Extreme Hepatic Surgery and Other Strategies

Increasing Resectability in Colorectal Liver Metastases

Eduardo de Santibañes
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To my mentors,
Enrique Marcelo Beveraggi,
Thomas E. Starzl,
Víctor Pérez,
and Henri Bismuth,
with great gratitude.

And to all my trainees,
for sharing their passion with me.

Eduardo de Santibañes

Foreword

Liver surgery is always improving, and I wonder when it will stop. Probably never.

At the beginning, the liver was considered a bloody pouch that was too risky to operate on or even to get in. The first real changes occurred in the 1950s, and included the anatomy of Couinaud bringing a real road-map of the liver and the first true anatomical liver resection by Lortat Jacob. Then, until the early 1980s almost nothing happened. The real revolution was the first imaging technique of the liver, ultrasound, which for the first time made it possible to see inside the liver in vivo; at last, smaller tumors amenable to surgical treatment could be discovered. Now, the surgeon was able to use the segmental anatomy of Couinaud. This was soon followed by intraoperative ultrasound, now allowing the surgeon to use the anatomical map of the liver segments during surgery. All these advances permitted the description of a wide variety of anatomical liver resections from subsegmentectomies to extended hepatectomies. At the same time, different ways of clamping the liver vessels were developed for the best control of intraoperative bleeding, the first fear of the surgeon. During these two decades, liver surgery achieved its full development. According to the nature of the tumor, the size and number of nodules, and the quality of the parenchyma, the surgeon was now able to choose in the vast armamentarium of techniques the most suitable for the operable patient.

But there were limitations: too large or too numerous tumors to remove, or too small liver remnants could not be overcome. We entered a new area, with the objectives of changing the tumor and/or to changing the liver. Changing the tumor included chemoembolization for hepatocellular carcinoma, and more importantly in the Western world, the use of chemotherapy for colorectal metastases. Unresectable tumors were downsized to become operable, and in 1996, we introduced the concept of "resection of unresectable liver metastases": at the ASCO meeting in the same year, there were no communications on liver metastasis. On the other hand, changing the liver occurred with the use of portal vein embolization, which was able to increase volume of the future liver remnant to allow large or staged liver resections. The field of neoadjuvant therapies prior to liver resection was born, and opened a large avenue of research. These new concepts added to pure technical strategies that dealt with the tumoral load and the liver volume. This is the theme of this book: how to go to the extreme of our capabilities to treat the patient with this multiform spectrum of colorectal liver metastasis.

I have known Eduardo de Santibañes for more than 20 years. At the beginning, it was through Miguel Ciardullo, who trained with me at Paul Brousse in the mid-eighties before joining Eduardo. Then Eduardo and I became personal friends, and I admire his skills and leadership. Eduardo is surely one of the best expert liver surgeons in the world. He has brought together several other experts to produce this outstanding book that I think any liver surgeon will want to read in order to know what we may achieve today in the most difficult and extreme liver surgery.

Paris, France

Henri Bismuth

Preface

Colorectal carcinoma is the third most commonly diagnosed cancer in the world. Over 1.2 million patients are diagnosed each year, and more than half of these patients develop liver metastases during the course of their disease. Despite the several advances in the systemic treatments for these patients, radical surgery still plays the major role, as complete tumor removal offers the possibility of cure or transforms patients with an acute illness into patients with a chronic disease and a reasonable quality of life. Nonetheless, the emergence of highly effective modern chemotherapy has made it possible to rescue patients who once could not undergo surgical treatment, and has contributed to the modification of the paradigms regarding safe resection margins. Nowadays, surgical resection with curative intent is being offered to a greater amount of patients thanks to multimodal therapies that brief decades ago we would not have dreamed possible.

The field of liver surgery has experienced an exponential growth over the past 15 years, mainly owing to the introduction of more effective cancer drugs, improvements of imaging modalities, novel techniques of liver function evaluation, and improvements in anesthesia and intensive care, as well as several advances of the surgical technique itself. Over time, liver surgeons have been constantly pushing the frontiers of resectability by the introduction of several surgical innovations, but also by using diverse strategies to either increase the amount of liver to remain after resection and/or reduce the tumor size. The combination of systemic treatments, endovascular procedures, and local ablation therapies with surgery has led to the successful treatment of patients having high tumor loads and otherwise poor prognosis. From an oncological perspective, the increased knowledge concerning tumor biology and the evolution of the concept of resectability have also played key roles in maximizing the survival benefit of patients with colorectal liver metastases. The concept of resectability has changed over time, and is highly dependent on the physician's expertise. Nowadays, there is consensus that resectability should be judged by a multidisciplinary board in a case-by-case fashion, in specialized centers, and taking into account a risk/benefit perspective, the technical feasibility of achieving complete tumor resection, and the oncological rationality behind the approach.

In the present book, we aim to portray the multimodal management of patients with colorectal liver metastases, and to describe in full range the state-of-the-art surgical techniques and adjunct therapies that form the armamentarium for increasing resectability of patients with advanced disease. The

various strategies available are presented and illustrated, emphasizing the current trends and main advancements in each particular field.

This book would not have been produced without the invaluable contribution of worldwide leading experts from Argentina, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Pakistan, Spain, Switzerland, and the United States. Each of the authors of the different chapters have outstanding knowledge in the field, and have been pioneers in the development of the different strategies addressed in this book. I want to express my gratitude to these authors for their time and effort in writing informative, insightful, and up-to-date chapters. Finally, I would also like to thank the other editors, Victoria Ardiles, Fernando Alvarez, Virginia Cano Busnelli, and Martin de Santibañes, for their enthusiasm and remarkable dedication in the edition of this book.

I am convinced that the present book will be useful not only for junior and senior specialists in liver surgery who are frequently faced with clinical dilemmas of how best to care for a patient with advanced forms of colorectal liver metastases, but also for general surgeons who might be asked for an opinion, and even for general practitioners patientwho need to be aware of recent advances in order to implement a timely and accurate referral of the patient.

Buenos Aires, Argentina

Eduardo de Santibañes, MD, PhD

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Part I

Global Patient Evaluation and Oncological Assessment

Liver Surgical Anatomy

1

Henri Bismuth, Ruben Balzarotti,
and Pietro Majno

Introduction

Modern hepatic surgery, and in particular the surgery of liver metastases, on patients with advanced and recurrent disease, as well as chemotherapy-induced liver injury, demands the pursuit of the apparently conflicting goals of radicality and tissue-sparing. Successful procedures require a perfect knowledge of the vascular anatomy of the liver, commonly based on Couinaud's *ideal* representation that will be illustrated in detail. Alternative anatomical representations will be briefly presented, as they allow a better understanding of some surgical procedures such as central hepatectomies. We will argue that the best results will be obtained by deep understanding of the individual *real* anatomy of the patient, based on radiological reconstructions that are now more widely available on the surgeon's laptop, and on intraoperative ultrasound. In addition, we will detail the anatomical characteristics of some structures of the liver, such as features particular to individual segments, the glissonean pedicles, the hepatic veins, the vestigial structures such as the umbilical and Arantius' ligaments, and the surgical approaches and maneuvers that knowledge of these structures allows. The customized procedures that result go beyond the conventional segmental representation, are best described as *tailored territorial liver resections*, fit the concept of precision liver surgery to which the authors fully subscribe [1], and illustrate the evolution from surgical anatomy to anatomical surgery that was anticipated in earlier work [2].

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Classical Surgical Anatomy of the Liver

The morphological or gross anatomy of the liver reveals, from the superior (diaphragmatic) aspect, two lobes, the right and the left, separated by the round ligament and the falciform ligament, joining the round ligament to the vena cava (Fig. 1.1).

On the inferior aspect, the hepatic pedicle widens into the hepatic hilum, drawing grooves similar to an incomplete "H" (missing the left inferior limb). The upper limbs of the H, made of the gallbladder on the right and the round ligament on the left, create the borders of the

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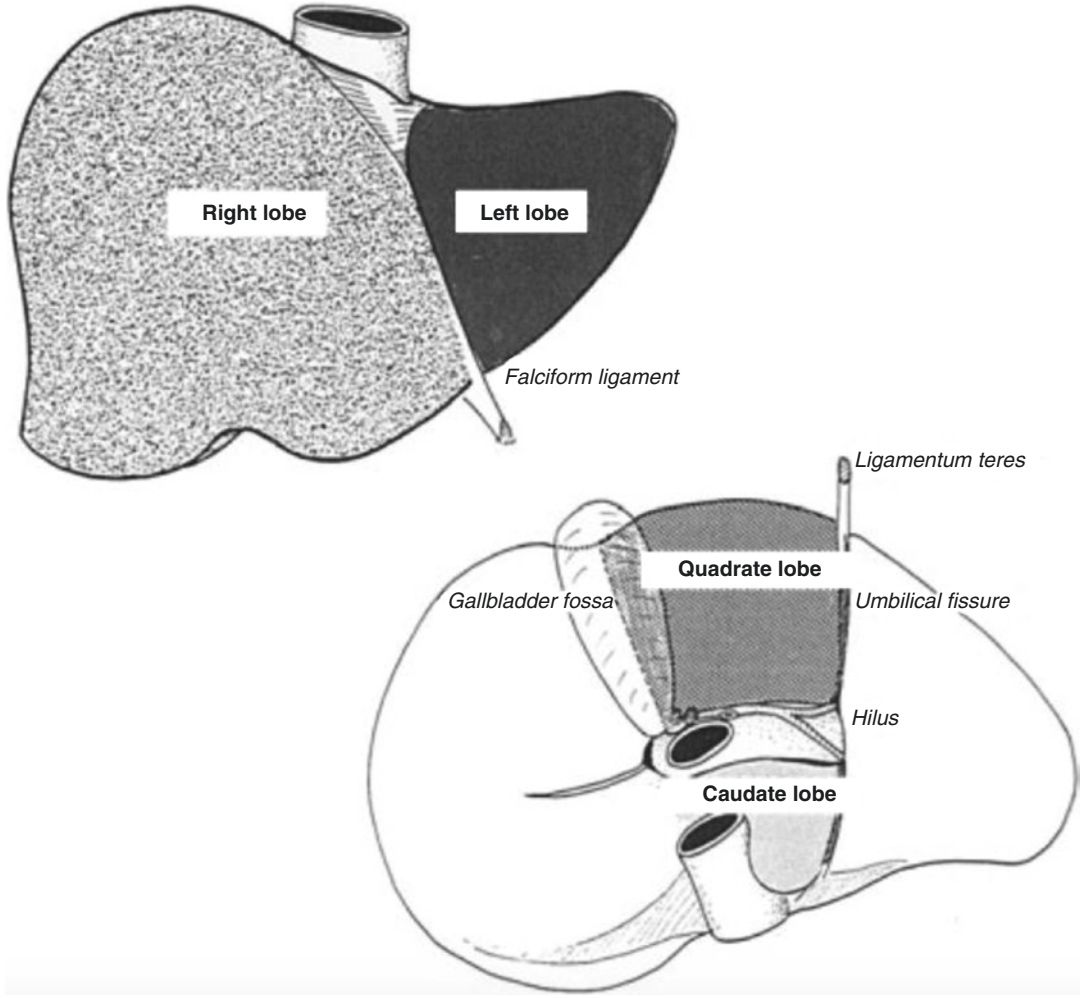

Fig. 1.1 Schematic representation of the gross appearance of the liver, with the macroscopical lobes. The external anatomical structures have little relation to the vascular anatomy (one exception is the round ligament)

quadrate lobe; the horizontal bar of the H, made of the left portal pedicle and the lower right limb, made of Arantius' ligament (joining the left portal vein to the confluent of the left and middle hepatic vein), create the boundaries of the caudate lobe, that encircles the vena cava.

Functional (Vascular) Anatomy

The morphological anatomy described above has little relation to the vascular anatomy of the liver, a point revealed from early anatomical drawings, but in particular from the work of Cantlie [3], Hjörtsjö [4], and Goldsmith and Woodburne [5], who identified separate vascular and biliary areas according to the branches of the portal pedicles.

It is the merit of the French anatomist Claude Couinaud [6] to have analyzed and systematized the vascular distribution of the main liver vessels into a scheme that is relatively constant and consensual. The scheme, popularized by an historical paper [2], is depicted in Fig. 1.2.

In Couinaud's representation, the three hepatic veins interdigitate with the portal pedicles as the fingers of two opposite hands. The vascular territories defined this way, the right and left LIVERS, on the first division of the portal vein,

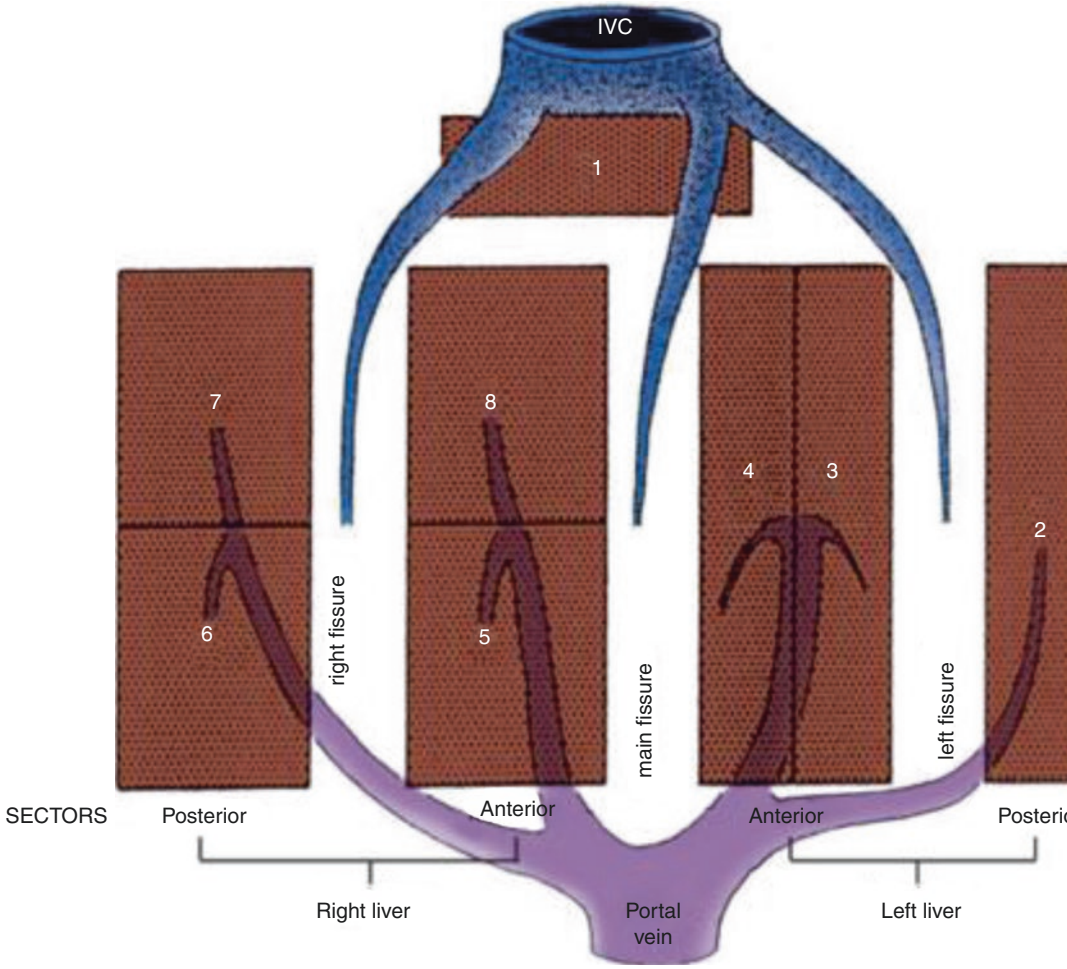

Fig. 1.2 Schematic representation of the vascular structure of the liver. The three hepatic veins and the four sectorial portal branches interdigitate like fingers of two opposing hands. The reader will notice the symmetry of the *right* and *left* liver, taking into account an anticlockwise rotation in the disposition of segment 4 and segment 3 (maybe because the round ligament retains the segments of the left liver from taking a position symmetrical to the right?). While segment 2 is embryologically a left posterior sector, it is practical to call it a segment because two segmental branches are generally not seen within it, and because this territory is small

and the SECTORS, on the second-order division, were further divided into SEGMENTS according to the distribution of third-order portal branches.

In extrapolating the above representation to obtain a closer fit to the morphological anatomy, Couinaud first postulated that there was only one segment (segment 2) in the lateral sector, and that there was a vertical plane rather than a horizontal plane dividing the medial sector into segment 3 and segment 4. Then, the sectors of the left liver fell into oblivion, leaving the simplified schemes with three segments in the left liver, illustrated in Fig. 1.3.

In this representation, the right and the left liver are defined by the bifurcation of the main portal vein. The middle hepatic vein runs in this plane, which can be *approximated* as the plane joining the gallbladder fossa to the vena cava, and corresponds to the main portal scissura or Cantlie's line. On the right, the right hepatic vein separates two sectors: the anterior sector, where the right anterior sectorial pedicle (second-order division) divides into two (third-order) segmental branches, and the same for a posterior sector. On the left, the portal vein runs first in a horizontal

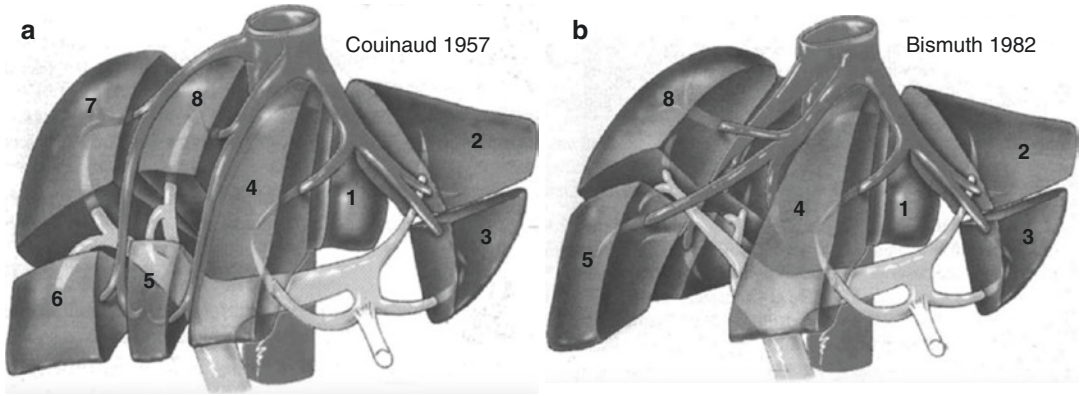

Fig. 1.3 (**a**) Schematic representation of Couinaud's segments. As an anatomist, Couinaud drew the liver "flattened out" on a dissecting table. In fact, segments 6 and 7 are posterior to segments 5 and 8, as illustrated by (**b**), a much more faithful reproduction of the radiological and surgical reality

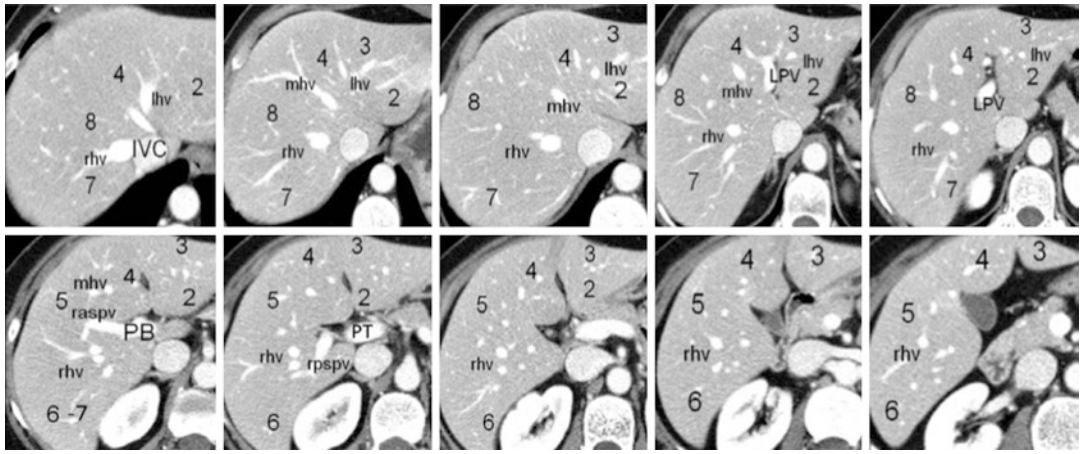

Fig. 1.4 Transposition of Couinaud's segmental representation in a modern axial radiological study (computerized axial tomography, venous phase). The vascular landmarks are easily recognized, and so are the segments (courtesy of Dr Pierre Loubeyre, Department of Radiology, University Hospitals of Geneva). *IVC* inferior vena cava, *lhv* left hepatic vein, *rhv* right hepatic vein, *mhv* middle hepatic vein, *LPV* left portal vein, *raspv* right anterior sector portal vein, *rpspv* right posterior dector portal vein

direction, then in the direction of the umbilical ligament, with a concave side encasing one segment, and on the convex side where two segments are separated by the left hepatic vein. The caudate lobe remains on the posterior side of the portal vein and surrounds the vena cava. Indeed, this anatomy is not exactly the one described by Couinaud. Couinaud described the two sectors of the right liver as paramedian and lateral (Fig. 1.3a). This corresponds to a liver that has been flattened out on the anatomist's table. The true three-dimensional liver was reestablished by naming the two sectors on the right as anterior and posterior, according to their position when the organ lies in the body and under the hands of the surgeon (Fig. 1.3b) [2].

Couinaud's classification has many advantages. The classification of the main territories according to the hepatic veins, that are easily recognized in particular in modern axial imaging, is convenient; with the second and third-order portal branching that can be assumed to occur at the level of the portal bifurcation, it establishes an unambiguous system of coordinates that defines the segments (Fig. 1.4), and therefore the position of focal lesions.

Also, in particular for some segments, there is a relatively good correspondence between the main anatomical planes of the common liver resections (right hepatectomy, left hepatectomy, left lobectomy) and Couinaud's anatomical description (Fig. 1.5).

On closer study, however, there are several inconsistencies of the (simplified) Couinaud scheme that need to be resolved.

From a theoretical point of view, the conceptual and embryological symmetry of the liver is not respected: if the analogy of the interdigitating hands and the order of the portal branches defining sectors and segments were to be respected, Couinaud would have insisted on a large left medial sector composed by segments 3 and 4, separated by a vertical division, and a small left lateral sector to the left of the left hepatic vein, where two segments cannot be individualized. This discrepancy was recognized in the 1982 paper popularizing Couinaud's classification [2] and underlined in our last paper [7].

What happens in this part of the liver is that the umbilical vein—coming from the left branch of the portal vein—is pulling out the portal branch and creates an additional division of this part of the liver, which is, in fact, if we put inside the portal branch, a single segment. The left medial sector becomes one segment, and segments 3 and 4 are indeed half-segments. The left

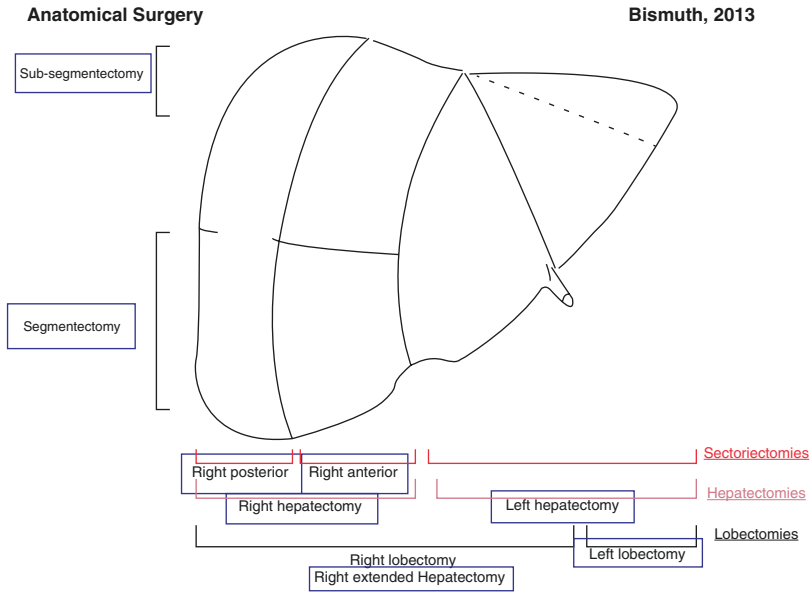

Fig. 1.5 The terminology of the hepatectomies consistent with Couinaud's classification. In *red* are indicated the most precise denominations of liver resections; left lobectomy is the preferred term of the bisegmentectomy 2-3, and right and left extended hepatectomies for the five or six segmentectomies on the right and the left. Alternatively, hepatectomies may be defined by the number and identification of the resected segments. For one segment removed: segmentectomy + number, 1–8. Resection of two segments: bisegmentectomy + numbers. For three segments: trisegmentectomy + numbers (for instance: trisegmentectomy 8-5-1). Central hepatectomy (it is better to avoid using the term middle hepatectomy) has to be defined by the segments removed: usually segments 5-8-4, but it may also include segment 1. Resection only of segment 4 is segmentectomy 4. As segment 4 is divided into two subsegments—4a, the upper one, and 4b, the lower one—each may be removed independently: subsegmentectomy 4a or 4b. Right or left hepatectomies are well defined. For the lobectomies, left lobectomy may also be called bisegmentectomy 2-3. Right lobectomy includes five segments (segments 4-5-6-7-8). Because this extension of the right hepatectomy may remove segment 1 instead of segment 4, it is better to say right extended hepatectomy to segment …*n*, which makes it possible to specify to which segment the right hepatectomy is extended: segment 4 or 1. Extension may involve two segments: 4 and 1, which is the 6-segmentectomy on the right, also called right hepatectomy extended to segments 1 and 4. The left extended hepatectomy to segments 1, 5, and 8 is the mirror resection on the left: left hepatectomy extended to segments 1, 5, and 8, or 6-segmentectomy on the left

lateral sector, only with segment 2, has to be united to the left medial sector that becomes one segment, and together they constitute one sector: one sector with two segments (Fig. 1.3b); this is in accordance with the usual description of Couinaud. In order not to change the numbers put by Couinaud, it is better to keep the numbers 3 and 4, knowing that these segments are in fact half-segments.

We arrive at the following description of the liver anatomy (Fig. 1.5):

- two hemilivers (right and left)
- three sectors (the right posterior, the right anterior, and the left)
- seven segments
  - six segments (each sector divided in two segments)
    - right posterior sector: segments 6 and 7
    - right anterior sector: segments 5 and 8
    - left sector: half segments 3–4 (as one segment) and segment 2
  - plus segment 1

It is in fact fortunate for the diffusion of Couinaud's segmental system that his obscure book was never translated, that neither he nor I (HB) insisted on this point in further papers, leading to the simplified but useful system diffusing in the world.

Alternative Representations

It is worthwhile for the experienced liver surgeon to whom this book is dedicated, to understand some points where the scheme of Couinaud does not fit the anatomical reality, better represented by alternative schemes or by a deeper understanding of Couinaud's work. This not for a sterile anatomical discussion, but because we believe that conceptualizing these alternatives allows to perform the radical yet conservative liver resection required in modern liver surgery [8].

From an embryological point of view, a scheme recognizing the symmetry of the right and the left liver does make sense. As an embryological recall, there are at the beginning two umbilical veins entering the right and the left liver, as illustrated in Fig. 1.6 [9]. This embryological point is not only evident in the anatomical variations where the gallbladder is located on the left side, but also in all the cases where a distribution of the whole right anterior sectorial branches or of the branches of segment 5 recall the pattern of the left portal vein (Fig. 1.7 [10], in

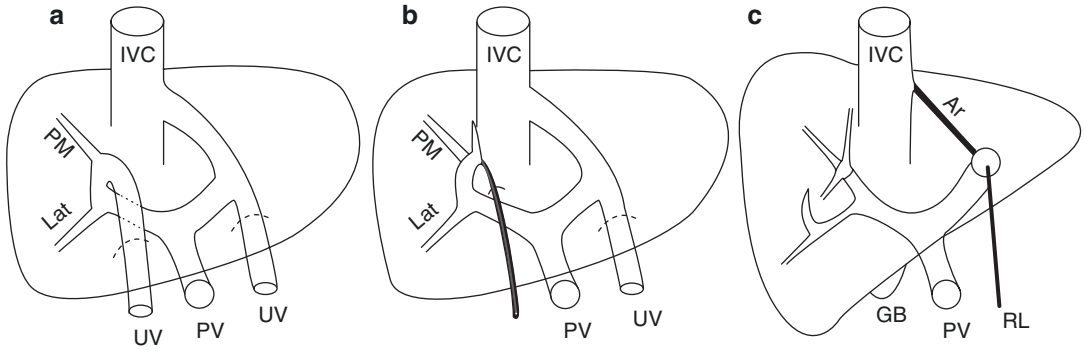

Fig. 1.6 Schematic representation of the development of the liver. (**a**) Two umbilical veins (UV) enter the right and the left portal vein (PV). (**b**) The right umbilical vein obliterates and the left umbilical vein remains. (**c**) The left umbilical vein obliterates and becomes the round ligament (RL), Arantius' canal obliterates into a ligament (AR). *PM* paramedian sector, *Lat* postero-lateral sector (modified with permission from Makuuchi Ann Surg 2013)

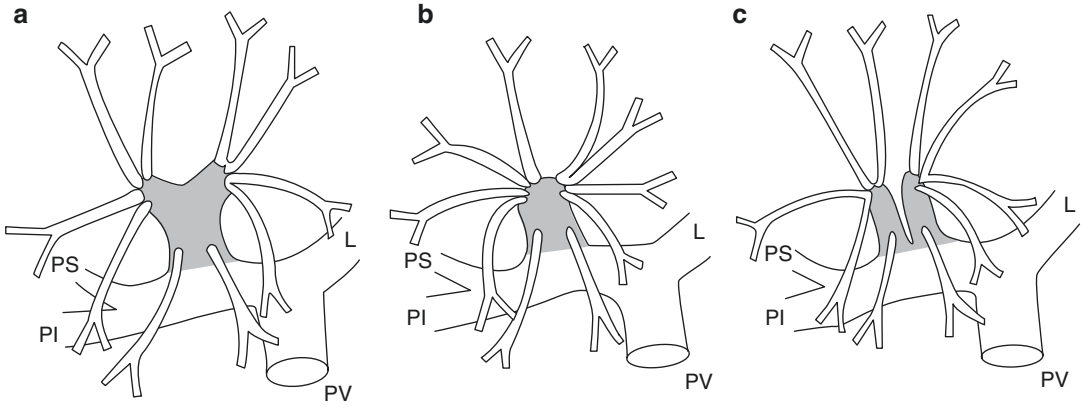

Fig. 1.7 Schematic representations of different patterns of the anterior sectorial branch (**a**, **b** and **c**), in cases where the remains of the right umbilical vein are more easily visible. The analogy with the branching of the left portal vein is obvious (reproduced with permission from Kogure Arch Surg 2002)

particular configurations (a) and (b), Fig. 1.8). In these cases, the surgeon can perform limited yet radical resections of territories in the anterior sector that keep the lateral branches of the traditional segments 5 and 8 well vascularized and drained by the right hepatic vein. The authors have performed, simply following the glissonean plane from the roof of the plate of the hilar bifurcation and ligating all the medial branches going to the left, some very satisfactory central hepatectomies, or resection of the posterior sector extended to part of the anterior sector and the right hepatic vein.

This situation, at least on the right, is well conceptualized by the representation of Hjörtsjö [4], where the right anterior sector is divided in a ventral and dorsal portion (Fig. 1.9). Hjörtsjö's representation also accounts for the apparently weird distribution of the segments of the left liver, in a symmetry and respect of the embryological development that can be developed further by the interested reader.

Similarly, central and lateral hepatectomies in the glissonean planes can be well conceptualized in the representation of Takasaki [11], where only three segments (+segment 1) are described (Fig. 1.10). In this representation, the left, middle, and lateral segment constitute approximately 30% of the liver each. We find Takasaki's representation more suitable for conceptualizing the larger hepatectomies needed for HCC in well-compensated cirrhotics than the finer resections that are needed in the surgery of liver metastases, in particular when multiple resections are needed.

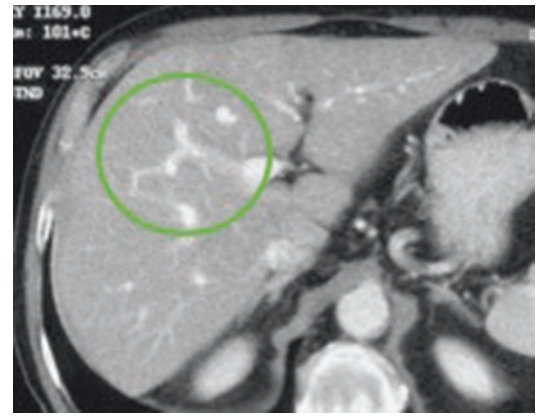

Fig. 1.8 CT scan of a patient in whom the similarity of the branching of the portal vein of Segment 5 (*green circle*) with the branching of the left portal vein can be recognized and exploited, for a resection of just the medial part of S5, leaving the lateral part intact. This case illustrates well the relevance of Hjörtsjö's representation.

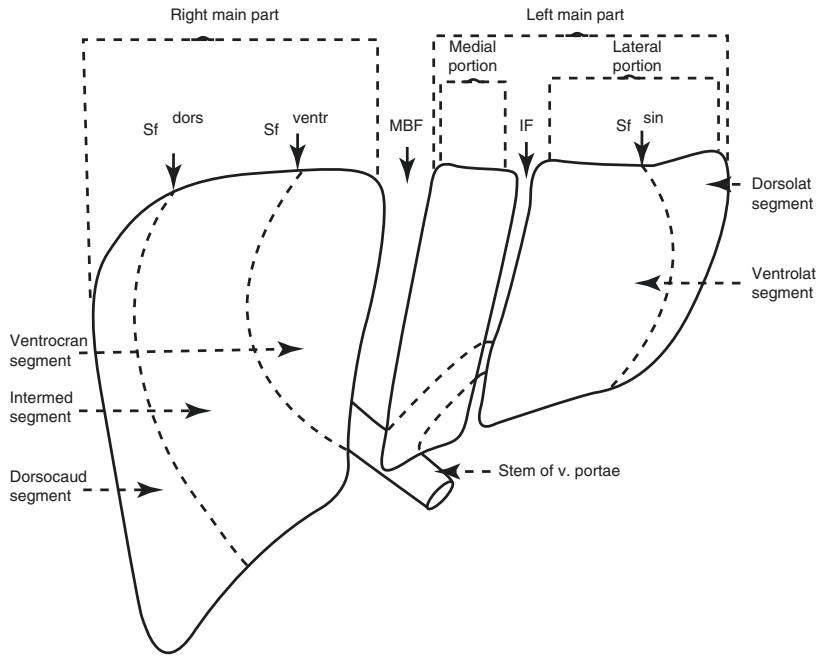

Fig. 1.9 Hjörtsjö's division of the liver into four portions (corresponding to Couinaud's sectors), each of which is divided into segments. This representation is interesting for conceptualizing the surgical anatomy of the anterior sector

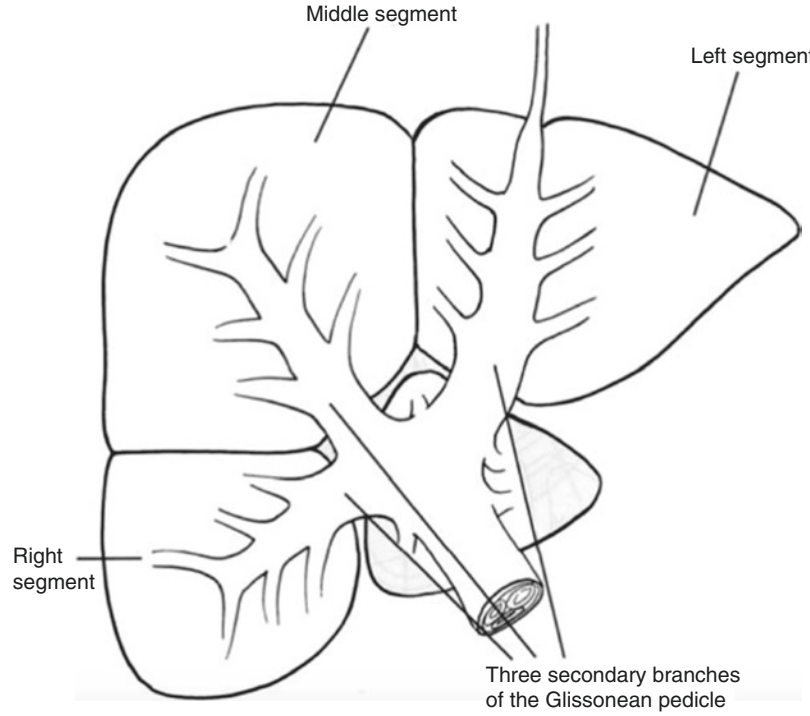

Fig. 1.10 Takasaki's representation, dividing the liver in three segments (+segment 1), separated by the three hepatic veins. This representation is particularly useful to guide resection in the intra-hepatic, extra-glissonean plane, or to perform central hepatectomies "pruning" the (secondary, in this case) branches medial or lateral to the main divisions of the portal vein

A More Independent Look at the Anatomies of the Liver

It appears from the above consideration that there is no unique representation of liver anatomy that satisfies all needs, and it is in fact the needs of the situation that have to guide the type of anatomical representation that is best used [8]. *For the localization of liver lesions*, the common language of the simplified Couinaud's scheme is unambiguous and consensual, and there is no necessity to change it. Besides, Couinaud's representation is useful to plot preoperatively all liver lesions that have to be found during the operation, a practice instituted by the authors in their units, on a chart such as the one in Fig. 1.11.

For the description of liver resections, we are probably in a period of transition, where the simple application of Couinaud's terms, based on a right liver and a left liver, and factually recognizing a morphological left lobe, is challenged by the Brisbane classification [12] that in our view has no appreciable added value (the new term, *section*, to define the left lobe is not useful nor does it have an embryological substrate). For the time being, we would simply describe the resection in terms of the Couinaud's segments that have been removed, cutting short any ambiguity.

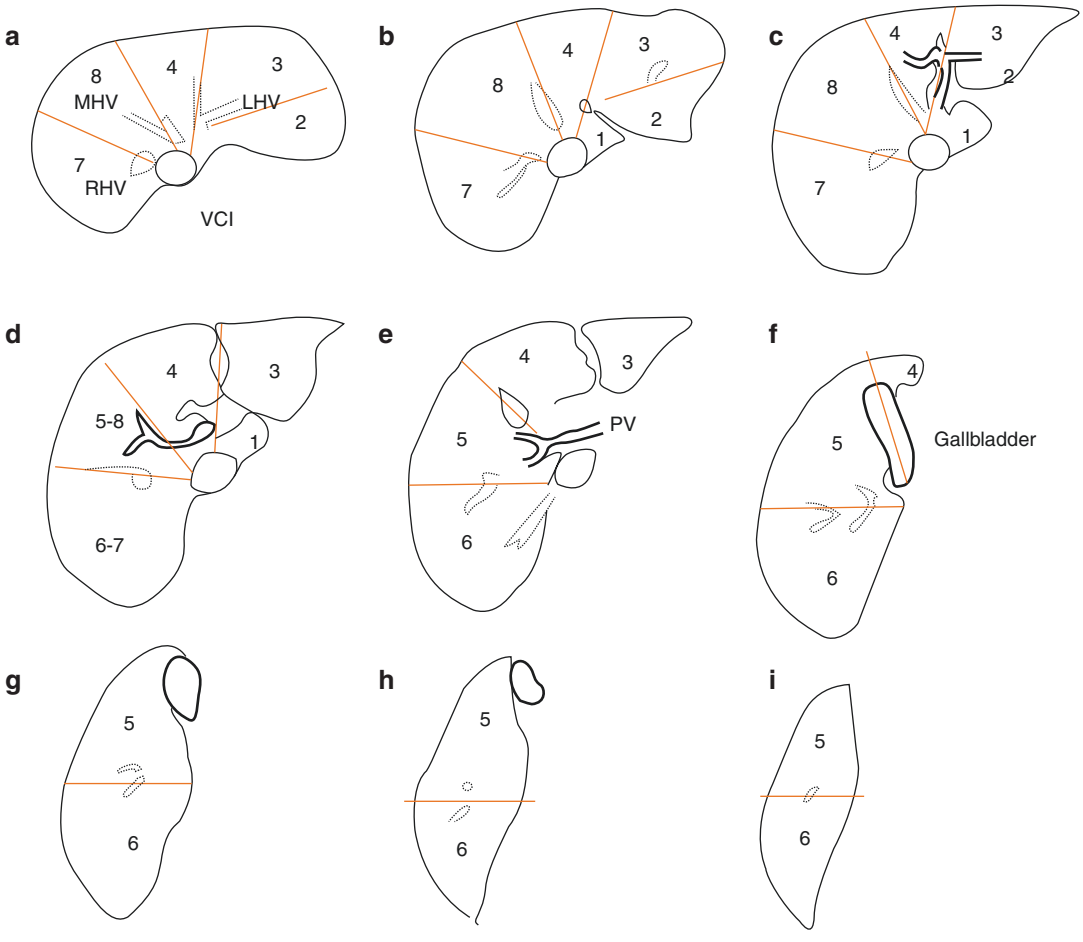

Fig. 1.11 Schematic chart with the main landmarks used for Couinaud's segmentation on different axial planes of the liver (**a** to **i**). Such a chart can be used to plot all the lesions that have to be identified during a liver resection. This particular model is freely available for download on the internet (www.compagnons-hb.org)

For the needs of advanced liver surgery, we anticipate that a freer approach based on the study of individual cases will turn out to be the most appropriate. This can be linked to the different representations of liver anatomy as illustrated above, but more importantly, to the real revolution that the transfer of radiological images from the radiology reporting room to the surgeons' laptop has started [13]. These new approaches have contributed to challenging the simplifications of Couinaud's scheme, and are indeed useful for the accurate planning of tailored territorial liver resections [8].

New radiological software, taking advantage of mathematical algorithms such as the nearest neighbor calculations, can depict the vascular territories with more precision and less prejudice than human-made segmentations, and are now commonly used in experienced units.

From the point of view of the anatomist, an unbiased view based on these models, on comparative anatomy and on mathematical analogies to other natural patterns such as fractals and crystals, can open new insights on the complexity of the liver. Representations that do not systematize the liver segments beyond the second order branches and leave the number of segments variable such as the 1-2-20 systems may offer the closest approximation to anatomical reality [14]. It is unlikely, however, that advances in this field will have short-term repercussions in surgical practice, where the preponderant need is a simple, reliable, and automatic segmentation starting from a standard axial imaging.

Surgical Anatomy and Anatomical Surgery of the Structures and Planes in the Liver

The above considerations on the surgical anatomy of the liver's vascular tree can be complemented by some comments on particular segments and structures of the liver, useful both for tailored territorial liver resections and for approaching lesions in awkward locations.

The Hilar Plate

The hilar plate is a layer of connective tissue that surrounds and accompanies the main liver vessels and bile ducts, separating them from the liver parenchyma. The denomination of this structure as a *plate* does not simplify its understanding. The plate is in fact a *tube* that surgical dissection can *transform* into a plate, when the surgeon opens the anterior peritoneum that in well-identified locations (listed below) constitutes the non-parenchymal side of this tube. This surgical transformation can take place only close to the central structures (Fig. 1.12), as follows:

- at the hilum (where it is possible to separate the portal vein, the hepatic arteries, and the bile ducts as far as the connective tissue joining them remains loose);
- on the right side once the gallbladder has been removed (exposing the vesicular, or gallbladder plate);
- on the left, when the peritoneum on the left pedicle is opened, exposing a transverse plate proximally and an umbilical plate more distally.

At the level of the biliary confluent, the bile duct can sometimes be separated from the hilar plate, but beyond this point the right and left hepatic bile ducts are contained in the tissue of the plate, and cannot be dissected from it. Also, it is generally not possible to dissect the portal vein and hepatic arteries beyond the bifurcation of the right portal branches, and beyond the umbilical portion of the left hepatic pedicle, as these vessels are completely encircled in the tube of connective tissue (here called the glissonean sheath), with no recognizable surgical plane (Fig. 1.12).

At the level of the umbilical portion of the portal vein, however, it is useful to distinguish three concentric planes, as illustrated in Fig. 1.13. These planes can be entered in the fat that surrounds the ventral side of the umbilical portion of the portal vein, and the left hilar plate can be unraveled to expose this structure from the inside,

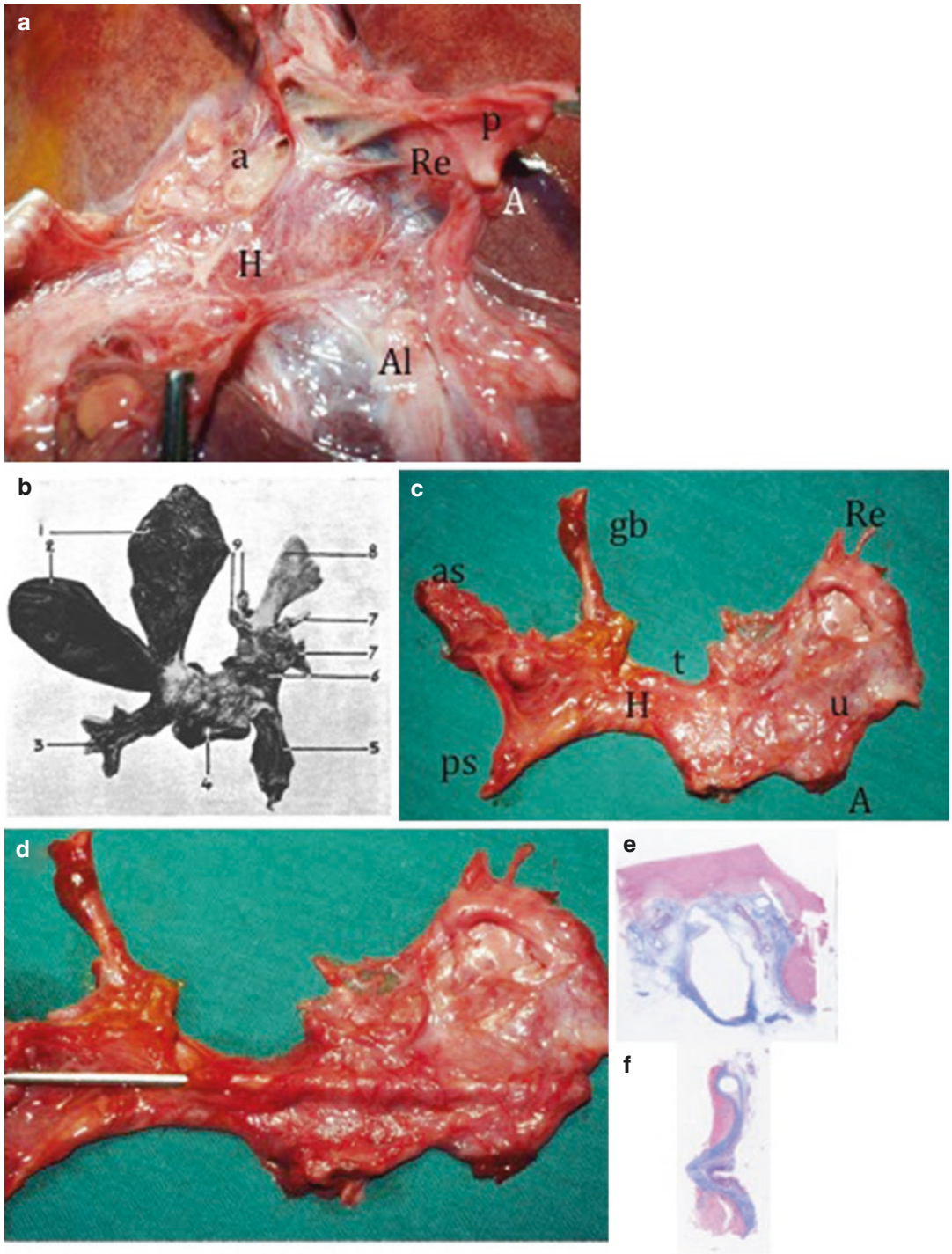

Fig. 1.12 (**a**) The hilar plate, in an anatomical dissections by the authors, after the portal vein, the hepatic artery and the common bile duct have been lifted and pulled to the left; (**b**) in the original illustration by Couinaud; (**c**) after removal of the portal vein, the hepatic artery and the parenchyma; (**d**) a probe enters the left bile duct, soon embedded into the plate in such a way that it cannot be dissected from it; (**e**, **f**) histological preparation of a transverse section at the hilum. The fibrous tissue is colored in *blue* and the liver parenchyma in *red*. It is obvious that the structure is a tube that can be prepared into a plate by dissection of the anterior peritoneal layer. The sheath is not symmetric, however, and the artery and the vein can be dissected from it as they are surrounded by loose connective tissue (courtesy of Prof. Laura Rubbia-Brandt, University of Geneva, Switzerland)

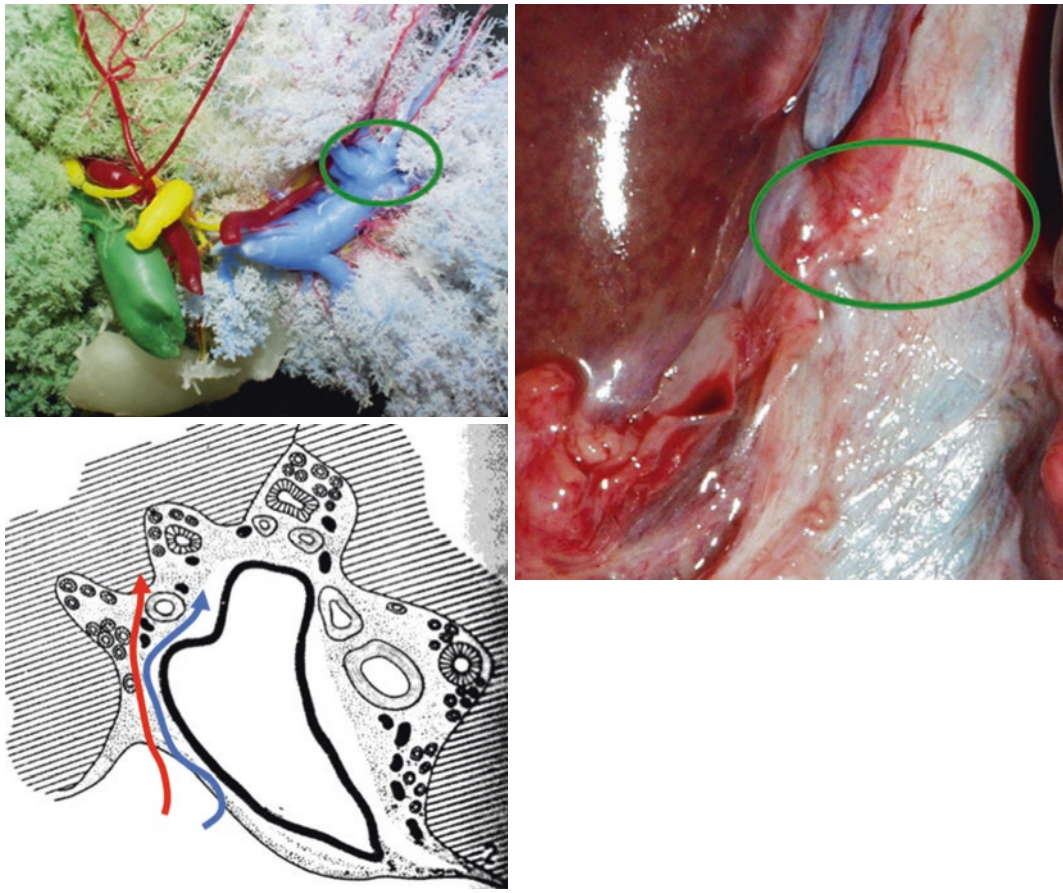

Fig. 1.13 The outermost layer is the one of the peritoneum anteriorly (*green oval*) and of the hilar plate posteriorly; the second layer is the one of the hepatic arteries (*red line*), and the third one of the portal vein (*blue line*)

to prepare it for the resection of Klatskin's tumors, or for the separation of metastases adhering to the hilar structures (Fig. 1.13).

Approaches to the Portal Pedicles

Clearly defined planes around the hilar plate (centrally) or the glissonean sheaths (beyond the second-order branches) can be found *within the liver parenchyma* (we say this to underline that when accessing these planes the surgeon has to enter frankly the liver tissue, rather than dissecting within a glissonean structure) at any level in the liver; the closer to the pedicle (once this has been identified from *within* the liver), the lower the chances of entering one of the hepatic veins, that in some locations run very close to the glissonean structures. The plane on the hilar plate can be entered, (generally with blunt dissection, such as the suction aspirator rather than with the tip of the ultrasonic dissector that can produce thermal injuries to the bile ducts) at the level of the portal bifurcation, to control the right or the left hepatic pedicles, or once the arterial and portal vessels have been dissected free and protected, for the transection of the bile ducts in the preparation of right or left liver grafts or when a the tumor close to the second order branches argues for a intra-hilar dissection rather than for a intrahepatic extra-glissonean approach for the control of the hepatic pedicles.

Also, the glissonean plane can be followed to expose and "prune" from the level of the portal

bifurcation the second or the third order branches to resect tumors in the anatomical, yet conservative approach detailed above, in particular for resections in segments 4, 5 and 8.

Arantius' Ligament

This is the remnant of Arantius' canal that takes the oxygenated blood from the left umbilical vein through the left portal vein to the right atrium in fetal life. Contrary to common belief, the ligament inserts not into the vena cava, but into the axilla between the middle and the left hepatic vein (Fig. 1.14). The ligament can then be isolated, pulled upwards and to the left, and used to separate the veins when the left hepatic vein has to be controlled [15]. On the portal side, cutting the origin of the ligament close to the portal vein (i.e., when the vein is freed from the umbilical and the transverse plate), is a key maneuver to gain length in the left portal vein or exposure in the umbilical plate (in Kasai's operation).

