma over the bleeding vessel [99]. However, it has been reported that this technique has given rise to a number of serious complications, such as extensive tissue necrosis which may lead to sepsis [105]. It may, nevertheless, be applicable in minor (grade I and grade II) liver injuries [106]. Fibrin glue has been proposed as an adjunctive technique. It is very effective in controlling oozing from the liver parenchyma and sealing small bile ducts. Report drawbacks include hypotension if it enters the circulation and some concern regarding viral transmission [54].

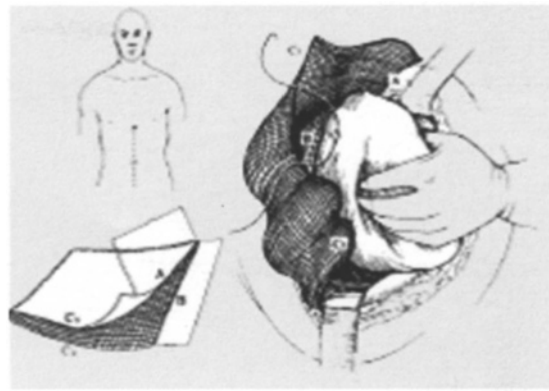

Fig. 36.11. Mesh wrapping.

36.9.2.7. *Anatomic Hepatic Resection*

Anatomic hepatic resection in severe hepatic trauma, presenting a mortality rate higher than 50%, is currently seldom performed, having been replaced by resectional debridement [107]. Exceptionally high mortality, when hepatic resection is attempted in the setting of complex liver trauma, is mainly attributed to the magnitude of the injury, shock, coagulopathy, acidosis and associated injuries [96]. Worthy of mention is the fact that when the same operation is performed by specialized hepatobiliary surgeons, mortality is significantly lower [108]. By definition, this resection is performed along anatomical planes and requires identification of portal structures. On the other hand, complications such as postoperative blood oozing, hemobilia, bile leak, and subphrenic abscess in the survivors undergoing anatomic resection appeared lower than in debridement groups [91]. Anatomic resection can be applied in patients with diffuse parenchymal damage, lacking a clear line of injury through which resection can easily be performed. Its main advantage is that it simultaneously removes the source of bleeding and the site of necrosis [109].

36.9.2.8. *Mesh Wrapping*

The use of this technique is particulary advocated for major parenchymal disruptions (grade III-IV) or for tamponade of large intrahepatic haematomas, in order to minimize the risk of a delayed rupture (fig. 36.11). It has the advantage that a relaparotomy is not routinely required. It is not indicated in situations were hepatic or juxtacaval vein injuries are suspected. If a mesh is placed on the right lobe of the liver, the gallbladder should be removed due to the increased danger of necrosis [110].

36.9.2.9. *Perihepatic Packing*

Perihepatic packing should be the first option for the majority of surgeons faced with severe liver injury (fig. 36.12) [56]. When routine procedures cannot control the bleeding, perihepatic packing is a well accepted technique for severe liver trauma with or without RHVI [91]. Perihepatic packing is performed by using roll gauze packed around the injured liver with or without the placement of a bowel bag [111]. Temporary packing has been used, particularly in patients with hypothermia, coagulopathy and severe acidosis or severe injuries in other intra-abdominal organs, as part of the three step damage control surgery. Its drawback is that the use of gauze packing in bleeding patients results in a 30% incidence of perihepatic abscess, which can be addressed with the timely removal of the gauze packing and adequate antibiotics administration [112, 113]. The packing technique involves manual approximation of the parenchyma followed by placing of dry abdominal packs around the liver and directly over the injury, in an attempt to tamponade the wound [114]. It is strongly emphasized that the gauzes should always be put around the liver and never inside the laceration.

36.9.2.10. *Drains*

Perihepatic drainage with a rubber tube is used in grade IV and grade V injury and has proven helpful in decreasing the incidence of subphrenic abscess and in

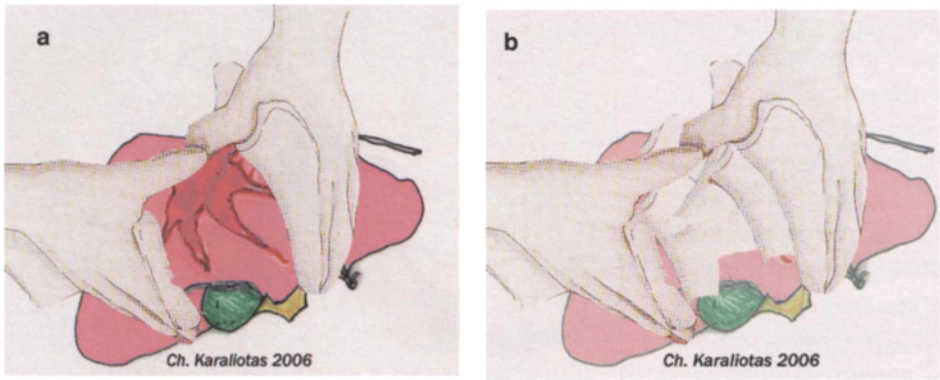

Fig. 36.12. a, Extend liver rupture. b. Perihepatic packing.

observing oozing of blood and bile. Closed rather than open drains are more beneficial because they provide an accurate record of the amount of the evacuated fluid as well as reducing septic complications [95].

36.9.2.11. *Intrahepatic Tamponade with Penrose Drains*

After penetrating liver trauma, the tract may be so long that tractomy would be very extensive. In such cases, several penrose drains can be passed through the tract under tension (fig. 36.13). Once the tension is released the drapes pull back and tamponade the tract. Alternatively, a balloon catheter may be inserted using the same principal [115].

36.9.2.12. *Damage Control Surgery on Liver Trauma*

Damage control (sometimes known as "damage limitation surgery" or "abbreviated laparotomy") is best defined as creating a suitable anatomical environment yet preventing the patient from progressing to an unsalvageable metabolic state. It is the rapid termination of an operation after control of life-threatening bleeding and contamination followed by correction of physiologic abnormalities and definitive management. This modern strategy involves a staged approach to multiply injured patients designed to avoid or correct the lethal triad of hypothermia, acidosis, and coagulopathy before definitive management of injuries [116]. The term damage control originates from the United States Navy, with reference to "the capacity of a ship to absorb damage and maintain mission integrity". This allowed for rapid assessment of the damage, thereafter instituting the best manner of sufficient temporary repair to facilitate expedient return to a controlled environment in port. This analogy of preventing a ship from sinking is even more relevant when one considers the anatomical and physiological damage inflicted on trauma patients [117].

These concepts included the rapid termination of the procedure after control of hemorrhage, continuation of aggressive ICU resuscitation, and return to the operating room for definitive care [118].

Damage control consists of three distinct parts namely initial abbreviated laparotomy ICU resuscitation, and subsequent reoperation for definitive repair.

There are several critical factors that demand for damage control: (a) pH less than 7.30; (b) temperature less than 35°C; (c) combined resuscitation and procedural time exceeding 90 minutes; (d) nonmechanical bleeding; and (e) transfusion requirements surpassing 10 units of packed red blood cells (PRBCs), which should obligate the surgeon to perform an abbreviated laparotomy the base deficit is worse than -18 mmol/L in a patient less than 55 years old [119].

Once the abdomen opening is completed, imme-

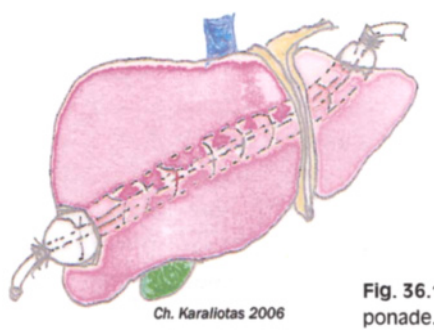

Fig. 36.13. Intrahepatic tamponade.

diate hemorrhage control should commence. The primary method of hemorrhage control for complex liver injuries is packing. Packing is performed using laparotomy pads placed with the goal to compress the source of hemorrhage. Retrohepatic vena caval injuries are treated by anterior packing of the liver, which compresses the vena cava. Other liver injuries frequently require anterior and posterior packing to compress the hepatic parenchyma. The goal is to tamponade bleeding while maintaining organ perfusion. Plastic drapes may be placed between the hepatic parenchyma and the packs to avoid displacement of clots when the packs are removed [114].

When bleeding is controlled, attention is then turned to the contamination control. After a quick inspection of the entire bowel, contamination containment is achieved through the use of simple suture closure or clamping of the visceral perforations. No reconstruction efforts should be made during damage control. Hollow viscus injuries are treated by resection of affected areas using stapling devices. Re-anastomosis is postponed until the patient is stabilized and returned to the operating room for definitive surgery. After controlling hemorrhage and contamination, a decision must be made concerning the temporary management of the abdominal wound. The goals of temporary closure include containment of the abdominal viscera, control of abdominal secretions, maintenance of pressure on tamponaded areas and optimizing the likelihood of ultimate abdominal closure (fig. 36.14) [114].

In cases where arterial bleeding persists, despite intraoperative efforts and damage control surgery, the patient should be transferred to the angiography suite and control of the bleeding by embolization should be performed before transfer to the ICU (fig. 36.15).

Once the abdomen has been temporarily closed, the second phase of the damage control sequence begins – ICU resuscitation with the team's focus on secondary resuscitation in an effort to rewarm the patient and correct the patient's acidosis and coagulopathy. During this effort, an emergent reoperation may ensue, as an unplanned event, in three types of clinical scenarios: (a) ongoing bleeding, (b) missed enteric injury resulting in systemic inflammatory response syndrome and shock, and (c) development of ACS. The aim at this juncture of the resuscitation is to control hemorrhage or contamination and, if necessary, decompress the peritoneal cavity [120]. Once hemodynamic stability has been achieved and the patient is warm and not coagulopathic, the decision to return to the OR for the definitive operation can be made. This return usually occurs within the first 12 to 48 hours after a damage control laparotomy (fig. 36.16).

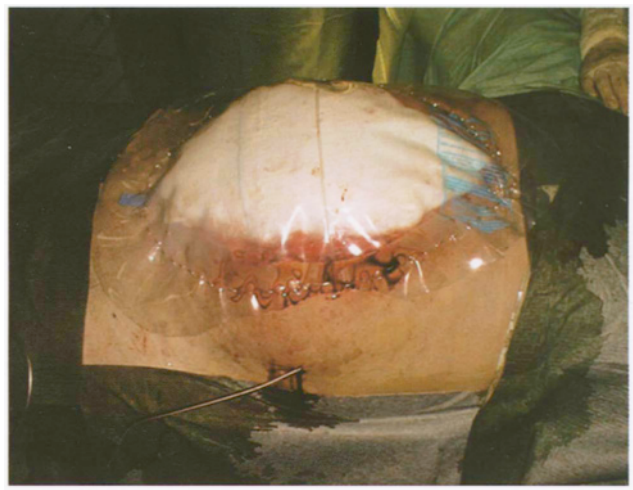

Fig. 36.14. Temporary abdominal closure.

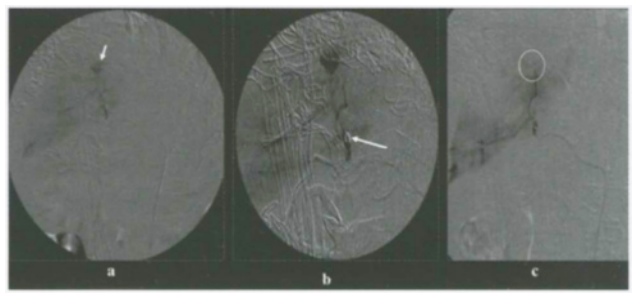

Fig. 36.15. After damage control surgery a patient with ongoing liver hemorrhage underwent angiography. The site of active bleeding was depicted (a, arrow). The bleeding vessel was embolized with coils (b, arrow), while the gauze packing radioopaque material can be seen. The bleeding was finally successfully controlled (c, circle).

Patients who undergo damage control procedures are at high risk of Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Failure (MOF) and death. The independent risk factors for ARDS in trauma patients include the presence of sepsis, transfusion of more than 15 units of packed red blood cells in 24 hours, pulmonary contusion and long bone fractures [18].

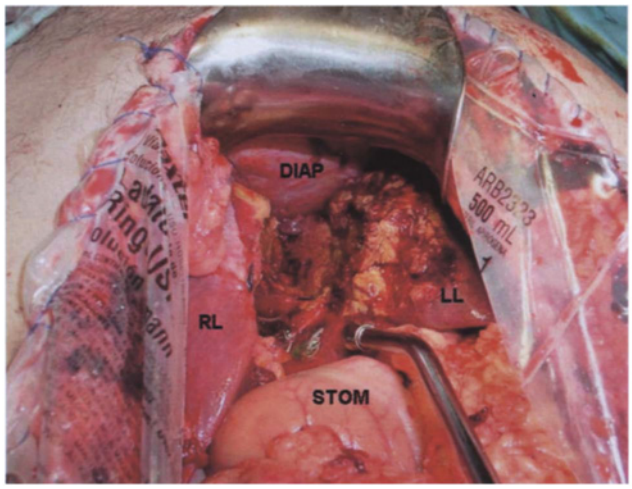

Fig. 36.16. Reoperation. Hepatic laceration after removal of packing.

36.9.3. Outcome

Complications in low grade hepatic injuries are related to associated injuries, whereas in high grade hepatic injuries they are related to the hepatic injury itself and resultant bleeding. The most frequent postoperative hepatic complications include coagulopathy, late hemorrhage, sepsis, pulmornary insufficiency (ARDS) and renal failure [13]. In these patients, an overall mortality ranging from 25-50% has been reported, 40% of which was not liver related [56, 100]. Major complications include ongoing haemorrhage, intraabdominal abscess, bilomas and biliary fistulas [13].

36.10. Conclusion

Despite major advances accomplished during the last 30 years in the management of liver trauma, it remains a deadly disease. Technological innovations such as spiral CT and contrast enhanced ultrasound as well as new applications of older technologies such as angiography and embolization, have contributed to the advent of non-surgical management. For those patients suffering major injury resulting in continuous bleeding and requiring emergency operation, timely application of the principles of damage control surgery is the best option and may be life saving.

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CHAPTER 37

HYDATID CYST OF THE LIVER

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37.1. Introduction - Life-Cycle, Species, Distribution

Hydatid disease of the liver is a parasitic zoonosis, caused by the larval cestode of the tapeworm Echinococcus granulosus [1-6]. The disease was firstly alluded to by Hippocrates. The disease is also mentioned in Talmud [7]. The characteristic of the disease is that the life-cycle typically involves two hosts.

The major "intermediate host" is a herbivore, mainly the sheep (in other cases is the pig, horse, camel etc) which is infected after ingestion of food contaminated with eggs passed from the faeces of the "definitive host", a carnivore mainly the dog [1, 2]. Humans are accidentally infected after ingesting tapeworm eggs [2] (fig. 37.1).

There are four species of Echinococcus (see table 37.1).

The E. granolosus is cosmopolitan; E. multilocularis is mainly limited to the Northern Hemisphere; the other two E. vogeli and E. Oligarthus are indigenous to central and south America.

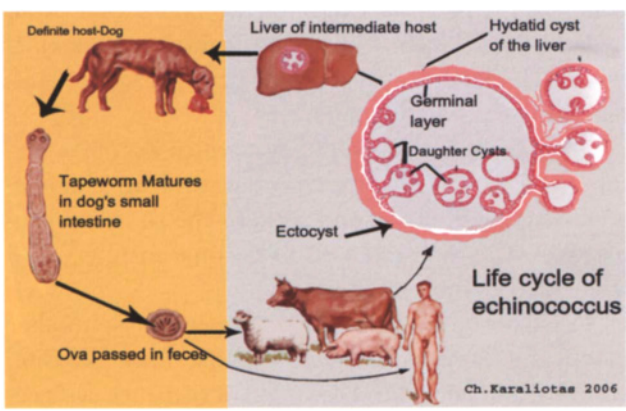


Fig. 37.1. Life cycle of ehcinococcus (by permission of Novartis from "The CIBA Collection of medical illustrations". Utterly redrawn by us).

Table 37.1. The diseases from different species of echinococcus.

Echinococcus species	Caused disease
• E. Granulosus	Hydatid cyst in man
• E. Multilocularis	Alveolar hydatid disease
• E. Vogeli	Polycystic form of hydatid disease
• E. Oligarthus	No confirmed involvement of man

The disease in uncommon in the USA and most of central Europe but remains endemic in Mediterranean countries, Middle East, Turkey, Africa, South America, Asia, Australia and New Zealand [1-3]. There is always a relationship between the definite and intermediate host. The farming practices and the close association which is perpetuated are the main causes of the disease's appearance to rural communities.

The relationship between the intermediate and definite host may be the cycle *Sheep-Dog*, which is dominant in Europe, Soviet Union, Western USA, Mexico and areas of South America and Australia. The *Horse-Dog* cycle is dominant in western areas of Europe, the UK and Ireland, while the *Pig-Dog* cycle in Eastern European regions, Soviet Union, south-eastern USA, Mexico and in Ventral American Countries.

Other associations, like *Goat-Dog*, *Donkey-Dog*, *Camel-Dog* and *Buffalo-Dog* are implicated in the life cycle, mainly in Eastern Mediterranean areas, North Africa, Middle East and India. Wolves and foxes are referred as definite hosts with intermediate hosts sylvan wild animals, resulting in the so called sylvatic cycle in Arctic and Sub-Arctic areas. Sometimes, the two different types of cycle, domestic and sylvatic may interact and human may be infected. This phenomenon very often occurs in Northern Canada and Alaska where indigenous Eskimos and Indians use to feed their hunting dogs on infected offal from moose (large deer living in North America) and reindeer.

37.2. Anatomy of the Parasite - Egg

The tapeworm Echinococcus is less than 0.5 cm in length and has anteriorly a scolex bearing two rows of keratinized hooks and four suckers. These structures, after ingestion, anchor the parasite to the intestinal mucosa of the dog host. Behind the scolex, there are the so called proglottides, 2-6 in number (see fig. 37.2). The terminal proglottis contains several hundred fertilized eggs. The last proglottis is shed every 1-2 weeks in the host faeces and the autolysis liberates the eggs. An infected dog may produce via "its proglottides" up to 120 million eggs every week.

The eggs spherical or ellipsoidal contain the true larval stage (the so called oncosphere with six hooks), host-independent stage, and are surrounded by several envelopes for high protection. The egg is resistant to temperatures from -30°C to 38°C, but susceptible to desiccation.

37.3. Lodging in the Liver-Cyst Structure and Fertility-Daughter Cyst - Secondary Cyst

The eggs penetrate the wall of the intestine of the intermediate host and via the bloodstream they first reach the liver [3, 6, 8], which is mostly affected (60%), proceeding to the lungs (30%), kidneys, brain, spleen, bone, kidney, mesocolon and potentially any other viscera where they develop hydatid cysts [1, 3, 6, 8]. The right lobe of the liver is affected more than the left (80%) and in 1/3 of the cases the cysts are multiple [8].

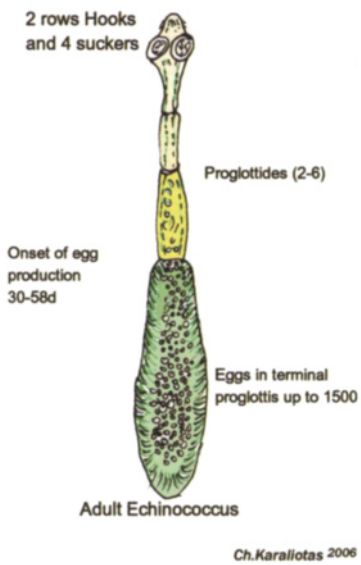


Fig. 37.2. Schematic representation of adult echinococcus taenia.

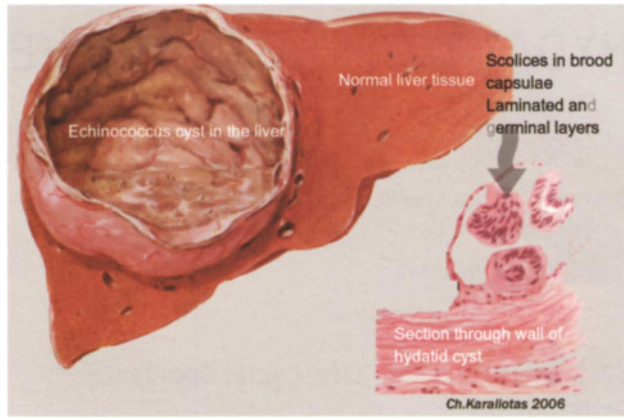


Fig. 37.3. Schematic representation of Liver Hydatid Cyst (by permission of Novartis from "The CIBA Collection of medical illustrations". Utterly redrawn by us).

After the egg has lodged in the liver, and after a hatching of some days (no more than 15) a series of reorganization occur. It includes a transformation and a differentiation of the oncosphere, resulting to a cystic form. At the same time a host reaction occurs and a fibrous adventitial layer is produced from the host liver or other tissue around the cystic form (see fig. 37.3).

The outer adventitial layer coming from the host is called ectocyst or pericyst (fig. 37.4). The two inner layers coming from parasite, the most inner germinal layer and the outer laminated layer together form the endocyst. The germinal layer secretes the laminated layer which is a mucopolysaccharide – protein-lipid complex [9, 10]. The cavity of the cyst contains the hydatid fluid which is clear and similar to interstitial fluid [11]. Old cyst may become calcified at the laminated and the ectocyst parts.

Fertility cyst is called the cyst which becomes mature (fertile), that is to say it produces the presumptive adult stage with hooks and suckers, the so called protoscolex. The time required to become mature varies from 10 to 20 months.

Daughter cysts are identical to the primary (mother cysts) and have both layers coming from parasite, germinal and laminate. The origin of daughter cysts remains controversial. Possibly a source of origin of daughter cysts are the released protoscolices from rup-

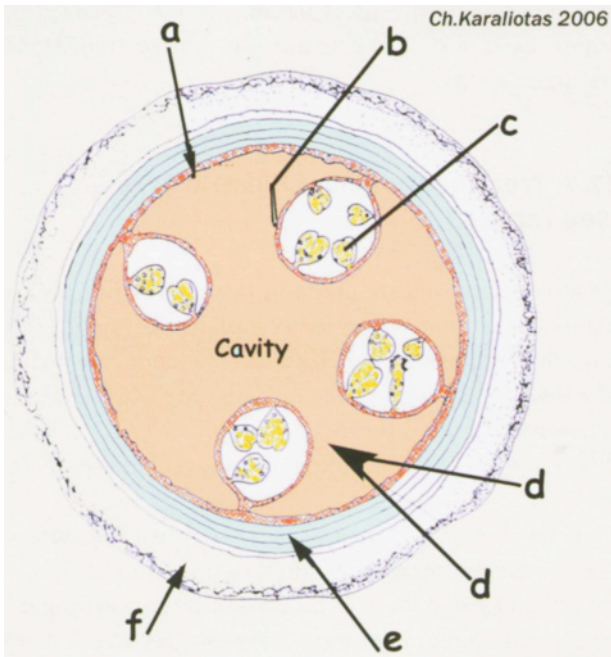


Fig. 37.4. Schematic representation of Liver Hydatid Cyst.
a) germinal layer,
b) daughter cyst,
c) scolices,
d) cavity of primary cyst,
e) laminated layer,
f) host response layer.

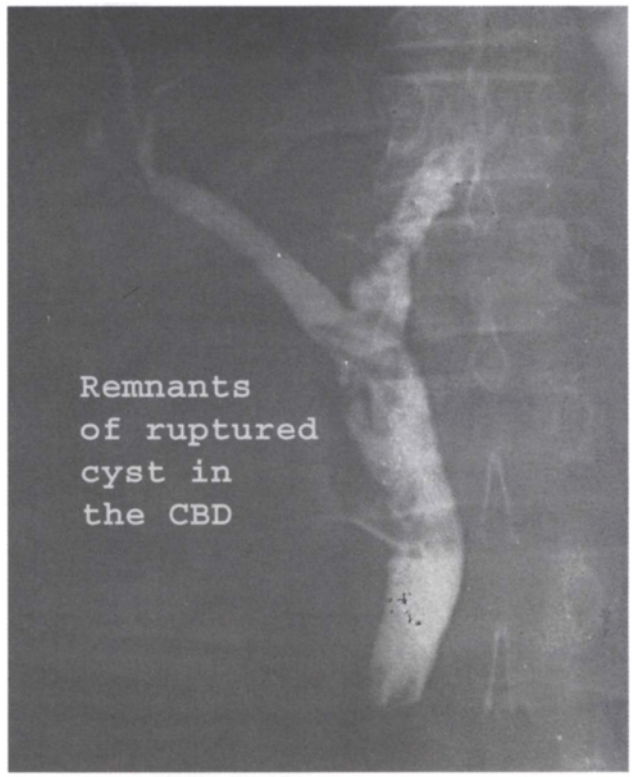


Fig. 37.5. Diagnostic ERCP in a case of obstructing jaundice in liver hydatid cyst. Rupture of liver hydatid cyst in the biliary tract. The cyst was ruptured in the left hepatic duct.

tured brood. Rogan and Richards in 1986 attained to produce cysts in vitro from ruptured brood capsule [12].

Secondary cysts are those developed from primary ruptured cysts and spillage of contents accidentally after trauma or during surgical management.

37.4. Clinical Presentation

The clinical presentation varies and depends on the presence of complications. Most of the cysts remain uncomplicated (82%) [2, 8] and the diagnosis is based mainly on clinical suspicion. The most common symptom in these cases is right upper quadrant pain, liver enlargement or palpable mass [2]. Moreover, in cases of complicated cysts the patients may present nausea, vomiting, weight loss, jaundice, or even fever and peritonitis [5]. This usually occurs in the remaining 18% with a rupture in the biliary tract causing biliocystic fistula (12%) (see fig. 37.5) or the thorax causing bilio-broncheal fistula leading to cholangiitis, biliptysis, chest pain, cough and haemoptysis. Rupture into the peritoneal cavity may lead to anaphylactic shock [5].

37.5. Diagnosis

In addition to the history and clinical examination, the diagnosis is based on a combination of imaging techniques. Ultrasound (U/S) is the major diagnostic tool while Computerized Tomography (CT) offers additional information, especially anatomical details in cases of recurrent or multiple cysts (fig. 37.6a). Imaging determines the morphology, location, number and size of the cysts as well as the status of the biliary tree and the other adjacent or distal organs [5]. Moreover serological or immunological tests (hemagglutination, immunoelectrophoresis) can confirm the nature of the cyst [2, 3, 6].

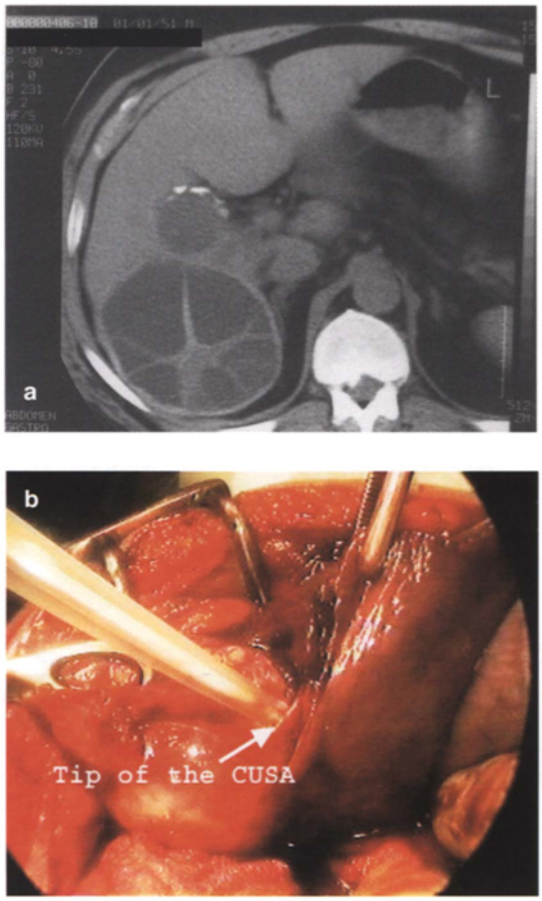


Fig. 37.6.
a. Primary Hydatid cysts in segments V and VI. The smaller cyst seems calcified. In the larger one, multidaughter cysts are clearly visualized.
b. The cysts were totally excised (pericystectomy) using CUSA.

37.6. Classification

Before any intervention, the nature of the cyst should be classified based on the imaging [8]. Based on U/S morphological appearance of liver hydatid cysts, the most acceptable classification is that of Gharbi et al [2, 3, 5, 13]. In this classification, type I reflects a cyst with a pure fluid collection and type V a cyst with a calcified, reflecting thick wall. Between these two extremes lie cysts with variable morphology (detached membrane/ slit wall in type II, multiple septa/daughter cysts in type III and high internal heterogenous echoes in type IV) all pathognomonic of a liver hydatid cyst [3, 5, 8]. The functional state of the parasite is taken into account in the more recent WHO classification where cysts are also classified as active, transitional and inactive [3].

37.7. Treatment of Liver Hydatid Cyst (See Table 37.2)

Treatment options are given in table 37.2. Surgery remains the gold standard for complete treatment [2, 3, 14] while in terms of medication, Albendazole (ABZ) in a dose 10-15 mg/kg/day in 2 divided doses and the active metabolite (after liver metabolism) ABZ sulfoxide seem to be the most effective adjuvant chemotherapy.

It has better GI absorption, tissue distribution and reaches higher intracystic fluid concentration [2, 3]. Despite the fact that there is no consensus concerning the perioperative regiment most authors agree to a 4 week postoperative/post procedure period while the preoperative scheme varies from none to 3 months.

The most popular regimen is that of 7 days before and 28 days after the procedure [5] which can be repeated after 2 weeks with another 28-day cycle. ABZ alone can lead to a cure rate of 10-30% and degeneration of the cyst up to 92% (usually between 50-70%). The treatment can fail in 20-30% of the cases [3, 15]. Despite the fact that the relapse rate is about 3-30% readministration of the ABZ is effective in up to 90% of these patients [3, 16]. The WHO recommends the treatment to start somewhere between 1 month and 4 days before surgery [3].

A systematic review of the literature published in 2004 concluded that chemotherapy alone is not a successful approach and that it needs to be combined with either percutaneous drainage or surgery which remain the cornerstone of treatment [2].

Table 37.2. Treatment options of Liver Hydatid Cyst.

- Chemotherapy.
- Percutaneous drainage.
- Surgery.
  - Radical.
  - Conservative.
    - Approach.
      - Open.
      - Laparoscopic.

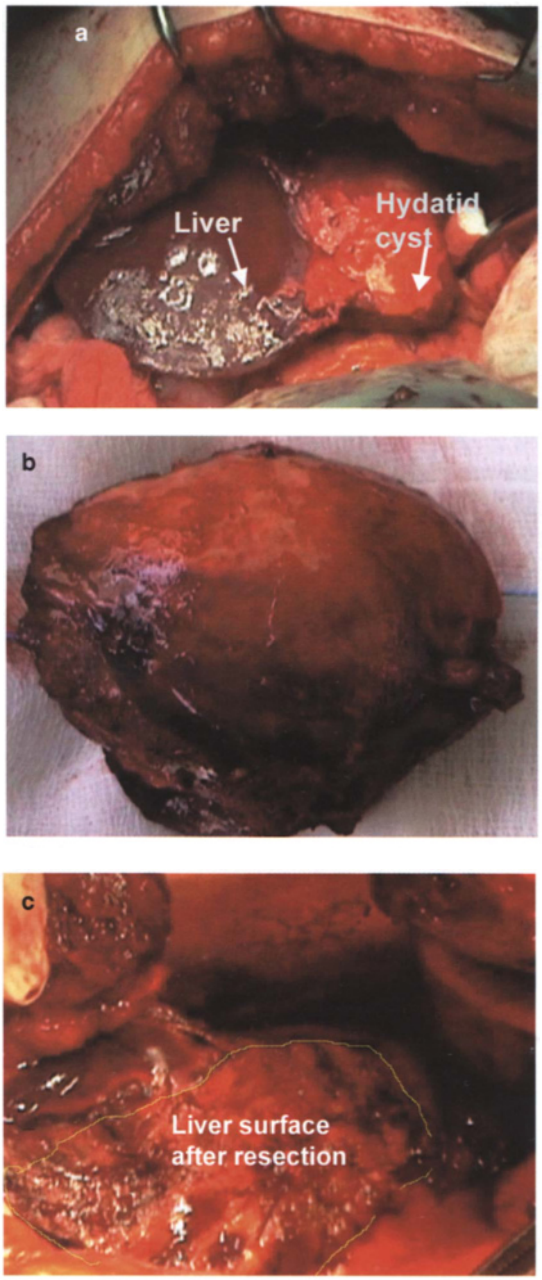


Fig. 37.7.
a. Hydatid cyst of the left liver lobe (segments II and III).
b. Resection of segments II and III.
c. Liver surface after liver resection.

There is insufficient evidence to corroborate more radical approach over a conservative one but it seems that omentoplasty added in any form of surgery is efficient in reducing complications especially abscess formation [2]. Another meta-analysis supports that the percutaneous drainage in combination with Albendazole is a safe and efficient treatment option with more clinical and parasitologic efficacy, lower complications and better postoperative recovery than conventional surgery [1].

37.8. Surgical Management/General Principles

The main principle of surgery is to eradicate the parasite, avoid spillage and obliterate the residual cavity [5]. The principal indications are given in table 37.3.

Table 37.3. Indications for surgery of Liver Hydatid Cyst [7].

- Superficial cysts that may rupture.
- Large cysts with many daughter cysts.
- Cystobiliary communication.
- Mass effect to vital organs.
- Infected cysts.
- Any extra hepatic localized cyst.

There are 2 types of surgical/interventional options: the radical and conservative approach.They aim either to eliminate the whole cyst and pericyst or safely expose the cyst, decompress it, evacuate the contents, sterilize it, control communication with the biliary tree and manage the residual cavity [3].

Known postoperative complications are: seroma, haematoma in the residual cavity, intraabdominal abscess, biliary fistula, spillage recurrence, anaphylaxis [5].

The techniques are classified as tables 37.4 and 37.5 show [17].

37.9. Radical Approach [2, 3, 8, 18]

These techniques eliminate the pericyst and reduce the likelihood of recurrence. Some authors support that morbidity and mortality is less, as is the hospital stay. However, they increase the operative risk for a benign disease and there are limitations of its application [2]. Voros et al support the radical excision, in order to prevent secondary disease from retained extracapsular (satellite) cysts. The authors consider the incidence of satellite cysts as high as 29,5 % [18].

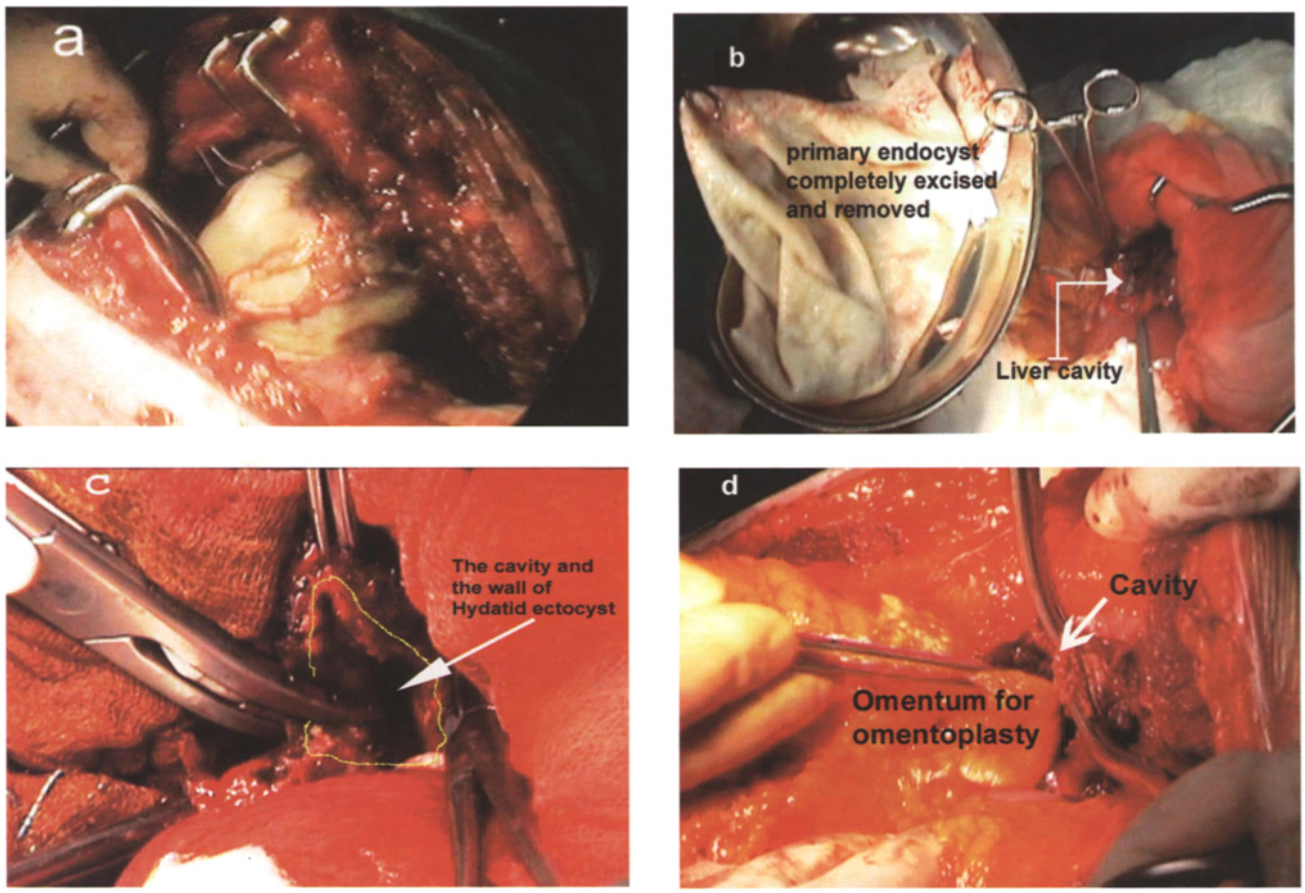


Fig. 37.8. Near total pericystectomy in liver hydatid cyst. a. Removal of the hydatid endocyst. b. Primary endocyst fully evacuated and removed. c. Near total pericystectomy , using Ligasure. d. Omentoplasty.

Table 37.4. Surgical techniques on liver hydatid cyst (fig. 37.6).

Radical approach	Conservative approach
• Pericystectomy (fig. 37.6b).	• External drainage.
• Cystectomy (fig. 37.10b).	• Wide roof excision (unroofing).
• Liver resection (fig. 37.7a, b, c).	• Evacuation and sterilization of the cavity.
	• Capitonnage.
	• Marsupialization.
	• Partial cystopericystectomy.
	• Near total pericystectomy (fig. 37.8 a, b, c).

Table 37.5. Management of the residual cavity in conservative procedures (minimize complications such as abscess formation, biliary cyst communication, bile leakage etc).

- External drain.
- Omentoplasty (fig. 37.8d).
- Capitonnage.
- Muscle flaps (myoplasty).

37.10. Conservative Approach [8, 19, 20, 21, 22]

These techniques are easier to perform with less operative risk but the recurrence rate is higher (10%-30%) [2, 3].

Bile staining of the interior wall of the cyst indicates cyst-biliary communication and the injection of scolicidal agents to the cavity should be avoided since they can lead to sclerosing cholangitis [3]. In cases with preoperative or intraoperative confirmed cyst - biliary tree communication the biliary branches should be found out and controlled either with suturing (see fig. 37.9), bile duct exploration or T-tube insertion (see table 37.6) [23].

Sometimes, when hydatid cysts are present in both liver and lung, or in the case of brocho-biliary fistula

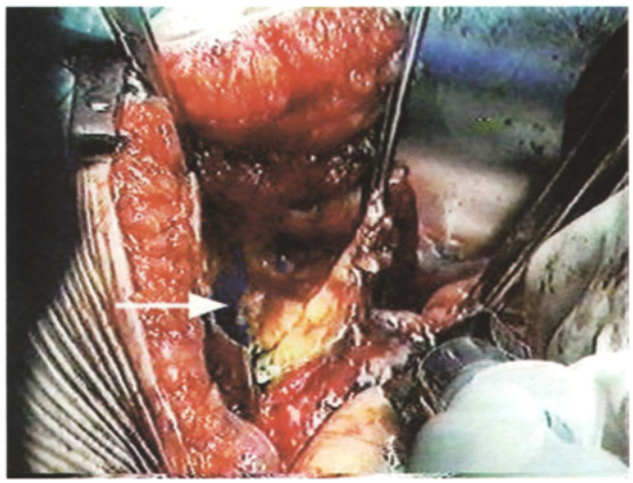
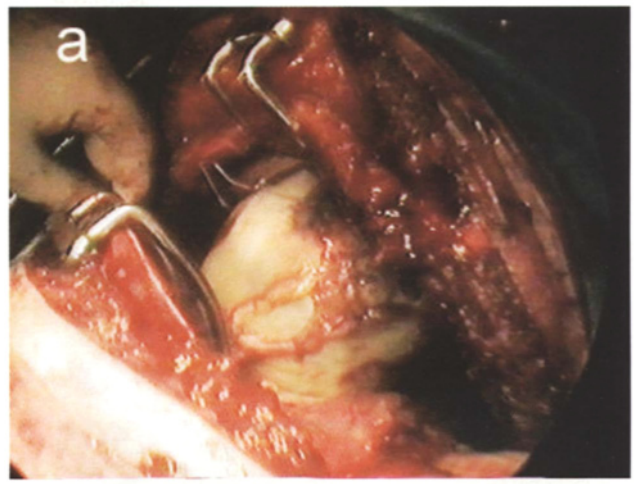


Fig. 37.9. Yellow wall of endocyst (host response layer) strongly supports the communication among cavity and small bile ducts. Since it is difficult to find out the exact points of bile leakage, we perform a retrograde infusion of "blue du methylene solution" via cystic or common bile duct. Blue staining of wall immediately appears. Suturing in obvious communication in order to prevent bile leakage postoperatively is performed.

Table 37.6. Management of bile duct - hydatid cyst wide communication [3,14].

- Choledochoduodenostomy.
- Roux-en-Y hepaticojejunostomy.
- Sphincteroplasty.
- T-tube drainage after exploration of the duct.
- Endoscopic exploration of the CBD can be used (ERCP and ES).



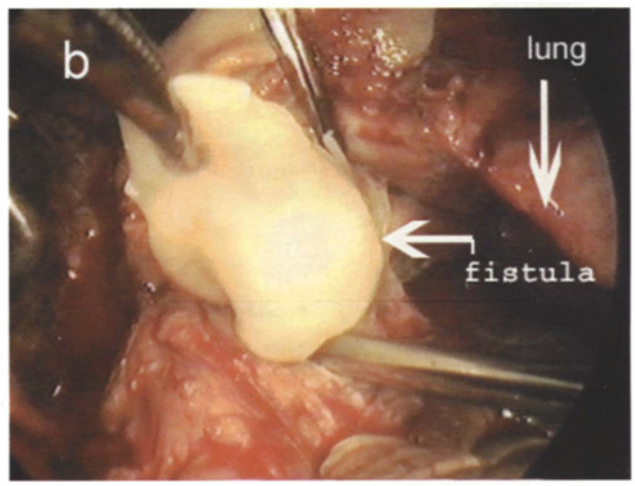


Fig. 37.10.
a. Right thoracotomy (combined excision of lung and liver hydatid cysts).
b. Right thoracotomy-removal of primary lung endocyst.

(see fig. 37.10, 37.11, 37.12) surgeons should consider the thoracotomy approach which offers an excellent access into the liver especially in those cysts lain on the superior-posterior liver segments. Beside the patient suffers only one incision. Many times a combined access by thoracotomy-laparoscopy is preferable.

37.11. Laparoscopic Management of Liver Hydatid Cysts (fig. 37.13)

Despite the advances of the laparoscopic technique and instrumentation, its application to liver surgery is not as popular as its longstanding use in other fields. The specific indication, safety and efficiency of its approach, particularly with regard to the management of hydatid cysts and liver malignancy, remain a subject of considerable controvercy. Meanwhile, increased experience and improvement in instrumentation have been conducive to a progressive expansion of indications. It is already, for example, a new-established approach for the management of benign liver solitary cysts. Nevertheless, the debate concerning the appropriate conditions and indications for management of liver hydatid cysts continues.

The safe laparoscopic approach of such cases demands surgical experience in both open and advanced laparoscopic liver surgery. The technique must be based on the same principles as conventional surgery and should only be applied to those cysts that are easily ac-

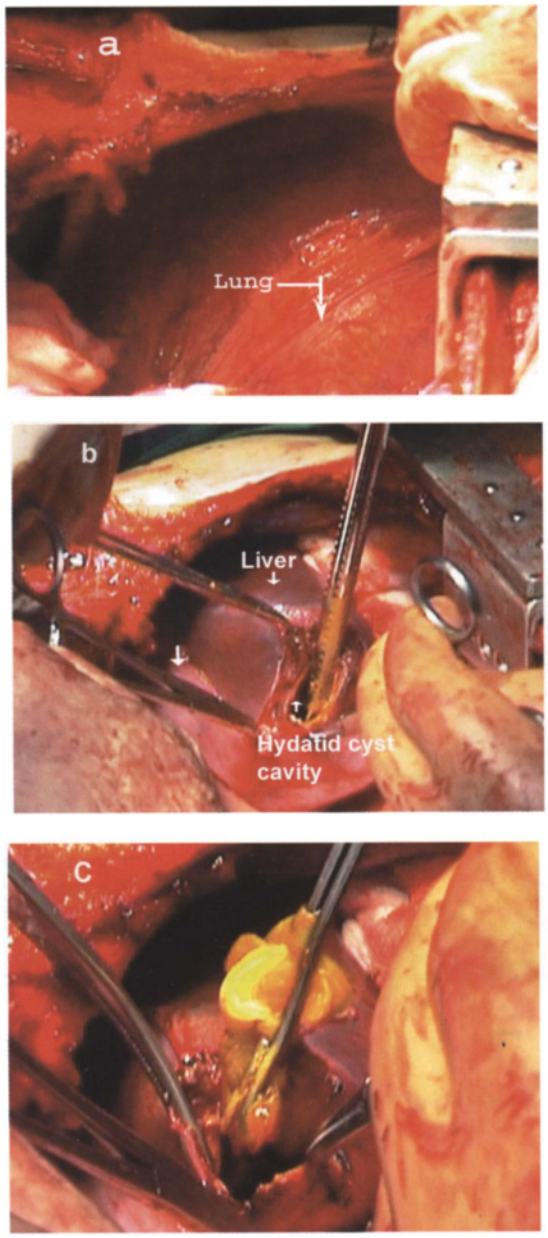


Fig. 37.11.
a. Transthoracic-transdiaphragmatic approach in difficult liver area for hydatid cyst excision (For example segment VII) near hepatic veins and vena cava.
b. Right thoracotomy. Hydatid cyst of segment VIII.
c. Removal of primary hydatid endocyst.

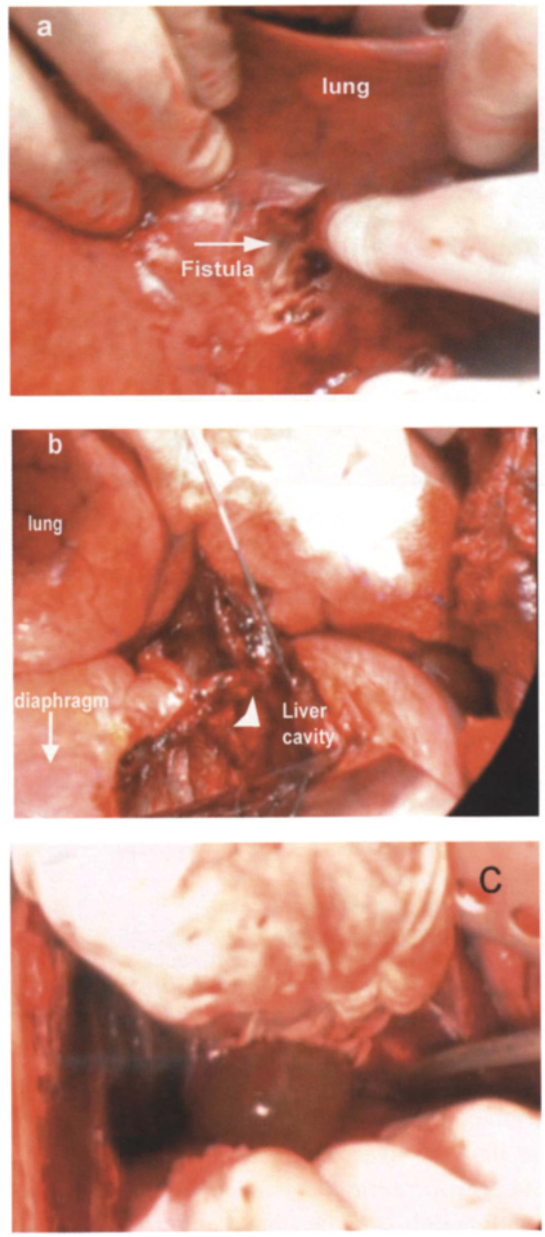


Fig. 37.12.
a. Lung fistula.
b. Liver cyst.
c. Daughter hydatid cyst removed from fistula.

cessible and only when appropriate equipment and technical support are available (table 37.7). Finally, adequate familiarization with the techniques is mantadory [19, 20, 24, 25].

The advantages provided by laparoscopic liver surgery are the better optics and easier control of a possible bile leakage from certain spots on the cyst wall, which represent communication between biliary tree and cyst cavity. Moreover, the postoperative course is better, the mean hospital stay shorter, the mobilization and the recovery of the patient quicker and the dis-

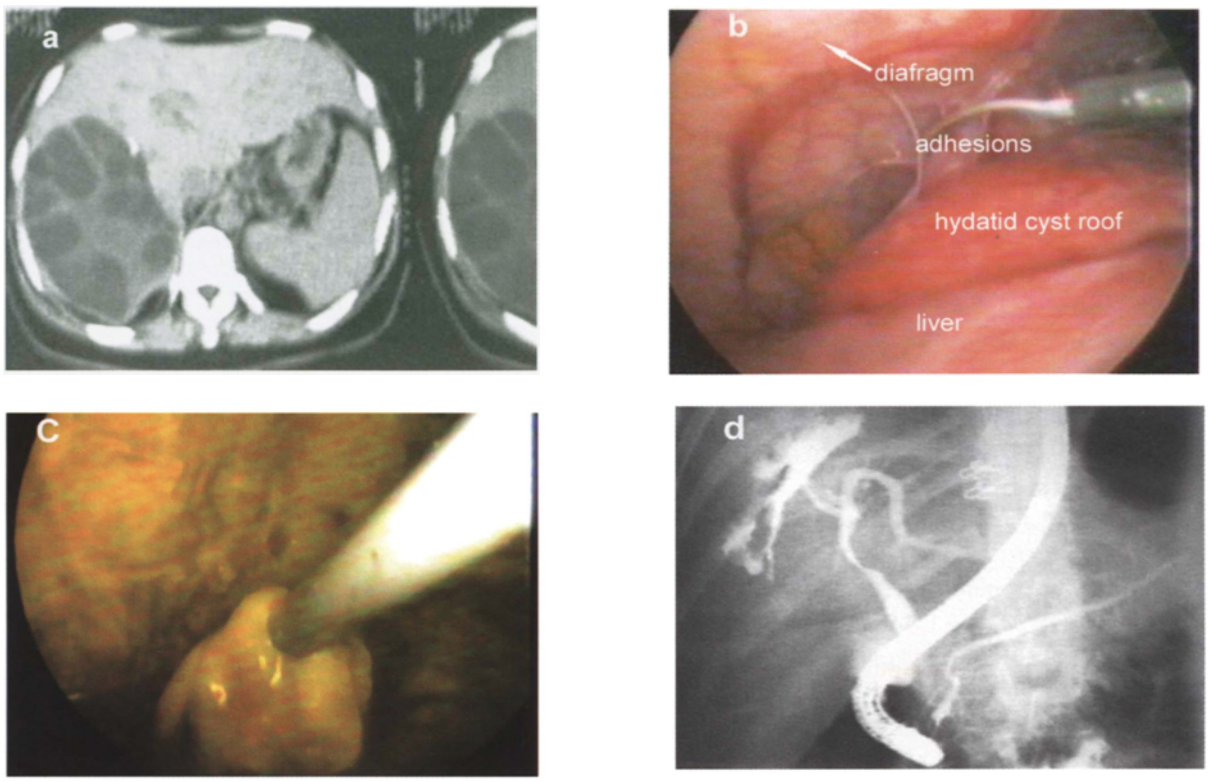


Fig. 37.13.
a. CT of liver hydatid cyst with many daughter cysts.
b. Laparoscopically management of hydatid cyst. Subdiaphragmatic surface of the liver and cyst
c. Laparoscopic view of inner wall of the endocyst, staining yellow.
d. ERCP sphincterotomy 6 days later (communication of the cyst with bile duct).

comfort of the patient less in comparison with the classic open methods. Finally, we have much better cosmetic results [24]. The laparoscopic technique, however, requires extreme caution in relation to haemostasis as a major hemorrhage is difficult to control and the risk of CO_2 infract is high.

Table 37.7. Contraindications for laparoscopic approach.

- Cholangiitis due to communication of the cyst with the biliary tree.
- Cirrhosis and advanced cardiac insufficiency.
- Complicated hydatid cysts with rupture or infection.
- Recurrent cysts.
- Contraindications related to the characteristics of the cyst:
  a. deep intraparenchymal cysts,
  b. cyst located in the posterior segments,
  c. cysts in proximity with the vena cava and hepatic veins,
  d. presence of >3 cysts and
  e. thick calcified wall cysts.

Moreover, the selection of the patients as well as their preoperative work-up study must be thorough and strict [25].

The principles of open surgery should always be respected: careful inspection and exploration of the abdominal cavity, mobilization of the liver, dissection and ligation (clips) of larger vessels, manipulations on the liver parenchyma, bleeding control and sampling for biopsies, bile-cystic communication identification and management [25].

Despite the fact that since 1992 [26] hydatid liver cysts have been submitted to the laparoscopic approach, current evidence comes from individual series, based on selected population and on studies that were neither randomized nor controlled.

Due to subsequent limited experience there is considerable debate on this approach.

Most of the authors agree that it is a safe and effe-

ctive technique with good early and late results, less surgical trauma, lower complication rate, less postoperative pain and need for analgesia, shorter hospital stay and recovery period, with early return to routine activities and jobs, with less morbidity from the wound.

One major concern is the risk of spillage and spreading of the cyst content in the abdominal cavity as well as the risk of anaphylactic shock.

Care must also be taken to neutralize and evacuate the entire germinal layer in order to prevent recurrence [8].

Laparoscopic approach should be applied to those cysts located in the anteriolateral liver segments (II-VI) [19, 20, 22, 24, 27].

Small partially calcified cysts in the anterior segments can be treated with pericystectomy (total excision) [22].

Larger cysts are treated with drainage; the cavity should be evacuated of the living elements and be sterilized. Additionally, external drainage or omentoplasty can be used [22, 28, 29].

The most debatable issue is whether spillage and contamination can effectively be avoided during the initial puncture and aspiration of the cyst.

In order to degenerate the cyst, antiparasitic medications like Albentazole and Meberazole, have been used pre and post operatively [6, 28] as well as of scolicidal agents pre and intraoperatively. Fixation of the cyst in the abdominal wall with specially designed trocars and suction with specific suction devices has also been proposed [14]. Furthermore, an assembled transparent cannula has been described in which a vacuum was created, while its tip adhered firmly to the cyst wall and through which main surgical maneuvers (puncture, parasite neutralization, and complete evacuation) were performed [31]. In an attempt to inactivate any spilled live parasites, Cetrimide (Scolicidal agent) has been used to fill the right sub-diaphragmatic space with the patient in trendelenburg position [14, 31]. Using gauzes soaked with hypertonic saline, as in the open approach, have also been suggested [14] (table 37.8).

Patients who are found preoperatively to have an obvious biliary communication (jaundice cholangiitis) can be treated with ERCP or biliary drainage procedure [14]. Also, if the cyst contains bilious fluid a communication with the biliary tree is possible and the use of scolicidal agent may lead to sclerosing cholangiitis [3, 14].

Table 37.8. Scolicidal agents used by various authors.

- Peroxide solution 10% (most effective) [6].
- Hypertonic saline 20%-30% for 5-10 min [5, 6, 8].
- Cetrimide 0,3% -1% for 4 to 10 minutes [6, 28].
- Chlororhexidine 0.05% [6].
- Alcohol/formalin.
  (Must be avoided since they are associated with sclerosing cholangitis if they reach the biliary tree) [6].
- Polyvinylpirrolidone and N/S [28, 30, 34].

37.12. Results: Literature Overview

The reported morbidity ranges from 8% to 25% while mortality is hardly reported. The mean hospitalization time is obviously less than that for open surgery and ranges between 3-12 days. The recurrence rate lies between 0 and 9% [3, 6, 8].

In the largest series (108 pts) the operating time was 80 min [40-180] with a follow up of 30 months [4-54]. A small percentage (3.6%) of the treated patients had recurrence [32].

Complications were observed in 11% of the patients but there was no mortality [2, 32].

Reported complications include: Biliary fistula, infection of the residual cavity and hepatic abscess, wound infection and recurrence. Moreover, risks involve uncontrollable haemorrhage, spillage in the peritoneal cavity, anaphylactic shock and echinococcal spreading during the initial puncture and aspiration [6, 33].

The hospital stay is about 8-10 days in the uncomplicated cases.

The results seem superior to those of the conventional approach but they are based on selected samples and possibly biased, influenced by the author's enthusiasm to present good results.

Therefore, current evidence supporting the laparoscopic approach, despite encouraging individual results, is insufficient to justify universal application of the technique [2] compelling the need for further prospective randomized and even multicenter studies to be done.

37.13. Technique

Albendazole (ABZ) seems to be an essential adjunct to laparoscopic surgery since, if administered perioperatively, it can prevent recurrences.

A prospective, controlled, randomized study demonstrated that administering Albendazole (10 mg/kg daily) for 1 month was successful in reducing the viability of the parasite by 72% and when administered for 3 months 94% [15].

There is no consensus regarding the duration of treatment but the most popular regiment is that of 7 days before and 28-day after the procedure [5] which can be repeated 2 weeks later (another 28 days cycle). Another effective regiment, for the same agent, without many side effects is a 28 days cycle before the operation and a 2nd a week after the operation and recovery [28]. Finally, regimens with 10 days preoperatively and 3 months postoperatively have been used [6, 14, 34]. In any event, liver enzymes should be checked regularly during the treatment.

37.14. Positioning and Exposure

The patient is positioned either on the inverted "Y" or the simple supine position. The surgeon is standing between the legs or on one side of the table while the assistants on same or the other side. Carbon monoxide pneumoperitonium is achieved either via a veress needle introduced through the umbilical region or by the open (Hasson) technique and abdominal pressure is kept between 12-13 mm Hg to minimize the risks of gas embolism (< 15 mm Hg). The 30 or 0 degree laparoscope is inserted through a subumbilical 10-12 mm trocar and explores the abdominal cavity. The patient is then placed in deep Trendelenburg position and tilted 30° to the right [34].

Two 5mm ports are inserted according to the site of the cyst and are used for palpation, grasping retracting or coagulation. A 10-12 mm subxiphoid trocar is used for the irrigator or suction device.

37.15. Assessment of the Liver Lesion

Inspection of the liver surface and of the position and appearance of the hydatid cyst as well as inspection for any other gross intraabdominal pathology must precede any further intervention.

Laparoscopic U/S is commonly used in liver surgery since it can partially compensate for the lack of tactile sensation and can help assess the size, location, relations and morphology of the liver lesions. It is the most sensitive technique for identifying small hepatic lesions (< 1 cm) [26].

A cholecystectomy and intraoperative cholangiogram can be performed if indicated or in order to improve exposure [26, 28], in which case it is advisable to be done as the first step in order to detect possible bile-cystic communication.

37.16. Conservative Management

37.16.1. Decompression and Inactivation/ Sterilization of the Cyst

The next and most difficult step is to decompress the cyst without spillage [26, 28] which involves controlled puncture and aspiration of the cyst without leaking in the peritoneal cavity and thereafter inactivation of the contents of the decompressed cyst.

Many methods have been described in the literature and with little concordance in the approach of this step of the operation.

37.16.2. Techniques that have been Used for Safe Decompression / Inactivation of the Cyst

- Transabdominal puncture and rapid aspiration via wide port, with simultaneous suction around the spot of the cyst puncture with the laparoscopic suction irrigation device in order to avoid dissemination. Deroofing and emptying of the cyst from the contents followed by sterilization of the cavity with scolicidal agents (Cetrimide 0,3%-1% for 4 to 10 minutes) [8, 28].
- Puncture of the cyst with a veress needle, rapid aspiration of the cyst fluid, reinjection with equivalent volume of scolicital agent (e.g. hypertonic saline 20% +/- Providone iodine 10%) [14, 34], removal after a certain amount of time (e.g. 10 minute) [14].
- Use of a special trocar to either suspend or fix the cyst against the abdominal wall (umbrella like trocar) and therefore minimize the chance of uncontrolled leakage.
- Use of a special perforator-grinder-aspirator (PGA) [8, 14, 34].
- Use of a special transparent cannula with bevelled tip and puncture under continuous suction [14, 34, 35].

- Manipulations aiming to protect the surgical area and avoid dissemination in case of leakage:
  a. Fill up the Right Upper Quadrant (RUQ) with Povidone iodine so as the liver is "drowned" into the solution before any aspiration [26].
  b. Surround the lesion with meshes filled with hypertonic saline [5, 14, 26].
  c. Flood the peritoneal cavity with peroxide solution 10% [6].
  d. Flood the peritoneal cavity with Hypertonic saline 30% [6, 8].
  e. Surround the cyst with gauzes soaked in polyvinylpirrolidone (Povidone Iodine) [30].
  f. Fill up the RUQ with Cetrimide so that the liver flows into the solution before any aspiration [3, 14, 35-37].

Some authors suggest that the use of peroxide is contraindicated since it can increase the intraperitoneal pressure and lead to gas embolus. If injected into the hydatid cyst it may increase intracystic pressure and lead to uncontrolled break of the cyst in the peritoneal cavity with all the unfortunate consequences (anaphylactic shock, seeding) [6, 26]. Complications can be compounded if the peroxide and the cyst contents pass into the biliary tree causing sclerosing inflammation or even gas embolus [6].

Generally speaking, as all manoeuvres are performed in a closed, small, confined space the results cannot be as predictable as in open surgery and complications like hyperosmolar, hypernatremic coma can arise following an attempt to inactivate the cyst contents or during lavage of the remnant cavity. Therefore, an irrigation with Povidone iodine or large amounts of N/S at the end of the procedure may decrease the risk of such complications [26].

If during the initial aspiration a bilious cystic fluid is aspirated a communication can be suspected and scolicital agents should be avoided. The cyst contents should be cleared mechanically [14].

37.16.3. Removal of the Contents of the Cyst and/or Part of the Cyst

All authors agree that the contents of the cysts and germinate membrane must always be aspirated and the cyst cavity explored for biliary communication.

When the cyst is decompressed and evacuated, a wide window in the cyst roof can be created using hook cautery or ultrasonic scissors enabling the laparoscopic camera and other laparoscopic instruments to enter the cyst. The camera and a variety of suction devices -that have been described in the literature- can be used for entering the cyst and aspirating the cyst content, the germinal epithelium and the daughter cysts, if there is any. It is suggested that the trocar and the suction device be wide (> 10 mm) [10].

37.17. Inactivation/Sterilization of the Cyst

It can be done either before or after the removal of the contents of the cyst according to the preference of the surgeon [28].

Injecting scolicidal solutions into the hydatid cyst and packing the operative field with sponges soaked in scolicidal agents have been used to avoid dissemination of the parasite during surgery. An in-vitro study compared 20% saline, 3% hydrogen peroxide, 1.5% cetrimide-0.15% chlorhexidine (10% Savlon), 95% ethyl alcohol, 10% polyvinylpirrolidone-iodine (Betadine). Savlon was found to be the least concentration - dependent scolicidal agent among those studied. Most sponges containing scolicidals killed the scolices after 15 min (20% saline, 95% ethyl alcohol, Betadine and 3% hydrogen peroxide) while lower concentrations of N/S (3% and 10%) were ineffective [38].

In another study based on animal model N/S, 10% Providone iodine, praziquantel, 10% hydrogen peroxide, 10% hypertonic saline, were compared. It was found that the most effective scolicidals were hydrogen peroxide and povidone iodine [39].

37.18. Assess Biliary-Cyst Communication and Treatment of the Residual Cavity

The laparoscopic camera has the advantage of the magnification and the cavity must be checked thoroughly for suspect points of bile leakage. If a leakage is suspected a cholangiogram may help and should be done at this point whereas if hydatid cyst content is identified inside the biliary tree, an open or endoscopic sphincterotomy is indicated [26].

They are controlled with application of clips, cautery or sutures in order to avoid bile leak [28].

In the case of a massive leak, a derivation of the remnant cavity using a "Roux-en-Y" jejunal loop is possible [26].

The operation can be accomplished with insertion of a drainage tube inside the cavity and with the suturing of the window. Alternatively, the operation can be accomplished by omentoplasty rather than external drainage achieving better results [2, 28].

It is recommended that all patients receive a perioperative regimen with Albendazole 10 mm/k/d divided in two doses usually from 7 days to one month before and for one month after to avoid recurrence in case of dissemination [2, 28].

38.19. Laparoscopic Radical Procedure

The aim of a radical procedure is to remove the pericyst and treat the residual cavity [28]. There is a risk of bleeding and gas embolism as well as technical difficulties, but, as experience in laparoscopic liver resections is increasing, this approach seems progressively more attractive. Nevertheless, the indications are limited to those cysts whose anatomic position favors the easy approach and these are the cysts located in the anterio-lateral liver segments (II-VI Couinaud) [19, 26] and mostly to relatively small cysts to avoid a major haemorrhage.

The laparoscopic ultrasound can define the anatomical relations with the vessels and ducts, as well as the actual size and position of the cyst allowing better vascular control. Vascular control can be achieved using endoclips, intracorporeal suturing, harmonic scalpel and ligasure [26]. Also electrical curved scissors and hook can be used [30]. Endoloops and complete vascular control of the larger vessels of the liver is mandatory before dividing them. The argon coagulant should not be used since it increases the risk of gas embolism [26]. Radiofrequencies (RF) have been used for non-anatomical liver resections and this can also be applied for hydatid cysts. With the completion of the resection a cholangiogram should be performed to identify possible biliary leaks; these should be controlled in the same way as has been described for non-radical operations. Injection of methylene-blue solution can help identify the leaking point [40]. The operation should always be completed with drainage of the area.

Main complications are: haemorrhage and liver decompencation with jaundice, deteriorated liver function tests, ascites and sometimes encephalopathy [26].

37.20. Conclusion

According to many authors, the laparoscopic management of liver hydatid cysts, seems to be a safe and effective technique with good early and late results. There is less surgical trauma, lower complication rate, less postoperative pain and need for analgesia, shorter hospital stay and recovery period with early return to routine activities and jobs and less morbidity from the wound. This approach demands experience in both open as well as in advanced laparoscopic liver surgery and is based on the same principles of conventional surgery.

It should only be applied when adequate experience and technical support is available and restricted to those cysts that are easily accessible.

Current evidence supports that percutaneous drainage in combination with Albendazole is a safe and efficient treatment option with more clinical and parasitologic efficacy, lower complications and better postoperative recovery than conventional surgery and should always considered as an alternative. On the contrary, the results for the laparoscopic approach come from individual series, based on selected population and from non randomized or controlled studies added to which the subsequent limited experience sparks a considerable debate on this approach.

The foremost concern is the risk of spillage and spreading of the cyst content in the abdominal cavity as well as the risk of anaphylactic shock.

Despite the fact that current results appear promising further well-planned randomized control studies are needed in order to arrive at safe conclusions regarding this approach.

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CHAPTER 38

HEPATIC ABSCESS

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38.1. Introduction

Hepatic abscess was recognized by Hippocrates as a favorable evolution of local or disseminated infection because it contained the inflammation in a favorable or more accessible location and, when mature, it was treated by incision/coagulation and drainage (i.e. surgery). Based on the quality of the evacuated pus a prognosis would be established. Hepatic abscesses would be invariably fatal, if the drained pus was malodorous, dark or somehow varied from the so-called optimum pus [1]. So, for centuries the treatment and grave prognosis of hepatic abscesses remained unchanged. In 1938, for the first time, Oschner et al. reported a 62% survival rate in series of patients with liver abscesses treated by surgical drainage [2]. Soon after, antibiotics were developed and further improved the prognosis of such a former lethal disease. Surgical drainage remained the mainstay of treatment until the first report of percutaneous drainage, in 1953 [3]. Despite the use of antibiotics and drainage, the mortality of the disease did not changed substantially until the introduction in the clinical practice of computer tomography, in the middle 1960s. Today, further improvements in diagnostic imaging, antibiotic therapy and the wide adoption of percutaneous drainage, have all contributed to improved outcomes in the management of hepatic abscess. These patients still remain mainly under the care of surgeons but they are actually treated mostly by interventional radiologists. Surgery, once the first line treatment, is reserved today for a very few selected cases. Nevertheless, even today hepatic abscess still carries a significant morbidity and a reported mortality ranging from 2.5% up to 30%. This is mainly the result of the shifting pattern of demographics (older patients with associated co-morbidities) and etiology of disease. An increasing number of older patients develop hepatic abscess secondary to ascending cholangitis because of malignant lesions of the biliary tract. Final prognosis is ultimately dictated by the primary disease. For the successful management of hepatic abscesses, early diagnosis and treatment from a multidisciplinary team of specialists is required. For didactic reasons, hepatic abscesses are categorized as pyogenic and amebic, depending on the causative organism. Pyogenic hepatic abscesses are due to bacterial or occasionally fungal infection, while amebic abscesses are caused by the protozoon Entamoeba histolityca. Both conditions share common features and they may overlap considerably in their clinical manifestation but there are major differences in their pathogenesis, clinical course, complications and treatment so, they are considered separately in this chapter.