Approaches to the Hepatic Veins

An avascular plane can be generally be dissected between the vena cava and segment 1, from the infrahepatic side to the space between the right hepatic vein and the common trunk [16]. The control of the right hepatic vein is relatively straightforward, once the ligament that links the right and left side of segment 1 is cut (hepatocaval, or Makuuchi's

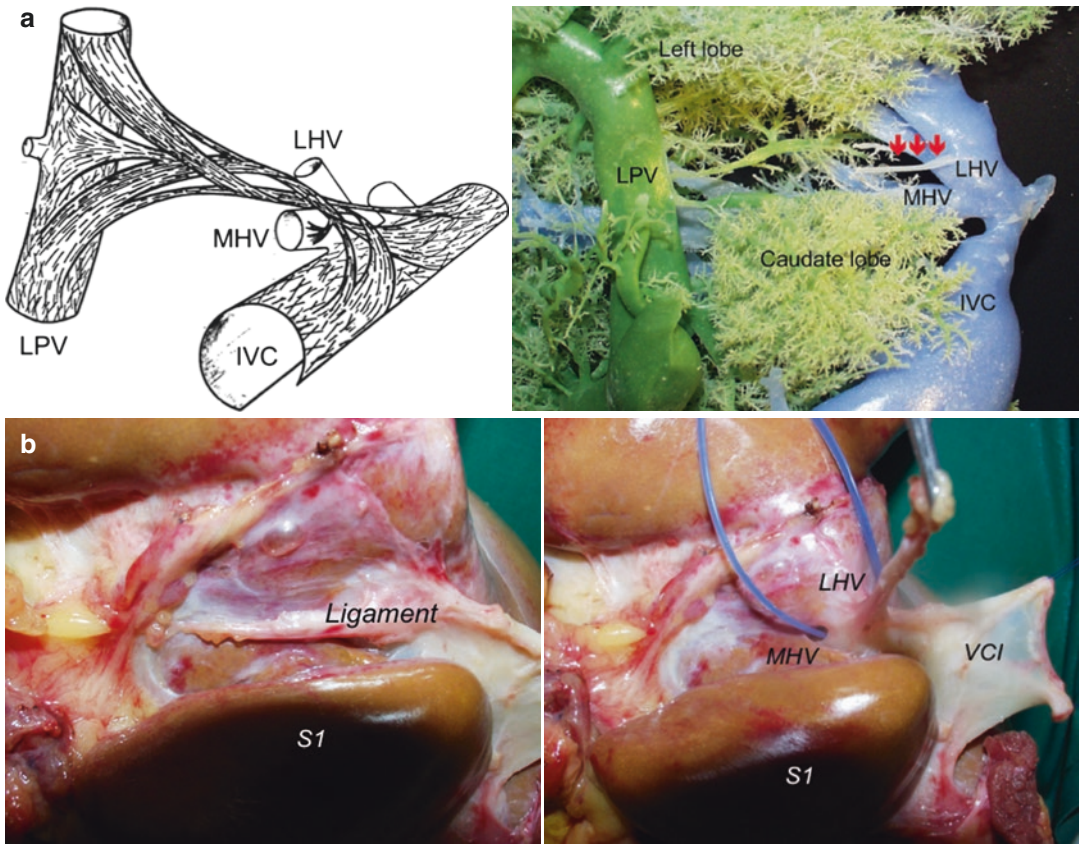

Fig. 1.14 (**a**) Corrosion cast showing the hepatic veins and a vestigial vein (the three red arrows) within Arantius's ligament inserting on the left hepatic vein; (**b**) Pulling on Arantius' ligament makes it possible to expose the passage between the left and the middle hepatic veins; in fact, this maneuver can be used to expose all the veins in the region (*left*, *middle* and *common* trunk), provided the right planes are entered

ligament), to expose a longer segment of the right hepatic vein and of vena cava on the right.

The control of the left hepatic vein using Arantius' ligament has been described above, and the only caveat is that sometimes there are two veins, and only one can be encircled, or that a large intermediate vein can be injured if the dissection from above and below is careless, or ultrasound has not been performed.

The access to the common trunk uses a different plane than the left hepatic vein, although traction on Arantius' ligament can also be used. The entry point on the left is accessed opening the peritoneum between the upper part of S1 and the vena cava (these entry points can be recognized in Fig. 1.14), and remaining close to the vena cava when a blunt right angle dissector is passed in this window to the angle between the common trunk and the right hepatic vein. The middle hepatic vein can be then controlled by passing the tape in the orifice between the middle and the left.

Hepatic veins can be used as hallmarks of some types of liver resections, and the position of liver tumors can require the surgeon to expose the wall of the veins over a considerable length. Japanese authors have underlined the "Christmas tree" shape of the hepatic venous architecture: brush-like strokes with the dissector, directed *against* the sense of the blood flow, make it less likely that the instruments will enter the vein, and the small openings made during such dissections can be easily repaired or left to seal off spontaneously. Also, despite the common belief to the contrary, the wall of the hepatic veins close to the caval side often has an adventitial layer that can be used to separate the tumor from the vessel, to increase or verify the resection margin (this favoured by a desmoplastic reaction that occurs when liver metastases compress the vessel, Prof. Laura Rubbia-

Brandt, department of pathology, University of Geneva) (Fig. 1.15).

Segment 1

The question of whether there are two identifiable sub-segments in segment 1 can be put aside, considering it a corollary in the discussion for the need of anatomical detail, and will not be taken further. Besides this point, there are three interesting surgical features to segment 1:

– There is a notch separating the right and the left part of segment 1: this notch corresponds to the plane where the posterior (retroportal) phase of a right hepatectomy should start, because this is where the transection surface is narrower, and because this corresponds to the watershed between the main branches of the portal and the hepatic vein [17] (Fig. 1.16).

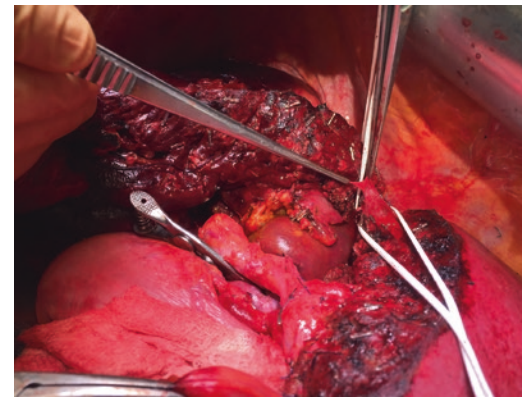

Fig. 1.15 Operative photograph of the denudation of the left hepatic vein. A fine adventitial layer can often be dissected in the wall of the vein, to increase the safety of the resection margin (courtesy of Prof. C. Toso)

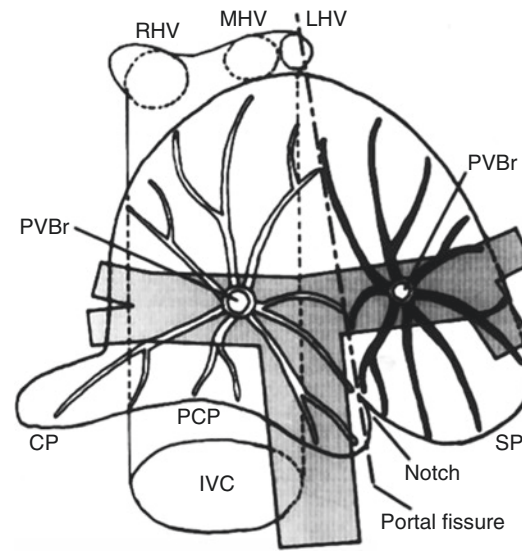

Fig. 1.16 Schematic representation of the anatomy of segment 1 (reproduced with permission from Kogure et al.)

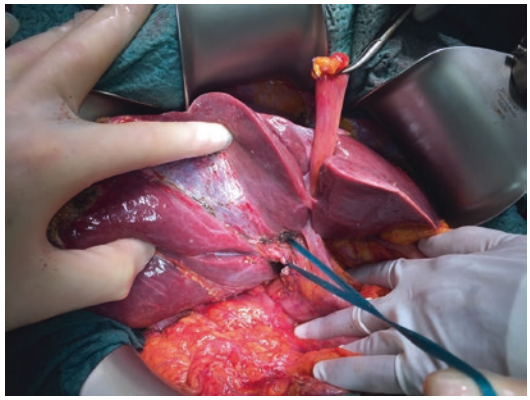

Fig. 1.17 Suprahilar control of the right hepatic pedicle

This notch corresponds to the exit point of a right-angle dissector passed for the suprahilar control of the right and the left hepatic pedicle, as explained above (Fig. 1.17).

– The hepatocaval ligament (Makuuchi's ligament) that has to be cut to expose safely the right hepatic vein during a right hepatectomy, is in fact a liver-to-liver ligament joining the right and left part of segment 1 behind the vena cava. A long tie can be left on it from the right, and retrieved from the left to start the separation of the dorsal part of Spigel's lobe.
– Arantius' ligament runs in a groove made by an extension of the umbilical plate, giving branches to segment 2 ventrally and segment 1 dorsally. The appropriate plane can be chosen to leave these structures intact on the side of the segment that is to be preserved.

Segment 8

There are relatively constant (sub-segmental) branches separating from the main segmental pedicle that continues *behind* the right hepatic vein, as in Fig. 1.18 (i.e., posteriorly and to the right, contrary to the schematic representation of Couinaud) [18]. This point has to be borne in mind when surgery exposing the right hepatic vein is performed (the surgeon relying on the discoloration of segment 8 can be led in the wrong plane, and resect the right hepatic vein, or reciprocally a disconnected part of S8 may be left in place).

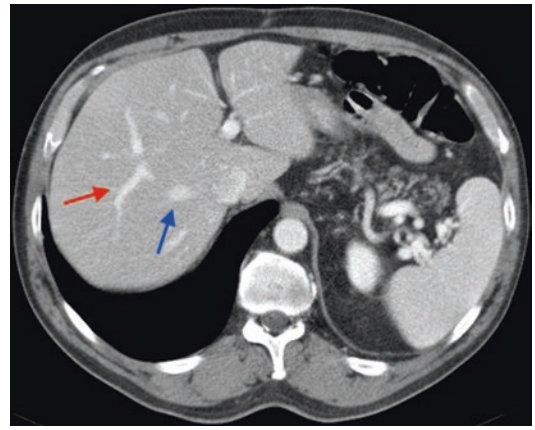

Fig. 1.18 CT scan at the level of the sub-segmental branches of S8. Branches from S8 (*red arrow*) extend behind the right hepatic vein (*blue arrow*)

Aknowledgement PM is indebted to Prof. Jean H. D. Fasel, Professor of Anatomy at the Universtity of Geneva, for transmitting his unprejudiced view on the discrepancies between the real liver anatomy and the theoretical anatomy of Couinaud, and for introducing him on the 1-2-20 concept of hepatic segmentation.

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Resectability Assessment with Diagnostic Imaging

2

Anthe Sterkenburg, Jan Müller, Marc-André Weber, and Peter Schemmer

Introduction

Colorectal cancer is the third most common cancer [1]. Up to 70% of patients develop distant metastases during the progress of the disease, most commonly located in the liver; in 30–40% of these patients, the metastatic spread is confined to the liver [2]. Without treatment, the median survival of colorectal liver metastases (CLM) is 6–8 months [3].

Liver resection is still a major pillar in the multidisciplinary treatment for CLM, and can increase the 5-year survival rate from 3.3 to 6.1% in patients without treatment, and up to 50–60% in patients undergoing curative liver resection for CLM [4, 5]. CLMs are resectable in about 20–30% of cases.

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Selection of Patients

About two-thirds of the patients still suffer from recurrences after resection of CLM. Since hepatic resection is still considered to be a major abdominal procedure which requires general anesthesia, careful patient selection is important. Several prognostic scoring systems have been used to predict the feasibility of hepatic resection of CLM and the factors that influence mortality after hepatectomy. The most important factors are the preoperative CEA serum level, the time that has passed between treatment of the primary colorectal tumor and discovery of the hepatic metastasis, the number of metastases, lymphatic spread, the size of the largest metastasis, and resection margin [6]. One of the most frequently used scoring systems is the clinical risk score (CRS) developed by Fong et al. [7]. This system categorizes patients into ‘low risk’ and ‘high risk’ groups for disease recurrence, with low-scoring patients having an overall median survival of 74 months and high-scoring patients having an overall median survival of 22 months.

The impact of age on the prognosis is still under discussion. The American College of Surgeons National Surgical Quality Improvement Program found that elderly patients are more prone to severe complications, and the difficulties in recovering from these often lead to an

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increased post-operative mortality rate [8]. This could be overcome, though, by careful postoperative planning and more intensive post-operative care.

Even with this scoring system, patients with CLM are not always identified and offered surgery with curative intent [9]. A significant number of tumors appear resectable in the retrospective evaluation of CT images performed by dedicated liver surgeons in a patient group treated with systemic, palliative regimens for CLM [10].

Patients with resectable CLM have a better prognosis when they undergo surgery than patients with resectable CLM who undergo systemic therapy. After liver resection, significantly longer overall survival (median, 56 months) was observed in the first group when compared to those undergoing treatment with systemic therapy for retrospectively resectable liver metastases (median, 27 months) [10]. It is therefore important to identify the patients with resectable CLM who would benefit from liver resection.

Several programs have been developed to help health-care professionals less experienced with the possibilities in hepatic surgery with their decision-making. Computer programs, such as Met-Assist and Oncosurge, give advice on treatment options based on the professional judgment of highly experienced surgeons [9, 11]. This program combines CT-imaging data sets with other prognostic factors.

But even when a group of highly experienced hepatic surgeons are asked to predict resectability based on CT-images alone, a lack of agreement can be seen in up to 50% of cases [12]. Hence, good preoperative imaging is crucial in the assessment of the resectability of CLM.

Assessment of Resectability Based on Imaging

Liver surgery assessment for resectability of CLM has changed rapidly over the past years, as more and more CLMs are assumed to be resectable. The current local requirements for resection is the ability to achieve a R0-situation via full resection of the metastases while maintaining adequate future liver remnant (FLR) with adequate perfusion and biliary drainage in order to keep appropriate liver function capacity [4]. The ability to predict the FLR is crucial, since the main factor for postoperative liver failure is a FLR that is unable to maintain hepatic function [13]. The required FLR is dependent on the preoperative synthetic capacity of the hepatic parenchyma. An otherwise healthy liver can be reduced to 30% capacity, whereas a liver that has developed injury, e.g., due to chemotherapy or cirrhosis, needs more FLR in order to maintain sufficient hepatic function [14]. Through preoperative portal vein embolization (PVE), first described by Makuuchi et al. [15], the FLR after resection can be increased. PVE induces atrophy of the ipsilateral hepatic lobe and compensatory hypertrophy of the contralateral lobe; it also increases the resectability rate of CLM, and leads to higher survival rates when compared to treatment using systemic therapy [16]. After resection, though, the remaining liver function does not increase linearly with the increase of FLR via PVE, and one should keep in mind that the liver function can still be insufficient.

The localization of CLM near important vascular structures, like the hepato–venous confluence or the inferior vena cava, greatly decreases resectability. To make careful preparation and vascular reconstruction possible without causing long warm ischemia times, ante situm liver resection has been developed. During this procedure, the hepatic veins are excised to enable mobilization of the liver. The infra- and supra-hepatic vena cava are cross-clamped, while a 4 °C cold preservation solution is perfused into the portal vein and drained through an incision of the infra- or supra-hepatic vena cava. After parenchymal resection, the hepatic veins are reconstructed. Through this technique, the cellular metabolism is slowed down by the induced hypothermia, which in turn allows for enough time to achieve precise resection and vascular reconstruction [17].

The resection margin has been under discussion for a long time, but the previously preferred margin of at least 1 cm seems to be of less importance nowadays. Even when the preoperatively predicted margin is greater than 1 cm, the number

of hepatic recurrences in CLM remains high, often making a second resection necessary [4]. It therefore seems more important to leave a sufficient FLR in order to make a necessary second resection possible.

Extrahepatic disease used to be one of the main factors of irresectability, but this has also changed over recent years. When colorectal cancer spreads to the lungs and resection of both lung metastases as well as CLM is possible, these are no longer considered to be definite contraindications for hepatic resection, since the impact of the hepatic lesion on survival is more significant than the impact of the lung metastases. Resection of the hepatic lesion should only be considered, however, when the extra-hepatic metastasis is surgically resectable or controllable via adjuvant therapies [18].

In small metastases, laparoscopic surgery could be a good surgical approach because it is associated with decreased blood loss and pain, lower overall complications, and a shorter hospital stay. In small hepatic lesions, the long-term survival for laparoscopic surgery is similar to that of the open surgical approach [19].

Imaging

The goal of preoperative imaging in CLM is to determine both the location and extent of the metastatic disease, as well as to describe the relation to critical structures for the surgeon. The surgical approach can be planned with consideration for tumor involvement in the hepatic inflow (artery and portal vein), the outflow (liver veins), and the resulting FLR. Further, extra-hepatic disease should be identified and assessed for optimal planning of multimodal treatment.

Regardless of the imaging technique used, some anatomical and physiological characteristics of the liver are relevant for imaging. The portal vein accounts for 75–80% of the blood supply to the liver, whereas the hepatic artery is responsible for the remaining 20–25%. Malignant lesions are almost exclusively supplied by the hepatic artery and, due to their vascular anatomy, tend to result in rapid rinsing of the contrast medium. In contrast-enhanced imaging, such as CT and MRI, malignant lesions show little contrast enhancement during the portal-venous phase. The hepatic parenchyma, however, shows the most enhancement during the portal-venous phase and the least during the hepatic arterial phase. This ultimately leads to a maximum contrast between liver and hepatic tissues during the portal-venous phase [20].

Ultrasound

Ultrasound imaging is a quick, non-invasive imaging modality which is particularly useful for the screening of patients with suspected CLM, and as a guideline for the biopsy of hepatic lesions. Ultrasound can also be used for distinguishing between patients with diffuse hepatic metastases who cannot receive hepatic resection, and patients with metastases that are only small in size and number or confined to a specific part of the liver; the latter could be potential candidates for curative resection [2]. The CLMs often appear as hypo-echoic lesions on ultrasound imaging; however, they may have the same echogenicity as normal liver parenchyma and may be recognized by the presence of a halo-sign, i.e., a peripheral zone with low echogenicity (Fig. 2.1). Sometimes, a bull's eye appearance—due to central necrosis or a target-type lesion resulting from regressive changes—may be observed [21].

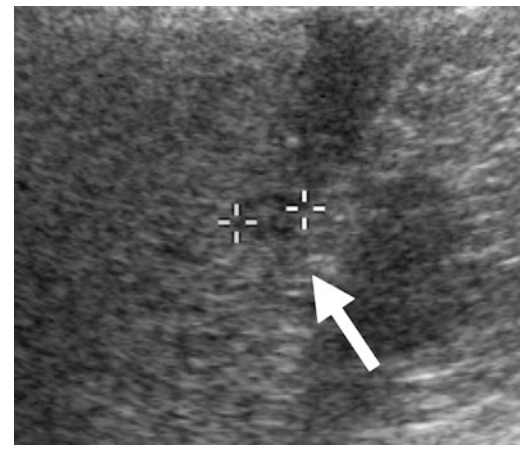

Fig. 2.1 Ultrasound (B-mode) of a CLM with a hypoechoic rim referred to as "halo-sign" (*arrow*)

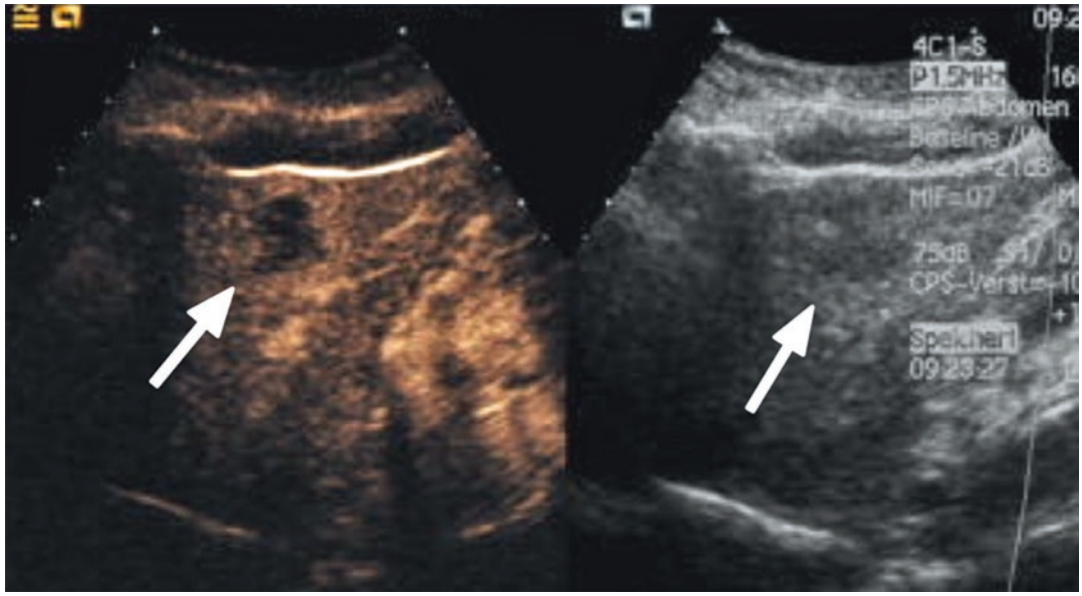

Fig. 2.2 CEUS [left image, Cadence™ contrast pulse sequencing (CPS) technology] of a CLM in the left liver lobe demonstrating peripheral and irregular central vascularization (*open arrow* pointing to peripheral microbubble accumulation within the lesion), the right image is the corresponding B-mode ultrasound image (*arrows*)

The use of contrast media improves the detection and characterization of hepatic lesions, and makes the differentiation between benign and malignant lesions more accurate; in particular, smaller and more numerous metastases can be detected by contrast-enhanced ultrasound (CEUS) in comparison to unenhanced CT [22, 23]. In CEUS, the arterial phase typically shows irregular tumor vessels and a wash-out pattern in the portal venous or late phase [23] (Fig. 2.2).

One of the largest disadvantages of ultrasound is the fact that the accuracy is highly user-dependent. Furthermore, it is hard to differentiate between hepatic fatty infiltration due to chemotherapy and malignant lesions. Patients who could be candidates for hepatic resection based on ultrasound imaging require further imaging in order to determine the appropriate therapeutic options.

Intraoperative ultrasound (IOUS) is standard procedure, and can be utilized to detect new lesions not seen during preoperative imaging; thus, it is useful for intraoperative staging and planning. Patients with multiple hepatic lesions benefit greatly from IOUS, since it is associated with higher detection rates for lesions that would have been otherwise missed via preoperative imaging. Contrast-enhanced ultrasound uses contrast not toxic to the liver, kidneys, or heart, and permits real-time visualization of the parenchymal micro-vasculature in order to aid in the planning of the resection. It can be used to identify small metastases that would have been overlooked during preoperative imaging, for example, in chemotherapy-induced parenchymal injury [24]. CE-IOUS is more sensitive than CT and MRI in detecting liver metastases, and can influence surgical management through the discovery of additional metastases, fewer metastases, benign lesions being wrongly diagnosed as metastases, and the vascular proximity to the tumor [25]. However, CE-IOUS is of no use in the preoperative surgical planning stage and is highly limited when applied to cases concerning liver steatosis and fibrosis.

CT

In a recent study, in which an unselected patient cohort and multiphase multi-detector row computed tomography (MDCT) were utilized, CEUS was shown to be significantly inferior to MDCT in the preoperative detection of hepatic metastases of colorectal cancer [26]. Generally, CT is a fast and relatively inexpensive imaging technique; its performance has been significantly improved

with the development of helical CT and MDCT. This increases the speed, acquisition, and resolution, thus enabling imaging of the liver during various phases of contrast enhancement. During a single breath-hold, imaging of the entire breast and abdomen can take place, thereby eliminating respiratory motion artifacts [20]. On the other hand, MDCT is considered to be the imaging modality of choice in CLM. MDCT can generate slices of the liver with a thickness of less than 1 mm, subsequently enabling high-quality reformatted multi-planar (MPR) and volumetric three-dimensional (3D VR) reconstructions [21]. These reconstructions demonstrate the main features of the CLM such as size, margin, and relationship with the vascular and biliary structure, as well as the remaining liver volume.

Intravenous iodinated contrast media can be used to help characterize hepatic lesions based on their enhancement patterns during different phases of contrast circulation in the liver [3, 27]. Early in the arterial phase, the hepatic arterial anatomy can be visualized, which is useful for surgical planning, whereas hyper-vascular lesions tend to show more degrees of enhancement when compared to the surrounding hepatic parenchyma during the late arterial phase. Hypo-vascular lesions, such as CLM, become more pronounced during the portal-venous phase (Fig. 2.3). Through vascular reconstruction, the hepatic arterial and portal-venous anatomy can be visualized, thus eliminating the need for conventional angiography for the surgical planning [20].

In CT scanning with arterioportography (CTAP), the contrast agent is injected into either the superior mesenteric artery or the splenic artery via a percutaneously placed catheter. Only the liver parenchyma is contrast-enhanced (as in the portal phase), due to the fact that metastases are almost solely perfused by the hepatic artery. This technique is superior to other imaging techniques in the detection of lesions smaller than 2 cm, but the specificity is relatively low and false-positive findings should be identified. In practice, CTAP currently does not play a role in the diagnostic work-up of liver metastases.

The limitations of contrast-enhanced CT are the increased risk of radiation exposure (especially when several contrast phases are acquired), possible allergic reactions to the contrast media utilized, and low sensitivity for lesions smaller than 1 cm. Furthermore, the presence of fatty liver, which often occurs after chemotherapy, decreases the sensitivity and specificity of CT.

The FLR can be calculated by CT-imaging. With the help of software programs, the proposed line of resection can be drawn and the remaining liver volume calculated as a percentage of the whole liver volume. The regenerative capacity of the liver can be determined by the assessment of the hepatic response to portal vein embolization (PVE). The hepatic volume is measured via CT-imaging before

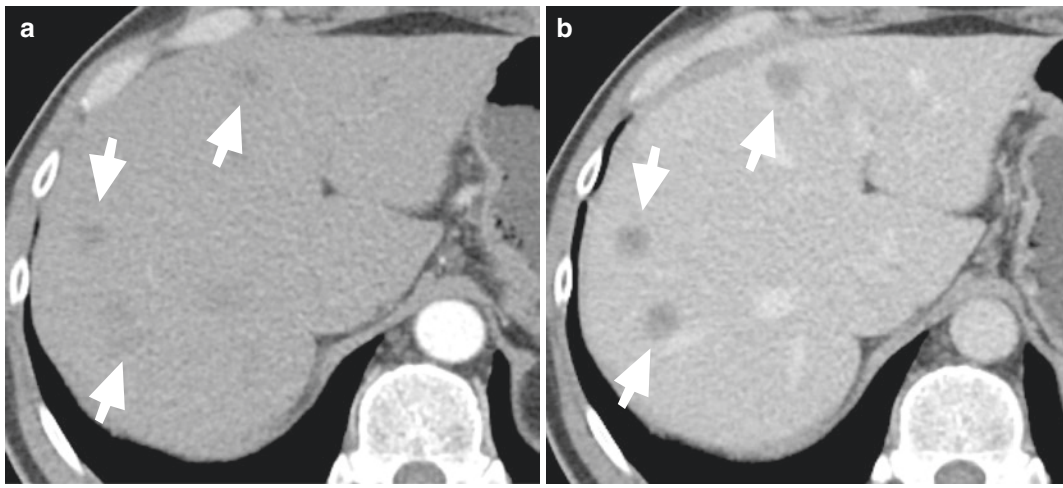

Fig. 2.3 CT of CLMs in arterial (**a**) and portal-venous phase (**b**). Due to the hypovascularity of CLMs portal-venous phase provides the best imaging contrast for lesion detection (*arrows*)

and 3 weeks after PVE. The occurrence of a minimum of 5% hypertrophy of the liver within these 3 weeks is considered acceptable. In the case of reduced hypertrophy, the FLR should be larger in order to maintain adequate liver function after resection [4]. This could be the case in hepatic cirrhosis or chemotherapy-induced injury. In incidents of underlying hepatic disease, the hepatic function can be further determined via indocyanine green clearance or lidocaine conversion tests [28].

MRI

In many studies, MRI has been found to have the greatest sensitivity and specificity when compared to FDG-PET and CT [29]. MRI uses the vastly differing properties of water and fat to generate images based on the proportion of these in normal and pathological tissue. It can provide greater liver-to-lesion contrast without the need for radiation and detects smaller lesions due to the lower resolution of the images. With faster imaging sequences, like T1-weighted spoiled gradient echo and T2-weighted turbo spin echo, image acquisition of the entire liver can take place in a single breath-hold, thus limiting motion artifacts. In T1-weighted images, CLMs have low signal intensity, with a central area of even lower intensity (doughnut sign); these sequences are mainly useful for the assessment of parenchymal fatty infiltration (Fig. 2.4a). In T2-images, CLMs have intermediate to high signal intensity, making these sequences useful for the differentiation between solid and non-solid lesions (Fig. 2.4b).

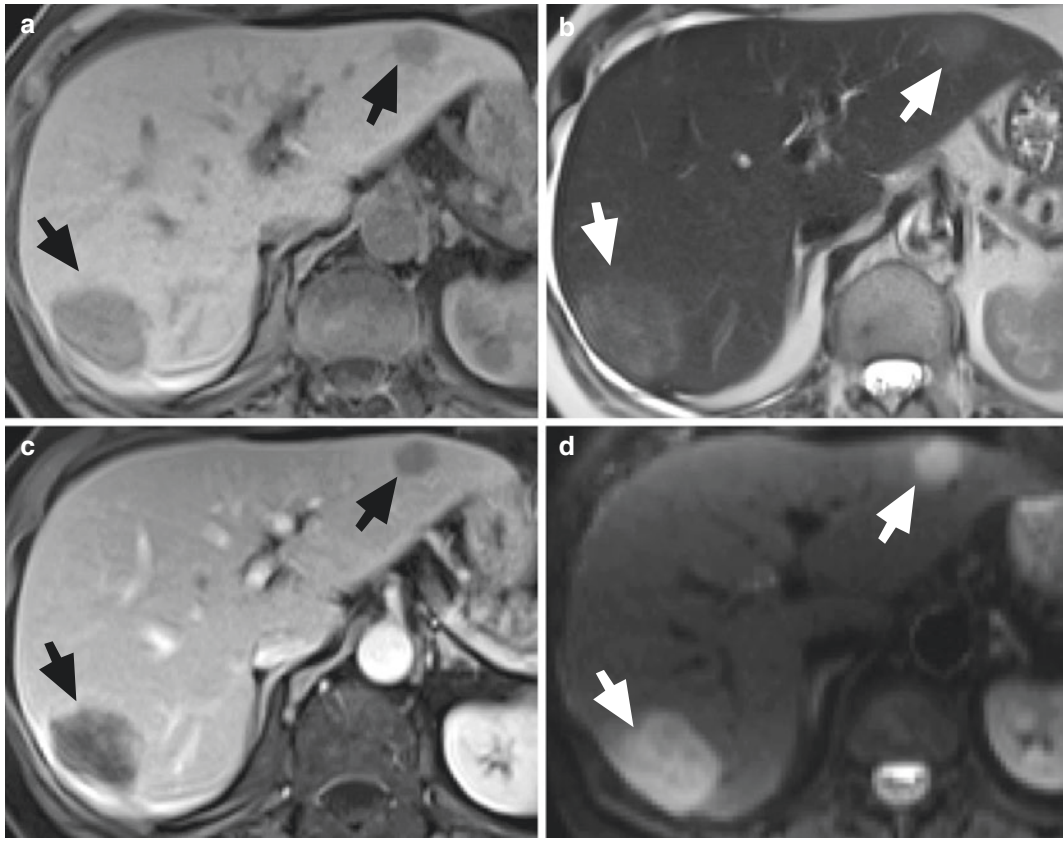

Fig. 2.4 MRI of bilobar CLMs (*arrows*). (**a**) T1-weighted: hypointense to surrounding liver parenchyma. (**b**) T2-weighted: slightly hyperintense signal. (**c**) portal-venous contrast with gadolinium: low heterogeneous lesion enhancement. (**d**) DWI: markedly hyperintense signal as sign for hypercellularity

The addition of diffusion-weighted imaging (DWI) to MRI improves the detection of CLM smaller than 1 cm, especially in unenhanced MRI examinations. DWI prevalently increases specificity/negative predictive value in gadoxetate disodium (Gd-EOB-DTPA)-enhanced examinations [30]. The technique uses the Brownian motion of water in tissues: the random movement of water which is modified by numerous interactions with intracellular organelles, cellular membranes, and macromolecules. Any architectural changes in tissues, such as the increased cellularity commonly seen in tumor tissue, can restrict the Brownian motion [31]. These changes in motion can be quantified by the calculation of the apparent diffusion coefficient (ADC), where the ADC is inversely correlated to the tumor cellularity [21] (Fig. 2.4d). Nowadays, these sequences are routinely used for MRI of the liver in many centers.

Contrast-enhanced MRI is equally as sensitive as CTAP, however, it has the advantage of the occurrence of fewer false positive findings [20]. Two types of contrast media are used in MRI: extra-cellular media and tissue-specific media. The most often used extra-cellular media are paramagnetic chelates of gadolinium. In the delayed arterial phase, CLMs have a cauliflower-like appearance with intense peripheral enhancement. Gadolinium-based contrast media are excreted by the kidneys, and may cause acute renal reactions such as contrast-induced nephropathy or (on rare occasions) nephrogenic systemic fibrosis, especially when macrocyclic gadolinium-chelates are used [32]. Therefore, the glomerular filtration rate should be taken into account when considering the administration of gadolinium contrast media [21]. Guidelines provided by the European Society of Urogenital Radiology are readily available [33].

The tissue-specific contrast media, superparamagnetic iron oxide (SPIO), is selectively absorbed by the reticulo-endothelial system of the normal liver parenchyma, spleen, and lymph nodes. There is a shortening of the T2 relaxation time, thus decreasing signal intensity in the liver parenchyma. Since malignant lesions almost completely lack a reticulo-endothelial system, the CLMs appear as high signal lesions in T2-weighted images. This is a highly sensitive method for small focal liver lesions [27, 34, 35]. The infusion time of SPIO is relatively long (30 min), which in turn prolongs the study time and is associated with side-effects such as lower back pain and hypotension. Given this, the use of SPIO for liver imaging has decreased in popularity during the last years.

Godobenate dimeglumine (gd-BOPTA) is a contrast medium which combines the properties of an extra-cellular agent and a tissue-specific agent, therefore making both dynamic imaging and delayed phase imaging possible. Whereas dynamic phase imaging is important for lesion characterization, delayed phase imaging can increase the sensitivity. Even though sensitivity may not be as high as SPIO-MRI, the tumor characterization is more specific, which is especially important in cases with both benign and malignant lesions [20].

Another contrast agent is gadoxetate disodium (Gd-EOB-DTPA), which makes a comprehensive evaluation of the liver with the acquisition of both dynamic and hepatocyte phase images possible. This can potentially provide additional information that could be useful in the detection and characterization of small liver lesions [36]. A growing number of articles in the literature have demonstrated the usefulness of the hepatobiliary-specific MRI contrast agent, Gd-EOB-DTPA, in liver imaging. When using Gd-EOB-DTPA, there is no contrast-agent uptake in the liver-specific late phase of the metastases; instead, they appear distinctly hypo-intense and thus often enable reliable delineation from normal liver parenchyma [37]. In a recent study, significantly more patients with CLM in the Gd-EOB-DTPA-MRI group were considered to be eligible for surgery (39.3% vs 31.0%), and 26.7% for MRI with standard extra-cellular contrast-media and contrast-enhanced MDCT

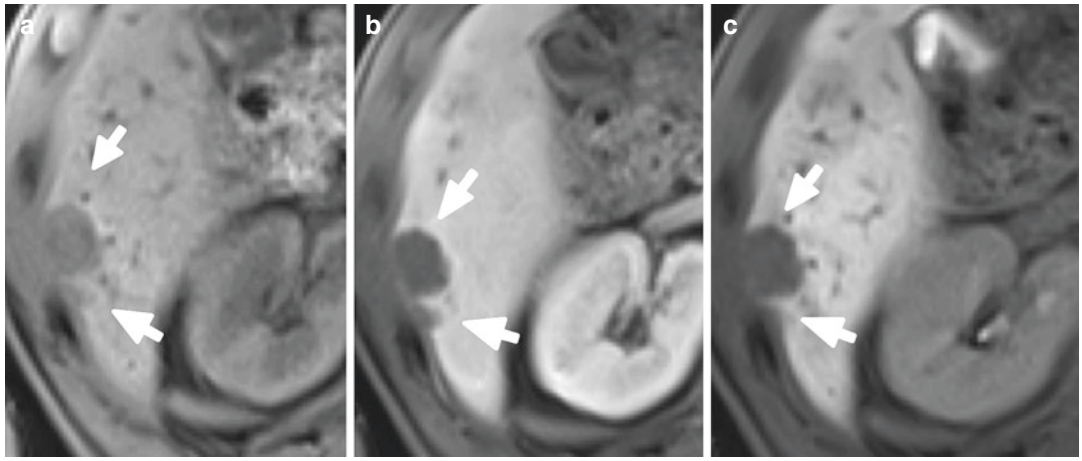

Fig. 2.5 Two adjacent CLMs in liver segment VI (*arrows*). (**a**) Hypointense signal in unenhanced T1w MRI. No contrast uptake 60 s (**b**) and 10 min (**c**) after administration of gadoxetate disodium. Hepatobiliary phase (**c**) reveals extrahapetic origin of the lesion

[38]. MRI has low sensitivity for extra-hepatic lesions, for example in the peritoneum and chest; it could therefore be used for the evaluation of small, unclear liver lesions detected on CT or in patients with allergies to iodinated contrast agents. MRI requires relatively more compliance from the patient, such as commands for inhalation and longer periods of lying still. Patients who are unable to hold their breath for more than 15 s are usually poor candidates for MRI (Fig. 2.5).

FGD-PET

FDG-PET uses the increased glucose metabolism in tumor cells (the Warburg effect), where a radioactive tracer is accumulated in cells with increased hypermetabolism. Since metabolic abnormalities usually precede anatomical changes in malignant tumors, FDG-PET improves early detection of CLM. Furthermore, FDG-PET can be used to search the entire body for the presence of early signs of extra-hepatic disease such as peritoneal metastases and lymph node involvement before liver surgery [34]. In a meta-analysis, the use of FDG-PET was shown to affect clinical management through the detection of additional liver metastases and/or extra-hepatic disease, mostly resulting in the switch from the intended curative surgery to a palliative treatment course. Nonetheless, the survival rate tended not to differ between the patients selected for surgery with and without FDG-PET [39] (Fig. 2.6).

On its own, liver parenchyma has a high metabolic activity, thus making it hard to distinguish small hepatic metastases from normal liver tissue. The sensitivity of FDG-PET is further reduced after neo-adjuvant treatment due to size reduction of the hepatic lesion and the reduction in metabolic activity of the remaining tumor tissue [39]. Furthermore, FDG-PET is unable to provide precise anatomical localization of the detected lesion. On a positive note, this limitation has been overcome with the advent of PET/CT and, more recently, PET/MRI hybrid-imaging modalities.

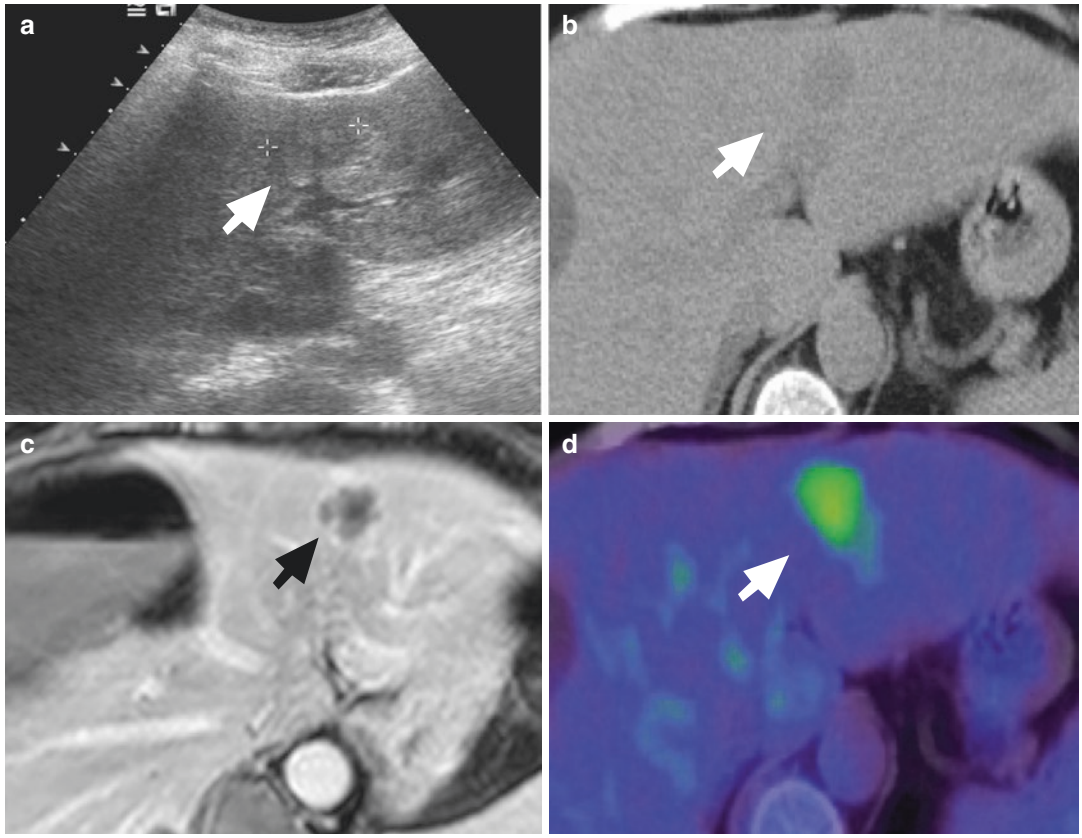

Fig. 2.6 The same CLM in different imaging modalities (*arrow*). Inhomogenous hypoechogenity in US (**a**). Hypodense to surrounding liver in unenhanced CT (**b**). Irregular vascularity in contrast-enhanced MRI (**c**). Strong FDG-uptake in PET-CT (**d**)

The combination of FDG-PET with CT allows for more accurate localization of the areas with increased metabolism, and improves the distinction between a physiological and pathological FDG-uptake (Fig. 2.7).

Due to the high costs and additional radiation exposure, FDG-PET/CT should be reserved for selected patients with a high risk of occult extrahepatic disease [11]. Furthermore, FDG-PET/CT can play a valuable role in the identification of the primary tumor, the follow-up after resection (in terms of detection of local or distant recurrence of the disease) and the monitoring of the tumor's response to therapy [21].

The combination of FDG-PET with MRI marries the detection of small lesions by MRI with the ability to visualize enhanced metabolism at the ablation site; this translates to possible improvements in the precise and early detection of progressive diseases. At present, there is insufficient data on the accuracy of this combined modality, since the hybrid devices needed are still rarely used [21]. A recent study reports that PET/MRI (including DWI) is comparable to PET/CT for the evaluation of colorectal cancer metastases, with a markedly higher accuracy when using combined imaging data than that obtained when both modalities are utilized separately [40].

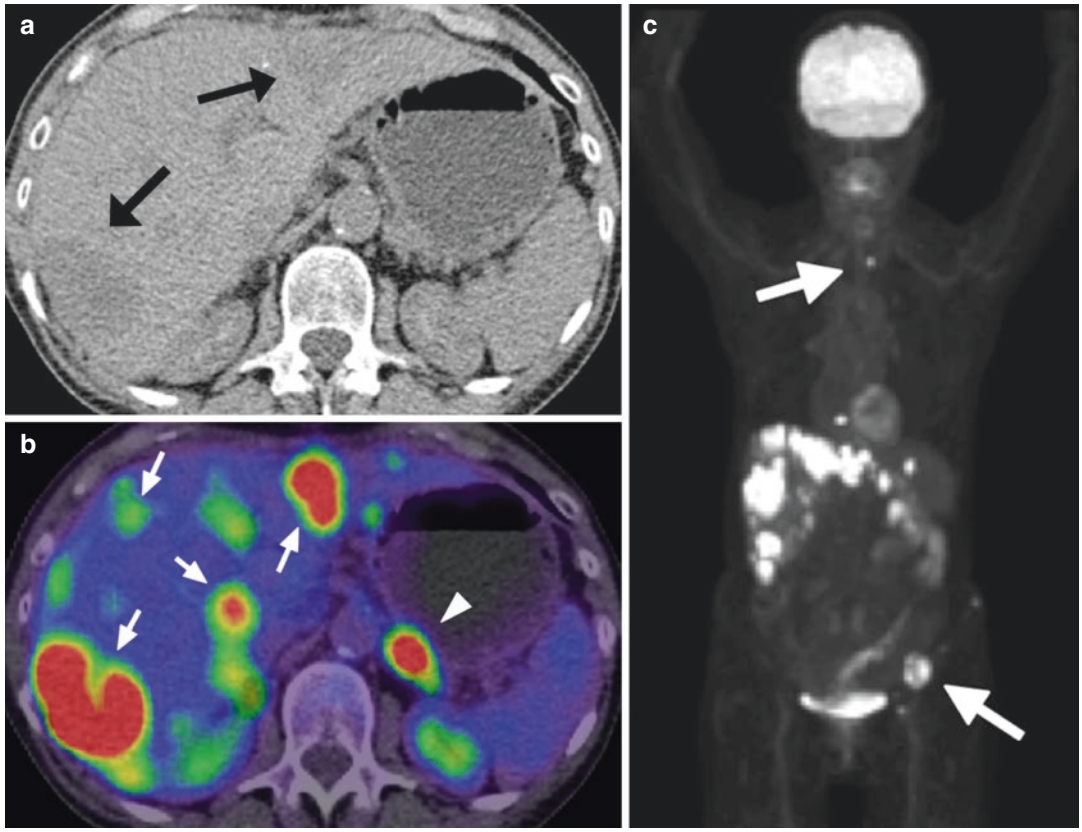

Fig. 2.7 Multiple CLMs (*arrows*) hypodense to surrounding liver in unenhanced CT (**a**). FDG-PET-CT (**b**) better demonstrates the true extent of disease due to strong lesion uptake, including disseminated liver metastasis (*arrows*) and metastasis of left adrenal gland (*arrowhead*). MIP (**c**) further visualizes bone metastases in the thoracic spine and left acetabulum (*arrows*)

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Preoperative Evaluation of Liver Function

3

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Introduction

Surgical treatment remains the only potentially curative treatment option for patients diagnosed with colorectal liver metastases. Hepatic resection has become more aggressive in the last decade, resulting in an increased rate of complex and extended resections being performed in specialized centers. This development has largely been made possible owing to thorough work-up of candidates for major hepatic resection, as well as new surgical techniques and improvements in the management of intraoperative and postoperative complications. Major hepatic resections are now established procedures in liver surgery, with an acceptable procedure-related mortality. At the same time, the number of patients qualifying for hepatic resection has increased as the limits of hepatic resection have been pushed further, with new modalities to manipulate liver volume and tumor using neoadjuvant chemotherapy, two-stage resection, portal vein embolization (PVE), and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS).

Postoperative outcomes mainly depend on the size and quality of the future liver remnant (FLR). Hepatic resection, when performed in the absence of sufficient FLR, inevitably leads to post-resectional liver failure, a severe and potentially life-threatening complication. The incidence of postoperative liver failure as reported in literature, ranges from 0.7 to 9.1% [1]. Management of post-resectional liver failure is mostly supportive and liver-failure-related mortality remains as high as 80% [1]. Apart from the volume of liver remnant after resection, postoperative function of the liver remnant is directly related to the quality of liver parenchyma which is mainly dictated by underlying diseases such as fibrosis/cirrhosis and steatosis, as well as by chemotherapy-induced liver injury [2–4].

Assessment of liver function is therefore crucial in the preoperative work-up of patients who are exposed to extreme hepatic resection. A wide spectrum of tests to assess FLR has become

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available in the last few years, attesting to the fact that the ideal methodology has yet to be defined. The aim of this overview is to discuss the current modalities available, and new perspectives in assessment of the future remnant liver in patients scheduled for major hepatic resection.

Definition of Liver Function

The liver is responsible for a spectrum of functions including the uptake, synthesis, biotransformation, and excretion of various endogenous and foreign substances, in which transporters play an important role [5, 6]. The liver also provides an immunological function, as the reticuloendothelial capacity of the liver plays a role in phagocytosis and clearance of micro-organisms and endotoxins from the portal blood [7]. The secretion of bile is an important end-point of liver function, and the production of bile immediately ceases when perfusion of the liver is arrested. The complexity of liver function is best reflected by our inability to restore full liver function during liver failure, insofar as liver-assist devices and bioartificial livers have not proven to fully substitute all the components of liver function yet [8, 9]. In addition, there is no liver function test available that measures all components of liver function.

Passive Liver Function Tests

The term liver function tests refers mostly to the set of laboratory blood assays of liver-related biochemical substances. None of these measured substances, however, truly represents liver function, as they measure products or by-products of the above-mentioned processes instead of the processes themselves.

Aminotransaminases

The aminotransaminase enzymes, aspartate transferase (AST) and alanine transferase (ALT), are exclusively intracellular enzymes, and their presence in plasma are therefore markers of liver injury [10]. Damaged hepatocyte cell membranes release their contents, including ALT and AST, into the extracellular space. The released enzymes enter the blood circulation, leading to an increase in plasma levels of ALT and AST that can be measured by routine clinical chemistry. Although a persisting release of these enzymes will ultimately result in the loss of liver functional capacity, they are not parameters of function per se. AST is predominantly present in cells of the liver, heart, skeletal muscles, and red blood cells. ALT is an enzyme primarily present in hepatocytes, and therefore a more specific indicator of liver damage than AST, as AST may also be elevated in diseases affecting other organs, making it an unspecific marker for hepatocellular damage.

Bilirubin

Plasma bilirubin concentration provides indirect information on the uptake, conjugation, and excretion function of the liver. Elevated plasma concentrations of bilirubin are specific markers for serious liver injury and therefore liver function loss. Importantly, bilirubin levels may also be influenced by non-hepatic factors such as an increased production as a result of e.g., hemolysis during sepsis [11]. Therefore, plasma bilirubin concentration is not a parameter of liver function per se. The plasma bilirubin concentration is often used in combination with other laboratory parameters of hepatocellular injury (e.g., AST, ALT, albumin levels) that constitute integral parts of clinical grading systems such as the Child–Pugh and MELD scores (see sections “Child–Pugh Score” and “MELD (Model for End-Stage Liver Disease) Score”, respectively).

Albumin and Coagulation Factor Synthesis

Albumin and proteins involved in secondary hemostasis and fibrinolysis, including vitamin K-dependent coagulation proteins (factors II, VII, IX, X, protein C, protein S, and protein Z),

as well as factor V, XIII, fibrinogen, antithrombin, α2-plasmin inhibitor, and plasminogen, are exclusively synthesized by the liver, and their plasma concentrations are therefore used as indirect indicators of liver synthesis function. Albumin, clotting factors, and coagulation parameters such as the international normalized ratio (INR) are measured by routine clinical chemistry. Albumin is also an important transport protein for fatty acids, bilirubin, and hormones [12]. In liver disease such as cirrhosis, there is a decrease in the synthesis of albumin and coagulation factors, resulting in an increase in prothrombin time (PT) and its derivative measures INR and prothrombin ratio, due to the reduced synthesis of coagulation factors.

Ammonia Elimination and Urea Production

One of the crucial metabolic functions of the liver is the conversion of ammonia into urea. In patients with an impaired liver function, the affected liver lacks the capacity to produce urea, which leads to hyperammonemia. At high concentrations, ammonia is a very potent neurotoxin that is known to induce astrocyte swelling in the brain, leading to hepatic encephalopathy [13]. Increased plasma ammonia levels are therefore indicative of severely compromised liver function, and most patients with hyperammonemia are not candidates for major liver resection. In the setting of post-resectional liver function, progressive increase in plasma ammonia is an ominous sign of remnant liver failure.

Hyaluronic Acid Clearance

Hyaluronic acid (HA) is composed of repeating disaccharide units of *N*-acetyl-D-glucosamine and D-glucuronate. HA is a glycosaminoglycan that is produced by connective tissue cells and synovial cells, and is taken up from the blood and metabolized primarily by the sinusoidal endothelial cells of the liver by HA receptor-mediated uptake and degradation [5, 6]. HA levels are low in normal liver tissue, but serum levels of HA increase in a variety of liver diseases, including liver fibrosis and cirrhosis [14–16]. Serum CD44, which is one of the cell surface receptors for HA, is also elevated in patients with chronic liver diseases, especially liver cirrhosis. However, CD44 is a cell surface adhesion molecule on numerous cells of non-hepatic origin. HA concentration in the blood may therefore not be considered a specific test for sinusoidal endothelial cell function.

Clinical Grading Systems

Child–Pugh Score

Clinical grading systems combine several biochemical parameters with clinical symptoms of insufficient liver function. The Child–Pugh score, a widely used clinical scoring system, includes total plasma bilirubin level, plasma albumin level, and PT, together with the presence or absence of encephalopathy and ascites. The scoring system is divided into class A, B, and C on the basis of a 1- and 2-year survival of 100% and 85%, 81% and 57%, and 45% and 35% respectively. The Child–Pugh scoring system is particularly useful in selecting patients with HCC and cirrhosis for resection or transplantation. In Western clinical practice, most class Child B and class Child C patients are candidates for transplantation, leaving class Child A patients eligible for resection. Patients with liver metastases usually have normal liver parenchyma and are typically classified as class Child A. In these patients, the Child–Pugh score has been shown to be quite variable, and may be unreliable for predicting the outcome of liver resections [17–19]. Therefore, additional clinical chemistry data (AST and ALT), blood clearance tests (such as the indocyanine green test and galactose elimination capacity test), and molecular imaging techniques (for example the ^{99m}Tc-galactosyl serum albumin scintigraphy and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy) may be employed to complement the Child–Pugh score [19].

MELD (Model for End-Stage Liver Disease) Score

The MELD score was originally developed to predict short-term survival in patients undergoing transcutaneous intrahepatic portosystemic shunt procedures (TIPS), and was later validated as an accurate predictor of survival among patients with end-stage liver disease awaiting transplantation [20]. The MELD score incorporates the serum bilirubin and creatinine levels and the INR [21, 22]. Although the MELD score is related to the risk of liver failure after surgery [22], survival cannot be accurately predicted in 15–20% of patients [22], and it does not predict morbidity or mortality after elective liver resection [23]. It is unclear whether the predictive power of the MELD score is superior to the Child-Pugh score, although the MELD score is quickly replacing the Child–Pugh score [24].

Volumetric Measurements: the Gold Standard

Current gold standard in the preoperative assessment of future remnant liver volume (FLR volume) is managed by computed tomography (CT) volumetry as initially described by Heymsfield et al. [25]. With this technique, the FLR volume can be calculated by manually tracing the liver contour in each sectional image and summing up the volume of all slices. The three-dimensional reconstruction is then used to calculate the non-tumorous liver volume, tumor volume, and FLR volume.

In most centers, a FLR volume of 20–30% is accepted as sufficient in patients without underlying parenchymal disease [26]. In patients with a compromised liver, a FLR volume of at least 40% is considered acceptable [27]. Insufficient FLR volume is associated with poor postoperative outcome as the frequency of major complications increases, including an increased occurrence of post-resectional liver failure and prolonged hospital stay [26, 28]. CT volumetry can be used as a tool in preoperative selection of patients for resection. When FLR volume is insufficient, CT volumetry is sequentially applied to monitor volume-increase of FLR after PVE or ALPPS, which is considered an important prognosticator of postoperative liver function [29]. The main advantage of CT volumetry is its non-invasive character; and because CT is frequently used as part of the diagnostic process, volumetric calculation can be carried out using the same CT imaging series.

However, preoperative assessment of liver function based on CT volumetry alone does come with important limitations. Firstly, tumor characteristics (e.g., small tumor size, multiple lesions) and liver characteristics (e.g., small or large liver due to compromised liver parenchyma) make CT volumetry an error-sensitive imaging technique [27, 30]. An important note to the latter is the uncertain correlation of CT volumetry with liver function and postoperative outcome [31]. FLR volume does not reflect function of FLR which might be impaired by underlying parenchyma disease or hepatic comorbidity such as fibrosis, cirrhosis, or steatosis. It is important to identify patients with compromised liver in order to interpret the volumetry results correctly [32]. This has become even more important, since many patients are now presented for resection after extensive induction or neoadjuvant chemotherapy, in which liver parenchyma is injured by post-chemotherapy steatosis or veno-occlusive disease [33]. In the absence of preoperative biopsies, parenchymal damage or disease is often unknown until after the resection specimen is examined. Secondly, the selection criteria for resection based on volumetric data are to be considered arbitrary as the minimal FLR volumes proposed in literature vary widely (10–40%), are based on different grades of hepatic disease, and have been established by different measuring methods [34]. Finally, CT volumetry can be used to monitor FLR volume after PVE and ALPPS [35]; however, as mentioned earlier, volume is not necessarily representative of FLR function. We recently showed a discrepancy between the volumetric and functional changes after PVE, in as much as FLR functional increase exceeded the volumetric increase [32].

Although CT volumetry is the current gold standard in the assessment of FLR, its role should be reconsidered due to the several limitations mentioned above. In order to better predict postoperative outcome, CT volumetry should be at least complemented with an additional liver function test.

Standardized CT Volumetry

In order to overcome some of the shortcomings of the traditional CT-volumetric assessment, adjustments were made to personalize this method. Urata et al. introduced a novel method of total liver volume estimation based on the finding that in adults without chronic liver disease, liver volume correlates linearly with body size and weight [36]. As this method was based on findings among an Asian population, it did not find application in Western countries. Vauthey et al. have introduced a modified method of total liver volume estimation based on Western patient characteristics: estimated total liver volume (eTLV) [cc] = −794.41 + 1267.28 × BSA [37]. The validity of this formula in estimation of total liver volume has been demonstrated several times [38–40]. The ratio of FLR volume measured by CT volumetry and eTLV is called the standardised FLR volume, and represents the percentage of liver that will remain after resection. The standardized FLR volume is described as an accurate method in prediction of postoperative outcome in patients with healthy liver parenchyma who underwent extended resection. The frequency of complications was shown to have increased when standardized FLR volume was <20% of eTLV [39–41]. According to Ribero et al., the thresholds for safe hepatic resections using standardized FLR volume should be set to 20% in patients with normal livers, 30% in patients with chemotherapy-related liver injury, and 40% in case of chronic liver disease. PVE should be considered in patients who do not meet these criteria [39, 40, 42]. However, this method also has limitations, namely it may not be reliable in patients who undergo repeated hepatectomies or in patients with a borderline FLR volume-eTLV ratio.

Body Weight Ratio

Truant et al. introduced a novel formula, consisting of the ratio of FLR volume measured by CT volumetry and body weight (FLRV-BWR) [43]. The concept originates from assessment of potential donors in living-donor liver transplantation surgery where the minimum graft volume is estimated as 0.8% of the recipient's weight, although, in emergency cases, a graft volume of 0.6% of the recipient's weight is accepted [44–47]. Truant and associates found that patients with a FLR volume <0.5% of their body weight are at risk for post-resectional liver failure and ensuing mortality. They concluded that the FLRV-BWR method is more reliable as predictor of postoperative course in non-cirrhotic patients than traditional CT volumetry [47].

Standardized volumetry and FLRV-BWR were compared in a small retrospective study including 68 patients showing equal ability of both methods to predict postoperative outcome after major resection [48, 49]. Despite these promising results, the main limitation of CT-volumetric methods remains the fact that volumetric estimation of FLR does not take into account the quality of the liver tissue and therefore, is not reliable as a predictor of function in patients with compromised livers.

Dynamic Quantitative Liver Tests

Other tools used in the assessment of FLR are the dynamic quantitative liver function tests. Quantitative liver function tests are based on the capacity of the liver to clear the administered agent that is mostly or exclusively cleared by the liver. Distinctive for quantitative liver function tests is their non-invasive character. Furthermore, as they address one of the liver's true processes they provide more reliable information in the setting of preoperative liver function assessment, especially in patients with unknown underlying

liver disease. Several of the most common quantitative liver function tests are discussed below.

Indocyanine Green Clearance Test

The Indocyanine Green (ICG) clearance test is worldwide the most commonly used quantitative liver function test in clinical practice, especially in liver surgery. Once introduced as a modality for the measurement of blood flow, it is now mainly used for the assessment of liver function [34]. ICG is a highly protein-bound, water-soluble anionic organic tricarbocyanine dye. It was first introduced by Caesar et al. in 1961 [50]. After intravenous injection it is taken up by organic anion-transporting polypeptides (OATPs) and Na^+-taurocholate co-transporting polypeptides (NTCPs) [51]. Subsequently, ICG is removed from the blood exclusively by the liver and excreted into the bile without intrahepatic conjugation [52]. ATP-dependent, export pump multidrug-resistance associated protein 2 (MRP 2) is responsible for the excretion of ICG [53, 54]. This test reflects the capacity of the liver to excrete organic anions, such as bilirubin.

After an overnight fast, 0.5 mg/kg of ICG is administered intravenously. Clearance of the agent is measured by serum sampling or pulse dye densitometry using a transcutaneous optical sensor. The ICG clearance test is performed after an overnight fast, as food consumption stimulates hepatic function and bile flow, and may influence the test results. The results can be expressed as various parameters: the plasma disappearance rate, ICG elimination rate constant, or the percentage of retained ICG 15 min after administration (ICG-R15), of which ICG-R15 is most commonly used. Although several studies have found an additional value of the ICG test in predicting safe liver resection, there is no consensus on the safety limit, as they vary from 14 to 20% ICG-R15 [55–57]. ICG-R15 has also been proposed as a component of an algorithm together with bilirubin and ascites for the prediction of the safety of liver resection, especially in patients with chronic liver disease [58–60]. The authors report non or close to non mortality after resection when using the proposed decision tree. The preoperative ICG elimination rate constant is also described as a valuable parameter in evaluating liver functional reserve [61].

Despite its widespread use, ICG has several limiting factors as well. The uptake of ICG can be impaired in the presence of hyperbilirubinemia, since the uptake is managed by similar transporters for both ICG and bilirubin. Furthermore, the ICG clearance test depends on overall liver blood flow, meaning that the test is less reliable in patients with non-flow-depending hepatic diseases, such as intrahepatic shunting or sinusoidal capillarization [58]. In order to avoid these shortcomings, interpretation of the ICG test should be done with caution. Moreover, the ICG test provides information on total liver function, while segmental differences in liver function might exist which can be of great significance, especially in the setting of major liver resection.

Galactose Elimination Capacity (GEC) Test

The galactose elimination test determines the metabolic capacity of the liver. Galactose in free form enters hepatocytes from the blood [62] and is phosphorylated intracellularly to galactose-1-phosphate by galactokinase. Galactose-1-phosphate is then converted to glucose-1-phosphate by the action of four enzymes in the Leloir pathway [63, 64]. Galactose is administered intravenously, and the GEC is calculated from serial serum samples from 20 to 50 min postinjection, making the test somewhat time-consuming.

The GEC has shown prognostic significance in chronic liver disease [65, 66], such as fulminant hepatic failure [67], primary biliary cirrhosis [68–70], and chronic active hepatitis [66, 69, 71]. Abnormal clearance has also been frequently observed in patients with metastatic liver neoplasms [69]. A low GEC-value can predict postoperative complications and death, whereas a high GEC-value is associated with longer survival [66].

As is the case with most liver function tests, alterations in environmental conditions or liver metabolism will affect test outcomes. Galactose is an essential component of membrane glycoproteins and glycolipids. During liver regeneration, an increased membrane synthesis can lead to an augmented galactose demand [72]. Furthermore, galactose can be converted into glucose, which is used as an energy source during anaerobic respiration, especially during fasting [72]. As a result, altered galactose kinetics during, for example, liver regeneration and fasting [72, 73] may provide false-positive results with respect to liver function.

Lidocaine Clearance (MEGX) Test

Lidocaine is taken up by hepatocytes and metabolized into monoethylglycinexylidide (MEGX), the *N*-deethylated metabolite, by the cytochrome P450 3A pathway [74]. MEGX is subsequently converted to glycinexylidide (GX) in the liver through sequential oxidative *N*-dealkylation [75] and *N*-deethylation [76]. MEGX can be measured by high-performance liquid chromatography [77–79], gas–liquid chromatography [80], or by enzyme-linked immunosorbent assay [75] in blood samples before and 15 min after intravenous injection of lidocaine (1 mg/kg). Lidocaine has a relatively high extraction rate, as a result of which this liver function test is dependent on hepatic blood flow in addition to hepatic cytochrome P450 activity [75].

The clearance of lidocaine is reduced in chronic liver disease, with prolongation of its half-life, and MEGX levels decrease gradually with time when liver injury progresses [76, 81]. Decreased MEGX levels have been correlated with increased complication rates after liver resection [82], especially in patients with cirrhosis or hepatocellular carcinomas (HCCs) [82]. The MEGX test has been widely used in the liver transplantation setting, both for the evaluation of liver function in potential donors and for the prediction of survival after transplantation [75, 83, 84]. A hepatic resection can be performed safely with a MEGX-value of <25 ng/ml [82].

Two considerable disadvantages of the MEGX test have been reported, and therefore this method has been largely abandoned. Firstly, there are variations in cytochrome P450 activity in the general population, with the consequence that in (stable) liver patients a broad range of MEGX production levels have been found [74]. This is probably due to the complexity of the pharmaco- and enzyme kinetics associated with lidocaine and its metabolic end-products, which rely on intrahepatic blood flow, uptake of lidocaine, conversion of lidocaine to MEGX, MEGX export out of the cell, and conversion of MEGX to GX. Secondly, other medications interfere with the cytochrome P450 system [76, 85] and can influence MEGX kinetics and thus skew the interpretation of liver function. Moreover, as is the case with other blood clearance tests, the MEGX test only provides information about the global liver function.

Scintigraphic Liver Function Tests

^{99m}Tc-labeled diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy and hepatobiliary scintigraphy (HBS) with ^{99m}Tc-labeled iminodiacetic acid derivates are the most common representatives of this group. Although the two methods are based on different principles, both provide quantitative and visual information on total and regional hepatic function. ^{99m}Tc-GSA scintigraphy and ^{99m}Tc-mebrofenin HBS are discussed in this section.

^{99m}Tc-GSA Scintigraphy

The asialoglycoprotein receptor is specific for asialoglycoproteins, which are formed after the removal of sialic acid from endogenous glycoproteins by sialidases. Asialoglycoproteins bind to asialoglycoprotein receptors on the hepatocyte sinusoidal surface and are subsequently taken up

by receptor-mediated endocytosis and delivered to lysosomes for degradation. Chronic liver disease is associated with a decrease in the amount of asialoglycoprotein receptors [17] and accumulation of plasma asialoglycoproteins [17, 86, 87]. The ^{99m}Tc-labeled asialoglycoprotein analog, ^{99m}Tc-GSA, was clinically introduced as a new scintigraphy agent for imaging of the human hepatic receptor [88, 89]. ^{99m}Tc-GSA is commercially available in an instant labelling kit in Japan [88]. The liver is the only uptake site for ^{99m}Tc-GSA, which makes it an ideal agent for liver function assessment. Furthermore, the uptake of ^{99m}Tc-GSA is not affected by high bilirubin serum levels, making the ^{99m}Tc-GSA scintigraphy applicable even in cholestatic patients [90].

^{99m}Tc-GSA is intravenously injected, after which a gamma camera is positioned over the heart and the liver of the patient. Regions of interest (ROIs) are generated, enabling the calculation of the hepatic uptake and blood clearance of the agent. Multiple other parameters can be calculated using different kinetic models [91–94]. Due to the complexity of these suggested models, they are not widely used in clinical practice, leaving hepatic uptake and blood clearance ratio as the most commonly used parameters. Both can be determined from planar dynamic ^{99m}Tc-GSA scintigraphy. The clinical usefulness of planar dynamic ^{99m}Tc-GSA scintigraphy in hepatic surgery has frequently been described. Many studies have shown ^{99m}Tc-GSA scintigraphy to be a reliable method for preoperative prediction of postoperative outcome after liver resection, including major complications [95–98]. Prediction of postoperative complications based on hepatic uptake ratio has been proposed several times, although post-resectional liver failure has been observed also in patients with relatively normal uptake of ^{99m}Tc-GSA, probably because planar dynamic ^{99m}Tc-GSA does not provide information on regional liver function [95, 97, 98].

Although hepatic uptake and blood clearance ratio of ^{99m}Tc-GSA have been used for the last 20 years, results can be influenced by scatter effects, body movements or inter-operator and inter-institutional differences [88, 97–99]. A novel parameter was introduced in order to overcome these shortcomings, i.e., the index of convexity, a parameter that is generated from the shape of the liver time–activity curve. Miki et al. demonstrated that this parameter correlated well with conventional liver tests and was superior to the standard parameters in differentiating healthy and cirrhotic livers [100].

Another new kinetic model of ^{99m}Tc-GSA scintigraphy is the uptake index. The uptake index has been developed to show the speed of receptor-mediated endocytosis of ^{99}Tc GSA. Uptake index is the ratio of the rate of transport of ^{99}Tc GSA through the hepatic cell membrane from the total plasma ^{99}Tc GSA, at any given time. As this model correlated with traditional serological tests, the authors of this method expect this model to gain popularity in the field of assessment of liver function [101].

In order to improve the assessment of regional liver function and to measure the functional liver volume, ^{99m}Tc-GSA scintigraphy was combined with static single-proton emission computed tomography–CT (SPECT-CT). The great advantage of ^{99m}Tc-GSA SPECT-CT is the ability to distinguish functional liver tissue from non-functional liver tissue [102]. This is especially important in patients with advanced liver disease in whom the liver volume is not corresponding to the amount of functional hepatocytes, e.g., patients with advanced fibrosis who do maintain at least the initial liver volume over a longer period of time, whereas the amount of functional hepatocytes is decreased. Nowadays ^{99m}Tc-GSA scintigraphy can be performed with dynamic SPECT-CT, allowing a three-dimensional measurement of ^{99m}Tc-GSA uptake. Liver uptake ratio and liver uptake density can be calculated from dynamic SPECT-CT acquisitions. Dynamic SPECT-CT has proven valuable for the preoperative prediction op–postoperative outcome after liver surgery [102]. The liver uptake ratio of the FLR was shown to correlate well with postoperative liver function parameters, and is considered a useful tool in preoperative assessment [103]. Furthermore, functional

liver volume can be estimated correctly using ^{99m}Tc-GSA SPECT-CT [104].

The applicability of ^{99m}Tc-GSA SPECT-CT in monitoring FLR after PVE has been evaluated several times. In cirrhotic and non-cirrhotic patients, the increase of FLR function after PVE was found to be more pronounced compared to the volumetric increase measured with CT volumetry [105, 106]. Currently the changes in FLR after PVE are monitored by CT volumetry; this finding implies that GSA could be of additional value in the management of patients who underwent PVE because of insufficient FLR.

Another field where ^{99m}Tc-GSA SPECT-CT could possibly find its use is the monitoring of liver regeneration after hepatic resection. Several studies report a more advanced increase in liver function versus increase in volume [107–109], although the available studies do not deliver clear evidence for this statement due to methodological and analytical errors, leaving this question to be answered in the future.

Recently, there has been an increasing interest in combining the validated ability of GSA in targeting the asialoglycoproteins receptor concentration with positron emission tomography (PET) because of its excellent imaging resolution and quantifying qualities. For this purpose GSA needs to be labelled with gallium-68 (^{68}Ga). From the PET images, ROIs of the heart and the liver are generated, followed by generation of time–activity curves and corresponding parameters (t50 and t90). The GSA labelling techniques, the metabolic stability, and the imaging properties of ^{68}Ga-GSA were investigated and compared to standard ^{99}Tc-GSA in an animal study showing promising results for the future use of ^{68}Ga-GSA PET in the assessment of liver function [110].

HBS with IDA Derivates

^{99m}Tc-IDA agents were introduced in 1976 by Loberg et al. [111] These lidocain analogs are transported to the liver bound to albumin, and dissociate from albumin in the hepatic space of Disse. Thereafter, they are taken up by the hepatocytes, a process similar to the uptake of unconjugated bilirubin. Unlike unconjugated bilirubin, ^{99m}Tc-IDA agents do not undergo any biotransformation after hepatic uptake, and are directly excreted into the bile canaliculi in the same manner as other substances such as conjugated bilirubin, hormones, and drugs. Hepatic uptake represents one of the main hepatic processes [112, 113].

^{99m}Tc-mebrofenin is the most hepatic specific ^{99m}Tc-IDA derivative [51, 114]. The uptake of mebrofenin is managed by OATPB1 and OATP1B3 [51]. Hepatic uptake of IDA agents via OATPs can be influenced by high serum bilirubin levels, as the same transporters are involved in the uptake of organic anions such as bilirubin. Of all available IDA agents, ^{99m}Tc-mebrofenin shows the lowest displacement by bilirubin in cases of hyperbilirubinaemia. The excretion of mebrofenin is most likely facilitated by MRP2 [53, 114]. The uptake, excretion, and lack of hepatic biotransformation of the IDA agents are similar to ICG. These properties make IDA agents suitable for the imaging of the hepatobiliary system and for its use in diagnosis of different biliary diseases [111, 112, 115]. The application of IDA agents for the assessment of liver function was first proposed in 1994, and has recently been elaborated by our group for risk assessment of patients considered for major liver resection [116]. The high hepatic uptake, low displacement by bilirubin and, furthermore, low urinary excretion make mebrofenin the most suitable IDA agent for hepatic function assessment.

Camera-based measurement of the relative hepatic uptake rate was developed by Ekman et al. [117]. After intravenous injection of freshly prepared ^{99m}Tc-mebrofenin, dynamic scintigraphy is performed with a gamma camera. Also here, the uptake of ^{99m}Tc-mebrofenin is calculated by determining ROIs around the heart, the liver, and the total field of view. Based on the ROIs, three time–activity curves can be generated. Using these parameters, it is possible to calculate the hepatic mebrofenin uptake ratio. Subsequently, the uptake ratio is divided by the body surface area (BSA) and expressed

as %/min/m^2 in order to compensate for differences in individual metabolic requirements, similarly to the standardized volumetry method introduced by Vauthey et al. to individualize CT-volumetric assessment of FLR. This technique makes it possible to generate other ROIs, e.g., the FLR, which makes it possible to estimate specifically the function of the FLR [118].

The use of ^{99m}Tc-mebrofenin HBS for preoperative assessment of liver function in patients undergoing liver surgery was first described by Erdogan et al. The hepatic uptake of mebrofenin can be calculated in the same way as for ICG. The mebrofenin uptake rate strongly correlated with the ICG clearance test [119]. Preoperatively measured FLR function with ^{99m}Tc-mebrofenin HBS proved to correlate with postoperative FLR function on postoperative day 1 [120]. Furthermore, in patients without parenchymal disease undergoing partial liver resection, preoperative measurement of ^{99m}Tc-mebrofenin uptake by FLR was more accurate in prediction of postoperative liver insufficiency and liver insufficiency related mortality than was preoperative measurement of FLR volume [31]. Dinant et al. described a risk of postoperative liver failure of 56% in patients with a hepatic ^{99m}Tc-mebrofenin FLR uptake below 2.5%/min/m^2, compared to 3% in patients with uptake above 3%/min/m^2. In surgical populations with and without compromised liver parenchyma, the cut-off value was validated at 2.69/min/m^2, making HBS more valuable in predicting postoperative liver failure compared to CT volumetry [121]. One single cut-off value for patients with compromised or non-compromised livers makes ^{99m}Tc-mebrofenin HBS an even more suitable liver function test in clinical practice, as underlying liver disease often is unknown or poorly defined until resection has taken place. Liver biopsies are not taken routinely as the distribution of compromised parenchyma in the liver is not homogeneous, leading to sampling errors, and because of the risk of biopsy-related complications [122–124]. This fact increases the value of ^{99m}Tc-mebrofenin HBS in daily practice.

The planar dynamic technique was developed in the era of single-head gamma cameras. Using this technique, in anterior view, the function of right liver segments is underestimated due to attenuation. With the availability of dual-head gamma cameras, it is now possible to perform dual-head dynamic acquisition and subsequent calculation of a geometrical mean hepatic uptake. However, the two-dimensional planar images lack the ability to assess detailed liver function on a segmental level. Therefore, a three-dimensional SPECT-CT has been devised for additional adequate anatomical information. As described by De Graaf et al., combination of the dynamic HBS with SPECT-CT delivers visible and quantitative information with regard to segmental liver function, and therefore is an accurate measure of FLR function (Fig. 3.1) [125–127].

^{99m}Tc-mebrofenin HBS with SPECT-CT is gaining applicability in patients undergoing PVE. Recent reports have indicated that the increase in the FLR function is more pronounced than the increase in the FLR volume [125]. This finding suggests that the time interval between PVE and liver resection should not be determined by volumetric parameters alone. Another possible application of HBS in this group of patients is the selection of candidates for PVE, as prediction of liver failure on the basis of function of the FLR can be done more accurate by HBS.

Monitoring of regeneration of liver function after resection is another potential application of HBS. As Bennink et al. already described, volumetric regeneration after partial liver resection does not correlate with functional regeneration measured with HBS, while the latter has been shown to correlate with ICG clearance [120].

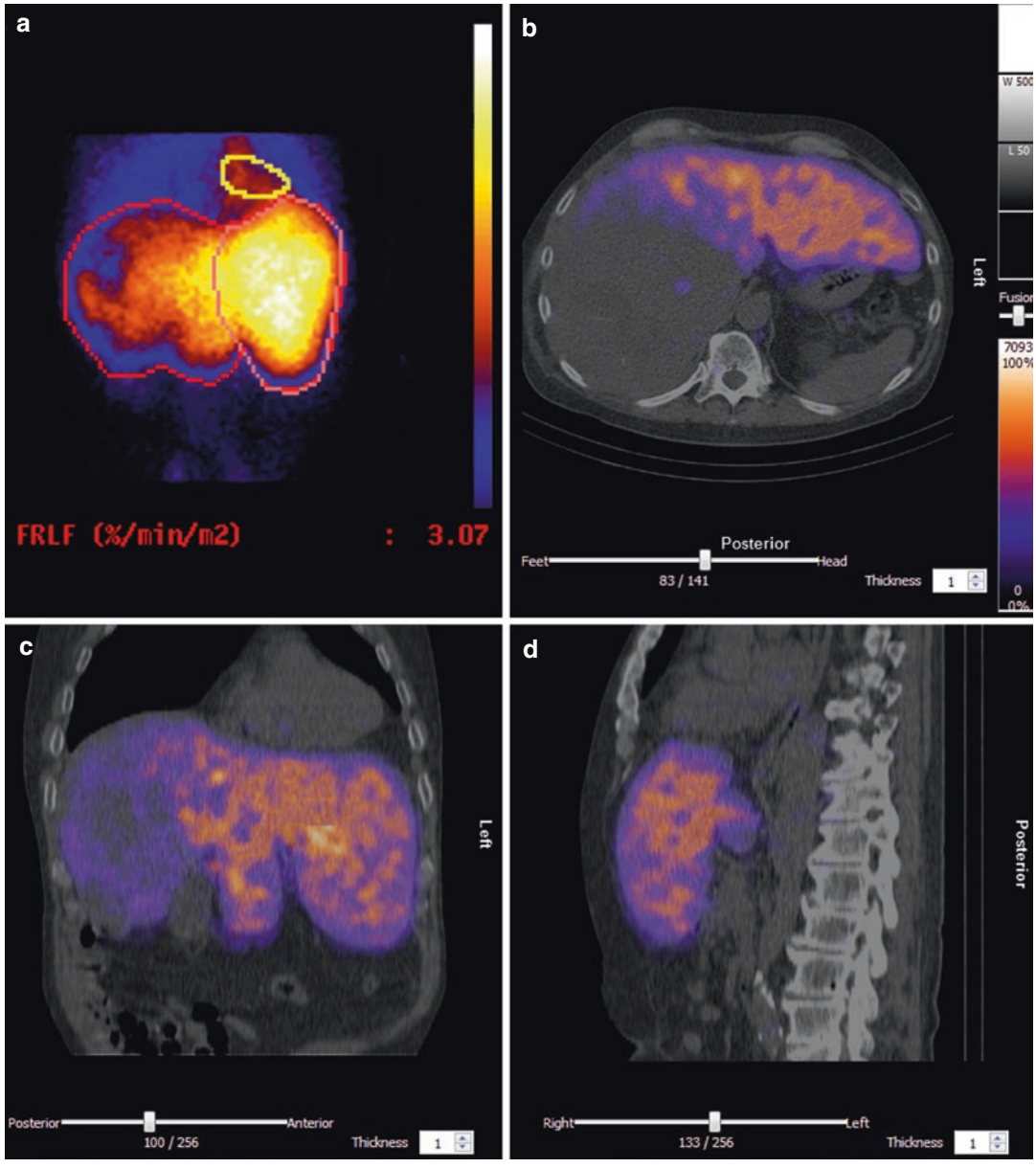

Fig. 3.1 Preoperative hepatobiliary scintigraphy in a 56-year-old male patient with a large resectable HCC in the right liver segments. Summed dynamic scintigraphy (**a**) showing hypertrophy and function of the left liver segments. The future remnant liver function was determined at 3.07%/min/m^2. Transverse (**b**), coronal (**c**) and sagittal (**d**) SPECT-lowdoseCT planes of the liver showing a large non-functional mass in the right liver and hypertrophy of left liver segments with sufficient function for safe right hemihepatectomy

Other Modalities for Assessment of Liver Function

Bioenergetic Tests

A key determinant of liver functional status and reserve is the energy state of the organ. The availability of adenosine triphosphate (ATP) is therefore critical for the maintenance of integrity and function of liver cells, particularly since the liver is the most metabolically active organ. When the ATP-generating ability of liver cells is compromised, as is the case in chronic parenchymal disease, the energy status of the liver decreases. This in turn leads to compensatory suppression of energy-consuming processes such as active ion transport and protein and nucleic acid synthesis [128]. The latter is important for liver cell proliferation, which is a key feature of liver regeneration. Assessment of the energy state of the liver therefore provides direct information on the liver functional reserve.

The liver functional reserve can be estimated by measurement of ketone bodies, which reflect the redox state in liver mitochondria (i.e., the site of ATP production) [129]. These are determined by the redox tolerance index (RTI), which is reflected in a 100-fold cumulative enhancement of ketone body ratio relative to glucose level (100 × AKBR/A glucose) [129]. Furthermore, it can be estimated by 31-phosphorus (^{31}P) magnetic resonance spectroscopy. The naturally abundant ^{31}P isotope constitutes an important element in molecules such as tri- and diphosphate nucleotides that play a central role biological energy metabolism [130, 131].

^{13}C-Methacetin Breath Test, LiMAx

There is a broad spectrum of ^{13}C-breath tests available. The principle of the ^{13}C-methacetin breath (LiMAx) test is based on the activity of cytochrome P450 1A2 (CYP1A2) system, an enzyme system that is exclusively expressed in the liver. The activity of this enzyme system proved to be reduced in patients with severe chronic liver disease, regardless of cholestasis [132]. CYP1A2 is distributed through the whole functional unit of the liver [133], and is not affected by drugs or genetic variation [133]. ^{13}C-methacetin, the agent used to measure the activity of CYP1A2, is exclusively metabolized by the CYP1A2 [134]. ^{13}C-methacetin is instantly metabolized into paracetamol and $^{13}CO_2$, after which $^{13}CO_2$ is excreted through the lungs. This causes alternations in the normal $^{13}CO_2/^{12}CO_2$ ratio in patients' breath [135]. In this manner, the ^{13}C-methacetin breath test provides quantitative information on hepatic function.

After a minimum of 6 h fast, the base line of $^{13}CO_2/^{12}CO_2$ ratio is measured. Subsequently, 2 mg/kg body weight (BW) 13C-labeled methacetin is intravenously administered to the patient. Changes in the $^{13}CO_2/^{12}CO_2$ ratio are analyzed by a modified, non-dispersive, isotope-selective infrared spectroscopy-based device during 60 min after injection of the agent. The expired air is collected using a specially designed facemask. The results are expressed as μg/kg/h [136].

The LiMAx test is a non-invasive and easy to perform test which makes it an attractive option in clinical practice. The cut-off value of normal LiMAx readout is set at 311–575 μg/kg/h [136]. While LiMax assesses total liver functional capacity, the test can be used to measure the FRL function by combining LiMAx test with CT-volumetric analysis of FLR [136]. The authors assume that the percentage of liver function attributed to the FLR equals the percentage of FLR volume; however, this method does not take into account regional differences in liver function. On the other hand, preoperative FLR LiMAx values correlated with the LiMAx values measured on the first postoperative day. LiMAx value on postoperative day 1 has also been described as a predictor of post-resectional liver failure and liver failure related mortality. The same research group proposed a decision tree based on the LiMAx results which is supposed to help the surgeon to decide between resection and alternative or additional therapies such as PVE, neoadjuvant treatment, and palliative therapy [137]. The value of this algorithm and the proposed cut-off values await further clinical assessment in a prospective setting.

The LiMAx test has also been proposed as a tool in the monitoring of functional recovery after hepatic resection. Test readouts showed that functional recovery of the liver remnant was completed significantly faster compared to volumetric recovery. With this knowledge, the authors suggested tailored management for patients with sufficient recovery [138]. Because this test is based on the activity of an enzyme system, it is uncertain, however, if the readouts are influenced by the resection. In order to validate LiMAx in this setting, the expression of the enzyme system should be investigated.

The LiMAx test has recently been explored in patients undergoing PVE [139]. In this study, the LiMax was used to visualize the changes in FRL function in the time between PVE and major liver resection, showing an increase in FLR function after PVE. Furthermore, they found that function of FLR post-resection was lower in comparison to the preoperatively calculated function, which they explain as loss of function due to intraoperative injury. The authors plead that an overestimation-margin of the FLR is needed preoperatively in order to compensate for this loss, which is an interesting point that could contribute to safety management in liver surgery, especially in patients who are scheduled for complex resections.

The major limitation of the ^{13}C-breath tests is the assumption that the contribution of FLR to total liver function is equal to the proportion of FLR to total liver volume. Malinowski et al. advocate in their study that the distribution of liver function does not change after PVE [139]. The FLR function measured with LiMax shortly after PVE did not differ from FLR function measured before PVE. Furthermore, they found that overestimation of FLR function preoperatively was not different between PVE and non-PVE patients. However, both arguments attest to the fact that the test is based on indirect measurement of liver function. Inhomogeneous distribution of liver function throughout the liver has been demonstrated using scintigraphic methods [105, 140, 141] and MRI as well [142].

Another difficulty in the application of the Limax test is that the test results are potentially affected by several factors such as hemodialysis, smoking, nutrition, and visceral hemodynamics [137]. Also, members of the CYP1A family are considerably downregulated in hepatocellular carcinomas, rendering the test less universal in use for the whole population of patients requiring liver resection [143].

The greatest advantage of the LiMax test is its non-invasive character. This permits a more intensive frequency of measurement of total liver function in the setting of prospective studies. Currently, little is known of the changes in total liver function in the course of the work-up before resection, e.g., neoadjuvant chemotherapy. Using Limax, a mild impairment of liver function has been shown [144]; however, this study should be repeated in a lager cohort of patients before any conclusions can be drawn.

Assessment of Liver Function Using Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is well established as a liver imaging technique. MRI provides accurate anatomical information and has recently also been introduced as a potential technique for preoperative assessment of liver function [145–147]. The use of contrast-enhanced MRI (CE-MRI) with gadolinium-based contrast agents allows more accurate depiction of benign or malign liver lesions than with CT [148]. Contrast-enhanced MRI is already part of the standard preoperative work-up in patients scheduled for major liver resection in various centers over the world.

Gd-EOB-DTPA is a liver-specific contrast agent. Approximately 50% of the circulating agent is excreted by the hepatocytes. The excretion of the remaining 50% is managed by the kidneys. The uptake of Gd-EOB-DTPA from the liver sinusoids is managed by the OATPs and the NTCPs [149–153], while the MRP2 excrete Gd-EOB-DTPA into the bile canaliculi [154, 155]. Excretion occurs without prior biotransformation. The pharmacokinetic properties of Gd-EOB-DTPA, including the uptake and excretion transporter proteins, are similar

to those of mebrofenin as used in ^{99m}Tc-HBS, suggesting that this technique is of potential use in the assessment of liver function.

The concept of using CE-MRI with Gd-EOB-DTPA in the evaluation of liver function was first introduced in 1993 [151]. Subsequently, several studies have been published showing correlation between MR imaging with Gd-EOB-DTPA and liver function in an animal model [156–161]. Recently, data on assessment of liver function using MRI with Gd-EOB-DTPA in humans have been published, all of them confirming the possibility of liver function assessment using MRI [162–169].

In a preliminary study, Saito et al. retrospectively reviewed data of 28 patients who had undergone several quantitative functional tests as well as a standard 5-phase CE-MRI with Gd-EOB-DTPA during work-up for liver resection [147]. They compared the intracellular contrast agent uptake rate and extracellular volume with the results of ICG and GSA tests, and found statistically significant correlations between the uptake rate and the reference tests. These data indicate that Gd-EOB-DTPA CE-MRI, even in its simplest form, may already be of use for estimation of liver function. Future studies should target the additional value of dynamic contrast enhanced MRI. This would allow a more thorough analysis of the time versus signal intensity curve, as more data are acquired during and after administration of the contrast agent.

Functional imaging with MRI-Gd-EOB-DTPA facilitates assessment of total and regional liver function in a similar way as scintigraphic modalities [169]. The latter, however, require additional CT imaging examinations in order to reach sufficient resolution which forms an additional burden for the patient. Since MRI does not use ionizing irradiation, the patient burden is lower. Furthermore, CT imaging used in combination with scintigraphic methods is usually insufficient for diagnostic purposes, while MR imaging provides high-quality information that can be used in the preoperative work-up of the patient. Given that MRI now allows the segmental assessment of steatosis and can be used to assess fibrosis, this makes it a potential one-stop-shop modality for both liver anatomy and function [170–173]. Another advantage is that Gd-EOB-DTPA uptake is reliable in patients with and without compromised liver parenchyma [162, 166, 167]. Hence, although the use of MRI with Gd-EOB-DTPA for liver function assessment is still under investigation, the evidence up to now shows promising results, and offers the attractive prospect of combining diagnostic and functional imaging in one procedure.

Discussion

Improvement of short-term and long-term survival after extensive liver surgery has been the main focus of liver surgeons during the last two decades. Modern surgical techniques have not only contributed to the reduction of procedure-related morbidity and mortality, but have also led to undertaking more extensive and even extreme hepatic resections in specialized centers. In parallel with these developments, postoperative liver failure has remained the most feared complication, as the treatment options are very limited and outcome often turns out to be lethal. Accurate preoperative assessment of FLR is essential in order to foresee postoperative liver dysfunction and to install alternative strategies, such as resection after portal vein embolization or two-stage resection.

In patients with liver-specific diseases, accurate assessment of liver function is critical for the selection of treatment options. Treatment of HCC in cirrhotic patients, i.e., by liver resection or transplantation, is determined by the severity of underlying liver disease. In cirrhosis, fibrosis is accompanied by a reduction of functional hepatocytes that is characterized by fibrous tissue septa that separate hepatocyte nodules, leading to altered resistance to blood flow in the liver and portal hypertension [174, 175]. The most commonly used liver function tests in cirrhotic patients include plasma aminotransferases, bilirubin clearance, albumin levels, PT, HA uptake, the Child–Pugh classification, and the ICG test.

Liver steatosis and steatohepatitis are associated with an increased risk of partial liver resection of intrahepatic tumors, especially after

neo-adjuvant chemotherapy, or in living donor liver transplantation [3]. When CT volumetry is used as a prognostic tool for surgical outcome, a functional overestimation can be made in patients with steatosis. The accumulation of triacylglycerols in hepatocytes leads to hepatocyte enlargement in combination with steatosis-induced perfusion defects; i.e., phenomena that distort the actual liver function when deduced from CT scans. Increases in liver fat infiltration reduce liver blood flow and hepatic microcirculation, which in turn affect the extent to which molecules such as ICG can reach hepatocytes. ICG clearance and ^{99m}Tc-mebrofenin HBS therefore possess the potential to assess hepatic function in steatotic livers, because of the combination of impaired parenchymal perfusion and liver dysfunction [176].

Prolonged cholestasis produces hepatocellular injury and fibrosis. The uptake of ^{99m}Tc-mebrofenin and ICG is impaired under these conditions, due to competitive uptake of bilirubin and ICG/mebrofenin by the same cellular transporter systems. Although this impaired uptake still reflects the uptake function of the liver at that specific time, it does not represent the function of the liver after surgery once the biliairy obstruction is resolved. Preoperative assessment of liver function using the ICG clearance test or ^{99m}Tc-mebrofenin HBS therefore requires complete biliary drainage in patients, with concomitant obstruction of (part of) the biliary tree, as seen in hilar cholangiocarcinoma. Alternatively, when percutaneous transhepatic biliary drainage has been performed, ICG or mebrofenin excretion can be measured directly in the drained bile.

The current gold standard, CT volumetry, uses volumetric parameters in the prediction of post-resectional outcome. However, FLR volume does not necessarily correlate with FLR function, especially in patients with a compromised liver parenchyma. Three quantitative liver function tests, i.e., ^{99m}Tc-GSA, ^{99m}Tc-mebrofenin HBS, and the LiMAx test, have shown a discrepancy in functional versus volumetric increase after PVE. From this we can assume that judgement of FLR should not be based on volumetric parameters only. Furthermore, routine preoperative liver biopsy is considered controversial due to possible complications and a high probability of sampling errors. Given the fact that the quality of FLR parenchyma remains unknown until the resection specimen has been examined, additional quantitative liver function tests are advised in the preoperative selection of patients for major resection, or for timing of resection after preoperative PVE. The exception obviously is the patient with FLR volume that greatly exceeds the minimum volume and in whom no parenchymal disease is anticipated.

The ICG clearance test was the first quantitative liver test to be introduced. Even though it has found wide applicability in liver surgery, it is reliable for preoperative assessment of liver function only in a select patient population (with cirrhosis) which makes the ICG clearance test less universally applicable. With this knowledge, hepatobiliary surgeons should focus on newer methods that are able to overcome the shortcomings of the older methods.

As mentioned above, underlying parenchymal disease is one of two major challenges in the assessment of hepatic function, making most of the available tests less suitable in the overall patient population. ^{99m}Tc-GSA, ^{99m}Tc-mebrofenin scintigraphy, and possibly the LiMAx test have brought solutions for this problem. Both ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin have been validated as preoperative liver function tests and correlated with post-resectional outcomes in several clinical studies involving patients with normal livers, as well as patients with parenchymal liver diseases.

The second major limitation of most quantitative liver function tests, such as the ICG clearance test and the LiMAx test, is the lack of accurate measurement of regional liver function, i.e., function of specifically the FRL. ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin HBS can be performed together with a single proton emission computed tomography CT (SPECT-CT), which offers the possibility to obtain at the same time anatomical as well as functional information of the FLR. The information is crucial in the setting of hepatic surgery. The choice which of the scintigraphic methods is to be preferred for the preoperative assessment of FLR function depends on the

facilities available. Although the two tests are based on different principles, both offer the possibility of measuring FLR function in both normal and compromised liver parenchyma, and are able to measure FLR function apart from total liver function. The only drawback of ^{99m}Tc-GSA is that it is not available in Western countries, whereas ^{99m}Tc-mebrofenin is inexpensive and freely available throughout the world. Both gamma camera and SPECT-CT possibilities are usually available in centers treating patients with hepatic disease, rendering implementation of the scintigraphic techniques less demanding.

Future opportunities in preoperative liver function assessment possibly lie in the field of MRI. The absence of radiation burden and the multi-purpose character of MRI potentially replace current quantitative liver function tests and CT volumetry, reducing costs at the same time. The similarity between the kinetics of scintigraphic agents and contrast agents used with MRI encourages further investigation of functional MRI, Notwithstanding the outlook on new modalities, the current quantitative liver function tests offer a chance to reduce postoperative liver failure, and therefore should be implemented in the regular preoperative work-up of patients considered for major liver resection.

Because of the complexity of liver function, one single test cannot represent overall liver function and accurately predict operative risk in any given patient considered for major liver resection [177, 178]. We still rely on the combination of clinical parameters and quantitative liver function tests to estimate liver functional reserve and to decide whether we can perform a safe resection in any patient presented to us. Scoring methods need to be developed in which clinical parameters, CT volumetric criteria, and the results of dynamic quantitative liver function tests guide our decision-making in patients requiring major liver resection [59]. Objective functional criteria are necessary to define patients at increased risk. Until appropriate scoring methods and objective functional criteria have become available, multiple tests measuring different components of liver function should be combined for the optimal assessment of liver function.

In conclusion, liver function involves a spectrum of metabolic functions, and there is not one test that can measure all functions at the same time. Laboratory blood assays and clinical scoring systems are unreliable in predicting post-resectional outcomes. Quantitative liver function tests mostly provide information on global liver function. Scintigraphic methods such as ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin HBS in combination with SPECT permit regional assessment of specifically, the FLR. MRI using Gd-EOB-DTPA has potential as a combined diagnostic and functional imaging technique in patients considered for liver resection. The ideal method for evaluation of liver function and surgical risk in patients considered for extreme liver resection should combine clinical parameters, volumetric data, and the results of dynamic quantitative liver function tests.

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Imaging-Based Preoperative Planning

4

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Introduction

Liver resection in the treatment of colorectal liver metastases, as for any other primary or secondary liver tumor, needs to be oncologically effective and surgically safe. The oncological goal of liver resection is the removal of all vital metastatic lesions, although debulking procedures may play a role in the future. From a surgical safety point of view, morbidity and mortality of liver resection arise, more than from any other cause, from postoperative hepatic insufficiency. Hence, the resection procedure must leave the patient with a sufficiently functioning liver remnant. In summary, both goals—oncological and functional resectability—need equal consideration, and for achieving each of them, imaging-based preoperative planning is paramount.

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Oncological Resectability

Imaging Techniques

Preoperative imaging of colorectal liver metastases should ideally identify all metastatic as well as all other benign or malignant lesions in the liver, as well as extrahepatic disease. Furthermore, it should provide an anatomical roadmap with the exact localization of each lesion within the segmental hepatic anatomy and its proximity to adjacent vasculature and bile ducts, to allow for proper resection planning.

Ultrasound

Transabdominal ultrasound (US) is the most widely used imaging tool [1]. It is highly available, inexpensive, easy to use, and allows for a good overview. Its sensitivity for the detection of metastatic lesions, however, is low, as it may miss more than 50% of liver metastases. In obese patients and steatotic livers, the diagnostic performance of transabdominal US can be even lower. High operator dependence as well as inadequate characterization of lesions and detection of extrahepatic disease are other challenges with US.

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Intraoperative Ultrasound

Intraoperative ultrasound (IOUS) provides significantly better performance and high-resolution imaging compared to conventional US [1, 2]. It has become a standard technique in most liver centers. Its particular strength is the detection of deep and non-palpable metastases during intraoperative exploration, and it can help localize metastases that have disappeared on other imaging modalities due to preoperative chemotherapy. Independent sensitivity rates of IOUS are difficult to report, as most lesions are already known from prior imaging studies. Use of IOUS in combination with dedicated US-contrast material can enhance its diagnostic value [3]. Furthermore, IOUS remains the only way to evaluate the topography of metastatic lesions and adjacent intrahepatic vasculature and bile ducts intraoperatively, which makes it a helpful tool, especially in complex resections [4].

Computed Tomography

Contrast-enhanced computed tomography (CT) overcomes many of the limitations of US. Its observer-dependent variability is considerably lower. Its availability is nearly as widespread as that of US, and shows significantly higher sensitivity for lesion detection [5]. With the use of multi-detector CTs, it has become very fast; a scan of the entire abdomen can be performed within less than 10 s. Its main strength is the excellent vascular visualization and mapping of the intrahepatic anatomy. This allows for better anatomical resection planning, and improves the assessment of tumorous vessel infiltration. For optimal vascular and lesion assessment, at least at the first time of imaging, the CT should be triphasic and consist of an arterial, portal-venous, and venous phase. Furthermore, it is the modality of choice for preoperative volumetric assessment [6]. Total liver volume, tumor volume, and the volume of the future liver remnant can be precisely calculated. Ideally, volumetric analysis should be done by the radiologist and the surgeon together to gain optimal results. Liver steatosis, which frequently occurs after chemotherapy, can be diagnosed if the attenuation of the liver is less than 40 Hounsfield units (HU) or if the attenuation is at least 10 HU less than the spleen in the non-contrast enhanced scan [7, 8].

The use of ionizing radiation is a drawback of CT imaging. In addition, its diagnostic performance is still not optimal. In a meta-analysis, the sensitivity was 74% for lesions larger than 1 cm and 47% for lesions smaller than 1 cm [5].

MRI

There are several reasons why MRI is the modality of choice for dedicated liver imaging [5, 9]. Sensitivity and specificity of colorectal liver lesion detection are considerably higher with MRI than with US or CT. T1- and T2-weighted native phases followed by contrast-enhanced dynamic phases and a delayed phase are today's minimum standard. Additional diffusion weighted imaging (DWI), which should also be performed routinely, further enhances the differentiation between different tumors, as especially benign lesions such as hemangiomas and cysts must be safely identified preoperatively [10–12]. The biliary tree can be imaged with a magnetic resonance cholangiopancreaticography (MRCP), which can be vital for the preoperative planning in patients with central lesions. Routinely performed chemical shift gradient-echo (GRE) imaging with in-phase and opposed-phase acquisitions permit assessment of steatosis [7].

The use of liver-specific contrast materials such as GD-BOPTA (Multihance, Bracco) or Gd-EOB (Eovist in the US, Primovist in Europe, Bayer Schering) provides even better sensitivity and specificity, especially in lesions smaller than 1 cm [13, 14]. This finding was proven to have a direct positive impact on resection planning. In a recently published prospective multicenter trial with 342 patients, intraoperative modifications of the planned resection strategy were more frequent

with preoperative CT-imaging than with conventional MRI, itself involving more frequent modifications than gadoxetic acid-enhanced MRI (47% vs 32% vs 28%). The higher diagnostic performance of MRI could also be shown comparing the radiologic and pathologic outcome [15]. Furthermore, the delayed hepatobiliary phase provides visualization of the biliary anatomy essential for preoperative planning [16].

FDG-PET-CT

Positron-emission computed tomography (PET-CT) mostly uses (F-18) fluorodeoxyglucose (FDG) as tracer, and is then called FDG-PET-CT. It primarily measures tumor metabolism and additionally provides the basic anatomy to allow for anatomic correlation. The diagnostic performance for lesion detection in the liver was inferior to MRI in several studies, albeit better than with conventional CT [17, 18]. As a whole body scan, FDG-PET-CT offers complete staging and preoperative detection of extrahepatic metastases such as lymph nodes, lung metastases, etc. [5]. The additional information provided by FDG-PET can improve patient selection, leading to longer survival times of treated patients [19].

As MRI is currently considered the best imaging modality for detecting colorectal liver metastases, and FDG-PET-CT is optimal for whole-body staging, a combination of both modalities would probably provide the best results. PET-MRI scanners are being evaluated in clinical studies, and may play a role in the future [20].

Imaging-Based Assessment of Oncological Resectability in a Multimodal Treatment Setting

The use of pre- and perioperative chemotherapy for colorectal liver metastases remains controversial when metastases are initially resectable, but it is widely and increasingly used, allowing better patient selection, assessment of sensitivity to chemotherapy, and possible downstaging of hepatic lesions [21, 22]. For patients with primarily irresectable metastases, it is the only initial treatment option offering a chance of secondary resectability [23]. This increasing preoperative use of chemotherapy has multiple repercussions not only on surgical decision making, timing of surgery, and liver regeneration, but also on the preoperative radiologic evaluation and diagnostic performance of the routinely used liver imaging techniques.

Impact of Preoperative Chemotherapy on the Diagnostic Performance of Liver Imaging

Preoperative chemotherapy seems to negatively impact the diagnostic performance of various imaging techniques for the evaluation of colorectal liver metastases. In a meta-analysis comprising a total of 11 papers with 223 patients and 906 colorectal hepatic lesions, pooled sensitivity estimates of MRI, CT, FDG-PET and FDG-PET/CT were 86%, 70%, 55%, and 52% respectively, in patients after chemotherapy. In chemonaive patients, sensitivity rates were 81% for CT, 81% for FDG-PET, and 71% for FDG-PET/CT. The negative impact of preoperative chemotherapy on the diagnostic performance was most obvious for FDG-PET and PET-CT, while MRI appears to be the best performing imaging modality after chemotherapy.

Radiological Assessment of the Oncological Response to Preoperative Chemotherapy

A comprehensive preoperative evaluation of the response to systemic neoadjuvant or "downsizing" therapy is warranted to [1] confirm the indication to liver resection, [2] to adequately plan or modify the intended surgical strategy, and [3] also to predict survival.

In a first step, the response to preoperative systemic therapy is assessed using the response

evaluation criteria in solid tumours (RECIST). Determining the change in the sum of diameters of all pre-defined target lesions after treatment, patients are classified as having a stable disease (SD), progressive disease (PD), partial (radiologic) response (PR), or complete (radiologic) response (CR) [24, 25] (see Fig. 4.1). Such assessment of maximum tumor diameter by RECIST or modified RECIST, however, was shown not to be predictive of residual viable tumor burden [26]. With a special regard to targeted therapy, physiologic and metabolic changes may precede alterations in lesion size, and there is growing evidence that tumor burden and response, especially in the early phase, is more accurately reflected by calculating tumor volume or tumor viability [27] or dynamic imaging using CT-MRI perfusion, which can assess changes in tumor vascularity [28, 29].

Taking into account intermetastatic and intrametastatic genetic differences between and within lesions in a single patient [30], the heterogeneity in response to chemotherapy has been shown to be a significant prognostic factor that could be assessed radiologically and, thus, preoperatively [31]. For each lesion individually, the increase or decrease in diameter was measured in terms of percentages, and the maximum difference in response taken as a continuous variable. Based on the differences between the best and the least responding lesion, the response was classified as heterogeneous or mixed response (MR) with >30% difference, but all lesions showing similar behavior, true mixed response (TMR) with at least two lesions behaving differently (at least ±10%), or homogeneous response (HR). This being applied to patient groups according to RECIST, partial responders with a heterogeneous response pattern had a significantly poorer survival compared to patients with a homogeneous partial response [31].

Preoperative Radiological Assessment of Pathologic Response

A complete pathologic response (CPR) after preoperative chemotherapy was observed, in a cohort of 767 patients treated between 1985 and 2006, in 4% of cases [32]. In this study, a low-risk subset of patients younger than 60 years with metastases smaller than 3 cm and low CEA levels experienced CPR in 31% of cases, and high 10-year overall and disease-free survival rates of 68% and 69% respectively. None of the patients with CPR had evidence of complete radiologic response. Instead, only two out of 767 patients experienced a complete radiologic response but were found to have small remnant lesions intraoperatively [32]. Although more

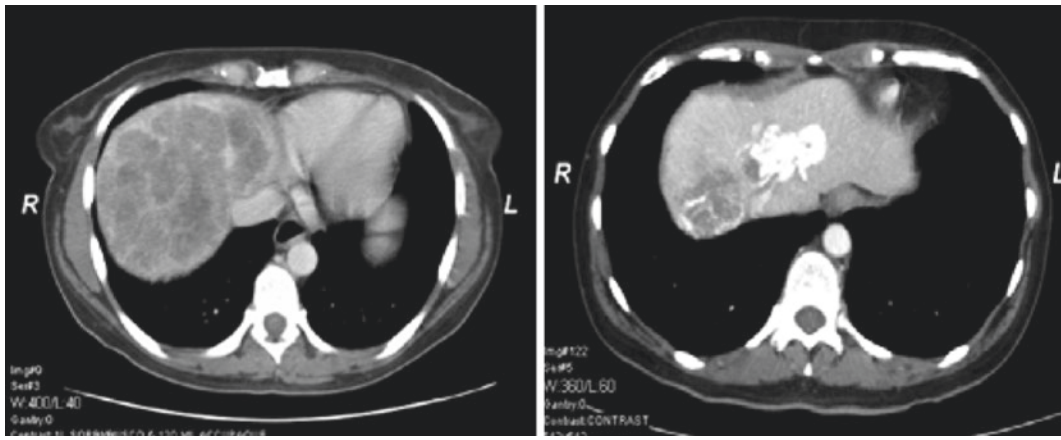

Fig. 4.1 CT-scan of a 38-year-old female patient with synchronous hepatic metastases from a rectosigmoid carcinoma before (*left*) and after (*right*) FOLFIRI/cetuximab chemotherapy showing a partial radiologic response

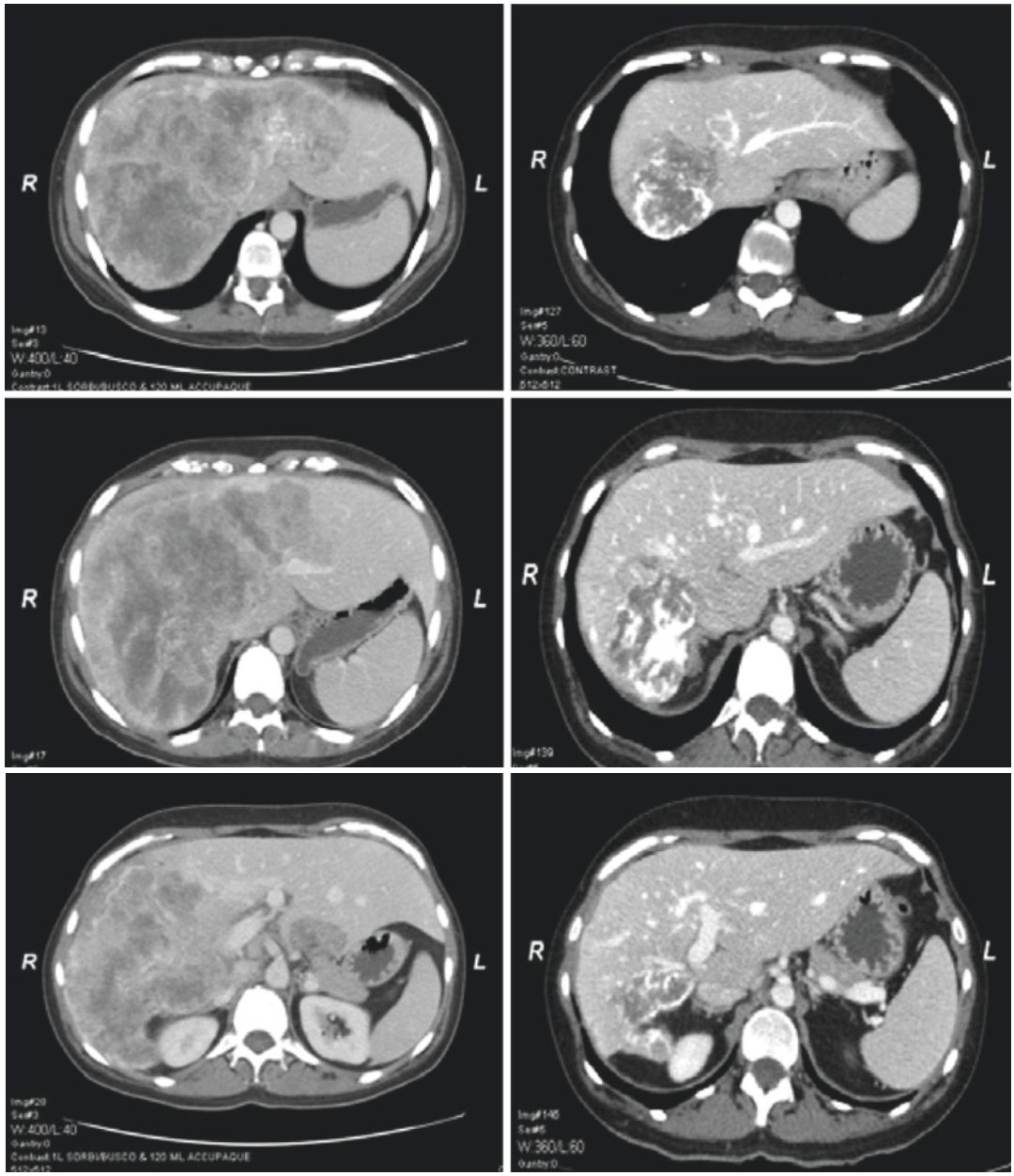

Fig. 4.1 (continued)

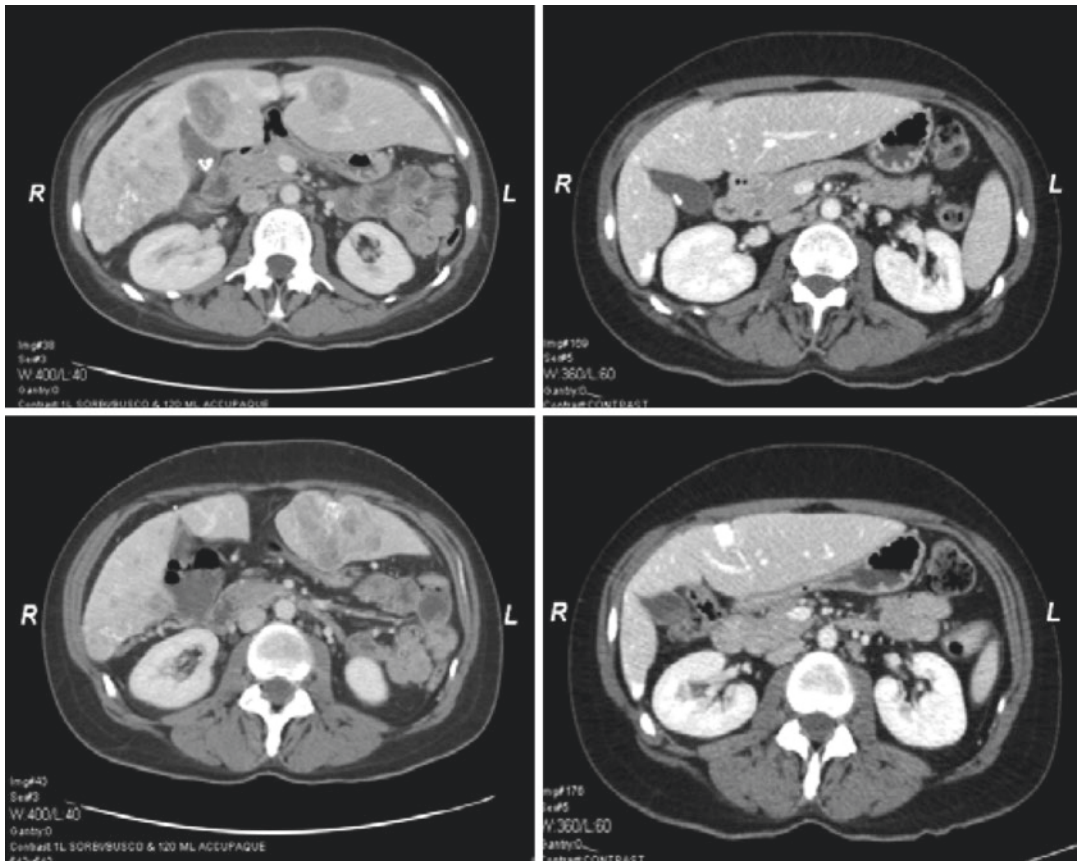

Fig. 4.1 (continued)

recent studies indicate a better diagnostic performance of gadoxetic-enhanced MR and diffusion weighted imaging in identifying patients with a complete pathologic response [33], the correlation of preoperative radiologic and postoperative pathologic response is far from being firm at this point, so patients with a radiologically assumed complete pathologic response should still be recommended resection of their hepatic lesions.