38.2. Pyogenic Hepatic Abscess

38.2.1. Incidence

Pyogenic liver abscess (PLA) has always been a rather rare finding. In autopsy series, the incidence of this condition has remained fairly invariable over the last fifty years, being between 0.01% and 0.60%, while the incidence based on hospital admissions ranges from 0.04% to 0.007% [4]. Since the advent of antibiotics and the early diagnosis and treatment of intra-abdominal infections, pyogenic liver abscesses occur less frequently. The peak incidence of the disease has shifted from the third and fourth decade to the sixth and seventh decades of life, a reflection of the shifted etiologic patterns. There is a slight male predominance of 58%.

38.2.2. Etiology and Pathogenesis

Pyogenic liver abscesses most commonly originate from

biliary and intestinal sources. The causes of hepatic abscesses are summarized in table 38.1.

Primary hepatic causes include trauma, tumor and ischemia. A small number of liver abscesses originate from secondary infection of neoplastic lesions either spontaneous but, most commonly, as a complication of an intervention such chemoemolization of a hepatocellular carcinoma. Risk factors for developing abscesses have been described, such as advanced age, tumor size greater than 5 cm, gas formation [5]. Every technique of interstitial destruction of liver tumors, ethanol injection, cryoblation, microwave and radiofrequency ablation (RAF), has been reported to be associated with liver abscess formation in a small number of cases. Cholangitis and liver abscess after percutaneous ablation therapy for liver tumors, has been reported in less than 1.5% of the patient treated and the presence of a bilioenteric anastomosis has been identified as the major risk factor [6, 7]. A high index of suspicion and prompt needle aspiration of the ablated lesion is need in patients with liver tumors who develop clinical signs of sepsis following such interventions [8]. Complicated, infected simple or parasitic cysts of the liver can also present as liver abscesses in a small percentage of patients.

Direct extension of an inflammation processes of neighboring to the liver organs, even penetration by ingested foreign bodies have been described as uncommon causes of hepatic abscess formation in a small number of patients [9]. Penetrating peptic ulcers or carcinomas of the upper GI tract, cholecystitis, pancreatitis, and perihepatic abscess could all lead to the development of a hepatic abscess especially in the cases of even small bilioenteric fistulas or communications.

The liver has a dual blood supply via the portal vein and hepatic artery and an amazing capacity of clearing the bloodstream from bacteria through the large number of its own fixed macrophages. When portal pyemia from any intra-abdominal infectious processes occurs, this natural capacity of the liver can be overwhelmed and hepatic abscesses may develop. Appendicitis was once the leading cause of hepatic abscess, while today only 20% of all liver abscesses are secondary to an infection from the drainage area of the portal vein, with diverticulitis, cancer of the GI tract with abscess formation, peritonitis and any intraperitoneal abscess to be the most common causes. Inflammatory bowel disease, pancreatitis, splenic infection and neonatal omphalitis can also lead to hepatic abscess formation via the portal circulation.

Table 38.1. Etiology of Pyogenic Liver Abscesses.

• Primary hepatic (trauma, tumor, cyst)	10%
• Direct extension	3%
• Arterial hematogenous spread	15%
• Portal circulation	22%
• Biliary tract	30%
• Cryptogenic	20%

Disseminated bacteremia, usually gram positive cocci from endocarditis or intravenous drug abuse, but also from any other septic foci, can lead to hepatic abscess formation via the systemic (hepatic artery) circulation. Occasional pathogens such as Pseudomonas species or Candida have been isolated from hepatic abscesses of immunocompromised patients with increasing frequency. Patients with AIDS, organ transplantation, hematological or other malignancy and children with granulomatoses or immunodeficiency syndromes can all develop single or multiple liver abscesses. Other conditions, associated with compromised host defenses, have also an increased risk of developing pyogenic liver abscess. Diabetes mellitus have been associated in 15-20% of patients or even more in some series with hepatic abscess development. Patients with end-stage renal disease (ESRD) on dialysis therapy have an increased susceptibility to bacterial infections and pyogenic liver abscesses developing in such patients have a high mortality rate [10]. Rarely bacteria that normally elicit granulomatous reactions, like brucellosis and tuberculosis, can cause hepatic abscess as a complication of a systemic infection.

Today, ascending cholangitis has replaced portal pyemia as the commonest cause of hepatic abscess formation in over the third of patients and is commonly associated with attempted interventions to alleviate biliary obstruction. Virtually every condition that partially obstructs the bile flow such as choledoholithiasis, benign and malignant strictures, cancer of the bile ducts or the pancreas can lead to liver abscess formation.

Finally, in 15-25% of cases the source cannot be determined, despite thorough clinical and radiological

investigation and they are classified as cryptogenic. It is postulated that they may develop liver abscess formation secondary to an unrecognized source within the portal system.

38.2.3. Morphology and Microbiology

Liver abscesses may be single or multiple. The majority of liver abscesses occur in the right liver, most commonly as a solitary mass. The rest of them are multiple and usually involve either lobes or the right side alone. Isolated or multiple abscesses in the left lobe only are rare. In a recent European report, 76% of the patients had single and 24% multiple PLAs (right lobe 65%, both lobes 22%) [12]. The site and distribution, as well as microbiology of the liver abscesses may give important clues about the underlying etiology. Single abscesses are more likely to be cryptogenic, while multiple are usually due to ascending cholangitis or hematogenous dissemination from a septic foci. Intraperitoneal septic processes give rise to single, predominately right sided abscesses, due to the preferential distribution of portal inflow from the superior mesenteric vein to the right side or simply due to the greater parenchymal mass of the right liver.

Virtually, every bacterium and fungus known to medical microbiology has been implicated as a causative agent of pyogenic hepatic abscesses. Usually, gram-negative aerobes are isolated from blood cultures and/or aspirates. E. coli and Klebsiella are the commonest microbes, reflecting the gastrointestinal origin of these infections in the majority of cases. In a significant number of cases, abscesses are polymicrobial. Lately, anaerobic organisms are more frequently isolated, due to better isolation and improvements in culture techniques. The most common isolates in pyogenic liver abscesses are summarized in table 38.2. Microbiology of liver abscesses could indicate the origin of the infection and carry a different prognosis. K. pneumonia is usually associated with single abscesses of unknown (cryptogenic) origin, while E. coli has been more commonly isolated from multiple abscesses of biliary origin [12]. K. pneumonia is commonly isolated from both blood cultures and aspirates in patients with diabetes mellitus or underlying biliary malignancy [11]. It is also the commonest isolate in Asian patients, both in Asia and the US [13], reported with an increasing frequency

Table 38.2. Microbiology of Pyogenic Liver Abscesses.

GRAM-POSITIVE AEROBES	
• Staphylococci	12%
• Streptococci	18%
• Enterococci	15%
• Others	2%
GRAM-NEGATIVE AEROBES	
• Escherichia coli	45%
• Klebsiella pneumoniae	35%
• Proteus	11%
• Pseudomonas aeruginosa	9%
• Others	7%
ANAEROBES	
• Bacteroides	8%
• Peptostreptococcus	6%
• Clostiridium	4%
• Others	3%
POLYMICROBIAL	40%

Represents median isolates from various reported series

in complex and severe liver abscesses referred to specialized hepatobiliary centers in Europe. In our own experience, K. pneumonia has also been isolated with an increasing frequency from patients with pyogenic liver abscesses of biliary origin, associated with diabetes mellitus and/or malignancy (unpublished data). In another study, K.pneumonia was cultured from specimens from all patients with gas-forming pyogenic liver abscess [14]. Gas formation was attributed to a mixed acid fermentation of glucose.

Liver abscesses occurring from bacteremia arising from a non-gastrointestinal septic focus are more likely to be monomicrobial, most frequently due to staphylococci or streptococci, while in immunodeficient and otherwise immunocompromised patients, fungi or opportunistic organisms may be isolated. Finally, rare cases of salmonella [15], tuberculosis [16] or actinomycosis [17] have been reported in the literature.

38.2.4. Clinical Manifestations

The clinical features may be relatively non specific,

while presentation can range from severe sepsis to an indolent course of malaise and anorexia. The commonest symptoms are fever, abdominal pain and jaundice (table 38.3). The symptoms and signs are either systemic or local. The systemic symptoms are those of sepsis: fever, chills and profound sweating. Malaise and anorexia occur early, along with weight loss, weakness, nausea, vomiting and lethargy. The most prominent local symptom is a dull, constant right upper quadrant pain. Localized tenderness and hepatomegaly may also be present, as well as positive Murphy's sign. Jaundice occurs less commonly. Finally, approximately 10% of patients present with signs of generalized peritonitis, due to intraperitoneal rupture of the abscess.

38.2.5. Laboratory Findings

They obviously reflect systemic infection as well as impairment of hepatic function. Leukocytosis is common and C-reactive protein and sedimentation rate are elevated. Up to two-thirds of patients are anemic, reflecting the chronicity of the clinical presentation or the underlying malignancy. More than 50% of patients have abnormal liver function tests. Alkaline phosphatase and transaminases are elevated in 60-80% of patients, while serum bilirubin is increased in a 30% of them. Serum albumin is usually low (70%), as a nonspecific response to inflammation. Prothrombin time and other coagulation parameters are usually impaired. Abnormalities in liver function tests are usually mild and do not correlate with the clinical picture of severe illness with hepatomegaly and sepsis. The alkaline phosphatase is the most constantly and significantly elevated. Blood cultures are positive in 30-60% of all patients while in 90% of the cases the causative organism can be grown from aspirated pus. Sterile cultures may be due to improper handling of specimens or prior administration of antibiotics. Gram stain of the aspirated pus is also imperative. It detects bacteria in the aspirated pus in 79%; the reported sensitivity and specificity of Gram stain of the liver abscess are 90% and 100% for Gram-positive cocci and 52% and 94% for Gram-negative bacilli [18]. Both blood cultures and Gram stains should always accompany aspirate cultures.

Table 38.3. Clinical manifestations of Pyogenic Liver Abscesses.

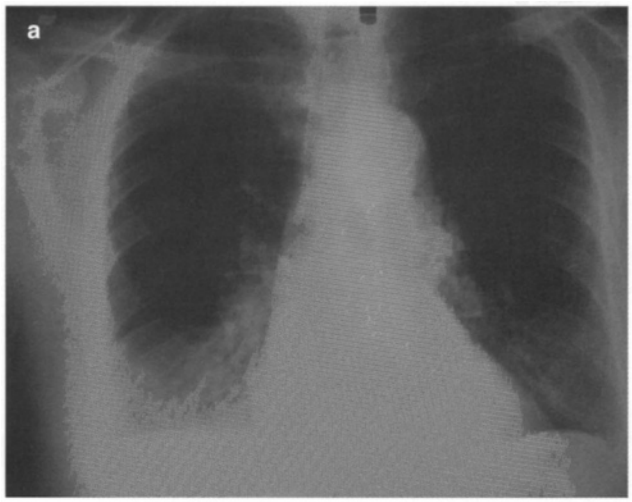
• Fever	83%
• Abdominal (RUQ) pain	63%
• Jaundice	50%
• Anorexia	77%
• Vomiting	27%
• Hepatomegaly	67%
• Septic shock	15%
• Lethargy	8%

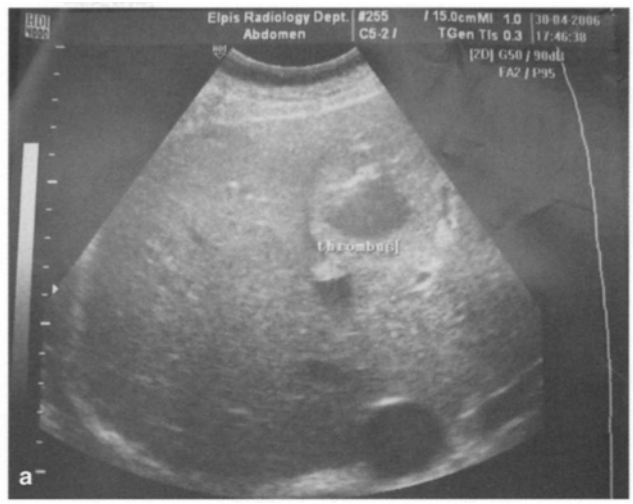
38.2.6. Radiological Evaluation

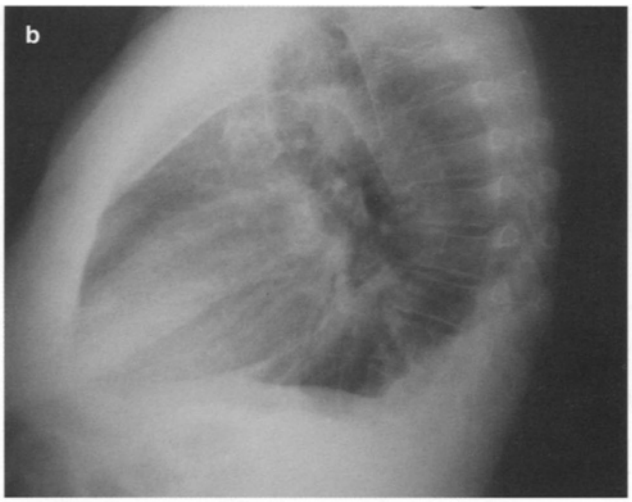
Imaging studies are essential for the diagnosis and treatment of liver abscess. Certain abnormalities observed on chest and plain abdominal x-ray studies may suggest the presence of a liver abscess but are non specific and of limited diagnostic value.

Chest radiograph may show an elevation of the right diaphragm, a right pleural infusion, atelectatic changes in the right lower lobe or obliteration of the costophrenic angle (fig. 38.1). The plain film of the abdomen may show signs of hepatomegaly, gas within the liver parenchyma, gas in a non-operated biliary tree and in the portal vein, suggesting liver abscess, septic cholangitis and bowel gangrene with portal pyophlebitis respectively. In rare cases, the presence of an ingested foreign body or other signs can been observed. Nuclear scans and angiography that were previously widely used, have become obsolete.

Ultrasonography (US), having 75-90% sensitivity, has replaced every other imaging study, as the method of choice for the initial evaluation of the liver. There are variations in the sonographic appearance of a liver abscess, depending mostly on the maturation of the process. Early on, the lesion tends to be less distinct and hyperechoic. It can be echogenic as well as nonechogenic. In the case of non-echoic lesions, variable amounts of internal echoes can be seen. As the abscess matures, the margins become better demarcated and the content typically hypoechoic (fig. 38.2). Occasionally, fluid interfaces can also be detected. Internal echoes can be visualized as a hyperechoic shadow behind the lesion, a useful sign to differentiate solid from fluid-containing lesions. When the pus is very







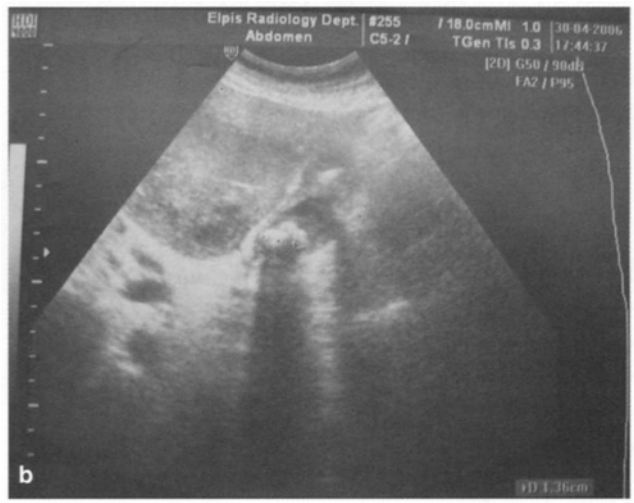


Fig. 38.2. a-b: Ultrasonography shows a characteristic hypoechoic lesion within liver parenchyma, associated with gallstones.

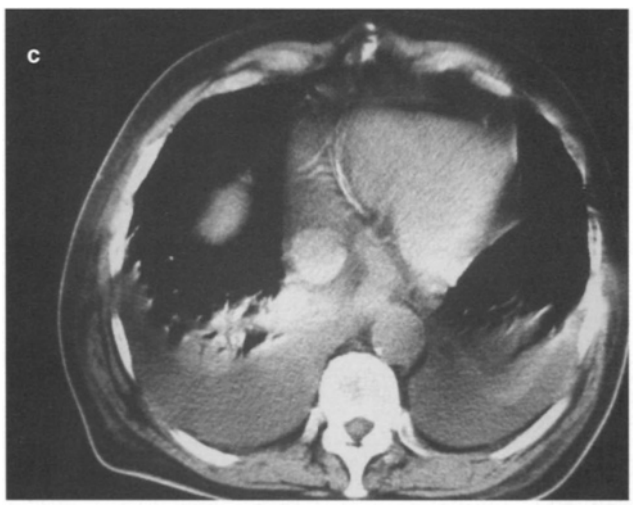


Fig. 38.1. a, b: Chest radiograph shows mild elevation and flattening of the right diaphragm. The patient was initially treated for lung infection. c: Chest CT shows bilateral pleural effusion and atelectasis/consolidation of the right lower lung.

thick or the abscess immature, it may be absent. Its absence does not exclude the diagnosis of a liver abscess. Finally, US may fail to detect multiple small abscesses or an abscess close to the diaphragm. US can also detect many pathological conditions, especially of the biliary tree, associated with the abscess formation. Furthermore, it can be used for a direct aspiration to confirm or treat the liver abscess.

Computed tomography (CT) is an ideal tool for diagnosis and treatment of hepatic abscess. It has a sensitivity of 97% or more and is more accurate than ultrasound in detecting and differentiating a liver abscess from other lesions. Pyogenic abscesses may be classified as either microabscesses (< 2 cm) or macroabsces-

ses. Pyogenic microabscesses may appear as multiple widely scattered lesions similar in distribution to fungal microabscesses in immunocompromised patients, or as a cluster of microabscesses that appear to coalesce focally [20, 21]. The diffuse miliary pattern is caused by staphylococcal infection in patients with generalized septicemia and usually involves both the liver and the spleen. The cluster pattern is associated with coliform bacteria and enteric organisms. It may well represent an early stage in the evolution of a large pyogenic abscess. On CT, a liver macroabscess appears typically as a single round or multiloculated mass with low attenuation. As with ultrasonography, there may be some variations in the appearance of hepatic abscess on CT [22]. A good quality contrast enhanced, three phases helical CT is imperative in the diagnosis, since it relies on the liver-to-lesion attenuation differences [23]. Typically, the lesion itself does not enhance on contrast injection and may be surrounded by a peripheral rim of contrast enhancement (fig. 38.3). It may be round or oval, but may have irregular or lobulated margin. It may be single, multiple or multiloculated. Early on, it may be less demarkated, mimicking tumors or other liver lesions. Gas bubbles or an air-fluid may be seen in only 20% but are diagnostic (fig. 38.4). If there are any doubts about the nature of the lesion, a fine needle aspiration should be performed under either US or CT guidance (fig. 38.5). It is a simple and safe procedure, which will not allow a diagnosis by a Gram stain, but also distinguishes a pyogenic from an amebic abscess, a tumor or a cystic lesion of the liver. An upper and lower abdomen CT scan should always be order in the first place as it may show the origin of the abscess being a silent clinically gastrointestinal abnormality (diverticulitis, cancer etc).

Magnetic resonance imaging (MRI) does not appear to offer any great advantage over CT in the characterization of infective local lesions in the liver. It has, though, a significant role in the diagnosis of biliary conditions associated with a liver abscess development mainly as MR cholangiography.

In conclusion, characteristic changes in US echogenicity, CT attenuation or MR imaging signal intensity and typical enhancement pattern can contribute to the diagnosis of hepatic abscesses and may be sufficient enough to obviate aspiration or histological examination. CT is particular helpful in revealing the presence of calcifications and gas and in detailing the enhancement patterns.

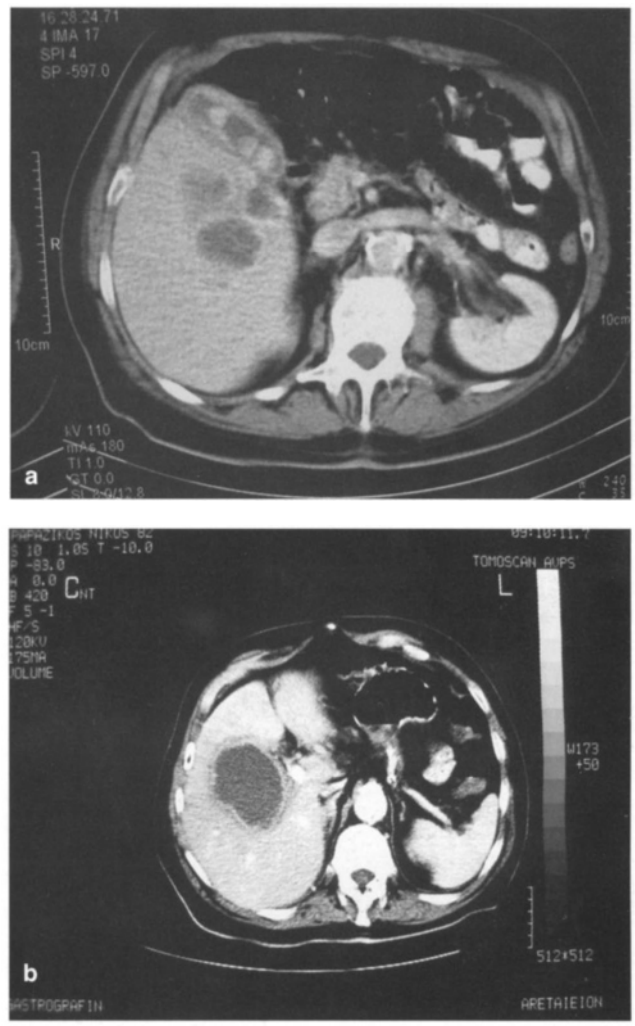


Fig. 38.3. a-b: Low attenuation area within the liver. Loculated liver abscess in close proximity with a mildly inflamed gallbladder full of stones. The lesion characteristically does not enhance on contrast injection, and is surrounded by a peripheral rim of contrast enhancement.

38.2.7. Diagnosis

The clinical manifestations of a pyogenic abscess may be highly variable. Patients may present with the classical triad of high fever, severe right sided abdominal pain and jaundice or may have a clinically occult (cold) abscess, which manifests only as weight loss and vague abdominal pain. Hepatic biochemical abnormalities, including slightly elevated alkaline phosphatase, trans-

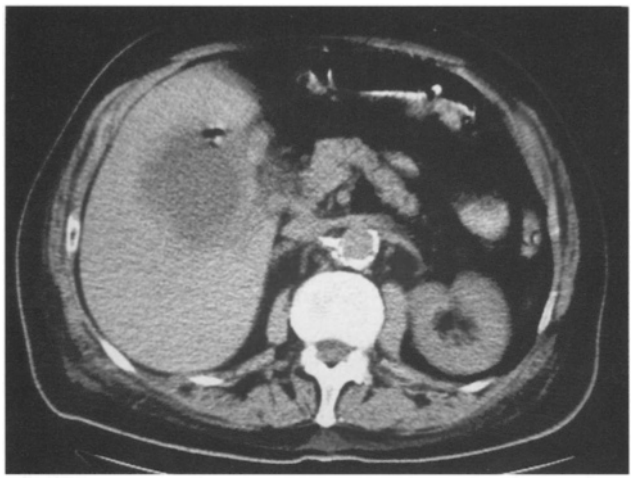


Fig. 38.4. Gas bubbles and air-fluid within a low attenuation liver lesion, characteristic of a liver abscess on CT imaging.

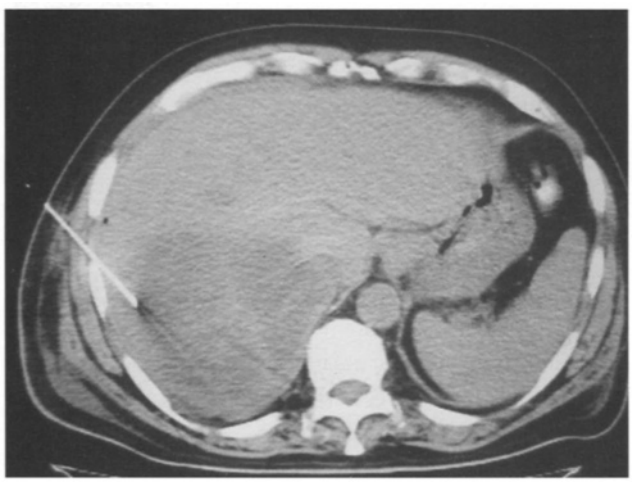


Fig. 38.5. Fine needle aspiration under CT guidance of a liver lesion, proved to be a liver abscess in the early stage of development. Differential diagnosis from a tumor or other focal lesion can be established safely.

aminases and hypoalbuminemia, are non specific. Early diagnosis and treatment is imperative in reducing morbidity and mortality rates, as well as the need for major surgery. It mainly relies on CT and US as they can reliably detect more than 90% of pyogenic abscesses. A vigorous search for the primary source of infection should be always attempted, because it's significant prognostic and therapeutic implications.

38.2.8. Differential Diagnosis

Differential diagnosis of pyogenic abscess includes all infective lesions of the liver, as well as benign and malignant tumors and complicated (infected) simple or parasitic liver cysts (table 38.4). Patients with amebic abscesses are usually more acutely ill, with high fever and abdominal pain; are younger, usually male and come from high-prevalence areas or have a history of recent travel to such areas. While both CT and US are sensitive in detection of amebic abscesses, it is difficult to differentiate from pyogenic abscesses. The amebic abscesses are typically oval or rounded, located near the liver capsule, with attenuation values indicative of complex fluid and an enhancing rim and hyperemia zone are common and somewhat characteristic for this lesion. Serum antibodies are positive in over 90% of patients with an amebic abscess and will establish the diagnosis. Secondary bacterial infection of hydatid cysts may mimic hepatic abscess and will be discussed later in this chapter. Fungal, tuberculosis, granulomatous diseases and other parasitic liver infections will be differentiated on clinical, radiological and serological grounds and the diagnosis established by aspiration/culture of the abscess content. Some times, pyolophlebitis and liver abscess can be misdiagnosed as hepatocellular carcinoma [25]. A cecal tumor with presumably hepatic metastasis can be in fact a pyogenic liver abscess, originating from an inflammatory bowel lesion [26], while solid organizing hepatic abscess mimicking hepatic tumors can be differentiated by the target appearance of the liver abscess on CT and MRI images [27]. In general, CT enhancement patterns and MR imaging signal intensity together with a dynamic interrogation of liver lesions will differentiate pyogenic abscess in the early stages of development from benign and malignant liver lesions. Fine needle aspiration and cytology may be necessary to confirm the diagnosis.

Table 38.4. Differential diagnosis of Pyogenic Liver Abscesses.

- Pyogenic abscess
- Amoebic abscess
- Parasitic liver cysts
- Tumor
- Infected simple liver cysts

38.2.9. Treatment

Once the diagnosis of liver abscess becomes a probability, based on clinical and/or radiological information, management comprises of antibiotic therapy and planning, performing and following-up a percutaneous drainage procedure. Finally, every effort should be made to identify and correct the source of infection, while surgery will be reserved for the treatment of very few cases.

38.2.10. Antibiotic Therapy

The treatment of all patients suspected or diagnosed with a liver abscess will start on antibiotics, independently of any other treatment modality employed. However, antibiotics alone are not sufficient in the treatment of liver abscesses, because bactericidal concentrations of antibiotics may be difficult to be achieved within a walled-off abscess. An adequate drainage procedure is therefore mandatory. Without drainage, mortality higher than 50% is reported, even today. The only indications for the use of antibiotic therapy alone are: (a) in proven cases of uncomplicated amebic liver abscess, (b) multiple small (< 2 cm) abscesses that cannot be drained percutaneously and (c) abscesses that fail repeated attempts at percutaneous drainage in patients who are too ill to undergo a surgical drainage procedure. The choice of antibiotics can be deducted from the microbiology of liver abscess. If the pathogenesis of the abscess is known, the underlying disease provides with some clues to the bacteriology and with that to the choice of antibiotics. As the microbiology of a liver abscess consists of one or more of pyogenic gram-positive cocci (staphylococci and streptococci), gram-negative enterobacteria (E. coli, Klebsiella, Enterobacter, Proteus etc) and anaerobic bacteria, the initial choice of antibiotics should consist either of a combination of an aminoglycoside and ampicillin with metronidazole or a second or third generation cephalosporin with metronidazole. Alternatively, a suitable broad-spectrum beta-lactam antibiotic with satisfactory anaerobic coverage, such as cefoxitin, moxalactam, carbapenems, piperacillin, ticarcillin or mezlocillin, could give reasonable coverage against the commonly isolated organisms. If the abscess occurs in the context of systemic sepsis, staphylococcus aureus or streptococci are the most common etiologic agents, and a penicillinase-resistant penicillin should be administered. If disseminated fungal infection is suspected, especially in immunocompromised patients, an antifungal agent should be given as well. The bacteriological diagnosis should however be established as soon as possible from the percutaneous aspirate and the antibiotic treatment should be modified according to the culture and sensitivity test results. If not drained, the recommended duration of treatment is 4 to 6 weeks in patients with multiple or large abscesses. This may be shortened for small or well-drained abscess, with fast response to appropriate treatment. Intravenous antibiotic therapy may be changed to appropriate oral antibiotic therapy after 2 weeks of systemic treatment. Finally, there is no evidence that antibiotics instilled in the abscess cavity have any advantage over appropriate systemic antibiotic therapy.

38.2.11. Percutaneous Drainage

It is currently the treatment of choice. It entails either a single or multiple percutaneous aspirations of the abscess cavity or a formal percutaneous large bore catheter drainage procedure, under US or CT guidance, with the Scheldinger technique (fig. 38.6). The exact methodology of the procedure is beyond the scope of this book. Local anesthesia and light sedation, proper planning of the procedure with, some times, further imaging to select the access route and appropriate medical preparation of the patient is required. The later should aim at minimizing the risk of hemorrhagic and septic complications. The procedure is ideally used in patients with single or multiple pyogenic abscesses, without concomitant intraabdominal pathology requiring surgical intervention. It is especially suitable in the management of cryptogenic abscesses. It may also used as an adjunct to operative or otherwise correction of the primary condition. It can also be used as a temporizing measure for critical ill patients with uncorrected primary pathology. In most series, the duration of catheter drainage required for resolution ranges from 2 to 14 days.

The first description of percutaneous treatment of a hepatic abscess was by simple needle aspiration and intracavitary antibiotic instillation [3]. Since then, a debate exists between aspiration alone and percutaneous catheter drainage. Percutaneous needle aspiration

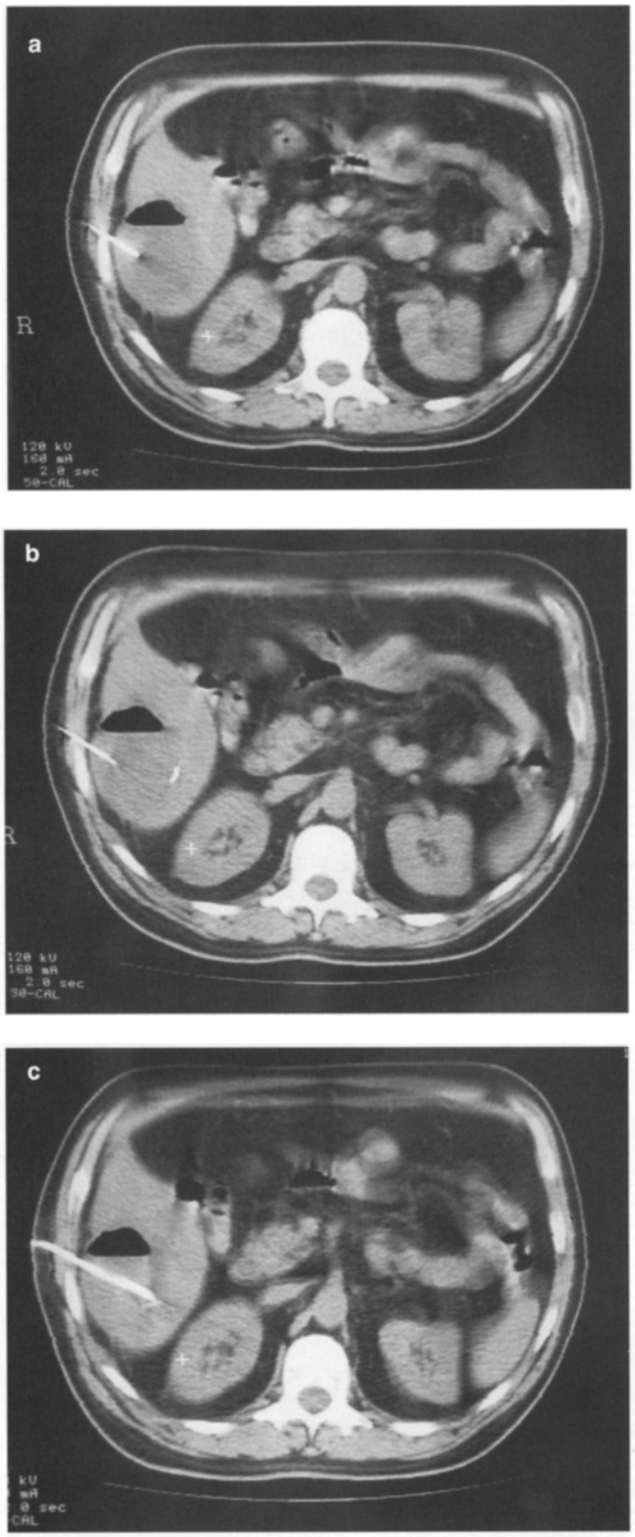


Fig. 38.6. a-b-c: Percutaneous catheter drainage under CT guidance of a liver abscess, by the Scheldinger technique: (a) needle aspiration of a liver abscess, (b) guide wire within the abscess cavity, replaced (c) by a large bore catheter (Courtesy of Dr. A. Koureas).

without catheter placement is favored in some institutions because a single needle aspiration will be adequate in 50% of patients. In a further percentage of patients, repeated attempts of aspiration will result in resolution and the risks of complications and patient discomfort, associated with the use of indwelling catheters, is avoided [28]. In a recent prospective study comparing catheter drainage with needle aspiration the needle group was associated with a higher treatment success rate, a shorter duration of hospital stay and a lower mortality rate, although the later was not statistically significant. Intermittent needle aspiration was found safer than and as effective as continuous catheter drainage and was considered a first-line drainage approach for the treatment pyogenic liver abscesses [29]. Contrary to this report, in another randomized comparison of the two approaches, catheter drainage resulted in complete resolution of all patients so treated, while needle aspiration had a 40% failure rate. Further more, hospital stay was significant shorter in the catheter drainage group [30]. Needle aspiration alone is more likely to be successful in relative small, unilocular abscesses without chronicity and communication with the biliary tree. Our own approach favors catheter drainage of all liver abscesses unless they are small or there are medical or patient related factors of increased risk for such catheter placement [31]. In a small number of patients, aspiration alone should be the first-line approach and if it fails, a percutaneous catheter or surgical drainage will follow.

Percutaneous drainage is not always possible [32]. In a recent study, it was associated with a 15% recurrence rate and a 3.9% mortality rate [33]. A failure rate of 20% has been also reported, which lead to a subsequent surgical intervention. Risk factors associated with failure of the initial non-operative management include multiloculated abscess, biliary communication, increased serum urea, creatinine or bilirubin. Presentation with rupture of the abscess was an independent risk factor. Further more, percutaneous drainage is associated with certain risks and complications. Although empyema is rare, pleural contamination should be considered, especially if the patient does not respond promptly. If a pleural effusion is present, a pleural tap and a tractogram will confirm or exclude the diagnosis.

38.2.12. Surgical Management

In approximately 10% of patients surgical intervention is required [34]. Table 38.5 shows the main indications for surgery. Open drainage of liver abscess is required in all complications, such as rupture into the pleura, pericardial or peritoneal cavities, in incomplete percutaneous drainage or uncorrected primary pathology. Indications for open drainage include multiloculated abscesses, not amenable to percutaneous drainage, and abscesses with biliary communications [35].

Radiological sign of "slough" within the abscess cavity indicate highly viscous material, not amenable to catheter drainage, and require open drainage [36]. In a recent prospective, randomized study comparing open to percutaneous drainage of large hepatic abscesses it was found that surgical drainage was superior to percutaneous approach in abscess larger than 5 cm. It was associated with less treatment failures, number of secondary procedures, shorter length of hospital stay and comparable morbidity and mortality rates. According to the authors, surgical drainage should be considered as first-line treatment of large liver abscesses [37]. This is the only study favoring surgery over percutaneous catheter drainage and should be considered carefully.

Failure to identify and correct the underlying intra-abdominal septic focus is one of the major reasons for treatment failure of a hepatic abscess, resulting in increased morbidity and mortality as well as prolonged hospitalization. Biliary tract benign and malignant lesions are the commonest sources of ascending cholangitis and liver abscess formation. Complicated gallstone disease still accounts for a significant number of these cases and may require either endoscopic procedures or emergency surgery to deal with both the primary condition and septic complications. From the other intraabdominal causes of liver abscess appendicitis has virtually disappeared as a cause of liver abscess, because of the earlier recognition and treatment, but diverticulitis and inflammatory bowel disease still remain important causes [36], as does colonic malignancy. In these cases, surgical correction of the primary cause and open drainage of the liver abscess is advocated (fig. 38.7).

Open surgical drainage can be performed by either a transperitoneal or an extraperitoneal approach. The extraperitoneal approach through the bed of the 12th rib or the transpleural approach through the bed of the 10th or 11th rib was the all times classical approach for drainage of a large abscess, located in the dome of the liver (fig. 38.8). In the past, an anterior subcostal incision with extraserous (extraperitoneal) approach would be employed for the drainage of an anterior hepatic

Table 38.5. Indications for surgical treatment of Pyogenic Liver Abscesses.

- Failure of percutaneous drainage
- Complications of percutaneous drainage
- Multiloculation
- Intraperitoneal rupture/signs of peritonitis
- Septic shock
- Co-existing pathology requiring surgical treatment
- Hepatolithiasis

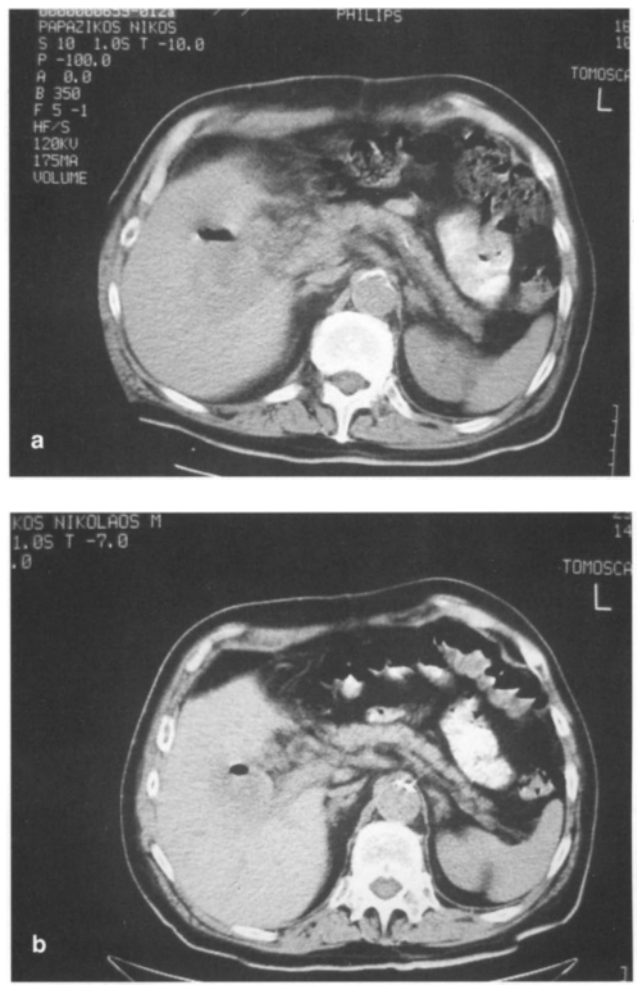


Fig. 38.7. Almost complete resolution of the liver abscess a month later, following open cholocystectomy and surgical drainage on the patient depicted on figures 38.1-38.4.

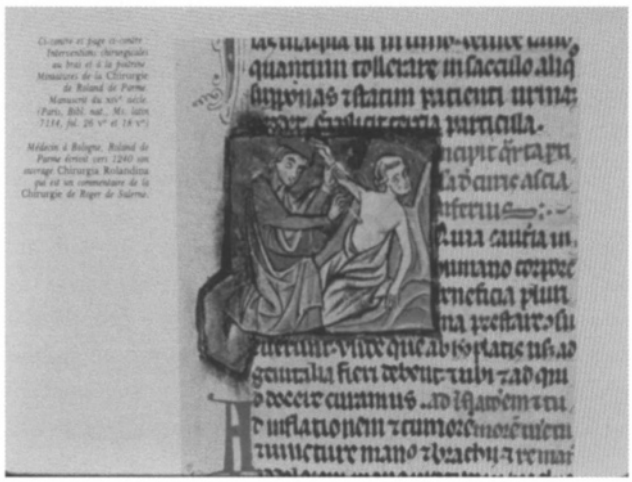


Fig. 38.8. The extraperitoneal approach through the bed of the 12th rib or the transpleural approach through the bed of the 10th or 11th rib was the all times classical approach for drainage of a large abscess located in the dome of the liver.

abscess. Avoidance of contamination of the peritoneal cavity was mandatory in the pre-antibiotics era. Since the introduction of antibiotics in clinical practice, the improvement in surgical techniques and the management of seriously ill patients, the transperitoneal approach became the gold standard as it confers the additional advantages of being able to drain all liver abscesses irrespectively of size and location within the liver, and being able to perform a thorough exploration of the abdomen and address the primary focus as well [33]. Direct palpation and blind needle aspirations have been replaced by intraoperative ultrasonography which can locate precisely any large or small hepatic abscess. Digital destruction of septations and loculations should lead to one large cavity, which could adequately be drained with large bore soft tubes brought out through a stab wound. Closed suction drains are favored by most surgeons. Adequate protections should be taken during the laparotomy for avoiding peritoneal contamination. Postoperative management requires prolonged antibiotic treatment and supportive care, even parenteral nutrition.

The postoperative complication rate is still significant, with recurrent abscess, abscess formation within the peritoneal cavity, metastatic abscess and mainly wound infection to be the most common causes of morbidity following open drainage of hepatic abscesses. If sepsis continued or recurred, repeated CT scans may be necessary to rule out the re-accumulation of pus within the liver, the appearance of additional abscesses or the development of a perihepatic collection.

Laparoscopic drainage of liver abscesses, combined with intravenous antibiotics, is a safe alternative for patients requiring surgical drainage, when medical treatment and percutaneous drainage have failed [38]. There have been numerous reports of successful laparoscopic management of liver abscesses, especially when intraoperative laparoscopic ultrasonography is employed [39, 40].

Finally, surgical drainage of the liver abscess may not be possible or sufficient enough for complete resolution of the liver abscess and hepatic resection may be required [32]. This is more common in cases of uncontrolled sepsis, multiloculated abscesses, infected or necrotic tumors, associated parenchymal destruction due to trauma, long standing biliary obstruction causing liver atrophy, hepatolithiasis or complicated hydatid disease. Hepatic resection may also be more suitable for definitive management of multiple liver abscesses, confined to one lobe of the liver.

38.2.13. Complications

The number of complications of the reported liver abscesses is small, but they may be underestimated. A complication rate as high as 21% has been recently reported [41] but, in that particular study, computer tomography findings were based on routine abscessograms demonstrating a particular high number of communications without direct clinical findings and surprisingly no mortality. Table 38.6 lists the most common complications associated with pyogenic hepatic ab-

Table 38.6. Complications of Pyogenic Liver Abscesses.

• Pleuropulmonary complications	8.6%
• Rupture into the peritoneal cavity	3.7%
• Vascular complications	3.7%
• Rupture into the pericardial cavity	1.2%
• Rupture into the gastrointestinal tract	1.2%
• Rupture into the retroperitoneum	1.2%
• Rupture into the bile ducts	1.2%
• Total of complications	21%

J Comput Assist Tomogr 2004, 28:311-317.

scesses. The pleuropulmonary complications of pyogenic liver abscesses include hepatobronchial fistula, lung abscess and consolidation, empyema and, most commonly, pleural infusion. Serous pleural effusion is common in a variety of subdiaphragmatic, perihepatic or intrahepatic infectious or collections and usually disappears, following treatment of the underlying disease. Rupture into the peritoneal cavity of a liver abscess leads to loculated perihepatic abscess or diffuse peritonitis. Patients are treated with percutaneous drainage of both the intrahepatic and intraperitoneal abscesses, but urgent surgery may be required. Vascular complications in the form of extrinsic compression of the inferior vena cava and portal vein thrombosis occur rarely. Rupture into the pericardial cavity is also quite rare, but is associated with a high mortality rate. It is usually reported in patients with an amebic abscess, though it has also been described in patients with a pyogenic abscess [42]. It is more commonly associated with a left lobe abscesses. Early diagnosis is of paramount importance and pericardiocentesis is a useful diagnostic and therapeutic tool. Rupture of a liver abscess into the bowel, as well as rupture into the retroperitoneum through the bare area of the liver, is extremely rare but has been described. On an abscessogram, opacification of the biliary tree has been reported either as a spontaneous rupture of a hepatic abscess into the bile ducts or, more probable, due an artificial communication following a percutaneous catheter placement. In another study in Taiwan, a 5.7% rate of spontaneous rupture of a liver abscess caused by Klebsiella was observed, and diabetes mellitus, large abscess size (greater than 8 cm), gas formation in the abscess and left hepatic lobe involvement were identified as independent risk factors [43]. Metastatic infections such as lung empyema, endophtalmitis, septic lung embolism, meningitis, epidural and renal abscesses were also observed in these patients at a rate of 14.3%. In another retrospective analysis of patients with pyogenic liver abscesses, diabetes mellitus, alcoholism, bacteremia and Klebsiella pneumoniae infection were associated with a 9.4% rate of extrahepatic metastatic infection. This study implies that the underlying host condition (compromised in diabetics and alcoholics) should play an important role in the development of septic metastases from pyogenic liver abscesses [44].

38.2.14. Outcome and Prognosis

Today, the overall mortality of hepatic abscess ranges from 2 to 35% [45, 46]. In the past, the number of abscesses, the causative bacteria as well as the origin of the infection, the mode of treatment, the presence of complications and the age of the patient had a significant impact on prognosis [47]. These parameters are less marked today. Risk factors are more consistently associated with poor outcome and include preoperative shock, hyperbilirubinemia, hypoalbuminemia, coagulopathy, leukocytosis, diabetes and the presence of malignancy [48]. Even today, the predominant E coli liver abscess has a relative high mortality rate, which is associated with underlying malignancy, multiple abscesses and profound hypoalbuminemia [12], whereas K. pneumoniae has become the predominant etiology for pyogenic liver abscess; mortality from this disease has decreased substantially [49]. With the advances in early diagnosis and treatment [50] by the liberal use of percutaneous drainage, antibiotic therapy and supportive care of these serious ill patients, it seems that the underlying causative pathology increasingly determines the outcome. In the series of patients with the highest mortality, a large percentage of patients suffered from a malignant disease [51].

In conclusion, even today, the overall mortality may be as high as 30%-40% in patients with multiple liver abscess, malignant biliary obstruction, inadequate drainage and immunodeficiency.

38.2.15. Pyogenic Liver Abscess in Children

In the developed world, pyogenic liver abscess is a rare diagnosis in children. Pyogenic liver abscess has been reported as the first manifestation of chronic granulomatous disease. The commonest isolated pathogen was Staphylococcus aureus. Because children are at increased risk of developing portal vein obstruction and portal hypertension, co-existent appendicitis, intra-abdominal sepsis and ascending pyelophlebitis must be sought. Prolonged intravenous antibiotic treatment combined with guided aspiration is highly effective [52].

38.2.16. Pyogenic Liver Abscess in Transplant Recipients

Liver transplant recipients consist a special subgroup of

patients with hepatic liver abscess. In addition to being on immunosuppressive medications, they also present specific complications, such as hepatic artery thrombosis and ischemic biliary strictures or bilomas which may lead to the development of hepatic abscesses. A range of causative pathogens, including Haemophilus parainluenza, Pseudomonas and Candida, have been reported [53, 54, 55]. In some reports, biliary reconstruction by Roux-en-Y hepaticojejunostomy has also been implicated as a risk factor.

38.3. Pyogenic Liver Abscess and Hydatid Cyst Disease

Hydatid disease is a severe and common parasitic disease, endemic to the Mediterranean basin and other sheep-raising areas. Ingested eggs of the tapeworm Echinococcus granulosus invade the intestinal mucosal wall and proceed to the liver via the portal venous system, where the surviving embryos become hydatid cysts. They remain dormant, but they may become infected and present themselves as liver abscesses. While history of recent travel or immigration to endemic areas, as well as the characteristic eosinophilia may suggest the diagnosis, unfortunately, serology is positive in only 25% of the patients. Differential diagnosis relies heavily on current imaging techniques. Ultrasonography findings vary and range from purely cystic to solid-appearing pseudotumors. Daughter cysts and the water-lily sign are characteristic but not always present. Calcifications may also be seen. At CT it appears as well defined, hypoattenuating lesion with a distinguishable wall. Coarse wall calcifications are present in 50% of cases and daughter cysts are identified in approximately 75% (fig. 38.9). MR imaging with its superior contrast resolution, can better demonstrate the pericyst, matrix and daughter cysts and establish the diagnosis [56]. Complicated, infected hydatid cysts, though, may well presented as typical liver abscess and only the existence of peripheral calcifications can be of help (fig. 38.10). Identification of hydatid cyst is considered to be of crucial importance, because percutaneous puncture should be avoided as it may lead to intraperitoneal dissemination of the infection. Percutaneous drainage and instillation of a sclerosing agent together with mebendazole treatment has been reported in the treatment of very selected cases of uncomplicated hydatid disease [57, 58, 59], but they should be consider as the exception to the rule. For the complicated with infection hydatid cyst of the liver, surgery is the treatment of choice.

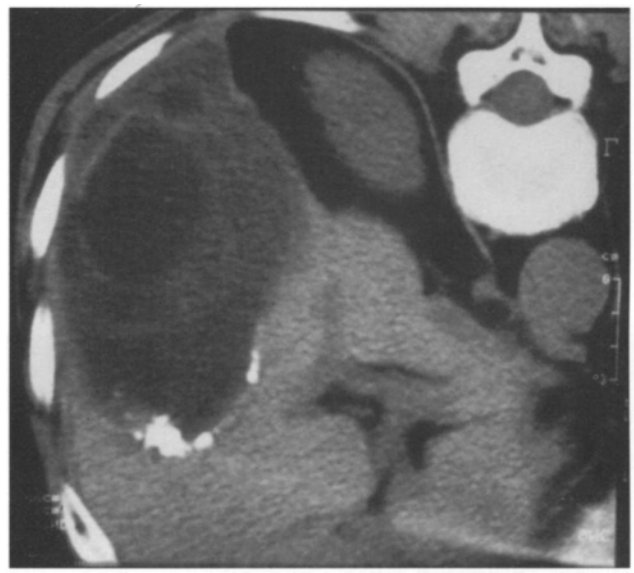


Fig. 38.9. Wall calcifications and daughter cysts depicted on CT scan help distinguishing between a liver abscess and complicated, infected hydatid cyst.

38.4. Amebic Abscess

38.4.1. Overview

Amebic colitis and amebic liver abscess were known since ancient years. Hippocrates recognized that, "Dysenteries..." when set with fever, intestinal discharges of a mixed character or with inflammation of the liver "...have a bad prognosis" [60].

However, more than 2000 years elapsed for Entero-amoeba histolytica to be identified as the cause of dysentery and death by the St. Petersburg physician Fedor Aleksandrovich, in 1875 [61]. In the ensuing years, clinical manifestations of the disease were defined, serological tests were developed and effective treatment was established. Despite all this progress, amebiasis is considered as the second or third leading cause of death amongst the parasitic diseases [62].

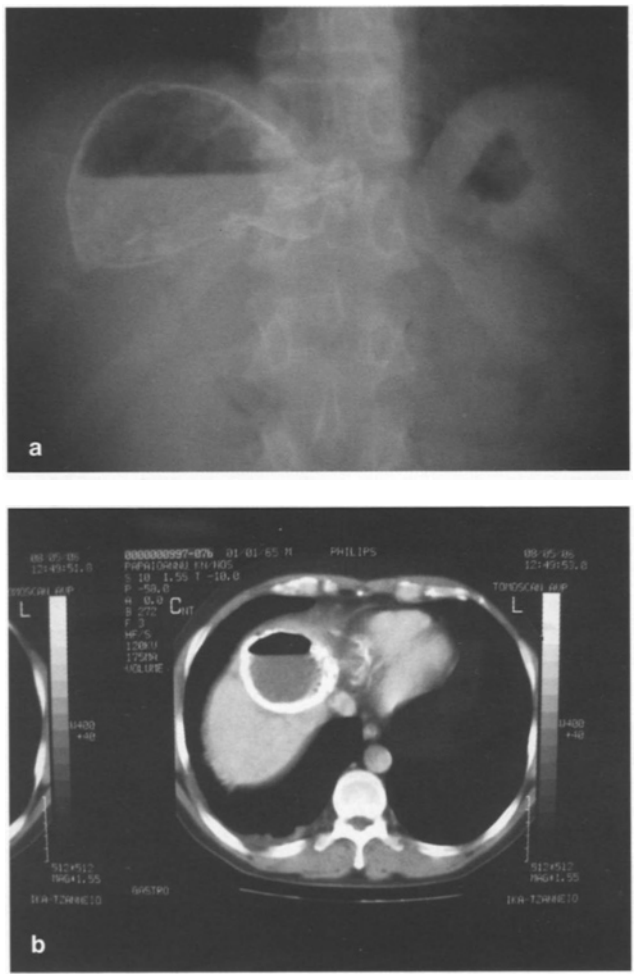


Fig. 38.10. (a) Plain abdominal x-ray shows a characteristic calcified hydatid cyst presenting as a liver abscess, (b) Complicated, infected hydatid cysts though may well show up as typical liver abscess on CT imaging but the presence of peripheral calcification reveals the true nature of the disease. Partial resection of hydatid cyst following attempted surgical drainage in a patient referred to us with clinical manifestations of a liver abscess.

38.4.2. Incidence

The disease is endemic worldwide, with an estimated 10% of the world's population being infected. It is most prevalent in India, Africa, the Far East and Central and South America. Less than 10% of the individuals are symptomatic and amebic dysentery is the commonest clinical manifestation of the invasive form. Hepatic abscess is the most common extra-intestinal form of the disease, occurring in 8.5% of the cases. In non-endemic regions, amebic liver abscess is limited to immigrants or recent travelers to an endemic area, chronically institutionalized patients and in a number of homosexual males. Amebic liver abscess mainly affects men, between the ages of 18 and 50, in whom the rate is 3-20 times higher than the rest population. There is a marked male predominance in amebic liver abscess, with men more commonly affected than women, with a ratio as high as 10:1.

38.4.3. Etiology and Pathogenesis

E. histolytica has a simple lifecycle, existing as either the infectious cyst form or the trophozoite stage. Most individuals are infected by ingestion of food or water contaminated with feces containing the cystic form, released in the small intestine as trophozoites. These invade the colonic mucosa and reach the liver through the portal system. They provoke enzymatic focal necrosis of hepatocytes, tissue infarction and multiple micro-abscesses that coalesce to develop into a single lesion, whose central cavity contains a homogenous thick fluid, reddish brown and yellow cooler, typically referred as "anchovy paste". The right lobe of the liver is involved in a single abscess, in over 90% of the cases. Multiple abscesses are found in only 10% of the cases. Amebic abscesses are usually bacteriologically sterile, but secondary bacterial infection has been reported.

38.4.4. Clinical Manifestations

Patients with amebic liver abscess are usually more acutely ill than patients with pyogenic abscesses. The clinical manifestations of hepatic amebiasis are so typical that may suggest the diagnosis in the areas where the disease is prevalent. Some days or months after the onset of classic dysentery, or as usually happen, without any symptoms or history of intestinal amebiasis, the clinical features begin to appear. The disease can occur in an acute and a chronic form [62]. In patients with acute onset, fever is generally present in more than 90% of the cases. It is often high, continuous or intermittent and accompanied by chills, weakness and profuse sweating. In chronic forms, the fever is low and is developing more gradually without chills or sweating. Abdominal pain is the earliest and most frequent complaint, present in almost all of the patients. It starts as a feeling of heaviness and soon it becomes a

severe sharp pain located over the right hypochondrium, chest or epigastrium, with radiation occasionally into the right shoulder. Patients may also complain of malaise, nausea, vomiting, anorexia and weight loss, while diarrhea may be present in about 2% of the cases. Jaundice is an unusual feature. Its appearance suggests the existence of large or multiple abscesses, bacterial infection and hepatic function derangement. Severe sepsis is generally less common than in pyogenic abscesses. Symptoms from the chest, such as dry cough, chest pain etc., may be present and an abnormal finding over the right lung base or localized intercostals tenderness can also be found in 47 and 38 percent respectively [63]. In over 80% of the cases, tender hepatomegaly is present. The clinical symptoms from a recent series of hepatic amebiasis in an endemic area are given in table 38.7.

38.4.5. Diagnosis

From the laboratory findings, a mild degree of normochromic or hypochromic anemia and a mild to moderate leukocytosis are usually present. Liver function tests are not very helpful. A moderate elevation of alkaline phosphatase as well as hypoalbuminemia and increased transaminases would suggest the possibility of a large abscess. The organism is not commonly detectable in the stool of these patients, but antiamebic antibodies are present in 90-95% of patients with amebic abscess and are detectable by haemagglutination or enzyme-linked immunoabsorbent assay (ELISA). However, serologic findings may be negative in acute disease (but positive at repeat testing performed within 7-10 days) and may be positive if the patient had amebiasis in the past. Among the available today serological tests, indirect hemagglutination (IHA) is a very sensitive test, being positive in 90-95% of patients with liver amebiasis but is replaced by ELISA techniques, which detect either IgG class or total immunoglobulin antibodies with 98% sensitivity and are especially helpfully in the early stages of hepatic amebiasis.

Table 38.7. Clinical symptoms of hepatic amebiasis.

Symptoms	Percentage of cases
• Fever	98
• Pain	100
• Hepatomegaly	80
• Jaundice	55
• Vomiting	43
• Diarrhea	36
• Weight loss	31

BJID 2003, 7:96-110

Radiology is also very important in the diagnosis and management of hepatic amebiasis. Chest radiograph is abnormal in 50% of the patients. An elevation of the right diaphragm, pleural effusion or infiltration at the base of the right lung is the most common findings. At ultrasonography, an amebic abscess may appear as a hypoechoic lesion, with low level internal echoes and absence of significant wall echoes. The lesion is typically oval or round and located near the liver capsule [64].

At contrast-enhanced CT, amebic abscesses usually appear as rounded, well-defined lesions, with attenuation values that indicate presence of complex fluid (10-20 HU). An enhancing wall 3-15 mm in thickness and a peripheral zone of edema around the abscess are common and somewhat characteristic for this lesion [65] Extrahepatic extension of amebic abscess is relatively common and can be easily diagnosed on CT.

At MRI imaging, amebic abscesses are homogeneous low signal intensity and high signal intensity on T1- and T2-weighted images respectively. Perilesional edema is seen on T2-weighted images in 50% of cases [66]. Despite a similarity with several diseases such as hepatoma, acute cholecystitis, parasitic cysts, subphrenic and pulmonary abscess provoked by bacteria, the differential diagnosis of hepatic amebiasis must be principally established against pyogenic abscess. Epidemiologic information of recent travel to or immigration form temperate climates, acute onset of fever and tender hepatomegaly, imaging studies and positive serology will establish the diagnosis. Sterile pus aspirated from the abscess, possible recovery of E. histolytica from the feces and rapid response to metronidazole treatment will further strength the diagnosis of amebic abscess.

38.4.6. Management

Contrary to pyogenic abscesses, amebic abscesses respond well to medical treatment. Metronidazole is the

drug of choice for the treatment of hepatic amebiasis because of its highly lethal action against the trophozoite form of the parasite, as well as the favorable pharmacokinetics. In critically ill patients, metronidazole is administrated at 500 mg by IV infusion every 8 hours, for five or ten days. By the oral route, 750 mg are given tid for 10 days. Most patients treated with metronidazole will improve within 3 to 4 days while cure has been reported in more than 90% of the cases. Newer imidazole derivatives, such as tinidazole and secnidazole, have been introduced in the clinical practice, while chloroquine and emetine can be also used in patients not responding to the imidazoles. Due to the short stay of imidazoles in the bowel lumen, a luminal amebicide such as diidohydroxyquin, tecloscan or ethophamide can be added to prevent relapses after treatment with metronidazole, even in the absence of symptoms of enteric amebiasis.

Needle aspiration is not usually required for the diagnosis or the treatment of amebic abscess. In the rare cases were serology is negative, aspiration may be necessary to differentiate amebic from pyogenic abscess. Pus aspirate from an amebic abscess may have the characteristic appearance of anchovy paste, is usually sterile and it may rarely demonstrate the trophozoites. By most of the reports [67, 68] needle aspiration or percutaneous catheter drainage of amebic abscess has not been proven to be necessary or to accelerate resolution of the amebic abscess compared to amebicidical treatment alone. Other reports observed faster clinical recovery and radiological resolution of the abscess with aspiration in addition to antiamebicides [69]. In our opinion, aspiration should be used in selected cases and not routinely. Indications for percutaneous drainage include large symptomatic abscess at increased risk of imminent rupture, poor response to medical treatment, contraindications to medical treatment such as pregnancy [70], and to exclude secondary bacterial infection. Drainage may also be used to treat complications of amebic abscess, while open surgery is reserved only for patients with secondary infections.

38.4.7. Complications

Most of the complications referred in the chapter of pyogenic abscess are valid for the amebic abscesses too. Intraperitoneal rupture occurs in 7-11% of the cases and can result in either a perihepatic abscess or in diffuse peritonitis [71]. Direct extension of the hepatic abscess into the chest is not uncommon, with a reported incidence of 4-7%. Rupture into the pleural cavity or into the bronchial tree is presented as empyema or consolidation/pulmonary abscess or with formation of a biliary-bronchial fistula [72]. Usually the thoracic complications of amebic abscesses are treated by percutaneous aspiration/drainage and drugs, without an operation. Rupture of an amebic abscess into the pericardium has been observed in less of 2% of all cases. Intraperitoneal or intarpericardial rupture of a left lobe amebic abscess is more likely to occur and a large amebic abscess in this site is an indication for a percutaneous drainage, to avoid the risk of such potential lethal complication [73].

38.4.8. Outcome and Prognosis

In general, the mortality associated with amebic liver abscess is less than 3% [72]. After the first episode, recurrence of amebic abscess is extremely rare, because the host develops immunity [73]. This concept has been lately challenged, as reports show that, in most individuals, the natural infections with E. histolytica do not seem to result in long term immunity to reinfection [74]. While no patient with uncomplicated amebic hepatic abscess should die, complications carry a dismal prognosis. Pulmonary complications carry a 6.2% mortality rate, amebic peritonitis due to intraperitoneal rupture a 18.4% mortality rate, while intrapericardial rupture of an amebic abscess is associated with 30-100% mortality rate. General speaking, complete resolution is the usual outcome of the amebic abscess, although on imaging studies it may take months for the complete resolution.

38.5. Conclusion

Pyogenic liver abscess is a rare disease but still associated with substantial mortality, due to the shifting pattern in the epidemiology and pathogenesis of the disease. A multi-disciplinary team approach is necessary for early diagnosis and effective management of the disease. Broad spectrum antibiotics with anaerobic coverage combined with percutaneous drainage is the

treatment of choice. Surgery, open or laparoscopic is reserved for selected cases.

In endemic areas, differential diagnosis of an infected hydatid cyst from a pyogenic abscess is of utmost importance, because of the risk of intraperitoneal dissemination during a percutaneous puncture.

Diagnosis of an amebic abscess is mainly by detection of serum antibodies, although history and imaging studies are highly suggestive. Complete resolution with medical treatment alone is the norm. Percutaneous or surgical drainage of an amebic abscess is rarely indicated.

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CHAPTER 39

BENIGN LIVER TUMOURS

Th. Mitellas, P. Brotzakis, Con. Ch. Karaliotas

39.1. Introduction

It is estimated that benign liver tumours affect about 20% of the general population. A great variety of benign liver tumours of different embryological origin can be encountered. The most common are listed in table 39.1.

Despite modern diagnostic techniques many benign liver tumours continue to represent an often difficult diagnostic dilemma, mainly because of overlapping radiographic and sometimes histological features [1]. Hemangiomas and cystic lesions are the exceptions to the rule of diagnostic uncertainty since they manifest very specific radiographic features. More than one third of benign liver tumours is estimated to require surgical exploration because of difficulty in achieving an accurate diagnosis. It must be stressed that benign liver disease could cause diagnostic confusion with both primary hepatocellular carcinoma or metastatic liver disease [2].

Diagnostic strategy: The diagnostic tools available when dealing with benign liver disease are listed in table 39.2. Complete history and a thorough physical examination accompanied by basic line blood tests, liver function tests and hepatic serology are imperative as well as tumour markers namely AFP, CEA and CA 19-9.

Table 39.1. Bening liver tumours.

- Lipomas - Angiolipomas.
- Leiomyomas.
- Hemangiomas - Hemangioendotheliomas.
- Hepatic adenomas.
- Biliary adenomas - cystadenomas.
- Hamartomas - Teratomas.
- Focal nodular hyperplasia.
- Nodular regenerative hyperplasia.
- Inflammatory pseudo tumours.

Table 39.2. Diagnostic Strategy in Benign Liver Tumours.

- History.
- Thorough physical examination.
- Base-line blood tests.
- Liver function tests.
- Hepatic serology.
- Tumour markers.
- Radiography.
  - Ultrasound.
  - CT scans.
  - MRI scans.
  - Tc 99^{m}-labeled red cells Scintigraphy.
- Liver biopsy.

Ultrasound is very helpful in distinguishing between solid and cystic lesions but further radiographic assessment with CT is usually necessary before establishing diagnosis. MRI could add further information in some cases. Positron emission tomography (PET) does not seem to be of much help in the differential diagnosis of benign liver lesions. Scanning with tagged red blood cells could sometimes be helpful in otherwise undiagnosed hemangiomas.

Liver biopsy should be the final step in the process of establishing diagnosis. All types of closed or open biopsies are used as well as laparoscopic needle biopsies. As stated by Crawford and recently by Gibbs et al., liver biopsies although extremely helpful might still pose diagnostic dilemmas because of overlapping cytological features between different types of benign liver disease [1, 2].

We shall further discuss some benign liver diseases of special diagnostic or therapeutic interest.

39.2. Haemangiomas

These are the most common benign liver tumors. The majority of lesions arises in the left lobe and is almost always of the cavernous type. Hemangiomas are about five times more common in females and this has been attributed to hormonal reasons. No malignant transformation has been documented. Fever or pain have been reported as the most common symptoms of liver hemangiomas but with lesions less than 4 cm in diameter symptomatology is almost always absent.

CT usually reveals typical peripheral nodular enhancement which when present establishes diagnosis. MRI helps in diagnosing small lesions of fewer than 2 cm in diameter [1].

Patients who manifest symptoms or have a potential hazard of rupture should be considered as candidates for surgery. It must be stated that spontaneous rupture is not frequently reported in literature and usually occurs in large lesions located laterally or in the undersurface of the liver (fig. 39.1, 39.2, 39.3) [1].

Segmentectomy, lobectomy or enucleation are the procedures of choice. Preoperative radiotherapy has also been recommended for the reduction of tumor size.

Excellent results for laparoscopic resections of hepatic hemangiomas as well as other benign liver lesions have recently been reported [3].