Complete Radiologic Response or the Disappeared Liver Metastasis

With the increasing use of highly efficient chemotherapeutic and biological agents in the treatment of colorectal liver metastases, a growing number of patients are experiencing a complete radiologic response—a phenomenon also called vanishing or disappearing liver metastases [34]. As mentioned earlier, reports differ to what extent lesions exhibiting a complete radiologic response were postoperatively found to have a CPR. While some authors have demonstrated only little correlation between response to chemotherapy on imaging and pathological examination [35, 36], others found a CPR in up to two thirds of disappeared metastases [37, 38].

Disappeared metastases can become a surgical challenge when neither intraoperative ultrasound (IOUS) nor digital palpation are able to localize the lesion. The latter aspect is a particular concern for deeply located metastases as well as during laparoscopic liver resections. Strategies to cope with disappeared metastases

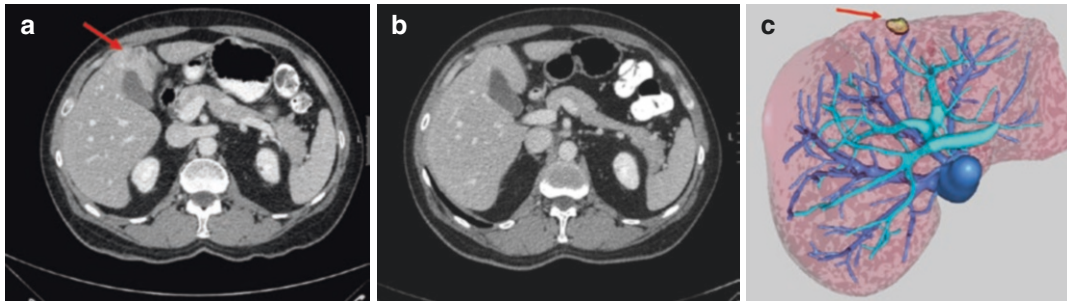

Fig. 4.2 A synchronous colorectal liver metastasis **a**, having completely disappeared after chemotherapy **b**. **c** 3D-fusion imaging

are [1] early restaging during preoperative chemotherapy after a few cycles and prompt resection before complete disappearance [34], marking of lesions with coils and resection after completion of preoperative chemotherapy [39], or pre-therapy imaging-based computer-assisted 3D-navigated open or laparoscopic resection [40] (Fig. 4.2a–c).

Functional Resectability

Assessment of the Functional Liver Remnant

The major cause of morbidity and mortality of a liver resection procedure is postoperative liver failure. In livers without underlying parenchymal disease, resections of up to 75–80% of the total liver volume are considered safe in most centers [41, 42]. In patients with compromised livers secondary to alcoholic or non-alcoholic steatohepatitis, viral hepatitis, or parenchymal alterations after hepatotoxic chemotherapy (steatosis, sinusoidal dilatation, etc.) removal of lower liver volumes can severely impact postoperative liver function, and a remnant volume of at least 40% is considered acceptable [43]. Size, parenchymal quality, and adequacy of the arterial and portal blood supply, as well as the venous and biliary drainage of the future liver remnant, are the factors that need to be considered in assessing functional resectability and eventually surgical decision-making.

Volumetric Assessment of the Liver

CT volumetry as initially proposed by Heymsfield [44] is the current gold standard, and allows a relatively precise calculation of the total liver volume, tumor volume, and volume of the future liver remnant (FLR) [45]. Since the size of the presumed FLR is only a surrogate marker of postoperative liver function, discrepancies between CT volumetry, liver function, and postoperative outcome can occur [46]. Calculating a standardized future liver remnant by correlating the size of the FLR with the estimated total liver volume can help to personalize volumetric measurements and better evaluate the risk of resection [47]. Total liver volume estimation has been described by Urata [48] in an Asian or by Vauthey [49] in a Western population. Alternatively, risk assessment can be achieved by correlating FLR and body weight [50], and either method has proven its ability to predict the postoperative outcome after extended hepatic resections [51].

Enzymatic Liver Function Testing

Enzymatic liver function tests such as the indocyanine-green-(ICG)-clearance or LiMAx-test can help assess global hepatic function, and have been evaluated as a useful additional tool in the preoperative work-up and risk assessment of hepatic resection [52]. With a special regard to liver resection for colorectal liver metastases and the high number of patients pretreated with

chemotherapy, an additional estimation of hepatic functional impairment after preoperative chemotherapy could potentially increase surgical safety.

The role of ICG-clearance seemed to be of limited value in assessing chemotherapy-associated liver injury [53]. In contrast, LiMAx has demonstrated a significant drop in enzymatic hepatic function after an oxaliplatin-based chemotherapy and a subsequent recovery within an average of 8 weeks after cessation of therapy. However, the pace of regeneration and time to functional recovery were highly different among patients [54]. Further studies are needed to corroborate the role of enzymatic liver function tests in liver surgery for colorectal metastases but could eventually impact surgical decision-making and timing of the procedure.

Imaging-Based Liver Function Testing

Imaging-based liver function tests were first developed in nuclear medicine and, compared to laboratory and enzymatic tests, have the advantage of additionally displaying the spatial distribution of liver function [55]. Using 99mTc-mebrofenin or 99mTc-galactosyl tracer scans, liver function can be assessed by planar scintigraphy. Single photon-emission computed tomography CT (SPECT-CT) offers hepatic function analysis in conjunction with 3D-volumetry, as does Gd-EOB-DTPA-enhanced MRI but featuring a higher temporal and spatial resolution than SPECT. MRI-based liver function assessment measures either biliary signal intensity during biliary elimination or the parenchymal contrast agent behavior over time by a region of interest analysis (see Fig. 4.3). It could be integrated seamlessly into the routine MRI-work-up at a relatively low expense [55].

The spatial distribution of liver function offered by imaging-based assessment could prove particularly helpful in the setting of hypertrophy induction following portal vein ligation or embolization, or as an intermittent assessment in between ALPPS steps (associating liver partition and portal vein ligation for staged hepatectomy).

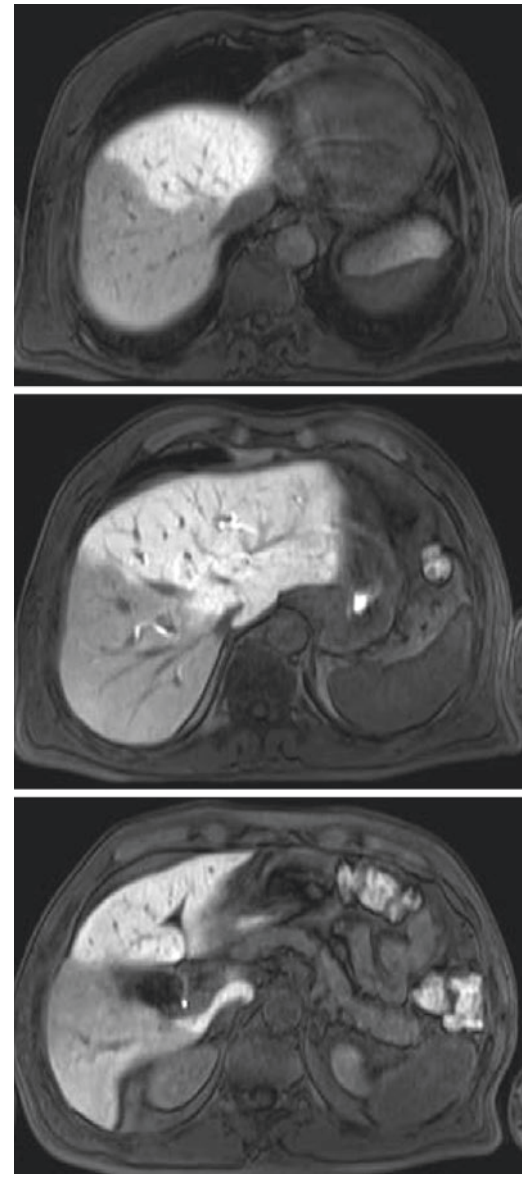

Fig. 4.3 Gd-EOB-enhanced MRI 4 weeks after right portal vein embolization, T1-VIBE sequence after 20 min with flip angle of 30°. MRI with an increased excitation angle clearly shows the different signal intensities of the embolized and the non-embolized liver segments corresponding to a different function ratio (from [55] with permission)

Computer-Assisted Virtual Resection Planning in the 3D Liver Model

Ongoing development in CT imaging-based computer assistance has enabled an optimal visualisation of the intrahepatic vascular branching

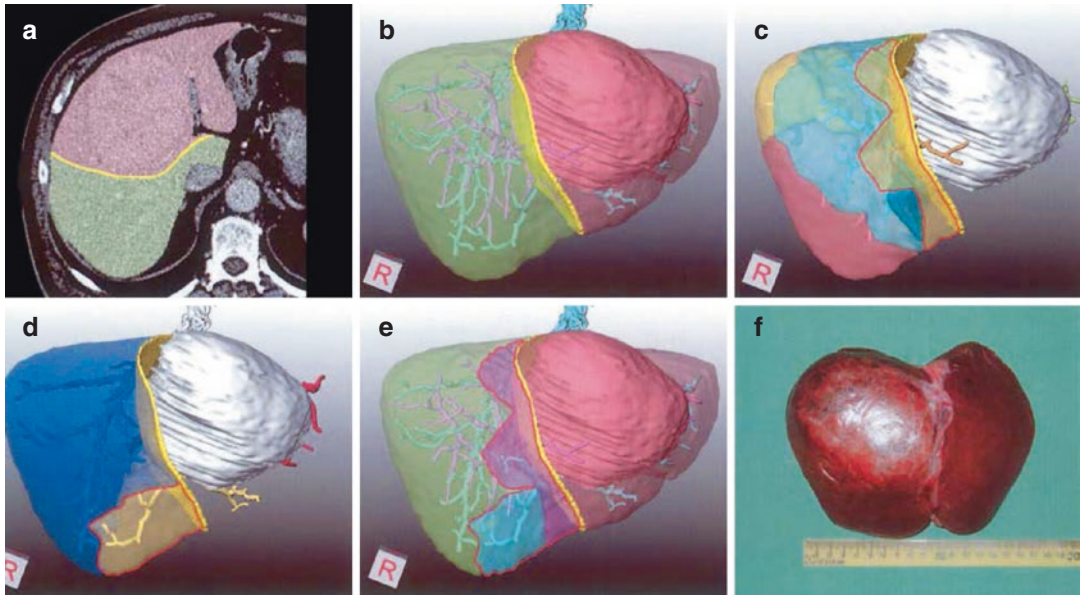

Fig. 4.4 Computation of volumetric risk for devascularization. **a** and **b** Transfer of the resection planned in Fig. 4.4a–c to the results of anatomic image evaluation as seen in Fig. 4.1. Portal vein, *magenta*; hepatic veins, *cyan*; plane of resection, *yellow*; remnant (remaining liver volume after resection planning in 2-dimensional computed tomography), *green*; and resected parenchyma, *red*. **c** Portal venous territories within remnant liver tissue. The *red-bordered* territory has been supplied by the dissected segment V branch and is exposed to devascularization after resection (accounting for 8% of the remaining tissue). **d** Territories within the remnant draining into the right hepatic vein (*blue*), and devascularized area (accounting for 6% of the remaining tissue) draining into a dissected small subbranch of the middle hepatic vein (*red bordered*). **e** Combined territories at risk for devascularization (accounting for 13% of the remaining tissue) for both blood supply and drainage (*red bordered*). Portal risk territory, *magenta*; risk for hepatic veins, *cyan*. Remaining functional liver volume after computer-assisted risk analysis (*green*), 679 ml. **f** Resection specimen after extended left hepatectomy. Ruler is in centimeters (from [61] with permission)

in a virtual 3D liver model, providing an individual territorial liver mapping as well as volume calculation of the corresponding vascular territories. Thus, liver resections can be planned with regard to the individual intrahepatic vascular anatomy and segmentation [56]. Resection planning is either fully automatic by the computer, with variable and freely selectable safety margins, or manually "free-hand" by the surgeon within the three-dimensionally reconstructed virtual liver [57]. The advantages of computer-assisted resection planning refer to a better assessment of functional resectability, since areas at risk for either devascularization or impaired venous drainage can be identified and precisely characterized preoperatively. Computer-assisted virtual resection planning, potentially combined with navigation, may evolve into a routine clinical practice in cases of complex and repeated liver resection for colorectal metastases in the future [40, 58–60] Fig. 4.4.

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Choosing the Best Strategy

5

Victoria Ardiles and Eduardo de Santibañes

Introduction

In the last two decades, advances in hepatic surgery have led to greater safety in the treatment of patients with primary and secondary liver tumors [1–4]. The morbidity associated with liver resections has decreased from 70% to 15–30% and the mortality from 15–25% to 2–5%. This has been accompanied by an increase in indications for resection. The reasons behind this improvement includes the progress in intraoperatory bleeding control with reduced perioperatory transfusions, a better control of septic complications, and an increase in knowledge with regard to the prevention and management of post-hepatectomy liver failure (PHLF). On the other hand, different innovations in imaging methods, refinements of the surgical techniques, and advances in local and systemic treatments, as well as the introduction of routine multidisciplinary patient care have allowed a gradual expansion of resectability criteria and the safe performance of highly complex liver surgery.

Modern liver surgery has undergone a paradigm shift with regard to resectability. Up until a few years ago, the main focus was placed on anatomical criteria, i.e., on the liver to be resected. In this approach, the number, size, and location of lesions were considered limiting factors to classify a patient with colorectal liver metastases (CLM) as resectable [5, 6]. In the last decade, the attention has shifted towards a functional approach, where the main focus is placed on what remains after resection, regardless of the specimen resected. Even though the number, size, and location of the lesions themselves are no longer a contraindication for surgery, they often require the use of new tactics and strategies for treatment. The current paradigm of resectability is defined by the possibility of achieving complete tumor resection with negative margins, preserving at least two contiguous segments with intact portal, arterial, and biliary flow [7]. However, the recently introduced associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) approach has allowed even more extensive liver resections, with a single liver segment left behind as sufficient liver remnant (Fig. 5.1) [8, 9].

Although multiple, large, and bilateral CLM are no longer a contraindication to resection, they represent a more advanced tumor or a more aggressive biological disease resulting in poorer prognosis. Long-term outcomes of patients with extensive CLM who require extreme treatments to be resected are worse than in those resected with unique metastasis [10, 11]. For this reason,

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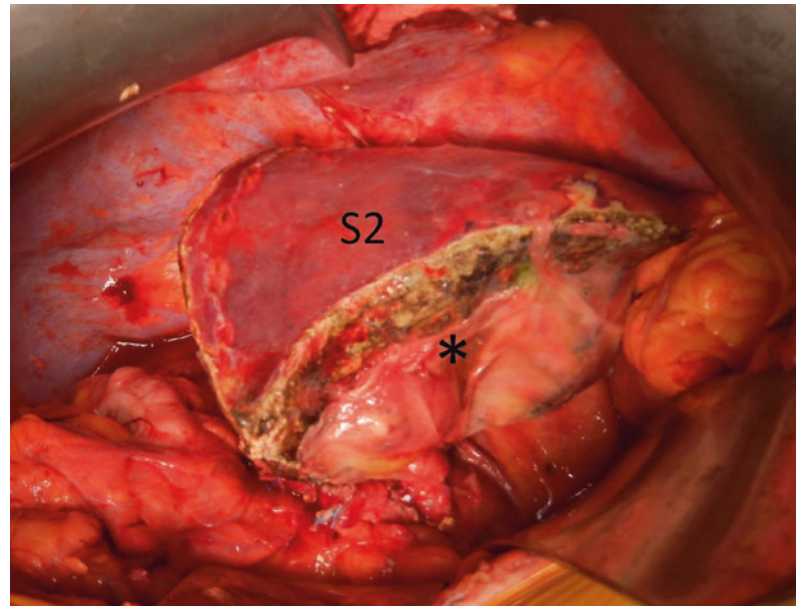

Fig. 5.1 Monosegment associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Only segment 2 (*S2*) was left as future liver remnant after a right trisectionectomy and anatomical resection of segment 3 (*asterisk*) in a patient with bilateral colorectal liver metastases

the assessment of each individual case by a multidisciplinary team is critical to offer the best treatment within the multiple strategies available.

Patient Selection

The selection of candidates for a given strategy requires both a general evaluation of the patient and a local evaluation of the liver parenchyma.

General Evaluation

The prevention of perioperative complications begins with an accurate assessment of the patient in order to optimize their clinical status and detect liable treatment conditions. Currently, there is no scale of global perioperative risk; hence patient's clinical risk and surgical risk evaluation are done separately. In general, liver resections are classified as high-risk surgeries due to functional implications, the possibility of bleeding, surgical position, and the duration of the procedure. Liver resections are also associated with a risk of cardiovascular (CV) events of around 5%. The ASA score (scale of the American Society of Anesthesiologists) is an assessment of the clinical status of the patient, not a risk scale, so it must be complemented with an assessment of CV and respiratory risk, especially in older patients and those with a related medical history. Acute renal failure in the postoperative period has been associated with increased mortality at 90 days posthepatectomy [12, 13]. Therefore, it is necessary to evaluate and optimize renal function before surgery, and to modify perioperative management, controlling renal perfusion and avoiding nephrotoxic drugs. Diabetic patients show an increased risk of infection, thrombosis, CV, and renal failure [14, 15]. Furthermore, liver regeneration may be reduced, with the consequent increased risk of PHLF, especially in patients who undergo major liver resections.

Advanced age is associated with an increased prevalence of comorbidities and disabilities. The aging process involves a decrease in the physiological reserves of vital organs (heart, liver, and kidney), therefore increasing the operative risk. In recent years, the concept of fragility has been developed, and is defined as the biological syndrome where the reserve and resistance to stressors reduce functionality progressively [16]. This deterioration leads to an increased vulnerability for adverse outcomes. The elderly patient group is not a homogeneous population as chronological age does not always reflect the biological age.

Therefore, the global evaluation of these patients should be carried out including not only comorbid conditions, but also geriatric syndromes and frailty (weight loss, weakness, low resistance, etc.). The fragility syndrome has been associated in several studies with an increased frequency of postoperative complications, prolonged hospitalization, and death [16]. The treatment strategy should therefore be tailored according to the existence of both patient- and liver-related operative risks.

Local Evaluation

In the treatment of liver tumors the surgeon must follow two contradictory objectives: (1) a complete resection of the tumor(s), and (2) the preservation of as much parenchyma as possible to prevent the development of PHLF, which is the most severe complication after major hepatic resections. Moreover, postoperative mortality has been related to PHLF in approximately half of patients [17]. Risk factors include previous parenchymal damage, long-course chemotherapy regimens, size and functional status of the liver remnant, and intraoperative ischemia developed by the surgeon. For this reason, it is essential to evaluate the quality and quantity of the remaining liver prior to surgery, as well as to detect portal hypertension at an early stage.

- *Evaluation of liver function:* this is usually performed by imaging methods and liver function tests. Patients with suspicion of liver parenchyma disease (fibrosis, inflammation, steatosis, chemotherapy-related liver injury) may require further evaluation with fibro-scan and a dynamic assessment of liver function. Liver biopsy in this context is rarely used, but can provide additional information in specific cases.
- *Evaluation of portal hypertension:* this is usually assessed by indirect methods such as the presence of ascites, thrombocytopenia, splenomegaly, spontaneous portocaval shunts, and esophageal varices. Even though patients with CLM rarely require invasive studies with direct measurement of portal vein pressure (PVP), its intraoperative measurement can be a useful indicator, since a PVP of 21 mmHg or greater has been identified as an independent predictor of PHLF and 90-day mortality after major hepatectomy in the noncirrhotic liver (Fig. 5.2) [18].
- *Evaluation of the liver remnant volume:* a small future liver remnant (FLR) is associated

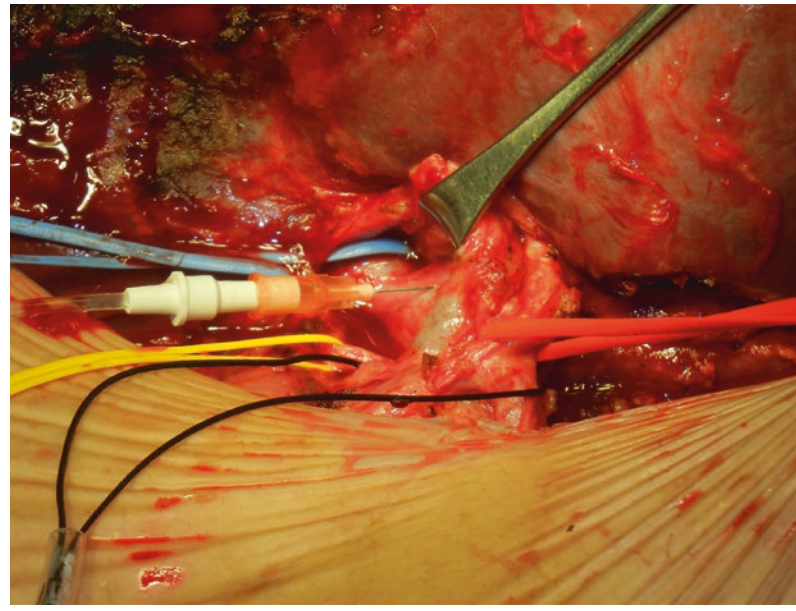

Fig. 5.2 Intraoperative measurement of the portal pressure by direct puncture of the main portal vein with a 25-gauge needle

with PHLF and increased postoperative morbidity and mortality. Because of this, volumetric assessment should be focused on the FLR volume. Usually, this volume is assessed in the same study performed to evaluate the tumor (either CT-scan or MRI). The surgeon must be involved in the process in order to delimit the planned FLR with the radiologist. In cases there are metastases in the FLR, these must be excluded from the overall calculation. The FLR can be expressed in absolute terms using volume units (ml or cc), or in relative terms as % over total liver volume or body weight (FLR/TLV or FLR/BW). The total liver volume should ideally be measured by volumetric analysis (excluding the tumor) or calculated as the standardized total liver volume using the formula: −794.41 + 1267.289 × body surface area (m^2; Mosteller formula) [19]. The FLR volume required for a safe resection in terms of PHLF risk is: 25–30% of the total liver volume (or ≥0.5% of FLR/BW ratio) in healthy livers, ≥30% in patients with steatosis damage or chemotherapy, and ≥40% in cirrhotic livers (or ≥0.8% of FLR/BW ratio) [20, 21]. The determination of FLR volume is also useful to monitor FLR growth after any of the procedures (portal vein embolization or ligation) that aim to induce FLR hypertrophy, allowing the calculation of the kinetic growth rate (KGR) expressed as either % or cc per day or weeks. The amount of the remnant liver is crucial, but its quality is also very important (presence of steatohepatitis, sinusoidal obstructive syndrome, cirrhosis, etc.). In these patients, in whom volumetric studies do not necessarily correlate with functionality, functional studies such as scintigraphy (99mTc-GSA, 99mTc-HBS), galactose elimination capacity, LIMAX test or indocyanine green clearence tests, might be of paramount help. However, except for the scintigraphic tests, most functional studies imply full liver functionality without discriminating the FLR (Fig. 5.3) [22].

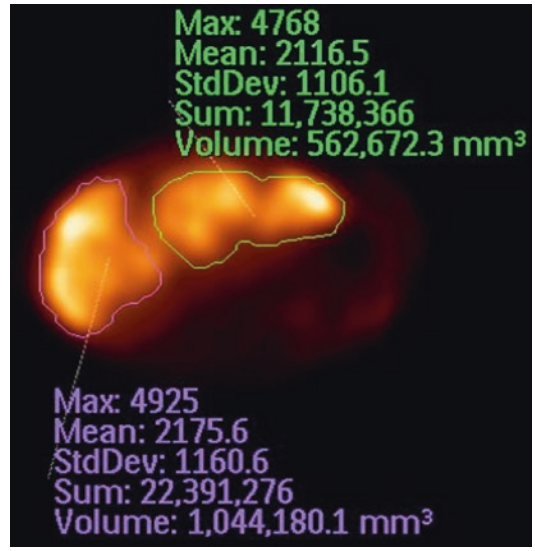

Fig. 5.3 Hepatobiliary scintigraphy to assess future liver remnant function before stage 2 in a patient undergoing the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) approach

Choosing the Best Strategy

The modern treatment of patients with CLM involve different tools that instead of competing, complement each other and are often applied sequentially. The right strategy is based on adequate selection and timing of application for each one of them. Every patient bearing CLM should be routinely discussed at a multidisciplinary tumor board including at a minimum a liver surgeon, an oncologist and a radiologist. If synchronic colorectal disease is present, a colorectal surgeon and radiation oncologist should by added to the team. Such a multidisciplinary approach has been demonstrated to offer better patient care and survival outcomes, as well as improved consistency, continuity, coordination, and cost-effectiveness of treatment [23]. Treatment eligibility should be determined taking into account the risk–benefit balance of each possible alternative, their feasibility, and oncological rationality. The several aspects that have to be considered with regard to imaging evaluation, chemotherapy, and surgery will be summarized in this section.

Imaging Considerations

Several advances in imaging methods have led to a more accurate preoperative staging at both local and systemic levels, and thus a better planning of treatment strategies. Imaging modalities in patients with CLM should provide information on the number, size, and location of metastasis, its relationship with vascular and biliary structures, and the presence of lymph node metastases in either the hepatic hilum or other locations. The presence of extrahepatic disease should also be evaluated. Currently, the most used methods for staging are magnetic resonance imaging (MRI), computed tomographic scan (CT-scan) and positron emission tomography scan (PET-scan) [24]. These last two studies can be merged for a better anatomical resolution. Despite having a lower sensitivity than MRI, the CT-scan is the most used method for the study of the liver and extrahepatic metastasis, remaining as the first-line diagnostic tool in most centers [24]. Modern multi-slice equipment with high definition as well as different phases of intravenous contrast makes possible reconstructions in any anatomical plane, and even three-dimensional vascular reconstructions (Angio-CT). An MRI with diffusion-weighted images has a higher sensitivity for the detection of CLM, reaching 100% in lesions larger than 1 cm [24]. It also makes it possible to distinguish the different soft tissues, so it is often used to define the metastatic nature of unspecific tumors observed in CT-scan. The systematization of the study protocol is very important to achieve excellent results. This includes axial planes, T2 sequences, T2 fat suppression, in- and out-phases, diffusion, and dynamic study with intravenous contrast. While MRI is used in most of the centers as second diagnostic line, it should be used as first line especially in patients who have received chemotherapy (in which TC has low sensitivity) or to detect small or missing lesions. The PET-scan has high sensitivity and specificity comparable to or even greater than CT-scan for initial staging of patients with liver metastasis. This study is useful to detect extrahepatic disease and to stage patients with recurrence in whom a new resection is planned. However, it has a weak anatomical definition and should be complemented by specific imaging studies.

Another key piece of information to define the surgical strategy provided by modern preoperative imaging concerns the liver anatomy itself, and the relationship between the metastatic disease and the different structures of the portal pedicle or hepatic veins. For example, the presence of an accessory hepatic vein (e.g., segment 6) could change the surgical approach, allowing certain parenchymal preserving strategies [25]. Therefore, the knowledge of normal liver anatomy and its variations is essential to plan the strategy, based on the information provided by the imaging studies.

Chemotherapy Considerations

The application of preoperative systemic chemotherapy in patients with CLM may be used in to ways: (1) as neoadjuvant therapy for resectable tumors, or (2) as conversion therapy to transform initially not resectable disease into resectable disease. The opportunity to convert a patient with an initially unresectable disease to resectable has further expanded the pool of patients who may benefit from surgery. This type of treatment requires intense collaboration between the team of surgeons and oncologists, who should reassess the treatment's response every 2–3 months and define the right time for liver resection. Liver metastasis should be resected as soon as they become technically resectable. This makes it possible to stay under the therapeutic window for response in order to avoid progression during treatment, which is associated with poor prognosis, but also to shorten the treatment duration and prevent liver damage.

Even though patients with response or stable disease under chemotherapy are those who benefit the most from surgical resection, recent evidence suggests that patients under progression but with less than three lesions, none of them larger than 5 cm and with a CEA of less than 200 ng/ml can have similar results to those without progressive disease [26]. Different chemotherapy regi-

mens, associated or not with monoclonal antibodies, have been studied with promising results, reaching high rates of post-treatment R0 resections in selected patients. However, intensive use of chemotherapy is not harmless for the liver parenchyma. In fact, the use of pre-hepatectomy chemotherapy has been associated with higher morbidity and mortality after resection, especially when more than five cycles are administered [27]. The different types of parenchymal injuries possible are associated with the use of specific drugs. The use of 5-fluorouracil has been associated with the development of liver steatosis, while irinotecan with steatosis and chemotherapy-associated steatohepatitis (CASH), which has been found to be a risk factor for postoperative morbidity and mortality [28]. On the other hand, oxaliplatin is associated with sinusoidal obstruction syndrome (SOS), which is related to increased risk of postoperative bleeding [29]. Some studies suggest that combining with bevacizumab (anti-VGF) may protect from this syndrome caused by oxaliplatin [30]. Although the use of anti-EGFR antibodies (cetuximab, panitumumab) has not been associated with increased risk of morbidity, a higher incidence of bleeding, impaired tissue healing and possible alterations in liver regeneration are described for bevacizumab [28]. However, these changes could be minimized if the medication is suspended at least 5 weeks before surgery [31].

Another problem with chemotherapy, more worrisome when using it as neoadjuvant treatment in patients with resectable disease, is the disappearance of metastasis in preoperative imaging. Some authors propose differentiating between those metastases that fade ("vanishing") in imaging but are visible during laparotomy, and those that are absent in imaging and cannot be detected during surgery ("missing"). Imaging studies have limitations in detecting small and superficial lesions; so the general consensus defines that patients should be explored surgically even if metastases are not visible on preoperative imaging [32]. Every lesion detected during laparotomy through visualization, palpation, and/or intraoperative ultrasonography ("vanishing metastasis"), should be ideally resected or at least treated with a local ablative method. One of the biggest challenges for a liver surgeon is the scenario of a disappearing metastasis on preoperative imaging that cannot be detected during surgery ("missing metastasis"). This scenario should be avoided when using preoperative chemotherapy, since complete tumor necrosis in these missing sites is exceptional (4–20%) and therefore there is a high risk of leaving microscopic disease behind [33, 34]. Given that complete pathologic response has been associated with an increased long-term survival, until a few years ago most experts recommended resection of parenchyma where metastases were located previously [33]. Even though nowadays there is not an absolute consensus, if a metastasis cannot be detected after careful and thorough palpation and intraoperative ultrasonography, blind resection should be avoided, and patients should be carefully followed by CEA and imaging methods in order to detect early recurrence if any.

Surgical Considerations

The evolution of liver surgery and chemotherapy regimens in the last 10 years has reduced the need of large liver resections [35]. Nowadays, a greater number of parenchymal sparing strategies are being performed (Fig. 5.4), which are considered by many the first-choice strategy because it preserves non-tumoral parenchyma, allows repeated resection in case of recurrence, and does not compromise oncological outcomes [25, 35, 36]. Parenchymal sparing resections might be particularly beneficial for patients with a high operative risk for major resection, who would otherwise not be candidates for resection. Intraoperative ultrasound confirms and extends previous findings, becoming essential for intraoperative decision- making [25].

The paradigm shift from large to parenchymal sparing resections was possible mainly due to a modification of the oncological concept of safe resection margins. In the 1990s, a lesion was considered non-resectable if it could not be resected with a margin of at least 1 cm [6]. Later on, not reaching this margin was not a contraindication but a strong recommendation [37]. Conversely, in

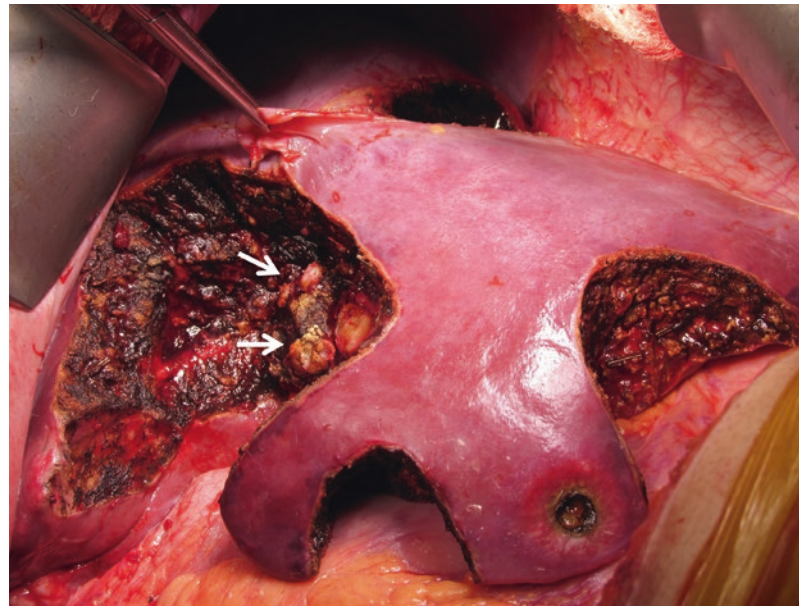

Fig. 5.4 Parenchymal sparing strategy in a patient with multiple bilateral liver metastases. A left hepatectomy is avoided by multiple atypical resections in segments 2, 3 and 4. Segment 4b pedicles emerging from the Rex's recessus are recognized in the resection surface (*white arrows*)

the last 15 years, various authors have shown comparable results with narrower margins and even with positive microscopic margins (R1) [38, 39]. However, the current consensus is that the thickness of the margin does not modify survival as long as it is negative (R0 resection), although R1 resection alone should not be a contraindication for surgery. Nowadays, unresectable extrahepatic metastases or unresectable primary tumor, prohibitive anesthesiological risk, and medical contraindications to hepatectomy still constitute contraindications for resection.

Despite the fact that parenchymal sparing minor resections are preferable in most patients, in certain cases the treatment of extensive tumor burden and/or unfavourable disease location requires the use of major liver resections, which carries a significant risk of PHLF when the FLR is regarded as insufficient. The old paradigm of resectability began to change with the introduction of different techniques to increase FLR volume, allowing safer major curative resections. Makucchi and coworkers described in 1990 the use of transileocolic portal vein embolization (PVE) to reduce PHLF in patients with hiliar cholangiocarcinoma [40]. The next breakthrough came a decade later, when the group from the Paul Brousse Hospital in Paris introduced a sequential surgical technique known as "two-stage hepatectomy", which removes multiple liver tumors, allowing the liver to regenerate between the two procedures [41]. Soon after, Belghiti and colleagues in France modified this approach by applying portal ligation and concomitant wedge resection of all tumors on the left side during the first surgery, followed a few weeks later by an extended right hepatectomy [42]. Finally, Jaeck and colleagues developed another two-stage approach for bilateral (predominantly right) disease, consisting of right PVE and resection of tumors located in the left liver during the first stage [43]. In 2009, a group from Seoul reported favourable results with the addition of sequential embolization of the hepatic vein 2 weeks after PVE, inducing a greater contralateral regeneration due to more liver damage than PVE alone [44]. Using this principle, Balzan et al. [45] developed an outflow modulation alternative to induce hypertrophy of insufficient segments 1 and 4. More specifically, in a first surgery a right hepatectomy combined with partial ligation of the left hepatic vein is performed, generating flow redistribution to segments 1 and 4, and therefore inducing its hypertrophy. In a second stage, a left lateral segmentectomy is completed.

To minimize the risk of PHLF in patients with a small FLR, all the previously mentioned strategies have been developed with satisfactory results in terms of safety. However, only 30–40% hypertrophy can be achieved in 1–3 months and up to 40% of patients treated with this approach are ultimately not amenable to resection due to tumor progression in the interval period or insufficient FLR hypertrophy [46]. Interestingly, in the MD Anderson PVE series, those patients that fail to complete the second stage do even worse than those patients treated with chemotherapy alone [47]. Many argue that early progression of malignant disease after PVE is beneficial for the selection of patients who were not destined to benefit from liver resection. What can not be evaluated in this case is when the progression of the disease avoids unnecessary surgery in a patient or prevents the salvage surgery.

The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently emerged as an option to avoid the high drop-outs of classical staged resections and PVE [8, 9]. This strategy induces a rapid and large FLR volume increase. The FLR hypertrophy observed with ALPPS is up to 200% over an average observation time of 1 week. However, the possibility of achieving a short-term hypertrophy and high resectability rates has been counteracted in initial series by an increased risk of morbidity and mortality [48]. Recently, an International Consensus Conference on ALLPS was held in Hamburg, Germany [49]. In this consensus conference, it was concluded that ALPPS has the potential to increase resectability in patients with high tumor load, and could be included as a part of the armamentarium of personalized treatment strategies in patients with CLM.

As the indications for surgical treatment of CLM have broadened, the use of multimodal therapies has also become more common. Nowadays, a patient with multiple bilateral disease should not be excluded from surgery if it is possible to treat all lesions with a combination of resection and local ablation techniques. This combined approach extends the limits of surgical treatment, where liver resection addresses the main tumor mass, and the residual tumor that cannot be resected is treated with local ablation [25, 35]. Thermal techniques using radiofrequency ablation (RFA) are the most commonly used methods. Other thermal ablative techniques include cryotherapy, laser interstitial thermotherapy, microwave coagulation therapy, hot saline injection, and high-intensity focused ultrasound. Ideally, lesions treated with RFA should be less than 25 mm in size, since technically successful ablation is possible in more than 90% of the cases [25]. This combined approach has not been associated with a compromise in disease-specific survival [25, 35].

Large CLM located at the hepatocaval confluence or compromising the inferior vena cava (IVC) are often not resectable using conventional techniques. To overcome this problem, different surgical procedures have been described. Ex-vivo resection techniques provide excellent accessibility to tumours placed around the IVC that otherwise would be unresectable [50]. These ex-vivo techniques include in-situ, ante-situ, and ex-situ resections. The two main problems regarding ex-vivo procedures are the low hepatic tolerance to warm ischemia and the splanchnic congestion secondary to vascular exclusion. Hypothermic hepatic perfusion and extracorporeal circulation with veno-venous bypass are two well-known strategies to avoid these complications [51]. More recently, a novel technique of ante-situ resection has been reported using a transitory intracorporeal veno-venous bypass between the portal vein and the IVC using a cadaveric saphenous graft [52].

Conclusions

The management of CLM has evolved over the past decades, with more patients now being offered surgery. The use of modern chemotherapeutic agents has contributed greatly to increase the resectability rates, and adjunct techniques to surgery have significantly improved outcomes. As a consequence, patients with advanced CLM are living longer than they did previously due to these major advances in treatment. Patient treatment should be routinely discussed by a multidisciplinary tumor board

including colorectal surgeons, liver surgeons, oncologists, radiation oncologists, radiologists and pathologists. Such a multidisciplinary approach has demonstrated to offer better patient care and survival outcomes, as well as improved consistency, continuity, coordination, and cost-effectiveness of treatment.

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Part II

Non-operative Multimodal Therapies

Conversion and Neoadjuvant Therapies

6

Jorge Pablo Grondona

Introduction

We define, as metastatic colorectal cancer (CRC), all cases of adenocarcinoma of the colon and/or rectum with documented secondary sites at the moment of diagnosis. The liver is the most common site for CLMs due to the enteric venous drainage via the portal circulation, with up to 50% of CRC patients developing liver metastases. Furthermore, the liver is the only site of metastasis in 35% of cases [1]. Globally, CRC is the commonest malignancy of the digestive tract and the third most common type of cancer, making up about 10% of all cases. It is more common in developed countries, where more than 65% of cases are found, and it is slightly less common in women than men [2, 3]. The majority of CRC develop sporadically; however, family history of CRC in a first-degree relative confers a two- to three-fold increased risk of disease. Environmental risk factors include obesity, physical inactivity, low fibre diet, and a high intake of red and processed meats [3]. The International Agency for Research on Cancer, the GLOBOCAN 2012, estimated the cancer incidence, mortality, and prevalence worldwide in 2012, and has published incidence and mortality of 27 major cancers for that year. They have reviewed the sources and methods used in compiling the national cancer incidence and mortality in 20 large "areas" of the world. Overall, there were 14.1 million new cases and 8.2 million deaths in 2012 [4]. The most commonly diagnosed cancers were lung (1.82 million), breast (1.67 million), and colorectal (1.36 million); the most common causes of cancer death were lung cancer (1.6 million deaths), liver cancer (745,000 deaths), and stomach cancer (723,000 deaths) [4]. For instance, GLOBOCAN 2012 published that the number of new CRC cases in all ages and both sexes in United States would be144,309 in 2015 (75,157 men and 69,152 women), and the number of deaths in all ages and both sexes would be 59,283 (31,434 men and 27,849 women) [4]. In our country, Argentina, the number of new CRC cases in all ages and both sexes would be 14,295 in 2015 (7626 men and 6669 women), and the number of deaths in all ages and both sexes would be 8391 (4537 men and 3854 women) [1]. In United States and in Argentina, CRC is the third most common cancer in both men and women and, the third leading cause in both sexes of cancer death in men and women [3]. Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States in the current year and compiles the most recent data on cancer incidence, mortality, and survival [2]. The overall cancer death rate in the

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Unites States decreased from 2151 (per 100,000 population) in 1991 to 1687 in 2011, a total relative decline of 22%. However, the magnitude of the decline varied by state of the country [2, 3]. CRC incidences rates also have been decreasing in United States for most of the past two decades, which has been attributed to both changes in risk factors and the uptake of CRC screening among adults 50 years and older. Further, from 2007 to 2011, incidence rates declined by 4.3% per year among adults 50 years of age and older, but increased by 1.8% per year among adults younger than age 50 [5]. CRC mortality rates have been declining since 1980 in men and since 1947 in women, with the decline accelerating in both sexes in the most recent time period. In addition, from 2007 to 2011, the overall death rate declined by 2.5% per year. This trend reflects declining incidence rates and improvements in early detection and treatment [5]. Treatments used for CRC may include some combination of surgery, radiation therapy, chemotherapy, and targeted therapy. Tumors that are confined within the wall of the colon may be curable with surgery, while cancer that has spread widely is usually not curable, with management focusing on improving quality of life and symptoms. Five-year survival rates in Western countries are around 60–65%. This, however, depends on how advanced the CRC is, whether or not all the cancer can be removed with surgery, and on the person's overall health. It is well known that the liver is the most common site of metastases from CRC [3, 4]. Approximately 15–20% of patients have liver metastases at diagnosis, and another 50% develop metastatic disease to the liver over the course of their disease [4–7]. For these patients, hepatic resection currently offers the best chance for long-term survival [6–9]. Related to the way of referring to disease-free survival versus progression-free survival, currently, there are trends in medical literature to change the word "disease" to "progression" because the first one has the wrong connotation of surviving without cancer disease, but the true situation is that the only way we can know whether the patient has a progression of disease or not is through imaging studies and/or blood tumor marker levels. Based on current evidence, the primary aim of treatment is to achieve a long progression-free survival (PFS) interval following resection. Whether or not initially resectable or unresectable CLMs are cured or at least whether a long overall survival (OS) duration is possible after complete resection of the metastases has improved significantly in recent years [6–8]. Although the reasons for this OS trend are not clear, contributing factors may include the use of newer preoperative imaging studies, increased use of chemotherapy, and salvage surgical therapy [9]. Adam, R and colleagues published in 2014 the results of "LiverMetSurvey" related to patient survival after a first liver operation for CLMs in a cohort of 23,444 cases coming from 302 surgical centers of 69 countries. A total of 22,210 were resected, and the other 1234 were not resected. The first group had 41% and 24% of OS at 5 and 10 years respectively, whereas the second group had only 9% at 5-year survival [7]. Advances in surgical and medical treatments have significantly changed the management of CLMs. In particular, new drugs and modern combination chemotherapy regimens, together with the improvement of surgical techniques, allow a potentially curative approach in an increasing number of patients. Nevertheless, there is no strong evidence for an optimal treatment strategy for CLMs, mainly because of the extensive heterogeneity in the patients [10]. In fact, in our opinion we believe that patients with CLMs are not all a unique population, because they are integrated by diverse clinical and biological subtypes that require different approaches. Moreover, the results of many published studies in this setting may be difficult to interpret, partly because the definitions of the various subgroups of patients are unclear and have overlapping between them.

Chemotherapeutic Agents: Overview and Toxicity

Early studies In the 1980s and 1990s, highlighting the publications of Adson, M and colleagues in 1984; Sugihara, K and colleagues in 1993 and Fong, Y and colleagues in 1997, had reported 5-year survival rates of 25–48% following

complete resection of the CLMs, in an era when the only active chemotherapeutic agent used was the antimetabolite 5-fluorouracil [11–13]. With increased use of systemic preoperative chemotherapy (SPC) for CLMs, clinical oncologists and liver surgeons are becoming more aware of the toxic effects of chemotherapy on liver parenchyma and how these changes affect postoperative outcome [14]. The entity "chemotherapy-associated liver injury or CALI" is described as the hepatotoxic effects of chemotherapy agents on the non-tumoral liver parenchyma. *Three types of CALI* are recognized: steatosis, steatohepatitis, and sinusoidal obstruction syndrome [15]. SPC alters the liver parenchyma in such way that it may increase the risks of liver resection [16]. Many studies have been published to assess the effects of SPC on the morphology of non-tumoral liver, which could produce histologic changes in the histology of the liver that may impact on surgical outcomes [17]. Pathologists have shown a wide spectrum of histopathological changes to the underlying liver parenchyma in resection specimens. The importance of CALI has been highlighted with regard to preoperative, operative, or early postoperative period [16]. Postoperative morbidity is correlated with the number of cycles of SPC administered before surgery, but not specifically due to the type of chemotherapy [16–18]. CALI can in particular prolong surgery and hospitalization, decrease accuracy of metastases at time of preoperative imaging assessment, increase risk of perioperative hemorrhage, postoperative risk for infections, lead to liver failure after major hepatectomy, cause portal hypertension with splenomegaly and ascites, and be responsible for persistent thrombocytopenia [18, 19]. It is mandatory that liver surgeons should have an adequate knowledge of the chemotherapy-associated hepatotoxicity [20]. However, with appropriate patient selection, liver resection for CLMs can be safely performed in patients treated with SPC [21]. Even though the association between chemotherapy and histopathologic changes has been well documented, the impact of chemotherapy-associated hepatotoxicity on surgical management of CLMs remains somewhat ill-defined. Many authors have concluded that the risk for postoperative complications in surgery of CLMs is related to the duration of SPC administration [14–16, 21–24]. Although the optimal regimen and duration of SPC is still being assessed, dialogue between clinical oncologists and liver surgeons regarding the timing of surgery is critical. Theoretically, a longer interval may provide the liver time to recover from any reversible hepatotoxic effect of chemotherapy. But on the other hand, a longer interval prior to hepatic resection may result in progression of disease. With this in mind, most liver surgeons will proceed with resection between 4 and 6 weeks after the last dose of chemotherapy [21–23]. SPC for CLMs induces regimen-specific hepatic changes that can affect patient outcome. Both response rate and toxicity should be considered when selecting preoperative chemotherapy in patients with CLMs [25].

Fluorouracil or 5-FU is a pyrimidine analog which is used in the treatment of cancer. It is a suicide inhibitor and works through irreversible inhibition of thymidylate synthase. It belongs to the family of so-called antimetabolite drugs [26]. 5-FU has remained as the backbone of systemic chemotherapy for CLMs for decades. This drug inhibits thymidylate synthase, thereby lowering production of pyrimidine thymidine for DNA synthesis.

Folinic acid or leucovorin (LV) is generally administered as calcium or sodium folinate (or leucovorin calcium/sodium). Folinic acid, also called 5-formyltetrahydrofolate, was first discovered in 1948 as a citrovorum factor and occasionally is still called by that name. Folinic acid should be distinguished from folic acid (vitamin B9). However, folinic acid is a vitamer (any combination of substances that together function as a vitamin) for folic acid, and has the full vitamin activity of it. LV is an adjuvant used in cancer chemotherapy involving the drug methotrexate. It is also used in synergistic combination with the chemotherapy agent 5-FU [27]. An updated meta-analysis published by Thirion, P and colleagues in 2004 demonstrated, on a large group of patients with advanced CRC, that infusional 5-FU and LV improves both overall response rate

(ORR) and OS compared with 5-FU alone, and that this benefit is consistent across various prognostic factors [28]. With the single-agent regimen of 5-FU, or 5-FU plus LV, tumor response in CLMs was seen in only 10–20% of those treated, which provided an OS of approximately a year in patients who were not candidates for an operation [27]. A multicenter study compared the therapeutic ratio of a monthly schedule of low-dose LV and 5-FU bolus with a bimonthly schedule of high-dose LV and 5-FU bolus plus continuous infusion in patients with advanced CRC. The conclusion of this study is that the bimonthly regimen was more effective and less toxic than the monthly regimen and definitely could increase the therapeutic ratio. However, there was no evidence of increased survival [29]. *Adverse effects*: 5-FU treatment can potentially include hepatotoxic effects on the non-tumoral liver parenchyma that have been reported as steatosis, which is a non-alcoholic fatty liver disease at the early stage and corresponds to accumulation of lipids in hepatocytes, and has a prevalence that ranges between 16–31% which may increase to 46–75% in patients with high alcohol consumption and/or obese [25]. From the transplant literature, is well known that *hepatic steatosis* can impair liver function and postoperative regeneration. In a study published by Kooby, D and colleagues in 2003 of 485 patients undergoing liver resections for hepatic tumors (325 steatotic livers and 160 matched controls), steatosis was found to be an independent predictor of postoperative complications on multivariate analysis ($p < 0.01$). Overall and infective complication rates of 62% and 43% for the marked steatosis group ($n = 102$) were significantly higher than in the control group, at 35% and 14% respectively ($p < 0.01$) [30]. Studies associating steatosis and 5-FU are mainly based on radiological evaluation; however, ultrasound sensitivity for diagnosis of steatosis is 60–94% and specificity is of 66–95%, while CT-scan sensitivity is 82% and specificity is 100%. Further, imaging does not distinguish steatosis from steatohepatitis [26]. Although 5-FU based chemotherapy may cause profound changes in liver parenchyma, it can be safely applied [31–33].

Capecitabine is the orally administered prodrug of 5-FU, which has lower hepatotoxicity and provides similar survival rates to those of an intravenous 5-FU/LV regimen. Capecitabine was more active than 5-FU/LV in the induction of objective tumor responses, and the times to PFS and OS were at least equivalent for capecitabine compared with the 5-FU/LV arm. In addition, capecitabine also demonstrated clinically meaningful benefits over the administration of bolus 5-FU/LV in terms of tolerability [34]. Chemotherapeutic regimens that combine continuous infusion 5-FU and LV with either oxaliplatin and irinotecan yielded ORR over 50% and provided a doubling of OS time in patients with unresectable disease [35, 36].

Oxaliplatin (oxal) is a platinum-based antineoplastic agent used in cancer chemotherapy that was discovered in 1976 at Nagoya City University by Professor Yoshinori Kidani. It is a novel platinum complex used for the treatment of metastatic CRC. It gained European approval in 1996, and in 2002 was approved by the U.S. Food and Drug Administration (FDA) [37]. According to in-vivo studies, the oxal fights against CRC through non-targeted cytotoxic effects. Like other platinum compounds, its cytotoxicity is thought to result from inhibition of DNA synthesis in cells. In particular, oxal forms inter- and intra-strand cross links in DNA, which prevent DNA replication and transcription, causing cell death [38]. Oxal is mainly used for treatment of CRC, in particular, in combination with other chemotherapy agents, including the regimen that is so-called FOLFOX, which consists of infusional 5-FU, LV, and oxal [35]. In clinical studies, oxal by itself has modest activity against advanced CRC. When compared with just 5-FU and LV administered according to the de Gramont regimen, a FOLFOX4 regimen produced no significant increase in OS, but did produce an improvement in PFS, which was the primary end-point of the phase III randomized trial [35]. Different drug doses and timed regimens—FOLFOX4, FOLFOX6, and FOLFOX7—have been evaluated, but no data support the superiority of any one over another in terms of patient OS. Recently, some authors have published that

FOLFOX is a feasible and safe option in patients with CLMs with severe liver dysfunction [39, 40].