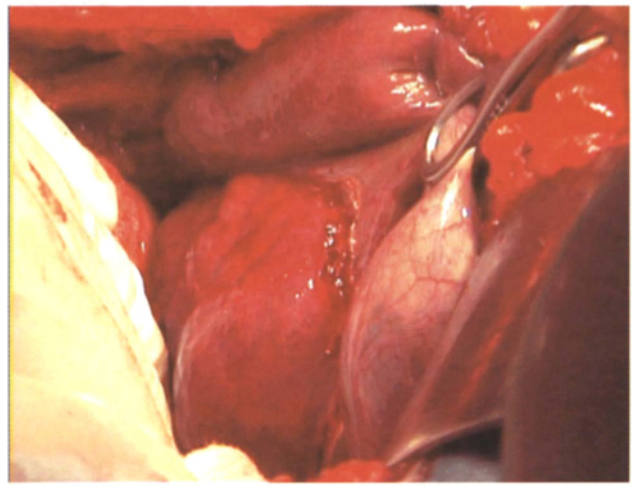

Fig. 39.1. Spontaneously ruptured liver haemangioma of segment V (inferior surface).

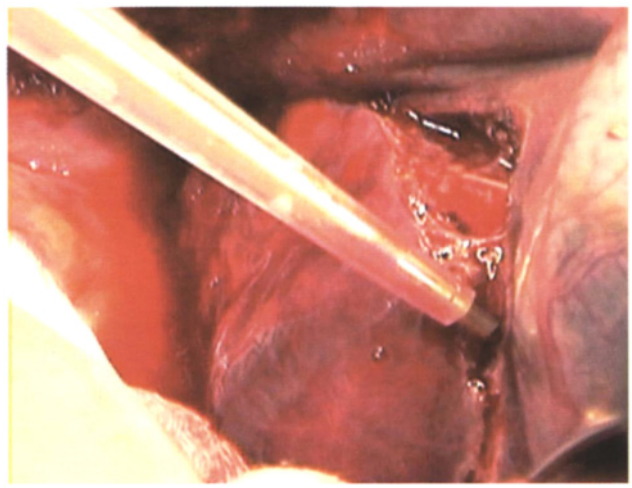

Fig. 39.2. Enucleation of haemangioma by the CUSA tip.

39.3. Cystadenoma

Is an uncommon, slow-growing tumor and is considered as a premalignant lesion [4]. Malignant transformation to cystadenocarcinoma is not uncommon, the pathogenesis of which is unknown. A congenital origin from an abnormal intrahepatic bile duct or from misplaced germ cells is possible

Usually it presents as a large multiloculated cystic tumor [5]. The lesions are located predominantly in the right lobe of the liver, but a third of them are found in the left lobe. It occurs predominantly in female patients between 30 and 50 years of age. It accounts for less than 5% of cystic neoplasm of the liver [6].

39.3.1. Symptoms

They mostly include chronic abdominal pain, abdomi-

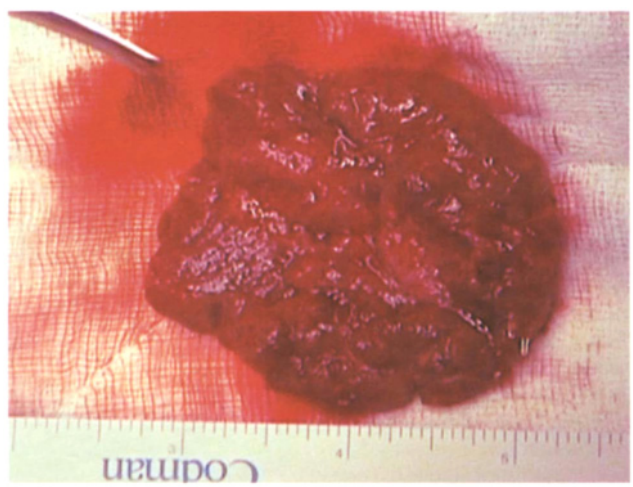

Fig. 39.3. Specimen of excised haemangioma.

nal discomfort and anorexia. Sepsis or cholangitis may occur and suggests an infected cystadenoma. Physical examination most often reveals tenderness in the right upper abdominal quadrant and, less often, an abdominal mass. However, in patients with a small cystadenoma, the disease may be asymptomatic and clinical examination may be normal. Liver function tests are normal. Serological tests for hydatid disease, which must be performed routinely, are negative. Histologically, the tumor appears as multilocular cyst with a single layer of biliary epithelium. Percutaneous aspiration provides a mucinous fluid, a strong argument favouring of the diagnosis of cystadenoma. If cystadenoma is complicated by cystadenocarcinoma, puncture of the cyst could reveal malignancy.

39.3.2. Radiologic Imaging

Computed tomography and ultrasonography are the most helpful examinations but have been diagnostic or highly suggestive in only 60% of cases. Computed tomography demonstrates multilocular cystic lesions with a regular or thick wall, with internal septations. Ultrasonography shows an anechoic mass with echogenic septations or papillary projections or both [7]. However, neither study can establish the diagnosis with certainty because some cystadenomas are unilocular. The MRI findings vary depending on the protein content of the fluid and the presence of an intracystic soft tissue component. Imaging findings are similar to cystadenocarcinoma, although the polypoid projection with pedunculated excrescence is more common in cystadenocarcinoma [8]. The tumor itself is avascular with multiple clusters of fine vessels in the periphery.

Endoscopic retrograde cholangiography shows displacement of the intrahepatic bile ducts by the tumor and no communication between the biliary tree and cystadenoma.

39.3.3. Laboratory Findings

Laboratory findings are normal for most patients, with the alpha-fetoprotein and carcinoembryonic antigen serum level reported to be normal [9]. However, recent studies have reported elevated serum levels of carbohydrate antigen (CA) 19-9, but their clinical significance remains controversial [10]. In contrast, measurement of carcinoembryonic antigen of the cystic fluid seems to be promising in the differential diagnosis of cystadenocarcinoma [11].

39.3.4. Treatment

Patients must be treated with liver resection even if they are asymptomatic. Aspiration is associated with a failure rate of 100% and partial excision with a recurrence rate of nearly 90%, while no failures in the total excision or liver resection occurred. Aspiration can be used as a temporary measure to alleviate symptoms while preparing the patient for a more definite procedure. If cystadenocarcinoma is suspected [12] surgical resection is mandatory. After surgical resection, recurrence is quite common. The three year survival rate following treatment of cystadenocarcinoma is 55% [13].

39.4. Von Meyenburg Complex

Bile duct hamartomas, also known as von Meyenburg complex, are relatively common benign lesions composed of a disorganized proliferation of bile ductules and fibrocollagenous stroma [14]. Radiologic studies are non specific, revealing multiple subcentimeter nonenhanced lesions [15]. Von Meyenburg complex is of no clinical importance, except that it mimicks metastasis or microabscess [16]. The recognition and identification of benign liver tumors is important since most of these tumors do not require any intervention.

39.4.1. Radiologic Imaging

The most common ultrasonographic pattern is that of multiple small hyperechogenic lesions (with or without posterior acoustic reverberation) with irregular margins. A less common finding is the "target" pattern with echogenic center and well defined limits. Further evaluation or treatment is not required.

39.5. Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is an inherited autosomal recessive malformation of the bile ducts that is sometimes referred to as Ductal Plate Malformation characterized by large, fibrotic portal spaces, containing multiple bile ductules, the main consequence of

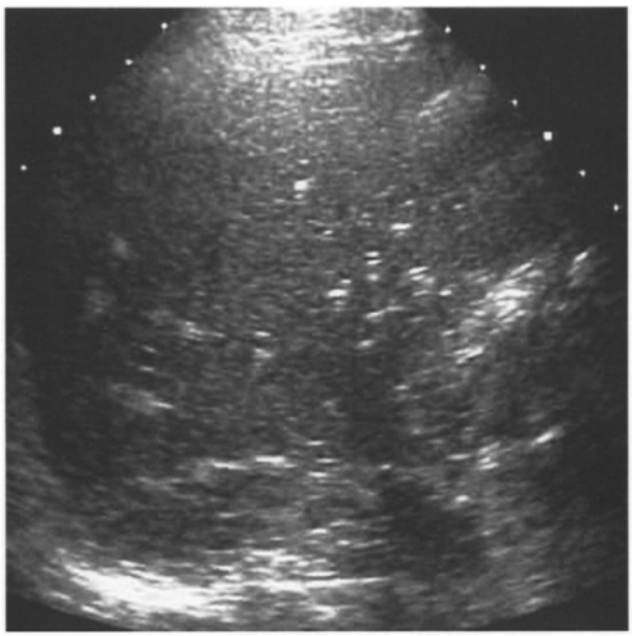

Fig. 39.4. In ultrasound, a finding like this is typical, showing numerable small calcifications in the liver.

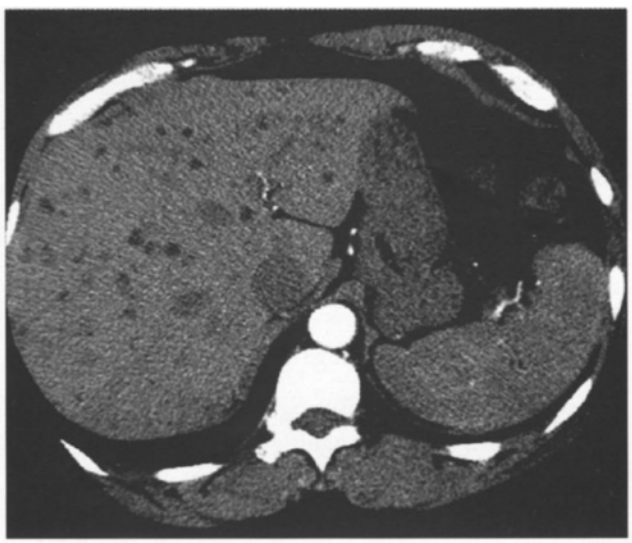

Fig. 39.5. CT scan of multiple Von Meyenburg Complexes. They are presented as non enhancing hepatic low density lesions.

which is portal hypertension. The disease was described by Grumbach and co-workers in 1954 as fibrocystic disease of the liver [17].

39.5.1. Anatomicopathologic Features

This malformation is associated with markedly increased portal spaces because of abundant scarring connective tissue in the portal tracts and bile ductules, more or less ectatic, (biliary ectasia) communicating with the biliary tree. It is uncommon for a person to have CHF without Autosomal Recessive Polycystic Kidney Disease (ARPKD). However if a person has ARPKD he also has some degree of CHF. The inherited defect in the kidneys and liver is the same. CHF has a highly variable clinical course and there are no guidelines that predict the prognosis. It must be emphasized that congenital hepatic fibrosis is not simply fibrosis and that bile ductular proliferation is an essential component of the lesion. Some bile ductules are so markedly dilated that they form microcysts; the microcysts communicate with the biliary tree.

It has been suggested that bile ductular proliferation might result from a disproportionate overgrowth of the biliary epithelium [18]. A Similar disorder affecting the epithelium of the large bile ducts might account for Caroli's syndrome associated with congenital hepatic fibrosis. A similar mechanism might explain the dilatation of the renal collecting tubules and the dilatation of pancreatic ducts, two extrahepatic malformations that may correlate with congenital hepatic fibrosis. They have been observed to degenerate into adenomatous and adenocarcinomatous neoplasia and are considered part of the adult polycystic disease.

39.5.2. Radiologic Imaging

The liver may be normal or enlarged in size. It may or may not be echogenic or coarse in appearance. Dilated intrahepatic biliary ducts, decreased visualization of peripheral portal veins or hypoplasia of the portal vein may be seen, even in the neonate. As fibrosis progreses, hepatosplenomegaly (enlarged liver and spleen) develops along with ultrasound findings of patchy echogenicity. Usually bile ducts are thin and hair-like in shape. In CHF, it is thought that fetal maturation of the portal tract and bile ducts never completes, resulting in an abnormal, bizarre configuration, hence ductal plate malformation.

39.5.3. Laboratory Findings

Magnetic Resonance Cholangiography (MRC) is an ef-

fective non-invasive diagnostic tool for evaluating portal hypertension and the biliary tree. Liver function tests usually remain normal. Even for symptomatic individuals, synthetic liver function is generally preserved, as the liver usually continues to excrete, synthesise, and regulate hormones and chemicals normally. Fibrosis tends to progress with age. Liver failure is not common, although severe liver involvement sometimes requires liver transplantation.

39.5.4. Clinical Presentation

The presentation and severity of symptoms varies greatly, from microscopic biopsy detection to severe clinical liver manifestations and complications. The disease is occasionally recognized as the first episode of gastrointestinal bleeding due to ruptured esophageal or gastric varices, which occurs usually between 5 and 20 years of age. In few cases the disease is recognized from symptoms due to blood disorders. In cases with hypersplenism, abdominal discomfort could be displayed due to an enlarged spleen or the presence of abdominal collateral venous circulation. The portal hypertension is caused by the abundant scarring of the connective tissue in the portal tracts. For some reason, these areas fill with scar tissue (fibrosis) creating blood flow resistance and turbulence. This slows blood flow resulting in a "backup pressure" within the vessels that feeds the portal vein. This backup pressure results in increased pressure in the portal vein (portal hypertension). When the blood flow obstruction is severe, blood flow may reverse, or may spontaneously bypass the liver. These shunts manifest as esophageal varices, hemarrhoids or dilated veins on the abdominal wall.

39.6. Focal Nodular Hyperplasia (FNH)

FNH is the second most common benign liver tumor. Usually an incidental finding and mostly asymptomatic, it affects premenopausal women in about 90 per cent of cases. Most lesions are solitary and rarely multifocal. Usually they consist of a central scar surrounded by hepatocytes, bile ducts and malformed blood vessels. A definitive capsule is absent. They may coexist with hemangiomas, adenomas or hepatocellular carcinomas but true malignant transformation has never been proved [16-17].

FNH pathogenesis is obscure. It has been attributed to abnormalities in portal or hepatic arterial blood flow. Its indicence has been reported to increase after blunt abdominal trauma, chemotherapy, use of oral contraceptives or even smoking [17].

CT scan, MRI or careful needle liver biopsy might be necessary to establish diagnosis [16].

Most cases of FNH need not to be treated. However hepatic resections should be undertaken in symptomatic lesions, lesions rapidly expanding or evidence of intranodular bleeding. Hepatic artery embolization could be of help to patients unsuitable for surgery [16-17].

39.7. Hepatocellular Adenoma

Hepatic adenomas are usually solitary encapsulated lesions containing bile producing hepatocytes but no bile ducts. They are more frequent in young females who use oral contraceptives. The use of other steroids has also been associated with adenoma [16].

Unlike FNH, adenomas have a marked tendency to bleeding or necrosis. Bleeding is mostly intra abdominal although intralesional bleeding is not rare.

Differential diagnosis of adenomas from hepatocellular carcinoma or other hypervascular lesions might prove very difficult. Difficulty in diagnosis and the potential risk of bleeding warrant surgical resection [17-18].

39.8. Nodular Regenerative Hyperplasia (NRH)

This lesion is usually associated with a variety of systemic disease affecting the liver. About half of the patients are cirrhotic or have portal hypertension.

Lesions might be solitary or diffuse. Severe coexisting disease renders surgery unnecessary if not hazardous. Laparoscopic wedge biopsy is recommended in order to document diagnosis [1, 19].

39.9. Inflammatory Pseudo-Tumour

This rare lesion is usually associated with lymphoma, primary sclerosing cholangitis or inflammatory bowel

disease. Polynesians are more prone to the disease. Biopsy is usually required to establish diagnosis. Surgical intervention is not required for this spontaneously resolved disease [2].

39.10. Peliosis Hepatis

Peliosis hepatis is a rare benign lesion that is characterized by the presence of diffuse blood-filled cystic spaces. It has been associated with the use of steroids, oral contraceptives or infection by Bartonella. Liver biopsy is usually necessary to confirm diagnosis. Treatment should be directed at the underlying disease [1, 20-21]. It is created as a result of sinusoidal dilatations forming large blood cysts scattered throughout the liver, grossly visible, measuring up to more than 1 cm in diameter This alteration is not unique to the liver. It may affect other organs with sinusoidal circulation. It has been reported in the spleen, endocrine organs (parathyroids) and may even affect lymph nodes, bone marrow, and lungs [17].

The blood cysts in the liver are of two types: the "parenchymal" type not lined by endothelial or Kupffer cells with the wall consisting of an uninterrupted thin layer of reticulin fibers, and "phleboectatic" type, lined by endothelial cells. They appear to represent an exaggeration of sinusoidal dilatation. They may cause no symptoms but when large and numerous they may cause jaundice, hepatic failure and may rupture and cause death by hemorrhage.

39.10.1. Causes of Peliosis

Drugs, especially long-term steroids treatment, estrogen, tamoxifen, immunoglobulin, (contraceptives, antineoplastic), metals (copper, arsenic), debilitating infections (tuberculosis, endocarditis AIDS), malignancy (hepatocellular carcinoma and adenoma) myeloproliferative disorders (myelofibrosis, polycythemia vera), lymphomas (Hodgkin disease), multiple myeloma, renal transplantation., and infections (tuberculosis). A peculiar type of peliosis is observed in patients with AIDS. Here, the blood cysts are surrounded by a fibromyxoid stroma, which contain locules filled with bacilli stainable with Warthin-Starry stain like the bacilli of cat scratch disease. This type is referred as "bacillary peliosis hepatis". The lesion is similar to "cutaneous bacillary angiomatosis" of the skin also seen in patients with AIDS. The bacteria in these lesions are sensitive to antibiotics, which will eradicate peliosis.

39.10.2. Radiologic Imaging

Radiologic features include cystic lesions with variable sizes. Sometimes, very small lesions are detected as noncystic or diffuse hepatic lesions [17].

Treatment should include withdrawal of the possible causative agents and specific treatment such as antibiotics in patients with either primary or secondary infections.

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CHAPTER 40

NON-PARASITIC DISEASES OF THE LIVER AND INTRAHEPATIC BILIARY TREE

P. Brotzakis, Th. Mitellas, Con. Ch. Karaliotas

40.1. Introduction

With the widespread use of sensitive imaging techniques, the frequency of non-parasitic liver cysts is increasingly reported. It is a rare clinical entity that is identify through the common use of computed tomography and ultrasonography [1-4]. Their reported prevalence is estimated to be between 0.8% and 3.8% [5] during routine abdominal ultrasound examinations.

They derive from a congenital malformation, inherited or non-inherited, of the intrahepatic bile ducts. The large majority of hepatic cysts are lined with a simple epithelial layer with cuboidal cells, suggesting a biliary origin. According to von Meyenburg, [6] embryologic maldevelopment leads to excessive numbers of intralobular ducts that progressively accumulate fluid and eventually become cystic.

Using simple imaging techniques such as ultrasound (US), they can be categorized as solitary or multiple and could be well differentiated from a solid hepatic tumor. Appropriate preoperative differentiation between congenital, parasitic, and neoplastic liver cysts by imaging techniques is crucial since treatment options may vary from observation in asymptomatic congenital liver cysts to surgical treatment in parasitic and neoplastic hepatic cysts.

Surgical management is warranted, when patients are symptomatic or when cysts cause complications, such as torsion [7], hemorrhage [8], rupture [9], infection [9], malignant degeneration [10], portal hypertension [11], or obstructive jaundice [12].

The treatment of choice is complete excision, enucleation, or resection when it can be performed safely. Partial excision can be used to alleviate symptoms in 43% of patients with polycystic liver disease. Aspiration can be used as a temporary measure to alleviate symptoms while preparing the patient for a more definite procedure. Other treatment options for minimally invasive therapy include laparoscopic treatment and alcohol sclerotherapy [13, 14].

40.2. Congenital Hepatic Cysts

Congenital hepatic cysts are uniformly benign, may be single or multiple, with a prevalence of only 0.14% to 0.3% in autopsy series. Solitary cysts are more common than polycystic disease. The pathogenesis of congenital hepatic cysts is unclear, but they most likely result from failure of intralobular bile ducts to fuse with interlobular bile ducts because of dysgenesis, stenosis, or obstruction. An alternative theory is that they are caused by congenital lymphatic obstruction.

40.2.1. Associated Diseases

The most commonly associated disease is polycystic kidney disease, encountered with polycystic liver disease in 45% of patients. The second most commonly associated finding is gallbladder disease, that is present in 17% of patients with simple hepatic cysts and in 16% of patients with cystadenoma. Gallbladder disease in patients with polycystic liver disease is absent.

40.2.2. Solitary Congenital Hepatic Cysts

Small cysts are usually found incidentally during radiologic examination or at laparotomy. Most cases are asymptomatic cysts. They are more common in females (about 3:1), usually occur in the right lobe, and are more often multilocular. There is no apparent genetic trans-

missibility or association with renal cysts. They are lined with cuboidal epithelium resembling bile duct epithelium and are filled with fluid that can be clear, mucoid, bloody, or bilious. Carcinoma can occur in a liver cyst but is extremely uncommon.

40.2.3. Anatomicopathologic Features

Simple cysts are predominantly located in the right lobe of the liver (83% of patients). Despite their pathogenesis, communication with the biliary duct is very rare, and simple cysts usually contain clear nonbilious fluid with a similar composition to plasma and are usually lined with cuboidal epithelium surrounded by basement membrane and fibrous tissue.

40.2.4. Clinical Presentation

Symptoms: Most hepatic cysts will not cause symptoms unless there is infection, haemorrhage or if they become very large. Symptomatic patients are often women in their 40s and 50s [15] with a cyst, generally larger than 5 cm. These conditions occur only in 10-16% of these patients. Thus, it is important to be strict in the selection of patients according to their symptoms and to focus on specifically cyst-related complaints [16]

The symptoms reported are those of pressure on adjacent organs, vague right upper quadrant discomfort or pain, with 75% experiencing a sensation of epigastric fullness or heaviness, and 17% early satiety, or nausea and vomiting or all the above symptoms.

Physical findings: On physical examination hepatomegaly or a palpable mass is the predominant finding in 42% of patients. Tenderness in the right upper abdominal quadrant is often found and respiratory symptoms may prevail if the cyst is large [17].

40.2.5. Complications

Though rare, they may include intracystic hemorrhage [8], secondary bacterial infection, torsion [7] (if pedunculated), and obstructive jaundice, [12] portal hypertension [11], from compression of extrahepatic ducts. In addition, malignant degeneration [10] and spontaneous rupture have been occasionally reported. In the absence of complications, laboratory abnormalities are uncommon.

40.2.6. Radiologic Imaging

CT and MRI are the radiologic studies that produced the highest diagnostic accuracy, followed closely by ultrasonography. Arteriography is useful and is also highly diagnostic in contrast with the results of nuclear scans of the liver, which is suggestive in only 40% to 50% of patients.

On ultrasonography, the cyst is unilocular, thin-walled, smooth in contour, and unechoic, while on CT and MRI, the cyst appears homogenous with water density without septations. Irregularities, septations, and calcifications of the cyst wall are suggestive of an infectious, neoplastic, or traumatic cause [1-4] (fig. 40.1, 40.2).

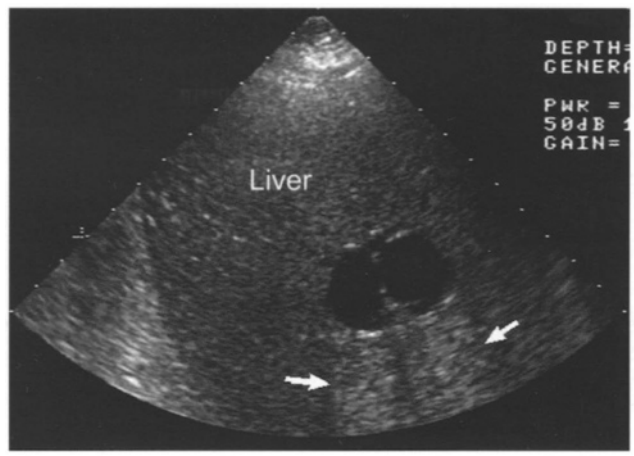

Fig. 40.1. Ultrasonography: A septated, round, unechoic area, 4-5 cm in diameter can be seen in the liver parenchyma, with relative enhancement (arrows) behind it.

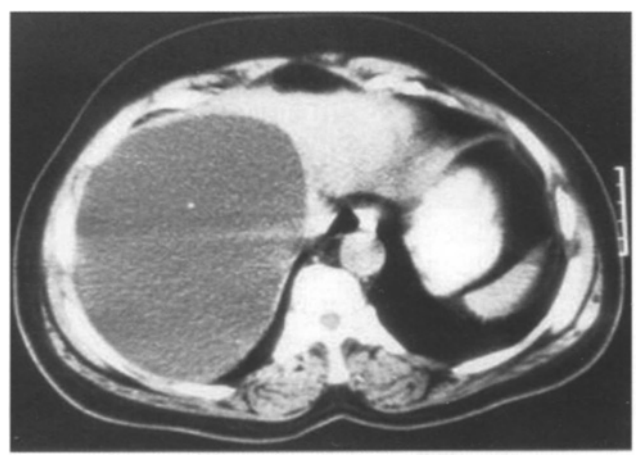

Fig. 40.2. CT scan of a right lobe liver cyst.

In cases of intracystic hemorrhage, the signal intensity is high, with fluid-fluid level, on both Tl- and T2-weighted images when mixed blood products are present [18].

In cases of an unidentified liver cyst, intraoperative aspiration of cystic fluid by a laparoscopic needle before fenestration and laboratory assessment of the fluid yielded the correct diagnosis and avoided massive abdominal flooding with hydatid content [19].

40.2.7. Treatment of Asymptomatic Solitary Hepatic Cyst

If there is no evidence of infection or malignancy, follow up is the only necessary measure. Neither percutaneous aspiration nor surgery is indicated. Cysts nearly always recur after simple aspiration. If there are internal echoes, however, the cyst should be aspirated under ultrasound or CT guidance for culture and cytology. If the cyst is discovered incidentally at laparotomy or laparoscopy, it should be aspirated (for Gram stain, culture, and cytology). If not infected, it should be left alone unless easily resectable.

40.2.7.1. *Treatment of Symptomatic Cysts*

The preferred treatment of symptomatic cases is US- or CT-guided percutaneous cyst aspiration followed by sclerotherapy with alcohol (or doxycycline). In patients suffering from chronic abdominal pain in whom its relation to the presence of liver cysts is questioned, the use of percutaneous aspiration as a pretherapeutic test is also recommended.[20] Percutaneous radiologically guided aspiration of hepatic cysts can also help to exclude other pathological entities, such as neoplastic cysts and liver abscess. [21] Surgical treatment is indicated for rupture, hemorrhage, and infection of the cyst and also if it is difficult to exclude malignancy or if biliary communication is present. [22]

A symptomatic, uninfected simple cyst is best treated by excision. The recurrence rate is low. Total excision includes any procedure that totally removes the cyst without considerable resection of surrounding hepatic tissue (i.e., enucleation or pericystectomy). Liver resection includes formal or extended lobectomy, segmentectomy, or wedge resection where a cuff of liver tissue around the cyst is removed. Wide deroofing of the cyst wall is a key factor in avoiding cyst recurrence. However, it also increases the risk of bleeding and biliary leak from the small vascular and biliary structures within the fenestrated hepatic edges. Larger cysts may be unroofed with free peritoneal drainage unless there is a history of hemorrhage or evidence of biliary communication. If the cyst communicates with the biliary system (grossly or by cholangiogram), the leak may be oversewn or the cyst drained by Roux-en-Y cystojejunostomy. Infected cysts should be drained externally and resected later or marsupialized. Of those patients who underwent partial excision, recurrences could be found in 38%. Recently laparoscopic fenestration and deroofing has been documented as safe and effective [23, 24]. The choice between open and laparoscopic surgery depends on the location of the cyst in the liver [25] (fig. 40.3).

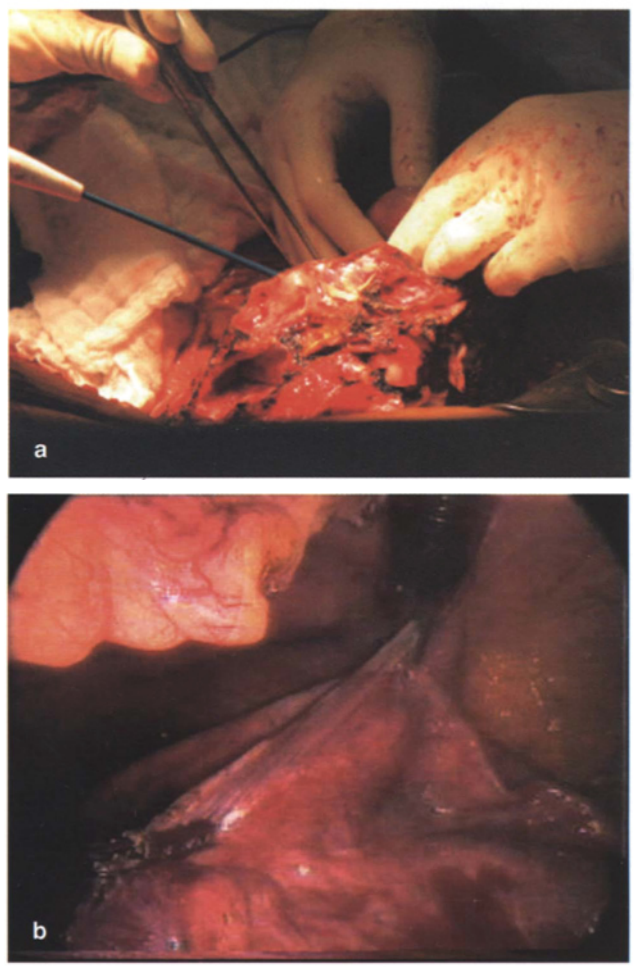

Fig. 40.3. a. Open laparotomy, liver cyst treatment with wide deroofing of the cyst wall. b. Large liver cyst laparoscopically evacuated before deroofing.

40.2.7.2. *Laparoscopic Technique*

The patient is placed in a left lateral reverse Trendelenburg position with a nasogastric tube and Foley catheter in place. A 10 mm Hasson cannula is inserted using the open technique through a right umbilical incision, and pneumoperitoneum is established. The cannula is replaced with a 30° laparoscope, two 5 mm trocars are inserted in the right flank, and a 10 mm trocar is inserted below the xyphoid under video guidance. After the cyst is located, it is punctured using a laparoscopic needle. Cystic fluid aspiration must be performed routinely during surgical exploration for cytologic examination. Most of the intracystic fluid is aspirated, avoiding intraperitoneal spillage.

Wide deroofing of the cyst roof must be performed according to the fenestration technique reported by Lin et al [26]. Electrocautery and harmonic shears are quite useful for the laparoscopic technique. Cystic wall speciments must be sent for biopsy. Bile leaks in the remnant walls must be ruled out by careful inspection, and in all cases a drain is left in place.

After wide deroofing, frozen pathological examination of the cystic wall should also be performed routinely to rule out a neoplastic cyst. Ablation of the cyst lining in the residual fenestrated cystic cavity can be achieved with argon beam coagulation to eliminate epithelial secreting cells and avoid cyst recurrence. Omentoplasty is an alternative technique but both could also be applied.

The biopsy specimen should be examined thoroughly to rule out cystadenoma or cystadenocarcinoma, and communication with the biliary tree should be excluded. When a communication is identified, complete excision is the treatment of choice.

Aspiration with injection of sclerosants has been used with some clinical success but is associated with a high rate of recurrence and should not be performed in the presence of infection, hemorrhage, or biliary communication [12, 27, 28].

40.2.8. *Polycystic Liver Disease*

Polycystic liver disease is a common manifestation of polycystic kidney disease and is associated with an autosomal dominant inheritance. In terms of severity, the disease has a wide range of expression.

Hepatic involvement is usually present, but children with severe perinatal and neonatal forms often die of renal failure. If they survive; the hepatic disease predominates as congenital hepatic fibrosis.

Adult polycystic disease is the most common cystic disease. It has autosomal dominant transmission with an incidence of 1:1000. In an autopsy study at UCLA Medical Center, adult polycystic liver disease was identified in 0.13% of all patients and in 93% of patients with polycystic kidney disease. However, in patients with polycystic liver disease, about 35% had an associated polycystic kidney disease [29]. Ten percent to 30% of patients with adult polycystic disease also have intracranial arterial aneurysms (fig. 40.4).

40.2.8.1. *Anatomicopathologic Features*

Hepatic Polycystic liver disease is always bilobar but has demonstrated a pattern of right lobar dominance in 18% of patients.

It may be microscopic or large, and the cysts generally contain clear fluid, similar to plasma in composi-

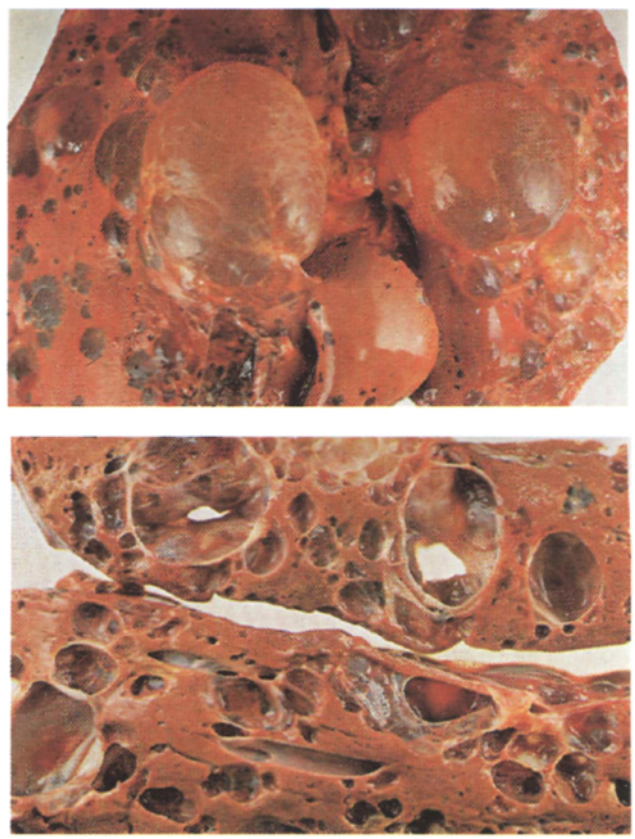

Fig. 40.4. Polycystic liver disease in hepatic specimen.

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40.2.7.1. *Treatment of Symptomatic Cysts*

The preferred treatment of symptomatic cases is US- or CT-guided percutaneous cyst aspiration followed by sclerotherapy with alcohol (or doxycycline). In patients suffering from chronic abdominal pain in whom its relation to the presence of liver cysts is questioned, the use of percutaneous aspiration as a pretherapeutic test is also recommended.[20] Percutaneous radiologically guided aspiration of hepatic cysts can also help to exclude other pathological entities, such as neoplastic cysts and liver abscess. [21] Surgical treatment is indicated for rupture, hemorrhage, and infection of the cyst and also if it is difficult to exclude malignancy or if biliary communication is present. [22]

A symptomatic, uninfected simple cyst is best treated by excision. The recurrence rate is low. Total excision includes any procedure that totally removes the cyst without considerable resection of surrounding hepatic tissue (i.e., enucleation or pericystectomy). Liver resection includes formal or extended lobectomy, segmentectomy, or wedge resection where a cuff of liver tissue around the cyst is removed. Wide deroofing of the cyst wall is a key factor in avoiding cyst recurrence. However, it also increases the risk of bleeding and biliary leak from the small vascular and biliary structures within the fenestrated hepatic edges. Larger cysts may be unroofed with free peritoneal drainage unless there is a history of hemorrhage or evidence of biliary communication. If the cyst communicates with the biliary system (grossly or by cholangiogram), the leak may be oversewn or the cyst drained by Roux-en-Y cystojejunostomy. Infected cysts should be drained externally and resected later or marsupialized. Of those patients who underwent partial excision, recurrences could be found in 38%. Recently laparoscopic fenestration and deroofing has been documented as safe and effective [23, 24]. The choice between open and laparoscopic surgery depends on the location of the cyst in the liver [25] (fig. 40.3).

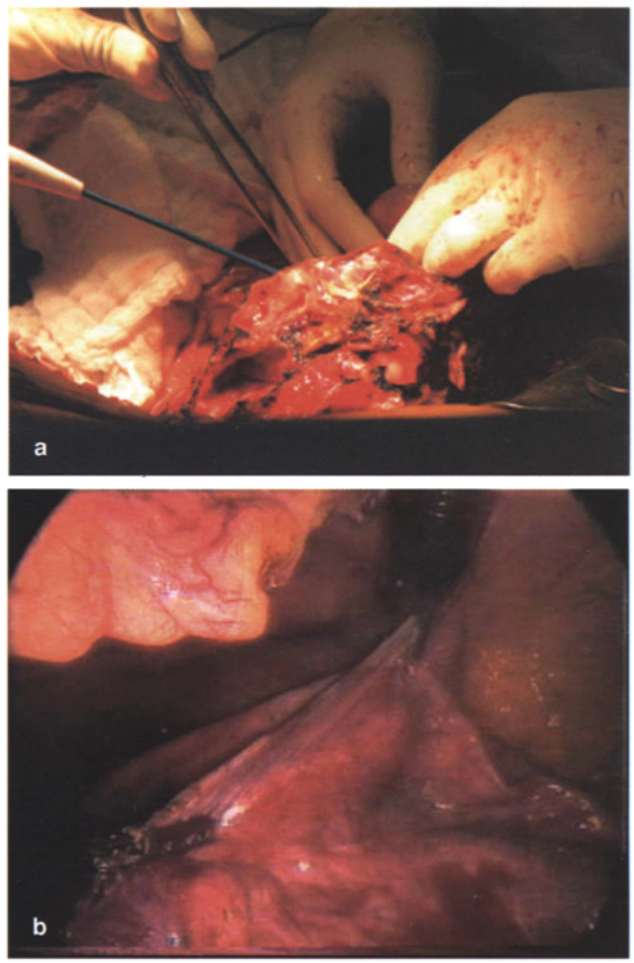

Fig. 40.3. a. Open laparotomy, liver cyst treatment with wide deroofing of the cyst wall. b. Large liver cyst laparoscopically evacuated before deroofing.

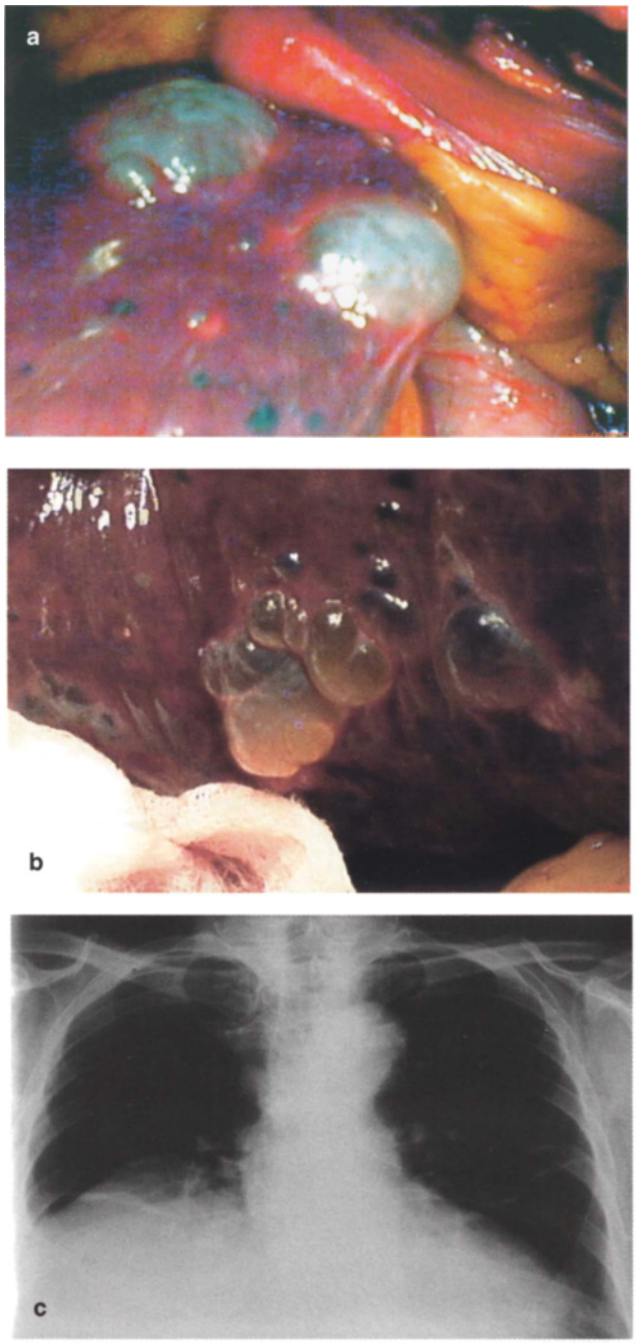

Fig. 40.7. a: Polycystic liver. b: Other appearance of multiple liver cysts. c: Rise of right hemidiaphragm in a symptomatic patient with multiple liver cysts.

plane of dissection [33, 34, 35]. Extensive and unresectable disease has recently been treated with liver orthotopic transplantation and can be of benefit in carefully selected patients especially on those with hepatomegaly and portal hypertension. Patients with associated renal failure may benefit from simultaneous kidney transplantation. Aspiration can be performed for temporary relief but is regarded as a poor treatment method because of a 100% rate of recurrence. The instillation of ethanol or Pantopaque in the cysts of polycystic liver disease, after aspiration, has been performed by other authors [35, 36], but longer follow-up study is needed in order to evaluate the procedure.

It is accepted that polycystic liver disease is a benign process in which the prognosis is determined by the extent of the kidney disease. However, in a series [37] of more than 100 patients with polycystic liver disease followed up for 28 years, polycystic kidney disease resulted in little morbidity, causing only 4 deaths. Hepatic failure directly attributable to cyst formation or compression has not been reported. This finding may be explained by the fact that the compressed liver parenchyma is histologically and morphologically normal. In fact, liver parenchyma as studied by computed tomography and plastic agar models is preserved in polycystic liver disease despite massive cystic involvement [38].

40.3. Acquired Hepatic Cysts

40.3.1. Traumatic Hepatic Cysts

They are false cysts (having no true epithelial lining) that result from a resolved subcapsular or intraparenchymal hematoma. The patient has a history of trauma. These cysts lack a capsule, and have a fibrotic wall that contains hemosiderin, but otherwise they are similar to solitary congenital cysts and should be treated in a conservative fashion.

40.3.2. Neoplastic Cysts

These cysts of the liver can be primary biliary cystadenomas or cystadenocarcinomas but more commonly are metastases from primary tumors, such as pancreatic or ovarian carcinomas. Alternatively, they may represent cystic degeneration of a solid primary or metastasis. Such malignancies taking a cystic form are uncommon but need to be taken into consideration when dealing with cystic hepatic disease. Confusion between a congenital and a neoplastic liver cyst could lead to

inappropriate treatment, exposing the patient to tumor recurrence, as recently reported [38]. Cystic neoplasms demonstrate typical features on imaging techniques, including the presence of thick irregular cyst walls, heterogeneous intracystic fluid and hypervascular internal septations [39-42].

However, in cases where the liver cysts are complicated by hemorrhage or superinfection, it can be difficult to differentiate between benign congenital liver cysts and cystic neoplasms on radiological examinations [43-45]. If during surgical exploration any unusual cystic fluid or cystic wall irregularity is encountered, then multiple frozen section biopsies should be taken in order to exclude a cystic neoplasm [45-47].

40.3.2.1. *Cystadenoma*

It is an uncommon, slow-growing tumor and is considered as a premalignant lesion. Malignant transformation to cystadenocarcinoma is not uncommon, the pathogenesis of which is unknown. (Details see later in the same chapter: Benign Liver Tumors).

40.4. Von Meyenburg Complex

It is hamartoma of bile duct (see in chapter 39 more details).

40.5. Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is an inherited autosomal recessive malformation of the bile ducts that is sometimes referred to as Ductal Plate Malformation characterized by large, fibrotic portal spaces, containing multiple bile ductules, the main consequence of which is portal hypertension. The disease was described by Grumbach and co-workers in 1954 as fibrocystic disease of the liver [48].

40.5.1. Anatomicopathologic Features

This malformation is associated with markedly increased portal spaces because of abundant scarring connective tissue in the portal tracts and bile ductules, more or less ectatic, (biliary ectasia) communicating with the biliary tree. It is uncommon for a person to have CHF without Autosomal Recessive Polycystic Kidney Disease (ARPKD). However if a person has ARPKD he also has some degree of CHF. The inherited defect in the kidneys and liver is the same. CHF has a highly variable clinical course and there are no guidelines that predict the prognosis. It must be emphasized that congenital hepatic fibrosis is not simply fibrosis and that bile ductular proliferation is an essential component of the lesion. Some bile ductules are so markedly dilated that they form microcysts; the microcysts communicate with the biliary tree.

It has been suggested that bile ductular proliferation might result from a disproportionate overgrowth of the biliary epithelium [49]. A similar disorder affecting the epithelium of the large bile ducts might account for Caroli's syndrome associated with congenital hepatic fibrosis. A similar mechanism might explain the dilatation of the renal collecting tubules and the dilatation of pancreatic ducts, two extrahepatic malformations that may correlate with congenital hepatic fibrosis. They have been observed to degenerate into adenomatous and adenocarcinomatous neoplasia and are considered part of the adult polycystic disease.

40.5.2. Radiologic Imaging

The liver may be normal or enlarged in size. It may or may not be echogenic or coarse in appearance. Dilated intrahepatic biliary ducts, decreased visualization of peripheral portal veins or hypoplasia of the portal vein may be seen, even in the neonate. As fibrosis progresses, hepatosplenomegaly (enlarged liver and spleen) develops along with ultrasound findings of patchy echogenicity. Usually bile ducts are thin and hairlike in shape. In CHF, it is thought that fetal maturation of the portal tract and bile ducts never completes, resulting in an abnormal, bizarre configuration, hence ductal plate malformation.

Laboratory findings: Magnetic Resonance Cholangiography (MRC) is an effective non-invasive diagnostic tool for evaluating portal hypertension and the biliary tree. Liver function tests usually remain normal. Even for symptomatic individuals, synthetic liver function is generally preserved, as the liver usually continues to excrete, synthesise, and regulate hormones and chemicals normally. Fibrosis tends to progress with age. Liver failure is not common, although severe liver involvement sometimes requires liver transplantation.

40.5.3. Clinical Presentation

Symptoms: The presentation and severity of symptoms varies greatly, from microscopic biopsy detection to severe clinical liver manifestations and complications. The disease is occasionally recognized as the first episode of gastrointestinal bleeding due to ruptured esophageal or gastric varices, which occurs usually between 5 and 20 years of age. In few cases the disease is recognized from symptoms due to blood disorders. In cases with hypersplenism, abdominal discomfort could be displayed due to an enlarged spleen or the presence of abdominal collateral venous circulation.The portal hypertension is caused by the abundant scarring of the connective tissue in the portal tracts. For some reason, these areas fill with scar tissue (fibrosis) creating blood flow resistance and turbulence. This slows blood flow resulting in a "backup pressure" within the vessels that feeds the portal vein. This backup pressure results in increased pressure in the portal vein (portal hypertension). When the blood flow obstruction is severe, blood flow may reverse, or may spontaneously bypass the liver. These shunts manifest as esophageal varices, hemorrhoids or dilated veins on the abdominal wall.

40.6. Caroli's Disease

Caroli disease is a rare, autosomal-recessive developmental disorder characterized by non-obstructive saccular of multifocal dilatation of intrahepatic bile ducts, multiple intrahepatic calculi and is associated with infantile and adult polycystic kidney disease and cystic renal dysplasia [49]. Caroli's disease may also be associated with choledochal cysts or medullary sponge kidney. Cholangiocarcinoma may be a complication. Cirrhosis of the liver mimics this condition and can be differentiated by biopsy. Caroli's disease is sometimes included in the classification of choledochal cyst, which is not appropriate since choledochal cysts occur in extrahepatic bile ducts and there is no renal involvement. While this condition generally involves the entire liver, it may be segmental or lobar.

40.6.1. Anatomicopathologic Features

Two forms of the disease have been described. The rare, so called pure form described by Jacqui Caroli is characterized by segmental saccular communicating intrahepatic bile duct dilatation, frequently accompanied by stone formation, recurrent cholangitis and hepatic abscess. The liver involvement can be diffuse, lobar or segmental. It usually presents in childhood and about 75% of affected patients are male. Areas of severe epithelial dysplasia or carcinoma in situ are rarely seen. Cholangiocarcinoma can develop in 7% of patients. Caroli's syndrome is another form that is more common and is associated with congenital hepatic fibrosis [51-52]. The dilatation of intrahepatic biliary ducts in usually less prominent. Both conditions result from malformation of the embryonic ductal plate at different levels of the biliary tree [52]. Macroscopically, the intrahepatic cystic dilatations are round or lanceolate, 1.0-4.5 cm in diameter, and may be separated by stretches of essentially normal duct. Inspissated bile or soft and friable bilirubin calculi may be detected in the lumen. The lumen contains admixtures of inspissated mucin and bile, calcareous material, or frank pus during bouts of acute cholangitis. Caroli's disease can be associated with congenital hepatic fibrosis and, rarely with infantile polycystic disease and even adult polycystic disease.

The multifocal dilatation may be diffuse, affecting the whole intrahepatic biliary tree (although it may be more marked in a part of the liver), or it may be confined to a part of the liver, often the left lobe or a segment of the left lobe. The pathogenesis of Caroli's disease seems to involve total or partial arrest of remodelling of the ductal plate of the larger intrahepatic bile ducts. In Caroli's "syndrome" (Caroli's disease with congenital hepatic fibrosis), the hereditary factor causing the arrest of remodelling seems to exert its influence, not only during the early period of bile duct embryogenesis but also later on during development of the more peripheral biliary ramifications (the interlobular bile ducts).

40.6.2. Clinical Symptoms

Include recurrent attacks of fever, right upper quadrant pain, and rarely jaundice. Jaundice occurs only when a stone blocks the common bile duct. Leucocytosis is observed typically when acute cholangitis develops. The main and often the only symptom of bacterial cho-

langitis due to Caroli's syndrome is fever without abdominal pain and jaundice.

Liver function tests are generally normal except during episodes of obstructive jaundice. Caroli's syndrome remains asymptomatic for the first 5 to 20 years of the patient's life and, in some cases, for life. In asymptomatic patients Caroli's syndrome remains unrecognized, and could only be revealed incidentally on an imaging investigation of the liver.

40.6.3. Radiologic Imaging

The diagnosis is established by cholangiography, ERCP, ultrasonography and CT scan. US is the best initial imaging study because it reveals the irregular dilatation of the large intrahepatic ducts. The dilated sacculi or cystic spaces appear as anechoic areas on ultrasound, and are hypodense on CT. On enhanced CT and MRI, the presence of tiny dots with strong enhancement within dilated intrahepatic ducts ("central dot" sign), reflecting intraluminal portal vein radicles, is a very suggestive finding of Caroli disease [53]. The fibrovascular bundles containing portal vein radicals and a branch of the hepatic artery bridging the sacculae appears as a central dot or a linear structure on CT, enhancing with contrast. This "central dot sign" described on CT [54] can be easily seen in ultrasound. Awareness of this finding can result in proper diagnosis and can avoid invasive tests for confirmation. The dilated cysts communicate with bile ducts. On color flow Doppler imaging, flow can be demonstrated within the linear strands [55]. Cholangiography shows diverticulum-like sacculi of intrahepatic bile ducts of varying sizes, shapes and distribution [56]. Calculi are common. The common bile duct is normal. Hepatic scintigraphy with Tc 99^m diethyl IDA shows the typical "beaded" appearance of dilated intrahepatic bile ducts. In Caroli's syndrome both CT and ultrasound show focal mild dilatation of intrahepatic bile ducts (2-3 mm). The liver shows changes of portal hypertension (shrunken liver, splenomegaly, splenic and esophageal varices and ascitis). Cholangiography shows typical findings of focal segmental dilatation. The MRCP findings in Caroli's disease are similar to those of ERCP [57].

40.6.4. Complications

In Caroli's disease they resemble those of Choledochal cyst and include recurrent cholangitis, abscess formation, septicaemia or pyaemia, intrahepatic lithiasis and amyloidosis. Cholangiocarcinomas, the commonest malignancy in patients with Caroli's disease, was previously reported in 7% to 14% of patients. Hepatocellular carcinoma occurs rarely. Despite the high incidence of malignancy in these patients there are currently no reliable methods for early detection of cholangiocarcinoma.

40.6.5. Surgical Treatment

Surgical treatment may be necessary for recurrent or refractory cholangitis and involves internal or external drainage procedures. Transhepatic decompression has been advocated. Segmental or lobar forms of Caroli's disease can be treated by partial hepatectomy and excellent results can be expected. Extracorporeal shock wave lithotripsy has been utilized for disintegration of intrahepatic bile duct stones. In the diffuse form without predominance of the cysts in any part of the liver, complicated by severe recurrent bacterial cholangitis, liver transplantation should be considered [58]. Administration of ursodiol is efficient in the prevention of lithiasis and in the treatment of intrahepatic stones [59]. Episodes of bacterial cholangitis are treated with antibiotics. Periodic administration of antibiotics to prevent recurrent bacterial cholangitis is efficacious in some patients. (Fig. 40.8, 40.9, 40.10, 40.11).

40.7. Peliosis Hepatica

Peliosis hepatis is a rare benign lesion that is characterized by the presence of diffuse blood-filled cystic spaces (see in chapter 39 more details).

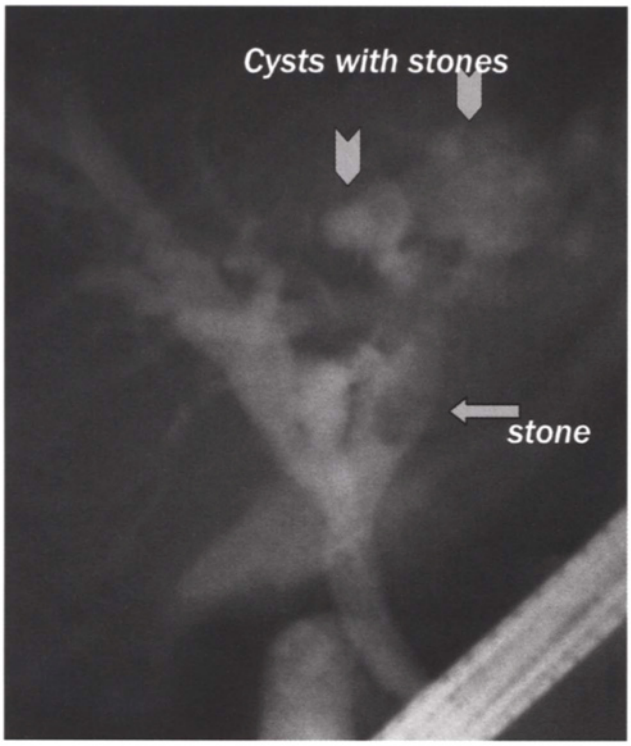

Fig. 40.8. Local Caroli's disease in left liver lobe (arrowheads). CBD lithiasis (arrow).

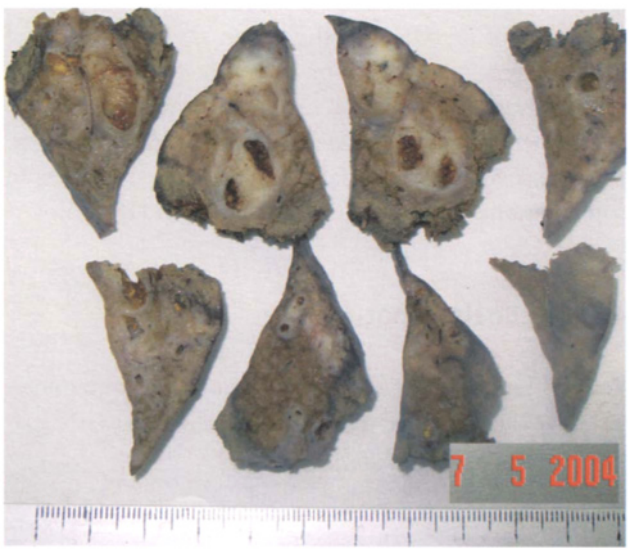

Fig. 40.9. Local Caroli's disease. Liver specimens after left hepatectomy.

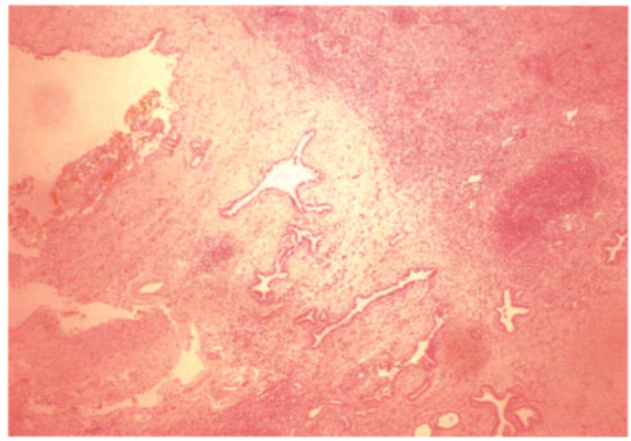

Fig. 40.10. Caroli disease. Liver parenchyma with fibrosis, inflanmation and bile ductules dilatations.

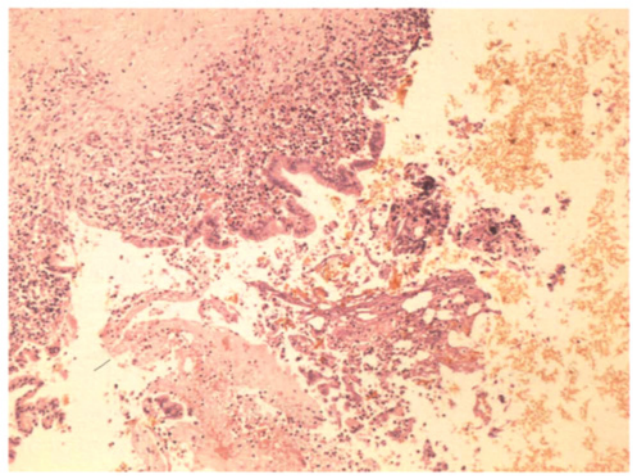

Fig. 40.11. Caroli's disease. Part of a bile ductule with cystic dilatation, intense acute parietal inflammation.

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SECTION 4

Chapter 41: Liver Transplantation

Chapter 42: Operative Data

Chapter 43: Living Donor Liver Transplantation

Chapter 44: Intensive Care Unit Management

Chapter 45: Perioperative Complications

Chapter 46: Outcome of Liver Transplantation in Special Categories of Patiens

Chapter 47: Computer Assisted Surgery Planning (CASP) in Adult-To-Adult Living Donor Liver Transplantation (ALDLT)

Chapter 48: Conclusion

CHAPTER 41

LIVER TRANSPLANTATION

41a. Liver Transplantation

C.E. Broelsch

41a.1. Introduction

Over the last three decades liver transplantation has become an established therapy for patients suffering from end-stage liver disease. In 1955, Welch reported the first attempt at experimental heterotopic grafting of a liver in a dog [1]. The first known experimental orthotopic liver transplantation (OLT) was reported by Cannon in 1956 at the University of California [2]. In 1963, Starzl performed a human-to-human OLT in a 3 year old child with congenital biliary atresia who died intraoperatively [3]. The following 2 transplant recipients lived for 22 days and 1 week, respectively [3]. In 1967, Starzl succesfully transplanted several patients [4].

The evolution of liver transplantation was paralleled by several major advances in the early 1980s such as the improvement of immunosuppressant regimens [5], organ preservation [6], surgical techniques [7] as well as improvement of post-operative management with reduction of infectious complications and prevention of disease recurrence.

Before the introduction of cyclosporin A (CSA) in the early 1980s, 5-year survival after OLT was about 20% [8]. The advent of CSA resulted in a dramatic reduction in the incidence of acute rejection, thus leading to widespread use throughout the 1980s, and 1990s. During the 1990s, tacrolimus (TAC) emerged as the mainstay immunosuppressive agent, with or without corticosteroides, in many transplant centers in the United States. New concepts in immunosuppressive therapy and improvement in patient management, operative techniques, and organ preservation have achieved 1 year and 5 year survival rates of 80% to 90% and 60% to 80%, respectively [9].

Today most common transplant indications are end-stage liver diseases with cirrhosis caused by viral hepatitis and alcoholic disease. Other common indications are metabolic or genetic disorders of the liver as well as acute liver failure. Also in selected cases of liver malignancies, liver transplantation is the therapy of choice in a continually increasing list of indications [10-11]. Approximately 50-70 out of 100.000 inhabitants are in need of liver transplantation.

The limited pool of cadaver donor organs prompted in the development of split-liver (SLT) techniques and living-donor liver transplantation (LDLT) as innovative techniques in adult liver transplantation [12-13]. Long-term patient and graft survival rates for these advanced techniques are comparable to those for whole organ transplantation procedures [14]. While split liver grafts are technically demanding, the use of living-donor-liver grafts incurs additional ethical problems. The benefits of living donation include decreased rates of graft dysfunction (lack of trauma and ischemia to the graft before retrieval), the ability to schedule an elective operation and the reduction of mortality and morbidity while waiting for a suitable graft. The main consideration is the potential risk for the donor and the difficulty of eliminating coercion in this life-saving situation. Thus, stringent medical and psychological criteria must form the basis of the selection criteria.

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41b. Indications for Liver Transplantation

S. Beckebaum, H. Lang, A. Frilling, G. Gerken

41b.1. General Considerations

Candidates for OLT must have irreversible acute or chronic end stage liver disease (table 41b.1). Virus or alcohol-induced liver cirrhosis constitute the most common disease indications in adults [1] (fig. 41b.1). In our department 28% of cirrhotic liver transplant recipients are transplanted for hepatitis C virus (HCV)-related liver disease and 26% undergo OLT for alcohol-related liver disease. Other indications include cholestatic liver disorders [primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), biliary atresia], hepatitis B virus (HBV) infection, autoimmune hepatitis, cystic fibrosis, inherited metabolic diseases (Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency), nonalcoholic steatohepatitis, nonmetastatic hepatocellular carcinoma, and acute virally-, toxin-, or drug-induced hepatic failure. The most common indications in children comprise biliary atresia and metabolic liver diseases.

Many attempts have been made to optimize the timing of liver transplantation for advanced chronic cholestatic liver diseases. A number of investigators have developed prognostic indices using clinical and laboratory parameters for prediction of survival in patients with PBC and PSC. The most popular model, the Mayo model, considers prognostic variables such as serum levels of bilirubin and albumin, age, prothrombin time, and the presence of peripheral edema including response to diuretic therapy. Apart from the prognostic model, the level of serum bilirubin is the most heavily weighted variable for prediction of survival. In patients with PSC, interventional endoscopic therapy may produce clinical and biochemical improvement and may prolong transplant-free survival.

Contraindications for OLT include active alcohol and drug abuse, extrahepatic malignancies, sepsis, uncontrolled pulmonary hypertension, and coexistent medical disorders such as unstable coronary artery disease, congestive heart failure, or severe lung disease.

OLT in patients with cholangiocellular carcinoma (CCC) reveals a high rate of recurrence and poor post-transplant survival. Concurrent illnesses that previously precluded consideration for OLT such as infection with human immunodeficiency virus (HIV), have been shown to be acceptable in selected cases with the introduction of potent antiretroviral therapy.

The patient status based on the Child-Pugh score (table 41b.2) and the length of time on the waiting list is still being considered in Europe. In 2002, the Organ

Table 41b.1. Reasons for acute or chronic liver failure potentially requiring liver transplantation.

- Chronic liver disease
  Post hepatitis cirrhosis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerotic cholangitis, Budd-Chiari syndrome, polycystic liver disease, Caroli's disease.
- Metabolic liver disease
  Wilson disease, hemochromatosis, Crigler-Najjar syndrome, α1-antitrypsin deficiency, Familial hypercholesterinemia, primary hyperoxaluria, haemophilia A, Tyrosinemia, Glycogenoses Type I and IV, Familial amyloidotic polyneuropathy, Gaucher's disease, Niemann-Pick disease, Erythropoietic protoporphyria.
- Acute liver failure.

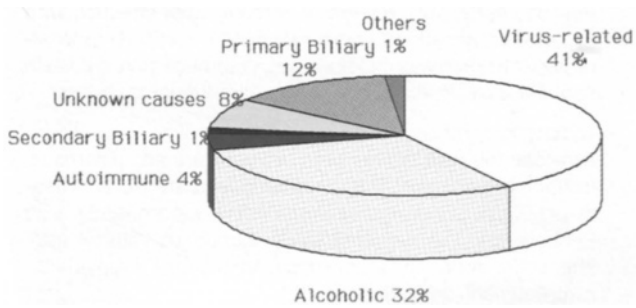

Fig. 41b.1. Indications for liver transplantation in cirrhotic patients (n = 31169) in Europe, during the period January 1988 to December 2004 (data kindly provided by European Liver Transplant Registry; http://www.eltr.org).

Table 41b.2. Child-Turcotte-Classification (Pugh-Modification).

• Points	1	2	3
Albumin (g/dl)	> 3.5	3.0-3.5	< 3.0
Bilirubin (mg/dl)	< 2.0	2.0-3.0	> 3.0
Ascites	no	manageable	refractory to therapy
Encephalopathy	no	light	severe
Quick-Value (%)	> 70	40-70	< 40
CTP-Score:	A (5-6)	B (7-9)	C (> 9)

Table 41b.3. Calculation of the MELD* Score.

$$\text{MELD Score} = 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}^{**}) + 0.643$$

* Model of end-stage liver disease.
** International Normalized Ratio.

Procurement and Transplantation Network (OPTN), along with the United Network of Organ Sharing (UNOS), developed a new system based on the model for end-stage liver disease (MELD, table 41b.3). The MELD score will soon be applied to transplant candidates in the Eurotransplant International Foundation organ procurement system.

A candidate is not considered for liver transplantation if his life expectancy is deemed greater without a transplant. Merion et al. reported that the adjusted relative mortality risk is significantly higher in transplanted patients than in those waiting for OLT with a MELD score of less than 152. Patients with MELD scores of 18 or higher derive significant survival benefit. Candidates with very high MELD scores have an extremely high waiting-list mortality whereas the post-transplant mortality risk seems to rise more gradually [2]. Those patients, whose calculated score is higher than 40 are aggregated with those whose MELD score is equal to 40.

The likelihood of relapse in patients transplanted for alcoholic liver disease is a major issue. It is our policy that patients with alcoholic liver disease must be abstinent for at least 6 months before liver transplantation. The Department of Psychosomatic Medicine and Psychotherapy at our university hospital established a group psychotherapy program with the aim of establishing alcohol abstinence and compliance of health behavior. Therapy consists of a 6-month program including 18 hours of group sessions. The alcohol concentration in the breath and alcohol metabolites in the urine is measured at every group session. Preliminary results presented by Erim et al (the 7th Annual Meeting of the European Association for Consultation Liaison Psychiatry and Psychosomatics and the 25th European Conference of Psychosomatic Research) suggest that structured cognitive-behavioral group therapy has a beneficial effect on the health behavior of these patients.

41b.2. Acute Liver Failure

The indication for liver transplantation in patients with acute liver failure must consider its etiology (table 41b.4). In principle, every chance should be given to allow recovery of liver function without liver transplantation, since acute liver failure frequently resolves with restitutio ad integrum, so avoiding a lifelong immune-suppression. If transplantation is deemed necessary, it must be performed without delay before prognosis worsens, hence patients with acute liver failure should be promptly transferred to a transplantation center.

The prognosis of acute liver failure is closely linked to the development of brain edema and a degree of encephalopathy. Therefore, the monitoring of intracranial pressure is of special significance. Beyond that, the general condition of the patient has a substantial influence on the success of a liver transplantation. Grade-IV encephalopathy, bleeding, as well as severe jaundice are considered particularly unfavourable. The great risk of septic complications following transplantation also accounts for high mortality. Furthermore, the duration of stay in the intensive care unit, intubation and the extent to which participation other organ systems are implicated (kidney failure, haemodynamic instability, ARDS etc.) are also of prognostic significance.

The necessity for a liver transplantation can be measured more closely by prognostic scores. The most important and most frequently used prognostic score

Table 41b.4. Reasons for acute liver failure.

- Viral disease
  Hepatitis A, Hepatitis B (with or without super infection with hepatitis D), Hepatitis C (extremely rare), Hepatitis E, other viral hepatitis (Herpes simplex viruses, Cytomegalovirus, Epstein Barr viruses, Varicella Zoster viruses, Para-influenza viruses).
- Toxicity/Idiosyncrasy
  Paracetamol, halo genius ores of hydrocarbons, Halothane, Isoflurane, Enflurane, INH, Rifampicin, Not steroid antirheumatics, Gold, Sulfonamides, Tetracycline, Ketoconazole, Mao Hemmer, tricyclic antidepressives, Allopurinol, Valproic acid, Phenytoin, Disulfiram, Methyldopa, Amiodarone, Propylthiouracil, Coumarin derivatives.
- Other causes
  Death cap (Amanita phalloides), acute pregnancy fat liver, Reye syndrome, Wilson's Disease, Budd-Chiari syndrome, Hyperthermia, Heat stroke.

Table 41b.5. King's College Criteria.

Patients with acute liver failure will also need a transplantation at security of bordering probability, if the following finding constellation is present.

In the case of paracetamol intoxication:

- pH < 7,3

or

- PTT > 100 sec and creatinine > 3.4 mg/dl and encephalopathy III° or IV°

In all other cases of acute liver failure:

- PTT > 100 sec (Quick < 7% or INR>6,7)

or at least 3 of the following criteria:

- Age < 10 years or > 40 years

unfavourable aetiology of the liver failure
(Cryptogenic hepatitis, halothane-hepatitis, intoxication with drugs)

- Jaundice > 7 days prior to the onset of encephalopathy

Table 41b.6. Clichy-Criteria.

By viral hepatitis:	Encephalopathy III° or IV° Factor V > 20% aged >30 Factor V < 30% aged < 30

in clinical practice is the "King's college criteria" (table 41b.5). This includes indices for liver transplantation, differentiating between acute liver failure due to paracetamol intoxication or due to other causes. A further score use to evaluate the necessity for transplantation in fulminant liver failure of viral genesis is "the Clichy criteria" (table 41b.6). This focuses on the age of the patient, the concentration of the coagulating factor V and the development of encephalopathy.

In patients with a transplant-worthy yet potentially reversible acute liver failure, the possibility of an auxiliary transplantation can be considered, in order to avoid lifelong immunosuppressive therapy. Favorable indications for an auxiliary transplantation may include fulminant hepatitis A, paracetamol intoxication as well as pregnancy fat liver. Auxiliary liver transplantation can be further discussed in fulminant hepatitis B (also with HDV co-infection) and halothane-induced acute liver failure. It should also be mentioned that particularly crucial to the consideration of auxiliary transplantation is the extent of liver cell necrosis and moreso the potential regeneration ability. However, since there are notable predictors for the latter, the practice of auxiliary liver transplantation nowadays has been virtually abandoned.

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41c. Patient Evaluation

V. Cicinnati, G. Gerken

Evaluation of a potential transplant candidate is a complex and time consuming process that requires a multidisciplinary approach. This process must identify extrahepatic diseases that may exclude the patient from transplantation or require treatment before surgical intervention. The protocol for evaluation of our potential transplant candidates as well as the potential contraindications to liver transplantation is demonstrated in tables 41c.1 and 41c.2.

Table 41c.1. Evaluation protocol for potential transplant candidates.

- Clinical evaluation: History and physical examination.
- Ultrasonography with Doppler.
- Lab tests: blood group, hematological tests, chemistry, coagulation profile, C-reactive protein, pregnancy test, thyroid function tests (TSH, T3, T4), immunoglobulines IgA, IgG, IgM, iron, transferring, ferritin, α-1 antitrypsin, ceruloplasmin, tumor markers (CEA, AFP, CA19-9), factors V, VII and VIII, protein C and S, urine sediment.
- First informed consent.
- Serology test: hepatitis A, B and C, HIV, CMV, HSV, EBV.
- Chest X-rays.
- Electrocardiogram, echocardiography, stress test (and if abnormal further cardiological screening).
- Pulmonary function testing.
- Upper and lower endoscopy.
- Abdominal MRI or "all in one" CT scan.
- Mammography (females >35 years).
- Physician consultations (gynecologist, urologist, cardiologist, neurologist, dentist, ENT physician).
- A meticulous psychosocial case review (Department of Psychosomatic Medicine and Psychotherapy).
- Anesthesiological consultation.
- Final informed consent.

Table 41c.2. Absolute and relative contraindications to liver transplantation.

- Absolute contraindications
  Sever cardiopulmonal disease, AIDS, florid sepsis, malignant secondary disease or metastasis of primary liver tumor, active alcohol or drug consumption.
- Relative contraindications
  Pronounced myodystrophia (strongly reduced general state), intrapulmonary Shunts, portal vein thrombosis, chronic renal failure, unstable social surrounding field, lacking of patient compliance.

41d. Pre-Transplantation Management Issues

S. Beckebaum, V. Cicinnati, A. Frilling

For patients with esophageal varices, non-selective beta-blockade remains the treatment of choice for prophylaxis of bleeding. In cases of recurrent variceal hemorrhage despite prior interventional endoscopic therapy or refractory ascites, transjugular intrahepatic portosystemic shunts (TIPS) have been used as an approach to lower portal pressure and as a bridging therapy for transplant candidates. The identification of predisposing factors and the application of lactulose and nonabsorbed antibiotics remain essential for prophylaxis and management of hepatic encephalopathy (HE). Hepatorenal syndrome (HRS) in end-stage liver disease patients is not infrequent. The probability of HRS occurrence among non-azotemic cirrhotic patients with ascites at 1, 2 and 5 years has been reported to be 18%, 32%, and 39-41%, respectively [1, 2]. Although its pathogenesis is complex, HRS has long been recognized as being reversible in cases of well-functioning OLT. However, depending on the duration and severity of HRS, the reversibility of HRS following liver transplantation is often delayed and incomplete. Special attention regarding specific, disease-related therapy prior to surgery should be given to transplant candidates undergoing OLT for HCC or virally-related liver diseases, especially hepatitis B.

41d.1. Waiting-List Monitoring of Hepatitis B Liver Transplant Candidates

Until about a decade ago, HBV infection was considered a contraindication to OLT, due to recurrent viral hepatitis that may lead to graft failure and the need for re-transplantation. The 3 year survival rate for replicative HBV patients without adequate antiviral treatment after OLT was only about 60% as opposed to survival rates of over 80% for patients with non-HBV-related liver diseases [3]. Efficient antiviral therapy is required for viremic patients awaiting OLT for HBV-related liver damage. The ultimate goal of treatment is suppression of viral replication to undetectable HBV-DNA titers

prior to OLT. Besides serial monitoring of serum HBV DNA, HBV sequence analysis, especially of the polymerase and the "a" epitope of the surface antigen, may be a requisite diagnostic tool in order to provide optimal therapeutic management for inhibition of viral replication before OLT. Interferon (IFN)-alpha is contraindicated for patients with decompensated liver diseases. Lamivudine (LAM) or adefovir (ADV) may be used as first-line therapy in replicative pre-transplant patients. Pre-transplant nucleoside analogue treatment can also be administered in advanced stages of liver cirrhosis and often leads to recompensation of liver disease and prolongation of pre-transplant survival. Treatment with ADV may lead to impairment of renal function. The dosage of the ADV interval should be adjusted for patients with creatinine clearance of less than 50 mL/min [4].

41d.2. Waiting-List Monitoring and Treatment of Hepatitis C Liver Transplant Candidates

Only a few studies have looked at the tolerability and efficacy of antiviral therapy in HCV patients before OLT [5-6]. Although pre-transplantation IFN-alpha therapy reduced HCV titers in some patients, adverse events associated with therapy were frequent [5]. These side-effects and the need for dose reduction or withdrawal often prevent efficient eradication of the virus in HCV patients awaiting liver transplantation. Furthermore, it has been shown that therapy is less effective in patients with advanced liver disease (Child Pugh B or C classification). In addition, animal studies and human trials of hepatitis C immunoglobulin for the prevention of post-OLT HCV have been disappointing in terms of HCV recurrence in the allograft [7-9].

41d.2.1. Adjunctive Treatment and Staging of Hepatocellular Carcinoma Transplant Candidates

Although OLT has been recognized as the most effective means of treating HCC patients who meet the Milan criteria (one tumor < 5 cm in diameter or up to three tumors each < 3 cm), success has been limited by long waiting times for transplantation, with disease progression or death while on the waiting list. Therefore both the OPTN and the UNOS established special rules for graft allocation to HCC transplant candidates [10]. Additional MELD points were awarded to HCC transplant candidates according to tumor size and number of tumors. This provided significant advantages for HCC candidates, because additional MELD scores were considered for both stage I and stage II lesions. As a result, 23% of the patients on the waiting list for OLT during 2002, were listed for HCC. These results prompted recent changes in organ allocation policy in 2003; the MELD score for patients with stage I and stage II lesions were lowered from 24 to 20 and from 27 to 24, respectively. Nine months later, all additional MELD scores were removed for stage I HCC.

Waiting-list drop-out rates may be reduced by the application of bridging therapies, such as transarterial chemoembolization, radiofrequency ablation, laser therapy, percutaneous ethanol injection, cryotherapy, and transarterial radiotherapy for downstaging of the tumor. Pretransplant tumor diagnosis is based upon established imaging criteria and/or alpha-fetoprotein (AFP) level. Liver biopsy may be performed in selected cases, such as in patients with tumor lesions smaller than 3 cm and normal AFP levels where discrimination between regenerative nodules and malignant tumors is difficult [11]. It is our policy to perform routine follow-up examinations (MRI or CT scans and bone scintigram) of HCC transplant candidates trimonthly for early detection of disease progression and extrahepatic tumor spread.

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CHAPTER 42

OPERATIVE DATA

42.1. Surgical Procedure Generally

G.C. Sotiropoulos, H. Lang, C.E. Broelsch

42.1.1. General Considerations

Despite some innovations in the area of the liver transplantation the orthotopic transplantation of a complete donor liver still remains the standard therapy for both chronic and acute liver failure. In principle, this requires the entire removal of patient's own liver. Hepatectomy, however, can take place with or without receipt of the retrohepatic vena cava, which influences the haemodynamics during the anhepatic phase.

Hepatectomy involving preservation of the retrohepatic vena cava –with the ensuing transplantation being performed by employing the Piggy-back technique– does not necessitate the release of the retrohepatic vena cava from the retroperitoneum. Instead, the liver is prepared from the vena cava. This operative step is temporally more complex than hepatectomy using the standard technique, as it requires good bleeding control as well as puncturing ligations of all dorsal veins leading from the liver into the vena cava. This preparation phase can additionally lead to increased bleedings from the liver due to very bad coagulation and end-stage liver cirrhosis. However, this pocedure clearly reduces risk of bleeding from retroperitoneal collaterals.

The advantage of cava preservation is improved haemodynamics of the patient, since the blood flow from the lower extremities and renal veins is continuously maintained. For further haemodynamic stabilization, the performance of a temporary portocaval shunt after end-to-site anastomosis between vena portae and vena cava could prove beneficial.

Hepatectomy with preservation of the retrohepatic vena cava is always considered necessary, if the available graft does not offer a suitable vena cava. This is usually the case in partial liver transplants (split liver transplantation or Living related Transplantation), where retrohepatic vena cava can only be assigned to one half liver (in case of split) and donor.

In cases of liver transplantation for malignant indications, a lymphadenectomy should, in principle, be performed in the liver hilum and along the common hepatic artery and the coeliac trunk. In rare cases, when attempting a more "radical" operation, operative extensions may be necessary (e.g. hepatectomy combined with a Whipple operation in the case of advanced Klatskin tumors or simultaneous resection of the intra-abdominal primary tumor during liver transplantation for neuroendocrine metastasis).

42.1.2. Urgent Hepatectomy

Rescue hepatectomy (e.g. due to haemodynamic instability in the case of acute liver failure or initial transplant non-function) must always be performed with preservation and/or with reconstruction of the retrohepatic vena cava, where the funcion of one portocaval end-to-side shunt (internal shunt) is obligatory.

42.1.3. Combined Liver and Kidney Transplantation

In combined liver and kidney transplantation, liver transplantation takes place first and, after closure of the abdomen over a second (inguinal) incision, the kidney is implanted into the right or left Fossa iliaca. Should there be a lack of space (as, for example, in polycystic liver and kidney disease) a simultaneous one-sided nephrectomy is mandatory. Due to the long duration of the operation and the large retroperitoneal wound surface as well as the necessary immunsuppression, these procedures are at risk of infectious complications. A two-stage procedure with primary nephrectomy prior to a scheduled combined liver and kidney transplantation may be meaningful in individual cases under few special criteria. In principle, the lack of space is caused by the liver. A space procurement by removal of a polycystic kidney prior to planned liver transplantation is viable if the general state of the patient is good. However, each additional operation prior to a successful transplantation relatively worsens operational conditions.

42.2. Donor Operation

G.C. Sotiropoulos, H. Lang, C.E. Broelsch

42.2.1. Full Size Liver Graft

Procurement of the cadaver liver graft is usually part of a multiorgan retrieval including kidneys, pancreas, heart and lung from heart beating but brain dead donors. The operation is performed in a standardized systematic way. The liver is generally removed after initial organ dissection and cold perfusion, when thoracic organs are already harvested.

To harvest the abdominal organs, a complete midline laparotomy from the xyphoid to the os pubis is performed. After careful exploration of the abdominal cavity for pathologies, the liver is examined for such macroscopic features as consistency, color and size.

The surgical strategy involves a partial mobilization of the liver with division of its major ligaments and dissection of the hilar structures. Perfusion catheters are placed into the lower abdominal aorta and portal vein. After cross-clamping of the abdominal aorta beneath the diaphragm and distal from the inserted cannula, cold perfusion is initiated. Additionally, the inferior mesenteric artery is ligated and the vena cava incised for the wash out of blood. After perfusion of the abdominal organs (protocol follows different specifications of the perfusion fluid), the liver is removed together with an aortic patch, preserving its anatomical structures which often varies (fig. 42.1-42.4). Its vascular pedicles are definitively isolated on the bench and prepared for anastomoses after a wash out of the bile duct.

The final decision regarding the suitability of a donor liver can only be made at the end of the procedure, when laboratory results, donor history and histology of the liver are conclusive.

42.2.2. Split Liver Graft

After laparotomy, the vascular and biliary structures are dissected and lobular branches are identified. Right and left branches of the bile duct, hepatic artery and portal vein are separated. The left and middle hepatic veins nearly always join to form a common trunk, which is isolated and divided from the inferior vena

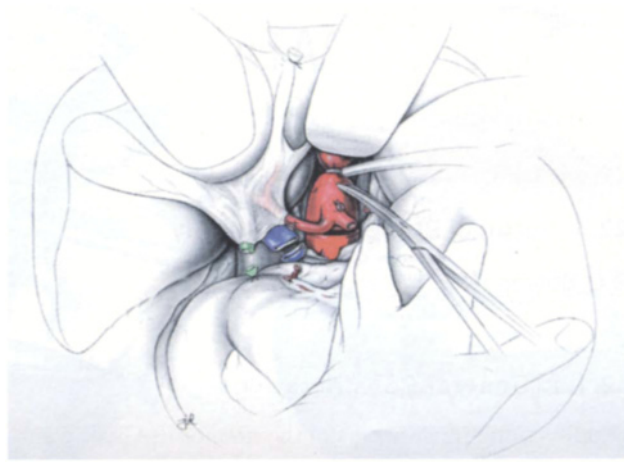


Fig. 42.1. Operative situs prior to liver harvesting: Dissection of bile duct and portal vein is followed by excision of celiac trunk with a corresponding aortic patch.

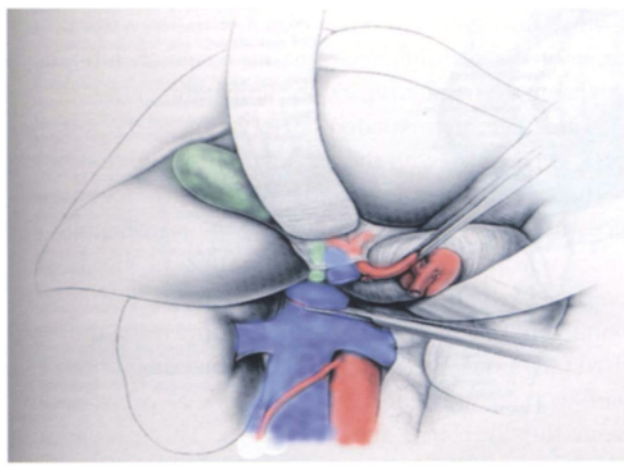


Fig. 42.2. Resection of the infrahepatic caval vein above the confluence of the renal veins.

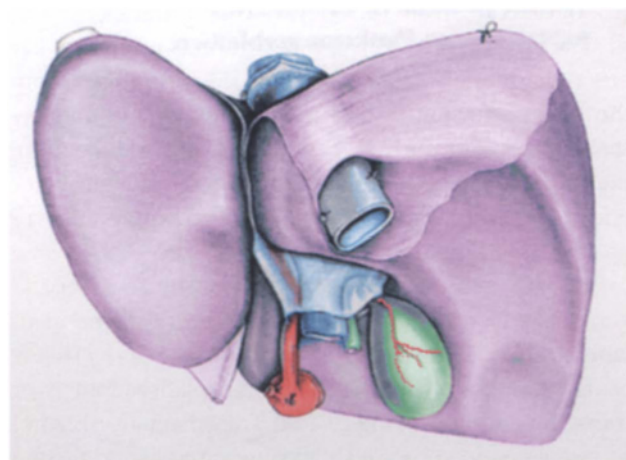


Fig. 42.3. Liver after harvesting.

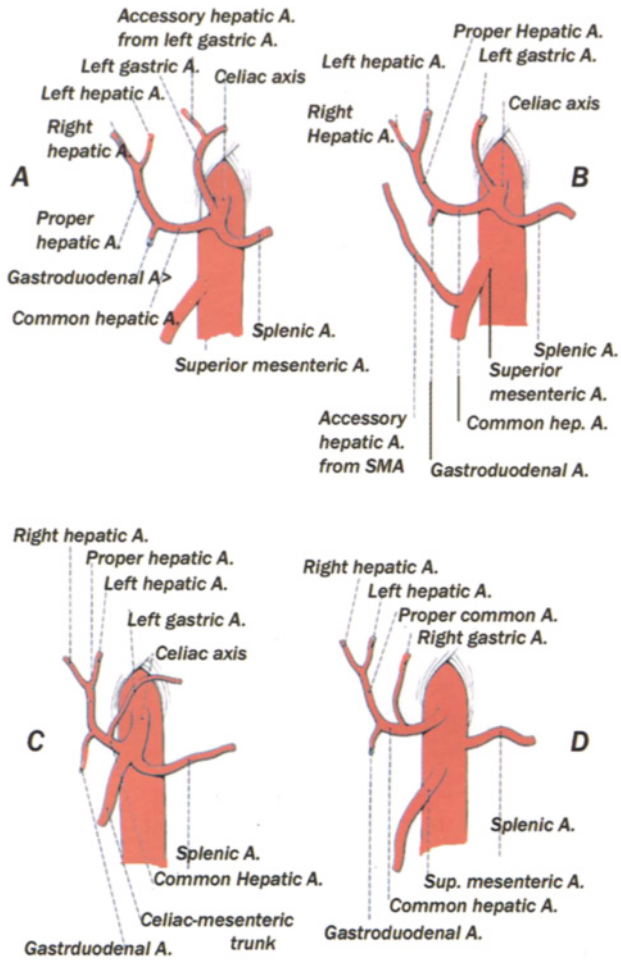


Fig. 42.4. Anatomical variations of the arterial supply of the liver.

cava. Depending on the recipient size, the parenchyma is dissected along the main portal fissure, separating the right and left side. Dissection of the hilar structures must be very limited to prevent ischemia of the bile ducts. The right side graft comprises liver segments I and V to VIII according to Couinaud. All common structures remain attached to the right graft. The retrohepatic vena cava is retained with the right graft, due to possible anatomical variations of its venous drainage. Vascular grafts can be interposed to increase the length of the vessels for anastomoses.

42.3. Recipient Operation

G.C. Sotiropoulos, C.E. Broelsch

The perfect timing for the surgical explantation and implantation must be determined. Cold ischemic time has to be kept minimal. Preparation of the donor organ is performed on a back-table. The donor liver must be examined for anatomical variations, potential injuries and quality.

Before laparotomy, a veno-venous bypass –if needed– can be administered by installation of large venous catheters via the femoral and subclavian/axillary vein (fig. 42.5). It entails decompression of the inferior vena cava and portal circulation using Gott shunts with returned flow into the superior vena cava through the subclavian/axillary vein. This can either be performed by puncture using the Seldinger technique or alternatively the conventional surgical technique after femoral and axillary venotomy. However, the veno-venous bypass is not universally accepted (table 42.1).

42.3.1. Hepatectomy

The upper abdomen is opened through a bilateral subcostal incision with a midline extension to the xyp-

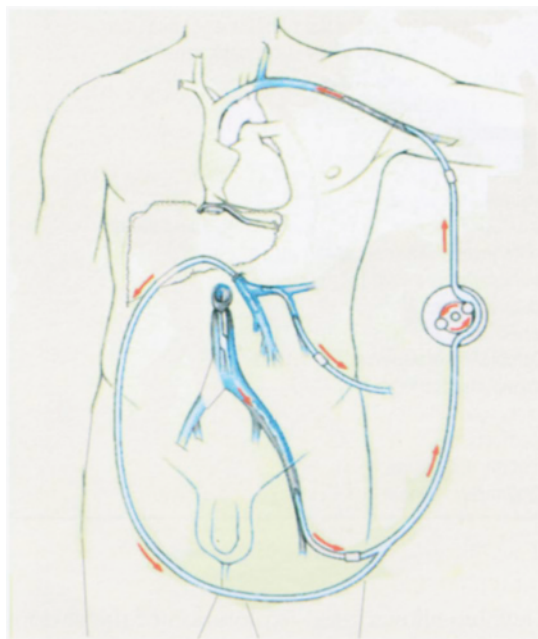


Fig. 42.5. Veno-venous bypass. The portal vein circulation can be drained through a catheter placed either in the superior or the inferior mesenteric vein.

Table 42.1. Surgical Steps in deceased donor liver transplantation; *steps in the case of performance of a veno-venous bypass.

Hepatectomy
- Preparation of the operatory field
- (Preparation of vascular approaches for the veno-venous bypass)*
- Laparotomy
- Suction of any ascitic spillage if present
- Xiphoid process excision
- Interruption of the round ligament
- Precision haemostatic control
- Sectioning of falciform ligament
- Positioning of abdominal retractors
- Approach to the hepato-duodenal ligament
- Interruption of peritoneal reflection and ligation of main collateral veins and lymphatics
- Identification and sectioning of hepatic artery
- Removal of peritoneal lymphnodes
- Preparation of the hepatic artery-The gastroduodenal artery may either be sectioned or kept in place until anastomosis
- Bile duct isolation-Bile duct sectioning
- Portal vein skeletonization from the hepatic hilum to the pancreas
- (Vevo-venous bypass)*
- (Axillary and saphenous veins cannulation)*
- (Portal vein cannulation)*
- (Preparation of circuit)*
- (Bypass activation)*
- Sectioning of left triangular ligament
- Sectioning of coronary ligament and access to frontal wall of the suprahepatic vena cava
- Interruption of right coronary ligament and freeing of the liver from the diafragm
- Interruption of hepatogastric ligament
- Interruption of peritoneal reflection medially to the vena cava
- Circumferential freeing of the suprahepatic vena cava
- Circumferential freeing of the subhepatic vena cava
- Clamping of suprahepatic cava
- Clamping of subhepatic cava
- Hepatectomy
- Retroperitoneal haemostasis

Transplant procedure
- Wash up of the liver reperfusion with albumin solution
- Suprahepatic vena cava anastomosis
- Subhepatic vena cava anastomosis
- Portal anastomosis
- Reperfusion
- (Completion of veno-venous bypass)*
- Arterial anastomosis
- Biliary anastomosis
- Haemostasis
- Abdominal drainage
- Abdominal closing

hoid, which allows good exploration of the abdominal cavity to assess the pathology. Previous surgery and severe portal hypertension can complicate the work. After dissection of overlying adhesions the left triangular and falciform ligaments are divided (fig. 42.6), followed by transection of the gastrohepatic ligament. Now the liver hilum can be reached and examined in detail. An organised portal vein thrombosis needs to be excluded and anatomic variations need to be detected. The dissection of the liver hilum is then started by careful opening of the covering peritoneal tissue of the hepatoduodenal ligament. The dissection of the hepatic artery, portal vein and common bile duct takes place very proximal in the hilum to preserve maximal length for the mentioned structures, which later need to be anastomosed with the graft. The hepatic artery should be divided first. Accessory vessels, e.g. additional left or right hepatic arteries occur often and need to be detected. The cystic and common bile ducts are then transected. While early transection of the artery, the portal vein is transected after complete mobilisation of the liver, prior to hepatectomy due to possible congestion in the mesentericoportal system. After skeletonization of the ligamentous structures including areolar, lymphatic and nerve tissue the mobilisation of the liver continues (fig. 42.7). The retrohepatic vena cava is prepared carefully under conditions of PEEP-ventilation to prevent air embolism. The liver can be excised from the retrohepatic vena cava leaving the entire vessel in place.

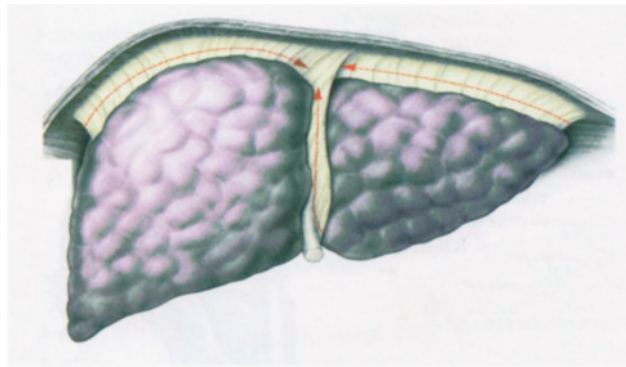


Fig. 42.6. Division of the right/left triangular and falciform ligaments.

If a full size orthotopic liver transplantation is planned a small segment of the retrohepatic vena cava can be removed after clamping (fig. 42.8). In certain such cases, the use of an extracorporeal veno-venous bypass is helpful in maintaining an adequate cardiac output and in achieving portal venous decompression.

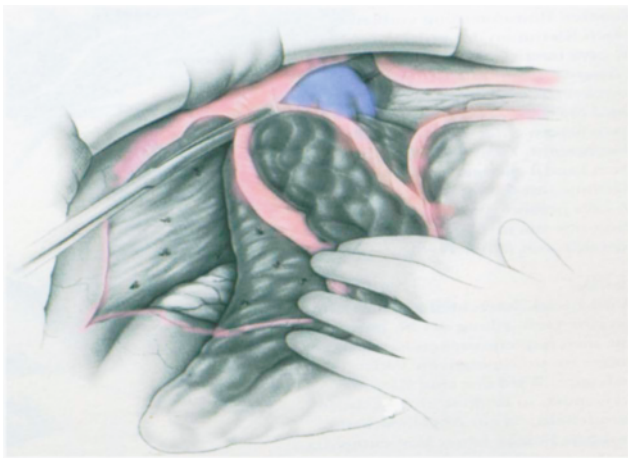


Fig. 42.7. Mobilisation of the right liver lobe.

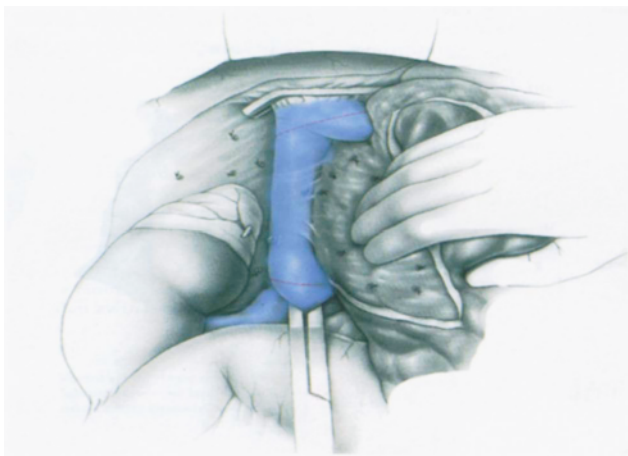


Fig. 42.8. Complete mobilisation of the liver, clamping of supra- and infrahepatic caval vein, transaction lines are marked for the case of "conventional" liver transplantation.

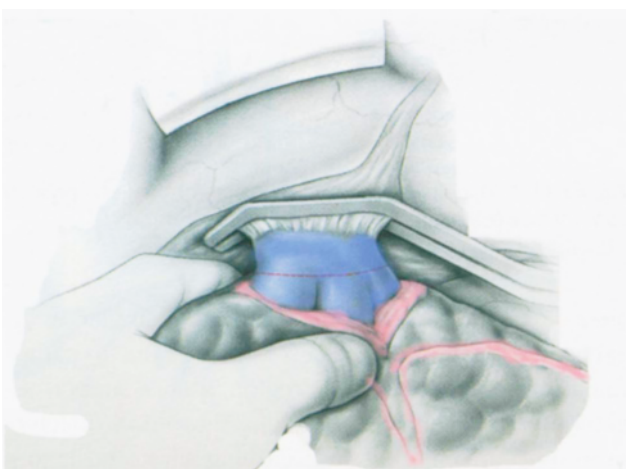


Fig. 42.9. Clamping of the suprahepatic caval vein. The dissection has to be performed as possible near to the liver surface.

The "piggy back" technique in full size liver transplantation and split liver transplant procedures requires that the accessory hepatic venous branches of the retrohepatic vena cava be dissected to preserve the caval segment. Therefore a vessel clamp is placed longitudinally across the posterior vena cava prior to hepatectomy to close the hepatic veins and maintain blood flow in the caval segment (fig. 42.10a-b). In such cases, an extracorporeal veno-venous bypass is not needed.

After completing the mobilization of the liver, hepatectomy is performed following dissection of the portal vein (fig. 42.9, 42.11a-b). Once the liver is removed, hemostasis can sometimes be difficult to achieve due to the development of coagulopathy in the anhepatic phase. Multiple techniques of hemostatic control like running sutures, cauterization with electrocautery or argon beam cauterization as well as pharmacological regiments are helpful.

42.3.2. Transplant Procedure

Whole liver grafts obtained from cadaver donors can retain the vena cava and therefore be transplanted using either the conventional or the "piggy back" technique.

The conventional technique involves the graft being placed in the operating field and kept cold, while vascular venous cuffs are prepared for anastomoses. Usually, anastomoses are performed in the following order: suprahepatic vena cava, infrahepatic vena cava, portal vein. After unclamping and reperfusion with blood, arterial anastomosis is performed followed by biliary anastomosis.

42.3.2.1. *Venous Anastomoses*

The upper caval anastomosis is reconstructed first (fig. 42.12). One suture is placed at each corner of the vessel to be sutured (non-absorbable material, e.g. 3-0 Prolene). The vessel will be run around in two halves of its circumference starting from the two corners, only the posterior half of which is sutured on the inside within the eversed vessel lumen. The suture must prevent stricture of the anastomosis and also ensure a perfect seal at reperfusion to prevent hemorrhage. After completing the lower caval anastomosis using the same technique, the liver is flushed using an albumin

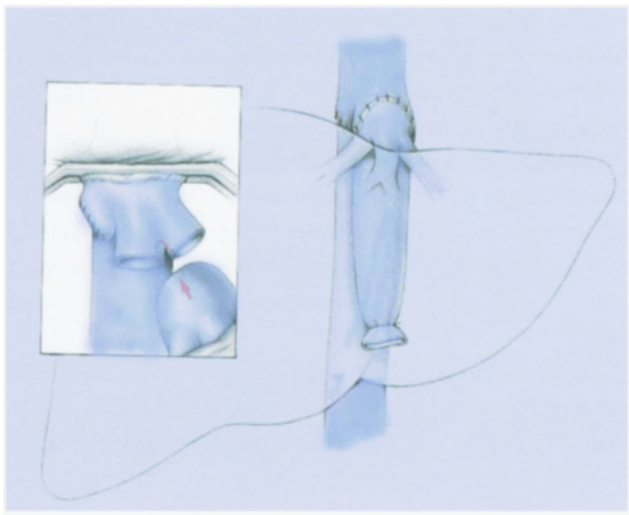


Fig. 42.10. a: "Piggyback" technique: The anastomosis can be performed between the supra-hepatic caval vein of the donor and the middle and left hepatic vein of the recipient.

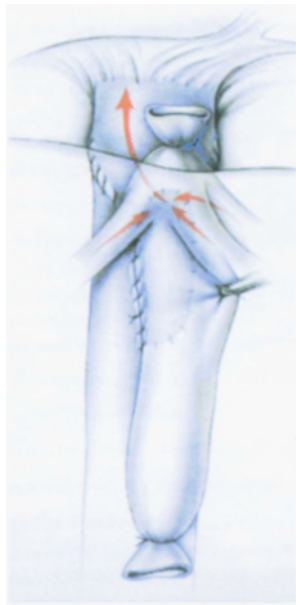


Fig. 42.10. b: "Piggyback" technique modification: Wide anastomosis between donor's and recipient's caval vein.

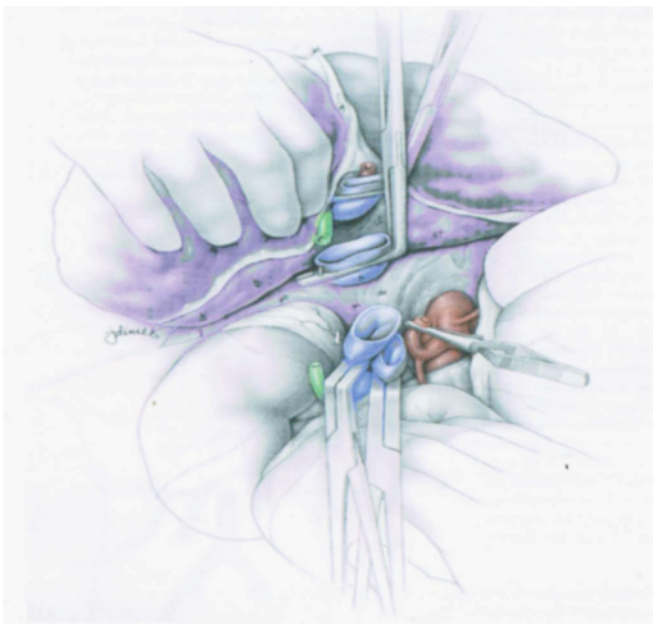


Fig. 42.11. a: Transection of hepatic artery, portal vein, bile duct and caval vein.

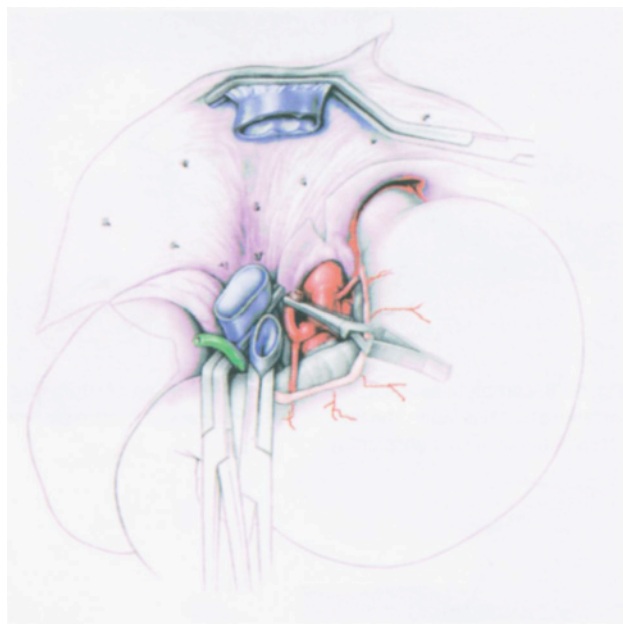
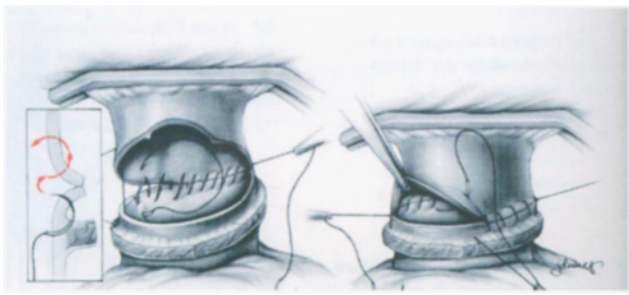


Fig. 42.11. b: Operative situs after removing of the liver- prior to conventional technique.

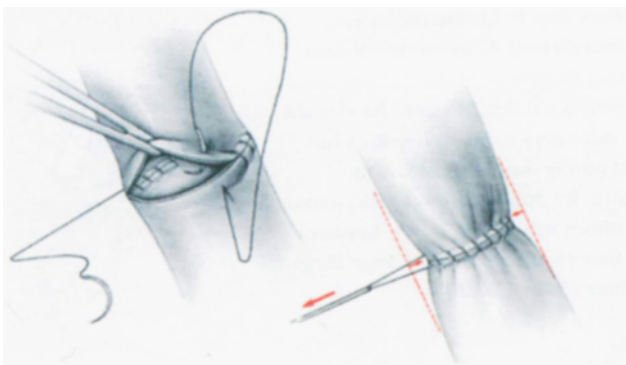
solution via the portal vein cannula to remove the preservation fluid, which could cause severe cardiac problems due to its high content of potassium. The portal cannula is removed after clamping. For portal venous reconstruction, both the donor and recipient vessel sides are trimmed to the appropriate length for anastomosis. The portal venous blood flow is usually restored after an end-to-end anastomosis using a similar surgical technique (fig. 42.13). In some cases, due to pathological changes in the portal region, special surgical techniques are needed such as like declotting or interposition of a vein graft with ensuing anastomosis to a patent confluence of the mesenteric and splenic vein.

After provisionally unclamping the suprahepatic ca-



a b

Fig. 42.12. Anastomosis of the suprahepatic caval vein.



a b

Fig. 42.13. Anastomosis of the portal vein.

val vein, the suture threads are tied following a complete distension of the portal anastomosis. After flushing the infrahepatic caval vein, the anastomosis is tied and clamps on infrahepatic caval vein and portal vein removed to start the reperfusion of the graft.

42.3.2.2. *Arterial Anastomosis*

An optimal positioning of the arterial anastomosis and size match are indispensable to guarantee an optimal blood flow. Magnifying loops are necessary for a perfect surgical technique. The arterial reconstruction is usually carried out as an end-to-end anastomosis (interrupted or running sutures, e.g. 6-0 or 7-0 Prolene) of the celiac trunk of the donor to the recipient vessel stump (fig. 42.14a-b). The anastomosis site depends on the length and caliber of the donor vessel which implies various possibilities of the hepatic artery reconstruction in the recipient e.g. at the proper hepatic artery level, near or at the gastroduodenal artery branch,

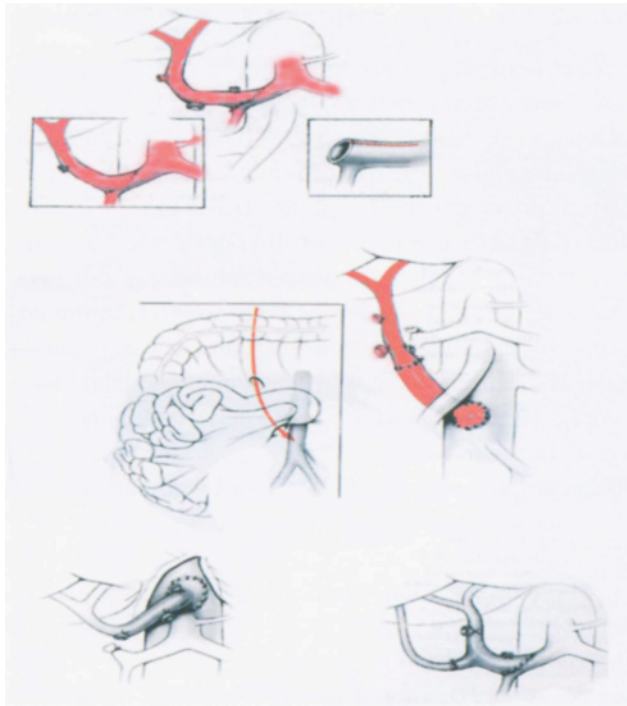


Fig. 42.14. a: Anastomosis of the hepatic artery in different techniques.

Fig. 42.14. b: Reconstruction of the hepatic artery through aortic segment, infrarenal and supra-celiac.

the common hepatic artery level or the proximal celiac axis. The openings of two branches can be interconnected to a resulting branch patch. Anastomosis can also be performed with a Carrel patch of the donor artery to the abdominal aorta of the recipient. After removing the vessel clamps, the liver is rearterialized.

Similar techniques are used in split liver and living donor liver transplantation where reconstruction without a sufficient arterial patch can sometimes be technically more demanding.

42.3.2.3. *Biliary Anastomosis*

Perfect hemostasis must be achieved before commercing biliary reconstruction, the final step in liver transplantation. Usually a physiologic choledochocholedochostomy end-to-end (duct-to-duct) anastomosis is preferred, providing the recipient duct is free of disease and of suitable size diameter. It is performed with interrupted or running absorbable sutures e.g. 6-0 PDS. Donor and recipient bile ducts are adjusted to the appropriate length while the recipient duct is trimmed back as much as is feasible to maintain maximum blood supply. The additional use of a T-tube stent is not universal but may help in the early postoperative course to decompress the anastomosis and examine the bile fluid. Intraoperatively the T-tube can be used to check the anastomosis for leaks (e.g. T-tube cholangiogram).

The end-to-end anastomosis is technically easy to achieve and allows later interventional diagnostic and therapeutic access to the biliary tract. In recipients with bile duct disease or previous bile duct surgery an end-to-side choledochojejunostomy is performed (fig. 42.15). The reconstruction is accomplished with a 40 cm long Roux-en-Y limb of the proximal jejunum.

42.3.2.4. *Special Considerations in Partial Liver Grafts*

In partial liver grafts of the cadaver right hemi-liver obtained by split liver technique (fig. 42.16) retaining the vena cava, transplantation using the conventional or "piggy back" technique is feasible (fig. 42.17). In grafts of the left liver obtained by split liver technique (living and cadaver donor) or the right hemi-liver of a living donor, the lack of the retrohepatic segment of the vena cava renders necessary the practice of "piggy back" or similar techniques in anastomosing the orifice

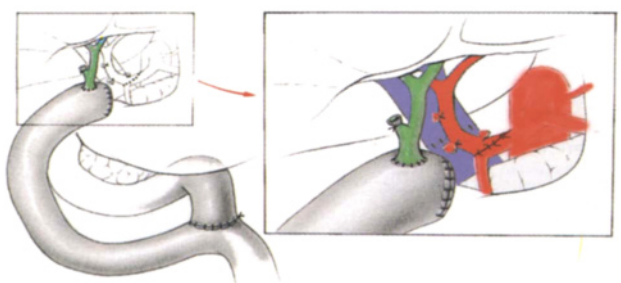


Fig. 42.15. Hepatico-jejunostomy.

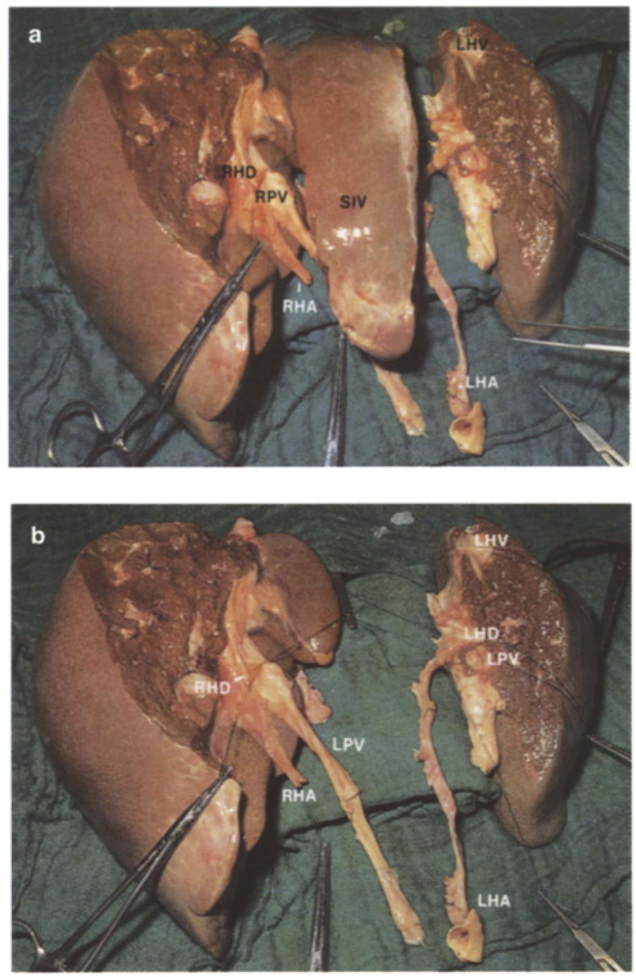


Fig. 42.16. a-b: Split liver grafts: The left lateral lobe can be removed initially and the segment IV subsequently from the right lobe. LHA: left hepatic artery; LPV: left portal vein; LHD: left hepatic duct; LHV: left hepatic vein; SIV: segment IV; RHA: right hepatic artery; RPV: right portal vein; RHD: right hepatic duct.

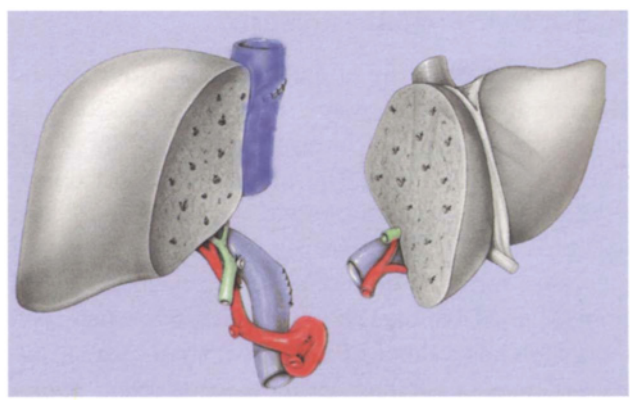


Fig. 42.17. Split liver transplantation: hepatic artery, portal vein and bile duct are left to the right graft.

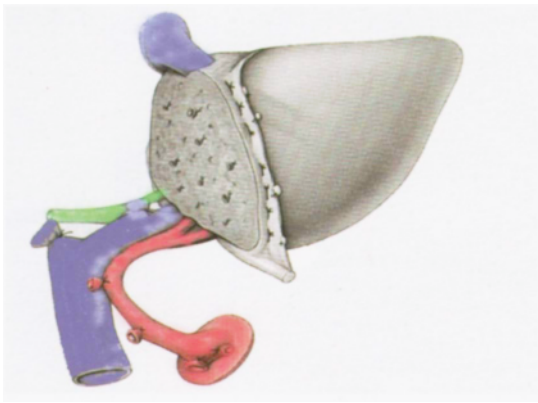


Fig. 42.18. Split liver transplantation: left lateral graft prepared to implantation.

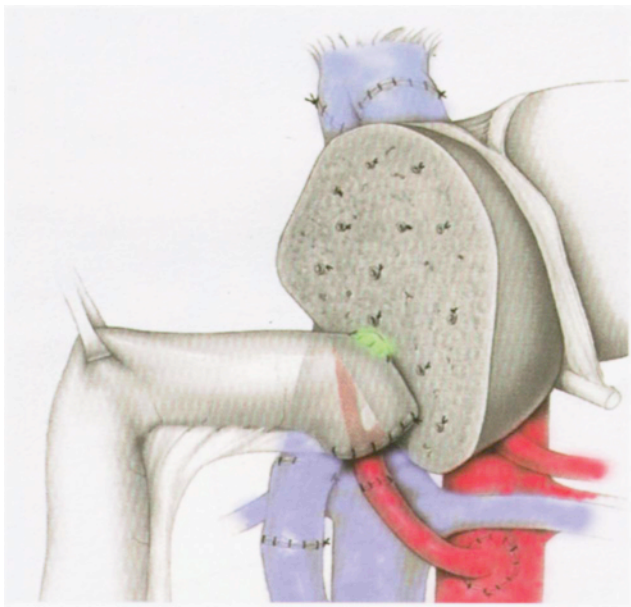


Fig. 42.19. Implantation of a left liver graft: Reconstruction of hepatic artery and portal vein.

of the hepatic veins laterally to the recipient cava (fig. 42.18). To perform an end-to-side anastomosis of the donor liver vein to the recipient caval vein, the orifice on the hepatic veins is modeled by dividing the septa and widening the incision on the vena cava. After completing the anastomosis and flushing the liver, the subhepatic donor caval stump is closed with a vascular stapler. All other anastomoses are performed using standard techniques as described earlier (fig. 42.19). In general it is necessary to resort to vascular graft when transplanting split liver grafts.

42.3.2.5. *Intraoperative Bleeding Problems*

Due to the portal hypertension with splenomegalia and corresponding thrombocytopenia as well as the limited coagulating function characterising cirrhotics, substantial bleeding complications can occur intraoperatively in the context of the hepatectomy. Apart from a careful staunching of bleeding, the early placement of a portal-femoro-axillary bypass with the aim of reducing the pressure in the outflow-area of the mesenteric vein, can substantially contribute to the reduction of the bleeding problem. After reperfusion of a good donor organ, a rapid improvement of the coagulation situation often with a spontaneously stoppage of diffuse bleedings, is to be expected. However, a hyperfibrinolysis can arise particularly in marginal donor organs after reperfusion, which can lead to a substantial bleeding inclination. Supply of the protease-inhibitors Aprotinin (100.000 IEh), best supported by an analysis of the hyperfibrinolysis by means of thrombelastogramm, can lead to a clear improvement of the coagulating situation.

42.3.2.6. *Conclusion of the Operation (Fig. 42.20)*

After careful hemostasis, suction drains are placed around and behind the liver. The abdomen is closed in layers and the skin margins are approximated.

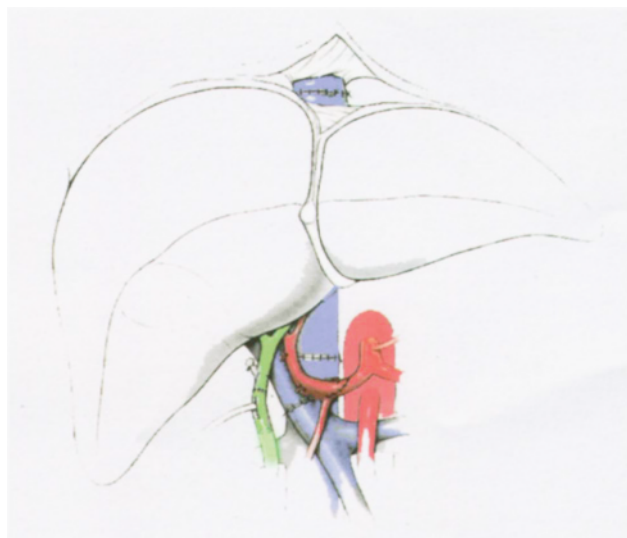


Fig. 42.20. Operative situs after orthotopic implantation of a full-size liver, conventional technique.

CHAPTER 43

LIVING DONOR LIVER TRANSPLANTATION

43.1. Historical Notes

S. Nadalin

43.1.1. Introduction

The disparity between organ demand and the cadaveric donor supply for children resulted initially in a pre-transplant mortality of around 25% and was disproportionately high compared with adult patients [1]. The problem of size mismatch and the different epidemiology of pediatric donorship and terminally diseased children was chiefly responsible for that situation [2]. This stimulated the development of technical innovations, based on the segmental anatomy of the liver, which facilitated transplanting parts of large deceased donor livers into smaller recipients.

The first step in solving the size mismatch problem was the introduction of reduced-size liver transplantation. The technique was originally described by Bismuth and Houssin [3] and entailed of performing a resection of the graft on the back table to reduce it to a size that fitted the small pediatric recipients [3-5]. Although reduced-size liver transplantation decreased the waiting list mortality of nearly 50% among children, it increased the number of adult patients on the waiting list, since the organs were withdrawn from the adult organ pool [6-7].

This problem was addressed by split liver transplantation (SLT), in which a deceased donor liver is divided into two parts for two recipients. The technique was first described by Pichlmayr in 1988 [8, 9]. It allowed the preparation of two split grafts by dividing all vascular and biliary structures and parenchyma for the benefit of two recipients, one receiving a right lobe graft and the other receiving a left lobe (segments 2-4) or left lateral (segments 2-3). The first series of SLT was reported by Broelsch and co-workers at the University of Chicago [10].

The results turned out not to be as expected, but revealed the "Achilles' heel" of the procedure: the cut edge of segment 4 and the biliary system. Hence, the presence of a poorly functioning graft placed both recipients in jeopardy and the increased re-transplantation rate [11]. The outcome was no real increase in donor organ availability for either pediatric or adult recipients. In addition, in regard to adults, a new phenomenon was discovered: the small for size graft syndrome, which prevented the expansion of hemiliver transplant between two adults [12].

All hope for SLT temporarily vanished until the increasing pressure on transplant surgeons prompted them to convert from extracorporeal split procedures of preserved organs to harvesting the donor organs in situ, thereby avoiding the likelihood of a non-viable transplant. Unfortunately, the wider application of the split technique is still hindered by both the lack of experience and unwillingness of some centers to split as well as by the logistics of sharing, making this procedure account for < 20% of all LT performed [13-14].

In the face of the drawback of reduced-size liver transplantation and SLT series and the growing need for liver grafts, the development of segmental LT from a living donor evolved as a natural consequence. The first experience was reported by Raia et al. in Brazil 1989, however the first two recipients died due to medical complications within the early perioperative period [15]. In 1990 the first successful case was published by Strong et al. from Australia. The recipient was a 15 month old child, living-related-liver-donation was performed from the mother [16]. In the early 1990 is Broelsch et al. established the first program for living related liver transplantation at the University of Chicago. He reported the first series of 20 cases under prospective scrutiny and was able to demonstrate the benefit of this procedure for both donor and recipient [17]. Equivalent results were obtained by the group of Tanaka et al. in Kyoto soon afterwards, proving the clinical effectiveness of LDLT in childre [18]. The procedure was gradually adopted more widely, especially in Asian countries, where cadaveric donors were scarce. In 1994, Yamaoka et al. first reported the

use of a right lobe for transplantation, and Marcos et al. demonstrated in their series of 30 patients that right lobe LDLT can be performed with minimal risk to the donor and recipient [19-20]. Up to now, almost 3500 adult-to-child and 2500 adult-to-adult LDLTs have been performed [21].

LDLT emerged as the only innovation to significantly expand the scarce donor pool in countries in which the growing demands of organs are not met by the shortage of available cadaveric grafts.

43.2. Indications, Donor Evaluation

G.C. Sotiropoulos, S. Nadalin

43.2.1. Introduction

In order to optimize the ratio of donor risks to recipient benefits, it is necessary to revise the current selection criteria, to assure that risk factors are estimated for each individual case [22]. For the donors' safety, liver biopsy is routinely performed in all candidates for ALDLT at our transplant center, irrespective of age and body mass index. From April 1998 to August 2004, liver biopsy was performed in 337 potential living donors at the University Hospital Essen, Germany; 21% of these candidates were excluded from donation due to liver steatosis or nonsteatotic hepatopathy [23]. Our strategy is to limit the macroscopic fat content to less than 10%, and even lower when the planned resection volume exceeds 60%. The evaluation of the donors is a cost-effective yet time-consuming process. Clinical examinations, imaging studies, special examinations, biochemical parameters, and psychosocial evaluation prior to donation varies from center to center and has been described elsewhere [24]. In Germany, the cost of evaluation, hospital admission, surgical procedure, and follow-up examinations of donors is covered by the recipient's insurance. Due to the increasing number of potential candidates and the more stringent selection criteria, rejection of potential donors has been reported in about 69%-86% of cases [24-25]. The advantages of LDLT include the feasibility of performing the operation when medically indicated and the short duration of cold ischemia. Initially, segments II and III of the left lateral liver grafts or segments II-IV of the left liver grafts were transplanted. Nowadays, right liver harvesting is generally the chosen procedure for ALDLT; in selected cases the left liver is used if the volume is estimated to be > 40% of the recipient standard liver volume. No anatomical vascular variances seem to be an absolute contraindication for hepatectomy, even though a double right portal vein constitutes a technical challenge in the recipient anastomoses. Some centers refuse donors with a documented biliary anomaly, e.g. a second right hepatic duct draining into the left hepatic duct, as it poses an increased risk of postoperative complications in the recipient [26]. Contraindications include blood group incompatibility and viral infection of the allograft with hepatitis B or C virus for recipients with non hepatitis B- or non hepatitis C-related liver disease. However, donors with cured hepatitis B (positive anti-hepatitis B surface (HBs) status) are not considered an absolute contraindication.

43.3. Special Operative Considerations

M. Malagó, C.E. Broelsch

43.3.1. Donor's Operation

Nowadays the donor's left lateral hemihepatectomy represents a standardized procedure [27]. In addition, the right hemihepatectomy is almost standardized worldwide [28-33], but some points of discussion are still open. One major point of debate is whether the middle hepatic vein (MHV) should be harvested or not in the case of right or left hemihepatectomy. Based on radiological studies on partition of the venous vascular anatomy of the liver [34-35], as well as our own surgical experience [33, 36] (fig. 43.1-43.5, 43.6a-d, 43.7a-b), we can state that the MHV can be harvested without causing any outflow decompensation in the residual liver [33, 37-39]. Additionally, by performing a "carving" resection along the MHV (fig. 43.8-43.9), a volume-sparing resection could also be performed [36].

It is well known that the division of the right hepatic duct is one of the most important steps in donor hepatectomy, potentially influencing both the outcome of the anastomosis in the recipient and the safety of the donor. Therefore, an intraoperative cholangiogram should be performed whenever standard preoperative

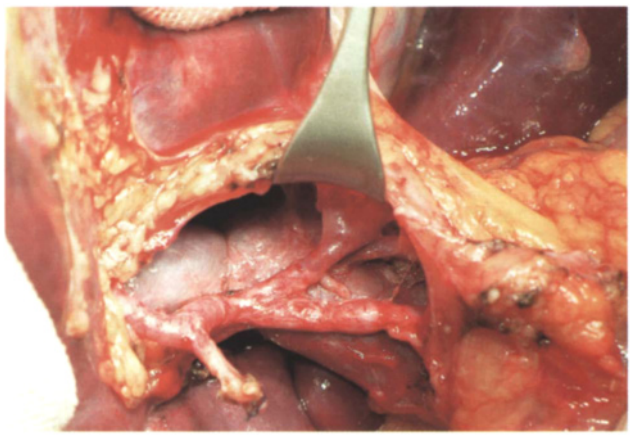


Fig. 43.1. a. Lymphadenectomy in liver hilum.

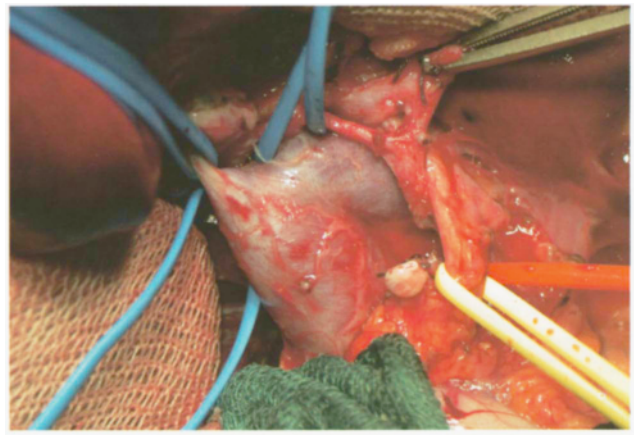


Fig. 43.1. b. Anatomical variations: portal vein trifurcation.

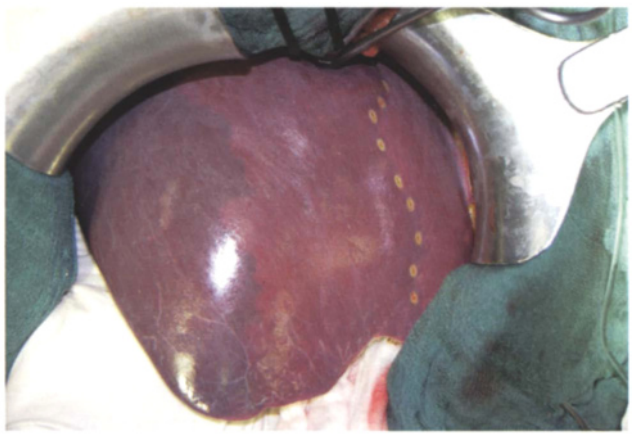
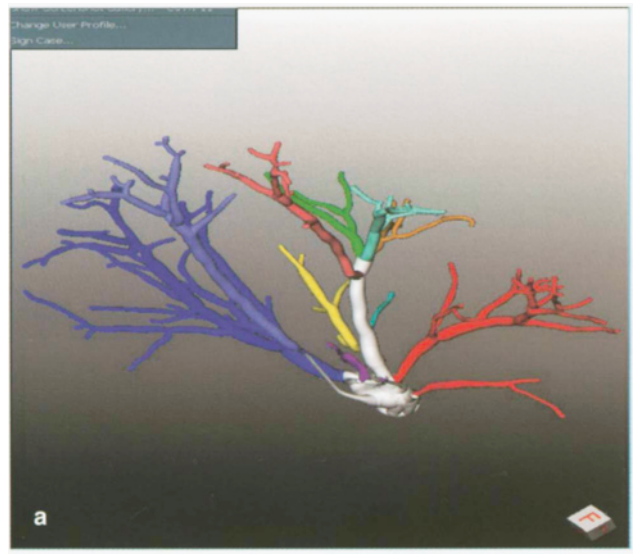


Fig. 43.2. "Malago Manoeuvre" virtual simulated: (a) versus real in situ (b) After completing the hilar dissection (bile duct transection already performed) and before starting liver transection, the territorial RHV/MHV dominance relationship (preliminary pre-operatively simulated) is checked in situ. First right hemi-Pringle clamping (right portal vein and right hepatic artery) shows the demarcation line on the liver surface. Then, RHV at the level of confluence is clamped, and right hepatic artery is declamped giving up a demarcation line between the drainage territory of right hepatic vein (posterior sector S6/7 dusky) and middle hepatic vein (potential venous congestion in the marginal zone S5/8 on the right graft). The virtual and real images can be compared and the decision on MHV inclusion into right hemiliver graft versus reconstruction of its tributaries V5V8 is definitely made.

imaging protocols (i.e. MRI or CT) fail to provide reliable information on the anatomy of the biliary tree. Based on the 3-D pictures alone, provided by the all-in-one CT, we avoided an intraoperative cholangiogram in the last 71 cases, and no biliary complication in the donors was observed.



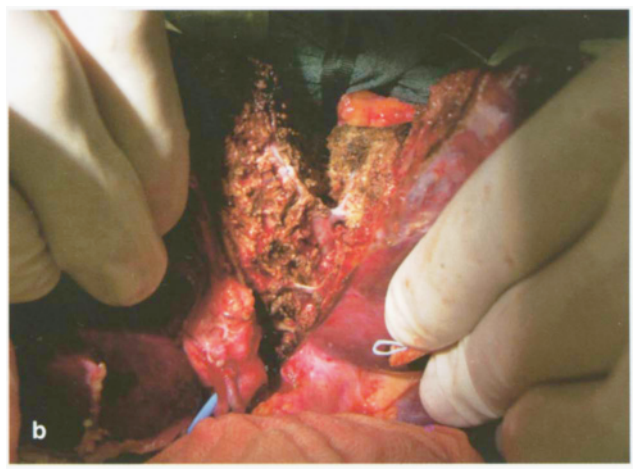


Fig. 43.3. a-b. 3D/Reality: Situs with dissection of middle hepatic vein (MHV) showing the branches demonstrated in 3D reconstruction.

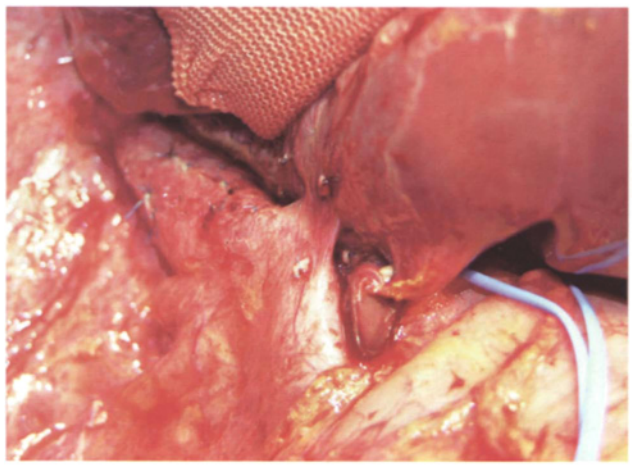


Fig. 43.4. Retrohepatic caval vein with inferior hepatic vein.

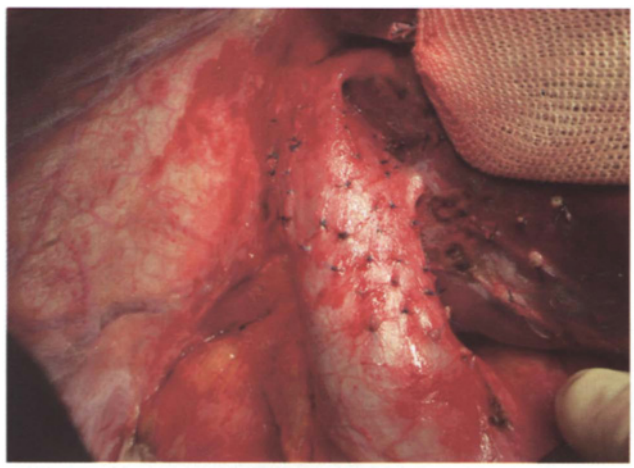


Fig. 43.5. Retrohepatic caval vein.

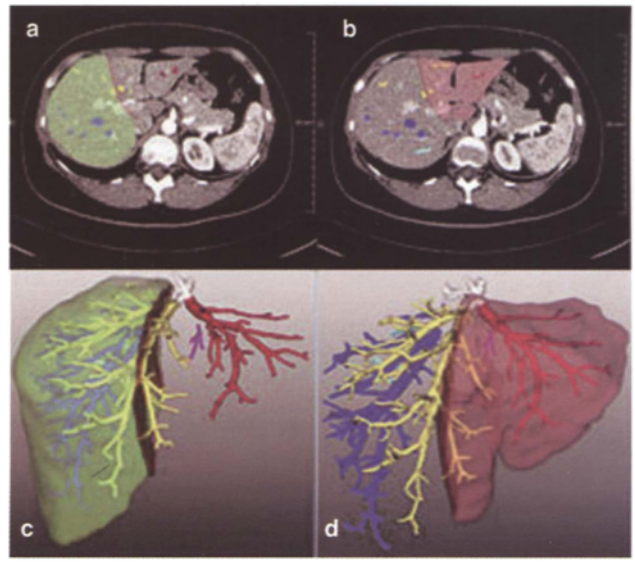


Fig. 43.6. a-d. Donor virtual hepatectomy. "Carving technique". Cranial view, 3-dimensional reconstruction. The plane of transection runs along the course of the MHV – 2D view (3ab). The MHV is "carved" out of the surrounding hepatic parenchyma – 3D view (3cd). RHV (blue), MHV (yellow), LHV (red), right graft (green), left liver remnant (brown).

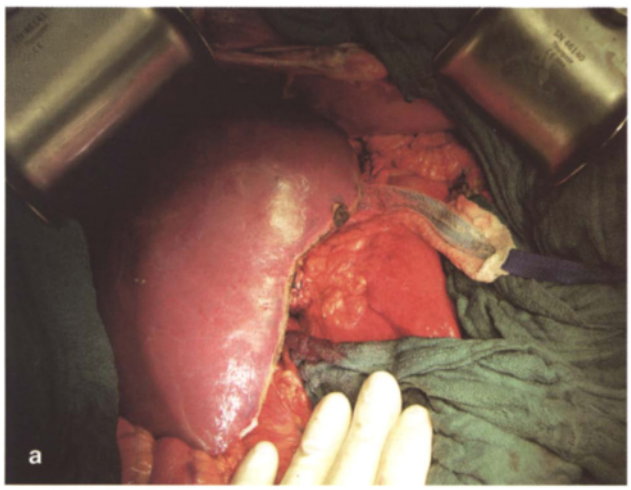
The method and timing of biliary dissection should also be mentioned. Although most centers perform the bile duct division at the end of the parenchymal transection, we are convinced that an early suprahilar bile duct division should be performed before the parenchymal transection [33] (fig. 43.10). The technique of hepatic duct probing and early division is safe, it preserves the vascular supply of the hepatic duct and allows an excellent yield of a single orifice for the recipient anastomosis. Moreover, it provides a precise definition of the anatomy of the hepatic duct confluence and facilitates one of the most challenging elements of donor hepatectomy.

Careful preparation and blood-saving surgery will significantly lower postoperative morbidity. The use of a cell saver is indicated. The procedure is performed either without hilar occlusion or by using only intermittent clamping. For the parenchymal transaction, ultrasound or waterjet dissectors can be used in combination with electrocautery. After the removal, the graft is flushed with either UW or HTK solution; no difference between the two solutions has been reported.

43.3.2. Recipient's Operation

43.3.2.1. *Timing of the Operation*

Generally, the recipient's operation follows the donor's operation in a timely fashion, with the possibility of overlapping in the case of two teams of experienced transplant surgeons, with a consequent reduction in the cold ischemic time for the graft. Notwithstanding, the clinical condition of the recipient and the indication for transplantation can both dictate a change in the sequence of the surgeries. For example, in patients with advanced HCC, the exploration of the recipient should precede the donor's hepatectomy.