Adverse effects: First of all, *neurotoxicity* due to oxal-based chemotherapy is their main toxicity and is focalized as a peripheral neuropathy [41]. The symptoms are progressive, involving numbness, tingling, intense pain and hypersensitivity to cold, beginning in the hands and feet and sometimes involving the arms and legs, often with deficits in proprioception. This neurotoxicity sometimes is very annoying for patients and they suffer a lot with these symptoms [41]. Further, this adverse effect can be maintained for a long time after finished the oxal-based chemotherapy [30]. Other side-effects are fatigue, nausea, vomiting, diarrhea, neutropenia (low number of a type of white blood cells), ototoxicity (occasionally hearing loss), and persistent hiccups. Further, extravasations if oxal leaks from the infusion vein may cause severe damage to the connective tissues [31]. In addition, some patients may experience an allergic reaction to platinum-containing drugs. This is more common in women. Oxal has less ototoxicity and nephrotoxicity than cisplatin and carboplatin [37]. In patients with CLMs, chemotherapy-induced hepatic injury is associated with *increased splenic volume*, thrombocytopenia, and decreased long-term survival. Slade, J and colleagues described in 2009 the use of oxal-based chemotherapy in six patients with stage III or IV CRC who developed evidence of non-cirrhotic portal hypertension. These patients developed complications of portal hypertension, including esophageal or hemorrhoidal varices with bleeding, splenomegaly with associated thrombocytopenia, and ascites. In each case, oxal-induced hepatic sinusoidal injury was identified as the most likely factor contributing to the development of non-cirrhotic portal hypertension [32, 33]. Simpson, A and colleagues reported in 2015 the relationship between change in splenic volume after SPC and the development of postoperative complications. The study group consisted of 80 patients who underwent resection of CLMs; half received SPC with oxal for 6 months before resection (n = 40) and the other half did not (n = 40). They concluded that the presence of CLMs and SPC is associated with higher splenic volume. Percent splenic volume increase after 6 months of chemotherapy can aid preoperative risk stratification, as it was an independent predictor of major postoperative complications [34]. Finally, splenomegaly would decrease in size over 1–3 years after end of oxal-based chemotherapy [32, 34]. Specific hepatotoxic effects on the non-tumoral liver parenchyma have been reported, and are included in the so-called "sinusoidal obstruction syndrome or SOS", formerly veno-occlusive disease, which is a well-established complication of hematopoietic stem cell transplantation, pyrrolizidine alkaloid intoxication, and widely used chemotherapeutic agents such as oxal [42, 43]. SPC frequently causes morphological lesions that involve the hepatic microvasculature [44, 45]. Macroscopically, liver has typically a blue-red marbled appearance, commonly so-called "blue liver" [17]. SOS is the consequence of an initial toxicity to sinusoidal endothelial cells. Histologically, it is characterized by centrilobular sinusoidal dilation, often associated with erythrocyte extravasations in perisinusoidal space (hemorrhage), compatible with a rupture of sinusoidal wall. It is occasionally associated with persinusoidal fibrosis and centrilobular vein obstruction, to peliosis or development of nodular regenerative hyperplasia [46]. Sinusoidal injury has been shown to persist several months after end of chemotherapy, and fibrosis may progress [24, 33]. A case of systemic capillary leak syndrome was reported in association with oxal-based chemotherapy [31]. Rubbia-Brandt, L and colleagues showed in 2004 that 44 (51%) of the 87 post-chemotherapy liver resection specimens had sinusoidal dilatation and hemorrhage, related to rupture of the sinusoidal barrier. In contrast, the 66 livers treated by surgery alone remained normal. Light microscopy, electron microscopy, and immunohistochemistry using antibodies against endothelial cells (CD31) and hepatic stellate cells (alpha-SM actin, CRBP-1) were performed to identify the sinusoidal wall integrity [15]. The main hepatic lesion induced by preoperative oxal-based chemotherapy in patients with CLMs is vascular and not steatosis [42]. Detailed pathologic analysis has determined that the most severe

vascular lesions are associated with increased intraoperative blood transfusions [15]. Tamandl, D and colleagues published in 2011 that the patients who developed grades 2 or 3 of hepatic sinusoidal dilatation had a significantly shorter PFS (HR: 2.05; 95% CI, 1.23–3.39, $p = 0.005$) and OS (HR: 2.90; 95% CI, 1.61–6.19, $p < .001$) than patients without this alteration. Those cases also had significantly more intrahepatic recurrences (66.7% vs 30.5%, $p = 0.003$). So, these authors conclude that SOS due to oxal-based chemotherapy may not only compromise perioperative outcome, but in addition can lead to early recurrence and could decrease survival in the long term. Strategies to prevent this condition are clearly needed [47]. To those who have resectable disease, there is a price to be paid in the development of chemotherapy-induced hepatic injuries [42, 45, 48]. There are *four degrees of sinusoidal dilatation* described: G0: absent, G1: mild, with centrilobular involvement but limited to one-third of the surface lobular, G2: moderate, with centrilobular involvement but limited to two-third of the surface lobular, and G3: severe, with complete lobular involvement [15]. Prolonged SPC alters liver parenchyma and increased morbidity after major resection under total hepatic vascular exclusion, but it does not increase operative mortality. This should be taken into consideration before deciding a major liver resection in patients who have received SPC [16]. Morbidity rate in patients with SOS is about 36%, and it is well demonstrated that this is correlated to number of cycles oxal-based chemotherapy [46]. SOS is well associated with the use of oxal-based chemotherapy, and represents a spectrum of hepatotoxicity, with nodular regenerative hyperplasia (NRH) representing the most significant degree of injury [19]. Morris-Stiff, G and colleagues published in 2014 a study to determine the prevalence of NRH in patients undergoing resection of CLMs, and to evaluate its impact on outcome, and they concluded that NRH is not an uncommon finding amongst patients with SOS in patients having received oxal-based chemotherapy. However, data on outcome would suggest no increased morbidity and mortality associated with the presence of NRH [49]. Even though multiple studies have shown that patients with damaged livers have higher perioperative morbidity and mortality rates than those with healthy livers, others have directly compared perioperative outcome with and without SPC, and have not been able to significantly demonstrate this phenomenon [22]. The reason for this discrepancy probably lies in factors of timing and dose of SPC treatments and extent of hepatic resection. Moreover, age and oxal predispose for the development of sinusoidal dilatation; therefore, caution must be taken in old patients treated with oxal [50, 51]. Prolonged SPC treatments and short intervals between the cessation of chemotherapy and surgery have been found to be associated with significantly increased morbidity [22, 24]. Finally, better comprehension of the molecular events underlying chemotherapy-associated hepatic injury might also be a source of help in patient management. Global gene analysis has shown activation of several pathways in human liver with oxal-related SOS, namely acute phase response, coagulation, fibrosis/hepatic stellate cell activation, oxidative stress, hypoxia, and angiogenesis [43]. This provides new insights into mechanisms underlying CALI in humans and potential targets relating to its diagnosis, prevention, and treatment. Activation of vascular endothelial growth factor and coagulation pathways could explain, at a molecular level, the clinical observations that bevacizumab and aspirin have preventive effect in SOS [46, 52, 53]. Ribero, D and colleagues reported in 2007 that the addition of bevacizumab to oxal-based chemotherapy *reduced the incidence of SOS* of any grade by half (27% vs 54%) and lowered severe, grade 2–3 sinusoidal dilation (8% vs 28%) to about a third of reviewed pathologic specimens [52]. In patients treated by oxal-based chemotherapy, aspirin intake appears to be associated with a reduced risk of sinusoidal lesions but should be tested in a randomized phase II study [54].

Irinotecan (irino) is a topoisomerase I inhibitor which prevents DNA unwinding and results in failure of DNA replication, DNA strand breaks, and cell death. During its development, it was known as CPT-11 [55, 56]. DNA topoisomerases are the targets of important anticancer and antibacterial drugs. Irino is activated by hydrolysis to SN-38, an inhibitor of topoisomerase I. This is

then inactivated by glucuronidation by uridine diphosphate glucoronosyltransferase 1A1 (UGT1A1). The inhibition of topoisomerase I by the active metabolite SN-38 eventually leads to inhibition of both DNA replication and transcriptions [55, 56]. In 1996, Irino received accelerated approval by the FDA and then full approval in 1998. Its main use is in CRC, in particular in combination with other chemotherapy agents. In a randomized trial that evaluated irino in patients with unresectable CLMs, OS after irino alone was equivalent to that of patients treated with standard bolus 5-FU/LV, but the combination of irino and 5-FU/LV improved OS by 2.2 months over 5-FU/LV alone (14.8 vs 12.6 months; $p = 0.04$) [57]. The current regimen is so-called FOLFIRI, which consists of infusional 5-FU, LV, and irino, and was associated in early publications in the 2000s with further improvement in OS (17.4 vs 14.1 months; $p = 0.03$) [58].

Adverse effects: The most significant side effects of irino are severe *diarrhea* and extreme *suppression of the immune system* [56]. Irino-associated diarrhea is severe and clinically significant, sometimes leading to severe dehydration requiring hospitalization or intensive care unit admission. This side-effect is managed with the aggressive use of anti-diarrheal such as loperamide or co-phenotrope after the first loose bowel movement [48]. The immune system is adversely impacted by irino. This is reflected in dramatically lowered white blood cell counts in the blood, in particular the neutrophils. The patient may experience a period of *neutropenia* (a clinically significant decrease of neutrophils in the blood) while the bone marrow increases white-cell production to compensate [48]. Several specific forms of liver injury have been associated with various chemotherapeutic regimens, including steatosis and steatohepatitis with prolonged treatment with 5-FU or with irino-based therapy. Hepatotoxic effects on the non-tumoral liver parenchyma have been reported, and are included in the so-called "Chemotherapy associated steatohepatitis or CASH" [59]. *Steatohepatitis* diagnosis is based on a histological triad: steatosis, balloonisation, and rich inflammation. Macroscopically, liver has typically yellow appearance, commonly so-called "yellow liver" [60]. The progressive features of CASH will begin in the early stages as steatosis, continuing in an intermediate step as steatohepatitis and then with lobular inflammation and finally, in the late stage with the hepatocyte necrosis that will finish in liver cirrhosis [61]. It has been shown at large that steatohepatitis is associated with an increase in morbidity and occasionally mortality after hepatic surgery and patients with CLMs were recommended that the chemotherapy regimen should be carefully considered because the risk of hepatotoxicity is significant [15, 17]. Vauthey, J and colleagues reported in 2006 a systematically analyzed hepatic injury in 158 patients treated with varying SPC regimens for CLMs, and correlated them to postoperative outcomes after hepatic resection [17]. This study distinguished steatosis and steatohepatitis as separate pathologic findings, and demonstrated that steatohepatitis induced by irinotecan-based chemotherapy was associated with an increase in 90-day mortality following major hepatectomy for CLMs (14.7% vs 1.4%, no steatohepatitis; $p = 0.001$). Furthermore, patients with steatohepatitis have a higher risk of death from postoperative liver failure compared with all other patients (6% vs 1%; $p = 0.01$) [17]. *Morbidity rate* in patients with CASH is *about 33%*, and it is well demonstrated that this correlated to the number of cycles of irino-based chemotherapy [17]. Analysis of the impact of steatosis on outcome after liver resection suggests that morbidity is increased but not mortality. While steatohepatitis may be associated with increased 90-day mortality due to liver failure after surgery [62], irino-based regimens are associated with increased risks of CASH, and consequently there is an increase in morbidity and mortality rates after hepatectomy, especially after major liver resections; therefore, it is important that liver surgeons should have an adequate knowledge of the chemotherapy-associated hepatotoxicity [44]. Over a 10-year period, approximately 9–20% of patients with steatohepatitis have developed cirrhosis. Of these cirrhotic patients, 22–33% of them have developed end-stage liver disease. Incidence of chronic liver disease is however not

yet evaluated, particularly for patients who receive multiple cycles of adjuvant or maintenance chemotherapy and, despite an apparent initial indolent course, delayed complications could develop [60].

An open question therefore is whether CALI, notably SOS and NRH, are reversible once the cause has stopped, and in which time frame. In the short term, histological persistence of SOS and NRH in the setting of two-stage hepatectomy was observed, suggesting that there is no advantage in delaying an operation in terms of tumor response to chemotherapy. In the long term, the issue is more open: the analogy with settings in which NRH and portal hypertension was noted 2–3 years after treatment, suggests that changes are not always reversible, and persistent SOS, NRH, and even fibrosis may occur several months after end of chemotherapy.

Molecular Targeted Agents: Overview and Toxicity

In the third millennium, the integration of molecularly targeted agents, such as bevacizumab, cetuximab, and panitumumab into treatment strategies has further increased response rates to an impressive 70% [52]. Further, by combining surgery with these newer chemotherapeutic agents and regimens, 5-year survival rates approach 50–60% following hepatic resection of CLMs [11, 53, 54]. The epidermal growth factor receptor (EGFR), also called ErbB-1 and HER1 in humans, is a trans-membrane glycoprotein receptor [38, 63]. The EGFR is a member of the human epidermal growth factor receptor (HER-erbB family of receptor tyrosine kinases). It is selectively activated by ligands belonging to the epidermal growth factor family of the peptide growth factors. The receptor auto-phosphorylation leads to the activation of multitude pathways, including the RAS/RAF mitogen-activated protein kinase MAPK, the PI3K/AKT, and the JAK/STAT3 pathways, which can be responsible for cancer cell proliferation, survival, invasion, metastases, and neo-angiogenesis [64]. Currently, two monoclonal antibodies target EGFR; the chimeric IgG1 moAb *cetuximab* and the fully humanized IgG2 moAb *panitumumab* have been developed and introduced into clinical practice. By binding the EGFR extracellular domain, these moAbs inhibit its dimerization, its subsequent phosphorylation and its downstream signaling [64]. EGFR amplification and EGFR gene copy number variation have also been investigated, but only a small amount of evidence can support their use as predictive markers of response [65]. The *KRAS test* was the first genetic test to guide treatment of CRC. Currently, this KRAS testing should be performed on all presenting cases of CLMs to ensure access to this treatment option [51]. Approximately 30–40% of CRC patients carry alterations or mutations in the KRAS gene which are associated with lack of activity of anti-EGFR moAbs [58]. In our group (Grondona, J and colleagues), since 2009 to 2014, in a total of 300 KRAS tests, 109 KRAS gene mutations were observed (36.66%). The concordance between the primary tumor and metastasis is high, with only 3–7% of the discordant tumors. Most mutations occur in Exon 1, codons 12 and 13; Exon 3, codon 61, and Exon 4, codon 146 of the KRAS gene. The result of these mutations is the constitutive activation of signaling pathways KRAS. Multiple studies have shown that patients with tumors harboring mutations in KRAS are unlikely to benefit from therapy anti-EGFR antibody, either as monotherapy or in combination with chemotherapy [66, 67]. So, the presence of these mutations correlates with primary resistance to anti-EGFR moAbs [57]. In the last decade, one of the questions of the researches undertaken was whether chemotherapy can cause RAS mutations. A study by Kawamoto, Y and colleagues in 2012 demonstrated that the mutational status of predictive biomarker genes were not altered by FOLFOX therapy [68]. Related to RAS family, the two most common isoforms in CLMs are KRAS/NRAS, both together so-called *ALL RAS*. Several groups have been focusing on the molecular analysis of additional genes involved in the downstream of the EGFR signaling such as BRAF, NRAS, and PIK3CA. *BRAF* is one of the primary downstream effectors of

KRAS signaling, and the V600E point mutation is the most common alteration that involves this gene, with a frequency in CLMs of about 9–10%. Some retrospective studies suggest that the BRAF/V600E mutation is associated with an unfavorable prognosis regardless of the treatment administered, and with primary resistance to anti-EGFR moAbs. Based on data from different clinical trials, the authors cannot conclude if the BRAF/V600E mutation is a negative predictive marker of response to anti-EGFR moAbs. *NRAS mutations* in the gene occur in approximately 1–6% of CRC. Tumors without alterations in any NRAS, BRAF, and PI3K genes are associated with good response to anti-EGFR antibody therapy. On the contrary, All RAS (KRAS/NRAS) mutation can be considered as the first negative marker indicative of response to anti-EGFR agents in CLMs. RAS mutation predicts early lung recurrence and worse OS after curative resection of CLMs. This information may be used to individualize systemic and local tumor-directed therapies and follow-up strategies [69]. Currently, the information provided by the RAS mutation status for patient selection is the only one with robust evidence and which warrants its clinical application for cost-effective use of anti-EGFR agents in CLMs. Therefore, choice of the biologic agent to add to the doublet chemotherapy could be individualized based on the RAS status and the clinical scenario [36]. The array of chemotherapeutic and molecular targeted agents available to treat CRC and CLMs is growing. As such, patients who were not typically considered candidates for liver-directed surgery for CLMs are now sometimes considered for potentially curative resection. With the incorporation of targeted therapies in routine cancer therapy, it is imperative that the array of toxicities associated with these agents are well-recognized and managed, especially since these toxicities are different from those seen with conventional cytotoxic agents [60]. The development of targeted therapies is a major breakthrough in the treatment of cancer in general [61, 70].

Cetuximab (cetux) is an EGFR inhibitor used for the treatment of CLMs, metastatic non-small-cell lung cancer, and head and neck cancer. It is a chimeric (mouse/human) monoclonal immunoglobulin G that recognizes and binds to the extracellular domain of the EGFR. Binding of cetux to this receptor does not cause receptor activation, but rather results in a steric interference with the ligand binding site. This effectively prevents ligand activation of the receptor [38]. Cetux has sometimes been used as first-line therapy of unresectable CLMs. By competitively blocking the transmembrane tyrosine kinase EGFR, this agent inhibits cell growth, induces apoptosis, and decreases matrix metalloproteinase and VEGF production; however, the effectiveness of this drug seems to be significantly dependent on the wild-type phenotype of KRAS, as this protein is part of the downstream signal-transduction pathway of EGFR. The benefits of cetux in CLMs are well documented in clinical trials, and are acknowledged in the approval and licensing of this agent. Results from the CRYSTAL study showed that for patients with wild-type KRAS, the addition of cetux to FOLFIRI as first-line treatment for CLMs increases the response rate to 59% compared with 43% using FOLFIRI alone ($p = 0.003$). Further, a slight increase in PFS was found (9.9 vs 8.7 months; $p = 0.017$), but all these benefits were not seen among patients with KRAS mutations [70]. The OPUS study was constructed similarly and assessed the addition of cetux to FOLFOX, and it also showed benefits for the KRAS wild-type subgroup (61% vs 37%; $p = 0.011$) but not for patients with KRAS mutations [66]. In the last decade, the definition of "tumor shrinkage" was widespread, which refers to "contraction or shrinking" of a liver metastasis due to the chemotherapy effect. *Early tumor shrinkage*, namely 20% or more at the eighth week, was experienced by 64% of patients in the CRYSTAL study and 69% of patients in the OPUS study. In addition, early tumor shrinkage translated into a long-term clinical benefit of 12 months median PFS and 28 months median OS in the CRYSTAL study and 12 months median PFS and 26 months median OS in the OPUS study. In 2009, the FDA approved cetux for treatment of CLMs with KRAS wild-type, since it had little or no effect in CRC harboring a KRAS mutation [71]. The iden-

tification of biomarkers associated with disease control, including All RAS mutation status in patients treated with cetux, is changing the current management of CLMs. Based on the CRYSTAL and OPUS studies, the American Society of Clinical Oncology published in 2009 a consensus statement that patients who have CLMs with KRAS mutations in codon 12 or 13 were unaffected by EGFR inhibition, and they recommended that anti-EGFR drugs not be used as part of the treatment regimen for this patient population [72]. The CELIM study randomized patients with unresectable CLMs to receive FOLFOX plus cetux or FOLFIRI plus cetux in a non-blinded fashion. Response rates for the 53 patients in each arm were similar (68% and 57%; p = not significant). But, when analyzed for KRAS mutation, an impressive ORR of 70% was found for the wild-type group. Following a median of eight cycles, complete resection was achieved in 41 patients (34%), suggesting that this regimen was useful for converting unresectable cases to resectable ones [73]. In a secondary analysis, 68 patients were included in a retrospective reevaluation by seven experienced liver surgeons. Twenty-two patients (32%) were considered to be resectable based on initial staging imaging studies, which increased to 41 patients (60%) based on restaging of studies after chemotherapy (p = 0.001). This study concludes that chemotherapy plus cetux yields high ORR compared with historical controls, and leads to a significant increase in resectability [54]. It is interesting to compare the process and liver resection rates in cetux trials in liver- limited KRAS wild-type studies. An interesting observation of the design of four major trials about the evaluation of resectability rate is as follows: in the CRYSTAL and OPUS studies the decision of liver surgery was carried out by clinical oncologists with 13% and 16% of liver resection rate respectively, and in the CELIM and POCHER trials the decision of liver surgery was discussed by MDT with the participation of *liver surgeons*, with 34% and 60% of liver resection rate respectively. So, this is one of the main items of evidence concerning the interdisciplinary management of CLMs. Finally, KRAS mutational status was shown to be a highly predictive selection criterion in relation to the treatment decision regarding the addition of cetux to FOLFOX-4 for previously untreated patients with CLMs [66].

Panitumumab (panit) was developed by immunization of transgenic mice (Xeno mouse) that are able to produce human immunoglobulin light and heavy chains. After immunization of these animals, a specific clone of B cells that produced an antibody against EGFR was selected and immortalized in Chinese hamster ovary cells. These cells are then used for the full-scale manufacture of the 100% human antibody [67, 74]. Panit works by binding to the extracellular domain of the EGFR, and prevents its activation. This results in halting of the cascade of intracellular signals dependent on this receptor [67]. In 2006, the FDA approved panit for the treatment of patients with CLMs and KRAS wild-type with disease progression on or following chemotherapy regimens based on 5-FU, oxal, or irino. In 2007, it was approved by the European Medicines Agency (EMEA) for the treatment of refractory EGFR-expression of CLMs in patients with non-mutated KRAS [74]. In 2009, the FDA updated the labels of two anti-EGFR monoclonal antibody drugs (cetux and panit) indicated for the treatment of CLMs, to include information about KRAS mutations. This was the result of a study, which demonstrated lack of benefit with panit in patients who carried NRAS mutations [64]. Although they both target the EGFR, panit (IgG2) and cetux (IgG1) differ in their isotype, and they might differ in their mechanism of action. Monoclonal antibodies of the IgG1 isotype may activate the complement pathway and mediate antibody-dependent cellular cytotoxicity [65]. It is not clear at this time if one drug is superior to the other [66].

Adverse effects: Cetux and panit represent an effective treatment option for patients affected by CLMs; furthermore, they are relatively devoid of systemic toxicities, which are commonly observed with standard cytotoxic chemotherapy [75]. Both have been associated with *skin toxicity/rash*, fatigue, nausea and/or vomiting, diarrhea, renal toxicity and decreased magnesium

levels [76, 77]. Often, the patients do not develop anemia or neutropenia and usually have no occurrence of hypersensitivity reactions [78, 79]. Lv, Z and Ning, J conducted a meta-analysis in 2014 to evaluate the efficacy and toxicity of adding cetux to oxal-based or irino-based chemotherapeutic regimens for the treatment of patients with CLMs with wild-type/mutated KRAS tumors. These authors conclude that the incidence of grade 3/4 adverse events, including skin toxicity/rash, diarrhea, hypertension, anorexia, and mucositis/stomatitis, was slightly higher in the combined therapy group than in the chemotherapy-only group [80]. A number of cancer therapy agents are cleared by the kidney and may affect renal function, including cytotoxic chemotherapy agents, molecular targeted therapies, analgesics, antibiotics, radiopharmaceuticals and radiation therapy, and bone-targeted therapies [23]. EGFR inhibitors cause electrolyte imbalances including hypomagnesaemia and hypokalaemia, due to the direct *nephrotoxic effect* of the drug on renal tubules. Cetux may also result in renal tubular acidosis [81]. Discerning the renal adverse effects resulting from these agents is essential for safe treatment strategies, particularly in those with pre-existing renal disease [81]. Clinical and molecular predictive markers of response are under active evaluation in order to better select patients who could benefit from anti-EGFR treatment, with the aim of both optimizing patient outcomes and avoiding unnecessary toxicities [30]. The majority of patients treated with EGFR inhibitors will experience *dermatologic toxicities*, most notably the *papulo-pustular skin rash*, which can impact quality-of-life and affect adherence to therapy. Often, this skin rash is mainly noted in the sun-exposed parts of the body, such as the face or chest [71, 75]. Skin toxicity was classified in 2014 according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0. The most common skin toxicity was an *acne-like skin rash* (80% of patients) and paronychia (20%). Other side-effects were trichomegaly, hypertrichosis, and allergic reactions [82, 83]. In addition, the severe papulo-pustular rash and xerosis may be clinical predictors of good response to anti-EGFR therapy. Patients who develop the skin rash should be treated promptly because suboptimal treatment of these adverse effects can lead to delays in taking the prescribed dose of anti-EGFR or certainly to interruption of therapy [77, 78, 83]. A proper care of low-grade toxicities is well recommended in order to reduce progression to high-grade toxicities and the resulting risk of hospitalization, which really impacts on costs [84, 85]. At the start of treatment with EGFR inhibitors, proper patient education about the skin rash associated with these monoclonal antibodies, and the implementation of a pre-emptive, comprehensive skin toxicity program significantly contribute to improving adherence to therapy, optimizing anti-EGFR therapy, and maintaining quality-of-life [75, 83]. Previous experience from clinical trials shows that in some cases proper care and prevention can improve the quality of patients' lives [82, 85]. Oral antibiotics may be needed for worsening skin rash, such as one accompanied with blisters and ulcers. Otherwise, topical steroid creams such as hydrocortisone may help [85]. Gibson, T and colleagues showed in 2006 the results of a phase III trial which compared panit as a single agent to provide supportive care in patients with previously treated CLMs, and they reported skin-rash toxicity in 90% of patients, with increased severity significantly *correlated* with improved medium OS [74]. Jaka, A and colleagues reported in 2015 that 81.9% of the patients developed a papulo-pustular rash. Patients who received the most cycles of treatment with the EGFR inhibitors were at the highest risk of developing the rash, and these patients also had the most severe rash reactions ($p = 0.03$) [77]. In addition, *all of the patients who exhibited a complete tumor response had the rash*, and the incidence of such rash was lower in patients with poor tumor response ($p = 0.03$) [77]. Many authors have shown that early acne-like rash predicts superior outcome among patients treated with anti-EGFRs [74, 77, 80, 82, 84].

Bevacizumab (Bev) is a monoclonal antibody which is an angiogenesis inhibitor that slows the growth of new blood vessels and, has shown promising preclinical and clinical activity against metastatic CRC, particularly in combination with

chemotherapy [13]. Bev is a recombinant humanized monoclonal antibody, whose main action is the inhibition of the function of a natural protein called vascular endothelial growth factor A (VEGF-A) that stimulates new blood vessel formation [4]. VEGF-A is a chemical signal that stimulates angiogenesis in a variety of diseases, especially in cancer. So, this monoclonal antibody specifically blocks the angiogenesis by inhibition of VEGF-A [14]. Bev is produced in a mammalian Chinese hamster ovary cell expression system in a nutrient medium, and was the first commercially available angiogenesis inhibitor. Bev decreases micro-vascular density and integrity and reduces interstitial tumor pressure in vivo, potentially increasing local delivery of other concurrently administered cytotoxic drugs [86]. Because most malignant tumors are highly dependent on angiogenesis it is expected that bev could stop or delay growth of tumors [87]. Hurwitz, H and colleagues demonstrated in 2004 the benefits of adding bev to systemic chemotherapy for CLMs. In a randomized controlled double-blinded trial, they compared bolus 5-FU/LV plus irino in conjunction with either bev ($n = 402$) or placebo ($n = 411$). Patients in the bev group had an almost 5-month improvement in median survival compared with the placebo group (20.3 vs 15.6 months; $p < .001$), and they had an increase in median PFS (10.6 vs 6.5 months; $p < .001$) [88]. Bev was approved by the FDA for certain metastatic cancers. In 2004, it received its first approval, for treatment for metastatic CRC when used with standard chemotherapy (as first-line treatment) and with 5-FU-based therapy for second-line metastatic CRC [87]. In 2005, it was approved by the European Medicine Agency (EMA) for use in metastatic CRC. In patients having CLMs with KRAS, mutated tumors could be treated in the preoperative period with bev given intravenously every 14 days, in combination with the chemotherapy drugs 5-FU, LV and oxal or irino [89].

Adverse effects: Although studies have confirmed the survival benefit of bev, the toxic side-effects caused by this monoclonal antibody should also be considered [90]. Bev inhibits the growth of blood vessels, which is part of the body's normal healing and maintenance. The body produces new blood vessels in wound-healing, and as collateral circulation around blocked or atherosclerotic blood vessels. One concern is that bev interferes with these normal processes, and worsens conditions such as coronary artery disease or peripheral artery disease. These effects are largely avoided in ophthalmological use since the drug is introduced directly into the eye, thus minimizing any effects on the rest of the body [90, 91]. The most frequent adverse reactions to bev are hypertension, renal toxicity, and proteinuria, heightened risk of bleeding and thrombosis, and wound-healing abnormalities [91–93]. *Arterial hypertension* is the most common bev-associated adverse event, which has been correlated with the biological inhibition of the vascular endothelial growth factor-related pathway, and may represent a possible clinical marker for treatment efficacy [91, 94]. Chun-Ying Qu and colleagues reported in 2015 that Grade 3 hypertension was higher in the bev plus irino, 5-FU, and LV arm than in the placebo arm (11% vs 2% respectively) [95]. Although in several studies the results showed that the incidence of hypertension (≥grade 3) in the treatment group was approximately five times higher than that of the control group, other published studies have confirmed that this side-effect can be well controlled by oral antihypertensive agents [95]. Scartozzi, E and colleagues showed in 2009 that bev-induced hypertension may represent an interesting prognostic factor for clinical outcome in advanced CRC patients receiving first-line bev [94]. Anti-VEGFs agents including bev, aflibercept (VEGF trap), and anti-VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) all cause hypertension, whereas some of them result in proteinuria [81]. The incidence, severity, and pattern of renal toxicities may vary according to the respective target of the drug. The early diagnosis and prompt treatment of these renal alterations are essential in daily practice where molecular targeted therapies have a definitive role in the armamentarium used in many cancers [23, 81]. The risk of thromboembolic events are the deep vein thrombosis, pulmonary embolism, transient ischemic attack, and acute mesen-

teric ischemia. However, incidences of overall thromboembolic events were not statistically different between the bev/irino and the control arms [95]. Bev could produce abnormalities of *wound-healing*. In this group are included wound dehiscence, ecchymosis, subcutaneous serum collection, bleeding, and wound infection [92]. Treatment with bev prior to surgery may be associated with increased wound infections and dehiscences, attributable to inhibition of neovascularization of the healing wound. Wound healing complications were *increased* in patients who had major surgery during bev therapy. In order to diminish or avoid abnormalities of wound-healing, the current recommendation is still to wait at least 28 days from cessation of bev to proceed with surgery, although many liver surgeons prefer to wait 6 weeks [96]. Gruenberger, T and colleagues showed in 2008 that bev can be safely administered until 5 weeks before liver resection in patients with CLMs without increasing the rate of surgical or wound healing complications or severity of bleeding. This is one of the early studies that showed that neoadjuvant bev does not affect liver regeneration after resection [97]. For the aforementioned reasons, it has been recommended that a period of 6 weeks should elapse following the cessation of bev administration before the hepatic resection [92]. Severe but very infrequent side-effects are *gastrointestinal tract perforations*. These risks include gastrointestinal free intra-abdominal perforation, fistula formation, intra-abdominal abscess, and free air under the diaphragm without identified source. All of them are rare, but are serious complications which may be fatal [95]. Nasal septum perforation and renal thrombotic microangiopathy have been also reported [98]. In December 2010, the FDA warned of the risk of developing perforations in the body, including in the nose, stomach, and intestines, in patients treated with bev. In 2013, F. Hoffmann-La Roche, the Swiss global health-care company that produces bev announced that the drug had been associated with 52 cases of necrotizing fasciitis between 1997 and 2012, of whom 17 patients died. Chun-Ying Qu and colleagues, have shown in 2015 that although the incidence of gastrointestinal perforation caused by bev increased by approximately threefold in the treatment group compared with that of the control group, the incidence in eight studies including one meta-analysis is relatively low (approximately 1–1.5%), suggesting that in this issue bev is safe and non-toxic [95]. The *contraindications of bev use* include hypersensitivity to its active components or to recombinant monoclonal antibodies, pregnancy, lactation, wound-healing risk complications, severe arterial hypertension, proteinuria, arterial thromboembolic episodes, congestive heart failure, cardiomyopathy [92]. Several meta-analyses suggest that cancer therapy with bev is associated with a slightly elevated risk for developing any serious adverse effects. The incidence of adverse reactions can be limited by effective monitoring and prevention during the course of treatment with this monoclonal antibody [93]. The addition of bev to standard chemotherapy before resection of CLMs does not seem to increase postoperative morbidity. Caution should be given to extended resections (more than three liver segments) and synchronous bowel anastomoses [99]. The higher risks for adverse effects in patients treated with bev should be weighed against its benefits, and be considered by the MDT approach [92, 93].

In conclusion: (1) consensus between many researchers affirm that anti-VEGFs and anti-EGFRs targeted antibodies have increased efficacy of chemotherapy in first-, second- and third-line treatment, (2) patients with liver limited metastatic disease who have response to chemotherapy in combination with targeted antibodies have more chance of curative resection, (3) widespread use of KRAS testing could permit oncologists and liver surgeons to be able to tailor SPC and increased efficacy of different chemotherapeutic regimens, and (4) for the near future, there is the need to have new prognostic markers (to provide information on outcome independent of the therapy that is used) and also new predictive markers (to provide information on outcome with regard to a specific therapy, such as KRAS testing) to increase the efficacy of treatment armamentarium and decrease the toxicity of the drugs. Further, some markers can have both predictive and prognostic value.

Criteria to Define Resectability in Colorectal Liver Metastases

Today, in some medical centers worldwide, patients diagnosed at a metastatic stage appear to be wrongly directed towards a palliative strategy, and thus they can lose a real chance for survival. This probably results from initial misguidance, lack of knowledge of the disease, and the absence of an initial assessment of the resectability of the metastases by a specialized surgeon capable of this evaluation. Progress in recent years in the multimodal management of these patients has led to a clear increase in the resectability rate of CLMs and has improved their prognosis. Planning the right therapeutic approaches for individual patients is becoming more complex, and it requires a close multidisciplinary collaboration between surgical and medical oncologists. A relevant message for the management of CLMs is the importance of a strong and interactive multidisciplinary team (MDT) to plan the care and cure for these patients [100, 101]. This interdisciplinary team (a so-called *tumor committee* or *tumor board*) is handled by a case-manager and integrates liver surgeons, clinical oncologists, pathologists, gastroenterologists, and specialists in image-study diagnosis, in order to discuss altogether the oncologic case studies with which they are presented at each meeting [102]. The treatment of disseminated CRC is no longer the domain of only one physician or of one medical group with the same specialty [11]. A proportion of diagnosis and treatment decisions in patients with CLMs could be changed by the discussion in the MDT [12–14]. In two studies with 699 people, working in groups of 2–5, converging evidence of the general collective intelligence factor that explains that a group's performance is stronger than the maximum individual intelligence of such a group was found [15]. Treatment of CLMs must always be established in an MDT discussion with an analysis of prognostic factors and resectability [3]. The real paradigm shift is the approach to patients with CLMs by an interdisciplinary group where the backbones are the clinical oncologist and the surgeon specialized in liver surgery [5]. In our opinion, the MDT is essential in the assessment and decision-making concerning CLMs to ensure that patients receive optimal care and, further a regular follow-up and re discussion if is necessary should be established for each individual case. In conclusion, currently, the assessment and follow-up of individual cases of CLMs by MDT is mandatory.

No agreed definition of resectability has been reached by several panels of oncologists and liver surgeons considering the treatment of CLMs. The resectability very probably differs from one hospital to another, and depends on the available equipment and the level of surgical expertise. The definition also depends, understandably, on patient-specific data, such as general health, co-morbidities, nutritional status, and more specifically, the presence of a possible underlying liver disease [103]. Currently, with subsequent confirmation that a patient with CLMs is medically fit for general anesthesia and major abdominal surgery, determination of resectability falls into *two domains*: *oncological and technical*. From an oncological perspective, evaluation of extrahepatic disease and response to any delivered SPC are the main considerations. From a technical perspective, the ability to remove all viable tumors with negative margins and adequate functional liver remnant are prioritized [104]. With regard to *oncological considerations*, extrahepatic disease in patients with CRC who also have liver metastases should no longer be considered an absolute contraindication to hepatectomy [105]. The most common sites of extrahepatic disease include recurrent CRC involvement, intra-abdominal lymph node involvement, and lung metastases [106]. However, the presence of extrahepatic disease that is not durably controllable with chemotherapy and/or resection should contraindicate liver resection, although various groups of researchers have reported long-term post-hepatectomy survivals in highly selected patients with clinically apparent extrahepatic disease at all these sites [7]. Currently, patients who have responded to SPC and harbor extrahepatic disease that is amenable to surgical resection, for instance isolated portal lymphadenopathy, could be considered for hepatic resection; and in other patients

expected to have long-term control with adjuvant therapies of the extrahepatic disease, for instance a small-volume lung disease, could be considered as well as liver resection. With regard to *technical considerations*, CLMs were historically divided into three or four groups in order to classify the liver metastases according to the possibility of surgical resection. In the 90s, there was a discussion about how to define whether CLMs were or not resectable, and two main issues were evaluated: when all macroscopic disease could be removed, and when enough healthy liver remnant could be left in place with adequate portal inflow, biliary drainage, and hepatic vein outflow [5, 95]. However, one of the *first classifications* of patients were published in 2007 by clinical oncologists, Schmoll, H and colleagues, and consisted of *three groups* as follows: Group 1; patients with metastases that might become resectable, Group 2; patients with unresectable metastases with high tumor burden and/or tumor-related symptoms, and Group 3; patients with unresectable asymptomatic metastases and low aggressive disease [107]. Later, the Group 0 was added by the same authors, which included patients who were initially resectable [89]. The definition of resectable CLMs has changed over the years, and now focuses on *all visible liver metastases* while preserving at least 20–25% liver remnant with adequate vascular supply and biliary drainage, with the expectation that a resection would render the patient able to stay free of macroscopic evidence of disease [108]. Some liver surgeons have defined the resectability in CLMs in *four groups* of patients that were differentiated as follows: Group 1; initially resectable, Group 2; not optimally resectable, Group 3; unresectable that could become resectable, and Group 4; unresectable that will never be likely to be resected [3, 108, 109]. The criteria of resectability included estimated residual liver volume, the number and localization of lesions, and the resection margins. Co-existing medical conditions need to be taken into account. Age per se is not a limiting factor [4]. Recently, an established practical approach is to subdivide patients into four clinically defined groups based on last *ESMO Clinical practice guidelines* published in 2014:

- Group 0; primarily technically R0-resectable liver metastases. Upfront resection is an option, specifically when metastases are limited in number and size. The *goal* is to cure and/or to reduce relapse rate. Chemotherapy intensity is nothing or in some cases is moderate (FOLFOX)
- Group 1; potentially resectable metastasis with curative intention but not upfront R0. The *goal* is objective response and tumor shrinkage. The *most active induction chemotherapy* should be selected upfront in this group
- Group 2; multiple metastasis/sites by definition never or unlikely to be resectable, rapid progression and/or associated symptoms and/or co-morbidities allowing intensive treatment. The *goal* is disease control and symptom improvement. The treatment intention is upfront active combination of at least doublets
- Group 3; never-resectable metastatic disease, without present or imminent mild symptoms and with limited risk for rapid deterioration. The *goal* is disease control and to preserve the quality of life. The treatment depends on performance status and patient preference. Single agent or doublet low toxicity or only palliative care [103, 110].

In our opinion, one definition with widespread consensus of *resectability of CLMs* is the ability to remove surgically, with clear microscopic margins (R0), all metastases, without compromising postoperative liver function because of the insufficiency of either the remaining liver volume or biliary and venous vascularization and drainage. Although a surgical margin of 5–10 mm is considered optimal currently, anticipation of at least a *microscopically negative margin* (1 mm) should be included in the definition of resectability [111, 112]. More recently, the ability to accurately predict the future liver remnant (FLR) volume and function have added to our ability to select resectable cases [97]. In addition, it is difficult to define

an absolute value for remaining liver volume because this varies from one patient to another in a multifactorial manner [113]. Liver volumetry has allowed quantification of the anticipated FLR [114]. This has facilitated stratification of the risk of liver failure after major liver resection, and therefore the selection of candidates who may benefit from hypertrophy of liver remnant [113]. The *liver volume values* most frequently reported in the literature are 20% for a healthy liver, 30% in patients who underwent numerous cycles of SPC, and 40% in patients with an underlying liver disease that impairs their functional hepatic reserve [114]. Moreover, *unresectability* is defined with one or more of the following criteria: (1) no possibility of upfront R0/R1 resection of all lesions, (2) less than 30% residual liver volume after resection and, (3) metastases in contact with major vessels of the FLR [115]. For insufficient FLR volume, currently there are some surgical procedures that may improve or enhance the normal parenchyma, such as percutaneous portal vein embolization or intra-operative portal vein occlusion, two-stage liver resection, combined liver resection and contra-lateral tumor destruction, and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [115]. Only *20% of patients* with CLMs meet the principal criterion, that is to say resectability, for receiving surgical treatment. It is therefore important to optimize their management to increase surgical treatment and thereby improve the prognosis of this disease [104].

In conclusion, the technical feasibility of hepatic resection should be based on *three criteria* related to the remaining liver following resection: (1) the anticipated ability to conserve two contiguous segments, (2) the skill to keep adequate vascular inflow and outflow as well as biliary drainage, and (3) the awaited capacity to preserve adequate FLR.

Response Imaging Evaluation in Colorectal Liver Metastases

Imaging studies are a major component in the evaluation of patients for the screening, staging, and surveillance of CRC. Several modalities are available; these include ultrasound (US), abdominal computed tomography (CT), magnetic resonance imaging (MRI), 18-F-FDG positron emission tomography (FDG-PET), and FDG-PET-CT [116, 117]. US is operator-dependent, plays a limited role in the diagnosis of CLMs, and has generally low sensitivity for detection, especially for small lesions. When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions [118]. MRI and CT are the best currently available and reproducible methods to measure target lesions selected for response assessment [7]. The choice of CT or MRI for preoperative assessment of CLMs depends on local expertise and availability, CT being limited by radiation dose and further, by limited accuracy for characterization of small lesions. MRI lacks ionizing radiation, offers higher contrast resolution, and provides the possibility of performing multiparametric imaging, combining T1, T2 and diffusion-weighted imaging with dynamic multiphases imaging. Currently, MRI is considered the most accurate non-invasive imaging technique for detection of CLMs, and is probably the best choice for a precise preoperative detection of CLMs, particularly for diagnosing small lesions under 10 mm in diameter [117, 119]. Related to this, FDG-PET and FDG-PET-CT in the preoperative imaging evaluation of CLMs have a role mostly for detection of extrahepatic metastatic disease [7]. While there are many sophisticated new methods to explore *response to treatment* such as perfusion studies, diffusion-weighted imaging with MRI, and texture evaluation which is still at the development stage, at present, in clinical practice, tumor response in CLMs can be evaluated from *three different perspectives*: (1) change in tumor size, (2) morphologic change unrelated to size, and (3) functional imaging, essentially FDG-PET. For the *first perspective*, the established methods for evaluation rely on changes in tumor size as defined by WHO and RECIST criteria. A situation is evolving with discrepancies between responses based on both methods, and advances in molecular imaging and image processing are opening new opportunities for response evaluation [104]. The

WHO criteria, the first attempt at standardization, use bidimensional measurements and were supplanted in 2000 by the RECIST criteria. Such criteria were published in *February 2000* by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group. RECIST, which means "Response Evaluation Criteria in Solid Tumors" is a set of published rules that define when cancer patients improve or respond, stay the same or stable, worsen or progress during treatments. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumors use RECIST criteria [118]. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. It is considered measurable disease, in the presence of at least one measurable lesion. The standard criteria used to evaluate tumor response by RECIST were developed to assess tumor shrinkage after cytotoxic chemotherapy, and may be limited in assessing response to biologic agents, which have a cytostatic mechanism of action [120]. Target lesions should be selected on the basis of their size, that is to say the lesions with the longest diameter. Since 2009, RECIST has undergone modifications in its rules, and the major changes include the number of lesions to be assessed, which has been reduced from a maximum of ten to five lesions. Thus, it is the sum of maximal transverse diameters of up to five target lesions [111]. RECIST evaluation of target lesions are defined as follows: (1) complete response (CR); disappearance of all target lesions, (2) partial response (PR); at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, (3) stable disease (SD); neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD recorded since the treatment started, and (4) progressive disease (PD); at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions [118]. In summary, many authors have shown that change in tumor size is a strong indicator of response, but the problem is the arbitrary choice of cut-off values. The need for 30% decrease in tumor size derives from historical data collected at a time where precise measurement was impossible. Currently, the new imaging techniques available allow better estimation. Several studies have shown that *an early decrease in size of 10%* correlates better with outcome than the established 30% decreased by RECIST [104]. The *second perspective* of evaluating tumor response is morphologic change unrelated to size which is recognized as a valid indicator of response, particularly with target therapy. In this situation, modifications of the tumor texture, enhancement, and margins have been shown to be a reflection of response, regardless of change in tumor size. This was first observed with gastrointestinal stromal tumor (GIST); similar observations have been since made in CLMs treated with bev. Moreover, by evoking necrosis and cavitation, evaluation based on tumor size alone, as is done in the RECIST criteria, is no longer an adequate method. New molecular and functional imaging techniques are currently being developing [97]. Finally, in the last decade several authors have reported that tumor metabolic response to SPC could be quantified by FDG-PET as predictive of prognosis in patients undergoing resection of CLMs. Assessing metabolic response uniquely characterizes tumor biology, which may allow future optimization of patients and treatment selection [121]. In special cases, FDG-PET imaging is a useful tool for assessing treatment response and predicting clinical outcome in patients with CLMs who undergo chemotherapy before liver resection [122].

In conclusion: (1) MRI is currently the best choice for a precise preoperative mapping of CLMs, particularly for diagnosing small lesions, (2) RECIST criteria are not used currently in clinical practice to judge response to chemotherapy in CLMs and further, is imperfect particularly when bev is used, (3) an early decrease in size of 10% in CLMs is considered a radiologic

response to chemotherapy, (4) modifications of the tumor texture, enhancement, and margins as well as necrosis and cavitation have been shown to be a reflection of tumor response to chemotherapy, (5) if an abdominal CT was carried out in order to detect CLMs, the diagnosis and assessment of resectability should be completed with MRI, and (6) the role of FDG-PET to evaluate treatment response in CLMs remains to be defined.

In our opinion, imaging studies are the cornerstone of response evaluation in oncology, and resectability or not must be evaluated by multidisciplinary review.

Disappearing Liver Metastases and Tumor Response

Disappearing liver metastases (DLMs) are also called by other authors missing or vanishing liver metastases. However, the verb disappear according to the Cambridge Advanced Learner's Dictionary means "go where it is impossible to be seen or found" [123]. So, applying this word in relation to CLMs in the context of DLMs refers to a hepatic lesion that is impossible to see or find in the same anatomical liver site that was localized by imaging studies and/or surgical exploration. Therefore, in our opinion we definitely prefer to call these lesions DLMs. A dramatic response to SPC in some patients with multiple bilateral and initially unresectable CLMs sometimes leads to their partial or complete disappearance from imaging studies [98]. DLMs are likely to become in more frequent in the near future due to the widespread use of highly efficient chemotherapy. This creates a new set of issues for managing patients with CLMs following neoadjuvant or conversion chemotherapy. The question remains whether these lesions are undetectable, but still present and therefore likely to grow back [99]. During SPC, some CLMs disappear on serial imaging. This disappearance may represent either a complete radiological response (CRR) or a simple reduction in the sensitivity of imaging during chemotherapy that could lead to a misinterpretation of the assessment of the patient [124]. From the start of the third millennium, the reported concordance between a CRR with complete pathological response (CPR) has been variable, ranging from 20% to 100%. Early evidence have been reported by Elias, D and colleagues in 2004 on 11 patients in whom at least one of the CLMs disappeared on imaging and could not be localized at laparotomy. Local recurrence was seen in three of these patients (27%), with a median follow-up time of 31.1 months. It was concluded in this initial report with small sample size that disappearance of CLMs after SPC on high-quality imaging studies and after intraoperative liver exploration resulted in their definitive cure in approximately 70% of cases [125]. Subsequently, on the contrary, Benoist, S and colleagues in 2006 reported on 66 CLMs that disappeared radiographically following SPC, which represented 20% of all lesions in the cohort. At the time of exploration, 31 lesions (47%) could not be identified, even with intra-operative ultrasonography, and they were consequentially not removed. After 1 year of follow-up, 23 (74%) of these lesions recurred. Of the other 35 liver lesions (53%) identified and removed at surgery, 32 (91%) contained viable disease, suggesting that tumors are still present, even when they disappear on imaging. Thus, it was concluded that 55 of the original 66 lesions (83%) harbored residual viable disease [126]. In our opinion, based on this study, many liver surgeons began to manage these patients with a clear surgical exploration tendency. One year later, Rubbia-Brandt, L and colleagues published in 2007 a study in order to characterize histological response to chemotherapy of CLMs, evaluate efficacy of different chemotherapies schemas on histologic response, and determine whether tumor regression grading (TRG) of CLMs predicts clinical outcome [127]. The TRG scoring system is as following: TRG1; absence of residual cancer and large amount of fibrosis that is CPR, TGR2; rare residual cancer cells scattered throughout the fibrosis, TRG3; more residual tumor cells but fibrosis predominates, TRG4; residual cancer cells predominate over fibrosis, and TRG5; only tumor cells that usually correspond to the cases without chemotherapy treatment [117]. Histological tumor regression of

CLMs to chemotherapy *corresponds to fibrosis* overgrowth that replaces the malignant cells, and not to the increase of intra-tumoral necrosis [127]. In a study published by Blazer, D and colleagues in 2008, related to 305 patients who received a median of five cycles of oxal and irino-based chemotherapy, with or without bev, prior to hepatic resection, a pathological response with no residual histological evidence of tumor or TRG1 was observed in 9% of cases, a major response (1–49% residual cells) was seen in 36%, and a minor response (up to 50% residual cancer cells) was seen in 55% of tumors in the resection specimen. The 5-year survival rates for these three groups were 75%, 56%, and 33% respectively ($p < .05$) [128]. So, CPR to SPC was independently associated with improved survival on multivariate analysis [128]. In addition, Adam, R and colleagues reported in 2008 that only 4% of patients had a CPR in a series of 767 patients who underwent liver resection after SPC for CLMs [129]. However, this study had the problem that the cohort involved a heterogeneous group of patients with initially resectable and unresectable disease, including some patients with extrahepatic disease. Further, in this study it was observed that a CPR may occur in almost one-third of objective chemoresponders with an age up to 60 years, with metastases up to 3 cm in diameter, and with low CEA values [129]. As with the Blazer study, patients with a CPR ($n = 29$) had an excellent 5-year survival, which reached 76% compared with 45% for patients without this kind of response ($p = .004$) [128, 129]. Other report, by Chun, Y and colleagues in 2009 represents an early assessment of the correlation between radiographic and histologic findings, and how they correlate with patient outcome [110]. In this study, they assessed the association of morphologic radiologic response with pathologic response. A total of 234 lesions were examined from 50 patients who underwent hepatic resection after treatment with bev. In the cohort that had an "optimal" morphologic radiologic response, the median number of residual tumor cells was 20%. In contrast, patients who had an "incomplete or absent" response had 50–70% residual tumor cells on pathologic assessment and had a shorter median survival than the responder group [110]. Further, an interesting study by Auer, R and colleagues reported in 2010 a CPR of 65% [124]. Many authors have shown that after SPC, a pathological response of CLMs increasingly occurs, but such responses are not frequently CPR [126, 130]. It is mandatory that DLMs on preoperative CT-scan should be systematically confirmed by a second imaging modality, ideally MRI. With increasing efficacy of SPC or CLMs, more patients will present with one or more DLMs on preoperative cross-sectional imaging [131]. Currently, it is well demonstrated that MRI is more accurate than CT for the evaluation of liver metastases [116]. Among patients with DLMs, an extensive search of the lesions, including full mobilization of the liver, palpation, and intraoperative ultrasound, should be conducted at the time of surgery. The variability in the reported ability to detect DLMs at the time of surgery is undoubtedly multifactorial, but may be related to the quality of preoperative imaging, since some of the CLMs may disappear or may be hardly detectable with surgical exploration and intra-operative ultrasound. Zalinski, S and colleagues reported in 2009 a new technique to mark small lesions with coils before chemotherapy. This technique facilitates the resection of small lesions likely to disappear after SPC [132]. Further, Takahashi, M and colleagues reported in 2012 about the use of lipid-stabilized perfluorobutane microbubbles as an intra-operative ultrasound contrast agent, in order to improve the identification of DLMs and mainly the detection of isoechoic ultrasound lesions [133]. The incidence of DLMs ranges from 5 to 38% in most reported series [124–126, 134–136]. However, incidence is dependent on the extent and sensitivity of preoperative imaging. In addition, disappearance is associated with high tumor number, longer duration of chemotherapy, and small lesion size [107]. It should be noted that among groups such as those at the Gustave Roussy Institute of Paris and The Memorial Sloan Kettering Cancer Center of New York which employ hepatic arterial infusion therapy, the incidence of CPR is much higher [124, 125, 134]. Specifically, Elias, D and colleagues reported a CPR rate of 86% among patients treated with

hepatic arterial infusion therapy prior to surgery, versus 22% for those treated with SPC alone [125, 134]. Recently, a new definition was reported of "true complete response", as either a CPR (no tumor detected in the resection specimen) or a durable complete clinical response (CCR), which is defined as the DLMs not recurring on follow-up imaging studies for a period of time (usually 1 year) [114]. Gruenberger, T and colleagues reported in 2012 that the pathologic tumor response was further defined as the "objective measurement of residual cancer cells in resected tissue", which has been identified as a reliable prognostic factor in patients with CRC receiving SPC and has been shown to correlate with improved OS after resection of CLMs [7]. Expanded surgical intervention in CLMs and improved chemotherapy led to an increasing problem of DLMs. Treatment of those continues to evolve, and poses a real challenge for liver surgeons [136]. Currently, studies are appearing with an improvement in the CPR rates, such as the one published by Zendel, A and colleagues in 2014 about the influence of CPR on CLMs who received SPC on long-term survival after hepatectomy. Of 472 CLMs evaluated, 86 were no longer visible from images after SPC (14 out of 86 metastases are not included because were treated with local ablation). Of the remaining 72 metastases, only 22 (30.6%) were microscopically persistent metastases or recurrences in situ [109]. Most studies have noted a higher rate of intrahepatic recurrence among patients with DLMs left untreated, compared with patients in whom all initial sites of disease were resected. In several series, recurrent DLMs have been reported to occur in more than one-half of patients in whom the DLMs were not resected [104]. With regard to OS, patients with DLMs have a reported 5-year survival ranging from 40 to 80%. Several studies have noted no statically significant difference in OS among patients with some untreated DLMs versus those in whom all original DLMs sites were treated [131, 135]. The management of patients with DLMs, that is, CLMs that disappear under chemotherapy and are undetectable intraoperatively and finally are "left in place", continues to be controversial [106]. Moreover, up to the 2010s the collected data suggested that all original sites of CLMs should be addressed surgically or with ablative therapy if possible, even if they are no longer present on re-staging imaging, as they are likely to harbor viable malignant cells that may progress at some point. But today, these statements are a matter of debate and currently, the MDT has a great challenge when all original liver metastatic sites are not detected and some questions emerge about how patients should be managed. One of the therapeutic attitudes could be to go forward and operate without preoperative evidence of residual disease. On the contrary, the current attitude of the majority of the authors is to wait to see some evidence of recurrent liver disease before surgical approach. A *complex clinical situation* is a patient that has had *mixed response* characterized by some DLMs but also other areas of residual macroscopic disease, where the clinical approach is more controversial. Further, there is no evidence about what could be the role of a "chemotherapy break" as a provocative test to determine a durable complete response.

In conclusion: (1) patients with DLMs should undergo an MRI to better look for signs of residual disease in order to better delineate whether the patient has had a CRR, (2) CRR does not always signify a CPR, (3) currently, "true complete response" (CPR and/or CCR) is the best way to select patients with DLMs, (4) the traditional dogma stipulating an obligatory "blind liver resection" of the initially affected part of the liver is no longer acceptable, and (5) TRG Rubbia–Brandt scoring system should be considered when evaluating efficacy of SPC for CLMs. Therefore, in our opinion, pathologists in liver surgical centers should adopt this scoring system in order to homogenize the pathological reports that would be published in various future studies.