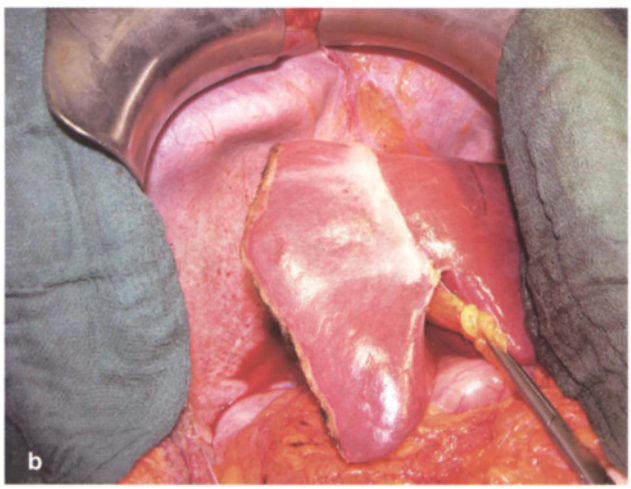


Fig. 43.7. a-b. Malagó partition ("carving technique"), intraoperative view. Right liver graft by recipient including the MHV (a); left remnant liver by donor (b).

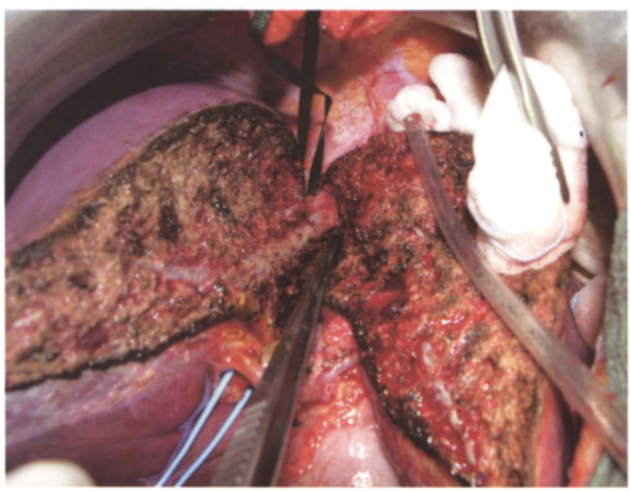


Fig. 43.8. "Carving technique".

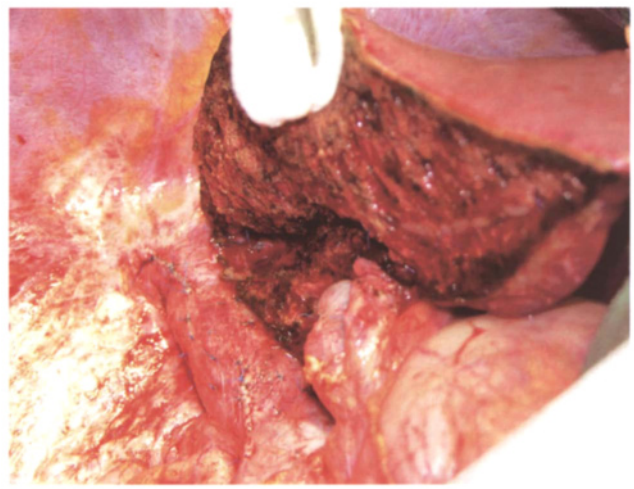


Fig. 43.9. Sulcus after right hepatectomy in carving technique by donor.

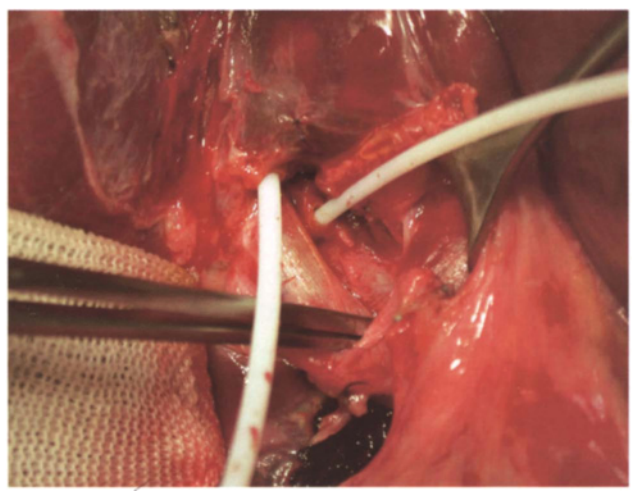


Fig. 43.10. Bile duct dissection with 2 bile ducts in right LDLT.

43.3.2.2. *Technical Aspects of Recipient's Hepatectomy*

The retrohepatic inferior vena cava (IVC) should always be preserved and completely mobilized to guarantee an optimal IVC occlusion in cases of complicated outflow reconstruction. A temporary porto-caval bypass can be used selectively in the case of patients with severe portal hypertension and previous abdominal surgery or a foreseeable long anhepatic period. The indications for systemic veno-venous bypass (VVB) are still controversial [40]. In the case of planned duct-duct biliary anastomosis, the dissection of the bile duct should

be extended deeply into the hilar plate [41-42]. The time of completion of the hepatectomy (removal of the recipient's own liver) depends on the availability of the graft and on the clinical and hemodynamic condition of the recipient.

43.3.2.3. *Benching the Graft (Fig. 43.11)*

The better understanding of the venous flow the more time-consuming and complicated benching of the right graft becames. The "blanket" technique [36] (fig. 43.12, fig. 43.13, 43.14, 43.15) which maximizes the venous outflow by reconnecting all major veins, draining the graft in one sinlge large conduit is considered a "state of the art" procedure.

43.3.2.4. *Implantation of the Graft*

Great emphasis should be placed on the hepatic outflow tract to prevent graft congestion, a key problem leading to early postoperative graft dysfunction. Given that the rapid regeneration of the graft could cause kinking, compression, or torsion of the outflow tracts, a wide cavotomy of subdiaphragmatic IVC joining the triangulation of the three hepatic veins became mandatory in right LDLT (fig. 43.16). The wide cavotomy (triangle-shaped), combined with a single large venous conduit, can protect the outflow even in the instance of medial graft rotation (fig. 43.17).

The portal vein is generally anastomosed to the mainportal vein of the recipient. In the presence of multiple branches of the right portal vein, a single anastomosis using a common patch is preferred.

The graft hepatic artery is anastomosed to the proper, right or left, hepatic artery. The bile duct(s) are reconstructed by using a Roux-en-Y loop or are anastomosed in an end-to-end/end-to-side fashion with or without insertion of a T-tube [42-43].

43.3.2.5. *Size Mismatching of the Graft*

In cases of marginal (< 0.8) graft volume body weight ratio (GVBWR) and presence of portal hypertension (> 20 mmHg), a small for size syndrome may develop in a short time. It is mainly caused by a hypertensive high portal flow, graft congestion, and consequent reduction of arterial flow, which can lead to enhanced hepatocyte injury with consequent graft dysfunction

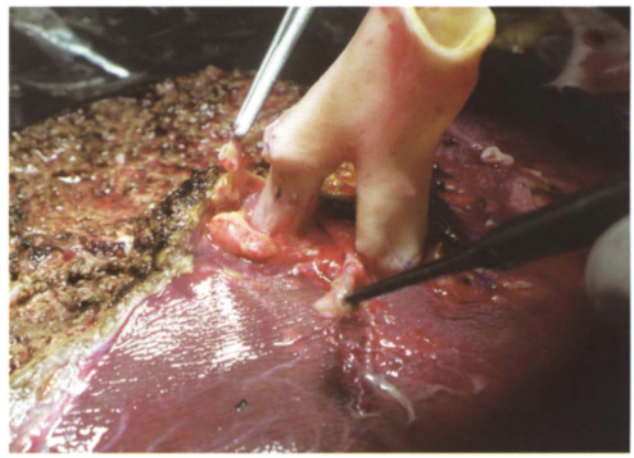


Fig. 43.11. Right liver graft with 2 arteries and 2 portal veins. Reconstruction with allogenic iliac vessel.

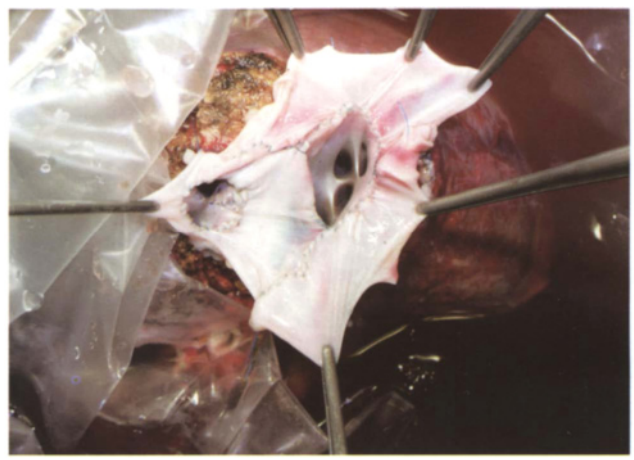


Fig. 43.12. "Blanket technique".

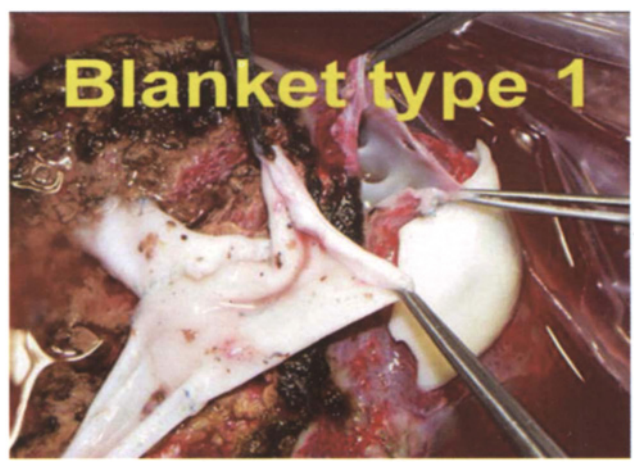


Fig. 43.13. Tree vs four holes: Common outflow tract, by "blanket" like venous graft-interposition: RHV-separate ostium, MHV separate ostium (if included into graft), HV 8 separate ostium (if no MHV included into graft, then HV 8/5 on separate ostium).

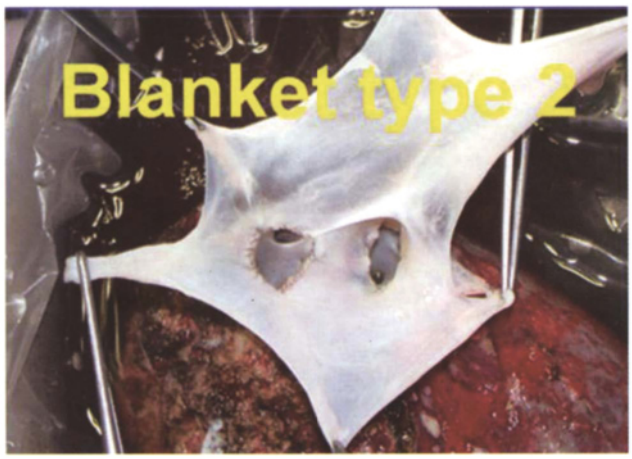


Fig. 43.14. Two holes: Common outflow tract, by "blanket" like venous graft-interposition: RHV-separate ostium, MHV/HV 8 venoplastic (separate ostium).

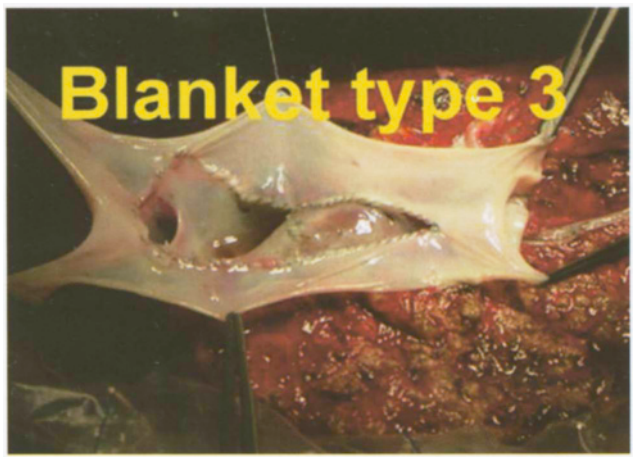


Fig. 43.15. One hole: Common outflow tract, by "blanket" like venous graft-interposition: RHV/MHV/HV 8 venoplastic (one ostium).

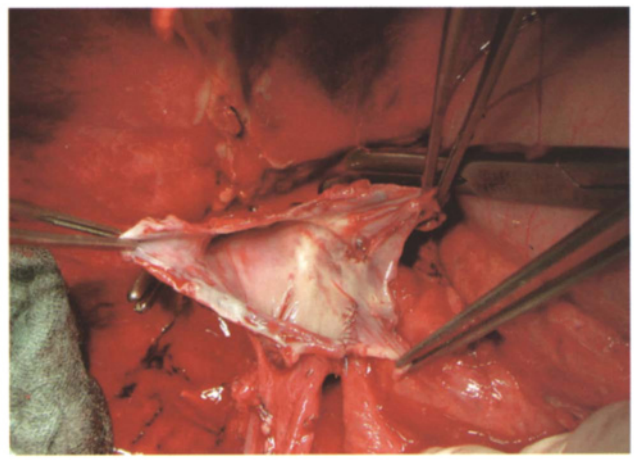


Fig. 43.16. Cavotomy by recipient.

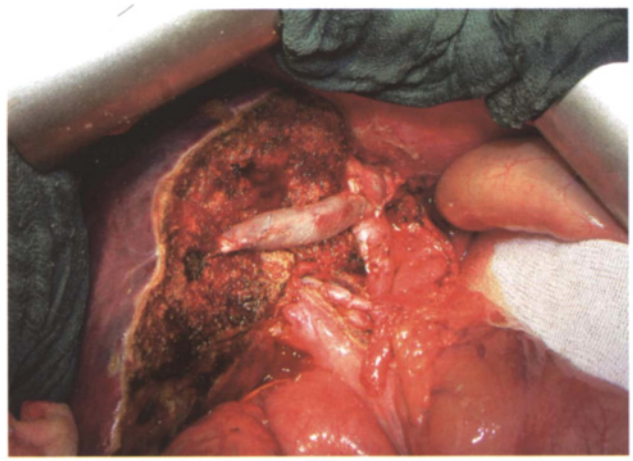


Fig. 43.17. Ancestral blanket.

up to graft loss. In this regard, different surgical solutions with different results have been proposed and can be summarized in two groups, represented by our group and the group from Hong Kong, mainly oriented in maximizing the venous outflow by harvesting the NHV and performing a wide singular venous conduit [32, 36-37]. The other school of thought aims to reduce portal flow, indirectly through the ligature of splenic artery [44], or directly by means of a mesocaval shunt [45-46], or hemi-portal shunt [47]. The actual trend is in reality a combination of the two schools according to individual patient's requirements, mainly based on intraoperative hemodynamic monitoring of portal and arterial flows and pressures.

43.4. Outcome

G.C. Sotiropoulos, M. Malagó

The early results of ALDLT were very promising, with a 1-year patient survival rate of 87% and 2 year patient and graft survival of around 75% [48]. The surgical procedures for LDLT are technically more challenging than those for cadaver liver transplantation. In the recipient operation, bile duct reconstruction has proven to be the most challenging part of the procedure with biliary complications ranging between 15% and 60% [49].

Regarding donor outcome, morbidity rates between 0% and 67% have been reported [50]. The most common complications include wound infection, pulmonary pro-

blems, vascular thrombosis with biliary leaks, strictures, and incisional hernia. Biliary complications occur in up to 7% of donors [49]. Complications occur more frequently in donors of the right graft than of the left. Sugarawa et al. recently reported ten donor deaths in their review of the literature [49]. Liver regeneration –documented with imaging studies and confirmed by normalization of bilirubin, liver enzymes, and synthesis parameters– occurs within 2-3 weeks after surgery. LDLT should be performed only by established transplant centers with the appropriate medical expertise [51].

43.5. Extended Indications

G.C. Sotiropoulos, M. Malagó

43.5.1. Living Donor Liver Transplantation for Hepatocellular Carcinoma

The application of the Milan criteria to HCC candidates has resulted in 75% overall patient survival and 83% overall tumor-free survival at 4 years post-transplant [52]. However, limitations of clinical staging systems prior to OLT lead to underestimation of HCC stage in 15-22% of cases and overestimation of HCC stage in 10% of cases [53-55]. Even with the current sophisticated imaging techniques, tumor staging is inaccurate in up to 20-30% of patients. Detection of small lesions (< 2 cm) in end-stage cirrhotic livers is still a major problem clearly shown by the reported differences among "radiological" and "pathological" Milan criteria in several series, as well as by the high rates of "incidentally found HCCs" [56-58]. Retrospective analysis of data from the University of Pittsburgh Medical Center revealed that 27%-49% of transplanted patients who did not meet the Milan criteria experienced long-term survival and nearly 50% remained tumor-free at a mean follow-up of 3.3 years [59]. Whether the criteria for HCC with LDLT should be expanded, remains a controversial subject. In accordance with the critiria of the University of California, San Francisco (a single lesion < 6.5 cm or up to three nodules with the largest lesion < 4.5 cm and with a total diameter < 8 cm, without gross vascular invasion), Yao et al. reported recurrence-free 1 year and 3 year survival rates of 93% and 85%, respectively [54]. The Barcelona Clinic Liver Cancer Group has proposed considering patients acceptable for LDLT if they have a single tumor < 7 cm, up to three nodules < 7.5 cm, or up to five lesions < 3 cm [60]. Cheng et al. found significant advantages for HCC patients undergoing this "fast-track" transplantation as opposed to deceased donor liver transplantation, with survival rates of 86% vs. 71% at 1 year and 68% vs. 42% at 5 years [61]. Hwang et al. in the multicenter Korean study reported 3 year survival rates of 66.4% and 62.6% for patients beyond the Milan criteria who underwent deceased donor or living donor liver transplantation, respectively [62], whilst the corresponding 3 year survival rates for patients exceeding the University of California of San Francisco criteria were 68% and 58.5% respectively [62]. Todo et al. in the multicenter Japan study on living donor liver transplantation for HCC reported 3 year survival rates of 60.4% for patients exceeding the Milan criteria [63]. In our transplant center, patients are considered suitable LDLT recipients if they have no evidence of extrahepatic tumor or portal vein/tumor thrombosis and if the serial levels of alpha- fetoprotein are no higher than 1000 ng/ml [62]. Furthermore, cirrhosis-related parameters, recipient's age and physical condition are evaluated, since they constitute important factors affecting hospital mortality [64]. The value of adjuvant/ neo-adjuvant therapies for transplanted HCC patients [65] or of new immunosuppressive agents with strong antiproliferative and eventually tumor inhibiting effects may also be considered [66-67].

The current worldwide trend to "expand" the Milan criteria therefore seems to be justified. However, prospective multicenter randomized analyses should be undertaken in order to establish a consensus of "how far to go" with the listing criteria for patients with HCC and cirrhosis. Longer follow-up, multicenter cooperation and identification of biological markers responsible for the "carcinogenesis" of HCC using modern methods of molecular biology may in future be the key to better defining "patients at risk" for LT. However, ethical issues also need to be considered, as well as the potential risks and benefits to a living donor and HCC recipient with extended standard criteria taken into account.

43.5.2. Extended End-Stage Liver Disease

LDLT for patients with decompensated end-stage liver

disease (UNOS 2A, MELD > 30) is a somewhat controversial issue. Nevertheless, the fact remains that these patients are most in need of a timely liver transplant. In our series, patients and graft survival rates were only 43%. Notwithstanding the high mortality rate, no donors had regrets about the procedure, and all donors state that they would donate again if placed in the same position. LDLT represents a timely and effective alternative to DDLT in decompensated end-stage liver disease. Nonetheless, the ethical concerns regarding risks and benefits for both donor and recipient should be discussed.

43.6. Ethical Considerations

M. Malagó, C.E. Broelsch

LDLT has always been accompanied by ethical concerns, mainly related to the risk imposed on the donor [68-69]. Over the past decade, it has been proven that LDLT significantly increases the donor pool and that the outcome is equal or even superior to DDLT. In this context, the risk/benefit ratio for the recipient is clearly in favor of LDLT [70]. Applying the principle of justice to LDLT is also complex, and it is questionable whether a procedure that violates the principle "above all, do no harm" can be justified. Furthermore, ongoing ethical discussions concerned themselves with questions such as who should receive a living donor transplant. While some argue that stable patients with chronic liver disease, before hepatic decompensation, benefit the most from LDLT, others maintain that very ill patients are precisely the ones who should be offered LDLT [71]. This argument can also be stended to those patients who cannot currently be placed on the waiting list due to advanced cancer, but for whom LDLT offers the only effective option. There is an ongoing debate concerning patients with acute hepatic failure, even though several reports have shown that patients with acute hepatic failure can be well served by LDLT [71-72].

Who, then, should donate? LDLT is guided by two main principles: 1) donor morbidity and mortality must be kept to a minimum; and 2) graft and recipient survival should be as high as in full size LDLT. The exact risk to the living donor is not known. The evidence from several surveys and subjective assessments indicates that donor mortality is somewhere between 0.2 and 1% and morbidity as high as 60% [73]. Trotter reported that a complete recovery required more than 3 months in 75% of all donors [74]. Despite all this, recent studies have shown a significant benefit for the donor. Liver donors reported satisfaction and increased self-esteem. In a study by Karliova et al. 92% of all donors would opt to donate again [75]. A high degree of preoperative information enabled the donors to have a realistic view of the operation and its potential complications and further explained the overall positive retrospective rating.

Clearly, donor safety is paramount in LDLT, while the risks and benefits to the donors will undoubtedly be debated by ethicists.

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CHAPTER 44

INTENSIVE CARE UNIT MANAGEMENT

G.C. Sotiropoulos, H. Lang

44.1. Cardiovascular and Pulmonary Monitoring

In the early post transplant period, an intensive medical monitoring is necessary with frequent controls of the vital parameters [1-2]. Whilst post operative artificial ventilation is not mandatory, it is almost without exception, the rule. Stable transplant patients with good general condition can usually be extubated within 6 hours after the transplantation.

44.2. Support with Vasoactive Substances

After transplantation of critical organs with initially poor function, support with prostaglandins (for example Flolan: 4-5 ng/kg min) for the improvement of the liver blood circulation is recommended. Possible side effects of prostaglandins (hypotension, inhibition of platelets aggregation; cave: platelets < 30.000 µl) may be considered.

44.3. Volume Therapy - Electrolyte Balance

Volume therapy is performed on the basis of the central venous pressure, or, better on the basis of pulmonary arterial pressure (PAP) and wedge pressure, measured over a Swan-Ganz- catheter. Crystalloids and colloids substances are used.

Special attention should be given to the correction of hyponatremia. Due to the danger of a heavy pontine or extrapontine myelolysis, hyponatremias may be balanced only very slowly. Pronounced hyponatremias <120 mmol/l should be compensated for during a period of two to three days.

44.4. Coagulation Substitution

The substitution of coagulating factors requires an exact assessment of the coagulating situation. The most reliable value is that of the concentration of coagulating factor V. In the absence of bleeding tendency, values of factor V > 25% do not require substitution supply of plasma. Excessive substitution of coagulating factors influences and hampers the evaluation of the synthesis of the transplanted liver. Antithrombin III should be intensively controlled and be substituted at values < 60-70%. This applies in particular to patients with an increased risk of thrombosis (for example patients with Budd Chiari syndrome).

Without signs of bleeding, the substitution of platelets is only indicated at values under 20.000/µl, while in bleeding situations the supply of platelets should be considered at values under 50.000/µl.

44.5. Nutrition Therapy

The energy requirement after liver transplantation during the first two post transplant weeks is approximately 30-35 kcal/kg/Day. The supply of non protein energy should amount to, for instance, the 1.3 × the basic conversion in relation to the glucose – fat ratio, (e.g. of 60:40 and/or 50:50). In the context of post transplant aggressive metabolism, early postoperative disturbance of the glucose metabolism with insulin resistance can be manifest. In these cases the glucose supply should be reduced, since an increase of the insulin supply does not lead to any improvement of the glucose metabolism. Owing to the smaller influence of RES after liver transplantation, emulsions from MCT/LCT fats seem to be favourable in comparison to pure LCT emulsions. For protein metabolism, the supply of stan-

dard amino-acid solutions is sufficient. The early post transplant period usually displays a negative nitrogen balance. Nevertheless, protein supply should not exceed 1,0-1,5 g albumin/kg/Day, since an increase of protein conversion with an increase of urea production can occur.

Enteral nutrition should be given preference over parenteral nutrition and should begin as early as possible after the transplantation. In this respect, patients with assumed long stay in ICU and poor physical condition, the intraoperative placement of a duodenal nutrition catheter or a fin-needle-catheter-jejunostomy, may prove helpful.

44.6. Postoperative Laboratory Controls

Laboratory values should be controlled very closely, in the first postoperative hours i.e. every 8 hours (liver values, coagulating controls, electrolytes etc). Close control of the hemoglobin value should take place close in conjuction with the clinical process.

44.7. Smear Tests, Microbiological Investigations

Routinely, wound smears as well as bacteriological investigations of trachea secretions and urine are carried out twice weekly. Furthermore, the determination of the Candida titter (AGAC) and viral marker (VZV, CMV, EBV, HSV) can prove significant. Clinical suspicion should prompt further examinations.

44.8. Antibiotic Therapy and Selective Intestinal Decontamination

A perioperative antibiotic therapy of 24 hours is usually sufficient; in exceptional cases (i.e. post spontaneous bacterial peritonitis or post cholangitis by primary sclerosing cholangitis) long-term therapy may be indicated. The selective intestine decontamination (colistin-sulfate 100mg; gentamycine 80mg, amphothericin B 6,6 g as well as non biliary tree-active antibiotic) is standard practice and should be administered for 2 to 3 weeks post transplant.

44.9. Prophylaxis Against Candida Infections of the Pharyngo-Oral Cavity - Viral Prophylaxis

For the prophylaxis of pharyngo-oral Candida infections an oral application of Amphomoronal should commence from the first post transplant day 4 times daily for 4 to 6 weeks.

A general prophylaxis against viral infections is neither possible nor meaningful. However, prophylactic treatment of Ganciclovir against Cytomegalovirus should be administered to protect IgG CMV negative recipients from IgG CMV positive donors.

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CHAPTER 45

PERIOPERATIVE COMPLICATIONS

45a. PERIOPERATIVE COMPLICATIONS

H. Lang, G.C. Sotiropoulos

During the last 2 decades patient and graft survival have dramatically improved (fig. 45a.1). Despite advances in organ preservation and technical procedures, postoperative complications due to preservation/reperfusion injury have not markedly decreased over the past several years. Perioperative ischemic injuries include hepatocellular damage during cold ischemia time from prolonged preservation and warm ischemia during implantation of the allograft. Typical histological features of preservation and reperfusion injury include centrilobular pallor and ballooning degeneration of hepatocytes. Bile duct cells are more sensitive to reperfusion injury than hepatocytes [1], resulting in increased levels of bilirubin, gamma-glutamyl [1] transpeptidase (γGT), and alkaline phosphatase (AP). Vascular complications such as hepatic artery thrombosis (HAT) or stenosis occur in 1.6%-10.5% and up to 5% of patients, respectively. HAT may lead to large bile duct injuries, requiring retransplantation in many patients. Hepatic failure due to HAT is more common in the early postoperative period and can be managed with thrombectomy. Late HAT is managed by interventional endoscopic retrograde cholangiography (ERC) in cases of bile duct strictures and may require retransplantation in the long-term, should ERC not be successful. Early portal vein thrombosis is rare (< 1%) but may lead to graft loss if not revascularized. Our institution's protocol advocates Doppler exams of the hepatic artery and portal vein being performed every 8 hours in the early postoperative period.

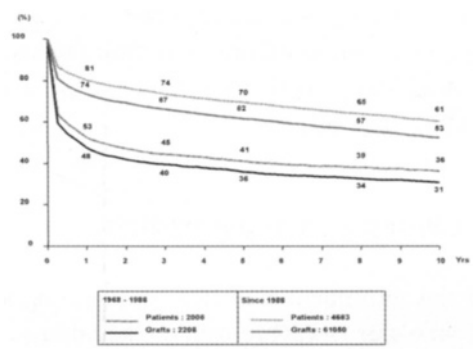

Fig. 45a.1. Patient and graft survival between May 1968 and December 2004 (data taken from European Liver Transplant Registry; http://www.eltr.org).

Primary non functioning graft (PNFG) may be clinically obvious immediately after revascularization of the allograft. Early signs of liver dysfunction include prolonged coagulation times, persistently elevated liver enzymes (transaminases, cholestasis parameter), rising lactate, and hypoglycemic episodes. PNFG is a critical situation and requires immediate retransplantation.

Bacterial infections represent a major cause of morbidity and mortality in the early posttransplant period. Correct differentiation between colonization and true infection is important. Reported risk factors for infections include advanced age, accompanying renal insufficiency, malnutrition, and a high number of perioperative blood product transfusions. Low pretransplantation hemoglobin, high pretransplantation bilirubin, return to surgery and prolonged therapy with ciprofloxacin have been found to be independent variables for predicting fungal infection [2].

The clinical symptoms of acute liver rejection are unspecific and may manifest as fever, right upper quadrant pain, and malaise. A liver biopsy is indispensable for confirming the diagnosis of acute rejection. High dose corticosteroids (3 days of 500-1000 mg methylprednisolone) are the first-line treatment for acute rejection.

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45b. LONG-TERM COMPLICATIONS AFTER LIVER TRANSPLALNTATION

S. Beckebaum, V. Cicinnati, A. Frilling, G. Gerken

Due to excellent results in the short-term outcome after liver transplantation, attention has shifted to reducing long-term complications. Seyam et al. investigated late mortality in more than 1000 patients transplanted between 1982 and 1999. Of the 129 who did not survive within this time period, 56% died of side-effects associated with long-term immunosuppression including malignancies and renal impairment, 22% died of vascular complications, and 15% suffered liver organ failure due to recurrent disease [1].

45b.1. Opportunistic Infections

Opportunistic infections are primarily viral and fungal in origin. Cytomegalovirus (CMV) is a frequent cause of infection in the post-transplant setting. Diagnostic assays, such as CMV pp65 Ag and quantitative PCR have demonstrated similar efficacy for the diagnosis and monitoring of CMV infection in liver transplant recipients [2]. Persistent CMV infection has been shown in patients with chronic rejection [3]. Valganciclovir is an oral prodrug for ganciclovir [4] and has various advantages over the original formulation (10 times higher bioavailability, lower application frequency, lower occurrence of resistance). A high viral load of Epstein-Barr infection and a high level of immunosuppression are reported as risk factors for post-transplant lymphoproliferative disease (PTLD) [5]. The clinical presentation varies and may manifest as an impaired general condition with fatigue, weight loss, tonsillitis, lymph node enlargement, and gastrointestinal symptoms. PTLD is more frequent in children after organ transplantation, but still represents 15% of tumors in adults. The treatment includes modulating the immunosuppressive regimen and applying antiviral drugs such as acyclovir or ganciclovir, and as a second step, treatment with anti-CD20 monoclonal antibodies if CD20 positive tumor cells are detectable.

The clinical manifestation of infection with human herpes virus-6 may vary between asymptomatic infection to severe symptoms [6]. Other viral pathogens include herpes simplex virus and varicella. Fungal infections in transplanted patients include infection with Candida sp., Aspergillus, Cryptoccocus, and Histoplasma. Early diagnosis and careful management of disseminated fungal infections are necessary to avoid high morbidity and mortality rates.

45b.2. Chronic Rejection

Advances in immunosuppressive regimens have greatly reduced the incidence of rejection and allograft failure. Chronic rejection begins within weeks to months or years after OLT and affects about 4% to 8% of patients [7]. Risk factors for chronic rejection include alloimmune immunologic injury and nonimmunologic factors such as older donor age, prolonged cold ischemia, and donor atherosclerosis. The most widely recognized manifestation of chronic rejection is obliterative arteriopathy [8]. Chronic rejection may appear indolently and might only become apparent as liver test injury abnomalities (γGT, AP, bilirubin, transaminases). The diagnosis needs to be confirmed by histopathologic examination. It is important to recognize chronic rejection in the early stages in order to avoid irreversible damage to the allograft. The first therapeutic approach is generally treatment with corticosteroids. At our transplant center and in some others, this step is often accompanied by switching the baseline immunosuppression from CSA to TAC and initiating mycophenolate mofetil (MMF) rescue therapy [9]. A recent study investigating the efficacy and safety of anti-interleukin (IL -2) receptor antibodies (daclizumab and basiliximab) for steroid-resistant rejection revealed a poor histologic response to chronic rejection but successful resolution (75%) in patients with acute cellular rejection [10].

45b.3. CNI-Induced Nephrotoxicity

Despite the introduction of new immunosuppressive agents (table 45b.1), CNI remain the key drugs of most immunosuppressive regimens. Both CSA and TAC inhibit the calcineurin-calmodulin complex and therefore IL-2 production. Complications of CNI, including

Table 45b.1. Immunosuppressive Drugs in Liver Transplantation.

Immunosuppressant Class	Immunosuppressant Agent
• Corticosteroids	• Prednisone, prednisolone
• Calcineurin inhibitors	• Cyclosporin A, tacrolimus
• Antimetabolites	• Mycophenolate mofetil, azathioprine
• TOR inhibitors	• Sirolimus, everolimus.
• Polyclonal antilymphocyte antibodies	• Antithymocyte globulin (ATG)
• Monoclonal anti-CD3 antibodies	• Muromonab-CD3 (OKT3)
• Anti-IL-2 receptor antibodies	• Basiliximab, daclizumab
• Anti-CD52 monoclonal antibodies	• Alemtuzumab (campath-1H)
• Investigational immunosuppressive agents	• FK778 (leflunomide analogue) • FTY720 (synthetic analogue of sphingosine) • WHI-P-154 (JAK3/STAT inhibitor) • LEA29Y (CTLA4-Ig)

nephrotoxicity, diabetes, hypertension, and hyperlipidemia, have a major effect on morbidity and mortality within the transplant setting. CSA monitoring has traditionally been performed by measuring predose "trough" blood concentrations (C0). The development of a 2 hour post-dose CSA (C2) monitoring strategy has emerged as a more sensitive approach for assessing the pharmacokinetics and provides greater precision in the optimization of dosing than C0 measurements. The incidence of chronic, CSA-induced, mild to moderate nephrotoxicity (serum creatinine > 125 and < 200 umol/L) is high and varies in different studies between 23.3% and 78.0%. The incidence of severe chronic renal failure ranges from 4-28%, and the incidence of end-stage renal insufficiency resulting in hemodialysis is 1.4-7.9% [11].

In OLT patients with CNI-induced nephrotoxicity, a complete replacement of CNI with conversion to MMF bears an increased risk of acute rejection ranging from 0% to 60% [12-15]. MMF inhibits inosine monophosphate dehydrogenase, a critical enzyme in the de novo pathway of purine synthesis. It may be used for acute or chronic rejection, recurrent autoimmune disease, and corticosteroid resistance.

Results from previous studies with immunosuppressive regimens including MMF and reduced CNI treatment suggest a significant improvement in renal function in this patient group [16-18]. In contrast, Neau-Cransac et al. [19] and Gonwa et al. [20] did not find a significant renal function improvement after withdrawal of CNI and introduction of MMF. We investigated the impact of combined MMF and minimized CNI therapy on cardiovascular risk factors, liver parameters, and renal function [21]. We randomized 32 patients with CNI-induced renal dysfunction to either a) continue their current CNI dose or b) to receive MMF up to a dose of 1000 mg twice per day followed by stepwise reduction of CNI (TAC trough levels < 4 ng/ml, CSA trough levels < 50 ng/ml). Three months after conversion therapy, we observed a significant decrease in the mean values of serum creatinine (from 1.88 ± 0.36 to 1.58 ± 0.33 mg/dL; $p < 0.001$), serum urea (from 39.2 ± 11.8 to 29.9 ± 9.59 mg/dL; $p < 0.001$), and GFR (from 51.4 ± 10.8 to 61.6 ± 14.1 mL/min; $p < 0.001$, fig. 45b.1). Interestingly, renal function improved even in long-term liver transplant recipients (5.6 ± 3.6 years; range 2-13 years), which suggests at least a partial reversibility of CNI-induced renal damage.

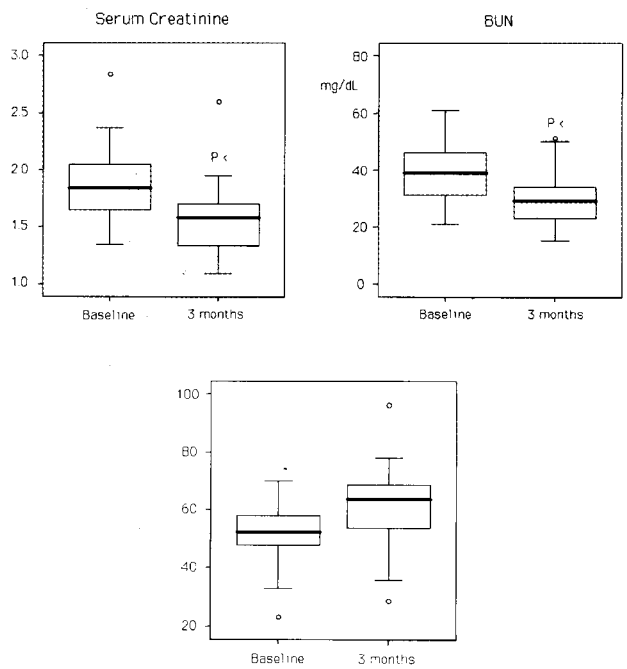

Fig. 45b.1. Significant improvement of renal function 3 months after switch from CNI therapy to combined MMF and minimal dose CNI therapy in liver transplant patients (n = 21) at the University Hospital Essen, Germany.

Sirolimus (SRL) is a macrolide isolated from Streptomyces hygroscopius. It binds to a highly conserved cellular protein, FKBP12, and to the rapamycin/FKBP12 complex targets, and it inactivates mTOR, which is considered as a master switch for cell cycle progression [22]. Side-effects of SRL include increased incidence of wound infection and dehiscence, hyperlipidemia, thrombocytopenia, leucopenia, and anemia. The antifibrotic effect of SRL may provide an explanation for impaired wound healing [23]. There is also evidence that SRL has been associated with an increased risk of HAT. However a recent study by Dunkelberg et al. with 170 patients receiving SRL as primary immunosuppression failed to demonstrate an association between SRL therapy and increased prevalence of HAT and wound complications [24]. SRL is currently being investigated in clinical studies as an alternative or complementary agent to CNI [25-27].

A second TOR inhibitor, everolimus (ERL), may exhibit improved bioavailability and a shorter half-life than SRL. Phase I trials have shown that ERL is generally well-tolerated [28]. The different mechanisms of action of ERL and CNI give rise to synergistic immunosuppressive properties. The use of ERL in combination with CSA allows for a strong reduction of CSA dose. The use of IL-2 receptor antagonists at induction is presently being considered in ongoing studies as part of CNI-sparing or steroid-sparing regimens.

45b.4. Other Side Effects of CNI

Beside potential nephrotoxicity, CNI therapy is associated with side-effects which include tremor, headache, electrolyte abnormalities, hyperuricemia, hepatotoxicity, and gastrointestinal symptoms. Neurotoxicity, including tremor, paresthesia, muscle weakness, and seizures, more often occurs in TAC-treated patients; whereas, gingival hyperplasia and hirsutism are associated with CSA treatment.

Cardiovascular side-effects due to CNI and steroids include hyperlipidemia, hypertension, and impaired glucose tolerance. The increased risk of myositis should be considered in patients treated with statins for hyperlipoproteinemia [29]. At our center, therapy with statins is given consideration only for patients with a risk profile for cardiovascular morbidity.

There is ongoing discussion on steroid avoidance due to dyslipidemia, osteoporosis, the development of cataracts, weight gain, hypertension, and a deleterious impact on glucose control. The Ochsner Clinic investigated the efficacy of polyclonal rabbit anti-thymocyte globulin (RATG) induction followed by TAC monotherapy in a randomized, prospective trial [30]. Compared to the control group with steroids, the RATG plus TAC group had a lower incidence of posttransplant diabetes, CMV infection, and steroid-requiring rejections. Other research groups have reported encouraging findings with steroid-free protocols including basiliximab induction therapy [31-32].

The prevalence of new-onset diabetes mellitus after OLT, has been reported to occur in 9% to 21% of patients [33-34]. The prevalence of posttransplant diabetes is even higher if co-factors such as hepatitis C are present. In various studies, the diabetogenic potential has been reported to be higher in patients receiving TAC than in those receiving CSA. In contrast, CSA has a more pronounced effect on lipid levels. CSA can act by modulating the activity of the LDL receptor or by inhibiting the bile acid 26-hydroxylase that induces bile acid synthesis from cholesterol.

44b.5. De Novo Malignancies

Malignancies in transplant patients occur 4-5 times more frequently than in the general population. This phenomenon is associated with immunosuppression and carcinogenic viruses. The highest risks in the transplant setting are cancers of the skin and PTLD, which range from 6% to 70% and 4.3% to 30%, respectively [35]. An annual routine dermatological follow-up exam is highly recommended for transplant patients. Patients transplanted for PSC have an increased risk of colon cancer. Recent studies reported a significantly higher incidence of aerodigestive cancer including lung cancer among patients who underwent OLT for alcohol-related liver disease [35-36]. SRL exerts antiangiogenic activities that are linked to a decrease in production of vascular endothelial growth factor (VEGF) and to a markedly inhibited response of vascular endothelial cells to stimulation by VEGF [37]. Furthermore, the ability of SRL to increase the expression of E-cadherin suggests a candidate mechanism for its ability to block

regional tumor growth and for inhibiting metastatic progression. Therefore, not only patients transplanted for HCC but also those with de novo malignancies after transplantation should be given special consideration for SRL-based immunosuppressive regimens.

45b.6. Biliary Complications

Biliary strictures are one of the most common complications after liver transplantation, with a reported incidence of 5.8-34% [38]. Risk factors contributing to biliary strictures include ischemia/reperfusion injuries, prolonged warm and cold ischemia times, bacterial and viral infections especially CMV, age cross match, acute and chronic rejection, a small-for-size graft, HAT, ABO blood incompatibility, hepatotoxic drugs, and recurrent viral or cholestatic disease. The spectrum of biliary complications has changed within recent years, due to the introduction of reduced size, split liver, and LDLT. In the LDLT recipient, 18% of biliary complications have been reported in various centers in the United States, 15% in European centers, and 32% in Japanese centers. There is no consensus among centers regarding standardized biliary anastomosis techniques; some favor a hepatico-jejunostomy with or without stenting of the anastomosis, but others prefer a direct hepaticocholedochostomy [39]. Novel radiological methods such as magnetic resonance cholangiopancreaticography (MRCP) have been introduced as diagnostic tools for biliary complications.

Biliary leaks generally occur as an early post-transplant complication; whereas, strictures may develop postoperatively over months and years. ERC or percutaneous transhepatic cholangiography (PTC) have often been used as the primary approach, leaving surgical intervention for those who are non-responsive to endoscopical interventions. The long-term efficacy and safety of endoscopic techniques have been evaluated in various transplant centers [40-42]. Non-anastomotic strictures are commonly associated with a less favorable response to interventional endoscopic therapy, in comparison to anastomosis stenosis. An Austrian group found anastomotic strictures in 12.6% of patients transplanted between October 1992 and December 2003 and non-anastomic strictures in 3.7% of them [38]. Interventional endoscopic procedures were effective in 77% of patients with anastomosis stenosis; whereas treatment of non-anastomotic strictures showed long-term effectiveness in 63% of patients. A surgical approach was required in 7.4% of transplant recipients.

At our center, results from 75 transplanted patients undergoing ERC for suspected anastomic strictures were retrospectively analyzed [41]. Interventional endoscopic treatment was successful in 22 of 25 patients. Balloon dilatation alone and combined dilatation and endoprotheses placement was efficacious in 89% and 87% of cases respectively, but recurrence occurred in 62% and 31% of cases respectively. We therefore use dilatation plus stenting with endoscopic reassessment. Repeated ERC sessions are performed with increasing endoprothesis diameter in trimonthly time intervals and double or triple parallel stenting in selected cases. Tung et al. have shown that up to 75% of patients were stent-free after 18 months of endoscopic intervention [43]. Medical treatment for bile duct strictures consists of UDCA and additional antibiotic treatment in stricture-induced cholangitis. Complications related to bilioenteric anastomosis require PTC or surgical intervention. Ampullary and sphincter of Oddi dysfunction occur in up to 5% of transplanted patients with typical signs of biliopancreatic reflux of contrast medium during ERC. Various centers have reported on endoscopic sphincterotomy or transpapillary stenting as endoscopic treatment [44-45]. In patients with biliary stones, endoscopic sphincterotomy and stone extraction have been reported to be successful in about 90% of patients [43].

45b.7. Metabolic Bone Disease

Metabolic bone disease is a common cause of morbidity and often results from therapy with corticosteroids. Screening with bone densitometry should begin before transplantation. Patients with reduced bone mineral density (BMD) should be administered calcium and vitamin D. Biphosphonate therapy should be considered for patients with increased risk for fractures.

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45c. RECURRENT DISEASES AFTER LIVER TRANSPLANTATION

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Disease recurrence may occur in patients with viral hepatitis, tumor disease, autoimmune diseases, and cholestatic liver diseases. With universal recurrence of HCV in all replicative patients, hepatitis C continues to pose one of the greatest challenges for preventing disease progression in the allograft.

45c.1. Recurrence of Hepatitis C in the Allograft

The influence of HCV infection on allograft histology is highly variable. The liver injury can vary from absent or mild disease despite high viral burden to cirrhosis in the allograft (approximately 25% of recipients) within 5 to 10 years of follow-up [1]. There are also patients who clear the virus either spontaneously or with antiviral therapy, but still have progression of liver fibrosis. After the diagnosis of cirrhosis, the decompensation risk [2] appears to be accelerated (17% and 42% at 6 and 12 months, respectively) and patient survival [3] is significantly decreased (66% and 30% at 1 and 5 years, respectively). HCV associated allograft injury is the most common cause of both death (28-39%) and graft failure (42%-43%) among HCV infected recipients, and retransplantation is the last option for these patients in the context of increasing demands for OLT [4]. Several studies have found that short- and medium-term patient and graft survival for HCV infected recipients are comparable to those for most other indications [5-6]. However, there are reports suggesting a greater relative risk of death and allograft failure in HCV positive recipients [7-8].

Several factors have been discussed that may accelerate HCV reinfection of the allograft (table 45c.1). There is insufficient data regarding the relationship between immunosuppressive agents and clinical expression of HCV recurrence. TAC and CSA do not seem to be significantly different [9-12] with respect to their impact on histologically-diagnosed hepatitis C recurrence (table 45c.2). Various studies have demonstrated

Table 45c.1. Factors that may accelerate histological progression in HCV patients after liver transplantation.

Donor factors	Donor age Donor fat content Ischemic time
Recipient factors	Recipient age Non-caucasian race Genotype 1b High pre-transplant viral load Bolus corticosteroids posttransplant Rapid tapering dose of corticosteroids posttransplant

Table 45c.2. Impact of immunosuppression on viremia and HCV recurrence.

Immunosuppressive agent	Viral load	Severity of HCV recurrence
Calcineurin inhibitors	No difference between cyclosporine A and tacrolimus	No difference between cyclosporine A and tacrolimus
Bolus corticosteroids	↑	
Azathioprine	↓ (in the replicon system)	Controversial discussion
Mycophenolate mofetil	Controversial discussion	Controversial discussion
T-lymphocyte depleting agents	Not known	Controversial discussion
Sirolimus	Not known	Not known

that long-term treatment with corticosteroids, slowly tapered off over time, may prevent progression to severe forms of recurrent disease [13-15]. In contrast, the boluses of methylprednisolone (MP) used for acute rejection episodes are deleterious to the HCV-related graft survival. This may be related to the one log increase in the serum HCV levels after a pulse of MP over a 2 week period [16] and a possible cytopathic mechanism of HCV-induced allograft injury in the context of higher levels of viremia [9].

Berenguer et al. [17] reported that induction with MMF is associated with more severe recurrence of HCV. Other investigators have found that MMF has no impact on patient survival, rejection, or rate of HCV recurrence in HCV-infected transplant recipients based on biochemical changes and histological findings [18]. A recent study showed significantly better patient survival and graft survival for HCV infected patients treated with MMF, TAC, and steroids than for patients

treated only with TAC and steroids, with 4-year patient survival rates of 79.5% vs. 73.8% and 4 year graft survival rates of 74.9% vs. 69.5% [19]. Other studies have shown a positive effect of MMF in combination with CNI tapered for 24 months on fibrosis progression, graft inflammation, and alanine aminotransferase levels [20]. This may be due to the antifibrotic effects of MMF through an antiproliferative effect on myofibroblast-like cells. The role of HCV RNA levels in determining severity of HCV recurrence remains controversial [11] with the single exception of the well-established relationship between very high viral loads and occurrence of cholestatic hepatitis.

Histological evaluation of posttransplant chronic hepatitis C has to be performed with special attention to the different composite patterns of liver damage, because the autoimmune hepatitis pattern might indicate the need for a more sustained immunosuppression. The presence of steatosis may identify patients with more predominant viral-induced graft failure who may profit from antiviral therapy.

There is increasing evidence that IFN-alpha and ribavirin therapy may prevent the development of cirrhosis, even in the absence of sustained viral response in a subset of patients. This treatment is however associated with more side-effects and is far less effective than in the non-transplant setting. The most applicable treatment strategy is treatment of recurrence with pegylated (PEG)-IFN-alpha and ribavirin, which results in a sustained viral response of 20-25%. We investigated the efficacy and safety of a treatment regimen including standard IFN-alpha-2b (2 MU/day) during the first 3 months, followed by PEG-IFN-alpha-2b administered subcutaneously at a dose of 1.5 mcg/kg once per week for the following 9 months. Ribavirin was administered concomitantly with IFN-alpha at a dose of 10-12 mg/kg/day. At the end of treatment, viral response (EOTVR), biochemical response (EOTBR), and histological response (EOTHR) were detectable in 43%, 44%, and 31% of patients, respectively. A sustained viral response was achieved in 25% of patients. These data are comparable with results from various antiviral treatment studies in transplanted HCV patients reported in the literature [21].

45c.2. Recurrence of Hepatitis B in the Allograft

Hepatitis B immunoglobulin (HBIG) has been widely adopted as an effective treatment strategy against recurrent HBV disease in posttransplant patients [22]. Potential adverse effects of HBIG are rare and include anaphylaxis, mercury toxicity, and transmission of blood borne infection. The HBIG dose regimen in most European centers aims to maintain the trough anti-HBs titers above 100 IU/L. Subsequent dosing, which is based on a fixed dose regimen including the administration of 10,000 IU HBIG intravenously (IV) during the anhepatic phase and 10,000 IU IV daily for the first week post-OLT followed by 10,000 IU IV monthly, has been used in various centers in the United States. Preventive HBIG monotherapy in posttransplant patients who are negative for hepatitis B envelope antigen (HbeAg) and HBV DNA is commonly associated with a low risk of recurrent HBV infection [23].

Immunosuppression and the anti-HBs-mediated immune pressure on HBV may culminate in the emergence and/or selection of immune escape HBV mutants. Most escape mutations that influence hepatitis B surface antigen (HBsAg) recognition by anti-HBs antibodies are located in the second "a" determinant loop. Variants with exchanges of amino acid 144 in HBV genotype A and 145 in genotype D were found in posttransplant patients receiving long-term polyclonal anti-HBs immunoprophylaxis [24]. A major concern of long-term LAM therapy is the emergence of mutations in the YMDD (tyrosine, methionine, aspartate, aspartate) motif of the DNA polymerase. About 70% of patients treated with LAM for 3 years develop B-domain L528M, C-domain M552I, or M552V mutations in the HBV polymerase region [25-26]. In the transplant setting, breakthrough infection has been found to occur more rapidly in up to 30% of patients within as little as 6 months of continuous therapy [27-28] due to the development of drug resistance [29]. Excellent long-term results of HBIG/LAM combination therapy with a 2-year patient survival of 94% has been reported by Steinmüller et al. in HBV patients transplanted between 1997 and 2000 [23]. This strategy differs from our transplant center's strategy. We have found that HBV recurrence in patients who have seroconversion, gain of antibodies, and negative HBV DNA before and after transplantation, have an

extremely low risk for HBV recurrence under passive immunoprophylaxis. Thus, careful determination of the indication for LAM therapy is required in HBV recipients who do not display any evidence of viral replication before and after OLT. These patients receive HBIG monotherapy and undergo regular monitoring of virological, biochemical, and histological parameters. Liver tissue assessment routinely includes immunohistochemistry and PCR using HBV-specific primers. HBIG therapy is individualized in our transplant center according to anti-HBs titers and aims to maintain trough levels above 100 IU/L.

Resistance to LAM and HBIG may cause severe graft reinfection and progression to fulminant hepatic failure, due to fibrosing cholestatic hepatitis. Newer nucleoside analogues have been investigated for their antiviral potential against YMDD mutants and some of them may serve as a rescue treatment against LAM and HBIG-resistant viral strains. Several in vitro and in vivo studies have already confirmed that ADV has a potent antiviral efficiency against lamivudine-resistant strains [30-32]. The development of ADV resistance has been reported in 3% of patients after 2 years of therapy and in 18% after 4 years [33].

Schiff et al. reported on a study which included 131 liver transplant patients with LAM resistance [34]. Treatment for 48 weeks resulted in a significant decline in HBV DNA levels by 4.4 log10 copies/mL. Data from an international, multicenter, double-blind, placebo-controlled, phase III clinical trial in patients with chronic HBV infection showed that 64% of patients exhibited significant improvement in liver histology after 48 weeks of therapy with 10 mg of ADV. Treatment also resulted in a median HBV DNA reduction of 3.91 log 10 copies/mL, and normalization of alanine aminotransferase (ALT) levels occurred in 72% of patients, as compared to 29% in the placebo group [35]. Data from clinical studies with tenofovir (TNV) in HBV-infected patients are limited. Promising results have been obtained in the transplant setting, which suggests that TNV may be another potential option for the treatment of patients with LAM-resistant strains. In contrast to ADV, elevations of serum creatinine have not been observed during TNV therapy. Thus, TNV may be of particular interest for those transplant patients who have pre-existing progressive renal insufficiency due to nephrotoxicity of various immunosuppressive agents [36]. Entecavir was recently approved by the US Food and Drug Administration for the treatment of chronic hepatitis B, and it has been shown to be active against strains resistant to LAM and ADV. A large phase III study has demonstrated that HBeAg positive patients treated with entecavir at a dose of 0.5 mg for 48 weeks developed a more pronounced decrease in HBV DNA titer than those with LAM therapy [37]. More results from multicenter studies are warranted in order to determine the efficacy of entecavir in the liver transplant setting.

45c.3. Recurrence of Cholestatic Liver Diseases and Autoimmune Hepatitis

Data about the frequency of disease recurrence varies widely in the literature, but most investigators report recurrent PBC rates in up to one-third of patients at 10 years [38-39]. Diagnosis of PBC in the transplanted liver is usually more challenging than diagnosis in the native liver. Immunoglobulin M and anti-mitochondrial antibodies (AMA) often persist, and elevated cholestatic enzymes may be due to other causes of bile duct damage. Histology is usually required, and the detection of granulomatous cholangitis is necessary for the diagnosis of recurrent PBC.

Some investigators have found that CSA-based immunosuppressive therapy is associated with lower recurrence rates as compared to TAC-based immunosuppression [40-41]. There is not yet sufficient data about the impact of UDCA treatment after OLT on the rate of disease recurrence. Although matching is considered important for kidney transplantation, the significance of HLA testing for liver transplant patients has often been questioned. A study at the University of Pittsburg, on 3261 liver transplantation patients suggested that a mismatch between the donor and the recipient decreases the risk of disease recurrence in PBC patients (results were presented at the American Transplant Congress, Transplant 2002, in Washington, DC). They found that 35% of patients with 2 HLA-DR matches had disease recurrence, as compared to 10% of PBC patients with only 1 match or complete mismatching. A similar tendency has been observed by Hashimoto et al. for LDLT recipients [42].

The reported recurrence rate for PSC after OLT ranges between 8.6% and 25% [43-44]. Histopathological

findings in PSC include fibrous cholangitis, fibro-obliterative lesions, ductopenia, and biliary fibrosis. In a recent study at the Mayo clinic, recurrence of PSC was defined by strict cholangiographic and histological criteria in patients with PSC, in whom other causes of bile duct strictures were absent [44]. However, due to the lack of a histological gold standard, the diagnosis of PSC recurrence is based primarily on cholangiographic features. Seddon et al. investigated the clinical course of ulcerative colitis in recipients transplanted for PSC [45]. Interestingly, despite immunosuppression, significantly higher relapse rates and a significantly higher corticosteroids requirement were detected, with 20% of the patients becoming corticosteroid dependent after OLT [45]. Results from various studies have not revealed any differences in the overall patient survival or graft survival in patients with or without recurrent disease [43-44].

AIH recurrence has been reported in 10-35% of patients within a follow-up period of 5 years [46-47]. A long-term follow-up study (> 10 years) by a French group, found AIH recurrence in 41% of the patients. The authors recommended regular liver biopsies, because histological signs precede abnormal biochemical liver values in about one-fourth of patients [46]. The diagnosis of recurrent AIH may include histological features, the presence of autoantibodies, and increased gammaglobulins. The majority of published studies did not confirm a posttransplantation prognostic role of antibodies in patients undergoing OLT for AIH. Conflicting data exist regarding the presence of specific HLA antigens that predispose patients to AIH recurrence after liver transplantation [47]. Histological signs of recurrence include interface hepatitis, lymphoplasmocytic infiltration, and/or lobular involvement. In an analysis of data from 28 patients with AIH between 1987 and 1999, Vogel et al. found a 5 year survival rate of 78.2%, which was not significantly different from controls with genetic liver diseases [48]. Patients had more episodes of acute rejection though, in comparison to the control group.

45c.4. Tumor Recurrence

The results of early studies of OLT for HCC were disappointing. More than 60% of patients developed tumor recurrence within the first two transplant years [49-51]. Early studies reported 1-year survival rates of 42-71% and 5-year survival rates of 20-45% [52-53]. Five-year survival data for HCC patients showed an increase from 25.3% in the late 1980s to 61.1% in the late 1990s [54]. Currently, there are 1-year survival rates up to 80%, 5-year survival rates up to 70%, and a recurrence rate of 10-15% in patients fulfilling the Milan criteria [54-55]. A transplant group from the Mount Sinai Hospital retrospectively analyzed the records of 311 HCC patients transplanted between September 1988 and September 2002 [56]. Of these patients, the 5 year survival was significantly lower for patients with recurrence (22%) compared to those without recurrence (64%). In an analysis of predictors of survival and tumor-free survival in a cohort of 155 OLT recipients, Zavaglia et al. found that the histological grade of differentiation and macroscopic vascular invasion are independent predictors of survival and tumor recurrence in patients receiving liver transplants for HCC [55].

In Asian countries, HCC has emerged as the most frequent indication for LDLT. A Japanese group investigated the outcome of LDLT in 316 adult recipients with HCC [57]. When the Milan criteria were fulfilled, 3-year patient survival and disease-free survival rates were 78.7% and 79.1%, respectively. In those who did not meet the Milan criteria, 3-year patient survival and disease-free survival rates were 60.4% and 52.6%, respectively.

The transplant group of the Mount Sinai Hospital, who reviewed the data from 36 LDLT patients with HCC, performed follow-up investigations utilizing CT scan and AFP levels trimonthly over a time period of 2 years [58]. Patients with tumor lesions ≥ 5 cm underwent doxorubicin chemotherapy intraoperatively and every 3 weeks for 6 cycles posttransplant. Fifty-three percent of the patients were beyond the UNOS priority criteria. The 2-year patient survival and recurrence-free survival were 60% and 74%, respectively. Bilobular distribution was the only significant multivariate risk factor for recurrence. Interestingly, although the tumor size exceeded 5 cm in one third of LDLT patients, the incidence of recurrence, the recurrence-free survival rate, and the patient survival rate were comparable to patients who underwent deceased liver transplantation. Several groups have therefore argued that

an expansion of criteria for LDLT is justified in HCC patients [57-58]. Others argue that the concept of fast-tracking impedes the selection of tumors with unfavorable biology and poor outcome [59]. Furthermore, there is an ethical dilemma about whether deceased organ transplantation should be considered in LDLT recipients with primary non-functioning allograft. Novel molecular biology techniques, such as genotyping for HCC, may be relevant for determining recurrence-free survival. Further data from prospective trials are needed to clarify the benefit of adjuvant treatments for these patient groups.

CCC is an unfavorable indication for liver transplantation. The largest series of patients with intrahepatic CCC was reported in the Data Analysis Booklet of the European Liver Transplant Registry, revealing 1 year, 3 year, and 8 year survival rates of 58%, 38%, and 23%, respectively [60]. Considering the limited donor organ availability and the clearly inferior outcome as compared to other indications, liver transplantation does not represent a suitable therapeutic approach for patients with CCC, except in a highly selected patient group with very early tumor stages. The Mayo Clinic protocol utilizing preoperative chemoirradiation and staging at laparotomy before proceeding to OLT might be applicable in selected cases and might improve outcome [61].

Metastatic lesions are a contraindication for OLT unless originating from neuroendocrine tumors (NET) [62-64]. These tumors may be hormone producing (peptide hormones or amines) or may present as nonfunctional tumors. They are characterized by slow growth and frequent metastasis to the liver, and their spread may be limited to the liver for protracted periods of time. Gastrointestinal carcinoid tumors represent the most common neuroendocrine tumors presenting with liver metastases. Five-year disease-free posttransplant survival rates of 24%-52% have been reported in literature [65-66]. Rosenau et al. retrospectively analyzed by immunohistochemistry the expression of Ki67, E-cadherin, and p53 in metastases of NET of the explanted livers [66]. They found that survival in patients with low Ki67 and regular E-cadherin staining was significantly better than in those with high Ki67 or aberrant E-cadherin expression. Further studies will elucidate if these biomarkers are beneficial for prognostication of posttransplant long-term survival in this patient group. The currently available data in patients transplanted for NET is limited and ususally restricted to small numbers of patients, which suggests that liver transplantation should be considered only in highly selected cases. Coppa et al. found that patients were suitable transplant candidates at a younger age (< 50 years), if the primary tumor is located in the gastrointestinal tract, drained by the portal venous system, and has been completely removed (extrahepatic lymphadenectomy), and if the disease has been stable for at least 6 months during the pretransplantation period [66]. Long-term results from prospective studies are needed to elucidate how to select patients with NET for OLT, to identify predictors for disease recurrence, and to determine the influence of the primary tumor site on patient posttransplant survival.

45c.5. Recurrent Alcohol Abuse after Liver Transplantation for Alcoholic Liver Disease

Alcoholic liver disease has become a leading cause of liver transplantation and represents the second most frequent transplant indication in Europe and the United States. Studies evaluating recurrent alcohol abuse have reported a mean incidence of relapse in one third of the patients ranging from 10% to 50% in up to 5 years of follow-up [67]. The role of the length of pretransplant abstinence as a predictor of posttransplant abstinence has been controversially discussed. Many studies have assessed possible risk factors for alcoholic relapse after liver transplantation. Perney et al. recently identified the following factors as risks for recidivism: a shorter length of abstinence before OLT, more than one pretransplant alcohol withdrawal, alcohol dependence, alcohol abuse in first relatives, and younger age [68]. It has been reported that patients transplanted for alcoholic liver disease reveal more frequent bacterial infections but fewer episodes of acute cellular rejection than those with other indications [68]. Bellamy et al. have found that severe chronic alcohol consumption after liver transplantation significantly decreases the medium and long-term survival [69], and our experience confirms this (unpublished data). Interestingly, compliance with medication and follow-up visits has been reported to be comparable in patients with and without relapse [68].

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CHAPTER 46

OUTCOME OF LIVER TRANSPLANTATION IN SPECIAL CATEGORIES OF PATIENS

46.1. Outcome of Liver Transplantation in HIV Patients

V. Cicinnati

Recent data suggest an acceptable outcome in highly selected HIV patients [1]. Fung et al. propose that HIV patients with renal failure, advanced malnutrition, opportunistic infections within the last 6 to 12 months, previous Kaposi's sarcoma, or JC polyoma viral infection should be considered contraindicated for OLT [1]. Between July 1998 and October 2001, five HIV-infected patients underwent OLT because of HBV-, HBV + HDV-, or HCV-induced liver cirrhosis at our transplant center. Retrospective analysis of the data revealed that three of the five patients died due to graft failure [2]. Norris et al. compared data from HIV-positive patients coinfected with HCV (n = 7) to those with non-HCV-related liver diseases (n = 7). In the non-HCV group, all patients were alive; whereas 5 of 7 HCV-coinfected patients died during a median follow-up of 1 year [3]. Vogel et al. retrospectively analyzed the data of 7 HIV-positive transplant recipients [4]. They found that the spectrum of postoperative complications including the course of recurrent hepatitis C infection and rate of rejection was not different from that in HIV-negative patients, except in one with Kaposi's sarcoma and multicentric Castleman's disease.

46.2. Experiences with Liver Transplantation in Inherited Metabolic Liver Diseases

V. Cicinnati

OLT is regarded as an effective treatment strategy for patients with Wilson's disease. Transplantation leads to partial correction of the defective metabolism by converting the copper kinetics from a homozygous to a heterozygote phenotype, thus providing posttransplant an adequate increase of ceruloplasmin levels and a decrease of urinary copper excretion. Schilsky et al. retrospectively investigated the outcome of 55 transplant recipients at centers in Europe and the United States [5]. They found a 1-year survival rate of 79%. Four out of 7 patients who manifested neurological and/or psychiatric complications had improvement of theses symptoms posttransplant. Nonetheless, OLT for neurological Wilson's disease without severe hepatic disease does not seem to be justified, given the added risk of operative procedure, the uncertainty of improvement of neurological symptoms, and the potential long-term complications of immunosuppression.

Alpha-1-antitrypsin deficiency is one of the most common genetic causes of liver disease in the world. Recent studies have suggested that a subgoup of PiZZ individuals are predisposed to liver damage, due to an insufficient degradation of mutant alpha 1-antitrypsin Z within the endoplasmatic reticulum [6]. A 1 year survival rate of 73% for adults has been reported in literature [7].

It has been shown that the survival of patients who undergo OLT for hereditary hemochromatosis is markedly lower in comparison to other indications [8]. Data on 5180 liver transplant recipients from 37 transplant centers, compared to patients with hemochromatosis, revealed 1 year survival rates of 79.4% vs 69.2% and 5 year survival rates of 53.8% vs. 43.1% [9]. Similar findings have been obtained from the UNOS revealing 1 year and 5 year survival rates of 69% and 55% in patients with hereditary hemochromatosis and secondary iron overload, as compared to 75% and 61% in those without iron overload [8]. In hemochromatosis, patients' metabolic defect resides in the small intestine; whereas, OLT cures metabolic defect in the liver. Con-

flicting and very limited data are available on recurrent iron deposition in the liver. Nonetheless, there is a need for careful monitoring of patients with hereditary hemochromatosis in order to determine whether iron reaccumulates in the allograft.

46.3. Outcome after Liver Transplantation for Acute Hepatic Failure

S. Beckebaum, V. Cicinnati

Acute hepatic failure (AHF) accounts for up to 12% of liver transplant activity. The most common causes of AHF include paracetamol overdose, idiosyncratic drugs (paracetamol, isoniazid/rifampicin, cumarins, ectasy, tricyclic antidepressants, etc.), hepatitis B, seronegative hepatitis, and pregnancy-related syndromes. In addition, Budd-Chiari syndrome, Wilson's disease, and in rare cases autoimmune disease may also present as AHF. Recent data revealed that survival in patients with AHF is inferior to that of recipients with nonacute indications for OLT within the first year but comparable in the long-term [10]. Early postoperative complications in patients transplanted for AHF include sepsis, multisystem organ failure, and primary graft failure. Serum creatinine concentrations above 200 mcmol/L pretransplant, non-white recipient race, donor body mass index > 35 and recipient age >50 years have been suggested as risk factors for post-transplant mortality [11]. A study correlating the causes of AHF and the transplant outcome has suggested that the best outcome is found in patients transplanted for Wilson's disease and the worst outcome in those transplanted for idiosyncratic drug reactions. The results in patients transplanted for AHF have improved within the last decade, due to 1) the establishment of prognostic models such as the King's College criteria and the Clichy criteria, 2) the option for living-liver donation, and 3) the introduction of the MELD score. Newer markers, including serum leukocyte cell-derived chemotaxin-2 level, serum phosphate, or cytochrome C, have been proposed as complementary tools for prognostication of the outcome in AHF.

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CHAPTER 47

COMPUTER ASSISTED SURGERY PLANNING (CASP) IN ADULT-TO-ADULT LIVING DONOR LIVER TRANSPLANTATION (ALDLT)

A. Radtke, G.C. Sotiropoulos, M. Malagó

47.1. Why Do We Need CASP?

A successful adult live donor liver transplantation (ALDT) depends on many factors. However the risk of the operation is considerable and donor safety remains central to this difficult venture! The selection and imaging of the live liver donor candidates are paramount for a good outcome.

47.1.1. Challenges in Donor Selection and Evaluation

Proper donor selection is probably the most critical aspect. The main goal of the evaluation process is to ensure the safety of the donor and provide the best quality graft for the recipient. Given that a live donor is a completely healthy person, there should not be any compromise in the acceptance of donor! Selection criteria vary around the world, but each program has precisely defined guidelines, that include a complex stepwise work up, progressing from initial screening tests to more detailed investigations [1]. Nowadays CT and MRI imaging has been given preference [2-4]. An appropriate donor/recipient match is the secret to the safety of the donor and optimal result for the recipient. The graft size and its anatomical properties must be optimally adjusted according to the recipient's characteristics, premorbid condition and especially the severity of his portal hypertension. Main reasons for donor refusal under these circumstances include:

- inadequate liver biopsy and clinical parameters,
- insufficient liver volume,

and less common:

- disadvantageous donor liver anatomy.

The donor evaluation program in Essen follows a five-step process [5-6]. CASP, based on the all-in-one CT protocol [7], contributes initially to the second phase of our evaluation program and is crucial for determining donor suitability by providing:

- sufficient prediction of optimal or minimal functional graft/remnant masses,
- detailed information on vascular/biliary liver anatomy.

When the prospective donor candidate has been conclusively accepted a detailed surgery plan using virtual 3-D CT image-based computer assistance is formulated [8].

47.1.2. Pitfalls in Liver Anatomy

One of the "weak points" in surgery planning for ALDLT is unquestionably the assessment of the anatomy of the graft. The vascular and biliary liver anatomy is known to be very irregular and characterised by a very high incidence of anatomical variations [1, 9]. Nearly each individual "hides" some kind of anatomic anomaly [10]. Anatomic variations of the biliary tract in particular are of considerable significance in ALDLT and may lead to troublesome complications in both the donor and recipient.

Although variations of the vascular or biliary anatomy may seldom represent a contraindication for donation [1, 5], cases with bile duct anomalies, particularly when associated with multiple right arteries, demonstrate an increased risk of short and long term biliary complication. Thus, a precise knowledge of hilar ana-

tomy is crucial to a thorough strategy of hilar dissection, determining in advance the level of transection within the hilar plate, and eventually the art of vascular and biliary reconstructions.

Preoperative imaging investigations should provide accurate detection of "complicate" anatomy in the donor liver, which would allow a safe surgical preparation and parenchymal transection. In this respect, reliable imaging is needed to depict donor candidates with multiple right hepatic ducts, rendering hilar dissection dangerous and biliary reconstruction precarious. Similarly, donors with a tiny main right hepatic artery in conjunction with an accessory right artery are at higher risk of arterial thrombosis or ischemic bile leakage in the early -and anastomotic stricture in the later- postoperative period, particularly when an additional bile duct trifurcation is present [11]. Cases bearing these types of anatomical irregularities are best excluded from donation of right liver graft.

47.1.3. Exceptions in Pathophysiology

Essential features characterising ALDLT comprise the combination of two disadvantageous phenomena:

- small for size-situation for both donor and recipient,
- portal hypertension (PHTN) in the recipient.

Central to ALDLT is the problem of small for size (SFS), exposing both donors and recipients to considerable risk! Splitting the liver into right and left hemilivers is closely associated with the potential risk of lethal SFS-injury for both donor and recipient.

In order to prevent a postoperative liver failure, ALDLT has drastically changed the criteria of donor selection, leading to re-evaluation of our knowledge concerning adequate or at least minimum functional liver mass for an adult individual.

The term small for size (SFS) first described by Emond et al [12] entails three diferent phenomena:

- Small for size-situation.
- Small for size-injury.
- Small for size-syndrome.

Small for size-situation signifies graft/remnant size smaller then that of the required liver weight usually calculated as % SLV or GVBWR (Graft Volume Body Weight Ratio) [5, 13]. According to this definition, all live donor grafts in adult recipients and all remnant livers in the donors are SFS-livers.

The biochemical features of SFS in blood tests include:

- cholestasis with elevated conjugated (indirect) bilirubin,
- prolongated prothrombin time,
- mild to moderate elevation of the aspartate transaminase (AST) levels.

The histological appearence of SFS is characterised by:

- bilirubin plugs in line with cholestasis,
- ischemia with multifocal necrosis mixed with areas of regeneration,
- hepatic artery thrombosis occurs secondary to these microscopic changes.

Although the safety of the donor constitutes a major priority, clinical experience has demonstrated that a graft liver bearing the handicap of total devascularisation, cold and warm ischemia and exposure to the imbalanced porto-arterial inflow due to portal hypertention in the recipient, is much more prone to complications and liver failure in the SFS-situaton than the remnant liver.

Small for size injury denotes graft/remnant liver injury related to the SFS-situation independent of and in addition to the injury due to cold/warm ischemia. The SFS-injury probably arises from the constellation of more than one unfavorable condition such as:

- reduced liver quality,
- inadequate liver quality,
- increased portal inflow and
- impaired venous outflow.

Portal hyperperfusion has proven to be the main mechanism of SFS-injury with both experimental models [14] and independent clinical data supporting the theory showing that excessive portal venous inflow is attributable to postoperative liver dysfunction and deteriorated clinical course [15-16]. This occurs both directly and because of hemodynamic interactions between portal vein and hepatic artery flow [17]. The latter has been shown to be inversely related to both graft size and to portal/hepatic venous flow in SFS-grafts.

Although portal venous pressure is considerably elevated in liver grafts of GWBWR (Graft Weight Body Weight Ratio) less than 0.8, additional donor and recipient factors may affect postoperative portal venous pressure irrespective of graft size. An increased risk of

graft/remnant liver dysfunction has been observed in fatty content of more than 30%.

SFS-injury releases, at microscopic level, a combination of pathological mechanisms as:

- tissue injury,
- exaggerated inflammatory response,
- exacerbated acute rejection,
- diminished synthetic function,
- inhibited cell proliferation.

A vicious pathogenic circle eventually determines the clinical outcome. A shear stress caused by increased portal inflow has been suggested as being responsible for the damage to the sinusoidal endothelial cells, collapse of the space of Disse and the sinusoidal congestion. These changes may subsequently be followed by:

- hepatocyte and mitochondrial swelling,
- hemorrhagic infiltrates,
- centrolobular necroses,
- intracellular cholestasis,
- microcirculatory failure.

Small for size syndrome (SFSS) is the clinical manifestation of SFS-injury by showing a combination of clinical symptoms which display a prolonged graft malfunction, resulting from too small a functional liver mass for a designated recipient or live liver donor. It is characterised by the appearance of:

- early encephalopathy,
- progressive intrahepatic cholestasis,
- prolonged severe coagulopathy,
- intractable ascites due to persistent portal hypertension.

Small for size graft or remnant livers display a transient SFS-situation in donor/recipient after ALDLT, that can progress in to the SFSS – usually an irreversible clinical condition.

However, in the clinical situation symptoms of SFSS can be difficult to differentiate from postoperative complications associated with technical problems or septic complications.

Interestingly, not every SFS graft or remnant liver fail! Therefore, liver size alone may not be responsible for the damage seen to the SFSS. Aside from the adequate functional liver mass (size, volume), and satisfied liver quality, several other donor and recipient factors (donors age, and BMI, premorbid condition of recipient etc.) influence the graft/remnant functionality.

It is already well known that the increased metabolic demand on one side and a hyperdynamic state on the other encountered in recipients, suffering from terminal liver disease, require an appropriately sized graft! Increased metabolic demand on functionally SFS-grafts predisposes to surgical and septic complications and consequently poor outcome. Hence, when too small a liver graft is transplanted in a severely ill patient, a complex competitive mechanism of an increased metabolic demand together with stimulation of hepatocyte proliferation expressing a hyperdynamic state will eventually lead to the critical symptoms of SFSS which having become irreversible then culminate in septic liver failure.

These complex issues can be resolved with the appropriate approach. In order to overcome small for size, several conceptual and technical modifications have been proposed:

1. Choice of "extended" right grafts including MHV in order to provide an equally sufficient venous drainage in both posterior and anterior sectors [18].
2. "Large" venous outflow reconstruction by using venous graft interposition to prevent occlusion at the outflow orifice by kinking or twisting caused by graft malposition [19].
3. "Dual" graft transplantation with the use of two left hemiliver grafts from two separate donors, in order to reduce the risk to the donor for SFS [20].
4. "Inflow modulation" procedures to reduce portal venous pressure together with the resulting portal hyperperfusion, as well as to protect the hepatic artery by choosing some specific flow manipulations as: ligature of splenic artery or hemi-portocaval shunting, or portal vein "wrapping" (in certain cases combined together) [21-23].
5. Temporary administration of hydrocortisone and prostaglandine E2 into the graft artery via catheter, within the first 2-4 weeks postoperatively, to prevent "early" arterial occlusion.

Potential changes seen in SFS could be ameliorated by proper venous outflow or/and portosystemic shunting. Sufficient outflow seems to be key solution to releasing the porto-arterial imbalance in portal hypertention (PHTN) and preventing severe tissue congestion,

which is associated with loss of functional and regenerative capacity leading eventually to graft/remnant liver failure. It was also found that a hemi-portocaval H shunt reduced portal pressures without decreasing overall blood flow to the liver. Thus, a temporary employment of partial portal decompression may also prove expedient in those recipients with severe portal hypertention receiving a SFS-graft.

47.1.4. Surgical Problems in Donor Hepatectomy

ALDLT led to re-evaluation of our concepts of liver partition, changing the approach to liver transection considerably! Only optimal grafts and unaffected remnant livers can provide adequate immediate function and rapid regeneration following the operation.

The donor operation for an adult recipient involves either a right hepatectomy entailing resection of segments V, VI, VII, and VIII or a left hepatectomy, involving segments II, III, and IV with or without caudate lobe [24-27].

The decision on the choice of graft type depends on:

- liver mass required for both recipients and donor,
- avoiding potential risk to the donor.

The kind of graft hepatecomy is dictated by the size of the donor and the intended recipient, but additionally by the individual metabolic demand expected in the recipient according to the severity of his illness and degree of portal hypertention (PHTN). The transection line for liver partition in the donor must be decided in keeping with the individual liver anatomy.

The surgical technique is widely accepted as one of the most important factors to influence outcome in both the donor and recipient, underlining the need for meticulous handling. Central to graft hepatectomy, however, is the exact course of the transection line, that always gives rise for justifiable concern. On one hand it has to follow the right/left porto-arterial (Pringle) demarcation boundary, to avoid marginal necrosis with resulting serious biliary and septic complications, but on the other hand the liver partition has to respect the individual territorial liver anatomy and preserve MHV drainage in the medial sectors of either liver part (segments IV, V, VIII).

The "double dilemma" in determining the optimal transection line addresses:

- dilemma of the "hepatic vein dominance relationships",
- dilemma of the territorial "MHV belonging pattern".

The controversy surrounding the optimal line of transection can be traced to the "discrepant" vascular liver anatomy consisting of a porto-arterial inflow pattern that divides the liver into two parts (Pringle-demarcation line), and a venous outflow provided by three main hepatic veins with their separate drainage territories.

There is virtually a "competition" between the left and right hemiliver in relation to the middle hepatic vein. Although the MHV drains both liver parts, it can be preserved by only one of them when performing a transection. The territories drained by the middle hepatic vein constitute the most vulnerable areas in the graft and remnant livers. Any outflow impairment can be particularly detrimental in recipients with relatively small grafts and significant portal hypertension, in whom an underlying small-for-size situation can result at most in graft failure or at best lead to severe biliary and/or vascular complications [28-29].

Despite the extreme complexicity of the operation, which encounters many technical difficulties and demands exceptional operative tactics, graft procurement from a live donor for an adult recipient has become a widely established procedure.

47.2. Conceptual Frame of CASP

47.2.1. All-In-One Protocol of Multiphasic CT Scan

Three-dimensional non-invasive imaging reconstruction is a multimodal process using modern imaging techniques. An excellent cross-sectional (2-D) image quality is the precondition for effective usage of 3-D visualisation tools. A mandatory component is the use of thin-sliced, multi-detector row CT scanners, representing a comprehensive diagnostic tool, combining the advantage of non-invasiveness and detailed information, obtained by excellent image quality.

Above all, a multiphasic CT scan has to provide sufficient contrast of the liver organ, especially in regard to the intrahepatic vascular and biliary tree, which allows for clear demarcation of the vascular structures from the surrounding parenchyma on the axial 2-D images.

CT imaging, as originally published by Schroeder T.

et al. [2], is performed at our institution employing a 16-row-Multidetector-CT-Scanner (Sensation16®, Siemens, Germany) using the following parameters: kVp 120, mAs 140-170, slice collimation 0.75 mm, feed/rotation 12 mm, and rotation time 0.5 sec.

The CT protocol includes successive acquisition of three image sets of the liver and simultanous intravenous administration of a biliary agent to visualise the biliary anatomy. The first image set, outlining the biliary system, is usually acquired 30 (+/- 5) minutes following intravenous short-infusion of 100 ml of a biliary contrast agent (Biliscopinß, Schering, Berlin, Germany). To delineate the hepatic vasculature patients receive 140ml of an iodinated contrast agent (Xenetix 300®, Guerbet GmbH, Sulzbach, Germany). This is administered intravenously by an automated injector system (CT 9000, Liebel-Flarsheim, Cincinnati, OH, USA) at a rate of 4 ml/s. Automated bolus tracking with bolus detection at the level of the ascending aorta assures accurate timing of the arterial phase. For the display of portal and hepatic venous anatomy, third and fourth CT image sets are acquired effectively 10 and 40 seconds following the arterial one. Reconstruction increments are of 1 mm for the arterial and 1mm for the venous scans.

All-in-one CT protocol however, bears a potential risk to the donor, which must be balanced against the true benefits of this concept in each individual case.

The troublesome disadvantages include:

- exposure to ionizing radiation,
- administration of considerable volumes of potentially nephrotoxic iodinated contrast agents,
- possible side effects associated with administration of the biliary contrast agent, ranging from mild and self-resolving symptoms to a lethal anaphylactic shock.

In this respect, carefully obtained donor histories, as well as a confirmation of normal renal and hepatic function prior to the CT examination are mandatory.

47.2.2. HepaVision – Software Assistant for 3-D Image Analysis

We describe herein our experience of image-based computer assistance using a non-commercial software prototype HepaVision (MeVis, Bremen). The mathematical background for the MeVis software is based on studies by Zahlten et al. and Selle et al. [30].

HepaVision offers the combined option of a 3-D reconstruction and a virtual simulation of the planned liver partition including visualisation of the Pringle demarcation line. It comprises:

- visualisation panel (3-D reconstruction, territorial mapping),
- calculation capacity (volumetry, risk analysis),
- virtual 3-D simulation.

Both the "visualisation" and "simulation" panels, used in conjunction, offer a comprehensive system portraying the "real intraoperative" situation.

The visualisation panel not only encompasses a 3-D display of liver anatomy, but also allows for "territorial mapping" dependent on the individual vascular/biliary anatomy [8]. In combination with the volume calculation, the surgeon is able to perform a "computed risk analysis" concentrating on the medial sectors (segments: IV, V, VIII) with a special focus on the venous dominance relationship [32]. By using the simulation pannel, difficult operative steps, such as the hilar dissection and parenchyma, transection can be analysed and exactly planned preoperatively.

The methodical steps of computed image analysis include:

- segmentation of liver parenchyma,
- segmentation/analysis of vascular/biliary systems,
- final fusion of both steps.

The use of mathematical models [30] enables the fusion of vascular analysis and liver segmentation results. All virtual data are managed by Intervention Planner – a special software module and can be displayed by a freely movable 3-D liver model, or superimposed on the axial 2-D CT slices.

47.2.2.1. *3-D Liver Model: Visualisation of Liver Parenchyma*

Visualisation of liver parenchyma is a main prerequisite for creating individual 3-D liver models. Three dimensional reconstruction of the real liver shape and its surface was a pioneering invention and has become a benchmark for 3-D visualisation quality! HepaVision software provides great potential by utilising the segmented data acquired from venous phase CT images (fig. 47.1 a-b).

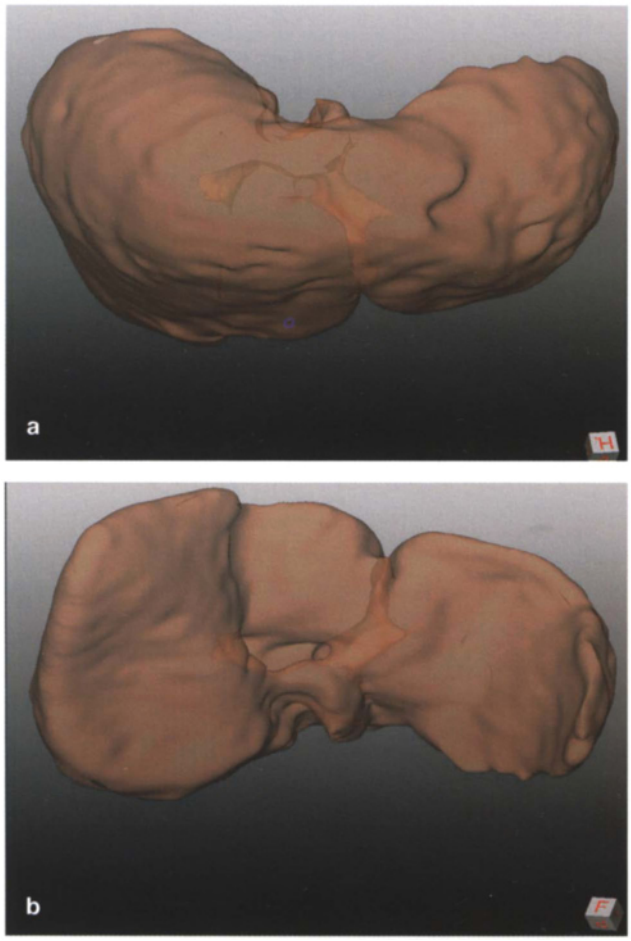


Fig. 47.1. a-b: 3-D reconstruction of donor liver, cranial view (a), caudal view (b).

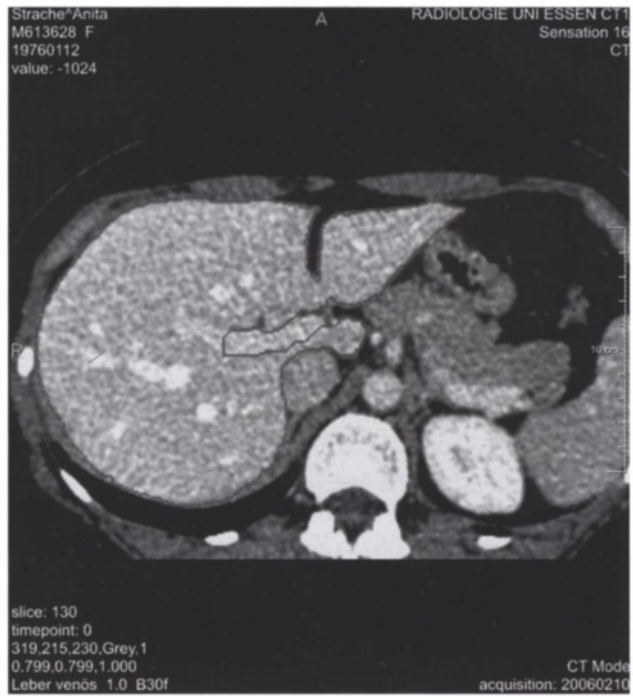


Fig. 47.2. Assessment of total liver volume (TLV). Liver contour was traced with a modified live-wire, semi-automated contour finding algorithm approach. The live-wire contour was obtained from venous phase 3-mm slice, axial, 2-D CT images.

Segmentation of the liver parenchyma represents a baseline step for both liver volume calculation and preoperative liver partition simulation. It is performed with a modified live-wire approach, a semi-automated contour finding algorithm, allowing for the calculation of total liver volume (TLV). The live-wire contours are interactively determined on a slice of the axial 2-D-CT images, every 3 mm, and the contours of intermediate slices can be automatically interpolated and optimised, by software, yielding volumetric calculation in mililitres (ml) (fig. 47.2).

47.2.2.2. *Territorial Liver Mapping: "Intrahepatic" Volume Calculation*

HepaVision has definitively "opened the gate" to a completely new concept of territorial visualisation. The mathematical fusion of the respective vascular and parenchyma segmentation-data, allows for the automatic calculation of individual vascular territories as described by D. Selle et al. [30]. The software offers the 3-D display of the portal venous segments (Couinaud segments: I-VIII) and their corresponding arterial, biliary, and hepatic venous territories (fig. 47.3-47.6 a-b). Additionally it enables the surgeon to obtain 3-D images of the subterritories belonging to the middle hepatic vein tributaries on each side ("fishbone" map), allowing for the prediction of venous outflow impairement in both marginal zones following the "virtual" liver partition (fig. 47.7 a-b). Selle et al. [31] demonstrated with the aim of anatomical specimens, a significant concordance between "virtual" Couinaud segments and "real" anatomical ones from liver casts. Although estimation of the volume of the individual segments or "territories" is difficult, it represents an essential part of planning the donor hepatectomy.

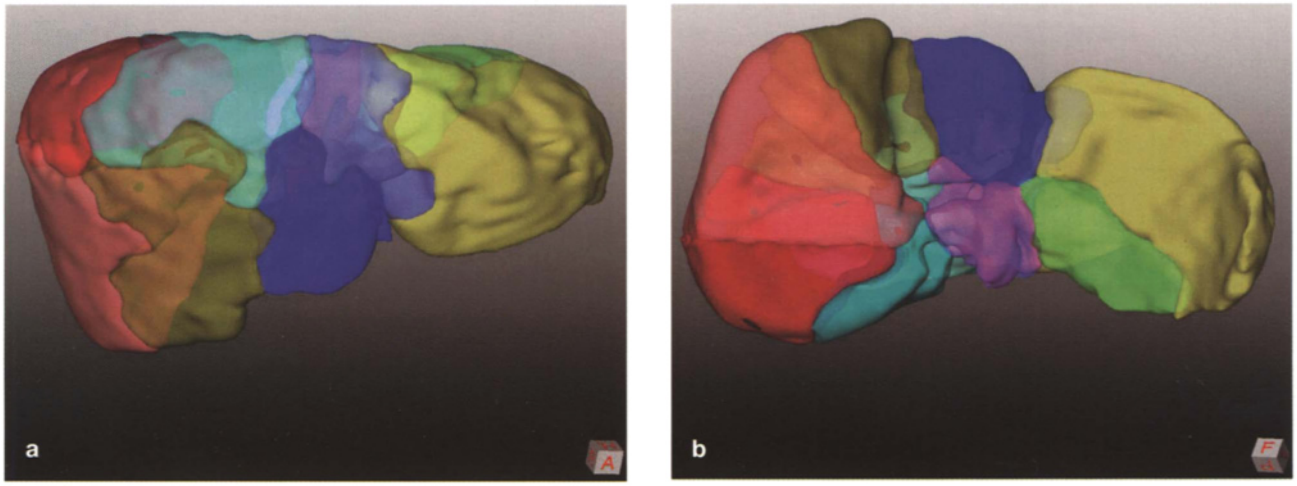


Fig. 47.3. a-b: 3-D reconstruction of Couinaud segments I-VIII, cranial view (a), caudal view (b).

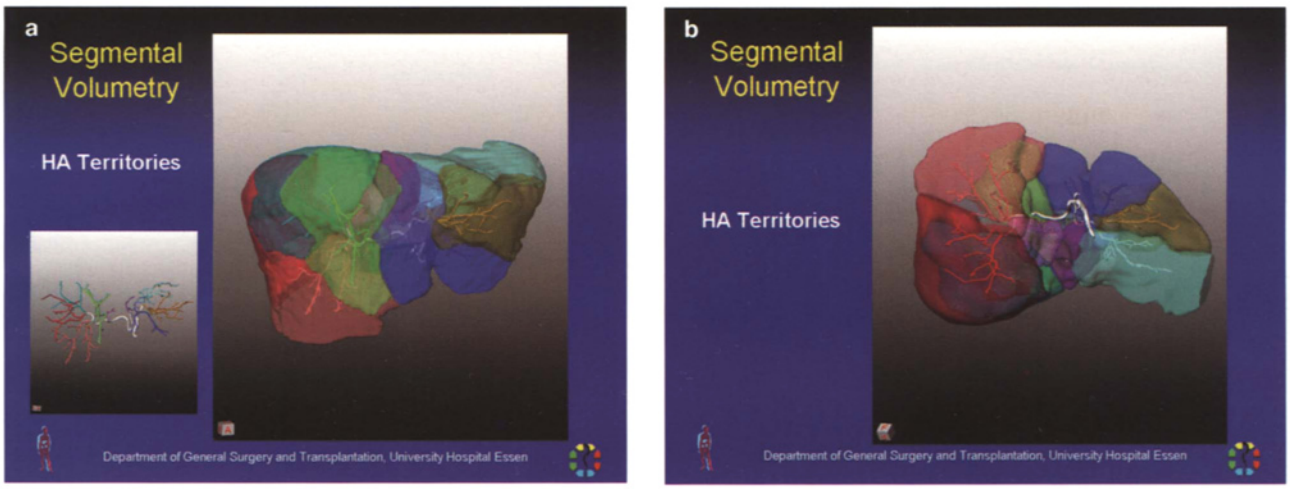


Fig. 47.4. a-b: 3-D reconstruction of hepatic artery territories, cranial view (a), caudal view (b).

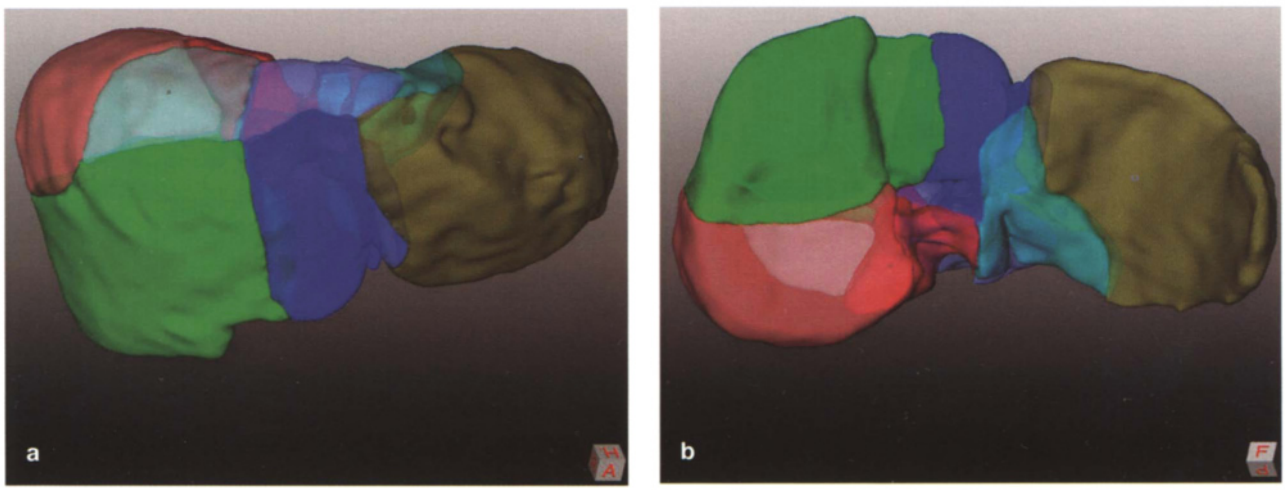


Fig. 47.5. a-b: 3-D reconstruction of bile duct territories, cranial view (a), caudal view (b).

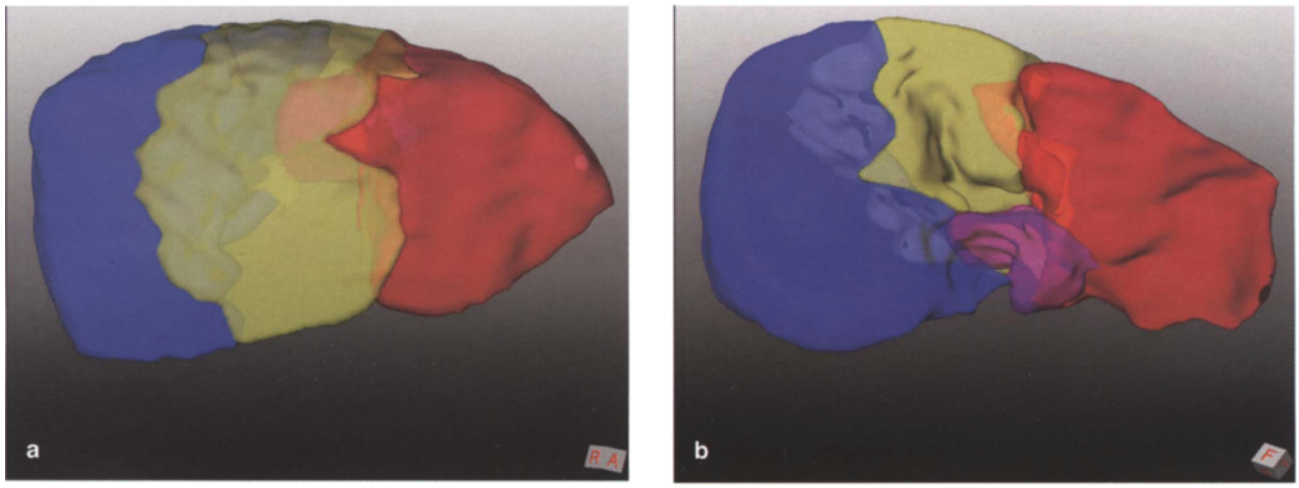


Fig. 47.6. a-b: 3-D reconstruction of hepatic venous territories, cranial view (a), caudal view (b), LHV (red), MHV (yellow), RHV (dark blue), caudate (purple).

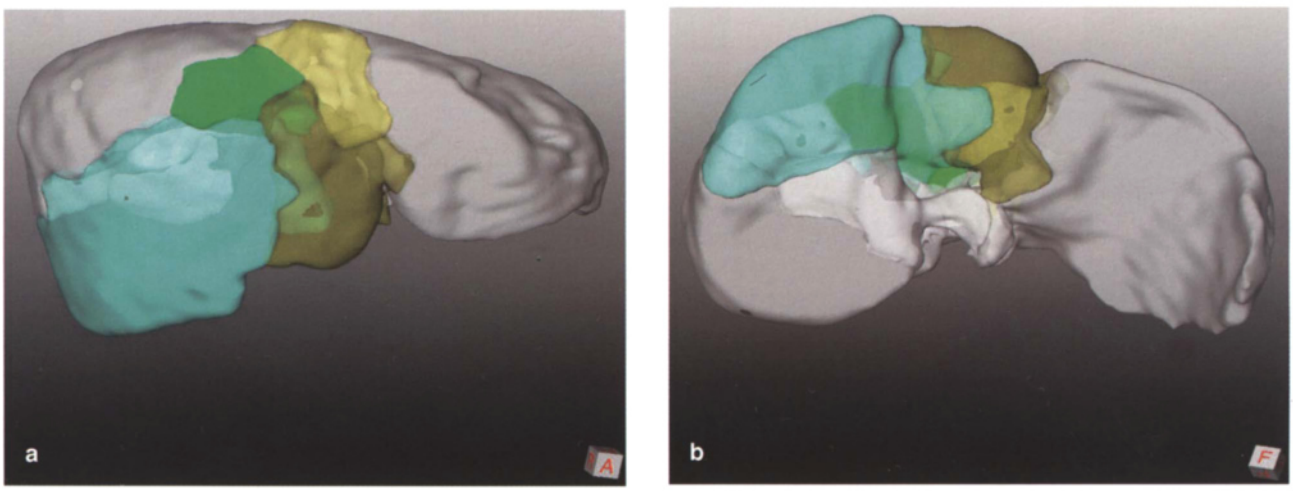


Fig. 47.7. a-b: 3-D reconstruction of MHV "fishbone" map, cranial view (a), caudal view (b), MHV 4a tributary (yellow), MHV 4b tributary (brown), MHV 8 tributary (green), MHV 5/6 tributary (cyan).

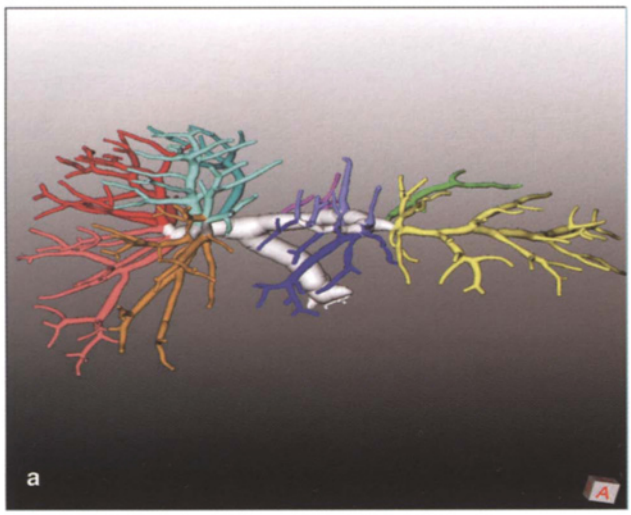
47.2.2.3. *3-D Vascular/Biliary Visualisation*

HepaVision offers a unique concept of "all in one" 3-D reconstruction of vascular and especially bile duct systems (fig. 47.8 a-b-c). Thanks to this feature, it is an excellent tool for non-invasive image analysis aiding the preoperative donor selection and simplifying surgery planning.

The technical challenges of "all in one" 3-D visualisation are:

- high image quality,
- precise image overlap.

During the initial processing, all relevant structures (portal and hepatic venous system, hepatic artery, biliary system) are extracted from the image data. Intrahepatic vessels are transformed into a hierarchical graph showing dependencies between branches and direction of blood flow. Relevant branches of subtrees are assigned different colors during exploration of the 3-dimensional vascular/biliary graphs. An accurate 3-D imaging of the intrahilar anatomy is paramount to planning the hilar dissection and determining the optimal transection line. Accurate entry into the segmental level of the vascular systems and the biliary tract is es-



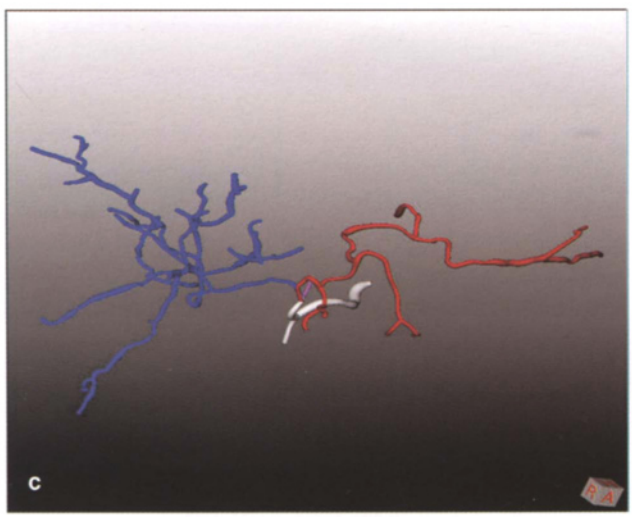


Fig. 47.8. a-b-c: 3-D reconstruction of vascular and biliary systems, portal vein (a), bile duct (b), hepatic artery (c).

sential to the visualisation of liver territories and reliable estimation of their volumes.

The use of registration alghorithms, as described by Preim et al. [32], enables the software to compile the acquired data in a single 3-D animation. The surgeon can display the vascular and biliary systems independently or simultaneously, allowing for an imaging overlap of all systems (fig. 47.9 a-b-c), which is subsequently verified in the "real" situation during surgery.

47.2.2.4. *Virtual Hepatectomy: Simulation in 3-D Liver Model*

Besides various kinds of volume calculation, virtual simulation is definitively a revolutionary tool offered to the surgeon for planning the donor operation. It has already proved to be most useful in clinical employment for oncologic resections [33-35].

Utilising the segmentation data, HepaVision provides interactive generation of resection proposals, with ilustration of marginal zones along the simulated transection line.

Different virtual resection lines can be simulated on a 3-D liver model, which offers optional display of vascular trees and territories. This 3-D visualisation not only allows for a better understanding of the liver anatomy, but also provides more precise and individualized views than the classic 2-D mode.

The volume of graft and remnant livers parenchyma is calculated separately for each liver partition proposal. In addition, the overlap of hepatic venous territories with territories arising from the manually (surgeon's line) and automatically defined (Pringle line) grafts and remnants can be calculated (fig. 47.10 a-b-c).

47.3. Surgery Planning: Strategic Work Up

ALDLT principally consists of two separate operations, donor hepatectomy and graft implantation, which are conceptually interrelated. This procedure is preferably conducted under elective conditions and must be planned very thoroughly. Both donor and recipient must meet criteria of suitability for ALDLT and the risks to both must be taken into serious consideration, should there be any concern, they should be excluded.

The main considerations during surgery planning for ALDLT entail:

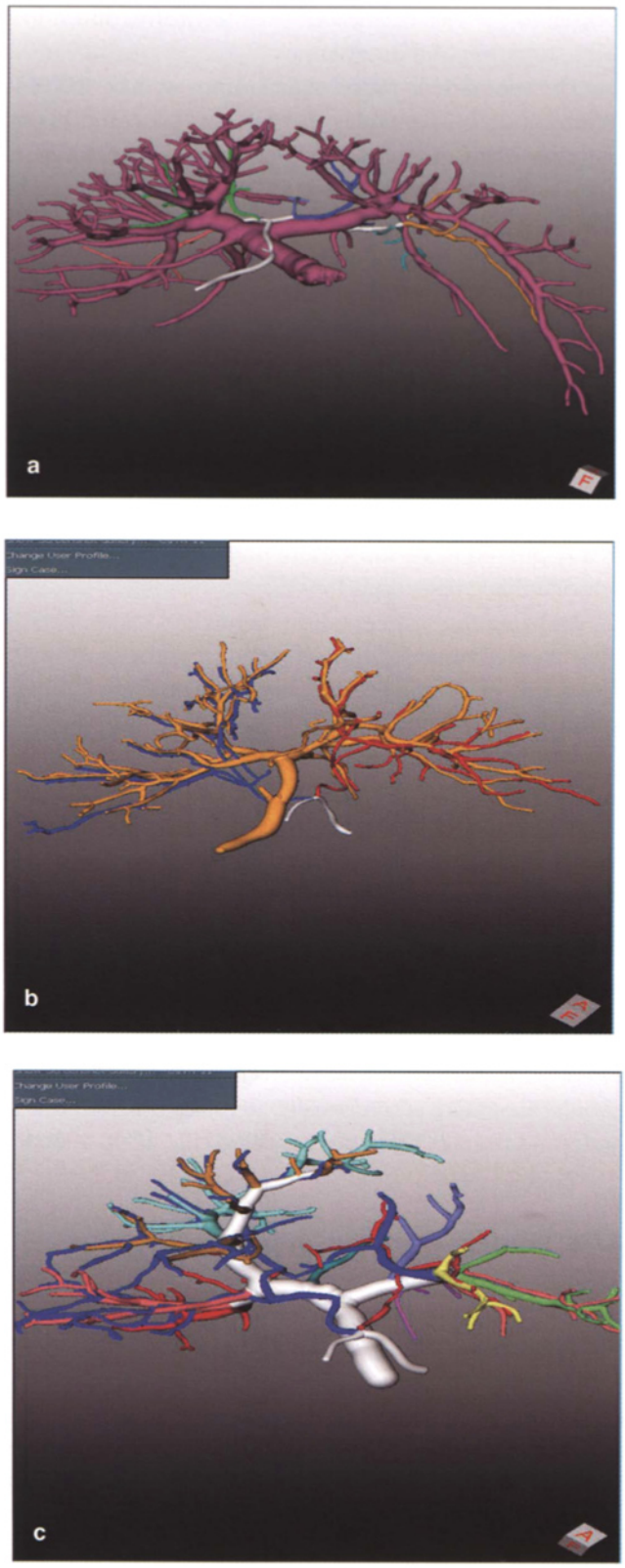


Fig. 47.9. a-b-c: 3-D reconstruction of vascular and biliary systems in overlap, PV/BD (a), HA/BD (b), HA/PV (c).

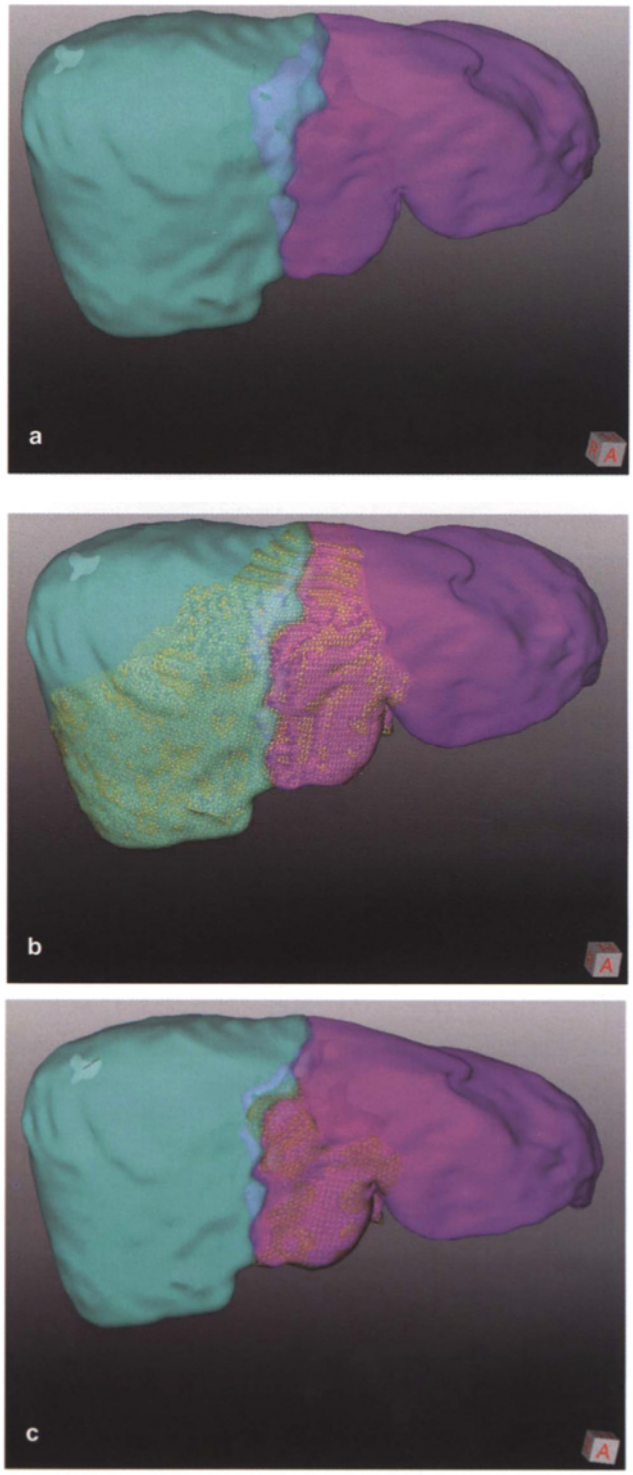


Fig. 47.10. a-b-c: 3-D reconstruction of Pringle demarcation line and hepatic venous territories in overlap, Pringle hemilivers: right vs left (a), Pringle demarcation line vs. MHV territory (b), Pringle demarcation line vs. MHV 4b sub-territory (c), right Pringle hemiliver (cyan), left Pringle hemiliver (purple), MHV Territory (yellow hatching), MHV 4b sub-territory (brown hatching).

- precise prediction of the functional reserve volumes of both graft and remnant livers,
- decision whether to use the right or left hemiliver as a graft,
- decision whether to include the MHV with the graft or to retain it in the remnant liver,
- decision on the appropriate venous outflow reconstruction in the graft.

The computer assisted surgery planning offered by the HepaVision software makes this much needed information rapidly and clearly available to the surgeon. It represents an essential component of the preoperative evaluation strategy.

While in the donor an insufficient functional volume in the remnant liver represents the main risk, there is a compromised perfusion of the graft in its "marginal zone" in the recipient, which can result in a fatal outcome. This may be attributed to an impaired arterial inflow or/and insufficient venous outflow [29]. Tissue congestion in the drainage territories of the MHV in the medial area of graft liver (segments V and VIII) can cause irreversible damage. Ischemia along the resection margin due to inadequate arterial inflow can lead to tissue necrosis with the risk of biliary leak and lethal sepsis.

47.3.1. 3D Hilar Vascular and Biliary Anatomy in the Donor Liver

Postoperative vascular and biliary complications are extremely dangerous and can require retransplantation! Thus, a clear understanding of the central (hilar) and peripheral (intrahepatic) anatomy is critical to success with this procedure.

The hilar vascular and biliary anatomy should not hide variations, which could place the donor and the recipient at risk of serious complications. Therefore it must be precisely evaluated pre- and intraoperatively.

In particular regard to recipients at high operative risk, who are critically ill or who receive relatively small grafts (SFS situation), additionally revealing unfavourable anatomical variations, such constellations themselves may considerably increase the risk of postoperative complications leading eventually to a fatal outcome.

"All in one" CT protocol provides a baseline for 3-D reconstruction images, which clearly depict potentially dangerous arterial, portal and biliary anomalies in the donor liver, thus minimizing the need for dissection close to the right and left bile ducts, enabling the entire left "hilar window" to be left undisturbed.

Anatomical variations essential in right graft hepatectomy, addressed by 3-D imaging (fig. 47.11-47.16):

- portal vein, and bile duct - trifurcations (fig. 47.11 a-b-c),
- short branched right bile duct ("short neck BD") (fig. 47.12 a-b),
- right sided caudate bile duct, with "cross over" course within the "right hilar window" (fig. 47.13 a-b-c),
- accessory "segment IX" branch of the portal vein "crossing over" the transection line (fig. 47.14 a-b-c),
- accessory hepatic arteries (fig. 47.15 a-b),
- sectorial branch of the right hepatic artery "undercrossing" the right bile duct (fig. 47.16),
- irregular segment IV branch arising from right hepatic artery.

A special advantage of the 3-D visualisation, provided by HepaVision, has been noted in the evaluation of the biliary tract anatomy. More specifically, the second/third-order branches (sectorial/segmental) can be analysed by the software with high accuracy, definitively replacing the need for the intraoperative cholangiography at our institution. In most centres, intraoperative cholangiography is necessary for establishing the most appropriate site of division of the right or left hepatic duct to avoid multiple hepatic duct openings in the graft and injury to the bile duct confluence.

Right liver grafts are known to have a higher incidence of vascular and biliary variants, than the left [36]. Multiple hepatic ducts have been found in 31% and irregular hepatic arteries in 23% of our patient cohort [8]. The combination of multiple right arteries and bile ducts is particularly detrimental, rendering arterial and biliary reconstructions risky.

The vascular anatomy of segment IV in the remnant liver, when the right hepatic graft is donated may prove challenging, as the arterial blood supply to the segment can completely or partially arise from the right hepatic artery. Similiarly portal inflow of right liver grafts, which usually originates from the right main branch, can in cases with PV trifurcation (about 18% in our cohort) hide a sectorial branch arising from the left portal vein (fig. 47.17).

Inadequate venous drainage of segment IV deprived of MHV 4a/b tributaries added to an impaired ar-

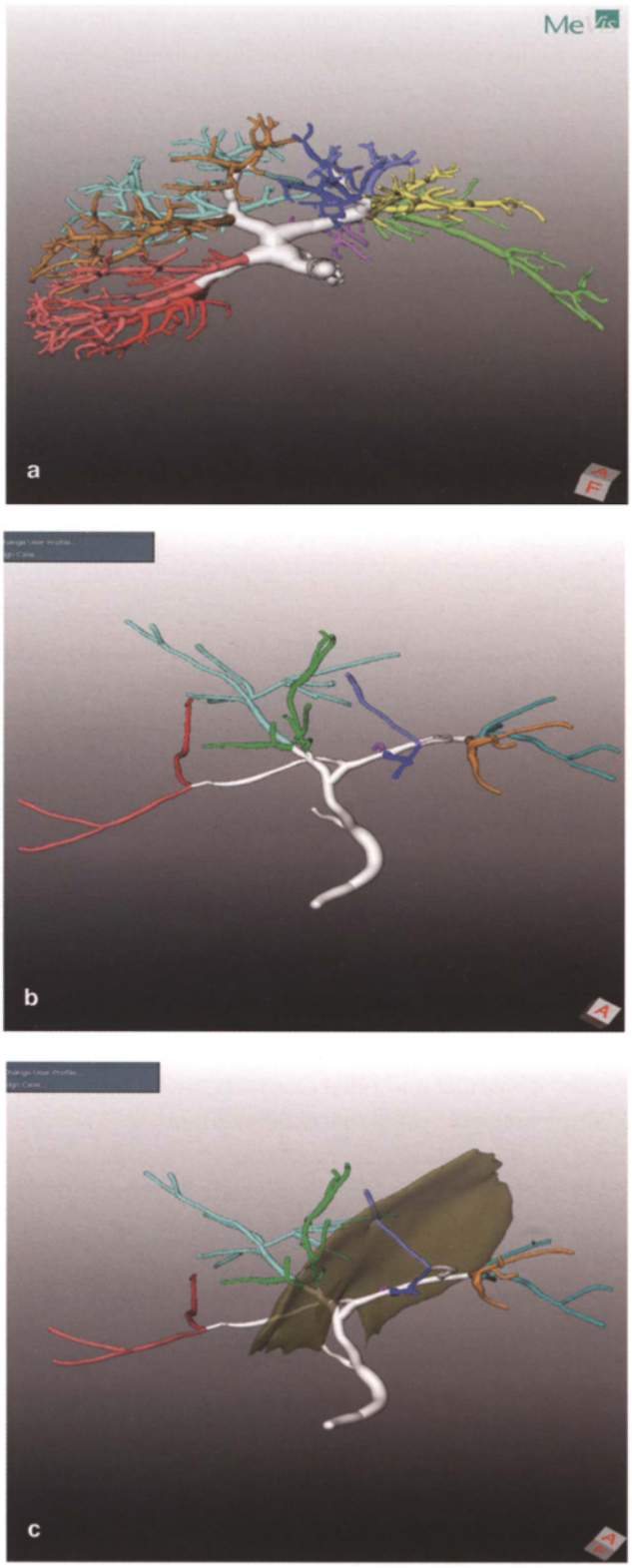


Fig. 47.11. a-b-c: 3-D reconstruction of hilar vascular/biliary variations, cranial view, PV trifurcation (a), bile duct trifurcation (b), bile duct trifurcation in overlap with the "virtual" transection line (c).

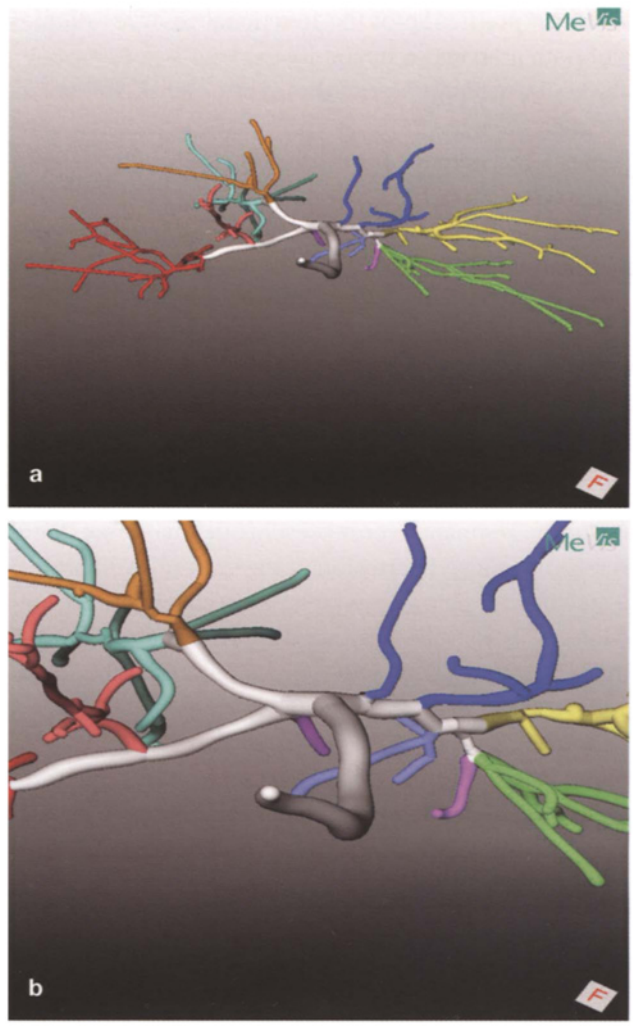
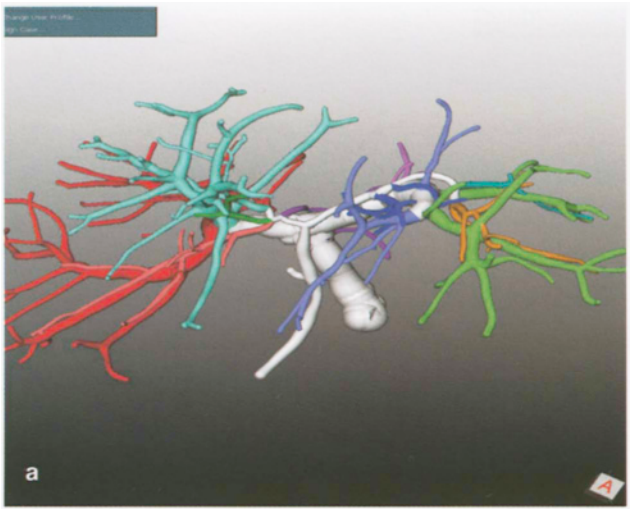
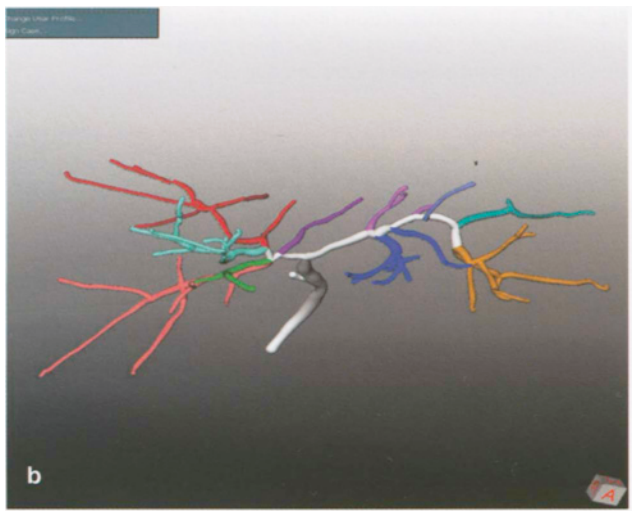


Fig. 47.12. a-b: 3-D reconstruction of right sided bile duct, with a "short neck" in the right hilar window, right caudal branch (dark purple).

terial supply due to detachment of an irregular segment IV branch from the right hepatic artery may result in atrophy of the segment or septic complications and biliary leakage in the donor. Therefore, careful preservation of the vasculature to segment IV is absolutely essential when performing right hemiliver graft procurement. The level of transection of the right HA and PV must be determined to accommodate the vascular anatomy of segment IV.

Other major complications of right graft donation include early bile leakage and late bile duct stricture at the anastomotic site caused by tactical mistakes or technical errors, associated with an error judgement





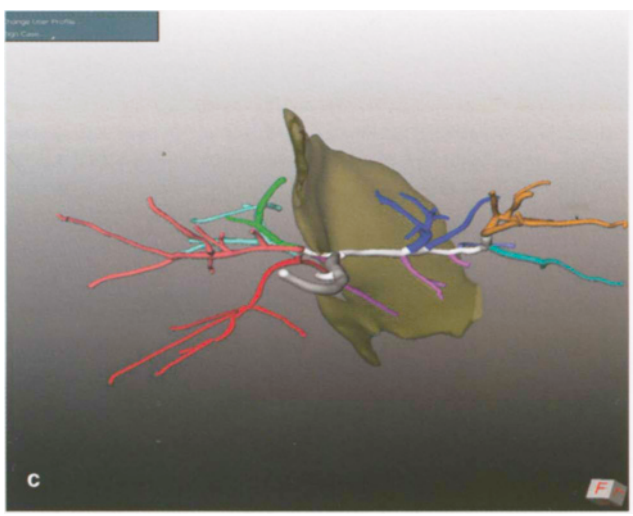
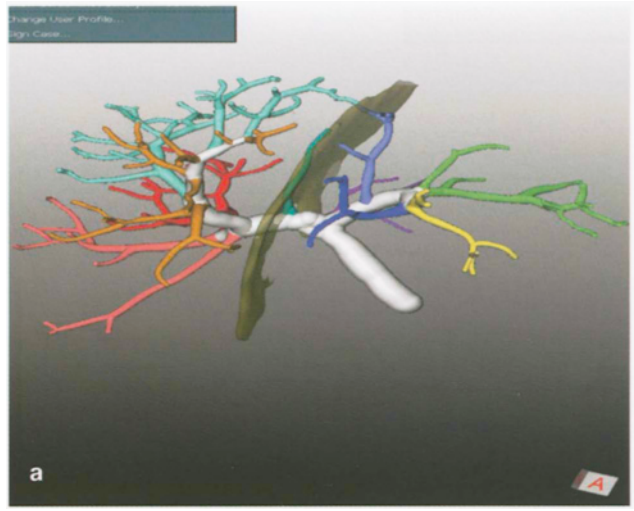
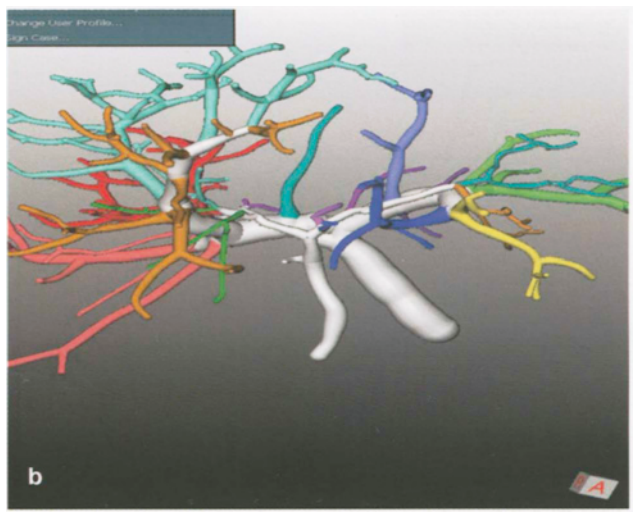


Fig. 47.13. a-b-c: 3-D reconstruction of right sided caudate bile duct (dark purple), with "cross over" course within the "right hilar window" in overlap with portal vein (a), selective view (b), in overlap with the "virtual" transection line (c).





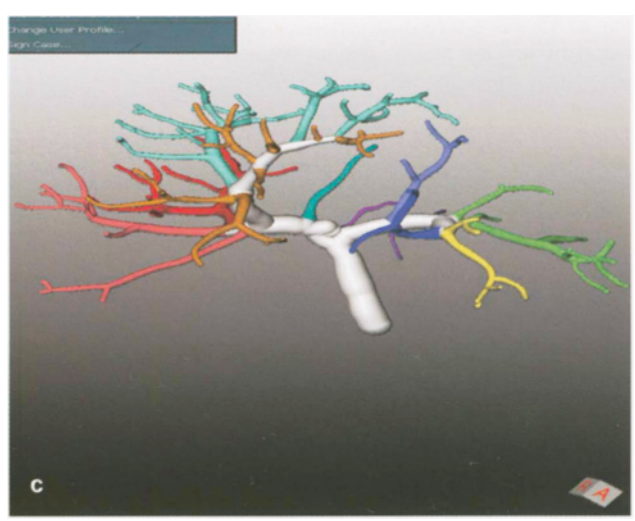


Fig. 47.14. a-b-c: 3-D reconstruction of accessory "segment IX" branch of the portal vein nearly "crossing over" the "virtual" transection line (dark cyan) (a), in overlap with the bile duct (b), selective view (c).

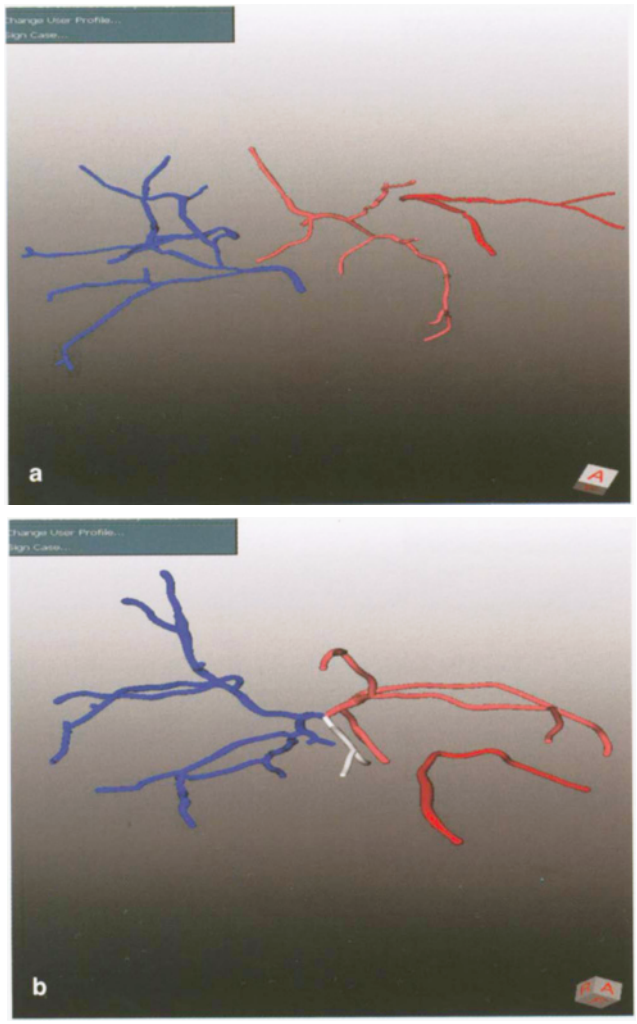


Fig. 47.15. a-b: 3-D reconstruction hepatic artery variations, replaced right- and left hepatic arteries (Michels type IV) (a), accessory left hepatic artery (Michels type II) (b).

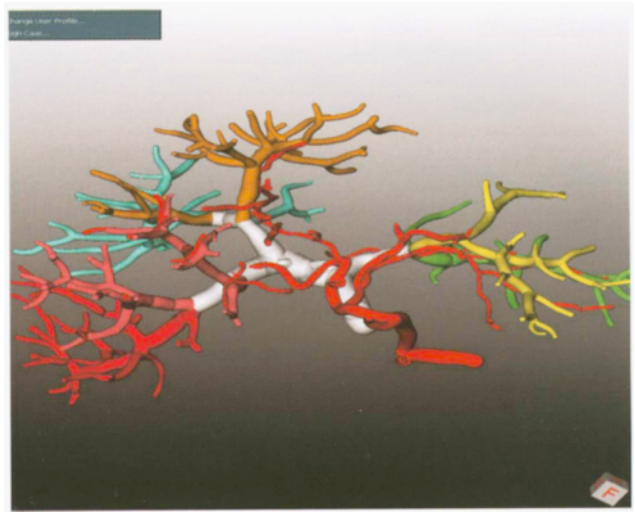


Fig. 47.16. 3-D reconstruction of sectorial branch of the right hepatic artery (red) "overcrossing" the right portal vein and "un-der-crossing" the right bile duct, intraoperative view.

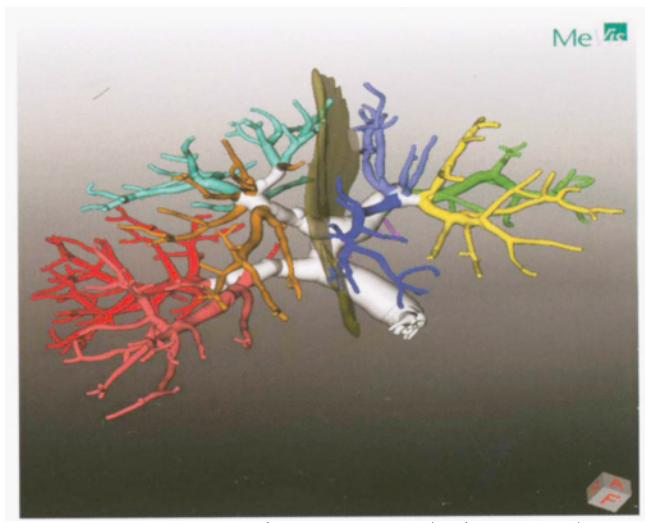


Fig. 47.17. 3-D reconstruction of PV trifurcation in overlap with the "virtual" transection line, right posterior sectorial PV branch arising from the left main PV branch.

and/or handling of "difficult" anatomy, eventually resulting in microcirculatory derangement of the bile duct.

Unquestionably, there is no situation more dangerous than the occlusion of the hepatic artery in the early postoperative period. "Loss of artery" is nearly always connected to "loss of graft" resulting in re-transplantation or death of the recipient! One of the most dangerous reasons for such a complication is the presence of a tiny right hepatic artery in the donor with or without a concomitant accessory artery. In such cases a considerable lumen disparity at the anastomotic site may lead to the intima dissection injury caused by the blood stream, resulting in an irreparable long distant occlusion extending deeply into the graft. HepaVision enables a precise analysis of the arterial properties in the donor liver by offering a combination of 3-D visualisation, depicting different anatomical anomalies, particularly the presence of multiple right hepatic arteries and the possibility of measuring the artery diameter, pointing to a probable lumen disparity in the recipient.

The superiority of CASP lies in an accurate mapping of the hilar anatomy in advance, with a special advantage of:

- enabling sufficient and safe exposure of portal vein and hepatic duct on the graft side (within the right hilar window), which requires minimal dissection "damage",
- preventing inadvertent ligation of significant branches supplying and draining the graft or remnant hemilivers,
- determining the optimal level of portal venous and bile duct division within the hilar plate.

Our strategy of stepwise hilar dissection for right graft hepatectomy entails:

- initial cholecystectomy and exploration of the calot's triangle,
- exposition of the right hepatic artery via cystic artery and its careful dissection proximally down to the bifurcation site (a. hep. propria), and distally into the right sided hilar plate (sectorial branching site),
- recognition of irregular segment IV branches (if present), arising from the right hepatic artery, which have to be carefully preserved,
- careful dissection of the right portal vein alongside its right border, upwards into the right sided hilar plate, and exposition of the portal bifurcation site,
- exposition and dissection of the right sided hilar plate by keeping away from the right portal vein and right hepatic artery,
- preliminary assessment of bile duct anatomy by deploying a probe, preferentially via the cystic duct or alternatively through mini-choledochotomy, in order to intentify the bifurcation site, and the right bile duct course within the right sided hilar plate
- definitive assessment (and confirmation of 3-D imaging reconstruction) of the vascular and biliary anatomy within the right hilar window including:
  - assessment of the length of the right bile duct (short vs. long neck BD),
  - analysis of the sectorial branching sites of the right portal vein, hepatic artery and bile duct and their overlap patterns,
  - recognition of the possible right or left caudate bile ducts, crossing over the intended (virtually simulated) transection line,
- preliminary incision of the right sided caudate lobe within the right hilar window after the right lobe was mobilised from the IVC including detachment of the small caudate veins, dissection and looping of the RHV and IHV if present,
- subsequently marking of the posterior boundary of parenchyma transection for the "hanging manoeuvre", alongside the "skeletonized" IVC between the RHV confluence and the "caudate incisional-notch" within the right sided hilar plate,
- detachment of the right sided hilar plate by underpassing it with a clamp, before parenchymal transaction in the hilus is undertaken, to avoid any troublesome bleeding, which would preclude precise recognition of the course and the length of the right hepatic duct within the right sided hilar plate,
- en block or stepwise division (preferably for bile duct trifurcation) of the right sided hilar plate including sharp division of right hepatic duct at the intended (virtually simulated) site, as follows:
  - upper border of the hilar plate,
  - only one right bile duct branch or separate anterior and posterior sectorial BD branches (BD trifurcation),
  - right sided caudate bile duct, crossing over the hilar plate,
  - lower border of the hilar plate at the site of "caudate incisional-notch",
- finally, marking the transection line at the hilar surface of the liver, alongside the gallbladder fossa.

It is always reasonable to break up the donor hepatectomy, if bile duct draining of the remnant liver were to be sacrificed to procure the graft or if division of the graft were to jeopardize the integrity of the common bile duct.

47.3.2. Preoperative Liver Volume Prediction: a New Approach

Size of the graft to be harvested is crucial to its function in both the recipient donor! The risk of graft loss increases with decreasing size [36].

To ensure a proper balance between liver regeneration and liver function the graft-volume-body weight-ratio (GVBWR) for the recipient should be nearly 1.0. Values below 0.8 GVBWR or a graft to standard liver volume ratio (%SLV) of less than 40%, both express a SFS-situation, being consistently featured by complicated and prolonged postoperative recovery, which can eventually lead to lethal SFSS [37]. The remnant liver should comprise at least 35-40% of donors SLV, or 0.75-0.8 GVBWR [38]. Although uniform GVBWR or

%SLV cut off values for the donors are still not defined, it is generally believed that a remnant liver volume of 30-35% of TLV and GVBWR of less than 0.7 is safe for donor survival.

In view of the optimal liver quality provided by live donors, the liver volume itself has been used to define a minimum functional liver mass required to obtain satisfactory outcome for the recipient and to predict the necessary volume to be retained in the remnant liver of the donor.