Neoadjuvant Chemotherapy and Resectable Colorectal Liver Metastases

First of all is important to clarify three definitions: (1) *preoperative chemotherapy* refers to a treatment given to patients before surgical resection,

(2) *neoadjuvant chemotherapy (NC)* refers to a treatment given to patients with resectable disease at initial presentation, and (3) *perioperative chemotherapy* refers to a therapeutic schema given to patients before and after surgical resection. The background to this issue is that the role of preoperative chemotherapy for resectable CLMs is still controversial [137]. It is generally accepted that resection of CLMs should be attempted whenever feasible. There is a need for clearly defined and widely applicable clinical criteria for the selection of patients who may benefit from hepatic resection for CLMs. Such criteria would also be useful for stratification of patients in clinical trials for this disease [138, 139]. As the efficacy of SPC is increasing, the number of patients who potentially benefit from NC, perioperative, and adjuvant chemotherapy is also growing. The traditional dogma of offering hepatic resection to only those patients with four or fewer lesions confined to one side of the liver no longer applies [89, 140, 141]. An early study published in 2008 by Nordlinger, B and colleagues of the EORTC Intergroup trial 40983, which was the *only randomized controlled trial* where a comparison was made between perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable CLMs [142]. In this trial, the primary end-point was PFS, and in patients who have received perioperative chemotherapy with the FOLFOX scheme the PFS was improved by 7–8% at 3 years, although the OS was not significantly longer. Further, in the chemotherapy arm, resection was possible in 159 patients (87.4%) compared with 170 patients in the surgery arm (97.3%), but the rates of R0 resections were almost identical (83% vs 83.5%) [141, 142]. In a subsequent update of the results presented by Nordlinger, B and colleagues in 2009, they have shown that the benefit in PFS in the perioperative chemotherapy arm was found to be statistically significant at 20.1 versus 14.3 months in the surgery arm (HR: 0.76, p = .026). These observations have suggested the importance of chemotherapy in the outcome for this group of patients. Further, perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of PFS in eligible and resected patients [110]. Recently, Nordlinger, B and colleagues confirmed in ASCO 2012 that in the follow-up at 8.5 years of the EORTC trial, despite increasing PFS there was no improvement in OS. Gruenberger, T and colleagues published in 2012 that SPC is now integral to the management of resectable patients, and conferring a PFS advantage over surgery alone in patients with upfront resectable disease [143]. Retrospective studies have confirmed the ability of NC to render some resectable CLMs [7, 89, 139]. The best group, so-called "ideal group" in CLMs, is for about 5–10%, and is represented by patients with easily resectable liver metastases and a low risk of relapse, and together these constitute the most controversial cases. This group includes patients with metachronous disease, with a few number of metastases (three or less), good intrahepatic location of those lesions, adequate radiological margins, and, no major poor prognostic factors [6]. In the other hand, we should consider in this category other patients with resectable CLMs but with high risk of relapse, including patients where liver resection is possible but is technically difficult because the lesions are close to the hepatic veins and/or portal branches. In addition, in this category another group of patients could have poor *prognostic factors* according to the *Fong Clinical Risk Score*: (1) primary tumor with lymph node metastasis, (2) progression-free interval less than 12 months, (3) tumor more than 5 cm in diameter, (4) multiple bilateral lesions and, (5) carcinoembryonic antigen (CEA) levels more than 100 ng/ml [108]. In this group, the NC has the advantage of prolonged PFS, but there is a clear influence of the number of factors that are involved [138, 140, 144]. The prognostic factors of CLM were identified, and then stratified according to the number of such prognostic factors into: (1) low-score group (L-group: score 0 or 1), and (2) high-score group (H-group: score 2 or 3). The overall 5-year survival rate was markedly higher in the L-group (68%) than in the H-group (26%, $p < 0.0001$). As for recurrence, tumor relapse more often was treated by resection in the L-group than in the H-group (p = 0.0339) [145]. Despite the wide variety of prognostic factors reported in the literature, John, S and colleagues published in 2014 a

study where they was only able to identify a preoperative CEA ≥ 200 ng/ml and the presence of tumor within 1 mm of the resection margin, where both could be of value in predicting survival. Such variables are likely to identify patients who may benefit from intensive follow-up to enable early aggressive treatment of recurrent disease [146]. R1 resection is a negative prognostic factor after liver resection for CLMs. The significance of R1 margins in the era of effective chemotherapy is unknown. Tranchart, H and colleagues reported in 2013 a study where on multivariate analysis, N (+) status of the CCR primary tumor ($p = 0.008$), presence of radiological occult disease ($p = 0.04$), and R1 resection ($p = 0.03$) were independent adverse predictors of OS. The N (+) status of the primary tumor ($p = 0.003$) and R1 resection ($p = 0.02$) were independent adverse predictors of PFS. Further, on multivariate analysis, use of postoperative chemotherapy was the only independent predictor of improved PFS ($p = 0.02$) in the R1 group. A positive resection margin remains a significant poor prognostic factor after liver resection for CLMs in the era of modern chemotherapy [147].

Mc Nally, G, Lloyd, D, and Grondona, J published in 2015 a study where the objective was to investigate the *prognostic value of serum CEA level* in CCR patients with liver metastases [148]. Such a serum CEA level was recorded at the point of *metastasis diagnosis*, differing from the majority of literature looking at preoperative liver resection CEA level. From January 2010 to December 2014, 138 patients with a diagnosis of CLMs were included in the study—population from Buenos Aires, Argentina and followed up over a 4-year period. The OS for all patients studied with a CEA < 100 ng/ml was significantly longer than for patients with CEA ≥ 100 ng/ml ($p < 0.001$). The 1-, 2-, and 3-year OS rates for the whole cohort were 73.6%, 56.6% and 53.8% respectively. In addition, for patients with unresectable metastases, a low CEA level (<100 ng/ml) was also associated with the increased overall survival ($p = 0.036$) [148]. In conclusion, in this cohort, the study indicated that a low CEA level (<100 ng/ml) measured at metastasis diagnosis was a *good prognostic indicator* for improving survival in patients with CLMs. These findings highlight the importance of measuring serum CEA levels in this group of patients at the time of liver metastasis diagnosis [148].

The EORTC 40983 trial and the majority of retrospective studies published in the 1990s and in the early 2000s did not find any OS advantage in patients treated with NC. Additional randomized high-quality studies are needed to shed light on this topic [144, 149]. Lehmann, K and colleagues analyzed in 2012 the literature (Pub Med) with a systematic review for publications related to liver surgery and chemotherapy according to the methodology recommended by the Cochrane Collaboration, and the conclusion was that for resectable lesions, studies on NC failed to convincingly demonstrate an OS benefit [150]. Taking into account the above, up to now, NC does not seem to improve the outcome of patients with solitary metachronous CLMs. In addition, it would probably be useful in multinodular disease (more than three lesions) despite being resectable [85]. It is well known that CLMs is a heterogeneous disease; therefore, Nigri, G and colleagues published in 2015 a systematic review in order to summarize all studies published from 2003 up to 2014 with regard to patients with initially resectable CLMs. Data were examined for information about indications, NC and adjuvant therapies, surgical treatments, perioperative results, and OS. They concluded that there is a lack of clear evidence on the role of NC in the treatment of resectable CLMs in the literature. Moreover, the majority of studies were retrospective, and there was high heterogeneity among them in the treatment protocols [149]. The effectiveness of perioperative chemotherapy for CLMs remains a matter of debate. In our opinion, there is a great difference based on whether we are evaluating CLMs in a synchronous or metachronous disease. Concerning *synchronous disease*, Slesser, A and colleagues published in 2015 a study where such patients were analyzed according to the following two different groups of treatments: (1) An upfront primary tumor resection, and (2) NC and then surgery. A univariate and multivariate analysis was performed to identify factors significantly contributing to progressive disease. Their

findings suggest that an upfront primary tumor resection in patients with synchronous CLMs will result in early progressive disease [151]. In addition, related to *metachronous disease* in our view there is a question: is perioperative chemotherapy useful for metachronous resectable CLMs? And moreover, what is the benefit or impact in the outcome of these patients related to OS and/or PFS and/or in the recurrence in the liver? All of these issues need to be validated in a future multi-center independent trial [95].

In summary, there are some *positive outcomes of preoperative chemotherapy*: Two of them are the clearest:

1. The possibility of increasing the complete resection rate
2. To decrease the extension of liver resection by the shrinkage of tumor [4, 133].

Other potential benefits of administering chemotherapy prior to hepatic resection are:

1. To assess the in-vivo response of disease, which means detecting chemo-responsiveness in vivo
2. To evaluate chemo-tolerance, which is valuable information for a future adjuvant therapy, facilitating postoperative chemotherapy planning. Therefore, a selection of patients who may actually benefit with liver surgery could be established. Borderline resectable patients may benefit from in-vivo response testing to systemic treatment
3. In resectable patients, it allows time for other sites with metastases may appear during that period
4. On the contrary, it could identify chemo-resistant patients and the aggressive disease [110, 141].

Finally, the *empiric advantage* could be the treatment or the eradication of the *micrometastases*, because of the hypothesis that the hepatic resection releases hepatotropic factors that could stimulate the growth of occult micrometastases elsewhere in the healthy liver, all of which should be tested in future studies.

On the other hand, there are several *potential negative outcomes of preoperative chemotherapy*:

1. First of all, the various drugs may produce adverse effects during the treatment and could result in partials interruptions or definitive suppressions of such chemotherapy
2. In patients that are candidates for liver surgery, one of the main cons could be the adverse effects of some drugs over the non-tumoral parenchyma that could conduct to a more complex surgery. In addition, the hepatotoxicity of some drugs may increase the risk of postoperative complications [152]
3. Further, the increase risk of disappearance of some or all liver metastases and the consequent problems in the resections of those patients
4. Finally, the worst scenario is the possibility of the progression of disease during NC.

In summary, related to the management of resectable CLMs and the possibility of giving them NC, in our opinion it has been well established that hepatic resection should be considered the standard of care for patients with resectable CLMs, but the benefits of using systemic chemotherapy for these patients have not been completely proven. Although many authors have published that systemic chemotherapy is likely to improve PFS, no differences in OS have been demonstrated to date. Therefore, in order to evaluate this issue, Araujo, R and colleagues published in 2015 the analysis of the systematic review and meta-analysis of studies published from January 1991 to December 2013 that were used to compare *surgery alone versus surgery plus chemotherapy* for patients with CLMs who underwent liver resection with curative intent. All randomized clinical trials were included in the study. Comparison of PFS and OS was performed using a fixed-effects model and the hazard ratio (HR). Four studies, totaling 1592 patients, reported on PFS, showing that chemotherapy (702 patients) relatively *improved PFS for 29% of the patients* (HR, 0.71; 95% CI, 0.61–0.83; $p < .001$). Concerning OS, five studies comprising 2475 patients were analyzed, and *chemotherapy* (1024

patients) relatively *improved OS rates for 23% of the patients* versus surgery alone (HR, 0.77; 95% CI, 0.67–0.88; $p < .001$). They concluded that this meta-analysis demonstrated that the use of chemotherapy for patients with CLMs who underwent resection with curative intent is a worthwhile strategy for improving both PFS and OS [153]. In conclusion, the combination of systemic chemotherapy plus hepatic resection is superior to resection alone for resectable patients with CLMs; however, in spite of this affirmation, it remains unclear whether such therapy is optimally given before, after, or both before and after surgery. Prospective randomized trials are needed to determine whether administering systemic therapy prior to, following, or both prior to and following hepatic resection for CLMs provides superior outcomes. Further, close multidisciplinary observation and communication are essential to avoid over-treating patients during SPC for CLMs. In our opinion, the role of personalizing cancer care and tailoring treatment at diagnosis is important. Further, the liver surgeon must be the gatekeeper for treatment of patients with CLMs.

Conversion Chemotherapy in Unresectable Colorectal Liver Metastases

Conversion chemotherapy (CC) refers to a treatment given to patients with unresectable disease at initial presentation. The meaning of *down-staging* in CLMs literally refers to lead a patient by using some chemotherapy treatment to a lower step down in a less severe disease stage. However, this is not true because patients with CLMs despite any successful treatment will always remain in CRC disease stage IV. Therefore, the correct name to use is *down-sizing*, which refers to the decrease in size and/or extension of a tumor due to the effects of chemotherapy treatment. Less than 20% of patients with CLMs are initially resectable, and of those cases PFS in 5 years is about 20–25%, with a high hepatic recurrence rate [89, 154]. Down-sizing for resection in the setting of metastatic disease that is deemed unresectable at the time of presentation but potentially resectable after a major clinical response should be considered a standard approach. The best management choice in CRC patients with unresectable liver-only metastases would be represented by CC aiming to reduce liver cancer deposits, thereby permitting curative surgery. The possibility of curative liver surgery significantly prolongs the outcome for patients with CLMs. More prospective randomized trials are required to define the conversion rates with biological drugs [107]. Bismuth, H and colleagues published in 1996 the first study aimed at the provision of chemotherapy to patients with unresectable CLMs and the subsequent "conversion" of some of them for hepatic surgery [92]. This data were updated by Adam, R and colleagues in 2004 with a series of 1439 patients who underwent resection of CLMs. Among these, a group of 1104 patients were described who were initially considered to have unresectable disease based on large tumor size, poor tumor location, multinodularity, or presence of extrahepatic disease. After receiving an average of ten cycles of systemic chemotherapy (5-FU and chronomodulated oxal), 138 patients (12.5%) demonstrated enough response to become anatomically resectable, but within the median follow-up time of 49 months, 111 of these patients (80%) recurred, and such recurrence was limited to the liver in 29% of cases. Five-year OS and PFS were 33% and 22% respectively, both of which were lower than for those patients considered resectable prior to chemotherapy (48% and 30% respectively; $p = 0.01$) [109]. Since those early retrospective reports, some prospective trials have provided additional data concerning outcomes of CC, but few studies report on long-term outcome after resection. CC is a reasonable strategy for managing CLMs; however, this group of patients must know that the benefit of resection following conversion is lower than if they had presented with resectable disease at the outset [8]. One possible use of chemotherapy for patients with initially unresectable CLMs is for downsizing tumors to the point where they become amenable to a complete resection. This treatment strategy is commonly referred to as conversion therapy, as opposed to neoadjuvant

therapy, which is designated to those patients with resectable disease at initial presentation. When patients are considered for resection of CLMs, questions arise about the best timing of the liver surgery: sequential or simultaneous, which includes surgery of the primary tumor or liver-first reversed approach for the management in synchronous disease, and especially the applicability and timing of chemotherapy. Classical and reversed managements of CLMs are associated with similar PFS and OS rates when successfully completed [155]. The definition of a treatment aim is important for both the integration of a multimodal approach, and for the choice of a first-line systemic treatment. In patients with large and/or multiple CLMs, the technical limits of curative surgery can be overcome by both reducing tumor volume with preoperative chemotherapy and, by increasing the *future liver remnant (FLR)*. One of the main procedures to achieve this goal is portal vein embolization (PVE). Therefore, preoperative PVE is used to promote compensatory hypertrophy in patients whose FLR may be insufficient to support them during the recovery phase following major hepatic resection. PVE increases the safety of hepatectomy for patients with marginal hepatic reserve. The average increase of the estimated FLR is between 8 and 16% at 2–4 weeks after PVE, depending on the measurement technique and the underlying liver disease [113, 156, 157]. Long-term survival has been found to be comparable for patients with and without PVE before major hepatic resection for CLMs, at 38% at 5 years [158]. Given the cytotoxic nature of chemotherapeutic agents and their ability to hinder cell proliferation, the question arises whether liver regeneration and hypertrophy are altered by concurrent chemotherapy. During the 1990s, chemotherapy was generally discontinued before PVE because it was alleged to impair hypertrophy of the FLR. However, currently it is well known that chemotherapy does not impair hypertrophy of the contralateral liver after PVE. One of the early reports to address this issue was from Goéré, D and colleagues in 2006, on ten patients who had no chemotherapy between PVE and surgery whose outcomes were compared with data from another ten patients who had continuous chemotherapy. No significant difference was observed in FLR growth between the groups [159], but the problem of this study was a small sample size. In order to address this issue Covey, A and colleagues in 2008 reported a study of 100 patients undergoing PVE before resection of CLMs, 43 of whom received concurrent chemotherapy of various regimens. This study found no statistically significant difference in liver growth between the patients who had concurrent chemotherapy treatment and those who did not (22% vs 26%; p = NS) [160]. In addition, similar results were presented by Zorzi, D and colleagues in 2008, who showed no difference in FLR growth after PVE in patients treated without chemotherapy, those managed with chemotherapy, and those treated with chemotherapy that included bev (10.1% vs 8.8% vs 6.8%; p = NS) [161]. Several researches using animal models were presented, as reported by Bockhorn, M and colleagues in 2007, concerning the role of VEGF inhibitors, as targeted by bev, which have been shown to impair liver regeneration in animal (rat) models after partial hepatectomy [122]. With regard to this issue, Aussilhou, B and colleagues published a paper in 2009 in which they suggested that a bev-containing chemotherapy regimen impairs FLR hypertrophy after PVE. The authors found a significantly smaller increase in FLR in the bev-treated group (n = 13) compared with the group that did not receive bev (n = 27) in their regimens (561 + 171 cm^3 vs 667 + 213 cm^3; p = 0.031) [162]. Based on existing data, administration of systemic therapy appears to be acceptable around the time of PVE, but it may be prudent to avoid bev in these patients. Liver growth occurs after PVE even when cytotoxic chemotherapy is administered. Data concerning the impact of chemotherapy-induced liver injuries on liver regeneration after PVE are scant. A recent study by Tanaka, K and colleagues in 2010 showed that steatosis was associated with significantly lower hypertrophy volume after right PVE in 35 patients after hemi-hepatectomy [163]. Based on existing data, it appears safe to consider PVE in patients who receive chemotherapy prior to hepatic resection; however, the actual benefit

of PVE for this set of patients still remains unclear. In conclusion: (1) the recommendation for patients who are receiving chemotherapy is to limit the use of PVE to cases who will undergo major hepatic resection with a FLR less than 25–30%; however, (2) if chemotherapy is mandatory it can be safely continued until liver surgery, despite a PVE being indicated because it was necessary. This continuing chemotherapy while PVE is performed impaired neither the hypertrophy of the FLR volume nor the postoperative course after liver resection. Another new strategy to expand the criteria of resectability is the *two-stage hepatectomy*, which has been adopted for resection of advanced CLMs. Using this approach, complete resection is feasible in selected cases with bilateral CLMs. PVE or intraoperative portal vein ligation is often required after the first resection to promote hypertrophy of the FLR and to ensure sufficient FLR. In the first description by Adam, R and colleagues in 2000, the authors proposed to remove as many tumor sites as possible during the first operation, followed by a course of chemotherapy, with or without PVE, and second-stage resection to clear the remaining liver [164]. This strategy was then modified by Jaeck, D and colleagues in 2004 because of concerns of accelerated tumor growth during the regeneration period after major hepatectomy and PVE. The new strategy is to initially remove tumor in the FLR, clear one side of the liver in a usually smaller operation prior to PVE or intraoperative portal vein ligation, and resect the remaining tumor-bearing liver in a second operation [165]. This surgical approach can be combined with systemic chemotherapy, and is an effective treatment strategy for selected cases with advanced CLMs. These patients are at considerable risk of local and distant recurrence; however, the majority can be salvaged, and long-term survival can be achieved. One of the best long-term results was presented in a study by Chun, Y and colleagues in 2007. In this research, all patients received a course of modern oxal- or irino-based chemotherapy preoperatively, and 81% received additional chemotherapy postoperatively. With a median follow-up of 25 months, they reported an astonishing 3-year OS and PFS of 86% and 51% respectively, which was favorable when compared with patients who had a one-stage hepatectomy. Although this series presents a well-selected patient population, it demonstrates that in combination with modern chemotherapy, two-stage hepatectomy offers a chance of long-term survival for patients who would otherwise not be candidates for resection [166]. Although SPC did not impair liver hypertrophy, PVE and/or two-stage hepatectomy accompanied by SPC should be performed with particular care to minimize risk of liver failure after the procedure. De Santibañes, E and Clavien, P reported in 2012 on the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), which induces *accelerated growth* of small FLR to allow curative resection of CLMs. The ALLPS approach consisted of a portal vein ligation combined with in-situ splitting that induces rapid contralateral liver lobe hypertrophy, enabling two-staged extended hepatic resection in small-for-size settings [132]. Alvarez, F and colleagues published in 2015 a prospective study on the largest reported single-center experience which shows that ALPPS has acceptable morbidity and mortality, together with a high oncological feasibility and hypertrophic efficacy. Partial parenchymal transection seems to reduce morbidity without negatively impacting FLR volume hypertrophy [133]. Further, in 2015 the results of a multicenter analysis were reported in order to show that ALPPS offers a better chance of complete resection in patients with unresectable CLMs compared with conventional-staged hepatectomies [134]. Concerned that the CC might be toxic to the organ and may impair hepatic regeneration in the ALPPS approach, Kremer, M and colleagues published in 2015 a study that was performed to assess the procedure's effect on hypertrophy of the FLR. They analyzed 19 consecutive ALPPS patients, of whom 58% (n = 11) received CC because of CLMs. Hepatectomy was performed within 6–13 days after hepatic partition. Volumetry was performed before both liver partitioning and hepatectomy. The volume of the FLR in non-chemotherapy patients increased by 98 ± 35%, but the increase was 59 ± 22% in

patients who underwent CC (p = 0.027). Therefore, data presented here demonstrate for the first time that CC significantly impairs hypertrophy of the FLR after ALPPS [132]. Currently, progress in both liver surgery and anesthesia-critical care as well as the development of new strategies, that is to say chemotherapy combined with targeted treatments, PVE, two-stage hepatectomy, and the ALPPS approach, make it possible to envision more complex surgeries. With regard to the use of oxal in patients with marginally non-resectable CLMs, an early study was published in 2004 by Goldberg, R and colleagues, where they found that FOLFOX treatment was associated with a 4.5-month improvement in median OS compared with continuous infusion of 5-FU/LV alone (19.5 vs 15 months; $p = 0.001$). As no trial has found a difference in efficacy between the FOLFOX and FOLFIRI regimens, both remain first-line treatment options for SPC treatment of unresectable CLMs. FOLFOX is used primarily over FOLFIRI because of potentially debilitating diarrhea associated with the latter [167]. Long-term outcomes between primary resection and the secondary resection following SPC are continuing to be debated. It is the case that an important prospective study was published by Capussotti, L and colleagues in 2006, in which they found no statistical difference in OS after resection in 34 patients who were converted to resectable, compared with 116 patients who underwent immediate liver resection (median survival 41 vs 50 months, respectively; p = NS). Further, at a median follow-up of 35 months, a 94% recurrence rate was observed in the conversion group compared with 66% in the immediate-resection cohort (p = .001), and PFS was 9 months in the converted group compared with 37 months in the immediate-surgery group (p = .001). These authors also noted that extrahepatic recurrence after resection was greater in patients who were converted from unresectable to resectable [168]. In addition, another prospective study published by Nuzzo, G and colleagues in 2007 compared the outcomes of 60 initially resectable patients to that of a cohort of 15 patients with initially unresectable CLMs who underwent complete resection following conversion chemotherapy. This study also found no significant difference in OS between initially resectable and unresectable patients with a mean survival of 46 and 47 months, respectively (p = NS). Further, at a median follow-up of 34 months, disease recurrence rates were higher in initially unresectable patients (53%) than in those in the primarily resectable comparison group (28%), and 3-year PFS rates were 31% and 58% respectively (p = .004) [169]. The past 12 years have seen the clear recognition that the administration of chemotherapy to patients with initially unresectable CLMs can increase the number of patients who can undergo potentially curative secondary liver resection. Coupled with this, recent data have emerged that show that perioperative chemotherapy confers a PFS advantage over surgery alone in CRC patients with initially resectable liver disease [110]. The European CLMs Treatment Group is an international panel of 21 experts in colorectal oncology comprising liver surgeons and medical oncologists. This group reviewed the available evidence, and in 2009 the recommendation of this panel was that the majority of patients with CLM s should be treated upfront with chemotherapy ± targeted agents combined with surgery, irrespective of the initial resectability status of their metastases [110]. Lehmann, K and colleagues published in 2012 a systematically reviewed for publications for unresectable CLMs, related to combination regimens that result in enhanced tumor response and resectability rates up to 30%, although the additional benefit from targeted agents, such as bev or cetux, is marginal [150]. In addition, in this study they have shown that preoperative standard chemotherapy can be recommended for downsizing unresectable CLMs, but not for resectable lesions, for which adjuvant chemotherapy is preferred [150]. In marginally resectable patients, the conversion in first-line chemotherapy should be optimal and short. It could be optimal with triplets or doublets combined with targeted therapy. Moreover, to evaluate the response when anti-VEGF is used, there is probably more necrosis and less shrinkage, but with anti-EGFRs probably less necrosis, more shrinkage, and significantly higher rate of con-

version to resectability. Further, OS is better with cetux versus Bev, in KRAS wild-type [170]. For patients with initially unresectable KRAS wild-type CLMs, anti-EGFRs combined with chemotherapy improved the resectability of liver metastases and improved ORR and OS compared with chemotherapy alone [73, 170, 171]. Adam, R and colleagues, have published in 2012 that based on current evidence, the duration of CC should be as short as possible, and resection achieved as soon as technically possible in the absence of tumor progression. Therefore, a widespread recommendation for CC is to stop sooner rather than later. Optimal first-line CC, doublet, or triplet chemotherapy regimens, combined with targeted therapy, is advisable in potentially resectable patients. In this situation, at least four courses of first-line CC should be given, with assessment of tumor response every 2 months [7]. To avoid sub-optimal treatment, wait for 2 months of treatment before assessing definitively resectability of CLMs [109]. Folprecht, G and colleagues published in 2014 a favorable long-term OS for patients with initially suboptimal or unresectable CLMs who respond to CC and undergo secondary resection. Both FOLFOX plus cetux and FOLFIRI plus cetux appear to be appropriate regimens for "conversion" treatment in patients with KRAS codon 12/13/61 wild-type tumors. Thus, liver surgery can be considered curative or alternatively as an additional "line of therapy" in those patients who are not cured [172]. In addition, PFS was similar and OS was improved with panit versus bev when combined with FOLFOX6 in patients with wild-type KRAS exon 2 tumors. Patients with wild-type RAS tumors seemed to experience more clinical benefit with anti-EGFR therapy [104]. Cetux and panit in KRAS wild-type CRC and initially unresectable liver-limited disease have increased ORR and R0 resection rate by about 60%, and have reduced the risk of PFS by about 32%. This combination represents one of the preferred choices as conversion therapy in KRAS wild-type patients with unresectable CLMs [173]. One option is the intensification of the CC, with the addition of a third agent to these regimens has been shown to increase the response rates and the resection rates in this subset. In a phase-III trial published in 2007 by Falcone, A and colleagues, from the Gruppo Oncologico Nord-Ovest (GONO), they showed that the FOLFOXIRI regimen significantly increased the ORR and radical resection of metastases compared to FOLFIRI (15% vs 6% all patients and 36% vs 12% in liver metastases only, $p = .017$). It is important to take in the account toxicity profile of this intensified scheme, in particular the relatively high rate of severe hematological and gastrointestinal side-effects, suggesting that special care should be taken in the selection of patients suitable for this strategy [174].

Primrose, J and colleagues published in 2014 a provocative study that was the New EPOC trial, that is an English phase III randomized trial comparing CC with oxal/irino plus 5-FU and cetux pre- and postoperatively in patients with resectable RAS wild-type CLMs [175]. In this study, patients with KRAS exon 2 wild-type resectable or suboptimally resectable CLMs were randomized in a 1:1 ratio to receive chemotherapy with or without cetux before and after liver resection. The primary endpoint was PFS. With an overall median follow-up of 20.7 months (95% CI 17.9–25.6) and 123 (58%) of 212 required events observed, PFS was significantly shorter in the chemotherapy plus cetux group than in the chemotherapy-alone group (14.1 months [95% CI 11.8–15.9] versus 20.5 months [95% CI 16.8–26.7], hazard ratio 1.48, 95% CI 1.04–2.12, $p = 0.030$). This detriment was more substantial in patients with a better prognosis, and occurred even in those who responded to treatment. Possible explanations include the need for improved biomarker definition of patients, chemotherapy interaction, or a modification of the biomarker environment after SPC or surgery [175]. Because a randomized clinical trial comparing CC to adjuvant chemotherapy combined with resection of CLMs is lacking, this topic can only be addressed indirectly. Another recent single-arm phase-II study assessed a perioperative treatment with capecitabine, oxal, and bev in 56 patients with resectable CLMs, and at least one risk factor according to the Fong risk score. Radical resections were performed in 52 out of 56 patients. The study showed a high response rate (73.2%) and disease control rate (94.6%) with 11 complete pathological responses (8.9%).

The trial confirmed the safety and feasibility of bev in the preoperative setting [97].

Gruenberger, T and colleagues reported in 2015 the *OLIVIA study*, which is a multinational open-label phase II study conducted at 16 centers in Austria, France, Spain, and the UK [115]. Patients with unresectable CLMs were randomized to bev plus FOLFOX-6 or bev plus FOLFOXIRI. Unresectability was defined as ≥1 of the following criteria: no possibility of upfront R0/R1 resection of all lesions, <30% residual liver volume after resection, and metastases in contact with major vessels of the remnant liver. Resectability was evaluated by multidisciplinary review. The primary end point was overall resection rate (R0/R1/R2). The most common grade 3–5 adverse events were neutropenia (bev-FOLFOXIRI, 50% and bev-FOLFOX-6, 35%) and diarrhea (30% and 14% respectively). The conclusion of this study was that bev-FOLFOXIRI was associated with higher response and resection rates and prolonged PFS versus bev-FOLFOX-6 in patients with initially unresectable CLMs, and toxicity was increased but manageable with bev-FOLFOXIRI [115].

The combination of regional hepatic artery infusional (HAI) and SPC may downsize tumors and allow for complete resection and/or ablation in patients with extensive unresectable CLMs [176]. D' Angelica, M and colleagues published in 2015 that in patients with extensive unresectable CLMs, the majority of whom were previously treated, 47% were able to undergo complete resection after combined regional HAI chemotherapy and SPC. Conversion to resection is associated with prolonged survival. When feasible, surgical approach of CLMs is the treatment of choice. HAI chemotherapy effectively treats CLMs and the combination with SPC may downsize tumors and allow for complete resection and/or ablation [177]. Despite extensive disease, about 25% of patients with unresectable CLMs responded sufficiently to undergo complete resection and/or ablation. Combination HAI and SPC is an effective strategy to convert patients to complete resection with an associated excellent long-term survival [176, 177].

In conclusion:

1. Resectability should become the new endpoint in strategies involving chemotherapy in patients with unresectable CLMs
2. Variability in chemotherapy type, duration, and timing with respect to resection and a lack of standard definition of resectability make comparison impossible between different published studies
3. If chemotherapy is more efficient, it would give the best chance for surgery, and if the response is fast, there would a lesser risk of liver toxicity
4. As soon resectability is obtained, surgery should be scheduled
5. The first-line chemotherapy in unresectable CLMs patients should be: personalized to achieve efficacy and avoid undue cost; optimized to offer a better chance of resection, and at shortt as possible in order to avoid the detrimental effects of chemotherapy and to diminish the risk of DLMs and complete radiologic response
6. Again, MDT treatment is essential for improving clinical and survival outcomes.

Adjuvant Chemotherapy in Colorectal Liver Metastases

Adjuvant chemotherapy refers to a treatment given to patients after RO resection of liver metastases. Early evidence of the effect of adjuvant systemic chemotherapy (ASC) on resected patients was published by Figueras, J and colleagues in 2001. They reported on a series of 235 patients who underwent partial hepatectomy with curative intent. Of 180 patients considered for ASC with six cycles of 5-FU, only 99 were actually treated, and several patients received oxal in addition. Patients receiving ASC had an improved 5-year survival rate of 53%, compared with 25% for those intended to receive therapy but denied treatment, or for those who declined for other reasons ($p < .001$). Multivariate analysis revealed ASC as an independent predictor of survival, but the selection bias in this report limits the interpretation

of the results [178]. Consequently, if liver resection has been done without previous chemotherapy, they should receive ASC after R0 resection [4, 84]. Despite the lack of clear evidence supporting the effectiveness of ASC after curative liver resection, it has been widely used clinically [18, 20]. The largest retrospective multicenter study from Parks, R and colleagues that was published in 2007 included 247 patients treated with adjuvant 5-FU–based chemotherapy following resection of CLMs, and 518 patients who received no adjuvant treatment. They found an increase in OS with the use of ASC, with a 47-month median survival and a 5-year survival of 37% compared with 36 months and 31% respectively, for patients who did not receive chemotherapy ($p = 0.007$) [179]. This large study, with patients stratified by risk of recurrence, demonstrates that ASC, like a 5-FU-based regimen, prolongs OS after hepatic resection for CLMs [179]. The use of ASC in patients who have undergone resection of CLMs has the hypothetical benefit of decreased recurrence rates from addressing potential micrometastases before they begin growing up. Further, it has the aim to reduce the risk of recurrence and to improve patient OS. There are two theoretical rationales for ASC: (1) the presence of cancer cells "dormant" in the remaining liver, and (2) the benefit after surgery for stage III colorectal cancer. However, after curatively intended surgery, liver recurrences occur in about 50–60% of patients, despite the administration of ASC. In some reports, the ASC could be associated with better OS and PFS, mainly when the tumor diameter exceeds 5 cm in diameter [140]. In analogy to stage III disease, ASC or also so-called "pseudo-adjuvant chemotherapy" was assessed after the complete resection of all liver disease in two phase III trials using a similar design, but they were closed prematurely because of slow accrual. The pooled analysis based on individual data from these two trials was also published. This meta-analysis showed a marginal statistical significance in PFS ($p = 0.095$) and OS ($p = 0.058$) in favor of ASC [180]. Some recently published studies refer to the protocol of postoperative HAI oxal combined with ASC after curatively intended surgery, and they showed that it may significantly improve PFS of patients at high risk of hepatic recurrence compared with modern ASC alone. However, these results should be confirmed in randomized studies [127]. Treatment with ASC was independently associated with improved PFS and OS by multivariate analysis. However, based on recent evidence, irino and cetux have negative results, so they should be excluded in the adjuvant protocols [145–147]. In conclusion: (1) a schema of ASC may improve PFS and OS after RO liver resection, (2) ASC may prevent early intrahepatic recurrence, and (3) in patients who did not receive preoperative chemotherapy, ASC should always be given after surgery.

Liver Recurrence and Chemotherapy

Hepatic resection offers the best chance of cure in patients with CLMs, with 5-year survival rates exceeding about 45–50%. However, despite hepatic resection with curative intent, about two-thirds of resected patients will have a relapse, most often within the remnant liver. The majority of patients who develop recurrent CLMs relapse within the first 2 years after the hepatic resection [108, 144, 181]. Several studies have reported an association of various clinical factors with recurrence following liver resection, including number, size, and timing of occurrence of CLMs, node-positive primary disease, preoperative serum CEA level, incomplete (R1/2) resection, involvement of hepatic pedicle lymph-node, and the absence of ASC [181]. Postoperative chemotherapy reduces recurrence rates after R1 resection of CLMs [147]. Related to tumor shrinkage, during liver resection the surgeon should be aware of the appearance of a dangerous halo around CLMs that may require adaptation of the surgical technique to decrease the risk of local recurrence [182]. In addition, is well known that the prognosis of patients with disease recurrence within 6 months is much worse than for those with disease recurrence after 6 months [181]. OS of patients is today largely prolonged after treatment, allowing the possibility, at time of recurrence, to perform new cycles of SPC and iterative

hepatic surgery which could take place on livers which have been potentially compromised by former chemotherapy treatment [183]. Despite the multitude of prognostic studies regarding recurrence of CLMs after resection, there have been few reports identifying predictors for early disease recurrence. No agreement regarding predictors of survival after resection of CLMs has been reached [131, 171]. Predictors of recurrence would enable the MDT to prescribe prompt postoperative interventions against early recurrence in these patients. Narita, M and colleagues published in 2015 a study where the bio-markers *CD133*, *Survivin*, and *Bcl-2* were evaluated to assess a possible association between their intratumoral expression levels and early disease recurrence. CD133 is a cell-surface transmembrane glycoprotein, which has been reported as an important cancer-initiating cell marker. Survivin and BCL-2 are important markers of tumor cell resistance to apoptosis induction and resistance to chemotherapy. Narita, M and colleagues conclude that tumor expression levels of *CD133 and Survivin* may be a useful predictor of early intrahepatic recurrence after hepatectomy for CLMs. Administration of ASC may prevent early intrahepatic recurrence, and is currently strongly recommended [144]. Further, early recurrence risk is enhanced for extensive disease after poor preoperative disease control and inadequate surgical treatment, but it could be reduced after ASC. Although early recurrence negatively affects prognosis, re-resection may restore better survival. Several authors are in favor of giving chemotherapy before early recurrence resection [145]. Measurement of both *CEA and CA19-9* levels is strongly recommended for patients with CLMs treated with preoperative chemotherapy followed by hepatectomy, because normalization of serum CEA and/or CA19-9 levels after chemotherapy will demonstrate a good prognosis after curative hepatectomy. Moreover, if in the follow-up of this cases such blood tumors-marker levels increase, patients should be evaluated in order to explore a disease progression [146]. Araujo, R and colleagues reported in 2015 that a total of 318 consecutive resected patients were studied, with 168 patients (53%) experiencing recurrence within 2 years, and various postoperative *CEA cutoffs* were tested as independent predictors of recurrence. A postoperative *CEA* $\geq$ *15 ng/ml* had a specificity of 96% and positive predictive value of 82% for recurrence. Thus, this study demonstrates a postoperative CEA $\geq$ 15 ng/ml to be a predictive test for recurrence [184]. In summary, recurrence is common after CLMs resection, but about 27% of patients were able to undergo a potential salvage therapy. Approximately one-quarter of these experienced effective salvage therapy and may be cured. Potential salvage therapy is associated with long-term survival and possible cure, and therefore active surveillance after CLMs resection is justified [145]. In conclusion: (1) Preoperative chemotherapy is possible before resection of liver recurrence, and (2) The MDT approach is mandatory to decide the timing of chemotherapy in patients that suffer liver recurrence.

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Portal Vein Embolization

7

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The Future Liver Remnant and the Rationale for Portal Vein Embolization

Makuuchi et al. performed the first preoperative portal vein embolization (PVE) in 1982 before an extended hepatectomy for bile duct carcinoma [1]. PVE has proven to be an effective method, allowing major liver resections to be performed more safely [2, 3]. The aim of PVE is to increase the future liver remnant (FLR), thereby allowing liver resection with reduced risk of hepatic insufficiency and death. The risk of liver insufficiency is inversely proportional to the FLR.

Surgical Strategy and Preoperative Assessment of FLR

Evaluation of Candidates for Portal Vein Embolization

Adequate imaging is essential for staging as well as evaluation of resectability. Liver protocol computed tomography (three-phase CT) and magnetic resonance imaging (MRI) are the most common modalities utilized. In patients being evaluated for liver resection, the FLR is defined as the total liver volume minus the planned resected volume (Fig. 7.1). The volume of the FLR and subsequently risk of postoperative liver insufficiency and death may limit the surgical options in patients with bilateral or centrally placed colorectal liver metastases. Patients with large centrally located lesions involving two hepatic veins can be cleared with extended liver resection performed in one stage, but after PVE if the estimated FLR in insufficient. In patients with bilateral CLM, a two-stage hepatectomy with PVE between the two stages may be required to clear all disease located in the left (partial resection segment I, II and/or III) or right (partial resection of segment V, VIII, VI and/or VII) before performing right or left PVE and subsequently extended right or left resection of the liver with atrophied liver with the remaining disease (Fig. 7.2).

Due to the liver volume alterations occurring during embryology, the right liver represents on average 66% of the total liver volume, and left PVE is rarely indicated, as the right hemiliver to be preserved almost always represents sufficient sFLR. The left liver represents on average 33% of the total liver volume, and PVE is required in approximately 10% of patients undergoing right hepatectomy and in 75% of patients undergoing

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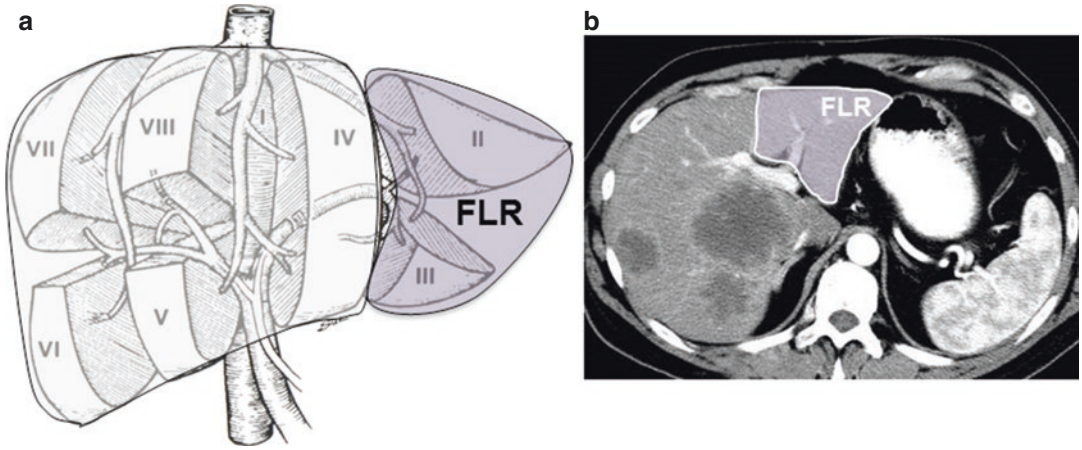

Fig. 7.1 Scheme (**a**) and CT scan (**b**) of the future liver remnant (FLR) in a patient undergoing evaluation for an extended right hepatectomy of segment 5–8 + segment 4 and 1. Segments 2 and 3 represent the FLR

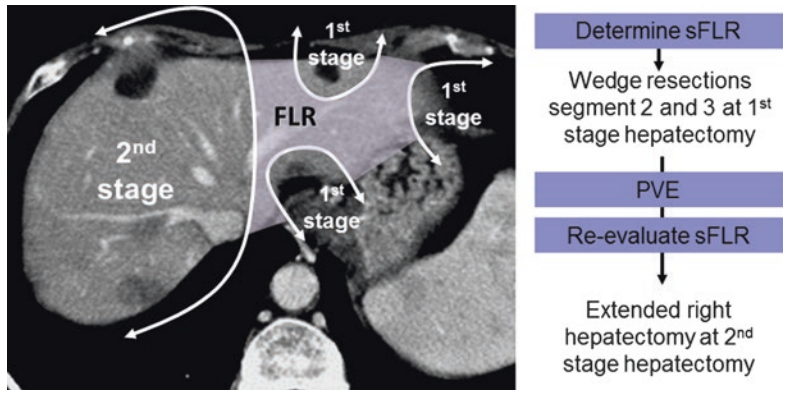

Fig. 7.2 Two-stage hepatectomy may be required to clear all metastatic liver disease in the case of multiple bilateral metastases. The FLR, usually segments 2 and 3 (± parts of 1 and 4), is cleared during the first surgical stage, followed by PVE. The sFLR is re-evaluated and if sufficient, the patient can undergo the planned extended right liver resection in a second surgical stage, usually 4–8 weeks after the portal vein embolization (PVE) was performed

extended right hepatectomy with preservation of only segment 2 and 3 (Figs. 7.3 and 7.4) [4].

There are two absolute contraindications for PVE: extensive ipsilateral tumor thrombus because most of the portal flow has already been diverted, and clinically evident portal vein hypertension because of the risk of bleeding varicies of the increased portal pressure from the procedure [5]. Renal insufficiency, coagulopathy, advanced liver fibrosis, and main portal vein thrombosis are conditions with increased risk of complication during or after PVE, and should be assessed as relative contraindications [2].

It is likely that as little as 10% sFLR may be sufficient in some patients with normal liver function [6]. However, a number of studies have demonstrated a significant impact on postoperative complications in patients with preoperative sFLR ≤20% [2, 3, 6]. Therefore, sFLR ≤20% is considered an evidence-based cut-off for PVE in the normal liver. The cut-off for preoperative PVE in the injured liver has not been explored to

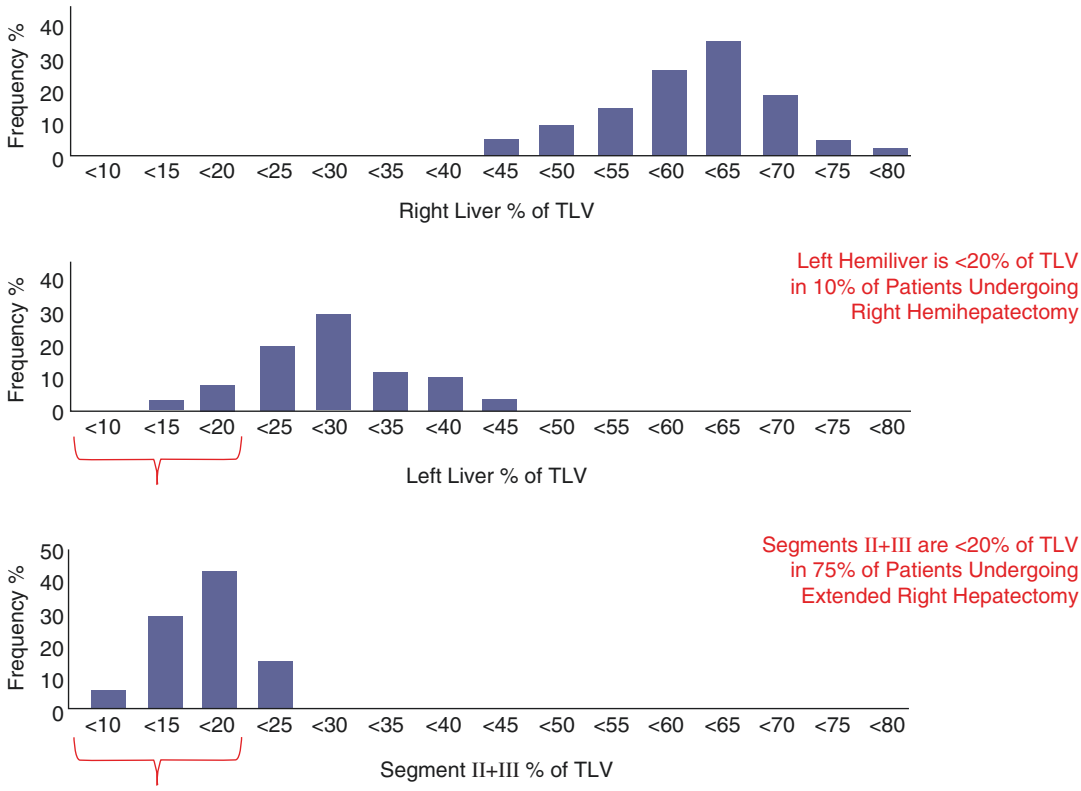

Fig. 7.3 Distributions of FLR volume of according to types of major hepatectomy. Adapted from Abdalla EK et al. *Surgery* 2004 [4] with permission

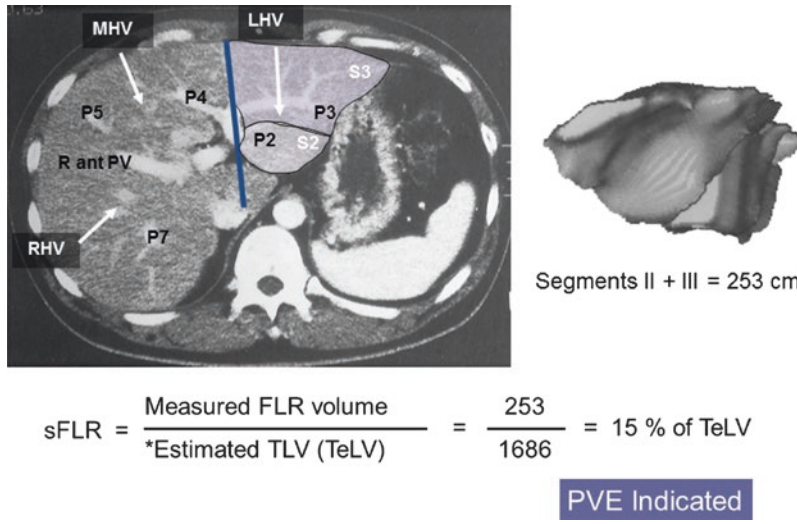

Fig. 7.4 Contrast-enhanced CT image of patient with colorectal liver metastases undergoing evaluation for PVE. Segments 2 and 3 represent the FLR, with a total volume of 253 ml. The sFLR was 15%, indicating need for PVE before liver resection. *Estimated total liver volume (TEL) is calculated to be 1,686 with the formula TEL = −794.41 + 1,267.28 × body surface area (BSA). *LHV* left hepatic vein, *MHV* middle hepatic vein, *RHV* right hepatic vein, *P* portal branch to segment, *S* segment, *R ant PV* right anterior portal vein

the same extent. However, studies have showed increased rates of postoperative complications and hepatic insufficiency after resection of liver with steatosis or chemotherapy-induced injury [7–9]. Many centers therefore consider the cut-off sFLR <30% an indication for PVE in these patients.

A substantial number of patients with cirrhosis are not candidates for major hepatic resection due to an unacceptable risk of perioperative death. However, patients with Child–Pugh class A cirrhosis are considered for resection if their sFLR is >40%. If sFLR is less than 40% but otherwise resectable, PVE is indicated [10]. This is supported by the findings of a prospective study showing decreased postoperative complications, ICU admissions, and length of hospital stay for patients with chronic liver disease who underwent PVE before resection [11]. Because of the severity of the liver injury occurring, the same cut-off for sFLR (>40%) has been suggested after prolonged biliary obstruction.

Preoperative Assessment of FLR

The FLR must be determined in patients who undergo evaluation for liver resection with a concern for insufficient volume. The most common method of measuring absolute FLR volume is to outline the FLR on axial slices from multiphase contrast-enhanced CT. Based on the area of the outlined FLR and the slice thickness, three-dimensional reconstructions are obtained and the absolute FLR volume can be calculated. However, the absolute FLR volume is inadequate for clinical decision-making, as larger patients require larger FLR. To account for this, most groups now use the ratio FLR to total liver volume (TLV), often termed standardized FLR (sFLR). Only functional non-tumor volume should be included when determining sFLR, and the TLV is calculated directly from three-dimensional computed tomography, subtracting the tumor volume. The main disadvantage with this method is the fact that determining the TLV is time-consuming and may not be accurate in patients with bile duct obstruction.

In our practice, the TLV is based on an estimated TLV (TEL). The TEL is based on the correlation between body surface area (BSA) and total liver volume [12]. Several formulas have been developed, but a meta-analysis found the most accurate to be: $\mathrm{TEL} = -794.41 + 1267.28 \times \mathrm{BSA}$ [12, 13]. BSA can be calculated using Mosteller's formula:

$$BSA = \sqrt{\frac{\text{height } [cm] \times \text{weight } [kg]}{3600}}$$

[14]. Furthermore, this method of calculating sFLR (FLR/TEL) has shown correlation with patient outcomes, and thus proven its clinical relevance [2, 6]. At MD Anderson Cancer Center, a web-based calculator has been design-based on these formulas to calculate the sFLR, degree of hypertrophy, and the kinetic growth rate (Fig. 7.5). The correlation between the BSA and the functional liver volume and the formula presented was developed in Western adults in the United States and Europe [12, 13]. It is important to note that TEL can vary between body size and race. Japanese patients have up to 19% larger livers compared to Caucasians for a given body weight. In some centers, especially in Asia, three-dimensional computer models are increasingly used to calculate FLR and sFLR based on the total liver volume.

The sFLR is estimated before and 3–4 weeks after PVE. If sFLR after PVE meet the resectability criteria, it is generally accepted that the planned resection can be performed within accepted risk of adverse events. At MD Anderson Cancer Center, the following cut-offs are used for FLR resectability criteria: normal liver >20%, liver pretreated with more than 3 months of chemotherapy >30%, cirrhosis >40% (Fig. 7.6) [6, 15–19]. While cirrhosis is rare in patients with CLM, an increasing number are heavily pretreated with chemotherapy. Obesity is increasing worldwide, and hepatic steatosis is also a more common finding which require >30% FLR for safe resection [17].

Input

000000	First Last	180	2015–01–01
MRN	Name	Height (cm)	PVE date (yyyy-mm-dd)

CT#1

2015–01–01	30	73	130	241	80
yyyy-mm-dd	Seg1	Seg2	Seg3	Seg4	Weight (kg)

CT#2

2015–02–15	42	143	170	410	79
yyyy-mm-dd	Seg1	Seg2	Seg3	Seg4	Weight (kg)

Output

	Pre EMBO[1]	Post EMBO[2]	Hypertrophy[3]	KGR[4]
Segment 1, 2 and 3	**13.4%**	**20.6%**	**7.2%**	**1.1%**
Segments 1, 2, 3 and 4	**27.2%**	**44.4%**	**17.1%**	**2.7%**
Segments 2 and 3	**11.7%**	**18.2%**	**6.5%**	**1%**

Fig. 7.5 Web-based calculator used to determine the degree of hypertrophy and kinetic growth rate (KGR) after PVE. Segment volumes are in ml (cm^3). Numbers are representative for a patient undergoing right PVE. The formulas used to calculate body surface area (BSA) [14] and total estimated liver volume (TEL) [12] are: $\mathrm{BSA} = \sqrt{\frac{\mathrm{Height}\ [\mathrm{cm}] \times \mathrm{weight}\ [\mathrm{kg}]}{3600}}$ and $\mathrm{TEL} = 794.41 + 1267.28 \times \mathrm{BSA}$. The calculations used to generate the output are: ${}^{1}\mathrm{Pre\ EMBO\ sFLR}\ (\mathrm{CT\#1}) = \frac{\mathrm{Seg2} + \mathrm{Seg3}(+\mathrm{Seg4})(+\mathrm{Seg1})}{\mathrm{Pre\ TEL}}$ and ${}^{2}\mathrm{Post\ EMBO\ sFLR}\ (\mathrm{CT\#2}) = \frac{\mathrm{Seg2} + \mathrm{Seg3}(+\mathrm{Seg4})(+\mathrm{Seg1})}{\mathrm{Post\ TEL}}$ and ${}^{3}\mathrm{Degree\ of\ Hypertrophy} = \mathrm{Post\ EMBO\ sFLR} - \mathrm{Pre\ EMBO\ sFLR}$ and ${}^{4}\mathrm{Kinetic\ growth\ rate}\ (\mathrm{KGR}) = \frac{\mathrm{Degree\ of\ Hypertrophy}}{\mathrm{Weeks\ Between\ CT\#2\ and\ PVE}}$

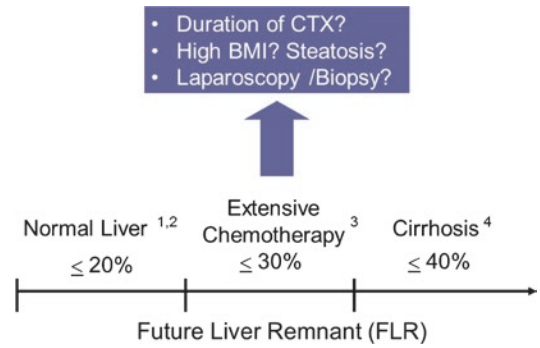

Fig. 7.6 Requirements for FLR depends on the underlying liver function. In the presence of liver injury, increased FLR is needed to allow safe liver resection with acceptable risk of hepatic insufficiency and death. [1]Abdalla et al. Arch Surg 2002, [2]Vauthey et al. Ann Surg 2004, [3]Azoulay et al. Ann Surg 2000, [4]Kubota Hepatology 1997. *CTX* chemotherapy *BMI* body mass index

Techniques of Portal Vein Embolization

Accessing the Portal Vein

The portal vein can be accessed for embolization during surgery, but with the increased experience within the field of interventional radiology, the percutaneous technique is currently the method of choice in most centers. Surgical PVE is usually performed via the ileocolic vein, while percutaneous PVE is performed ultrasound-guided transhepatic with catheter access through a distal branch of the ipsilateral or contralateral portal vein. The ipsilateral approach is often chosen due to safety reasons, as the FLR is left without risk of damage [20]. However, the ipsilateral approach may be technically more challenging, and holds a greater potential of peritoneal spillage of tumor cells. Reverse-curve catheters can be used to facilitate access to the segmental branches and cope with the increased technical challenge with the ipsilateral approach (Fig. 7.7).