Thus an accurate preoperative estimation of liver volumes represents a critical part of donor evaluation for ALDLT.

2-D CT imaging has been the "current standard" for TLV and graft/remnant volume estimations [1] with the recent application of MRI protocols also showing a similar accuracy for liver-volume prediction [2-3]. However, it is well known that computer systems mostly overestimate real volumes, showing error ratios of 5-36%, which can affect the concisely calculated functional reserve for both graft and remnant livers.

The challenge of accurate volume prediction for graft and remnant livers can lie in both the donor's individual characteristics, as well as the experience of the transplant team.

The potential sources of inaccuracy in the comparison of radiologically-derived volume assessment and the intraoperatively measured actual graft weight are multifactorial including various, as yet not fully understood, intrinsic and extrinsic factors:

- volume of blood perfusing the liver during CT/MRI scanning, responsible for overestimation of the weight measured of the non perfused (exsanguinated) liver graft at the back table,
- variable "compliance" of the liver in donors, dependant on many factors i.e. age, sex, fatty content etc,
- 1:1 conversion ratio for absolute liver weight (gm) and volume (ml) based on the experimental data that healthy liver parenchyma has almost the same tissue density as water,
- established formulae for BSA-derived estimation of liver and graft/remnant weights not reliably adjusted to the characteristics of different races or local populations,
- individual patient characteristics, especially the severity of recipient's ascites, fluid retention grade, and malnutritive condition, contributing to miscalculations of GVBWR or %SLV values,
- difficulty to exactly replicate the liver partition planned preoperatively in the real in situ situation without the use of reproducible liver partition models,
- phenomenon of "mismatched" virtual transections and intraoperative surgical planes at the time of the donor hepatectomy, due to lack of anatomical landmarks, identifiable on 2-D scans.

Our experience led us to establish an original strategy for graft - and remnant liver volume prediction. The Essen-modus, used for preoperative volume estimation, enables the transformation of the virtually simulated graft hepatectomy into a real in situ situation, mimicking the "bloodless" liver. The conceptual frame of this strategy allows for the calculation of total liver, graft -and remnant- volumes, based on the smallest CT phase, and in addition considers the intrahepatic vessel volume. It is widely known, that blood circulating in the intrahepatic vasculature at the time of imaging studies is associated with overestimations of graft-volumes when compared to actual graft weights measured intra-operatively on exsanguinated grafts at the back table [13].

The accurate prediction of the transection line requires reproducible liver partition models and anatomical landmarks, which can be easily identified. Cantlie's line, the standard landmark at most transplant centres, is extremely difficult to follow, especially on 2-D images. In contrast, the "carving" transection technique along the plane of the MHV-developed by our group [28] can be easily followed, leaving its left-or right-sided border exposed on the transection surface of the graft.

Our experience of HepaVision did not encounter any significant diversity in the predicted volumes when compared with the real values derived from the intraoperatively obtained graft weights. Thus we do not routinely use any "conversion factors" to adjust our preoperative virtual volume calculations.

47.3.3. Computed Risk Analysis: A New Concept

In ALDLT, donors and recipients are faced with an inevitable small-for-size situation (SFS), which may be ag-

gravated by graft/remnant swelling, expected early after transplantation.

Severe parenchyma congestion in the early postoperative course is attributable to some secondary loss of functional liver volume, which can lead to a functional-small for size situation (f-SFS) with a potentially fatal outcome for either donor or recipient [28].

The areas most prone to congestion are the right and left medial sectors (Couinaud's segments V-VIII, and IV respectively). However, because of the individually variable donor/recipient characteristics, the lower limit of graft and remnant size, in which a small-for-size syndrome (SFSS) can occur, is not clearly recognised.

The expansion of LDLT from the pediatric to adult recipient populations has been associated with a need to obtain imaging methods, which provide both anatomical and physiological information. The advent of 3-D reconstruction techniques has provided some of this valuable information. Several groups have already shown the advantage of CASP based on CT and MRI-imaging in surgery planning for ALDLT [35, 39].

Hepatic vein dominance relationships, drainage patterns, and anatomical variability must be carefully evaluated in surgery planning. Preoperative knowledge of hepatic vein mapping is crucial when deciding whether to reconstruct venous branches, in order to prevent compromise of the functional graft capacity.

The decision making for the donor hepatectomy addresses the major question of whether the middle hepatic vein (MHV) should be taken with the graft or retained with the remnant liver.

This constitutes one of the most difficult and problematic issues in ALDLT, especially when right grafts are used. To determine the most optimal solution for the donor and recipient, it is necessary to:

- define the MHV drainage volume in the "marginal zones" of both hemilivers,
- compare the anatomical (transectional) and functional (safely drained) graft/remnant hemiliver volumes.

The "computed risk analysis" offered by HepaVision software, usefully assists in the surgical decision making in both donor and recipient by addressing the aspect of the individually adjusted MHV management according to the appropriate donor/recipient-match.

HepaVision enables the surgeon to:

- distinguish various types of venous drainage patterns, based on territorial mapping, by considering the high anatomical diversity, often encountered in the right hemiliver,
- recognize the hepatic vein dominance relationships both in the whole liver and either hemiliver,
- define the "territorial belonging"of MHV to the right or left liver parts,
- predict the functional (rest) volumes with unaffected venous drainage for both graft and remnant hemilivers, after the liver partition was simulated.

This comprehensive information, originating from "computed risk analysis" and mainly focusing on the medial sectors in graft and remnant livers, allows for the definitive resolution of the dilemma of the MHV in surgery planning.

47.3.3.1. *Hepatic Veins - Territorial Dominance Relationship: New Definitions*

ALDLT has contributed greatly to our understanding of territorial liver anatomy.

The recognition of the individually variable venous dominance-relationship and MHV belonging-patterns is one of the major challenges in planning ALDLT and plays a key role in successful venous outflow management in both donor and recipient.

Our experience shows that 3-D imaging reconstructions, especially the territorial liver mapping, are a valuable adjunct to the conventional 2-D imaging analysis, and provide useful assistance in surgical decision-making for right graft ALDLT.

Although venous anatomy by itself is of great importance, a physiological complement is also an essential component. Together, they constitute what we have defined as "venous dominance" [40]. Our initial observations distinguished a marked variety of venous patterns associated with an even greater variety of liver volumes. This becomes especially prominent at the time when patterns of venous dominance are considered.

In order to define the venous drainage pattern of the liver based on anatomical properties, and subsequently outline the venous outflow in either graft or remnant hemilivers we proposed two definitions, aimed at hepatic vein dominance relationhip and territorial belonging of MHV.

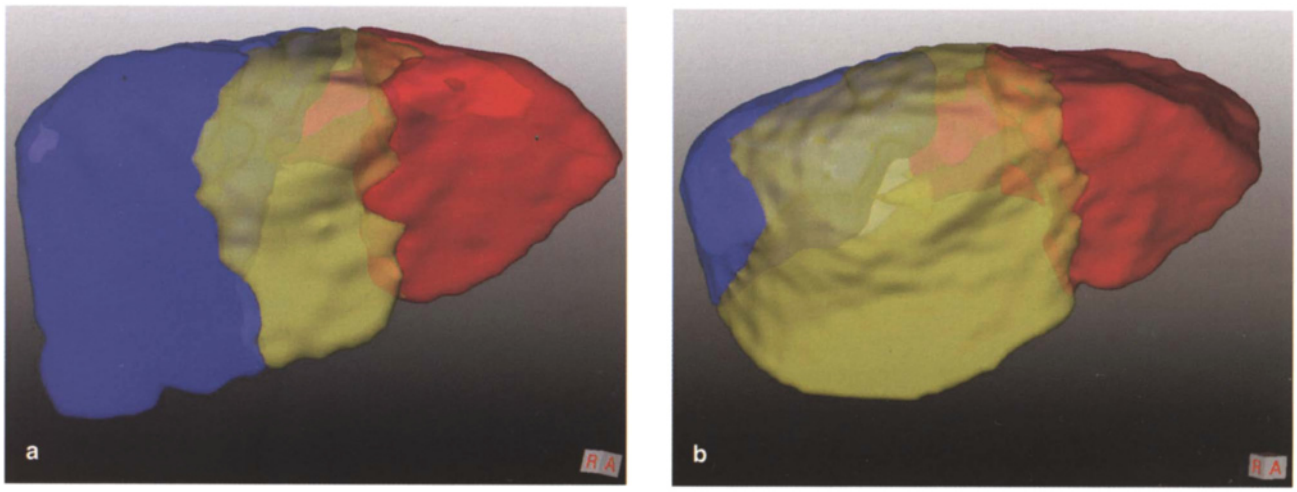


Fig. 47.18. a-b: 3-D reconstruction of total liver dominance definition (TLD), cranial view, dominant RHV (a), dominant MHV (b), RHV territory (blue), MHV territory (yellow), LHV territory (red).

Total liver dominance (TLD) (fig. 47.18 a-b)

According to this definition, the dominant hepatic vein territory (RHV, MHV, IHV, LHV) has the largest percentage of total liver volume (TLV).

Hemiliver dominance (HLD) (fig. 47.19 a-b-c-d)

Based on this definition, the dominant hepatic vein territory in the hemiliver (HL) is the one with the largest percentage of right or left hemiliver volumes.

Definition of the MHV "territorial" belonging (fig. 47.20 a-b-c-d)

This definition assigns the MHV belonging pattern in accordance to the ratio RHV/MHV in the right hemiliver, when compared to the ratio LHV/MHV in the left hemiliver. MHV belonging based on it is proportional volume contribution in the RHL and the LHL is assigned to the liver site with the smallest ratio.

Both dominance definitions (TLD vs. HLD) overlap, by providing independent mappings of the liver. Altogether, these definitions provide a helpful insight into venous dominance relationship, displaying the territorial belonging of MHV by taking into account the high individual RHV variability.

Our experience has shown, that:

- dominant RHV for the whole liver indicates that the RHV is also dominant in the right hemiliver,
- MHV belongs predominantly to the left hemiliver,
- right-sided MHV belonging is associated with high MHV volume drainage (up to 62% vol.) in the right hemiliver (fig. 47.21 a-b),
- LHV is predominantly dominant in the left hemiliver,
- MHV drainage volume in the left hemiliver is virtually equal regardless of its belonging pattern (mean range of 8% vol.).

Under these circumstances, the trend to include the MHV into the left hemiliver grafts or alternatively to reconstruct its left sided tributaries may be considered less dogmatic.

When analyzing the volume data, we generally consider the RHV and the inferior hepatic veins (IHV) (if present) as a single territory. However, when single RHV has been regarded out of complex with IHV, a "latent conversion" can be frequently encountered (50% of cases) from left-sided MHV belonging to the right-sided MHV belonging pattern.

Such findings highlight the necessity of MHV inclusion in the right graft unless the IHV is/are reconstructed in order to avoid congestive derangements.

47.3.3.2. *Hepatic Veins - Territorial Dominance Relationship: New Classification*

The purpose of developing a new nomenclature to include both anatomical and physiological attributes was to simplify the evaluation process of live donor candidates, and support the operation planning.

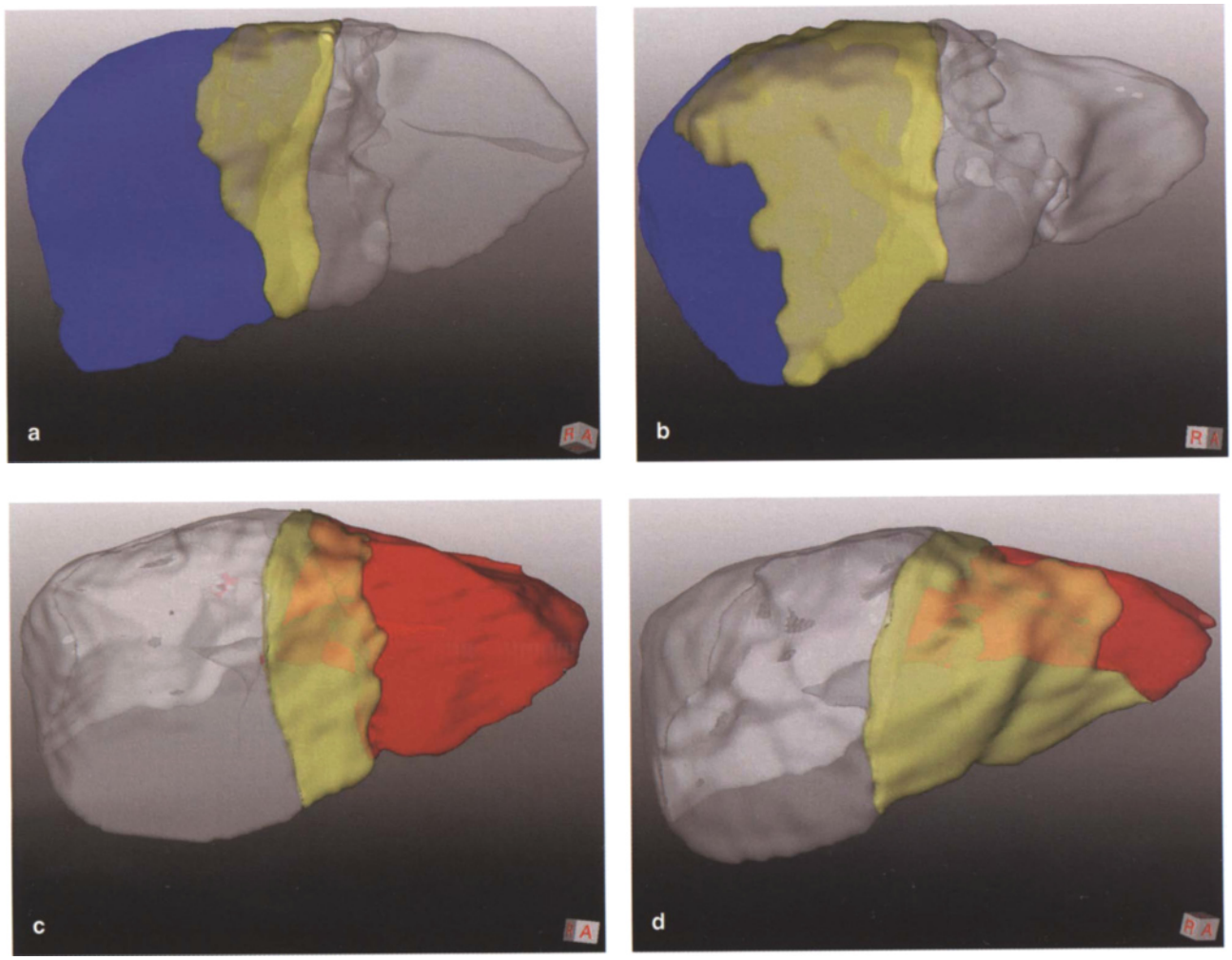


Fig. 47.19. a-b-c-d: 3-D reconstruction of hemiliver dominance definition (HLD), cranial view, right hemiliver (RHL): dominant RHV (a), dominant MHV (b), left hemiliver (LHL): dominant LHV (c), dominant MHV (d), RHV territory (blue), MHV territory (yellow), LHV territory (red).

When evaluating 3-D reconstructions, we are especially interested in the territorial hepatic venous anatomy, since vascular outflow, with its high degree of variability, is found to be equally or even more important than vascular inflow [21-22,28-29,42-43].

The assessment of the dominance relationships between the middle and right hepatic veins plays an essential role in planning right graft ALDLT. Our experience however, had proven that it is often difficult for the surgeon to provide complete information without stating, for example, whether the inferior hepatic veins (if present) are considered independently or as part of the RHV territory. The presence of significant accessory (inferior) hepatic veins is crucial to a later reconstruction policy.

Therefore, we proposed a combined anatomical and physiological classification of the various types of hepatic venous drainage patterns, in which venous dominance, following the TLD-definition is given especial consideration [41]. Although developed for live donor liver transplantation, the concepts proposed herein can also be successfully applied to non-transplant hepatic surgery

Dominance classification of the hepatic venous system in the whole liver according to TLD:

- 1 A: RHV dominant without anatomical IHV,
- 1 B: RHV anatomically with IHV,
- 1 Bx: RHV dominant together in complex with but not without IHV,
- 1 By: RHV dominant both with and without IHV.

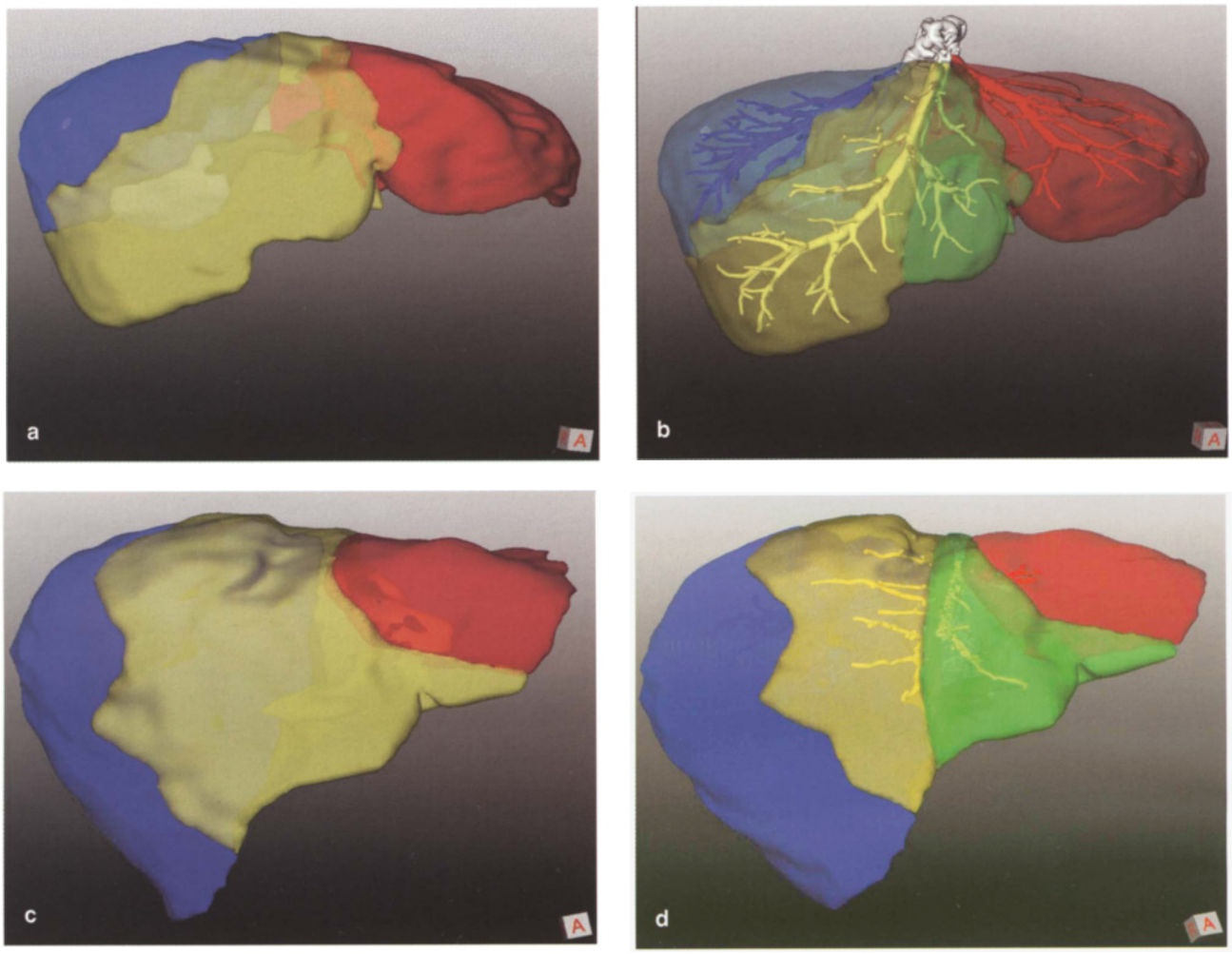


Fig. 47.20. a-b-c-d: 3-D reconstruction of territorial MHV belonging patterns, cranial view, right MHV belonger type (a+b), left MHV belonger type (c+d), RHV territory (blue), MHV territory (yellow + green), LHV territory (red).

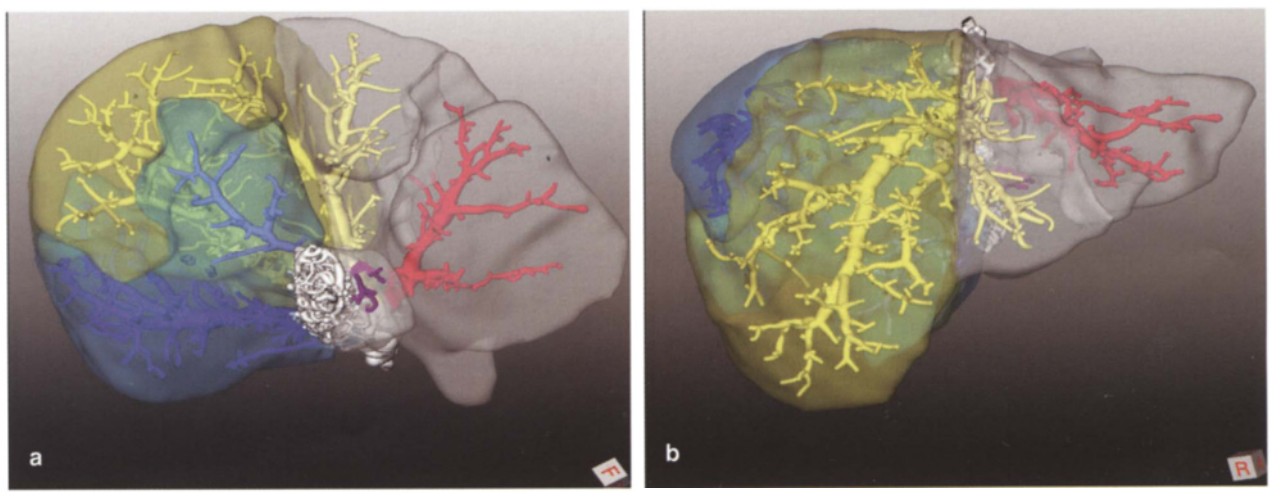


Fig. 47.21. a-b: 3-D reconstruction of a "territorial right belonger MHV type", cranial view (a), caudal view (b), huge MHV drainage territory in the right hemiliver (yellow), RHV territory (blue), left hemiliver (white).

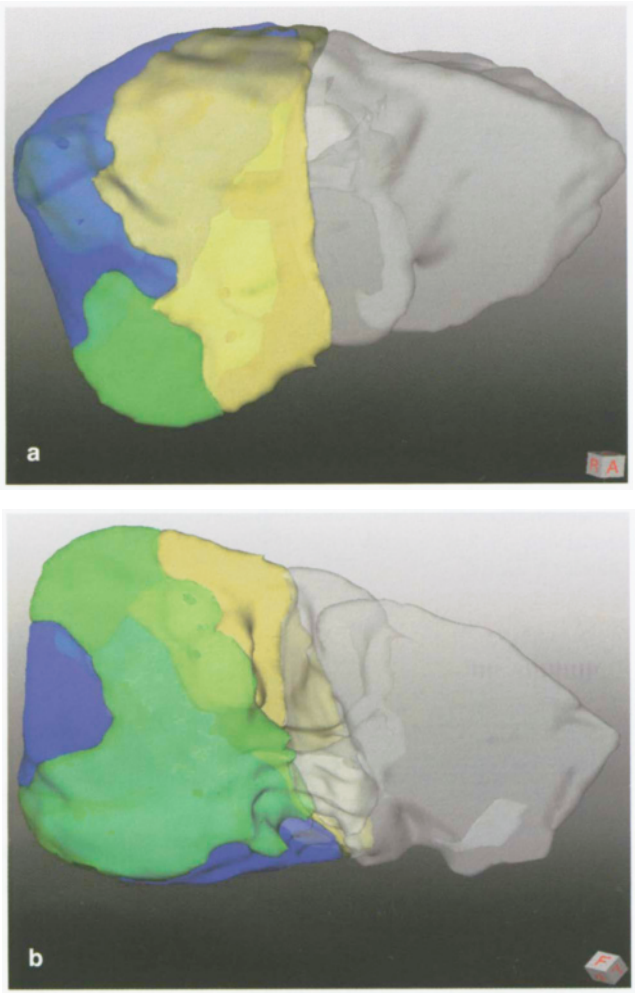


Fig. 47.22. a-b: 3-D reconstruction of a dominant RHV/IHV complex – type 1Bx, that hides a "latently" dominant MHV – type 2Bx, if the inferior vein (IHV) is taken out of volume calculation, cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), IHV territory (green), left hemiliver (white).

- 2 A: MHV dominant without anatomical IHV present,
- 2 B: MHV dominant when anatomical IHV present.
- 2 Bx: MHV dominant when RHV considered without IHV.
- 2By: MHV dominant when RHV considered either with or without IHV,
- 3 A: LHV dominant (when no anatomical IHV present),
- 3 B: LHV dominant (when anatomical IHV present),
- 3 Bx: LHV dominant when RHV considered without IHV,
- 3 By: LHV dominant when RHV considered either with or without IHV,
- 4 A: IHV dominant (when no anatomical RHV present),
- 4 B: IHV dominant (when anatomical RHV present),
- 5: other types.

We formulated our classification with the aim of allowing for the delineation of venous dominance and of RHV variability. Subsequently, we attempted to aid the better organization and categorization of the variants encountered within the hepatic venous system.

Our experience with 3-D liver mapping, show variations in hepatic vein dominance based on the presence of IHV. A dominant RHV/IHV complex with a prominent IHV-type 1Bx is capable of hiding a "latently dominant" MHV-type 2Bx (in total liver: 89% cases; in right hemiliver: 56% cases respectively) (fig. 47.22 a-b). According to this observation, in such cases the MHV belongs predominantly to the right hemiliver (78% of cases), and, given its greater dominance in the right hemiliver, should probably be included with the right hemiliver graft, when either its right sided tributaries are unsuitable for reconstruction or the IHV cannot be reconstructed.

The information gained from the volume analysis allows us to state that:

- right hemiliver graft is principally drained by the RHV (mean 55% vol) (fig. 47.18 a, 47.23). However, there are frequently accessory IHV from the right hemiliver (52% of cases), that drain directly into IVC (mean 16% vol), augmenting outflow from RHV drainage territory (fig. 47.24 a-b),

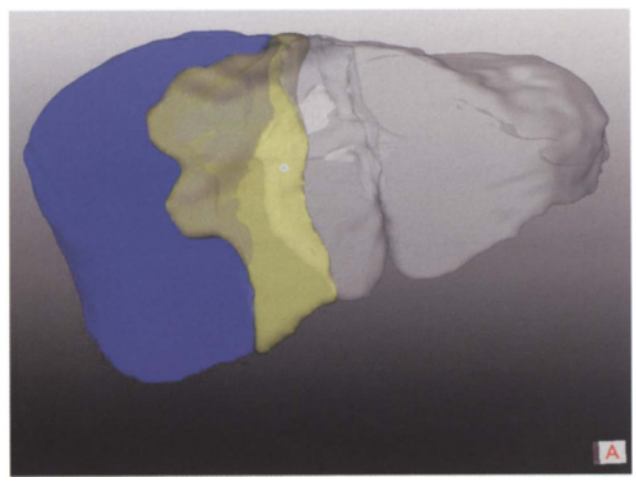


Fig. 47.23. 3-D reconstruction of RHV versus MHV drainage territories in the right hemiliver, cranial view (a), RHV territory (dark blue), MHV territory (yellow), left hemiliver (white).

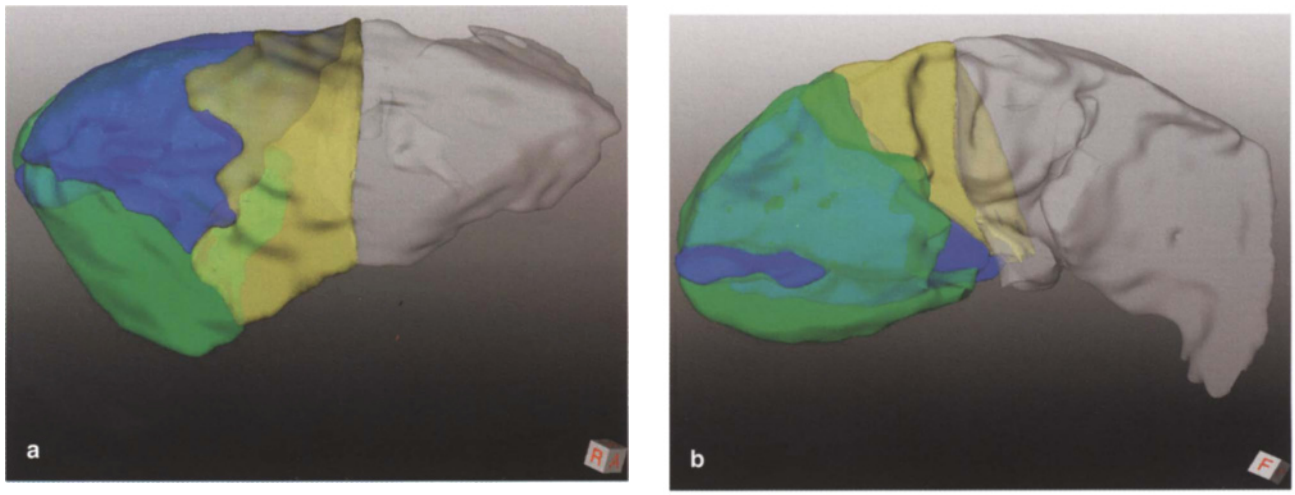


Fig. 47.24. a-b: 3-D reconstruction of a RHV/IHV complex, that contains an accessory (inferior) vein (IHV) draining directly from lateral sector of the right hemiliver into ICV, cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), IHV territory (green), left hemiliver (white).

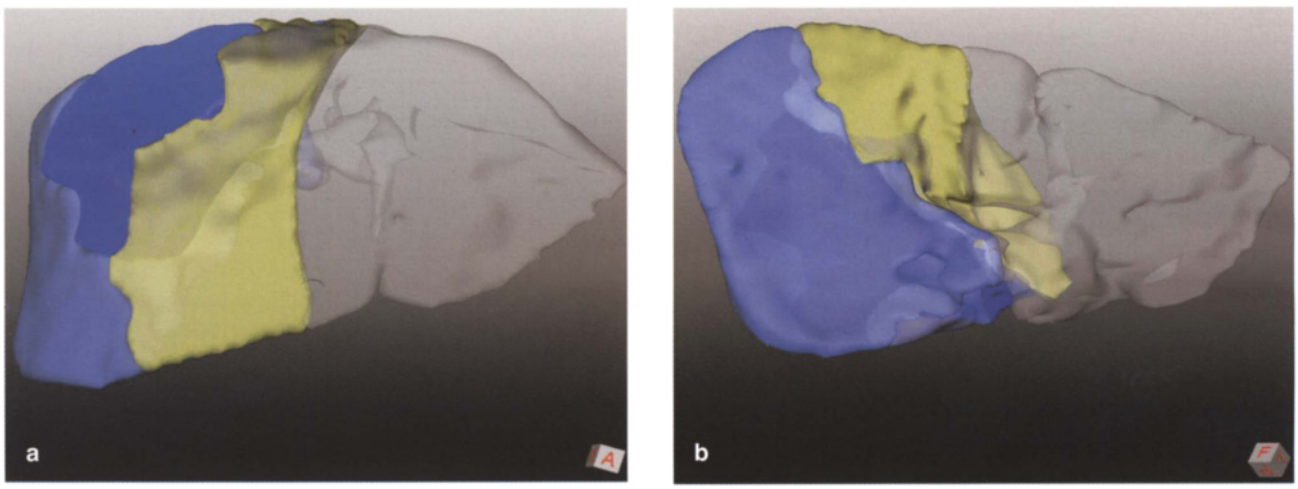


Fig. 47.25. a-b: 3-D reconstruction of a RHV/IHV complex, that contains a huge accessory (inferior) vein (IHV), draining the lateral sector of the right hemiliver, cranial view (a), caudal view (b), RHV territory (dark blue), MHV territory (yellow), IHV territory (bright blue), left hemiliver (white).

- IHV provides a mean 32% of venous drainage in the right lateral sector, and in some cases drains up to 25% of the right medial sector irrespective of the PV anatomy. Such cases require IHV reconstruction to prevent severe tissue congestion in the right hemiliver graft (fig. 47.25 a-b),
- dominant RHV without anatomical IHV – type 1A clearly dominates the right hemiliver (100% of cases; mean 71% vol.), and assigns MHV belonging to the left hemiliver in 76% of cases (fig. 47.26 a-b-c-d),
- dominant RHV/IHV complex shows a strong dominance in the right hemiliver, including a dominant HV by itself – type 1By (fig. 47.27 a-b-c-d). According to this observation, the MHV belongs to the left hemiliver (88% of cases) and its presence there is necessary to avoid venous congestion of the marginal zone (Couinaud's segments IVa/b),
- dominant MHV types 2A and 2By most often belong to the right hemiliver (67% of cases) and should be included with right hemiliver grafts to assure satisfactory venous outflow in the marginal zone of the graft (fig. 47.28 a-d, 47.29 a-d),
- drainage volume of dominant MHV types 2A and 2By in the right hemiliver grafts (mean 49% vol.), can so-

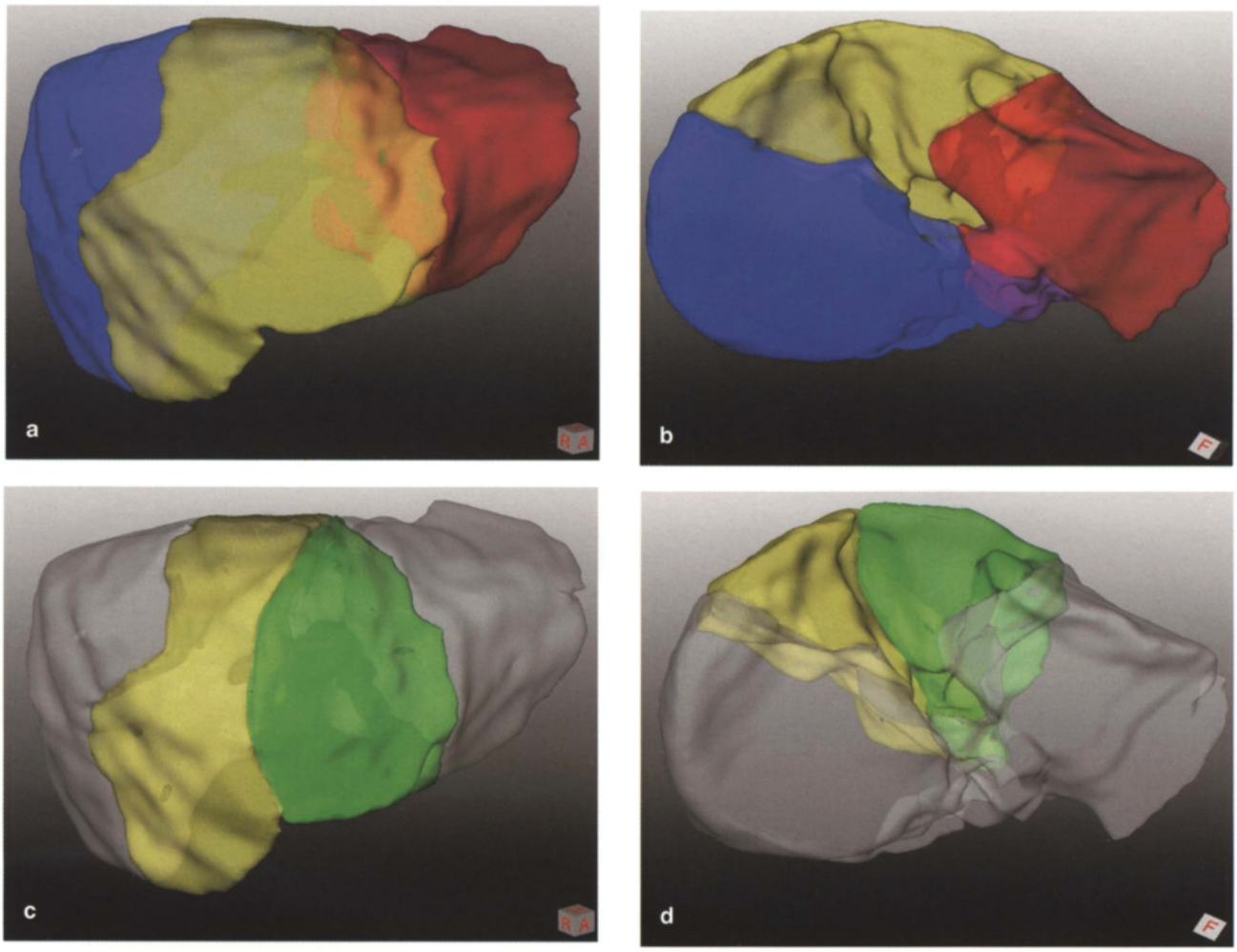


Fig. 47.26. a-b-c-d: 3-D reconstruction of a dominant RHV – type 1A, cranial view (a), caudal view (b), accompanied by a left MHV belonger type, cranial view (c), caudal view (d), RHV territory (blue), MHV territory (yellow), LHV territory (red), caudate (purple), MHV drainage volume in the right hemiliver (yellow), MHV drainage volume in the left hemiliver (green).

metimes significantly affect the venous outflow of the left hemiliver remnants (mean 41% vol.) (fig. 47.30 a-d, 47.31 a-d).

The overall incidence of hepatic vein types in our donor candidates, according to the proposed classification nomenclature, is given in the table 47.1.

We believe that the classification we propose may provide a universally applicable standard, and can ultimately serve as a guide in the decision of whether or not to include the MHV with right hemiliver grafts.

47.3.3.3. *Middle Hepatic Vein - Territory: "Fish Bone Map"*

The territories drained by the MHV are vulnerable to

Table 47.1

	Donor	
HV dominance type	HV characteristics	n = 94
1A	RHV without IHV	37
1Bx	RHV with IHV	18*
1By	RHV with or without IHV	24
2A	no anatomical IHV	8
2Bx (1Bx)	IHV excluded from calculation	16*
2By	RHV with or without IHV	7
3Bx (1Bx)	IHV excluded from calculation	2*

* Types 1Bx/2Bx/3Bx represent the same donor cohort (n = 18) including: 1Bx: RHV is only dominant together in complex with IHV; 2Bx: MHV is dominant when IHV was excluded from calculation; 3Bx: LHV is dominant when IHV was excluded from calculation.

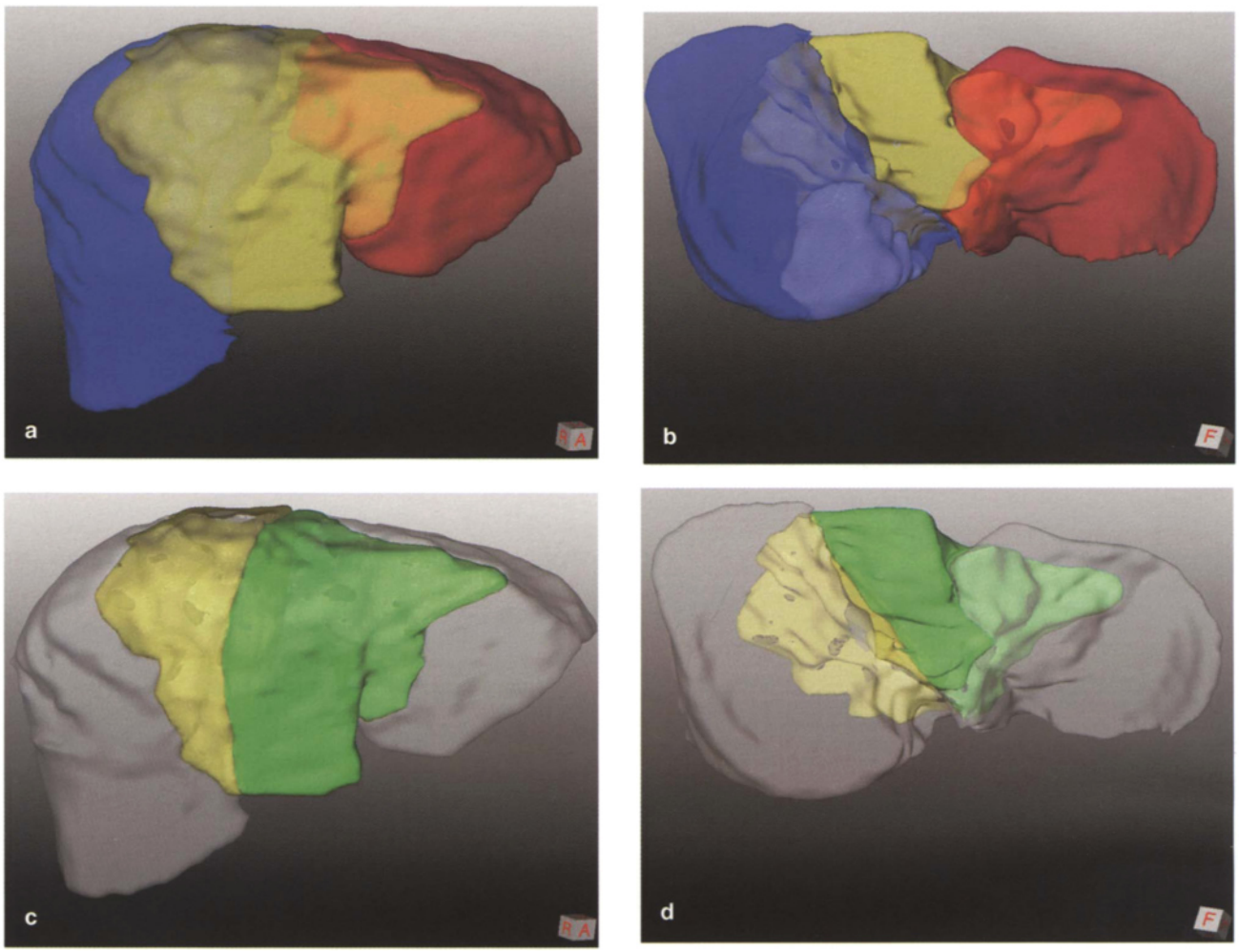


Fig. 47.27. a-b-c-d: 3-D reconstruction of a RHV/IHV complex – type 1By, including a dominant RHV by itself, cranial view (a), caudal view (b), RHV territory (dark blue), MHV territory (yellow), IHV territory (bright blue), LHV territory (red). MHV mostly belongs to the left hemiliver (territorial left MHV belonger type) (c+d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

venous outflow congestion depending on the type of liver partition employed. They constitute the most sensitive areas in the graft and remnant livers, particularly in cases of severe portal hypertension and/or small-for-size situations [28-29].

Pivotal to our concept of "venous outflow protection" is the finding of segmental congestion in the graft and remnant livers. In fact, many cases of graft loss can be attributed to unrecognized venous outflow dysfunction [28, 42]. In these cases, segmental or subsegmental venous territories developed venous congestion and became functionally affected.

HepaVision provides the surgeon with territorial liver mapping. On the basis of this comprehensive imaging information the surgeon can display the sub-territories on each side of the middle hepatic vein belonging to its tributaries ("fishbone"map), and recognize the areas of venous congestion in both graft and remnant livers, after the liver partition was simulated (fig. 47.32 a-b-c-d). The surgeon can subsequently decide on the inclusion of the MHV with graft or its retention in the remnant liver.

By virtue of having the possibility of displaying every singular sub-territory of the MHV and subsequently overlapping it with the respective portal segment or sector, the surgeon can simulate a map of potential ve-

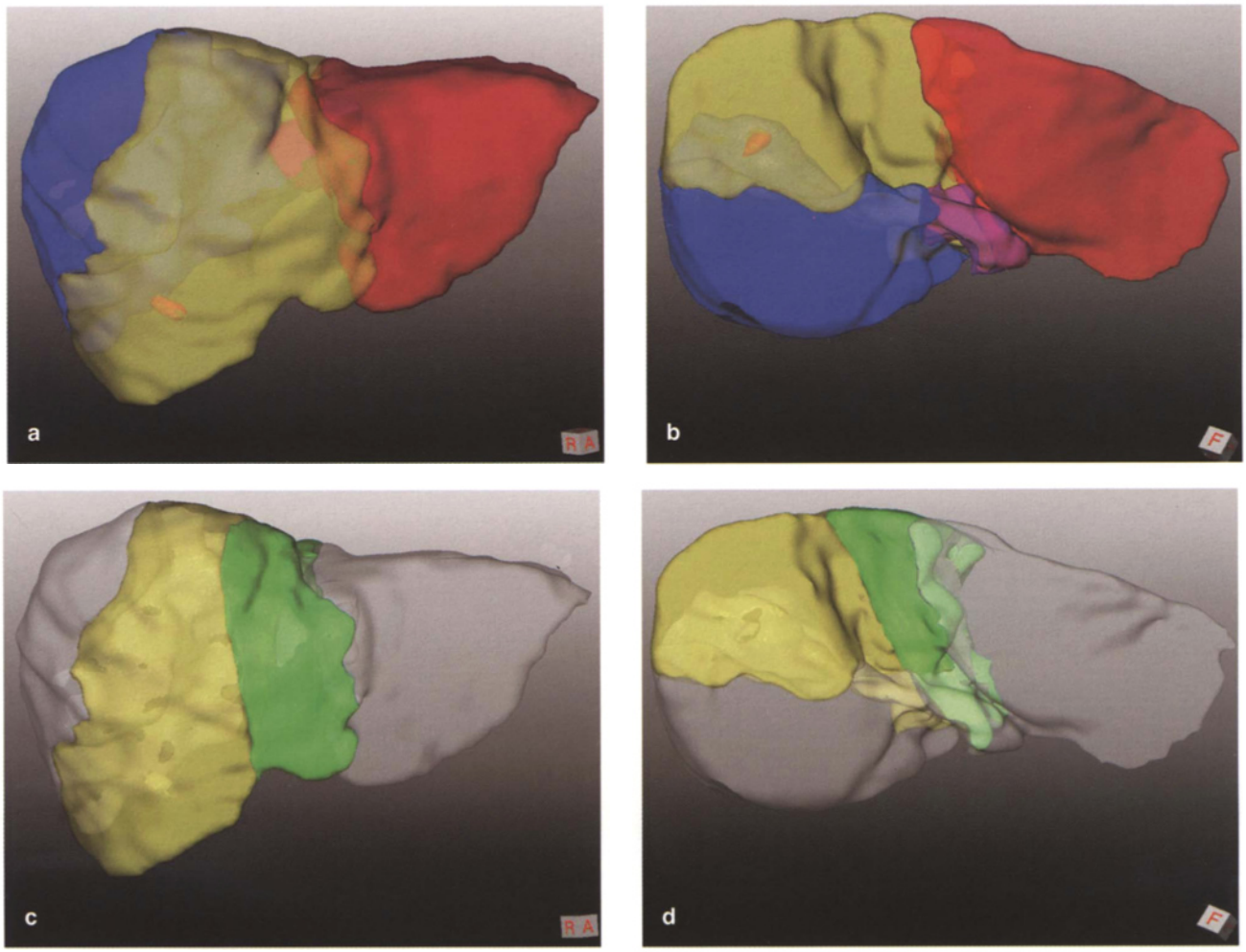


Fig. 47.28. a-b-c-d: 3-D reconstruction of a dominant MHV – type 2A (without anatomcal IHV present), cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), LHV territory (red), caudate (purple). MHV most often belongs to the right hemiliver (right MHV belonger type) (c+d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

nous outflow impairment and plan the appropriate reconstruction of MHV tributaries in the graft in cases where the MHV was left on the remnant side.

47.3.3.4. *Marginal Zones (Segments IV, V, VIII): Problem of Venous Drainage Impairment*

Given the limited functional volumes of graft and remnant livers, vascular mapping and preservation of vascular structures have acquired paramount importance in ALDLT.

Of special interest to the surgeon planning live donor hepatectomy is the middle hepatic vein. The MHV is shared by both medial areas of liver, and, from experience published in the literature, it is known that segments IV, V and VIII are especially prone to venous outflow impairment [15, 18-19, 26, 28-29, 42-43]. Thus, of special consideration in surgery planning is the adequate venous drainage in the "marginal zones" of both hemilivers.

The issue of how to cope with the middle hepatic vein remains controversial, particularly in right graft living donor liver transplantation [1, 24, 26, 28, 36, 42].

The virtual delineation of the marginal zones of both graft and remnant livers (Couinaud segments IV, V, VIII) enables the surgeon to evaluate and determine poten-

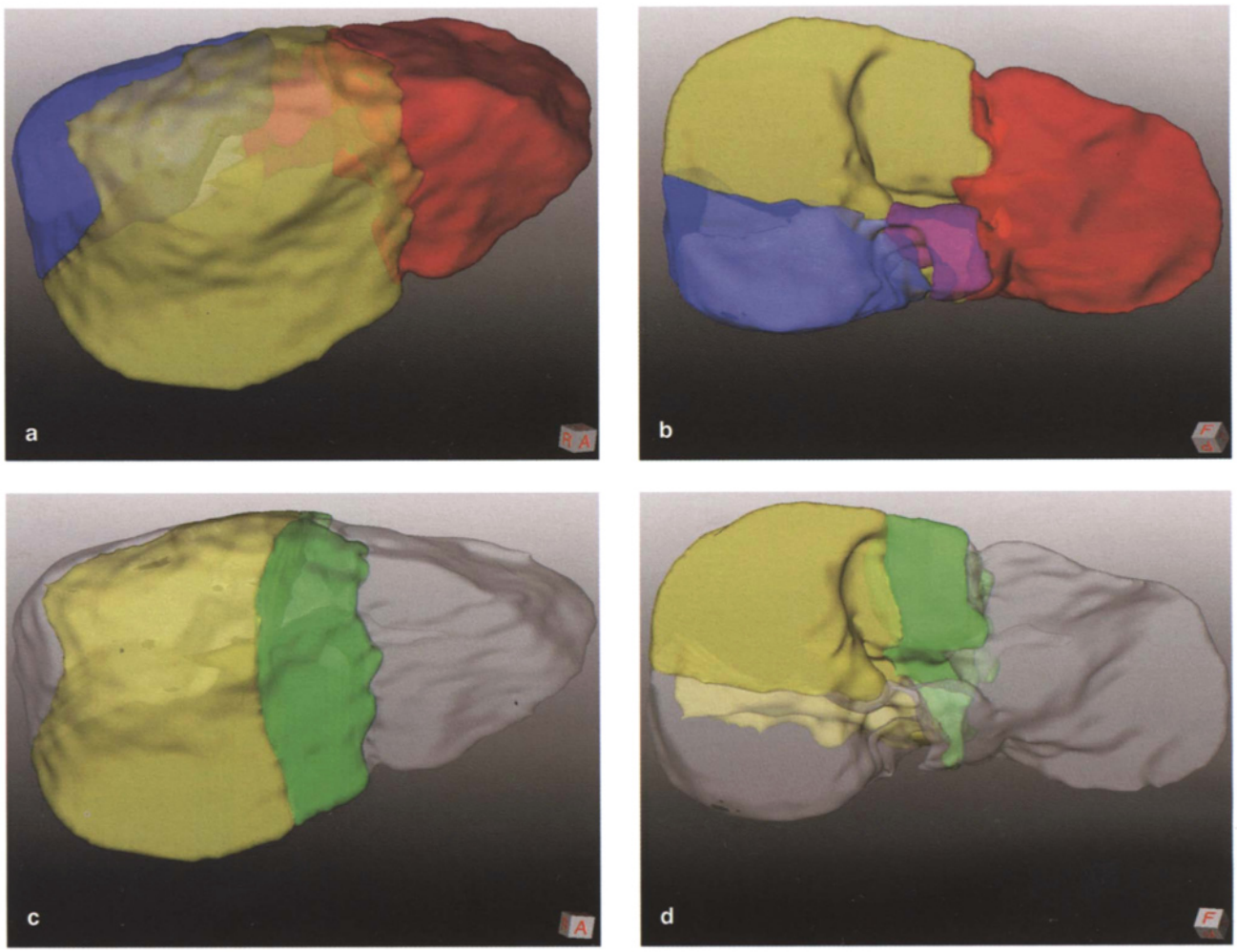


Fig. 47.29. a-b-c-d: 3-D reconstruction of a dominant MHV – type 2By (RHV considered either with or without anatomcal IHV), cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), LHV territory (red), caudate (purple). MHV most often belongs to the right hemiliver (right MHV belonger type) (c+d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

tial drainage impairments. The "virtual venous congestion" that we attempted to define in a virtual fashion, follows the clinical phenomena described separately by Lee et al [29] and Malagó et al [28]. Thus, in order to predict losses of functional liver volume, it is crucial to determine whether the MHV should be included with the graft or retained with the remnant. This is based on the assumption that, in a real situation, an inadequate venous drainage in the marginal zones of graft and/or remnant livers, would be associated with an additional loss of their functional capacity.

HepaVision allows for the accurate conceptualization of the MHV management, individually adjusted to the actual donor/recipient characteristics, by means of 3-D visualisation and territorial volume calculation of the MHV drainage hemi-territories in the marginal zones of the graft and remnant hemilivers (fig. 47.33 a-b).

The performance of the "Malago-manoeuvre" in vivo, in visualising the MHV/RHV territories in the right graft hemiliver (always before liver transection is carried out), greatly assists in deciding whether the MHV should be included, and whether IHV reconstruction should be performed. This permits the extrapolation of preoperative "virtual surgery" in the real in situ situation. Thus, Malago-manoeuvre allows for clinical validation of the "territorial venous mapping" derived from

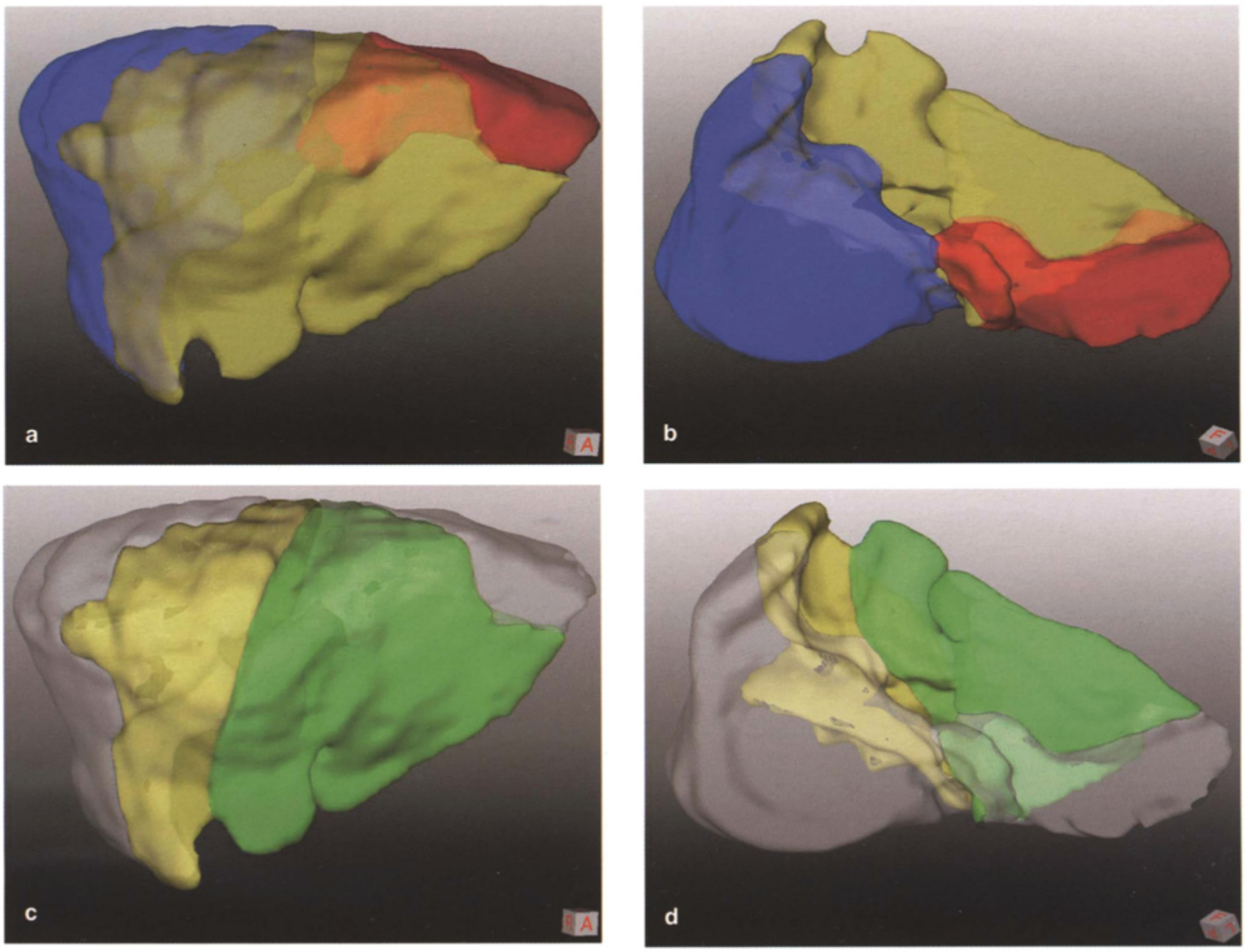


Fig. 47.30. a-b-c-d: 3-D reconstruction of dominant MHV – type 2A, cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), LHV territory (red). In such cases MHV sometimes belongs to the left hemiliver (left MHV belonger type), and can drain a large volume of the left hemiliver, cranial view (c), caudal view (d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

the "computed risk analysis". On the other hand, this manoeuvre represents a simple method, that can be succesfully adopted in right graft hepatectomy without use of advanced and expensive computer technology.

The background-hypothesis for "Malago-manoeuvre" is the assumption of "double" anatomical connections between the RHV and MHV branches, as first described by the Tokyo group [44]:
- via shunt veins (horizontal rescue veins),
- via PV branches (vertical rescue veins).

The stepwise performance of the "Malago manoeuvre" in vivo entails.

Step 1: right PV/HA clamped (always initially "total" right sided Pringle manoeuvre performed),
RHV clamped, MHV open,
No decolorisation in the right hemiliver because of the total right sided inflow occlusion.

Step 2: either right PV or HA clamped ("partial" right sided Pringle manoeuvre), RHV still clamped, MHV open.

Step 2A: right PV clamped, HA open.
"Slight" decolorisation of the RHV territory, since the "incomplete" (HA) –inflow is too

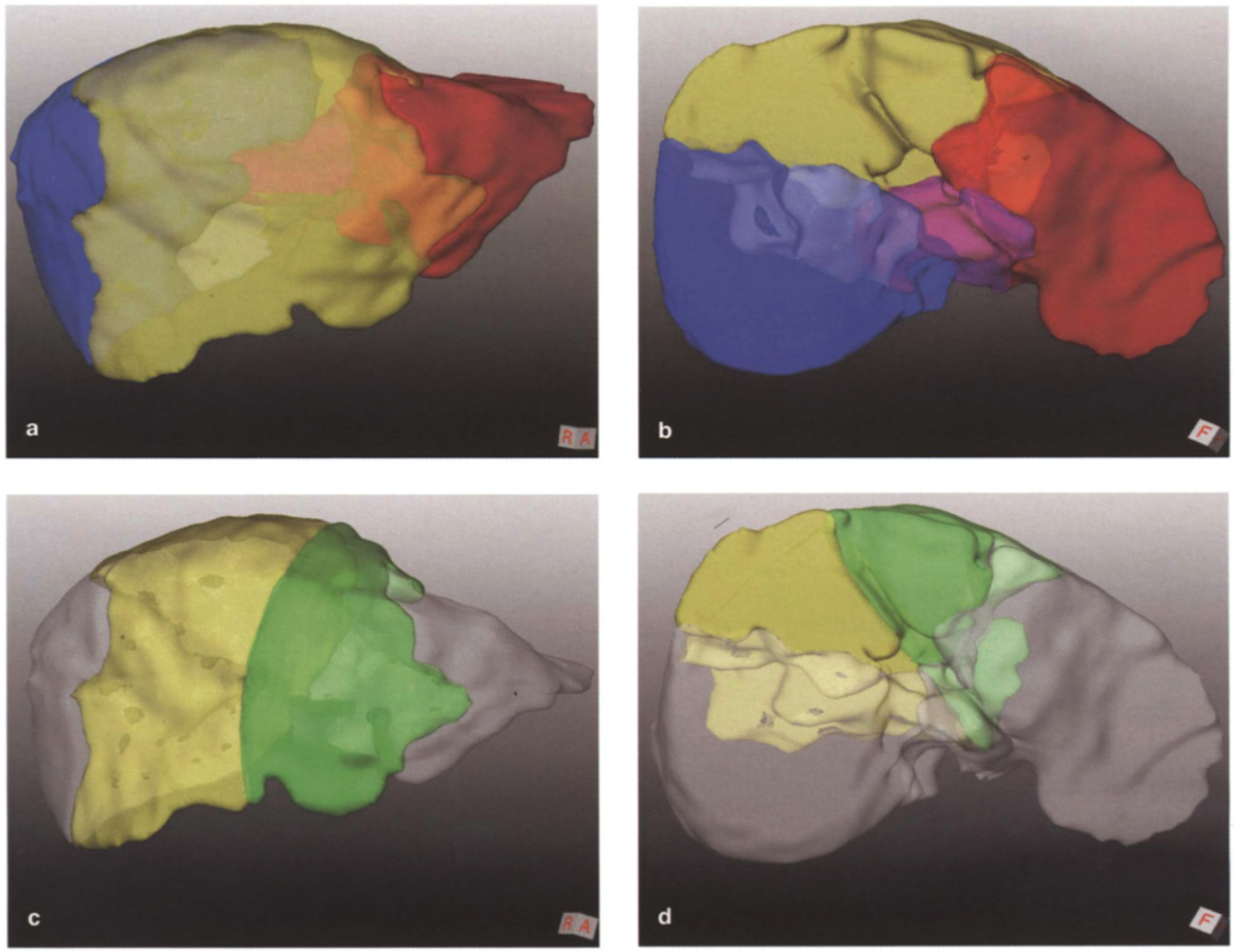


Fig. 47.31. a-b-c-d: 3-D reconstruction of dominant MHV – type 2By, cranial view (a), caudal view (b), RHV territory (blue), MHV territory (yellow), LHV territory (red). In such cases MHV sometimes belongs to the left hemiliver (left MHV belonger type), and can drain a large volume of the left hemiliver, cranial view (c), caudal view (d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

low to produce a significant outflow congestion in the RHV drainage territory that has been sufficiently drained into the MHV via both Makuuchi– shunts and PV branches.

Step 2B: right PV open, HA clamped.
"Moderate" decolorisation of the RHV territory, due to the compensatory right sided PV-over-perfusion causing a breakdown of the vertical rescue veins into the MHV, and revealing some stronger decolorisation as when the right PV was clamped (step 2A).

Step 3: right PV/HA open (right sided Pringle manoeuvre released), RHV still clamped, MHV open. "Strong" decolorisation in the RHV territory due to considerable congestion caused by the combined right sided PV/HA inflow, that consequently leads to reconvertion of both the horizontal rescue veins (Makuuchi shunts) back into the RHV drainage system, additionally causing the vertical rescue veins (PV-branches) to fail.

The conceptional difference between the "Malago-manoeuvre", which in vivo exactly replicates the virtually simulated boundary between the RHV and MHV drainage territories, and the originally proposed "Makuuchi manoeuvre" [44], is delineated in the table 47.2.

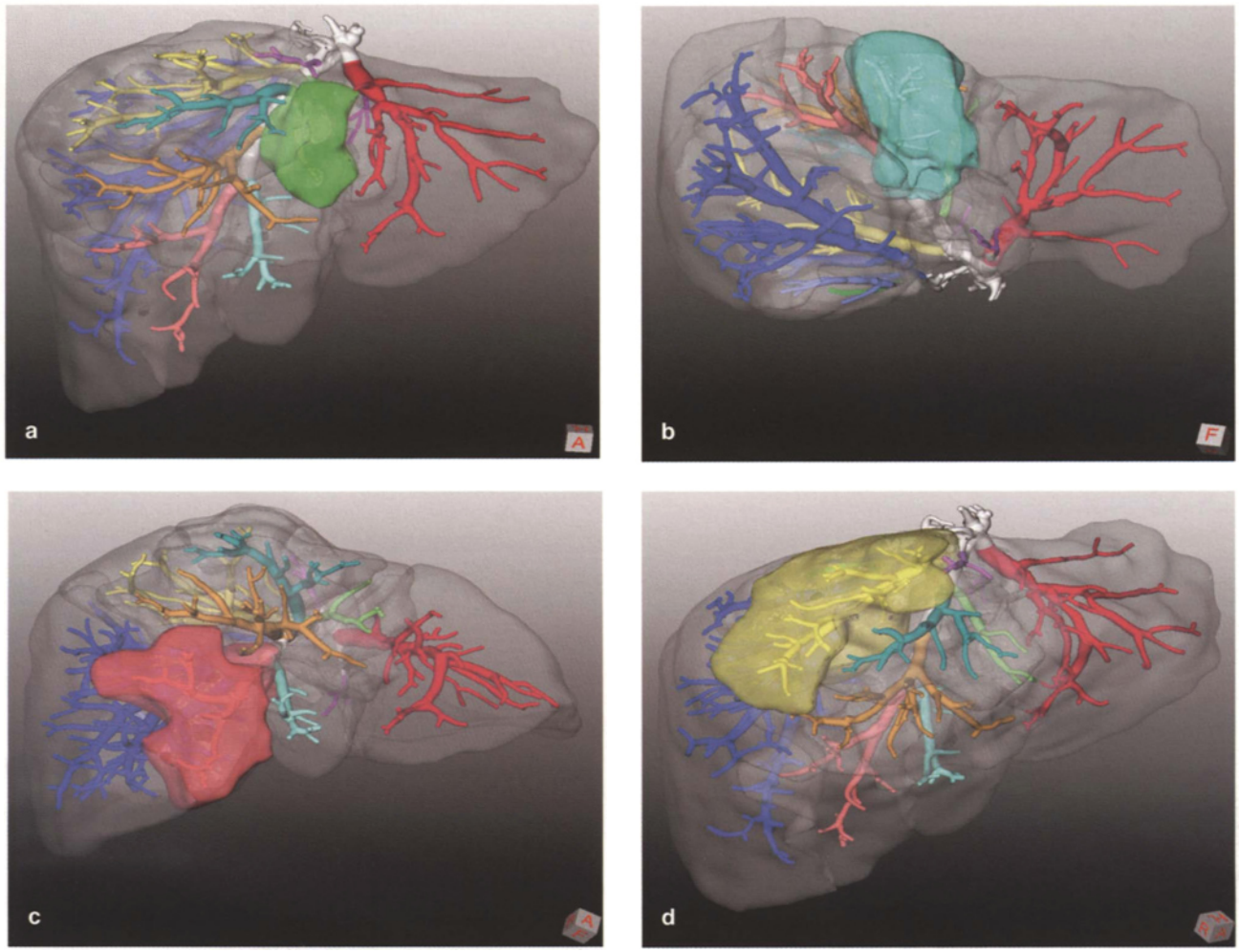


Fig. 47.32. a-b-c-d: 3-D reconstruction of the MHV tributaries and their territorial map ("fishbone map") – MHV 4a sub-territory (a), MHV 4b sub-territory (b), MHV 5 subterritory (c), MHV 8 sub-territory (d).

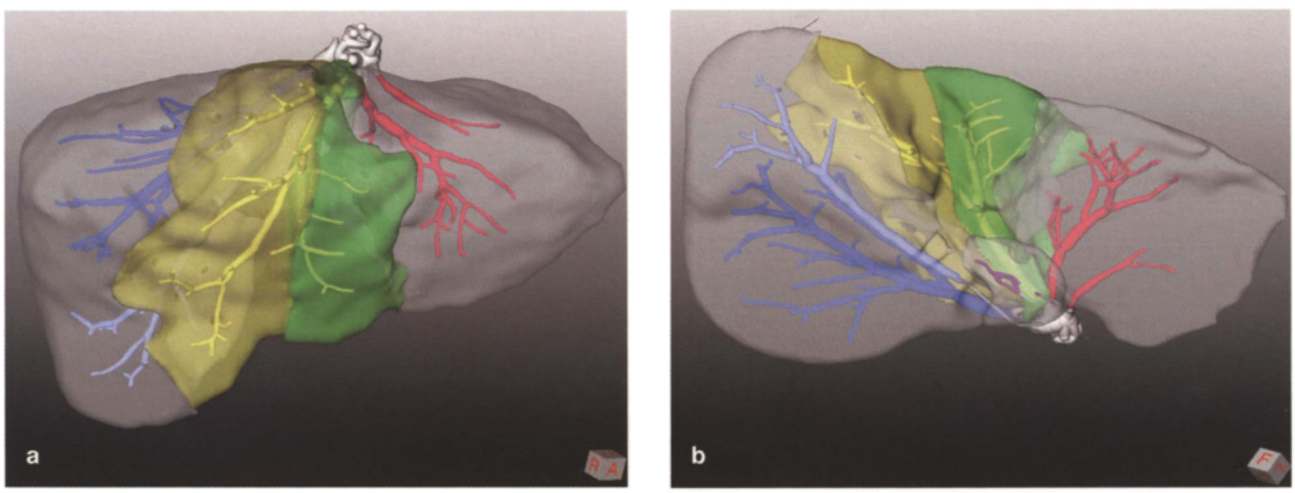


Fig. 47.33. a-b: 3-D reconstruction of the MHV drainage hemi-territories in the marginal zones of the graft and remnant hemilivers, cranial view (a), caudal view (b), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green), RHV/IHV (blue), MHV (yellow), LHV (red).

Table 47.2.

"Malago manoeuvre"	"Makuuchi manoeuvre"
conducted before parenchyma transection	conducted after parenchyma transection
visualised: RHV territory (dusky)	visualised: MHV territory (dusky)
accessible for clamping: RHV	accessible for clamping: MHV
decisive of MHV-inclusion/ retention	decisive of V5/V8-reconstruction

After conducting liver transection, a mirrored "inverted-Malago manoeuvre" is usually performed, allowing confirming visualisation of the MHV territory in the marginal zone of the right hemiliver graft. This can be achieved by clamping the MHV confluence instead of RHV (as previously described) (fig. 47.33 a-b).

The analysis of our volume data, derived from the computed risk analysis based on liver partition simulations has outlined the MHV drainage in the "marginal zone" of either hemilivers, considered as separate "hemi-territories", that are drained by the right- and left-sided MHV- tributaries (fig. 47.34 a-b-c-d). The data show no significant differences between the right-sided vs. left-sided MHV hemi-territory, ranging from 59-61% vol. vs. 39-41% vol. of the total-MHV territory.

47.3.3.5. *Anatomical vs Functional Graft/Remnant Volumes*

When the natural MHV drainage territory is divided at

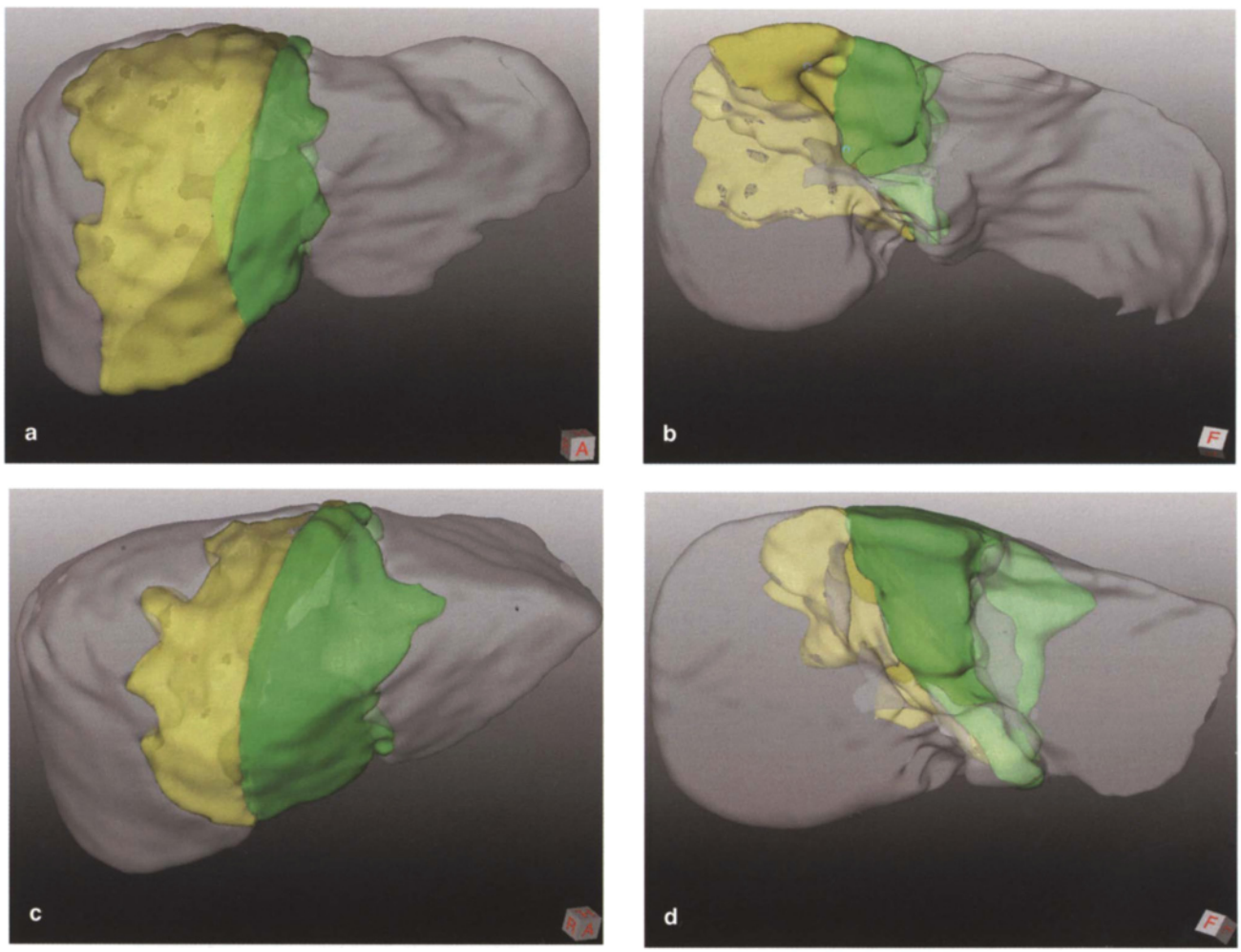


Fig. 47.34. a-b-c-d: 3-D reconstruction of the MHV drainage hemi-territories in the marginal zones of the graft and remnant hemilivers, "dominant" right sided MHV hemi-territory (a+b), "dominant" left sided MHV hemiterritory (c+d), MHV drainage in the right hemiliver (yellow), MHV drainage in the left hemiliver (green).

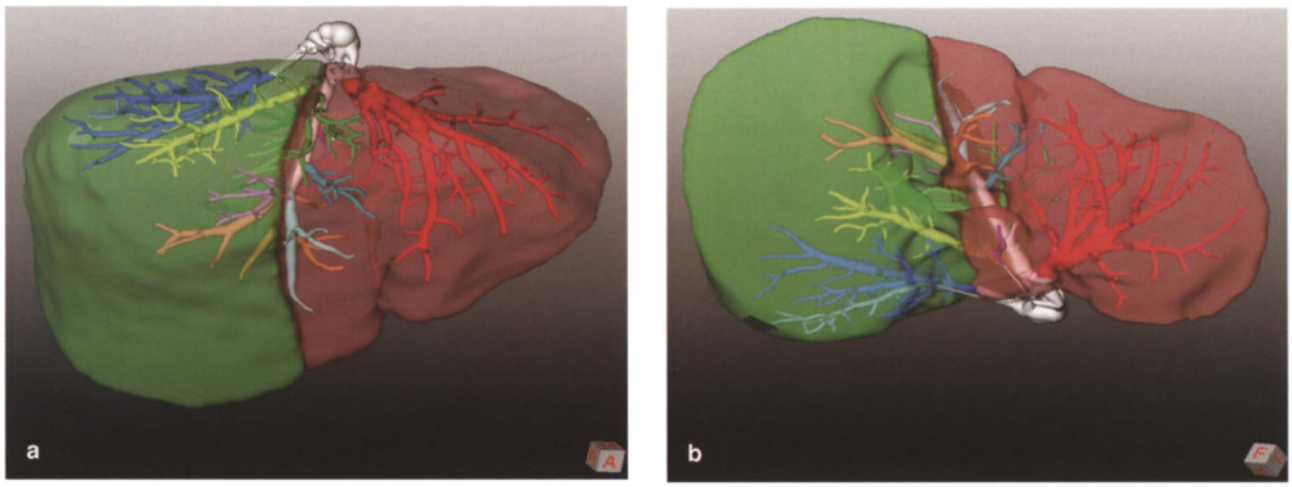


Fig. 47.35. a-b: Malago partition, 3-D reconstruction of the anatomical (resectional) graft/remnant hemiliver volumes, cranial view (a), caudal view (b), right graft hemiliver (green), left remnant hemiliver (brown), RHV (blue), LHV (red).

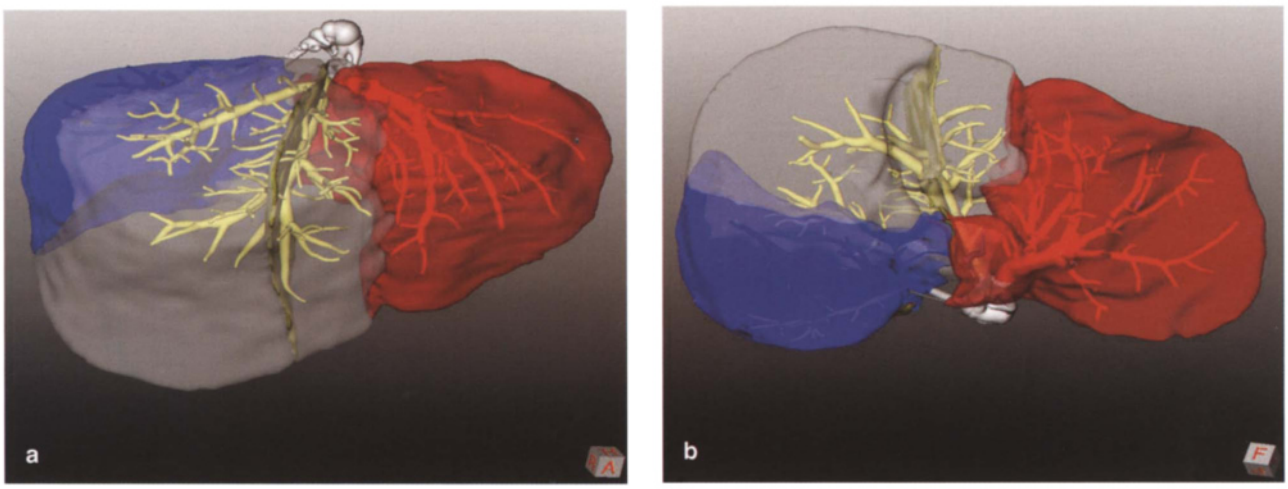


Fig. 47.36. a-b: 3-D reconstruction of the functional (rest) graft/ remnant volumes, defined as the retained, intactly drained, liver parenchyma, cranial view (a), caudal view (b), right (rest) graft hemiliver (blue), left (rest) remnant hemiliver (red), RHV (blue), MHV (yellow), LHV (red).

the time of liver partition, "marginal zones" of drainage are affected and the liver function capacity compromised.

Usually, only anatomical (resectional) volumes are routinely assessed for surgery planning (fig. 47.35 a-b). However much more important for the graft and remnant livers is the prediction of the functional (rest) liver volume, defined as the retained, intactly drained, unaffected by venous congestion or insufficient blood supply (fig. 47.36 a-b). Should volumes fall below a critical value, there is a high risk of a potentially lethal organ failure.

Venous congestion of part of the graft was found to be associated with physiological impairment of that area, potentially resulting in functional small-for-size syndrome (f-SFS), loss of graft and death of the recipient [28, 45]. Furthermore, a similar process could occur in the donor, leading to even more distressing consequences.

Thus, a precise knowledge of the "functional" volumes drained by the MHV and RHV is essential when planning the proper outflow reconstruction in right liver grafts.

In order to compare anatomical and functional vo-

lumes for both graft and remnant livers, we calculate the functional (rest) hemiliver volume by subtracting the right- and left-sided MHV drainage volumes ("marginal zones") from the anatomical right and left hemiliver volumes (fig. 47.33 a-b).

In order to translate these virtual data into the clinical situation we calculate initially anatomical-graft volume body weight ratio (a-GVBWR) based on the anatomical-(resectional)-hemiliver volumes and subsequently compare them with their functional values (f-GVBWR), derived from the functional-(rest)-hemiliver volumes.

Our "computed risk analysis" has shown that by following "virtual liver partition", a mean MHV volume drainage in the right- and left-hemilivers of 30-31% and 38-39% respectively can be expected. This involves some potential additional loss of drainage volume, contributed by the right- and left sided MHV tributaries and the subsequent decrease of the right- and left-hemiliver volumes. As a consequence, a further significant decrease in functional-GVBW- versus anatomical-GVBW-ratios can be expected for both right graft and left remnant hemilivers (table 47.3).

47.3.4. Donor Hepatectomy: Essen Concept

The "individual-graft-choice" policy, closely adjusted to the actual donor/recipient characteristics, and particularly aimed at the optimal donor/recipient match, is given overall preference at our institution.

A detailed analysis of graft failures due to small-for-size syndrome (SSFS) in our first recipients prompted us to implement newer computed technology in surgery planning.

The conceptual frame of our own policy for donor evaluation and surgery planning in the preparation of ALDLT is based on virtual 3-D CT image-derived computer assistance (CASP).

Table 47.3.

"computed risk analysis"	MHV drainage volume in the "marginal zones" right (V, SVIII) vs. left (IVA/B)	
donors n=94	right - hemiliver	left - hemiliver
% anatomical hemiliver-volume	mean 30-31% vol.	mean 38-39% vol.
SD	10	12

The "core" of HepaVision software-assistance is the "virtual risk analysis", mainly addressing the aspects of the appropriate liver transection and the individually adjusted MHV management at the donor hepatectomy.

Our experience, which included a "learning curve", led us to establish an original strategy together with a new surgical technique ("carving technique") for graft hepatectomy in conjunction with a new concept of venous outflow management in the graft ("blanket technique") [10, 19, 28].

Considering donor safety is a major priority and, given the fact of high graft vulnerability for SFS injury, the following aspects are central to surgery planning for right graft hepatectomy in the live donor:

- sufficient anatomical and functional volumes of graft and remnant livers are required,
- donor candidates revealing disadvantageous vascular/biliary anatomy should be depicted and, if in any doubt, best excluded from donation of right liver graft,
- MHV drainage territory in the "marginal zones" of both hemilivers must be estimated and offset against territories drained via RHV and LHV respectively. This allows for assessment of volume at risk for congestion in both the graft and remnant livers and their functional (rest) volumes,
- consequently the hepatic vein dominance relationship and the "territorial" MHV belonging pattern in the donor liver must be identified before deciding whether to include the MHV with the graft or retain it with the remnant liver. This "virtual" data must be subsequently related to the donor/recipients-GVBWR, and matched with the severity of recipient morbid condition, especially the degree of his portal hypertension,
- MHV tributaries on the graft side must be analysed for their potential amenability to reconstruction if the MHV is to be retained with the remnant liver,
- finally MHV 4A/8 tributaries and their drainage volumes must be analysed for the sake of their proper procurement and the most optimal reconstruction in the graft.

Our stepwise "virtual" pre- and intra-operative work up for right graft hepatectomy in the live donor entails:

3-D visualisation:

- intrahilar vascular and biliary anatomy,

- topographic anatomy ("fish bone") of MHV tributaries: MHV 8 vs. MHV 4A and MHV 5 vs. MHV 4B,
- topographic anatomy of umbilical vein tributaries: LHV 4A vs. MHV 4A and LHV 4B vs *MHV 4B:*
- anatomical MHV position in relation to the "virtual" Pringle demarcation line,
- anatomy of accessory (inferior) hepatic veins ("segmental belonging", size).

Volume calculation:
- total liver volume (TLV),
- "anatomical" (resectional) right- vs left-hemiliver volumes,
- intrahepatic vessel volume,
- PV (Couinaud) segments,
- HV drainage territories,
- MHV hemi-territories (right sided-MHV vs left sided-MHV in "marginal zones"),
- MHV sub-territories belonging to the separate MHV tributaries ("fish bone map").

Computed risk analysis:
- HV dominance relationships (TLD vs. HLD),
- "territorial" MHV belonging patterns,
- "functional" (safely drained) right- vs. left-hemiliver volumes.

Simulation in 3-D liver model:
- "virtual" Pringle demarcation line,
- HV territorial mapping,
- MHV – "fish bone map",
- MHV drainage territories in both "marginal zones" ("virtual Malago manoeuvre"),
- liver partition – "virtual" carving line.

47.3.4.1. *Right Hemiliver Graft Including MHV: Advantageous and Therefore Preferential*

The decision making for ALDLT addresses the main question of the type of graft to be chosen, while the MHV procurement remains a major point of controversy in ALDLT!

The right liver graft retrieval in the live donor is conceptually performed in two different ways: with the inclusion of MHV or without. If the MHV is retained with the left remnant liver, either MHV tributary V5/V8 draining the "marginal zone" (medial area) of the graft may or may not be reconstructed. The debate on the need to include the MHV in the right liver graft has been ongoing since the inception of ALDLT and to whether the middle hepatic vein should be procured with the graft or retained in the remnant liver remains controversial [1,18,20 24,26,28,38,42].

Advocates for the MHV inclusion with the right liver graft emphasize the particular graft vulnerability and argue that:

- MHV is indispensable for the sufficient drainage in the medial area of the graft (segments: V, VIII) and thus deprivation of the MHV would lead to graft congestion – giving rise to portal hyper-perfusion, due to persistent portal hypertention, an increase in porto-arterial imbalance, resulting in "reversed" drainage of hepatic artery via the portal vein in the medial sector (vertical rescue shunts), and excessive blood flow into the lateral sector, causing serious graft damage in both sectors and finally resulting in SFS syndrome (SFSS).

Advocates for retaining the MHV with the left liver remnant argue for increased donor safety and state that:
- collaterals are present via Makuuchi-shunts (horizontal rescue veins) between MHV and RHV branches reducing the danger of serious graft congestion.

However, it is unclear if and when donor and recipient develop sufficient collateral venous drainage via shunts ("rescue circulation") between RHV, MHV, and LHV, since the small collaterals (if present) usually open with delay, having individually variable patterns [46].

Although the drainage reconstruction in the "marginal zone", drained by the middle hepatic vein when a right liver graft is harvested, has been addressed by many groups, there is, as yet, no universally accepted policy [1, 24, 42].

Studies with postoperative CT or MRI controls show that the degree of venous congestion, measured in the medial sector of the graft, when the MHV is absent is not negligible and cases of ruptured right liver grafts have been reported [28,43].

According to our data, the MHV is unequivocally beneficial for the right liver graft, and the left remnant liver is most often not handicapped by its absence [8, 10, 28, 40]. Thus, the majority of living donor grafts donated to adult recipients at our institution are right

hemilivers including middle hepatic vein. Our experience shows that in such cases the functionally unaffected volume of harvested liver parenchyma is usually consistent with the recipients needs and the amount of functionally unrestricted remnant liver retained in the donors is enough to assure an uncomplicated postoperative recovery.

On this base, our centre adopted a flexible policy of performing right liver graft donation: with and without MHV depending on the individual donor/recipient match. Apart from the severity of the recipient's clinical condition, the degree of portal hypertension also plays an essential role in the decision. We have already learned that appropriate venous drainage is essential, particularly if graft-GVBWR is marginal or if the recipient has severe portal hypertension.

Our criteria for harvesting or retaining MHV in the remnant liver entail:

- intrinsic donor liver characteristics:
  - hilar (vascular/biliary) anatomy (right artery size, multiple right bile ducts etc),
  - territorial liver anatomy (HV dominance relationship, MHV belonging pattern, functional-rest-hemiliver volumes),
- recipient's clinical condition, especially the severity of PHNT),
- individual donor/recipient anatomical and functional GVBWR's.

The conceptual differences in the decision making for MHV inclusion with the right liver graft based on CASP, between Essen- and Kyoto- programs [36], have been delineated in the table 47.4.

The use of HepaVision software is able to:

- determine two different types of right hemiliver grafts based on the pattern of venous drainage RHV dominant graft vs MHV dominant graft – providing respectively the largest percentage of parenchymal drainage in the graft and remnant hemilivers,
- recognize two different MHV belonging patterns: left versus right belonger types based on their proportional volume contribution in the right and the left hemiliver,
- visualize the "marginal zones" in both graft and remnant hemilivers (segments-IV, V, and VIII), revealing potential drainage impairments and consequently predicting "additional loss" of the functional volume dependent on whether the MHV is included with the graft or retained with the remnant,
- determine the significance of accessory hepatic veins (if present) on the base of territorial venous mapping.

Table 47.4. Essen- versus Kyoto- criteria on MHV management for right liver graft ALDLT.

"Malago criteria"	"Tanaka criteria"
MHV belonging pattern and classification of HV dominance	RHV/MHV versus LHV/MHV dominance relationships
no cut-off volume for right/left MHV drainage hemi-territory	Cut-off volume for right/left MHV drainage hemi-territory: 35% vol. right/left hemilivers
functional (rest)-graft volume (0.8 < functional-GVBW > 0.8)	anatomical (resectional)-graft volume (1.0 < anatomical-GVBWR > 1.0)
other factors: intrinsic donor liver characteristics, recipient clinical condition, severity of PHTN!	other factors: donor age, steatosis etc.
donor refusal, if functional-remnant-GVBWR < 0.6	donor refusal, if remnant liver volume is < 30% SLV

Our decision on MHV management (inclusion/retention) is always based on the "computed risk analysis", that enables estimation of the virtual "functional" volumes of both graft and remnant hemilivers. Subsequently virtual "functional"-GVBW-ratios of graft and remnant livers are calculated. They portray potential volume restrictions associated with anticipated venous congestion of the marginal zones (segments IV, V, VIII) expected postoperatively. This comprehensive information in regard to the "virtual" liver graft must be subsequently adjusted to the intrinsic donor liver characteristics, especially the hilar vascular/biliary anatomy, as well as to the recipient's morbid condition, particularly take into consideration the severity of his portal hypertension with the resulting portal hyper-perfusion in the transplanted graft. However a "functional"-GVBWR for recipients in our series did not underscore 0.8, whereas a "functional"-GVBWR of 0.6 in the donor represented a cut-off value for us in this decision making.

The assumption that the removal of less tissue from the donor provides more safety for the donor proved to be unfounded. Healthy donors can compensate an extended right hepatectomy, providing it is performed with limited surgical trauma and without exposition to

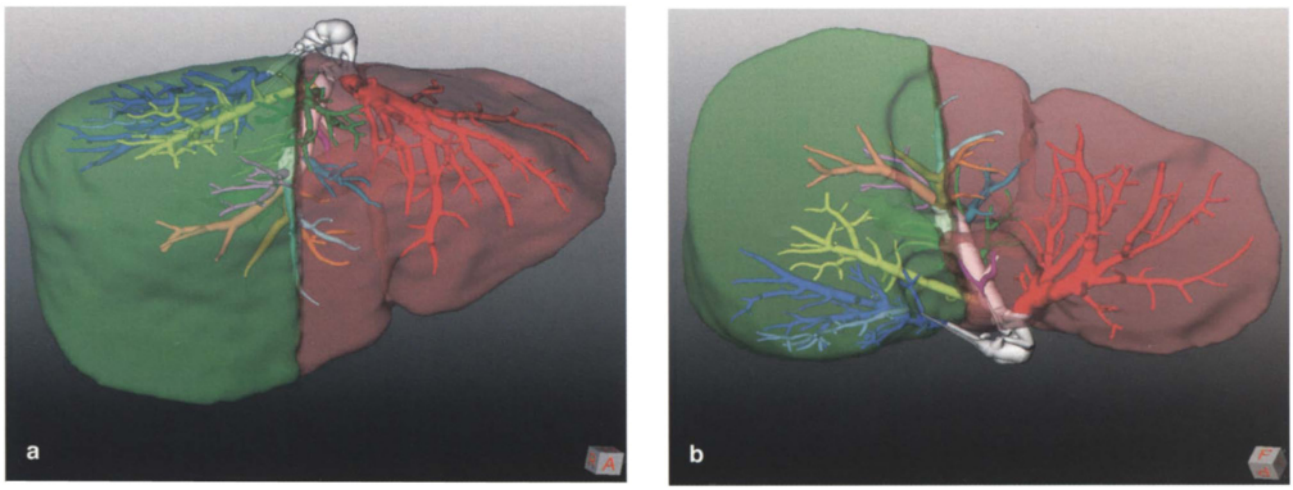


Fig. 47.37. a-b: Cantlie partition, 3-D reconstruction, cranial view (a), caudal view (b), right graft hemiliver (green), left remnant hemiliver (brown), RHV (blue), LHV (red).

the effects of portal hypertension during the post-operative recovery.

In our experience left graft donation, involving retrieval of segments II, III, IV with or without segment I, is suitable for adolescent and small recipients (under 60 kg), but is usually inadequate for adult recipients. In such cases MHV has always been included in the graft.

The choice of right liver graft including MHV seems in our opinion to be the most appropriate and convenient concept for preventing SFSS in the recipient, even if bearing some increased risk for the donor. Further clinical trials will show which type of graft can have the best outcome for both recipients and donors.

47.3.4.2. "Carving Technique" a New Liver Partition Philosophy: Outflow Oriented

The liver partition is performed by a variety of techniques, thus, the transection line differs according to the liver partition type.

The liver transection line is the "holy plane" and requires upmost attention during the graft hepatectomy. It must be determined by complying with the main principle: "do not pass into segments". If trespassing the segmental boundaries whilst performing a liver partition, marginal necroses can result on the transection surface of either hemilivers, eventually leading to severe septic or biliary complications.

On the other hand, it is well known, that even minimal modifications of the transection line can drastically change the outcome of donor and recipients, due to venous congestion in the marginal zones (medial areas) of graft and remnant livers, drained by the MHV branches, particularly in the setting of portal hyperperfusion and/or SFS-situation. Therefore the exact course of transection line must be analysed and planned individually, taking into account the intra- end extra donor hepatic anatomy.

Our strategy of "carving transection", based on the concept of right liver graft including MHV, is an alternative approach to the established world wide "Cantlie" method.

The Cantlie partition (fig. 47.37 a-b) is mainly "inflow oriented" by tracing the Pringle demarcation boundary and follows the "vascular ablation" principle. The Cantlie's plane of division is eventually traced by an imaginary line linking the gallbladder fossa to the confluence of the inferior vena cava (IVC). This transection entails the incidental detachment of tributaries on both sides of the MHV. In such cases, the MHV subterritories can develop venous congestion and become functionally impaired. The rationale for implementing the "Cantlie line" in standard liver surgery was probably based on the fear of damaging the MHV and causing severe bleeding. This approach keeps the surgeon away from the middle hepatic vein during the liver transection, and has been widely established for tumor resections when one part of the liver can be sacrificed and discarded.

The Malagó partition (fig. 47.35 a-b) on the other hand, is based on the "suprahepatic" approach, and is both inflow and drainage oriented. It is focused on the need to preserve an adequate venous outflow in the marginal areas of both right and left hemilivers while maintaining a secure inflow. The "carving technique", that follows the exact course of the MHV trunk, enables the preservation of small tributaries in both the graft and remnant hemilivers by means of their controlled transection, especially those of the contralateral marginal zone in the remnant. Sub-territorial microveins constituting "rescue circulations" are thought to play a bridging role in draining the marginal zones near the resection surface early after ALDLT, until venous shunts between the MHV and LHV or RHV spontaneously open [44, 46].

The conceptual differences in the liver partition for right graft hepatectomy, by following the "Malago"- versus "Cantlie"-lines, have been delineated in the table 47.5.

When comparing the anatomical and physiological chacteristics of venous drainage in the right hemiliver graft, the Cantlie partition is associated with devascularization of the marginal zone of the graft and remnant livers. This leads to a subsequent loss of drainage volume contributed by the MHV tributaries, as well as up to a mean 31% decrease of the right hemiliver graft volume (fig. 47.38 a). As a consequence, there is a significant decrease in functional-GVBW-versus anatomical-GVBW-ratios for right hemiliver graft with this partition type. In the Malagó partition the MHV is principally included with the graft to ensure intact drainage of its medial area. Thence, the anatomical right hemiliver graft volume is identical to its functional equivalent (fig. 47.38 b).

Table 47.5.

"Malago partition"	"Cantlie partition"
• outflow and inflow oriented	• inflow oriented
• follows exactly the MHV course in relation to the Pringle demarcation boundary	• follows virtual extrahepatic line linking GB fossa and ICV confluence
• includes MHV in one hemiliver and detaches contralateral MHV branches tightly by the MHV trunc	• Causes incidental detachment of right- and left-sided MHV branches
• protects venous drainage in both right/left medial areas	• causes drainage impairment due to devascularisation in both right/left medial areas
• prevents additional restriction of functional-graft/remnant volume	• causes additional restriction of functional-graft/remnant volume

The findings seem to suggest that given similar parenchymal volumes, the improved outflow obtained by including the MHV with the right hemiliver graft would improve recipient outcome without incurring additional risks to the donor. In such instances, the Malagó transection technique may provide a safer approach.

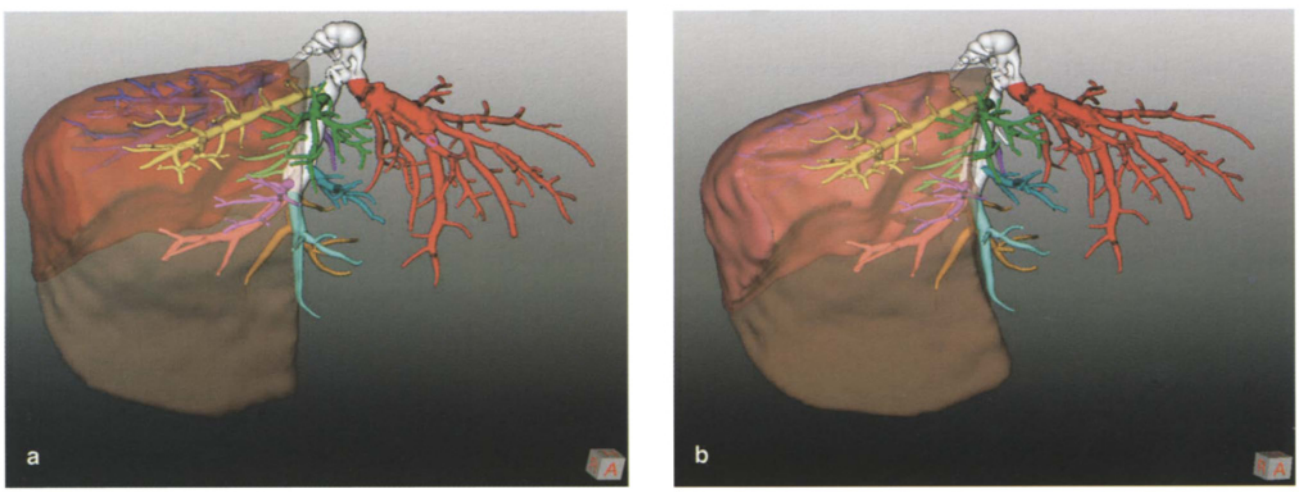


Fig. 47.38. a-b: 3-D reconstruction of the functional (rest) graft/ remnant volumes, defined as the retained, intactly drained, liver parenchyma, cranial view (a), caudal view (b), right (rest) graft hemiliver (blue), left (rest) remnant hemiliver (red), RHV (blue), MHV (yellow), LHV (red).

Another superiority of the "carving" transection concept in the clinical application is the potentiality of precise transformation from "virtual" surgery to the "real" in situ situation, thanks to excellently reproducible landmarks. This is particularly beneficial to:

- prediction of graft/remnant volumes,
- decision-making on MHV procurement.

47.3.4.3. *Strategy of MHV Harvest and Division of MHV 8 Versus MHV 4a Branches*

In our experience, the concept favouring the inclusion of the middle hepatic vein with the right liver graft by employing the "carving" transection technique offers the major advantage of optimal venous drainage in both lateral and medial area of the graft, while preventing severe tissue congestion in the remnant liver due to inadequate drainage in it's "marginal zone" (segments: IVa/b). The donor outcome shows no reproducible disadvantage of the MHV inclusion with the right graft, underscoring the fact that the remnant is more resistant than the graft due to the absence of PV hypertension in the donor. Moreover, the arterial perfusion can temporarily compensate for such deficiencies, as shown in CT controls obtained on postoperative follow up.

HepaVision software allows for the simulation of graft hepatectomy conducted on a 3-D liver model by following different liver partition types. Thanks to the additional display of venous trees and territories derived from the donors CT image data, exceptionally difficult operative steps, such as the "carving" transection, can be precisely planned and rehearsed in advance, making potential pitfalls more predictable. This allows excellent extrapolation of preoperative virtual surgery in the actual in situ situation.

Our concept of stepwise parenchyma transection according to "carving technique" for right graft hepatectomy entails (fig. 47.39 a-f):

- entrance into the corridor of "MHV-branching out",
- reaching of the "MHV crotch",
- following the course of the MHV-trunc,
- division of MHV trunc and harvest of MHV 8 versus MHV 4a tributaries.

In the "virtual" pre-operative and subsequently "real" intra-operative situations, the transection line is determined by initially simulating the Pringle demarcation line (right sided PV/HA clamped) and identifying the course of the middle hepatic vein in conjunction with the Pringle line, using ultrasound examination. While distinguishing the anatomical (right vs. left) MHV "belonger" pattern (fig. 47.40 a-b), the anatomical relationship of MHV tributaries from segments 8/4a and 5/4b must also be recognized. It will influence the level of the subsequent MHV division. However, while the transection line is being established, strong disparity between inflow and outflow oriented boundaries should be avoided, in order to minimize the volumes at risk (ischemia and congestion) along the transection surface of the graft and remnant livers.

Step 1. The entrance into the corridor of "MHV-branching out" between the liver margin and the MHV crotch can be determined, after have been marked:

- posterior boundary of parenchyma transection by right paracaval incision between: RHV – confluence and the caudate lobe,
- "caudate incisional-notch" within right sided hilar plate,
- transection line at the hilar surface of the liver by incision between the right sided hilar plate (already divided) and the anterior liver margin, through the gallbladder fossa (mostly running, within its left part or along its left boundary),
- Pringle demarcation line by right sided PV/HA clamping,
- course of the middle hepatic vein – projected on the diaphragmal surface of the liver using ultrasound examination,
- MHV crotch place – identified using ultrasound examination,
- course of MHV branches arising from the crotch-point away to segments: 5/4b – projected on the diaphragmal surface of the liver using ultrasound examination.

On the base of these preliminarly prepared landmarks, the course of the transection line can be continued on the diaphragmal surface of the liver, from the anterior liver margin to the MHV crotch-point, by passing a "narrow" window between the MHV branches to segments 5 and 4b, which are characterised by strongly diverse course.

The 3-D visualisation not only provides a better recognition of this "tricky" MHV anatomy, particularly at the crotch place but, thanks to the information derived

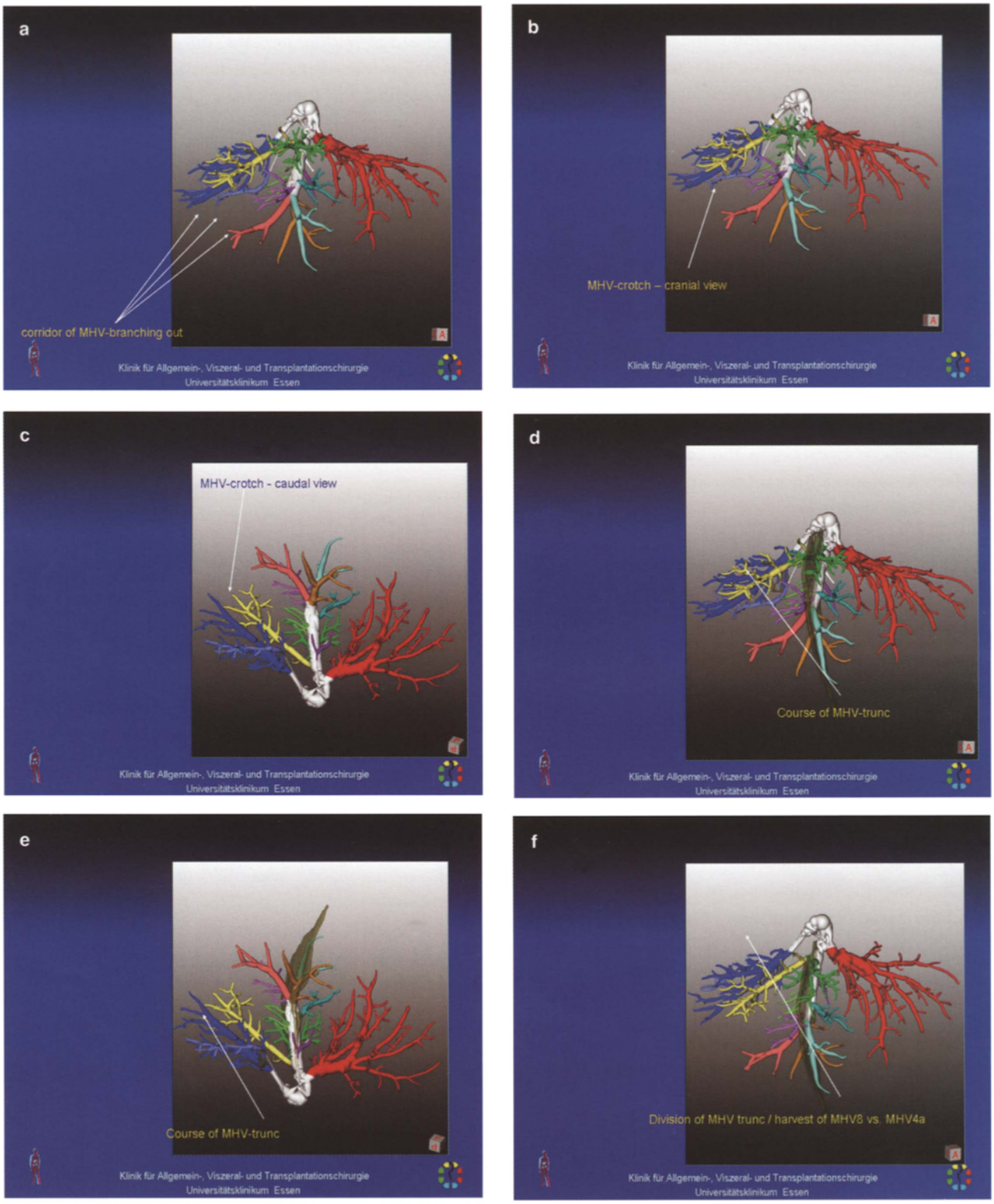


Fig. 47.39. a-f: Malago partition, 3-D reconstruction of the "carving" technique for right graft hepatectomy, entrance into the "corridor of MHV branching-out" (a), reaching of the "MHV-crotch" (b+c), following the course of MHV-trunc (d+e), division of MHV trunk and harvest of MHV8 versus MHV 4a tributaries (f).

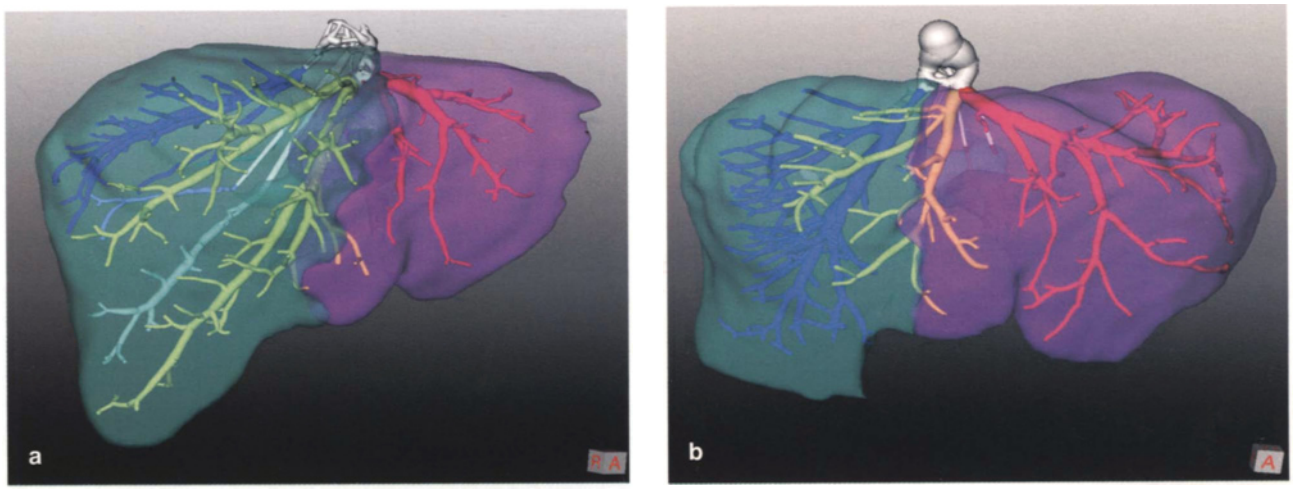


Fig. 47.40. a-b: 3-D reconstruction of the anatomical MHV belonger patterns: right sided type (a) versus left sided type (b), assigning the course of MHV in relation to the Pringle demarcation line, cranial view, right hemiliver (cyan), left hemiliver (purple), RHV (blue), MHV (yellow), LHV (red).

from the territorial mapping ("fishbone map") it also provides an excellently assist for reaching the proper decision on the most optimal course for parenchyma transection within the MHV-corridor (fig. 47.41 a-g).

Steps: 2 and 3. After reaching the "MHV-crotch", usually the MHV branches to segment 4b are ligated, and the MHV trunk is exposed. Due to the exceptionally high fragility of the MHV, it is of paramount importance not to damage the vein during the further dissection, to obviate severe bleeding. In this step, the plane of liver transection follows exactly the course of the MHV trunk, leaving its left-sided border exposed on the transected surface of the right liver graft. The MHV is almost always completely taken with the graft. In every instance, the MHV is initially identified by intraoperative ultrasound examination and subsequently "carved" out of the surrounding remnant liver parenchyma. The line of parenchyma transection on the diaphragmatic surface of the liver, lies exactly between the Pringle decolorisation-line and the "ultrasound-projection"-line of the MHV trunk, consistently tracing the virtual "avascular" hemiliver boundary. Thus, the assigned "carving" transection plane extends between the MHV trunk, being present deeply within the liver parenchyma and that "virtual hemiliver boundary"-line on the diaphragmatic surface of the liver. The real degree of "concavity" on the transection surface of the graft (vice versa: "convexity" on the remnant site) differs individually and depends on the anatomical MHV "belonger" pattern, which determines the width of the "virtual" strap between the Pringle decolorisation-line and the "ultrasound-projection"-line of the MHV trunk on the diaphragmatic surface of the liver.

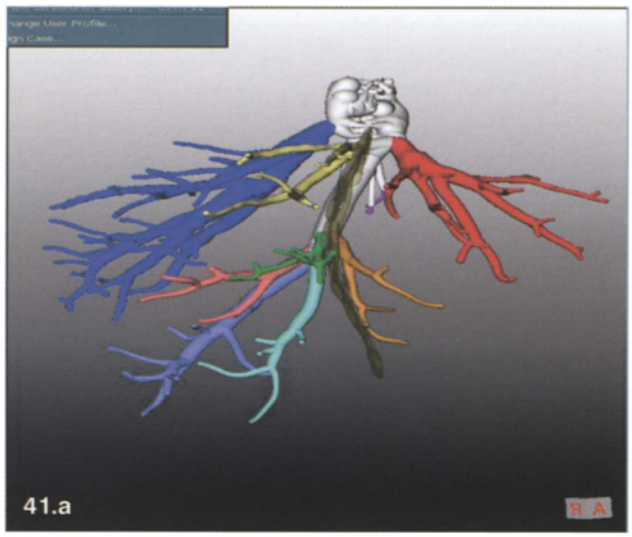
In case of left graft hepatectomy assigning the MHV trunk to the donor, the approach and dissection of the MHV is exactly mirrored, leaving the right sided MHV border exposed at the transection surface of the liver graft.

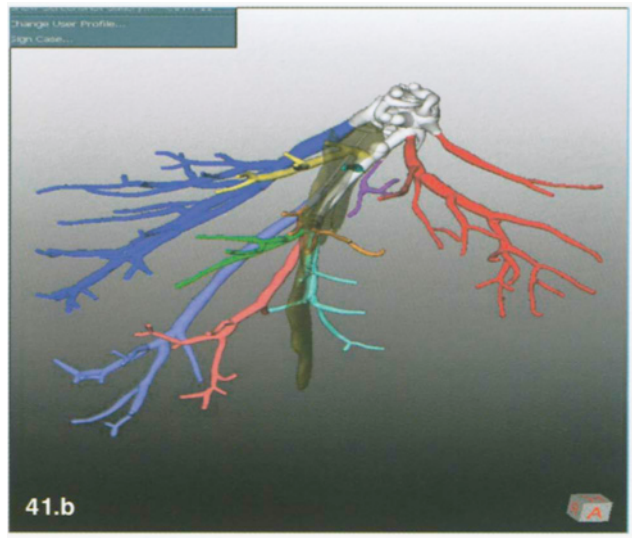
Because the MHV trunk lies in the posterior 1/3 of liver parenchyma, it is of enormous help to curry out the surgical dissection posteriorly in conjuction with the MHV course, passing both the MHV corridor from the hilar surface of the liver down to the crotch and subsequently "carving out" the MHV trunk from the parenchyma along the transection surface up to the confluence with LHV.

Step 4. Our strategy of MHV division and harvest of MHV 8 vs. MHV 4a tributaries depends on three preconditions:

- anatomy of the confluence MHV/LHV,
- anatomical MHV 8 vs. MHV 4a relationship,
- territorial MHV 8 vs. MHV 4a relationship,
- territorial MHV 4a vs. LHV 4A relationship.

According to these principles, the level of division of the MHV trunk depends on the anatomical configura-


41.a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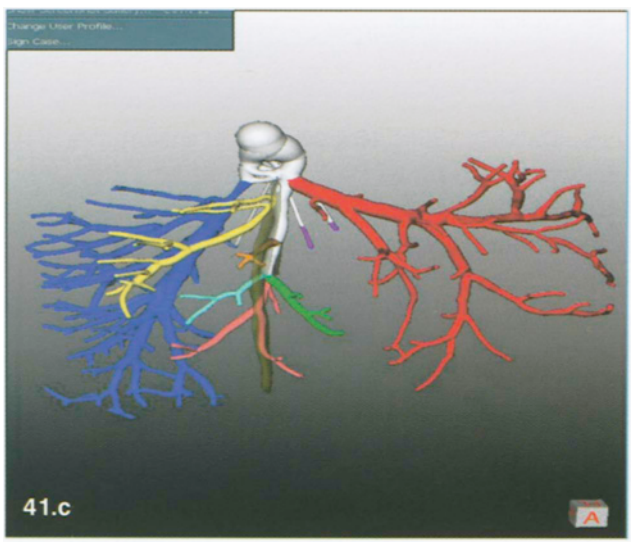
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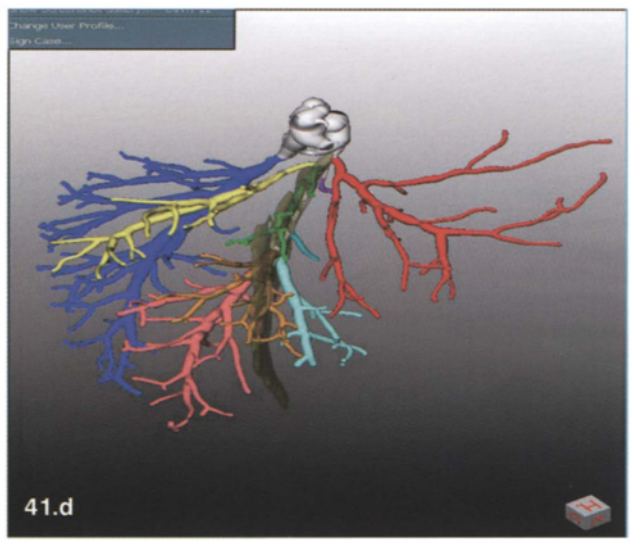
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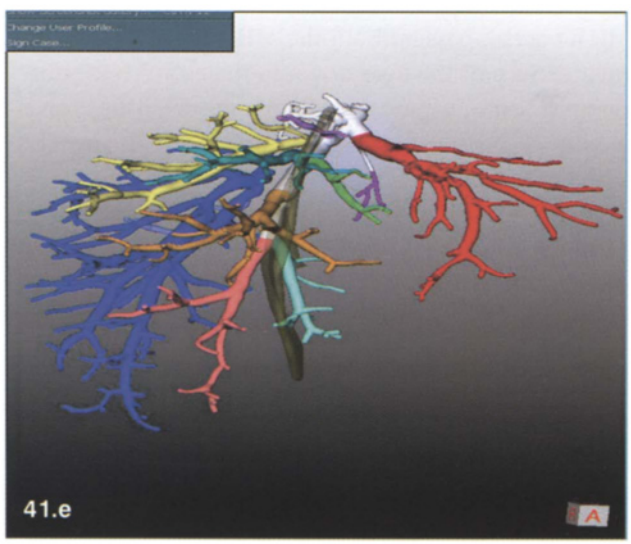
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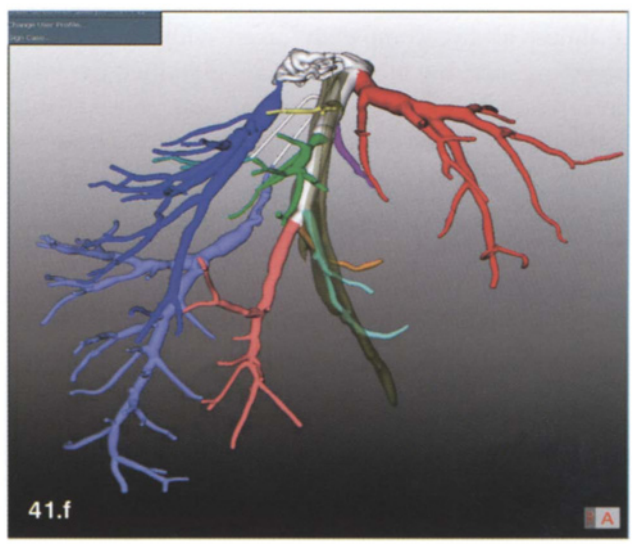
41.f

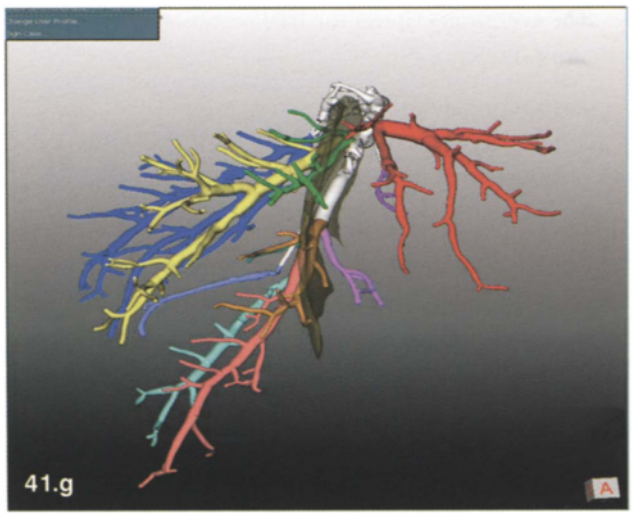

Fig. 47.41. a-g: Malago partition, 3-D reconstruction of the "carving" technique for right graft hepatectomy, different course of the "virtual" transaction line on the diaphragmal surface of the liver between the anterior liver margin and ICV confluence. RHV (blue), LHV (red).

tion of MHV branches to segment 4a vs. segment 8 as determined by their site (level) of confluence into the MHV trunk, as well as on the volume of their drainage territories. Additionally, the territorial relationship between MHV 4a tributary and LHV 4a plays another essential role in reaching this decision. Thus, MHV 4a tributaries can be either sacrificed or preserved on an individual basis, depending on the impact of the volume of LHV 4a, MHV 4a, or MHV 8 on the remnant liver volume and on the graft itself. The anatomy of the confluence MHV/LHV is often not important for this decision. However, in cases when the MHV discharges into LHV distally from the confluence or vice versa there is a connection between the umbilical vein and the MHV trunk, lower than the confluence level of MHV/LHV; the distal MHV trunk is divided, leaving a "long" stump in the remnant liver, to secure its venous outflow.

Based on these findings, three possible situations are anticipated in the 3D liver model:

MHV type 1: The middle hepatic vein can be dissected proximally to its confluence with the LHV, divided at this level and retained entirely with the right liver graft, leaving "no" stump in the left remnant liver. In such cases, the MHV 4a tributary is sacrificed, the MHV 8 branch is always procured en block with the MHV, and the MHV is kept with the right liver graft.

MHV type 2: The middle hepatic vein is divided somewhat distally from, but still close to, its confluence with the LHV, leaving a "short" stump in the left remnant liver. In such case, the MHV 4a tributary is either sacrificed or preserved, while the MHV 8 branch is always included with the right liver graft and harvested "en bloc" or separate, depending on the level of its junction with the MHV trunk.

In cases of MHV types 1 and 2, the middle hepatic vein has been entirely retained with the right graft.

MHV type 3: The middle hepatic vein is divided far distal to its confluence with the LHV, leaving a fairly "long" stump and retaining the distal MHV trunk with the right liver graft. This is happening case when the junction of the 4a tributary with the MHV trunk is encountered distally to that of the segment 8 tributary. For donor safety, it is indispensable such MHV 4a branch to remain preserved on the MHV stump in the left remnant liver, while segment MHV 8 branch must be separately reconstructed by a "blanket"-shaped grafting.

In case of MHV types 3, the middle hepatic vein is incompletely retained with the right graft.

When the left liver graft is transplanted, the entire MHV is always retained with the graft and divided at the level of confluence with the LHV.

Contradictive to our "flexible" policy, aiming at the individually adjusted harvest of MHV 4a tributaries in the right graft ALDLT, is the concept proposed by the Hong Kong-group, favouring the compulsory preservation of MHV 4a branches in the remnant liver, in order to secure the venous outflow in segment 4a, taking into account the inevitable deprivation of MHV drainage to segment 4b during right graft hepatectomy [43].

47.3.4.4. *"Common Outflow Reconstruction" an Original Strategy*

There is still no consensus agreement on the optimal type of reconstruction of tributaries of the MHV in either graft or remnant livers [43]. However, reports describing the dangers associated with small-for-size grafts and portal hyper-perfusion remind us of the importance of adequate venous drainage in the medial area of the graft [18-19, 28, 42].

Initially, efforts were aimed at optimizing arterial and venous inflow to the graft [21-22]. Our experience, as well as that of others, showed that the concept of

venous outflow was of equal if not greater, importance [18, 28-29, 43]. Nowadays, it is generally known, that a perfect venous outflow is the most important prerequisite in alleviating a SFS-injury in the graft. Thus, despite different technical considerations, there is a consensus agreement that adequate venous drainage is essential to optimize the viability of both graft and remnant, thus diminishing the risk of graft loss in the recipient and death in the donor [1,18,43].

We principally dismiss concepts preferring manipulation of inflow, without addressing appropriate outflow management. Based on the concept of right liver graft containing MHV, we developed our own strategy of venous outflow management in the graft [10]. Our original approach strictly reclining on our new surgical technique of parenchyma transection ("carving technique"), secures venous outflow in both medial and lateral areas of the graft and follows the principle of a "large" common outflow tract reconstruction, by means of "blanket"-like venous interposition grafting, that is anastomosed into a wide triangular opening on the anterior wall of the IVC, as published by Malago et al. [19].

The "virtual" surgery planning, offered by HepaVision, permits the recognition of principally three types of venous reconstruction, which have to be taken into account if the right liver graft is donated:

- middle hepatic vein (MHV), or/and its branches to segments: V and VIII (MHV 5 vs. MHV 8 tributaries),
- right hepatic vein (RHV), or/and its branch to segment VII (RHV 7 tributary),
- inferior (accessory) hepatic veins (IHV), mostly draining the lateral sector of the graft.

The decision on the appropriate venous outflow reconstruction in the right liver graft scrutinies following questions:

- when should MHV tributaries from segment 5 and 8 (MHV 5 and MHV 8) be reconstructed, if MHV retains with the remnant liver?
- when should IHV (if present) be reconstructed?
- which type of outflow reconstruction is optimal in the individual situation?

The management of tributary veins draining the "marginal zone" (medial area) of the right liver graft is usually much more challenging than the reconstruction of the inferior hepatic veins (IHV).

The common criteria for IHV reconstruction in such circumstances are [9]:

- cross-sectional diameter > 5 mm,
- adequate IHV distance from the RHV along the IVC,
- a positive "backflow"-test.

However, IHV branches smaller than 5mm in diameter may provide a significant and independent venous drainage of segments VI or VII, particularly in cases with portal vein trifurcation, which can alter the classical sectorial mapping, due to atypical segmental shift. Therefore, in such cases, reconstruction of IHV should be considered.

When compared with the conventional strategy of venous outflow management in the right liver graft, the "blanket"-outflow grafting bears the following advantageous qualities:

- "large" common outflow tract provides equally sufficient draining of the RHV and MHV territories, irrespective of the dominant relationship between RHV/MHV in the right hemiliver graft,
- veno(septo)plasties between RHV/MHV (sometimes additionally including: MHV 8 and IHV branches), which can lead to narrowing and/or occlusion of veins, are principally dispensable,
- number of openings created in the blanket-graft for linking together venous orifices of RHV, MHV, as well as MHV 5/8 tributaries and IHV branches, is not limited,
- "blanket"-shaped outflow conduit can act as a "springing pillow" and sufficiently "buffer" graft malpositions, due to a "graft-hypertrophy"-movement, and thus effectively prevents kinking, twisting and compression on the venous outflow orifice, as well as the associating severe congestive derangement.

Having considered different structural and technical variations of the blanket graft, we developed the following classification scheme.

Types I-IV: number of vein orifices within the blanket graft.
Types x/y: IHV included or not in the blanket graft.
Types a-e: MHV 5 or/and MHV 8 tributaries separately included or not in the blanket graft.

Classification of the blanket vein graft according to Malago.

- Type I: Blanket including 1 x hole orifice.
- Type II: Blanket including 2 x hole orifice.
- Type III: Blanket including 3 x hole orifice.
- Type IV: Blanket including > 3 x hole orifice.
- Type x: IHV included in blanket graft.
- Type y: IHV not included in blanket graft.

- Type a: MHV 5 tributary separately included into blanket graft by additional jump graft.
- Type b: MHV 8 tributary separately included into blanket graft by additional jump graft.
- Type c: MHV 5 and MHV8 tributaries separately included into blanket graft by additional jump graft.
- Type d: MHV 5 and MHV8 tributaries not separately included into blanket graft by additional jump graft.
- Type e: other MHV/RHV tributaries separately included into blanket graft by additional jump graft.

The conceptual differences in the outflow management of the right liver graft, between Essen –and Hong-Kong– programs [26,43,47], have been delineated in the table 47.6.

The superiority of our outflow management concept lies in its universality and roboust efficacy allowing a wide applicability, irrespective of the individual venous graft anatomy and yielding a satisfying long term patency.

Our strategy of stepwise outflow reconstruction in right liver graft comprises:

Phase I: (fig. 47.39-47.41) liver partition in the donor, performed according to the "carving" technique.

It determines, whether MHV should be included into graft or alternatively its branches to segments V and VIII must be separtately reconstructed in the recipient. Additionally, it enables for the procurement of MHV 8 tributaries at different levels of MHV confluence. Consequently, there is a different number and localisations of venous stumps (openings) encountered on the transaction surface.

Phase II: outflow reconstruction in the graft conducted by creating a blanket-shaped venous interposition graft on the bench table.

By using alloplastic venous material (blood group compatibility mandatory), obtained from our tissue bank, an appropriate interposition graft is tailored as follows:

- determination of the size and shape of the blanket must always assure, that,

Table 47.6.

"Malago outflow reconstruction"	"Fan outflow reconstruction"
• creation of "large" common outflow tract (conduit)	• creation of "large" "perfect" hepatic vein anastomosis (RHV/MHV/V8)
• use of "blanket" shaped-venous graft interposition-conduit with or without veno(septo)plasty	• use of veno(septo)plasty (no venous graft interposition) between MHV and RHV
• large (vertical triangle) subtotal opening of the anterior ICV wall	• narrow separate horizontal triangular orifice at the RHV side of the ICV, below the RHV stump, closed by suture
• IHV re-implanted into ICV separately or included in blanket-graft if cranial	• IHV always re-implanted into ICV separately
• MHV trunk always completely exposed at the transection surface of the graft liver	• MHV trunk not exposed at the transection surface of the graft liver
• 3 x different MHV types on the transection surface of the graft in dependence of MHV 4a sacrifice or retention in the remnant	• no differences of MHV in the graft because MHV 4a most often retained in the remnant
• sufficient protection from outflow occlusion by: kinking, twisting, compression due to graft malposition (blanket graft as a "springing pillow")	• high risk of outflow occlusion by: kinking, twisting, compression due to graft malposition unless "perfect" design of the anastomosis

- size of each blanket-border is exactly adjusted to the intended IVC opening in the recipient,
- length of each blanket-borders generally exceeds those of triangular IVC "window" by approx. 25-30%!
- particularly the left-sided anterior border of the blanket should be adequately sized for a sufficient covering of the left-sided diagonal border of triangular IVC "window",
- optimal topographic relationship of all venous orifices within the blanket is determined,
- veno(septo)plasty is always preliminarily performed (if advantageous), to reduce the number of venous orifices within the blanket,
- all venous stumps on the transection surface of the graft have been eventually sewn into the blanket at the prepared orifice places.

Phase III: Anastomosis between blanket graft and IVC opening in the recipient is conducted under a total proximal/distal cava clamping.

The graft implantation is done by performing an

anastomosis between the blanket graft and a wide triangular opening in the IVC. The septa between RHV/MHV and MHV/LHV confluence stumps are divided and fusioned into a large horizontal slot. For the IVC windowing, a wide venotomy of its anterior wall is utilised, extending from the confluence level, downwards well above the level of the renal veins.

- triangular IVC window delineates:
- upper horizontal border, a large horizontal slot, created by fusioning RHV/MHV/LHV confluence stumps,
- diagonal borders, extending proximally from the level of HV-confluence and distally well above the level of the renal veins or the intended IHV-replantation site with the distal IVC,
- triangular IVC opening should be designed shorter in the vertical –and longer in horizontal– diameters, especially when a separate IHV anastomosis with the distal IVC is required, in order to keep the distal triangle-spike far above the intended IHV/IVC anastomosis,
- MHV orifice should be positioned as cranially to the RHV orifice as possible,
- this special situation requires exact adjustment of size and length of the blanket borders to the triangular IVC opening, that has to be "stretched" particularly into its horizontal diameter
- especially left-sided anterior border of the blanket should be designed accordingly larger,
- veno(septo)plasty of the RHV/MHV is reasonable, to form a single venous orifice within the blanket, for keeping the distance between RHV/MHV stumps short (always preferential),
- in case of the need to restore segments V and VIII venous drainage in the right liver graft not containing the MHV, separate "jump grafts" from MHV 5 and MHV 8 tributaries are employed to join the common blanket orifice, thus establishing the continuity of venous drainage in the marginal area of graft.

The conduction of the anastomosis between the blanket graft and the triangular IVC opening is performed in a stepwise fashion as follows:

- preliminary placement of holding stitches in all corners of the triangular IVC window,
- performance of running stitches: one after another,
- firstly: restoring the right sided diagonal border of IVC triangle, starting from the right proximal corner downwards to the distal triangle spike,
- secondly: restoring the upper horizontal border starting from right to the left corners,
- finally: restoring the left sided diagonal border starting from the distal triangle spike upwards to the left upper corner.

Phase IV: separate clamping of the created venous outflow conduit, at the same time releasing of the proximal/distal caval clamps.

47.4. Conclusion

HepaVision software based on the "all in one" CT protocol proved to be a feasible and robust concept of CASP, enabling comprehensive evaluation of donor candidates in a single non invasive diagnostic fashion. The "virtual simulation" and "computed risk analysis", offered by HepaVision are a consistent concept of preoperative analysis, which has revolutionised the approach to surgery planning in ALDLT.

Our experience has shown that the use of computer technology in the preparation of ALDLT offers the following advantages:

- it reliably improves preoperative evaluation by enhancing the surgeon's anatomical and physiological knowledge of the individual donor,
- it increases the confidence of the surgical team when performing the graft hepatectomy and the subsequent graft implantation in the "real situation".

Consequently, by virtue of these features a high degree of donor safety can be achieved, while the recipient outcome can also benefit. Donor safety in particular benefits from the use of CASP in the preoperative evaluation. In this respect, the precise anatomical and functional volume calculation seems to be a key point, since the donor rejection rate resulting from inadequate graft/remnant liver volumes is substantial. Finally, correct MHV management and the 3-D visualisation of the bile duct anatomy are conceptual essentials in the preoperative decision making.

47.5. Outlook

Methods for computer assisted operation planning (CASP) in liver surgery, developed so far, are not fully adapted to the characteristics of living donor liver transplantation. For example, neither the segmental classification of smaller branches, in particular the hepatic arteries and bile ducts, nor the precise estimation of the individual vascular/biliary territories has yet been satisfactorily established.

Due to the significance of smaller blood vessels, especially arteries and bile ducts, in the planning of living donor liver transplantation, the development of more detailed algorithms for vascular segmentation is essential. Moreover, further developments in computer technology are required to make the software less sensitive and better compatible with routine CT protocols for commercial use.

While preoperative planning for ALDLT on the basis of CT data is feasible, the evaluation of healthy and mostly younger donor candidates demands further efforts to integrate MRI technology in CASP, in order to relieve future live donors of the radiation dose.

Another future – intended software application is one of more fundamental research, regarding liver regeneration after ALDLT. By employing the newest computed 3-D imaging technique that enables visualization of the vascular growth, the following aspects can be targeted:

- analysis of neo-macro-angiogenesis with special focus on the visualisation and quantification of the intrahepatic vascular growth (increase in vessel length and diameter) in both donors and recipients during liver regeneration,
- assessment of the "segment/territory-specific" regeneration in relation to the vascular growth, with special focus on the "segmental/territorial competition in graft vs. remnant livers.

These fundamental considerations can serve as a starting point for clinically relevant questions such as how a liver resection strategy can influence the regeneration and thus, which changes in preoperative planning can significantly contribute to the outcome of postoperative regeneration. Therefore, various regeneration models should be identified allowing detailed analysis of the regeneration process on the basis of the preoperative situation (e.g. SFS-situation, PHTN-condition), and the selected surgical technique (e.g. liver partition type, venous outflow sufficiency).

47.6. Abbreviations

CT: computed tomography;
MRI: magnetic resonance imaging;
TLV: total liver volume;
TLW: total liver weight;
GVBWR: graft volume body weight ratio;
GWBWR: graft weight body weight ratio;
ALDLT: adult living donor liver transplantation;
MHV: middle hepatic vein;
3-D: three dimensional;
PHTN: portal hypertentsion;
SFS: small-for-size;
SLV: split liver volume;
SFSS: small-for-size syndrome.

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CHAPTER 48

CONCLUSION

C.E. Broelsch

Liver transplantation is challenged by a shortage of organs and a prolonged waiting-list time. The large disparity between the number of available cadaver donor organs and recipients awaiting OLT has created an ongoing debate regarding the appropriate selection criteria. Novel surgical techniques, including split cadaveric livers, LDLT, and broadening the donor criteria towards acceptance of marginal donors have been used as strategies in order to expand the donor pool. The appliance of Computer Assisted Surgical Planing in Adult Living Donor Liver Transplantation represents a real challenge for transplant surgeons to perform a modern operation with high standards of safety for donor and recipient.

HCV has become the leading indication for cadaveric transplantation and LDLT in the United States, accounting for approximately 50% of all cases. Moreover, the number of patients with HCV cirrhosis continues to increase [1-2]. There is ongoing research aiming to define host or viral factors that predict recurrence, the impact of immunosuppressive regimens, and the appropriate timepoint and dose for antiviral treatment.

Due to the availability of antiviral drugs, the survival of patients undergoing OLT for HBV infection has dramatically improved and has become comparable to or even better than the survival of patients with non-virus-related liver diseases [3].

Data relating to the frequency of disease recurrence in cholestatic and autoimmune liver diseases vary widely in the literature, but excellent medium-term and long-term results have been reported.

Recent alcohol abuse is a contraindication to liver transplantation and most centers require 6 months of documented abstinence prior to OLT. Patients transplanted for alcohol-related liver damage experience fewer episodes of acute cellular rejection and chronic ductupenic rejection after liver transplantation than patients transplanted for non-alcoholic liver disease [4].

Liver transplantation in HCC patients provides excellent outcomes and low recurrence rates applying the Milan criteria. Living donation to transplant recipients with HCC who exceed the Milan criteria has been discussed controversially. CCC (Cholangiocellular Carcinoma) represents a contraindication for transplantation, except for highly selected cases with very early stage of disease. Combination with neoadjuvant chemoirradiation may further improve results after OLT.

Due to excellent short-term outcome after liver transplantation, attention has shifted to reducing long-term complications. Cardiovascular comorbidities due to metabolic complications, such as diabetes mellitus, dyslipidemia, obesity, and arterial hypertension, account for 30-70% of long-term morbidity. Chronic renal insufficiency appears in 50-80% of patients during long-term CNI therapy. Immunosuppressive drugs without renal side-effects, such as MMF and SRL, have been used increasingly as renal-sparing agents. The need for immunosuppression has to be balanced against drug-related side-effects. Possible routes to clinically relevant immune tolerance may include the application of tolerance-inducing immunotherapy, with or without low dose conventional immunosuppressants.

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