Agents Used for Embolization and the Technique

Agents used to embolize the portal vein must be easy and safe to deliver, cause complete occlusion preferably without any recanalization, and be well tolerated by the patient. A number of agents have been used to induce portal vein embolus, including *n*-butyl cyanoacrylate (NBCA) and ethiodized oil, fibrin glue, ethanol, and microparticles such as polyvinyl alcohol or trisacryl gelatin. To date, no study has convincingly demonstrated the superiority of any those, and the choice of agent is mostly operator-determined. After the PVE catheter has been maneuvered into place, the vascular sheet is secured and a flush portography is performed to assess the portal anatomy. The portal pressure is measured before the embolization takes place. At MD Anderson Cancer Center, a combination of trisacryl gelatin microspheres of various sizes and embolization coils are used. Small caliber

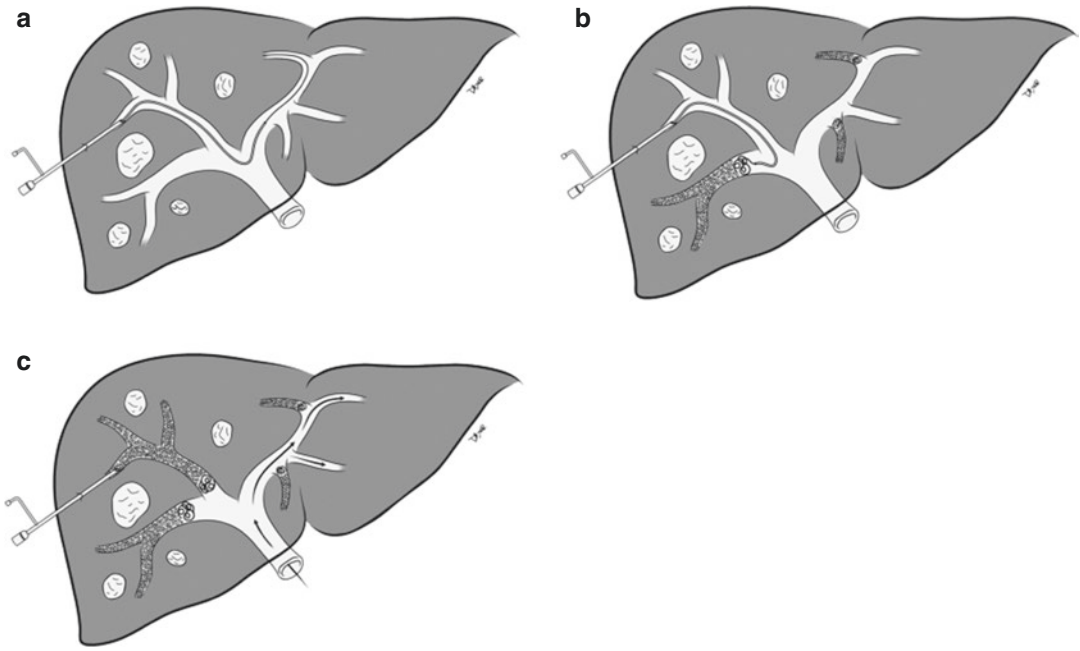

Fig. 7.7 Ipsilateral right portal vein embolization with embolization of segment 4 portal vein branches. The portal vein is entered via a distal branch of the right posterior portal vein, and the segment 4 embolization (a) is performed before embolization of the right posterior (b) and anterior (c) portal vein branch. The access tract is embolized to prevent capsular hemorrhage. Care should be taken to avoid puncturing tumor tissue due to potential peritoneal spillage of cancer cells when using the ipsilateral approach

microspheres are used initially to embolize smaller distal portal vein branches, followed by larger caliber microspheres in larger proximal portal vein branches. Upon complete stasis, embolization coils are placed proximally to prevent recanalization. Care must be taken in every step not to embolize non-target branches of the portal vein.

Embolization of Segment 4 Portal Vein Branches

Extended right hepatectomy involves resection of the middle hepatic vein and segment 4 or parts of segment 4. In cases where the left lateral section (segment 2 and 3) constitute the FLR, right PVE may not always ensure sufficient volume. This led to the idea that the superior and inferior segment 4 portal vein branches form the left portal vein could be co-embolized to increase atrophy of as much liver tissue to undergo resection as possible, and subsequently induce even further hypertrophy of the FLR (Figs. 7.7 and 7.8). Furthermore, segment 4 is at risk of increased growth in conventional right PVE, which may be unsuitable if segment 4 contains tumor and is planned to undergo resection [21, 22]. Since the late 1990s, several groups have published a significant increase in the degree of hypertrophy when segment 4 portal vein branches were co-embolized with the right portal vein (Fig. 7.9) [23, 24].

In patients where segment 4 is targeted for portal vein embolization, segment 4 embolization should be performed prior to the right portal vein embolization for safety reasons (Fig. 7.7). If non-target left portal vein

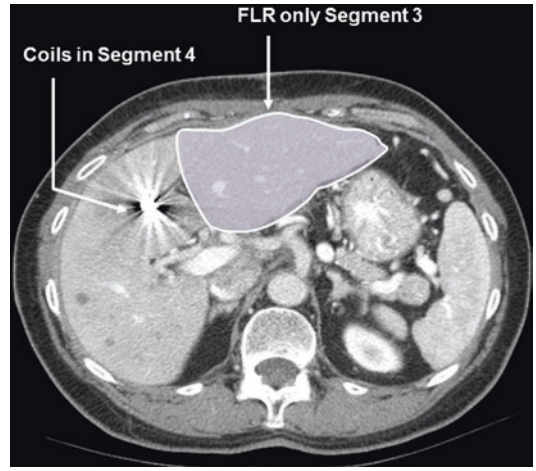

Fig. 7.9 Contrast-enhanced CT 4 weeks after right PVE with segment 4 embolization. The latter caused atrophy of segment 4 and increased hypertrophy of the left lateral segments, which in this patient represented the future liver remnant (FLR)

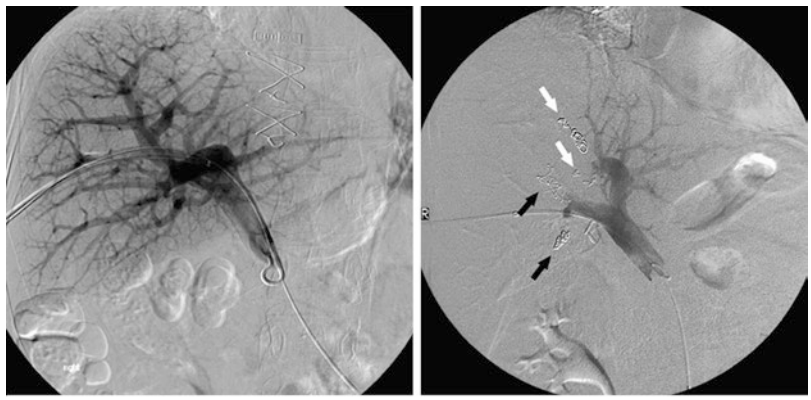

Fig. 7.8 Portogram with the catheter in the right portal vein before PVE showing a contrast-filled right portal vein three. Portogram with the catheter placed in the main portal vein after right PVE and embolization of segment 4 branches. *White arrows* indicate coils in the segment 4 branches. *Black arrows* indicate the right anterior and right posterior portal vein. Adapted from Madoff DC et al. J Vasc Interv Radiol 2005 [37] with permission

embolization or left portal vein injury occurs during the segment 4 embolization, the right portal vein embolization can be aborted. Furthermore, if the ipsilateral method is chosen, the technical aspects of replacing the catheters through the already embolized right portal vein may be challenging and cause dislodging of embolic material when maneuvering to segment 4 branches.

Measuring Effect and Outcome After Portal Vein Embolization

Degree of Hypertrophy

Observational studies have demonstrated that regeneration after PVE occurs slower than after hepatic resection, possibly due to apoptosis, as opposed to frank necrosis, which occurs after PVE [25]. The expected degree of hypertrophy is correlated with the degree of underlying liver disease. The normal liver may regenerate at a pace of up to 21 ml per day, while the same number for the cirrhotic patient may be 9 ml per day [26]. As such, sufficient hypertrophy can occur within 2 weeks in the normal liver, while regeneration may take >6 weeks in the cirrhotic. Degree of hypertrophy (DH) is the term used for the percent increase of the FLR when comparing pre-PVE and post-PVE sFLR. For example, the degree of hypertrophy is 10% if the total volume of segment 2 and 3 increased form 17 to 27% (Fig. 7.5).

Kinetic Growth Rate

Time is an important determinant for the degree of hypertrophy, which is often assessed as primary end-point for PVE. However, time is not included in the equation to determine the degree of hypertrophy. Furthermore, the risk of hepatic insufficiency and postoperative complications is lower in a patient reaching sufficient hypertrophy after 2 weeks, compared to a patient requiring 6 weeks to reach the same hypertrophy.

Kinetic growth rate (KGR) has been proposed as a tool to evaluate regeneration over time. To calculate KGR, the degree of hypertrophy is divided by the number of weeks from the PVE to the date of the post-PVE CT evaluation. A KGR >2% (meaning 2% FLR volume increase per week), is associated with low risk of hepatic insufficiency and mortality after major liver resection, irrespective of the sFLR. As such, KGR represents a functional measurement of the regenerative capacity of the liver after PVE. Caution should be taken if KGR <1% and salvage options after PVE should be considered or the second stage aborted, especially if the sFLR does not meet the resection criteria (Fig. 7.5).

Salvage Options After PVE Failure

In rare patients, PVE fails to cause hypertrophy of the FLR. These patients should be assessed for missed underlying liver disease explaining the absence of regeneration. Furthermore, depending on the technique and agent used to embolize the portal vein branches, the PVE may have been unsuccessful, or recanalization may have occurred. In such cases, a second attempt to embolize the portal vein can be attempted. Embolization of segment 4 portal vein branches can also be tried as a salvage option in patients when the FLR fails to regenerate after conventional right PVE.

There are three main factors limiting liver regeneration: portal inflow, bile outflow, and hepatic outflow. Embolization of the hepatic vein has been reported to induce sufficient liver regeneration in patients that previously have failed to regenerate after PVE (Fig. 7.10) [27, 28].

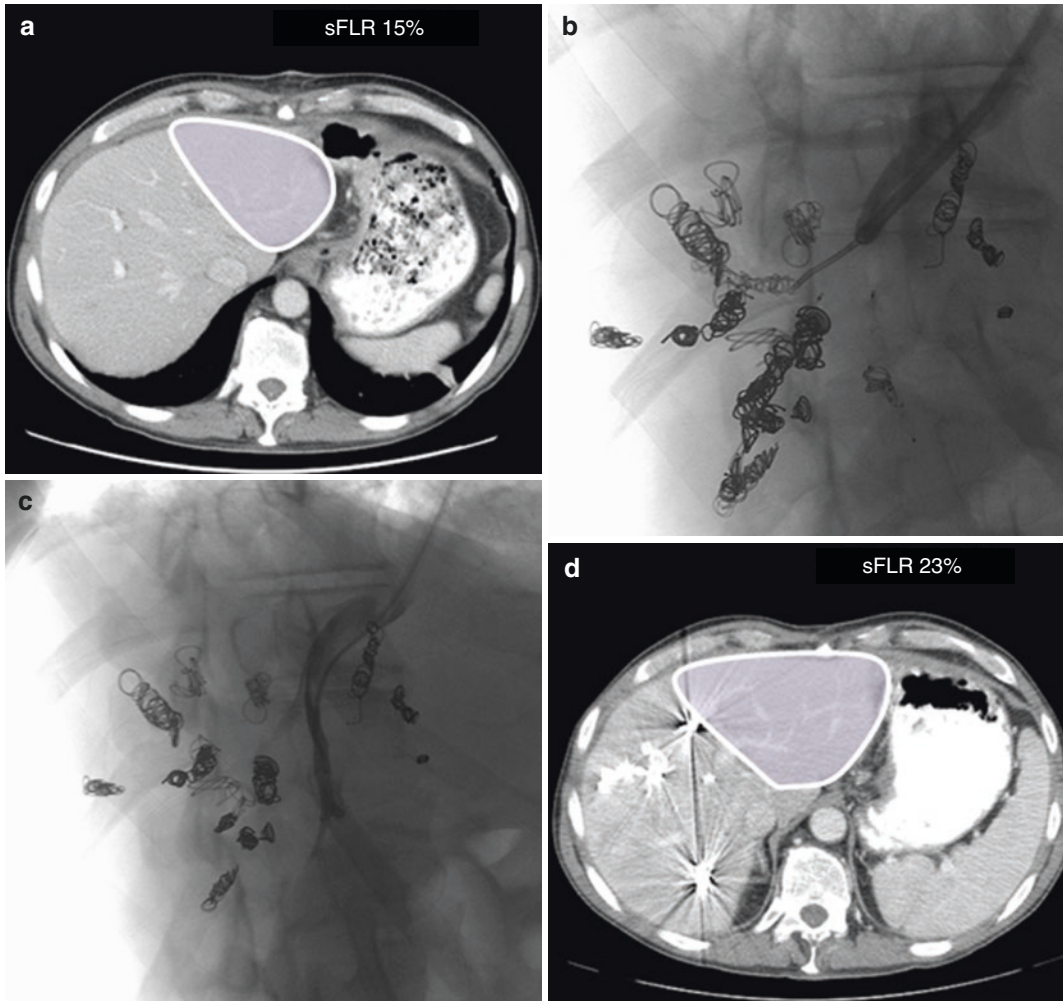

Fig. 7.10 Patient treated for CLM at MD Anderson Cancer Center. The patient was scheduled to undergo two-stage hepatectomy and PVE. **a** The liver failed to regenerate with insufficient sFLR at only 15% 6 weeks after right PVE with segment 4 embolization. **b** and **c** The patient underwent a second procedure with embolization of the middle hepatic vein. **d** CT image 8 weeks after embolization of the middle hepatic vein showed sufficient sFLR at 23%, and the patient underwent the planned extended right hepatectomy (**d**). The patient had an uncomplicated postoperative course, and was discharged at the postoperative day 7

Complications After PVE

The morbidity and procedure-related mortality after PVE is reported at 2.2% and 0%, respectively [29]. Non-target embolization, complete portal vein thrombosis, and recanalization of embolized segment are the most common PVE-specific complications. Subcapsular hematoma, hemobilia, hemoperitoneum, vascular injuries, pneumothorax, and cholangitis are among the most commonly reported complications after transhepatic procedures. The rate of major complications should not exceed 5% [30].

Oncologic Impact of PVE and Effect of Chemotherapy

PVE induces the release of growth factors to generate hypertrophy of normal liver tissue. Investigators have raised the concern that the same growth factors may stimulate tumor growth in the embolized liver, the FLR, or even promote the metastatic process. However, results from studies indicate that PVE does not cause tumor growth [2]. Furthermore, chemotherapy and targeted therapy with anti-angiogenic agent do not appear to affect liver regeneration after PVE [31].

Alternatives to Portal Vein Embolization and Additional Techniques to Induce Liver Hypertrophy

Associating Liver Partition and Portal Vein Ligation

In 2012, a European group reported a short-interval two-stage surgical approach, including initial liver parenchymal transection and right portal vein ligation in the first surgical stage, followed by completion hepatectomy within 7–10 days. The rationale for the method was the concept that parenchymal splitting and thereby division of collaterals would induce more rapid hypertrophy, allowing a shorter time interval between the first and the second stage, the latter where the extended right hepatectomy was completed [29, 32, 33]. In the literature, this method is referred to as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [34].

However, multiple concerns regarding this method have been raised. First, the rationale is not as obvious as initially believed. Interventional radiology techniques have improved, and with the recent addition of segment 4 embolization, the number of patients aborted from the second surgical stage is very low (3.5%) [35]. Second, the 4–6 week time interval between the procedures in patients undergoing conventional two-stage liver resection and PVE may provide a biological test-of-time, in which patients with rapid progressing disease may not benefit from the second stage. Third, preliminary data suggested a high incidence of major morbidity (40%) and inpatient mortality (12%) associated with ALPPS. One study comparing PVE and ALPPS for patients with small FLR reported that right PVE with segment IV PVE may offer equivalent FLR hypertrophy (62% vs 74%), but reduction in perioperative bile leak (5.8% vs 24%) or sepsis (0% vs 20%) compared to ALPPS [35]. Investigators have also questioned whether the extreme hypertrophy sometimes seen after ALPPS consists of functional liver tissue, or edema due to necrosis. Due to safety concerns, the majority of investigators still emphasize that the ALPPS method should be approached carefully and only in well-designed trials.

Portal Vein Ligation

Portal vein ligation (PVL) is a method that has been used as an alternative to PVE. When performed during the first stage of a planned two-stage hepatectomy, it saves the additional PVE procedure and may therefore be economically beneficial. However, there are several advantages of PVE compared to PVL. First, not all patients requiring portal vein ligation or embolization require two-stage hepatectomy. Second, with PVE the interventional radiologist strives to completely embolize small and larger branches of the portal vein, possibly reducing the potential of collateral circulation from the contralateral liver reaching the portal of the treated liver. In line with this, a retrospective study comparing the two methods suggested that PVE generates more hypertrophy and shorter hospital stay [36]. Third, PVE has proven to be associated with low morbidity and mortality rates, and is therefore considered very safe and minimally invasive for the patient.

Summary

- PVE is a safe procedure with low rates of major complications and nearly zero mortality.
- The sFLR takes account of the size of the patient, and is calculated by dividing the FLR determined by contrast-enhanced CT by the TEL, calculated based on the BSA of the patient.
- Currently, the indication guidelines for PVE are based on the sFLR: <20% in normal liver, <30% in liver pretreated with more than 3 months of chemotherapy, and <40% in the cirrhotic liver.
- Percutaneous transhepatic ipsilateral approach is the preferred technique due to safety concerns. The agent must be easy to deliver, well tolerated by the patient, and provide occlusion of the target portal branches. It is combined with coils to prevent recanalization.
- Right PVE is the most common procedure performed, as the left to right volume ratio usually greatly favors the right side of the liver. Left PVE is almost never needed.
- Embolization of segment 4 may be technically challenging, but has proven to be effective in addition to right PVE to increase the degree of hypertrophy before right hepatectomy is extended to include segment 4.
- DH and KGR are useful parameters to predict risk of hepatic insufficiency after liver resection. KGR is a functional measurement of the regenerative capacity of the liver after PVE.

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Intra-Arterial Chemotherapy

8

Rohit Chandwani and Michael I. D'Angelica

Introduction

Colorectal cancer is the third most common malignancy worldwide, with 1.3 million new cases in 2012 alone [1]. At the time of diagnosis, 25% of patients will have synchronous liver metastases; overall, up to 60% will develop hepatic metastases at some point in their disease course [2, 3]. That the liver is both the predominant site of metastatic colorectal cancer (mCRC) and frequently the only site of metastatic disease affords the opportunity to pursue liver-directed therapeutic options.

The liver-directed therapy with the most well-established effect on disease outcome is complete resection. Resection, in well-selected cases, offers the best opportunity for long-term survival and cure, with 5-year survival rates of 30–50% [4–6]. Many of these patients will recur, but frequently they can receive salvage therapy with resection [7]. However, only approximately 25% of patients with isolated colorectal liver metastases (CLM) are resectable at the time of first presentation [8]. Systemic chemotherapy—typically with 5-FU, leucovorin, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) in the first-line setting—offer response rates of 35–50%, with median survival in the range of 16–20 months [9]. With the recent addition of newer biologic agents that target VEGF, EGFR, or mutated BRAF, response rates are increased to 60% and median survival is increased to 26–28 months, but these results are typically in patients with KRAS wild-type tumors [10–12]. Moreover, neoadjuvant systemic chemotherapy converts only a minority of patients (25–30%) to surgical resectability [13, 14]. Furthermore, second-line systemic chemotherapy has very low response rates (in the range of 10–35%) [15, 16].

Together, these data illustrate that the majority of patients with hepatic metastases are neither resectable nor converted to resectability by standard chemotherapy. Because these patients have liver-only metastatic involvement, several forms of regional therapy have been explored. Among these are ablative treatments (cryoablation, radiofrequency ablation [RFA], microwave ablation [MWA], irreversible electroporation [IRE], transarterial embolization (bland, transarterial chemoembolization) [TACE], radioembolization (with ytrrium-90 [Y90]), and hepatic arterial infusion [HAI] chemotherapy). This chapter reviews the rationale, technical considerations, and outcomes of the last of these—intra-arterial chemotherapy.

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Rationale for Intra-Arterial Chemotherapy

The utility of intra-arterial chemotherapy is underscored by several key anatomic considerations. First, the liver has a dual blood supply, with normal hepatocytes deriving 2/3 of their blood flow via the portal vein, and the remaining 1/3 from the hepatic artery. In contrast, CLMs derive the bulk of their blood supply from the hepatic artery [17]. Injection of floxuridine (FUDR) into the hepatic artery has been shown to concentrate the drug 15-fold in tumor relative to normal parenchyma; injection into the portal vein has no such effect [18], Importantly, the presence of the gastroduodenal artery (GDA) is also crucial to the use of intra-arterial chemotherapy. Redundancy between the celiac axis and superior mesenteric artery (SMA) distribution allows for catheterization and distal ligation of the GDA without any resultant ischemia.

From a pharmacologic standpoint, the liver's function in drug metabolism is key to enabling first-pass extraction of chemotherapy administered via the hepatic arterial route. This can substantially elevate local concentrations of the chemotherapeutic agent, while minimizing systemic exposure. Several agents have been evaluated, and the pharmacologic properties of HAI administration of each are reviewed in Table 8.1. Most notably, FUDR features a short half-life (10 min) and high first-pass extraction (94–99%) that produce a 400-fold concentration of drug in the liver, with minimal spill-over into the general circulation [19]. As several chemotherapeutic agents have steep dose–response curves, higher doses of chemotherapy should translate into an increase in the degree to response.

Several clinical scenarios afford an opportunity for HAI therapy. Patients with unresectable CLM and no evidence of extrahepatic disease represent a large cohort who stand to benefit from a liver-directed therapy. In addition, HAI can be administered as an adjuvant therapy for patients undergoing definite surgical resection of CLMs. Recurrence after complete resection of CLM occurs in at least two-thirds of patients, and half of these recurrences will be limited to the liver [7, 20–23].

Table 8.1 Pharmacologic properties for hepatic arterial infusion of various agents

Agent	Half-life (min)	Fold increase in hepatic concentration
Bis-chloroethyl-nitrosurea	5	6–7
Cisplatin	20–30	4–7
Dichloromethotrexate	–	6–8
Doxorubicin	60	2
5-Fluorouracil (5-FU)	10	5–10
Floxuridine (FUDR)	10	100–400
Mitomycin C	10	6–8

Hepatic Arterial Infusion (HAI) Pump Therapy

Intra-arterial chemotherapy can be administered by the placement of hepatic arterial ports, percutaneously placed catheters, or hepatic arterial infusion (HAI) pumps. The most extensively studied of these modalities in CLM has been the HAI pump—an implantable infusion pump that delivers a continuous infusion of chemotherapy. Several chemotherapeutic agents can be administered via the pump, but FUDR is the most commonly given in the United States, while 5-FU has historically been used in Europe and Japan [24–26]. Patients with unresectable CLM or patients undergoing hepatectomy may undergo HAI pump placement, with or without concomitant colon resection.

Technical Considerations

Hepatic arterial infusion (HAI) pump placement requires careful assessment of the arterial anatomy of the liver, suitability of the abdominal wall, and the assessment of extrahepatic disease. The initial evaluation of a patient with mCRC should include cross-sectional imaging of the chest, abdomen, and pelvis, usually via computed tomography (CT) to look for radiographically evident extrahepatic disease. HAI pump

placement is generally not indicated in patients with apparent lung or peritoneal involvement. However, in carefully selected patients with minimal extrahepatic disease and a substantial burden of CLM, HAI treatment can be considered [27]. For patients with unresectable disease, a staging laparoscopy should be considered, as up to 1/3 of patients will have evident extrahepatic disease [28]. When extrahepatic disease is encountered and the judgment is that it is sufficient to preclude HAI pump placement, intraoperative frozen section is of obvious importance.

The preoperative evaluation should also consist of a CT arteriography to evaluate the hepatic arterial anatomy. Given standard anatomy, the preferred conduit for placement of the catheter is the gastroduodenal artery (GDA), as this is the side-branch immediately proximal to the proper hepatic artery. However, up to 34% of patients will have variant anatomy that requires special consideration [29]. The hepatic arterial anatomic variants are summarized in Table 8.2, and include replaced or accessory left and right hepatic arteries and combinations of multiple variants. Determination of the exact nature of the aberrant anatomy via careful review with the radiologist is imperative, as these findings impact the operative plan.

Suitability of the abdominal wall is also a key consideration, as patients with large ventral hernias or prior operations may have attenuated musculofascial layers of the abdominal wall. The operative plan usually consists of pump placement in the lower abdomen, typically on the left side to avoid the potential use of a future right subcostal incision. In obese patients with large subcutaneous spaces and in patients with large hernias, placement of the pump itself on the lower chest wall can enable location and access to the pump, as well as minimize the risk of flipping. Any one of a number of incisions can be employed for HAI pump placement, including an upper midline incision, right subcostal incision, or a limited hockey-stick incision. Of note, the pump itself should be placed in a subcutaneous pocket via a separate incision with tunneling of the catheter into the peritoneal cavity. Regardless of the incision type chosen, preoperative antibiotics are important in this setting, as are other standard preoperative precautions.

Intraoperatively, the hepatic artery and its branches should be carefully dissected and skeletonized. The right gastric artery should be divided, and the distal CHA, proximal proper hepatic artery (PHA), and GDA identified, encircled and freed from surrounding attachments. Proper identification and mobilization of these structures, including the entire extrapancreatic GDA, are critical. During this dissection, consideration should be given to removing portal lymph nodes in the vicinity of the CHA and the porta hepatis, as these can occasionally be interpreted as sources of extrahepatic perfusion. A cholecystectomy is also performed, as HAI therapy delivered to an in-situ gallbladder (via

Table 8.2 Summary of hepatic arterial anatomic variants

Variant	Daly et al. (1984) (n = 200) (%)	Michels (1966) (n = 200) (%)	Kemeny et al. (1986) (n = 100) (%)	Curley et al. [30] (n = 180) (%)	Allen et al. [31] (n = 265) (%)
Normal	70	55	50	63	63
Variant GDA	6	–	9	9	11
Accessory R hepatic	4	7	4	1	1
Replaced R hepatic	6	12	16	12	6
Accessory L hepatic	3.5	8	1	2	10
Replaced R hepatic	4	10	16	11	4
Other	5	2.5	1	2	5

Adapted from Allen PJ et al. [31]

the cystic artery) will cause chemical cholecystitis. All branches of the CHA, PHA, and GDA are divided and ligated to minimize perfusion of the pancreas, duodenum, or stomach by the pump. The left and right hepatic artery are similarly dissected for approximately 2 cm from the PHA origin to ligate any branches that may serve as conduits for extrahepatic perfusion [32]. Finally, a hepatic arterial pulse is palpated, while the GDA is temporarily occluded to ensure there is not retrograde flow in the GDA owing to celiac stenosis. If there is retrograde flow, an attempt to release the arcuate ligament may re-establish normal flow. If this is not successful, one can consider placing the catheter in the CHA, allowing flow to the liver through the GDA into the PHA.

Vascular control is obtained, and the distal GDA is ligated at its most distal point. In the case of standard anatomy, a transverse arteriotomy is made in the GDA, and the catheter is inserted up to the confluence with the hepatic artery. Positioning of the catheter tip is crucial, as the proximal GDA should neither be exposed to full concentrations of chemotherapeutic agent, nor should the catheter protrude into the lumen so far as to induce thrombosis. The optimal approach when there is aberrant anatomy is ligation of the aberrant vessel(s) and placement of the catheter in the GDA, as cross-perfusion is extremely reliable. Cross-perfusion is often visible at the time of operation, and occurs in almost everyone by 4 weeks after the operation. In a series of 52 patients with variant anatomy, all but one had adequate bilobar perfusion at 4 weeks [31]. Cannulation of a vessel other than the GDA is associated with a significantly elevated incidence of catheter-related complications and limited catheter durability, and is not preferred. When the GDA is not available, we generally prefer placement in the right or left hepatic artery (with ligation); in rare situations, vascular graft placement to create a "GDA" for catheter insertion is required. In the case of variant GDA anatomy, ligation of either in situ (left or right) hepatic artery may be necessary if the GDA arises from the contralateral vessel.

When placed at the time of major hepatectomy, the technical considerations are no different, except that the stump of the ligated arterial branch may be employed to perfuse the remnant liver if the GDA is not available. Of note, ligation of aberrant left or right arteries to a remnant liver for catheter placement should be performed with caution, as it may exacerbate postoperative liver dysfunction. In the face of a remnant liver perfused by a replaced hepatic artery, pump placement (into the GDA) should probably be deferred rather than employing direct cannulation of the replaced vessel.

The catheter is secured in place with silk ties, and the pump reservoir is placed in the pump pocket. Bilobar perfusion of the liver and the absence of extrahepatic perfusion are confirmed by either fluorescein or half-strength methylene blue injection into the side port of the pump. If extrahepatic perfusion is detected (most commonly to the duodenum and head of pancreas), a search for any vessel ensues with ligation and retesting. The catheter is then flushed with heparinized saline and wounds are closed. Postoperatively, perfusion is assessed by a radionuclide pump flow study using technetium 99m (^{99m}Tc)—sulfur colloid and ^{99m}Tc-labeled macroaggregated albumin (MAA). This study is used to detect extrahepatic perfusion (occurs in 5–7% of cases) that can usually be salvaged by angiographic intervention [33, 34]. Incomplete hepatic perfusion can also occur, but usually resolves on a repeat scan obtained a few weeks after the index study. If resolution is not apparent, there may be a missed accessory vessel not ligated at the first operation, and consideration to angiography should be given.

Alternative Modes of Intra-Arterial Chemotherapy

While the implantable hepatic artery infusion pump is the most commonly employed device, there are other means of access to the hepatic arterial tree. One of the earliest approaches was the placement of a subcutaneous port with

a catheter terminating in the hepatic artery. A large randomized MRC/EORTC study evaluating HAI 5-FU/leucovorin with systemic 5-FU/LV, however, featured a 36% rate of catheter-related complications that limited dose administration [24]. Subsequent studies exploring the role of IV oxaliplatin via HAI catheters placed in the GDA but using a subcutaneous pump showed significant improvement in the rate of catheter-associated complications of 10–15% [35].

Percutaneously placed catheters have also been explored. Arru et al. evaluated percutaneous axillary artery catheters as compared to implantable pumps, finding a 43% rate in the percutaneous group of an issue, causing either an interruption or end to treatment (versus 7% in the implantable pump group) [36]. Several studies have also attempted to develop and refine the use of intercostal artery catheters, either with a subcutaneous port or with an attached pump [37].

Recent attention has turned to minimally invasive surgical placement of implantable pumps. A number of initial case series established feasibility of a laparoscopic approach; the largest of these describes an experience with 38 patients, among whom there was one mortality and no pump-related morbidity [38]. Another series featuring 29 patients demonstrated that aberrant anatomy could be addressed safely via a laparoscopic approach and without significant perioperative morbidity [39]. Despite its widespread application, a robotic approach to HAI catheter and pump placement has yet to be studied in any systematic fashion.

Outcomes in Unresectable Disease

HAI pump chemotherapy for unresectable CLM has been extensively studied. Over the last 20 years, ten phase III trials (Table 8.3) comparing HAI with systemic chemotherapy have been conducted; three subsequent meta-analyses have evaluated these findings further still. Overall, there is relative concordance among the studies that response rates are higher with HAI. Nine of the ten studies employed FUDR as the HAI chemotherapeutic—each showed response rates of 42–62%, compared to response rates of 9–24% for systemic chemotherapy in these trials [45]. However, all of these studies employed older systemic regimens consisting of intravenous FUDR, 5-FU alone, or 5-FU/leucovorin, rather than modern regimens incorporating either irinotecan or oxaliplatin.

Despite the substantial increases in response rate, these studies have often failed to detect a difference in overall survival. Several factors have contributed to this phenomenon. Most

Table 8.3 Randomized trials of HAI therapy versus systemic chemotherapy for unresectable CLM

Study	Patients	HAI regimen	Systemic regimen	Response rates (HAI vs. systemic)	Overall survival (HAI vs. systemic)
MSKCC [40]	162	FUDR	FUDR	50% vs 20%	25% vs 20%
NCI (Chang, 1987)	143	FUDR	FUDR	42% vs 10%	44% vs 13%
NCOG [41]	64	FUDR	FUDR	62% vs 17%	30% vs 20%
City of Hope (Wagman, 1990)	41	FUDR	5-FU	55% vs 20%	–
Mayo (Martin, 1990)	69	FUDR	5-FU	48% vs 12%	–
French [42]	163	FUDR	5-FU	44% (HAI only)	22% vs 10%
HAPT [43]	100	FUDR	5-FU or BSC	–	–
German (Lorenz and Muller, 2000)	168	FUDR	5-FU/LV	43% vs 22%	–
EORTC [24]	290	5-FU/LV	5-FU/LV	22% vs 19%	–
CALGB [44]	135	FUDR/Dex	5-FU/LV	47% vs 24%	51% vs 35%

Adapted from Kemeny and Epstein (2012)

notably, early studies at MSKCC (99 patients) [40] and in the Northern California Oncology Group (NCOG) trial [41] both allowed crossover between groups (which occurred frequently), making an intention-to-treat analysis of overall survival meaningless. Those studies that did not allow for crossover and have shown differences in overall survival—namely the Hepatic Artery Pump trial (HAPT) and a French trial—are confounded by the fact that patients in the control arms frequently received only best supportive care rather than 5-FU [42, 43].

Among these ten studies comparing HAI with systemic chemotherapy, the CALGB 9481 trial is the most recent. In this trial, no crossover was permitted, and 134 patients were randomized to either systemic 5-FU/LV (via the Mayo Clinic regimen) or HAI (consisting of FUDR, LV, and dexamethasone). Dexamethasone was added in this series because of earlier data showing decreased biliary toxicity with the addition of steroid to HAI [46]. Again, response rates were significantly higher with HAI (47% vs 24%) and there was a significant improvement in overall survival (24.4 vs 20 months; $p = 0.0034$) [44].

Three meta-analyses of these trials have been performed, with variable results in determining a survival advantage. This inconsistency has been driven by variable exclusion criteria among the trials for either methodological reasons or because of concerns about study design—especially for those trials where some control patients received best supportive care only, or crossover was allowed. The most recent meta-analysis, published in 2007, includes all ten trials and attempts to account for their design flaws. The authors conclude that HAI was associated with a significantly elevated response rate (42.9% vs 18.4%), but this did not translate into an improvement in overall survival (hazard ratio 0.9; $p = 0.24$) [47]. Given the extreme heterogeneity of these trials, it remains difficult to draw any firm conclusions from these meta-analyses.

As mentioned above, these trials predate the development of modern and more effective systemic chemotherapeutic regimens incorporating oxaliplatin or irinotecan. In addition, several of these studies detected a high frequency of extrahepatic progression (40–70%) in patients treated with HAI. More recent studies have attempted to exploit the lack of systemic exposure to chemotherapy with HAI FUDR treatment, and evaluate the efficacy of HAI chemotherapy combined with systemic chemotherapy. The first of these studies involved 95 patients randomized to HAI FUDR with or without intravenous FUDR, and showed similar response rates (~60%) but higher extrahepatic recurrence in the HAI-only group (79% vs 56%; $p < .01$) [48].

Several phase I and II studies have since combined HAI with systemic chemotherapy (Table 8.4). The first of these evaluated 46 patients given HAI consisting of FUDR + dexamethasone in conjunction with systemic irinotecan; response rates were 74% in these pre-treated patients, with an overall survival (OS) of 20 months following pump placement [49]. Similar results were seen with addition of systemic FOLFOX (oxaliplatin +5-FU/leucovorin); in 15 patients, a response rate of 87% with a median OS of 22% was obtained [50]. The combination of oxaliplatin and irinotecan yielded the best results, with a pooled analysis of 49 patients showing a 92% response rate and an OS of 51 months for previously untreated patients and 35 months for previously treated patients. Also of note was that 47% of these individuals converted from unresectable to resectable disease

Table 8.4 Studies of HAI therapy combined with modern systemic therapy

Study	Patients	HAI regimen	Systemic regimen	Response rate (%)	Median overall survival (from pump placement)
Kemeny et al. [49]	56	FUDR/Dex	Irinotecan	74	20 months
Kemeny et al. (2005a)	15	FUDR/Dex	Oxaliplatin + irinotecan	90	28 months
Kemeny et al. (2005a)	21	FUDR/Dex	FOLFOX	87	22 months
Kemeny et al. (2005b)	37	FUDR/Dex	Sideport mitomycin C	70	20 months

Adapted from Kemeny and Epstein (2012)

[51]. A more recent phase II study with 49 patients (two-thirds previously treated) treated with HAI and modern systemic chemotherapy (initially with bevacizumab) showed high response rates of 76% and a conversion to resectability in 47% of the 49 patients. Median survival was 38 months for the whole cohort [52].

In addition to the extensive literature on FUDR, there are also data to support the use of oxaliplatin administered via HAI. In a phase II study to evaluate the efficacy of HAI oxaliplatin + systemic 5-FU/LV, 28 patients underwent placement of HAI catheters. The rate of catheter dysfunction was low, and the overall response rate was 64% [53]. A subsequent study in patients who previously failed systemic chemotherapy again showed a high response rate of 62% [54].

Together, these non-randomized phase I and early phase II studies demonstrate high response rates and long overall survival in patients given modern systemic chemotherapy in conjunction with HAI chemotherapy. Though these patients were non-randomized and selected, the response rates and survival data observed in these data are unprecedented in any cohort of patients with mCRC treated with systemic therapies alone. Moreover, as FOLFOX and FOLFIRI have become well-established standard first-line systemic regimens, HAI in the more recent era has most commonly been studied in the second-line setting. When one considers the low response rates for second- line systemic therapy (10–15%), combined HAI and systemic therapy has demonstrated remarkably high response and survival rates. Moving forward, these impressive results mandate randomized trials to isolate the specific effect of the addition of HAI therapy in patients with CLM, and to determine if intra-arterial chemotherapy should be pursued in a first-line or salvage setting for patients with unresectable disease.

Outcomes as Adjuvant Therapy Following Hepatic Resection

Following hepatic resection of CLM, at least two-thirds of patients will recur, and approximately half of these will have intrahepatic recurrence. The benefits of systemic chemotherapy alone in the adjuvant setting have been tested in randomized studies. Initial studies did not show a benefit to adjuvant 5FU chemotherapy [55]. Further, adjuvant FOLFIRI did not improve outcomes compared to 5FU alone [56]. The most well-known trial (EORTC 40983) which employed perioperative (pre and post-operative) FOLFOX4, demonstrated a minimal increase in progression-free survival (PFS) but did not show an improvement in overall survival [57, 58].

Several randomized studies have sought to determine if HAI chemotherapy diminishes the rate of recurrence and improves overall survival. In a study from our institution, 156 patients were randomized to adjuvant systemic 5-FU/LV or systemic 5-FU/LV + HAI FUDR. The addition of HAI in this population increased 2-year survival (86% vs 72%; $p = 0.03$), with median survival also increased in the HAI + systemic chemotherapy group (72 vs 59.3 months) [59]. At the 6-year follow-up, median PFS was significantly increased with HAI (31.3 vs 17.2 months; $p = 0.02$), as was hepatic PFS (not reached for HAI group vs 32.5 months; $p < 0.01$) [60]. A subsequent intergroup trial randomized 109 patients to resection alone versus resection with both FUDR via HAI and systemic 5-FU [61]. Recurrence-free survival (the primary endpoint) at 4 years was improved with adjuvant therapy (46% vs 25%; $p = 0.04$), but there was no difference observed in overall survival.

Retrospective analyses of patients undergoing liver resection have suggested that the administration of adjuvant HAI is associated with increased overall survival. One multivariate analysis of over 1,000 patients identified HAI as an independent predictor of survival, with a median OS of 68 months for HAI vs 50 months for no HAI [62]. Similarly, a retrospective analysis of 612 patients undergoing liver resection from 1985 to 1994 showed improved 10-year overall survival in those patients receiving HAI in the adjuvant setting (38% vs 15%) [63].

As before, these early randomized studies and retrospective analyses predated modern systemic chemotherapeutic regimens. Since then, small phase I and phase II

non-randomized studies combining adjuvant HAI with irinotecan and oxaliplatin have been performed. The first of these, performed in 96 patients, showed a 2-year survival of 89% in patients treated with HAI FUDR/dexamethasone + systemic irinotecan [64]. In a separate study, 35 patients were given FOLFOX in conjunction with HAI FUDR/dexamethasone, with a 4-year survival which was improved to 88% at a median follow-up of 43 months [65]. Further support for the effect of adjuvant HAI was observed in a retrospective case-matched analysis of 125 patients who received adjuvant systemic FOLFOX/FOLFIRI alone, and 125 patients who received FOLFOX/FOLFIRI combined with HAI-FUDR. Overall survival at 5 years was significantly greater in the HAI group (72% vs 52%; $p = 0.004$) [5].

A recent study examined the efficacy of HAI oxaliplatin in the adjuvant setting. Following surgical resection, 3-year disease-free survival was 33% in patients treated with HAI oxaliplatin + systemic 5-FU, compared to only 5% in patients treated with systemic chemotherapy alone [35]. As this study was non-randomized, further investigations are necessary to support the use of intra-arterial oxaliplatin.

In sum, the data supporting the use of intra-arterial chemotherapy via HAI in the adjuvant setting is similar to that for unresectable disease. Randomized studies comparing the combination of HAI and systemic 5-FU/leucovorin to the latter alone indicate that HAI probably improves both disease-free and overall survival. The more recent small-phase I and II studies that follow the introduction of irinotecan and oxaliplatin also suggest that there is probably a benefit to the addition of adjuvant HAI-FUDR. Nonetheless, while there are no randomized data to support the use of HAI-FUDR (as compared to modern systemic chemotherapy) in the adjuvant setting, it is important to recall that systemic chemotherapy also remains unproven as an effective adjuvant therapy. Further studies remain needed to establish the optimal adjuvant therapy following CLM resection.

Complications

Despite the abundance of evidence to suggest that HAI chemotherapy has a role in unresectable disease, adjuvant therapy, and as a means of conversion to resectability, the use of HAI is limited to only a few centers. The lack of widespread application is likely due to the complexity of managing the administration of HAI chemotherapy, and complications that can arise from both HAI placement and HAI therapy.

Early series reported the complication rate of HAI placement as anywhere between 12 and 41% [30, 34, 66]. More recently, a review of 544 patients at our institution revealed an overall pump-related morbidity of 22%, with a low operative mortality (30-day: 0.9%) [33]. Vascular complications comprised about half of the overall complications, and included thrombosis of the hepatic artery, arterial hemorrhage, and extrahepatic or incomplete perfusion of the liver. Catheter occlusion, dislodgment, or erosion constituted 25% of the total; pump failure, however, was quite low 5% at 6 months, and 16% at 2 years.

In the above series, the pump could be salvaged from complications in 45% of cases. Extrahepatic perfusion, for one, is typically addressed by proceeding directly to transfemoral angiogram and embolization of the culprit vessel. Only rarely is surgical ligation necessary. Similarly, incomplete perfusion is frequently due to a missed accessory vessel that can be angiographically addressed; following embolization, repeat ^{99m}Tc scan after 3–4 weeks demonstrates adequate crossover perfusion.

Arterial or catheter thrombosis are the most concerning complications, as these are typically difficult to salvage and preclude continued HAI therapy. However, these complication are quite rare—in our series, 13 cases (2%) of arterial thrombosis and 11 cases of catheter thrombosis occurred—and typically occurred late. Anticoagulation or thrombolytic therapy can salvage the former complication (31% of the time), but is of little use in the case of catheter thrombosis. Infectious complications are not common, but special attention must be paid to the pump

pocket during insertion. A low threshold is maintained postoperatively for the use of parenteral antibiotics if there are any skin changes that are concerning.

Finally, biliary sclerosis is an important consideration as a long-term complication of HAI therapy. In a study by Ito and colleagues, the incidence of biliary sclerosis was 5.5% among patients receiving adjuvant HAI FUDR and 2.2% in unresectable patients [62]. No patient died of biliary complications. Only rarely does sclerosis of the biliary tree, typically most pronounced in the common hepatic duct, ultimately require dilatation and/or stenting. Dose modifications and concomitant use of dexamethasone are critical, and generally anticipate and prevent this issue [46]. Other methods to reduce hepatic toxicity further have been explored—these include circadian administration of FUDR and alternating FUDR with 5-FU bolus [26, 67].

Conclusions

Intra-arterial chemotherapy for CLM has been extensively studied, with numerous studies having been performed over the last 30 years. Much of the literature is centered on the administration of FUDR along with dexamethasone, which is delivered by continuous HAI via an implantable pump attached to catheter terminating in the native gastroduodenal artery. In patients with unresectable CLM, the use of HAI chemotherapy is associated with high response rates in the first- and second-line setting, and frequent conversion to resectability. In patients undergoing definitive surgical resection, the addition of HAI chemotherapy appears to delay hepatic recurrence and increase overall survival. While the body of literature is limited in part by the absence of level I evidence in the era of modern systemic chemotherapy, there remains an abundance of retrospective and early-phase studies that indicate that HAI should be a key component of the armamentarium used to address metastatic colorectal cancer.

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Radioembolization

9

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Introduction

Surgical resection is the most effective method for improving survival in patients with colorectal liver metastasis (CLM). However, many patients are deemed unsuitable for liver resection, both at initial manifestation and/or at recurrence [1]. For these patients, the standard of care is systemic treatment with chemotherapy and/or molecular target agents. Eventually, the majority of patients will progress in the liver unless surgically resected, and there remains a high demand for effective treatments in chemo-refractory patients [2]. For these reasons, loco-regional liver therapies are increasingly being employed for the purposes of downstaging for subsequent resection, as an adjunct to improve resectability, and for improving palliative results [1, 2].

Over the last few decades, a number of intra-arterial liver-directed therapies for targeted treatment of CLM have been developed. These therapies are based on the principle that the majority of the blood supply to the liver tumors is originated from the hepatic artery, as opposed to the portal venous system that supplies the non-tumor liver parenchyma. The most widely used intra-arterial therapies for CLM are hepatic arterial infusion chemotherapy, transarterial chemoembolization, and radioembolization with yttrium-90 microspheres [2].

Radioembolization represents a valuable treatment option that is increasingly being considered as part of a multimodal treatment approach for the management of liver tumors. Yttrium-90 can deliver high cumulative doses of radiation preferentially to liver tumors, and has shown encouraging response rates with an excellent tolerance profile [3]. Indeed, accumulating evidence supports the safety and efficacy of this intra-arterial liver-directed treatment for the management of hepatic tumors in patients in whom the liver is the sole or dominant site of disease [3–6].

In this chapter we shall discuss the rationale, benefits, and limitations of radioembolization with yttrium-90 microspheres in the treatment of CLM.

Principles and Technique of Radioembolization

Radioembolization (RE) is defined as the intra-arterial delivery of micron-sized radioisotope-tagged particles that preferentially and permanently embed in tumor as opposed to normal tissue [3]. In the literature, this treatment is also named as selective internal radiation therapy or intra-arterial microsphere brachytherapy.

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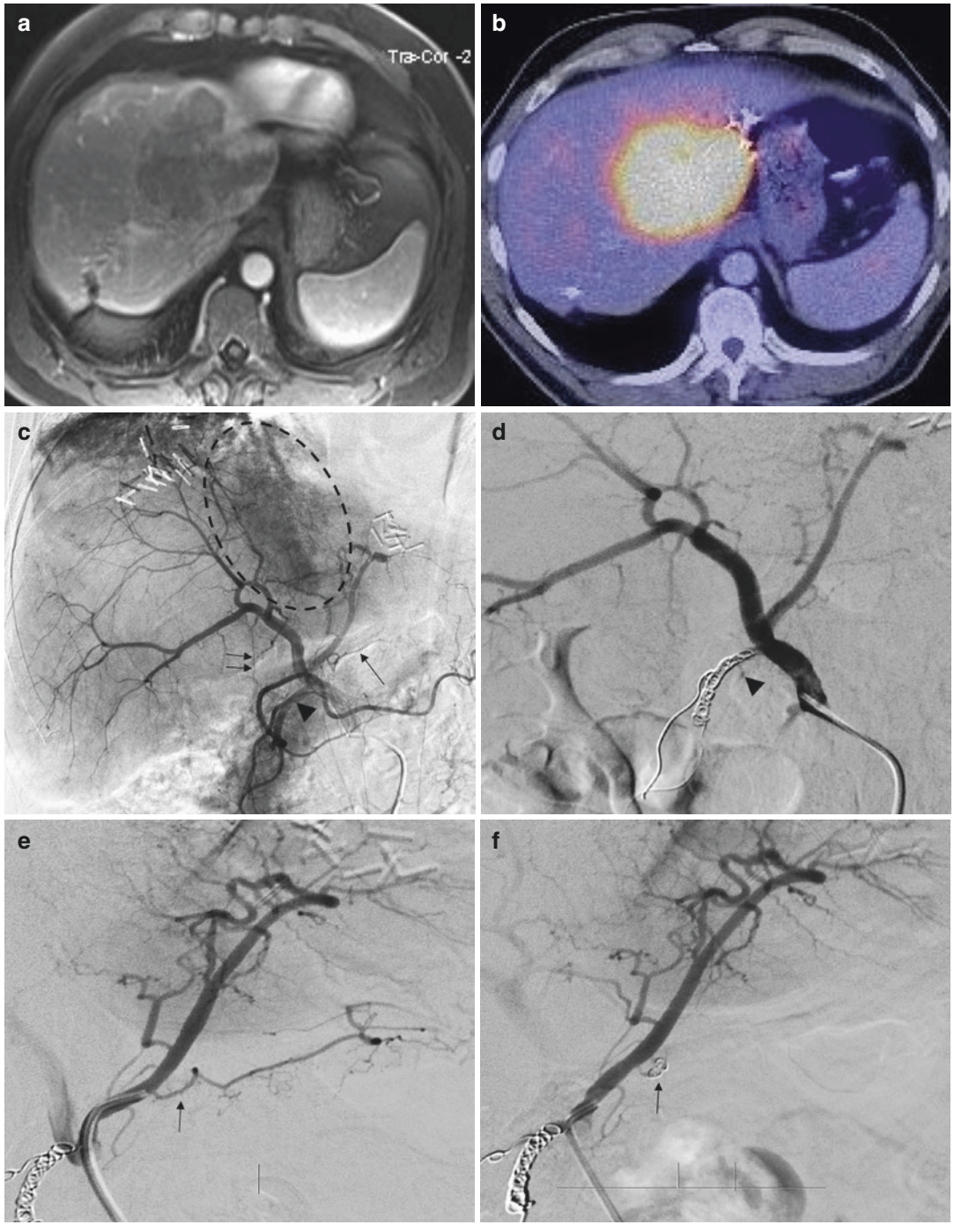
The aim of RE is to selectively target a high radiation dose to all metastasis within the liver regardless of their location, while limiting radiation to non-tumour liver parenchyma within tolerable levels. The preferential intra-arterial deposition of microspheres carrying a high-energy radiation source into the tumor capillary bed provides a tumoricidal dose of radiation (>120 Gy) that is absorbed over a limited time [3, 4]. The most commonly used radiopharmaceutical (high-energy radiation source) in the setting of RE is Yttrium-90 (Y90), a pure *B*-emitter with mean liver tissue penetration of 2.5 mm (maximum 11 mm). Given the short half-life of Y90 of 64 h, approximately 95% of the radiation dose is delivered within 11 days from treatment administration [3–5].

The preferential delivery of Y90 microspheres to liver tumors is based on several anatomic and pathologic factors that are unique to the liver and hepatic solid tumors, and follows the rationale of all modalities of intra-arterial liver therapies. It has long been established that normal liver parenchyma derives approximately 80% of its blood from the portal vein, whereas macroscopic liver tumors derive almost 100% of their blood supply from the hepatic artery [1, 2]. In addition, there is an increased microvascular density up to 20:1 ratio in liver tumors compared with normal liver parenchyma [1–4].

The size of the microspheres is critical to optimal implantation in the tumor vascular bed. To be effective, Y90 microspheres must be deposited within the network of tumor vessels (tumor capillary bed). As the median penetration of Y90 is 2.5 mm, any microsphere situated within the afferent tumor vessels, more than that distance from the tumor would probably not have a direct antitumor effect [3]. For this reason, the microspheres currently used for RE are small enough (average 32 μm) to allow optimal access and deposition within the tumor plexus, but large enough to prevent systemic passage through the capillary bed into the venous circulation [1].

The RE-Y90 procedure is performed in an angiographic suite provided with cone beam computed tomography (CBCT) under local anaesthesia, percutaneous femoral puncture, and on outpatient basis. It is a two-step procedure performed in 2–4 weeks interval: the preparation/simulation phase and the treatment phase [2, 7]. In the former, a liver arterial angiogram is performed to identify the arterial anatomy of the liver, potential arterial variants, tumor feeders, and extrahepatic branches coming off the hepatic arteries, which might require proximal coil embolization in this session in order to avoid Y90 microsphere delivery in these territories during the treatment phase [7]. The right gastric artery, and sometimes the falciform artery, should be coiled when left or medial lobe treatment is foreseen during the treatment phase. The gastroduodenal artery and cystic artery embolization is controversial when a right lobe treatment is foreseen, but it is highly recommended to deposit the injection catheter beyond its origins. The main concept is to avoid or otherwise embolize any arterial branch supplying an extrahepatic territory downstream of the final catheter position for microsphere injection [5, 7] (Fig. 9.1). In the same angiographic session, once the position of the catheter that will be used for the treatment phase is decided, a standard dose of technetium-99m-labeled macro

Fig. 9.1 Fifty-two-year-old male with recurrent CLM in the left lobe (liver resection was performed 4 years earlier) with liver progression despite three lines of chemotherapy. (**a**) Gadolinium-enhanced MRI. (**b**) PET-CT. (**c**) Hepatic angiogram at preparation phase shows tumor enhancement (*dotted circle*). Notice the right gastric (*arrow*), gastroduodenal (*arrowhead*) and falciform (*double arrow*) arteries. (**d**) Hepatic angiogram after gastroduodenal coil embolization (*arrowhead*). (**e**) Left hepatic angiogram clearly depicts the right gastric artery (*arrow*) supplying the lesser stomach curvature. (**f**) Left hepatic angiogram after right gastric artery coil embolization (*arrow*). Notice that the stomach is no longer supplied. (**g**) Selective angiogram of left hepatic artery (LHA) before Y90 infusion*. (**h**) Selective angiogram of middle hepatic artery (MHA) before Y90 infusion. (**i**) Follow-up PET-CT at 6 months after RE-Y90 showing complete response (no hyper metabolic activity) and calcification at the treatment site. *An ice pack was placed on the umbilical skin to induce flow arrest of distal falciform vessels (not shown)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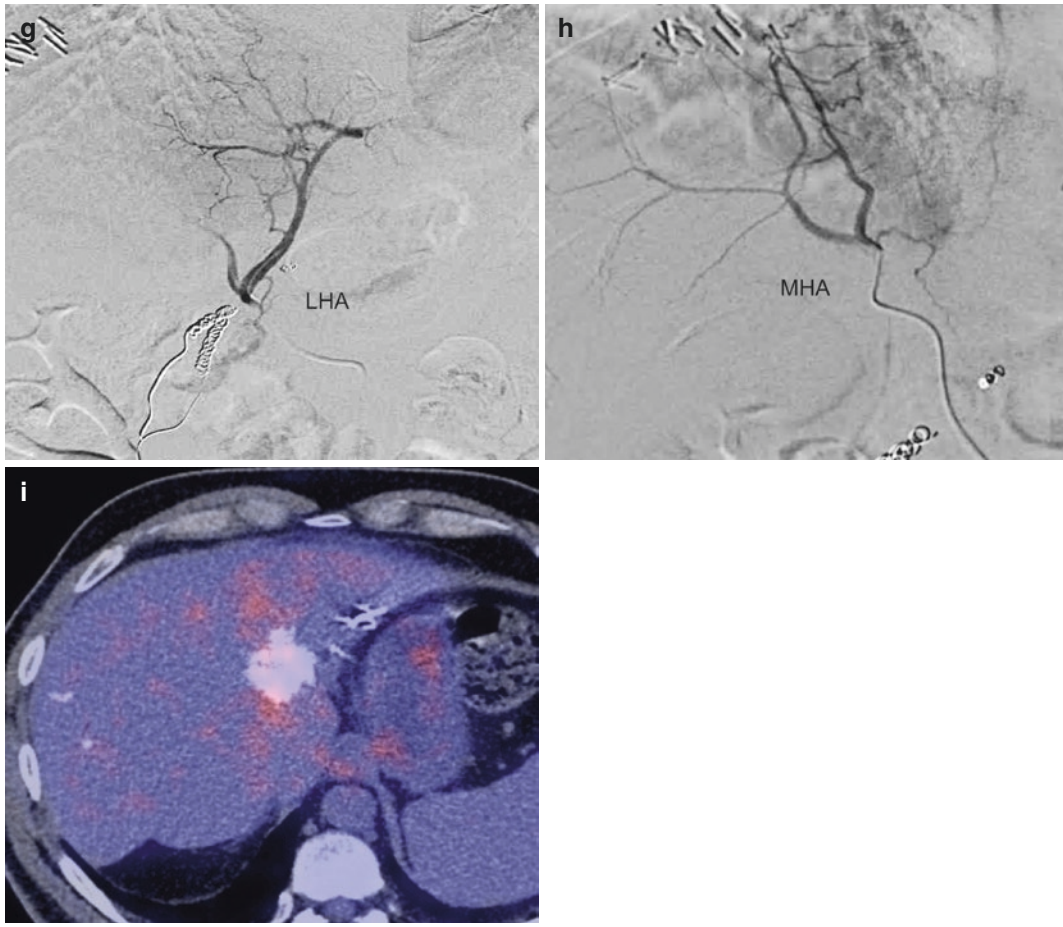

Fig. 9.1 (continued)

aggregated albumin (Tc99-MAA) is injected to check the distribution of the radio isotopic agent, simulating exactly what would be done in the second procedure. Planar and single-photon emission computed tomography are immediately obtained to identify potential extrahepatic deposits of Tc99-MAA, measure the lung shunt fraction (LSF), and to determine the intake ratio of the tumor relative to adjacent liver parenchyma. Once extrahepatic deposits of Tc99-MAA and a high LSF are ruled out, the dose of Y 90 to be delivered at the treatment phase is then calculated using a specific formula. Once the preparation/simulation phase is completed, the patient is rescheduled for the treatment phase (on average 2–4 weeks later) again as an outpatient (Fig. 9.2).

In the treatment phase, a new hepatic angiogram performed from the catheter is positioned in the exact position established during the simulation phase, and the liver vasculature is again verified in order to check the stability of the previous embolization of extrahepatic arteries and to rule out any new extrahepatic supply, preferentially using CBCT. Although uncommon, supplementary embolization may be performed if needed. In this session the Y90 microspheres are then slowly injected, mimicking the injection of Tc99-MAA at the simulation phase. The same day, before leaving hospital, a positron emission tomography (PET) or bremsstrahlung nuclear imaging is performed to check the intra arterial injected Y90 distribution.

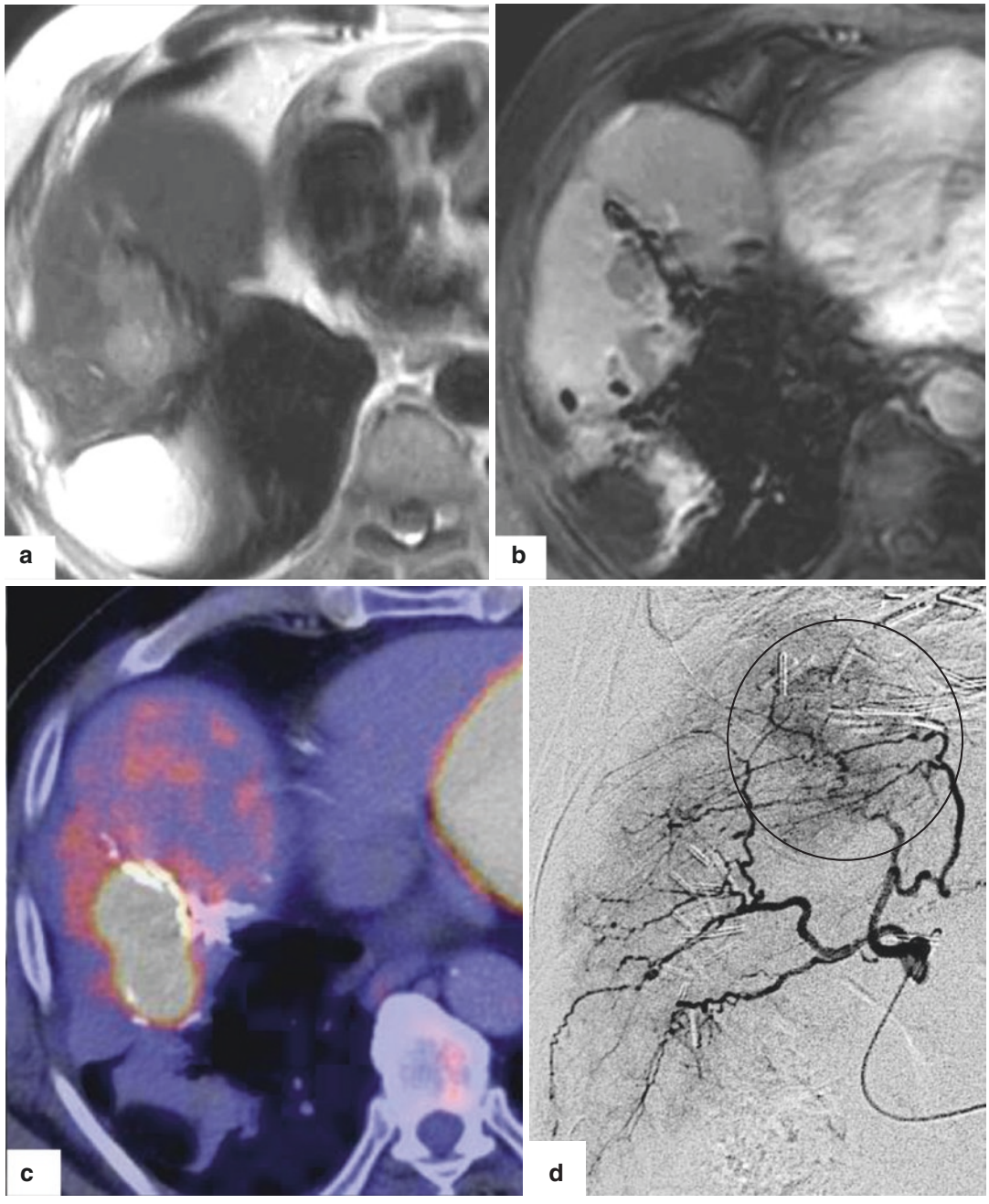

Fig. 9.2 Seventy-eight-year-old male with recurrent isolated CLM in segment VIII despite previous surgery and two lines of chemotherapy. (**a**) T2-weighted MRI. (**b**) Gadolinium-enhanced MRI. (**c**) PET-CT. (**d**) Selective angiography of segment V and VIII shows tumor enhancement (*circle*). (**e**) Intra-arterial CBCT confirms tumor enhancement in segment VIII (*dotted circle*). (**f**) MAA tumor uptake at SPECT-CT confirming correct catheter position for treatment. (**g**) T2-weighted MRI. (**h**) Gadolinium enhanced MRI at 3-month follow-up after RE-Y90 shows treatment response by tumor lack of enhancement and shrinkage (*arrows*). (**i**, **j**) Follow-up contrast-enhanced CT at 15 months confirms complete tumor response

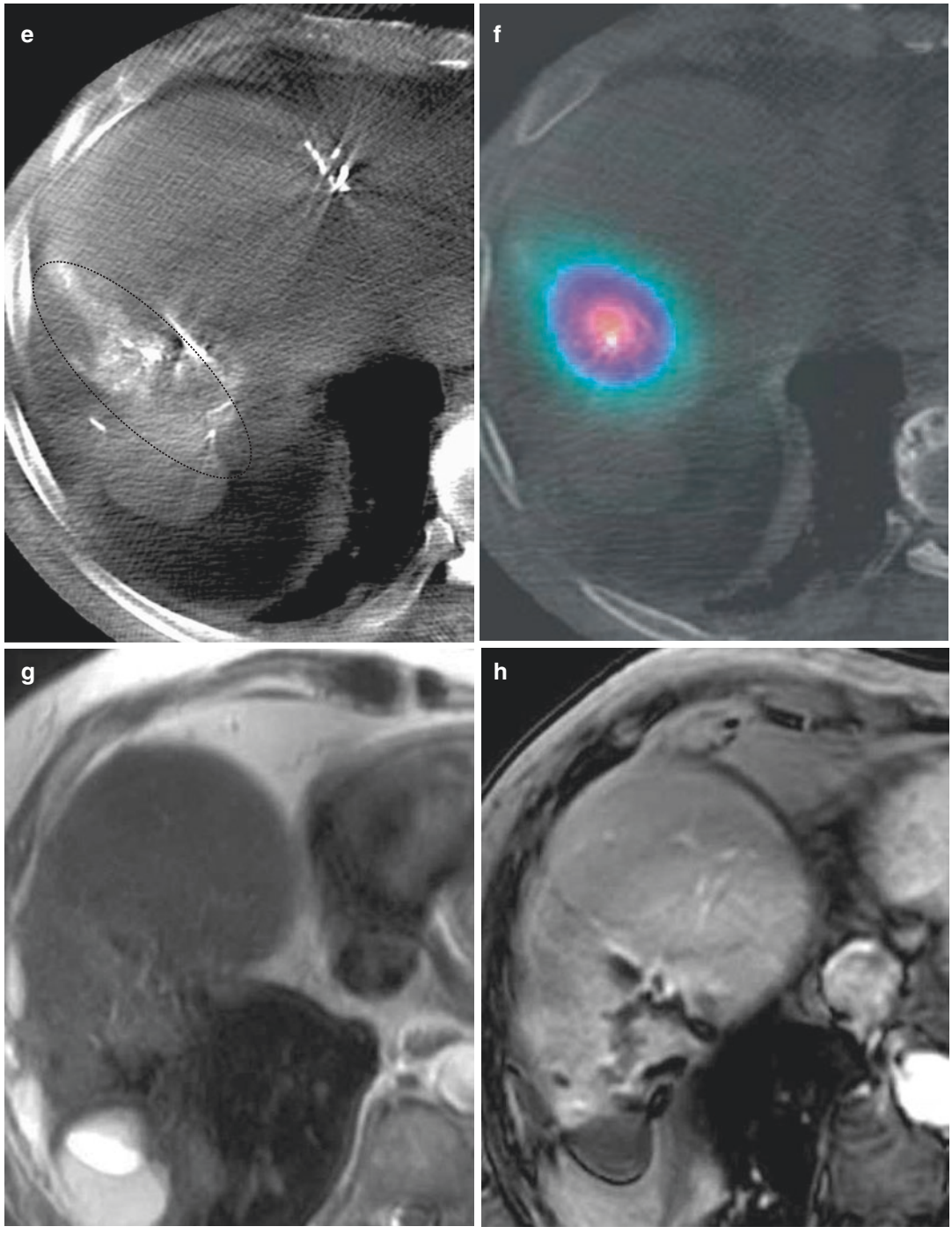

Fig. 9.2 (continued)

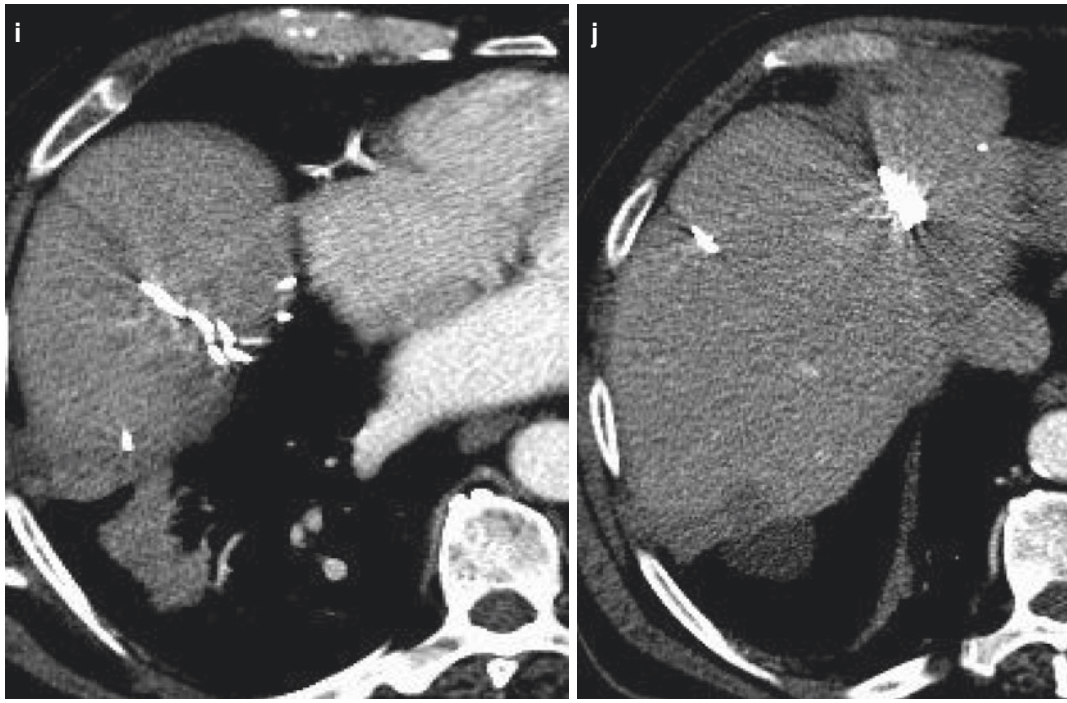

Fig. 9.2 (continued)

Indications, Contraindications, and Patient Selection

RE-Y90 in CLM is reserved for patients that are not candidates for surgical resection. A Consensus Panel Report by the Radioembolization Brachytherapy Oncology Consortium provides detailed guidelines for RE-Y90 eligibility and patient selection [3]. Main indications of RE-Y90 are suited in different clinical settings such as failed first- or second-line systemic chemotherapeutic regimens, salvage or palliative treatment and neoadjuvant therapy prior to surgical resection [2, 3, 6, 8]. Recent publications showed promising results of RE-Y90 in earlier metastatic disease associated with induction and maintenance chemotherapy, including level 1 evidence of better liver progression-free survival (PFS) when FOLFOX was associated to RE as first-line treatment [9, 10].

The best candidates for RE are patients with unresectable liver-only or liver-dominant tumor burden, preserved liver function, and good general clinical status [6]. Therefore, pre-treatment evaluation includes not only a clinical and laboratory check-up but also imaging studies, including a chest CT together with a three-phase MDCT and/or gadolinium-enhanced MRI of the liver, not only for assessment of liver tumor burden but to rule out or measure extrahepatic disease. A whole-body FDG-PET/CT may contribute to decision-making due to its high sensitivity for intrahepatic and extrahepatic tumor. Furthermore, therapy–response assessment is more accurate if a metabolic imaging has been performed before the RE-Y90, as well as MDCT or MRI.

In patients with excessive tumor burden and/or limited hepatic reserve, demonstrated by elevated levels of bilirubin (>3 mg/dl), elevated liver enzymes (AST/ALT 5 × upper normal limit), altered INR (>1.6), or reduced serum albumin (<3 g/dl), RE is contraindicated because of the risk of developing radiation-induced liver failure [3–8]. Patients with poor clinical condition

(Eastern Cooperative Oncology Group: ECOG >2) are also at a higher risk of developing severe side–effects, and treatment outcome is usually worse; therefore, the indication of RE is questionable in this clinical situation [3–8].

As in any other intra-arterial liver-directed therapy, the renal function and the biliary integrity should be monitored before treatment. Renal function impairment is a relative contraindication because of the use of iodine contrast media necessary to perform the diagnostic and therapeutic angiogram previous to RE-Y90. Patients with impaired biliary sphincter at the duodenum junction (biloenteric anastomoses, papillotomy, biliary stenting) may be at a higher risk of cholangitis and liver abscess formation in the follow-up weeks after RE, but this does not constitute an absolute contraindication [5, 7]. In a specific patient, these potential hazards have to be weighed against the potential benefit of the RE treatment.

In a small number of patients, RE could be contraindicated due to vascular abnormalities or the extent of lung shunting (lung exposure >30 Gy). These criteria are established at the work-up procedure performed by the interventional radiologist (preparation/simulation phase) before the RE-Y90 is confirmed, thereby preventing inappropriate treatment of the patient. The interventional radiologist may correct some cases of excessive shunting to the lung or gastrointestinal tract by proper vessel embolization, as described in previous paragraphs [6, 7]. Thus, an appropriate previous preparation/simulation test (low LSF, no extrahepatic deposits of Tc 99-MAA, acceptable dosimetry) is mandatory to perform the RE treatment safely.

Efficacy and Clinical Results

Multiple studies suggest that RE-Y90 is effective in slowing disease progression and improving survival. Localized high-dose tumor-directed radiation is an effective treatment for reducing the burden of CLM [4, 6, 8, 11–14]. A single treatment with RE induces profound cytoreduction of CLM in the liver, and significantly prolongs time to progression (TTP), PFS, and overall survival (OS), even among patients with highly chemo-refractory disease [3, 4]. The recruitment of a large proportion of these patients for RE has been among those with advanced, chemo-refractory disease [3–6, 15–17]. However, RE-Y90 has recently been shown to downsize tumors for potentially curative surgical resection in patients with earlier unresectable CLM that have received chemotherapy before or are chemo-refractory[18]. In clinical practice, RE-Y90 is integrated in the paradigm of management of CLM in three different settings: as first-line treatment, second-line treatment or as salvage therapy [4, 6, 9].

Radioembolization as First-Line Treatment

The current clinical data support the potential of RE-Y90 in downstaging and delaying liver disease progression in patients with CLM. Such findings provide opportunities to develop RE-Y90 treatment in patients with predominant liver disease to prolong first-line DFS and OS, and to impact positively on tumor downstaging for the potential of conversion to allow hepatic metastases resection [6, 9].

Two pioneering randomized clinical trials performed in the last decade showed the utility of RE-Y90 in the first-line treatment of patients with CLM, with encouraging results in terms of overall response rates (ORR), PFS, and OS [11, 12]. These studies compared the use of intra-arterial FUDR with and without RE and intravenous FU/LV with and without RE respectively, and clearly showed the benefits of RE-Y90. These studies have some limitations, such as the small size and the use of cytotoxic drugs that are not currently used as first-line treatments. To study the utility of RE-Y90 in the current paradigm of CLM chemotherapy regimens, three international randomized Phase III trials (the SIRFLOX, FOXFIRE and Global FOXFIRE) were conducted to report on the PFS and OS [10, 19, 20]. The SIRFLOX study showed improvement in liver PFS, with 31% reduction in risk of liver progression when combining RE-Y90 with FOLFOX, while not increasing toxicity [10].

The FOXFIRE and Global FOXFIRE are still ongoing, and will be powered to test the impact of RE-Y90 on OS [20].

Some authors suggest the incorporation of RE-Y90 in the first-line treatment, for the purpose of extending clinical benefits from maintenance therapy [9]. Indeed, the most common approach toward unresectable CLM involves the use of induction chemotherapy combined with bevacizumab. However, chemotherapy-induced toxicities encountered with combination regimens may lead in some patients to a milder maintenance form of treatment after few weeks of induction therapy. Maintenance therapy, usually fluoropyrimidine with bevacizumab, has limited efficacy and progression occurs in few months in the majority of patients. The combination of RE-Y90 during induction therapy or during maintenance therapy has the potential to prolong liver PFS, therefore improving patient outcome and delaying the need for more toxic second-line combination treatments [9]. Interestingly enough, the European Society of Medical Oncology (ESMO) consensus guidelines suggest that RE-Y90 of CLM in earlier treatment lines may be interesting as consolidation treatment [20].

Another beneficial possibility to combine RE-Y90 in the first-line setting is in those patients who cannot tolerate intensive chemotherapy. Aged patients with CLM and vascular comorbidities may be frail enough to be considered for combination chemotherapy or antiangiogenic agents. For such patients, first-line treatment is often limited to single agent 5-FU/LV or capecitabine monotherapy, a strategy associated with a median PFS of 4–5 months [9]. The integration of RE-Y90 with fluoropyrimidine in the first-line treatment of liver-predominant CLM has the potential of delaying progression without significantly impacting patients' performance status [9]. An advantage of RE-Y90 which should always be considered is its favorable toxicity profile when combined with fluoropyrimidine or FOLFOX, and yet it results in major clinical responses in the majority of the treated population [13].

The high efficacy of conversion therapy with aggressive chemotherapy such as FOLFOXFIRI discourages the initial use of RE-Y90 in CLM in the neoadjuvant setting, except for specific situations such as intolerance or inadequate initial response to induction chemotherapy [9]. However some authors suggest that RE-Y90 may be a good alternative in potential candidates for resection, but with small future liver remnant volume [8, 21, 22]. A matched-pair analysis comparing RE-Y90 with portal vein embolisation showed a lesser, but still pronounced benefit of RE-Y90 with regard to contralateral liver hypertrophy, following simultaneous treatment of the ipsilateral tumor load with Y90 [22].

Radioembolization as Second-Line Treatment

Limited prospective data exist on the second-line integration of RE-Y90 in combination with chemotherapy in the second-line treatment of metastatic colorectal cancer [9]. A Phase I clinical trial has evaluated the combination of irinotecan plus RE-Y90 in patients with CLM who failed at least one line of 5-FU- based treatment [14]. In this study, ORR was found in 48% of patients, with median PFS and OS considered favorable in comparison to second-line irinotecan therapy, where responses are historically <10% [14]. Median survival following RE-Y90 in the second-line setting after chemotherapy compares well with similar patients receiving second-line chemotherapy combined with aflibercept and bevacizumab beyond progression [18, 23]. These results are in line with the first-line clinical trials, and substantiate the potential of RE-Y90 in enhancing chemotherapy response and delaying tumor progression. Some authors suggest using this strategy in patients with KRAS or BRAF mutations with no further options of salvage therapy, to delay progression of liver disease [9].

Radioembolization as Salvage Treatment

Patients with CLM who are refractory to first- or second-line chemotherapy have a dismal prognosis, even with the newly developed antibiologic

agents. In this setting, several prospective studies have shown that RE-Y90 is safe and efficient alone or combined with a radio-sensitizing chemotherapy regimen as salvage therapy [3, 8, 12, 13, 16].

The results of clinical trials combining RE with second- or third-line chemotherapy indicate that an objective response may be seen in 30–48% of patients [8, 14]. Furthermore, studies in chemo-refractory patients have reported that disease progression is delayed following RE-Y90, and that survival is prolonged compared to either randomized, matched-pair, or historical controls [3, 15, 16]. The median survival following RE-Y90 in patients with two or three prior lines of chemotherapy respectively compares favorably with patients in a similar setting using regorafenib or placebo [23]. The evidence in the literature shows that, even among heavily pretreated patients, RE-Y90 appears to have a favorable risk/benefit profile and offer a more target approach for the management of dominant CLM [24]. This approach is confirmed by the ESMO consensus guidelines in CLM, which recommend the use of RE-Y90 for patients with liver-limited disease failing available chemotherapeutic options [21].

Side-Effects and Complications

For better tolerance of RE-Y90, some medications are regularly indicated before and after treatment, although side-effects and toxicity are low if the procedure is carefully performed. The most common side-effect of RE-Y90 is a mild post-embolization syndrome that occasionally may last some days after treatment [4, 5]. The most common side-effects include fatigue, nausea, and abdominal pain, the former being the most prominent symptom. Fever is uncommon but may be present as a consequence of the inflammatory effect of liver radiation or tumor necrosis, and should not be confused with bacterial infection. Symptomatic treatment of post-embolization includes corticoids, anti-emetics and analgesics starting the same day of treatment [4, 5, 7]. In some patients, nausea may last several days, occasionally being severe enough to require long-standing anti-emetic medication that should be continued until the symptoms subside. As organs adjacent to the liver may also receive radiation doses if microspheres are lodged on the periphery of the liver, some radiation gastritis is expected after treatment in such a case [4, 5]. Therefore, prophylactic pump proton inhibitors are commonly indicated before RE-Y90, and continued for at least 1 month after treatment [5, 7].

Severe complications are uncommon given correct patient selection, adequate pretreatment assessment (preparation/simulation phase), and a meticulous Y90 microsphere delivery during treatment. Anyway, serious complications of RE-Y90 have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than the liver [5, 25]. Non-target infusion of Y90 may lead to ulceration or bleeding in the gastro-intestinal tract and pancreatitis. The gastro-intestinal ulcers are resistant to medical therapy, and may need surgery [25]. These complications may be spared with careful analysis of pre-treatment angiography and SPECT-CT, together with the use of CBCT to rule out extrahepatic deposits of Tc-99 MAA or contrast medium. In addition, Y90 should be carefully delivered on the treatment day ,avoiding at all means arterial reflux or over-injection of the radioactive material [7].

Radiation-induced pneumonitis is another uncommon complication that may occur because of lung sensibility to radiation. It should be noticed that after any intra-arterial injection into the liver, a small fraction of the delivered substance is shunted into the lung through tumor arteriovenous shunts [4, 5]. The risk of radiation-induced pneumonitis can be somewhat predicted in the simulation phase by measuring the LSF by planar scintigraphy [3, 7, 26]. Pulmonary toxicity is avoided if the LSF is <20% or the accumulated lung dose <30 Gy [4, 5]. The symptoms indicating radiation pneumonitis include dry cough, progressive dyspnea, and restrictive ventilation deficits resulting in deteriorated lung function, and usually respond to corticoid therapy [5, 25].

Radiation-induced liver disease (REILD) is a rare complication, with an incidence ranging between 0–4% [5]. It results in various degrees of hepatic decompensation, and is indistinguishable from hepatic veno-occlusive disease [5, 25]. It is usually manifested clinically by the development of anicteric ascites and increased abdominal girth, as well as rapid weight gain with hypo albuminemia [5]. Although jaundice may be present, it is uncommon at presentation. Blood tests show normal or mild increase in the bilirubin levels, with a substantial increase of alkaline phosphatase. Several reports have indicated that REILD is more likely with liver tumor burden <70% and delivery dose to the liver <150 Gy [4, 5, 25]. Since radiation dose is related to liver toxicity, performing RE-Y90 in a repeated fractioned fashion is recommended to reduce the risk of liver toxicity, especially in patients with previous heavy chemotherapy treatment if a whole-liver treatment is needed [8, 26]. In such a case, Y90 is infused in the right hepatic artery separated by 4 weeks from infusion via the left hepatic artery. Prophylaxis with corticoids may be of benefit, and is regularly administered, as mentioned above. If REILD occurs despite cautious measures, treatment is instituted with diuretics, sodium restriction, and continuous corticoid therapy. Hepatotoxic drugs should be avoided, and in extreme cases a TIPS procedure may be of benefit.

Other complications such as radiation-induced cholecystitis and biliary tract injury are uncommon, and may be prevented with proper patient selection and by sparing the cystic artery before Y90 infusion [5, 7].

Follow-Up and Response Assessment

Follow-up is mandatory for results assessment and to detect eventual complications, as well to integrate this treatment among multimodality options. It is usually performed in a multidisciplinary fashion, and depends on the treatment plan of each patient.

Clinical evaluation and liver blood tests after RE-Y90 are recommended to determine the outcome of treatment. Contrast-enhanced CT or MRI and tumor biomarkers are performed for response assessment and to rule out intra- or extrahepatic new disease at 6 and 12 weeks. Oncologic responses at cross-sectional imaging are usually depicted after 3 months of treatment, with the best results shown after 6 months. Metabolic imaging under PET-CT may contribute to better response assessment if it has also has been performed at baseline.

The RECIST system is not an accurate method to assess oncologic response, as is the case with other imaging-guided liver-directed therapies. Indeed, tumor size after treatment does not reflect the number of viable tumor cells, tumor enhancement being a more reliable alternative. The most common imaging findings at cross-sectional images after RE-Y90 are liver edema congestion, and microinfarction that should not be mistaken for progression disease [4, 5]. These signs are reversible and are probably due to radiation inflammatory liver and tumor reactions. Tumor objective response may be demonstrated by tumor necrosis (absence of enhancing tumor at CT or MRI), but evidence of morphological changes may require 3 or more months after treatment. Tumor size reduction often may be observed at 6 months follow-up in good responders.

Since PET-CT has the ability to give information about tissue metabolic activity, comparison of a follow-up study to baseline PET-CT is highly contributive. In clinical practice, response is usually assessed clinically, by tumor markers and cross-sectional imaging as in any other type of treatment, but limitations of RECIST and the potential role of PET-CT should be considered.

Conclusions

RE-Y90 is a powerful tool in patients with liver metastasis due to the potential of augmenting regional response of systemic chemotherapies, and increases the number of patients who are candidates for resection. Application of this recently introduced liver-directed therapy might contribute to extending the benefits

of curative hepatic resection to a broader group of patients. Caution with regard to patient selection, treatment preparation, and performance is particularly important to prevent serious toxicity being associated with this highly efficacious treatment [4, 7]. Improvements in predicting dosimetry will lead to optimization of treatment outcome, even in borderline treatment candidates [26]. With the sustained accumulation of promising clinical results, RE-Y90 is moving forward from the salvage setting indication to its use in earlier stages of CLM. The optimal modern management of CLM requires a multidisciplinary team with various specialists including liver surgeon, medical oncologist, interventional radiologist, nuclear medicine physician, and others who have a thorough understanding of the latest diagnostic and therapeutic options.

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Part III

Surgical Strategies

Anesthetic Management

10

Francisco Carlos Bonofiglio

Introduction

In 1977, a multicentric study was published involving 621 hepatic resections. In this first report, average mortality stood at 13%, but reached a maximum level of 20% when they involved large resections. Intraoperative haemorrhage was pointed as the most important cause of mortality [1].

In the last two decades, the incorporation of new techniques, better knowledge in the perioperative care, and the development of sophisticated surgical equipment for bleeding control have succeeded in significantly decreasing haemorrhages and massive transfusions.

In the 1990s, mortality in hepatic resections had gone down to 5%, with a lower percentage in centres with high surgical volumes [2, 3].

This step forward has allowed for the geometric growth of the number of hepatic resection surgeries across the world, mainly due to the fact that it is the best treatment that can be offered to date for primary oncologic and metastatic injuries. Its potential in delaying the development of the disease and even offering a cure is higher than any other possible chemotherapy treatment. In a significant percentage of cases, surgical treatment represents the sole potential possibility of a cure [4–7] (Table 10.1).

Table 10.1 Hepatectomies indications

	Number of patients	Percentage (%)
Malignant pathologies	*826*	85.*86*
• Colon metastasis	552	61
• Neuroendocrine metastasis	22	2.9 4
• Metastasis of another origin	31	11.5 2.9
• Hepatocellular carcinoma	88	2.3
• Colangiocarcinoma	22	12
• Vesicular cancer	18	
• Others	93	
Benign pathologies	*136*	*14.14*
• Hemangiomas	36	26.5
• Live related donor	35	26
• Adenomas	23	17
• Focal nodular hyperplasia	21	15.5
• Hydatid cyst	8	5.9
• Others	13	9.5

Experience at the Hospital Italiano de Buenos Aires. *N*: 962 patients

Anatomy and Hepatic Physiology

It is vital for the anaesthesiologist carrying out perioperative care in hepatectomies to know the anatomy and physiology of the liver.

It is in these concepts that we shall find the bases for reducing haemorrhages and the way

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towards preventing the increase of cellular injury during the surgical ischemia periods.

Anatomic and Physiological Characteristics of the Liver with Surgical and Anaesthetic Relevance

The liver is the largest solid organ in the body, and weighs about 1.5 kg in an adult. It is placed in the right quadrant of the abdomen and is divided into four lobes: right, left, quadrate lobe, and caudate lobe.

At the same time, the right and left lobes are divided into segments which are defined by the distribution of arterial vessels and the biliary tree.

In the year 2000 in the city of Brisbane, a meeting of specialists was held with the objective of creating a definitive nomenclature to describe the different procedures on the liver. In subsequent years, this nomenclature has been adopted worldwide, and it is currently the most widely accepted one [8].

Hepatic surgery can be carried out according to lobe and segment distribution or disregarding this division.

Thus, the resection of a hepatic lobe will be called hemihepatectomy or right or left hepatectomy (Figs. 10.1 and 10.2).

At the same time, the resection of a single segment is called segmentectomy and when it involves two segments, bisegmentectomy.

The most important hepatic surgery involves the removal of the right or left lobe as well as one or two contralateral segments. This surgery is called hepatic trisegmentectomy [8].

Finally we call it an atypical hepatic resection when the cut on the hepatic tissue does not respect segmentary distribution.

It is important to bear in mind that this organ receives double circulation through the contribution of the portal vein and the hepatic artery. The latter, narrower, is responsible for between 25 and 30% of the hepatic flow but 60% of the oxygen available for this organ. The portal vein contributes 70% of the hepatic flow and 40% of the total oxygen [9].

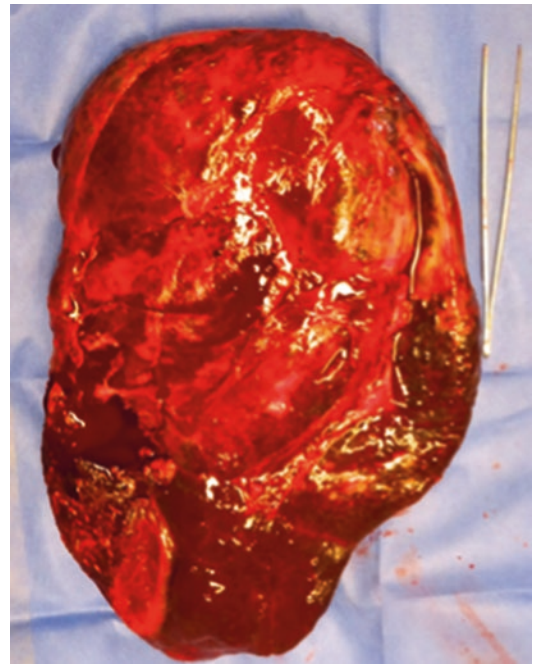

Fig. 10.1 Hepatic tumor

The portal vein branches ramify within the liver, and their division accompanies the hepatic sinusoids. Portal blood goes through these sinusoids and is collected by the centrilobular vein.

The hepatic artery branches run along the portal vein and finally transform into arterioles, precapillaries, and capillaries. Arterioles have sphincters which are part of the hepatic flow regulation [9].

After going through the hepatic sinusoids, blood coming from arterial and portal circulation is collected by three hepatic veins which drain their content into the vena cava [10].

Under normal circumstances, the liver extracts only 40% of the total oxygen delivered, but in patients under surgery or anaesthesia or suffering from diseases such as cirrhosis, the demand for oxygen may increase [9].

Hepatic flow represents about 25% of the total minute volume, which equals the delivery of about 1,500–1,800 ml of blood per minute [10].

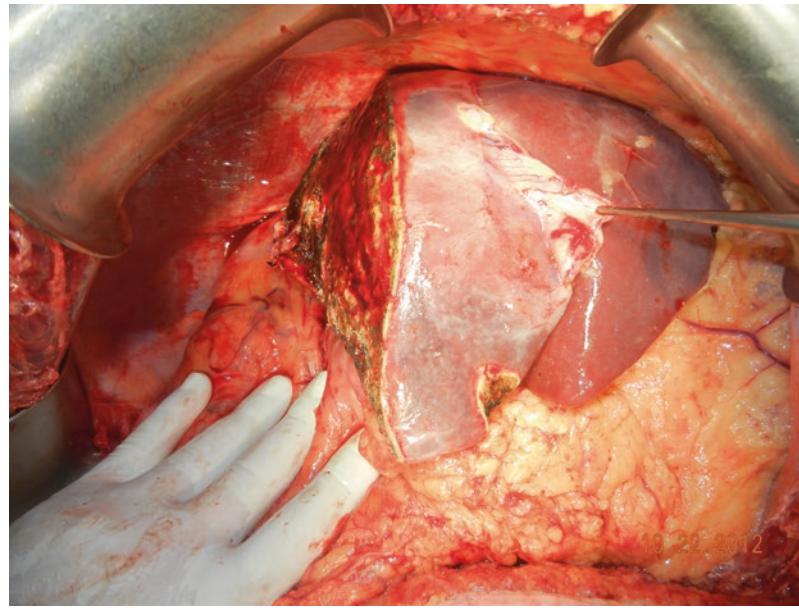

Fig. 10.2 Intraoperative photo of a right hepatectomy

There is a close relationship between the portal vein flow and the hepatic artery. When portal flow decreases, the hepatic artery complements it by increasing its flow [10].

While portal blood flow remains stable, the hepatic artery maintains an intrinsic self regulation system which keeps its volume constant in spite of the systemic pressure variations [11, 12].

Maintaining a stable blood flow towards this organ, under different hemodynamic conditions, is accounted for given the need to support the metabolism of endogenous and exogenous substances, even in critical clinical cases [9, 11, 12].

In other words, hepatic metabolism depends on the blood flow received in the time unit and only stops under extreme circumstances.

Hepatic irrigation is, therefore, an exception system, since it functionally does not respond to the same factors that lead to vasoconstriction or vasodilatation in the rest of the vascular tree.

The effects of the acid base or the concentration of oxygen only alter the diameter of the hepatic arterioles when they reach marginal conditions. Self-regulation would be controlled based on a neural type mechanism [13].

We should also mention, though with a lesser influence on this system:

- Cyclical alterations corresponding to spontaneous ventilation.
- Intrahepatic osmolarity.
- Excessive use of positive end-expiratory pressure (PEEP).
- Hypocapnia and hypercapnia.
- Surgery: surgery itself diminishes hepatic flow. Superior abdominal surgeries are those with the largest influence
- Anaesthesia: inhalatory anaesthetics decrease hepatic flow, although the most modern ones seem to do so in lower quantities (sevorane) and even increase it (isofluorane).
- Intravenous anaesthetics do not appear to have any influence over hepatic flow.

Hepatic Endothelium and Influence on Central Venous Pressure

The vascular endothelial cells in the hepatic sinusoid (mainly those corresponding to the portal vein branches), have fenestrations of a diameter

which varies between 100 and 500 nm, and are not supported on any basal membrane.

The importance of these fenestrations lies in that they place the blood perfused to the liver in direct contact with the hepatic interstice. In other words, there is no defence against the changes in hydrostatic pressure [9, 10].

The larger orifices are found in the centrilobular region. These can change their size as a response to intravascular pressures, the action of vasoactive drugs, and the presence of toxins [12].

As incoming blood is controlled by a self-regulating system, there is no possibility for the liver to receive excessive flow that would unproportionally increase the internal volume.

The only way of doing this is through the increase of the central venous pressure which exercises a retrograde strength on the vena cava and the suprahepatic vein. The increase of the central venous pressure successively leads to the increase of the hepatic volume, the increase in the filtration of liquids towards the interstice, a higher lymphatic flow, and finally to the formation of ascitic liquid [9].

The arterioles contract and ease the passage of liquids towards the interstice as a response to the higher central venous pressure.

However, thanks to the lymphatic system which can drain great volumes, there is no accumulation of interstitial fluid in the liver.

Lymphatic vessels have the ability of increasing the density of proteins in their interior. These increase until they reach plasmatic concentration. Thus, oncotic pressures are matched and the interstice does not become a fluid deposit. Additionally, the liver surface can exude liquid, thus ejecting its excess [9–11].

Before reaching this extreme situation, the liver becomes a fabulous blood reservoir due to the increase in its internal volume.

Carrying out a liver resection under these circumstances implies the real possibility of increasing the risk of provoking a significant haemorrhage during surgery.

Surgical Manoeuvres that Diminish Intraoperative Bleeding

Pringle Manoeuvre (PM)

First described by Pringle in 1908, it has proven effective in decreasing haemorrhage during the resection of the liver tissue [14]. It is frequently used, and it consists in temporarily occluding the hepatic artery and the portal vein, thus limiting the flow of blood into the liver, although this also results in an increased venous pressure in the mesenteric territory [15] (Fig. 10.3).

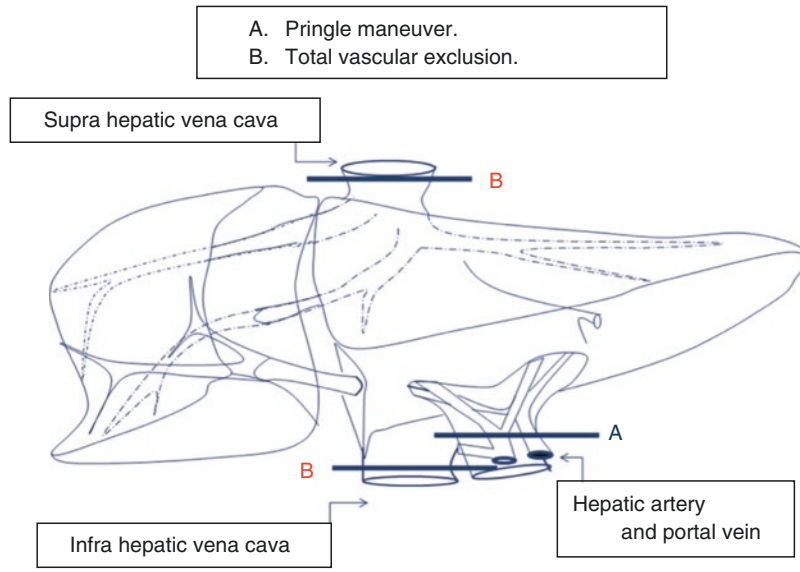

Fig. 10.3 Surgical maneuvers liver vascular occlusion

Hemodynamic repercussion during the PM is rare because it only diminishes the venous return in 15% of cases. The cardiovascular system slightly increases the systemic vascular resistance as a compensatory response, thereby limiting the drop in the arterial pressure. Through the administration of crystalloids, it is possible to maintain hemodynamic stability [16, 17].

In the 1990s, the PM was used continuously for 45 min and even up to an hour because the depth of the potential damage that could occur due to hepatic ischemia was not yet known [14].

During the PM, the lack of oxygen affects all liver cells, especially Kupffer cells which represent the largest fixed macrophage mass. When these cells are deprived of oxygen, they are an endless source of production of the tumour necrosis factor (TNF) and interleukins 1, 6, 8 and 10. IL 6 has been described as the cytokine that best correlates to postoperative complications [15, 17–19].

In order to mitigate the effects of continuous PM, intermittent clamping of the portal pedicle has been developed. This consists of occluding the pedicle for 15 min, removing the clamps for 5 min, and then starting the manoeuvre again.

This intermittent passage of the hepatic tissue through ischemia and reperfusion shows the development of hepatic tolerance to the lack of oxygen with decreased cell damage. Greater ischemic tolerance to this intermittent manoeuvre increases the total time it can be used [17, 20].

Total Vascular Exclusion (TVE)

This was described by Heaney and collaborators and initially associated to 30% mortality due to its use. As a result of this, it was quickly abandoned and only used again when the development of liver transplant programmes led into greater knowledge of the physiopathology of this surgical manoeuvre [21].

The classic vascular exclusion adds to the occlusion of the hepatic artery and the portal vein, and the clamping of the infrahepatic and the superior vena cava. Thus, we prevent retrograde flow of venous blood (Fig. 10.3).

There are variations of this manoeuvre described, with the intention of mitigating its risks; for example, the occlusion of the suprahepatic veins tributaries of the area to be resected, to avoid the total interruption of the flow of the cava. In these cases, the venous return remains undamaged [22].

Used less frequently than the Pringle manoeuvre, the TVE is useful in the resection of tumours adjacent to large vessels to diminish the risks of massive haemorrhage or air embolism [22].

This modality can also be intermitted, alternating periods of ischemia with periods when circulation is re-established to mitigate possible consequences due to the lack of oxygen [23].

Total occlusion of the vena cava damages the filling pressures of the right cardiac cavities, thus causing a drop in the venous return higher than 50% and, consequently, of the minute volume. Its clinical manifestation is a decrease in systemic arterial pressure, which receives an immediate compensatory response through the increase in the systemic vascular resistance (up to 80%), in an effort to decrease the arterial hypotension [22–24]. The anaesthesiologist can help these compensatory mechanisms through the administration of fluids and the use of vasoactive drugs. The intravenous use of fluids during this period must be carefully managed, since when the clamps are released, there can be saturation in the liver capacity and an increase of the haemorrhage from the exposed surface of the organ.

A persistent hypotension during TVE, in spite of the vasoactive drugs, is the main cause of interruption of the manoeuvre [24, 25].

As with PM, TVE should not be used for prolonged periods of time. The choice of an intermittent method allows for greater use of time [21] (Table 10.2).

Table 10.2 Differences between the Pringle manoeuver and total vascular exclusion

Pringle manoeuver	Total vascular exclusion
Greater number of transfusions	Greater number of complications
Greater ischemia/reperfusion effect	Greater hemodynamic instability
Shorter hospital stay	Technically difficult for the intermittent procedure

Morbimortality of the TVE has been related in different series studied with the amount of blood transfused, the clamping time, and the histology of the remaining liver [23].

The limitation of the haemorrhage during TVE is evident and in general, patients are operated on with scarce or no transfusional requirements [14, 26].

Anaesthetic Technique

When an anaesthesiologist is going to take part in a liver resection, he or she should assess the following considerations prior to the surgery: size of the liver resection to be carried out, clinical condition of the patient, preparation for surgery and necessary intraoperative monitoring, possibility of using Fast Track, and the place of post-operative care in the first few hours following surgery (Intensive Care Unit or Anaesthetic Recovery Unit).

Both inhalational anaesthesia and intravenous anaesthesia (total intravenous anaesthesia—TIVA) can be used in all their variations and without restrictions in liver resections. It will only be necessary to avoid those anaesthetics that diminish the hepatic flow, though they are practically out of use nowadays.

Monitoring should be according to the complexity of the surgery and the clinical condition of the patient. Routine monitoring in these types of surgery consists of: dynamic electrocardiography, capnography, oximetry, invasive arterial pressure, and periodic blood tests. Should TIVA be chosen for the anaesthetic technique, BIS is a vital monitor that must be accompanied by an adequate control of muscle relaxation. The control of central temperature and ST segment depression in DII and V5 must also be routine [27].

We should specially mention the central venous pressure (CVP) and its intraoperative control as a parameter highly related to bleeding in patients [28].

Monitoring of the CVP is up to now mandatory, although mini invasive monitoring could replace it in the future. With this method and only by using the invasive arterial pressure can be obtain constant values of systolic volume variation (SVV) or pulse pressure variation (PPV), which provide excellent guidance when restoring the blood [29].

Patients who require a liver resection surgery need at least two venous accesses as large as possible, given the potential need to administer fluids and homoderivatives quickly. Due to the need to measure CVP, one of these venous accesses needs to be central. All venous lines need to be located in the superior vena cava territory (arms and neck), since a vascular exclusion manoeuvre used would limit the desired administration of fluids [27].

Lately, crystalloids are the fluids of choice in high-risk patients, since colloids have been linked to higher renal failure and postoperative mortality [30–32].

Within the group of crystalloids, physiological solution is known for leading to hyperchloremia and acidosis. Both conditions are achieved with little volume, and are clearly damaging in procedures where the metabolic conditions can change quickly [32, 33].

Crystalloids which contain lactate are less criticized, mainly because they can maintain an artificial high level in plasma, which would lead us to conclude that the hyperlactacidemia present is the result of a poor postoperative evolution on the part of the patient [34].

The recommendation regarding the use of crystalloids basically consists of a very balanced solution such as Plasmalyte, whose osmolarity is close to plasmatic, thus contributing more acceptable metabolic results [35].

Nowadays, appropriate anaesthetic technique includes the use of protective mechanic ventilation to prevent pulmonary injury and postoperative complications. Generally speaking, a current volume between 6 and 8 ml/kg is sufficient for effective intraoperative ventilation in patients without prior pulmonary pathologies. The weight used in this equation needs to be ideal for each patient. Constant use of PEEP during mechanical ventilation will prevent pulmonary collapse and very probably the need for pulmonary recruitment with high peaks of positive pressure [36, 37].

Towards the end of the surgery, it is necessary to administer the necessary volume to re establish hemodynamic stability, without the need of pharmacological support or similar to the pre-surgical conditions.

It is desirable not to over-expand patients, among other considerations, because this will help to prevent later complications (e.g., oedemas, anastomosis filtrations).

The anaesthesiologist should have the ability to focus his intraoperative work on keeping the patient in an appropriate balanced metabolic condition which is pain-free and which bears an acceptable level of glycaemia, is normothermic, and has an appropriate concentration of Hb. Additionally, it should be hemodynamically stable, thus ensuring an appropriate consumption of oxygen and a convenient anaesthetic depth with enough muscle relaxation to allow for proper surgical work [38].

Relationship Between Central Venous Pressure (CVP) and Intraoperative Haemorrhage

The relationship between the intraoperative bleeding in liver surgery and CVP was explained in the section where we described the anatomical and physiological dependency between the endothelium, retrograde venous pressure, and intrahepatic blood volume.

Keeping a high CVP implies greater blood loss due to the accumulation of fluids in the liver. On the other hand, when the CVP is low, bleeding will not be a problem, but there might be a higher risk of air embolism [28, 39–43].

It is advisable to keep the CVP below 5 cm of H_2O, at the time of resection. During these periods, it will be necessary to use vasoconstrictive drugs such as phenylephrine or norepinephrine to maintain average arterial pressure between 50 and 60 mmHg [44–46] (Fig. 10.4).

Some authors propose replacing the CVP measure for pressure monitoring in a peripheral vein (in the arm) if it is at the same height as the right atrium. These researchers grant peripheral venous pressure (PVP) the same value as CVP because they have found an excellent correlation between the two parameters, with a discordance level of just 4% [47, 48].

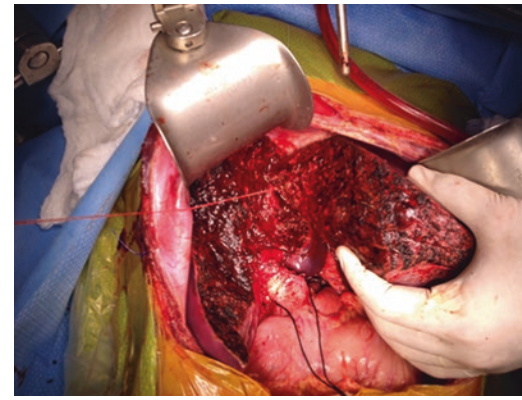

Fig. 10.4 Hepatic resection surgery with low central venous pressure. No bleeding is observed in the tissue

In order to achieve a CVP below 5 cm of H_2O, it is necessary to impose an intense restriction of the crystalloid infusion from the beginning of the surgery. This measure is frequently not enough on its own, and it is therefore necessary to resort to the administration of drugs in order to achieve the objective set.

The use of venous vasodilators has been described, but the use of diuretics can be a very effective way of obtaining very low levels of CVP without the need of other measures.

Furosemide (0.5 mg/kg), is normally injected in a single dose after obtaining the first basal CVP register at the beginning of the surgery. Its use necessarily implies the serial control of the potassium level in blood during the procedure.

Diuresis, generally speaking, is above 10 ml/kg towards the end of the surgery, which shows the extensive loss of fluids achieved. However, we should note a brief period of interperative oliguria when hypovolaemia is at its highest. Arterial pressure should be maintained through the administration of vasoconstrictive drugs until volemia is recovered at the end of the surgery.

When there is a drop in the effective volemia, the body responds with compensatory mechanisms to maintain constant arterial pressure. In a first phase, the activation of neurohormonal elements takes place which derive flow from the

muscle, skin, and splanchnic territory towards vital organs. Up until then, hypovolemia can result in minimal hemodynamic changes.

In more advanced stages, the activation of baroreceptors leads to the release of catecholamines with the subsequent increase in peripheral resistance. This course of action can partially compensate the fall in the venous return and maintain an arterial pressure close to the usual one. Finally, we should add the effect of the renin–angiotensin–aldosterone system, which increases the effect already begun by the sympathetic system [48–50].

The choice of vasoactive drugs to be used during this surgical moment lies within the spectrum of those which ease or even increase mechanisms of compensation. Phenylephrine is the first drug of choice since it behaves lightly and selectively on vascular resistance. A dose of 0.2–0.3 μg/kg/min is first administered, and later increased as necessary. It is unusual to reach a dose of 1 μg/kg/min and, generally, it is not necessary to add other drugs to ensure patients' hemodynamic stability. When thermodilution catheters have been used under these intraoperative conditions, vascular resistance figures registered have never gone above 1,300 dynas.seg.m^2 [51].

Once the hepatic resection period is over, it is necessary to re-establish volemia. Preventing haemorrhages and the absence of transfusions also appears to maintain an adequate immunological level, with considerable improvement in rates of infection. There are hypotheses that even support the possibility of a lower post operative tumoral recurrence [52].

Other Causes that Can Influence Intraoperative Bleeding

Undoubtedly, there are other causes that can strongly influence intraoperative bleeding during a liver reception.

One of them is PEEP, which when increasing transthoracic pressure during a part of the respiratory cycle, increases pressure on the inferior vena cava and its draining territory. There is a notable increase of bleeding if PEEP is maintained during the resection, even with very low CVP [53].

The other situation which can increase the loss of blood from the hepatic surface is Trendelenburg position which undoubtedly increases it, or that of reverse Trendelenburg which decreases it. Both situations can be related to the movement of the blood mass towards one or the other side of the body, according to which one is used [54].

Patients with Preoperative Morbility

The effect of chemotherapeutic drugs on the hepatic tissue does not go unnoticed. Drugs producing the greater organic changes are oxaliplatin, Avastin, and irinotecan, which provoke steatosis, sinusoidal obstruction, and fibrosis [55, 56]. When these patients are later operated on, it is more difficult to diminish the bleeding, even with an adequate reduction of CVP. During the postoperative stage, the changes on the tissue as a result of the chemotherapy increase the possibility of hepatic insufficiency [55]. The theoretical time in which these chemotherapy-associated pathologies diminish their potential to generate greater hepatic damage is 6 weeks after the last treatment [57, 58].

Smokers, diabetics, and morbidly obese patients represent another risk group in hepatic resections [58, 59].

Other Strategies to Diminish Bleeding

Avoiding blood transfusions during any type of surgery is nowadays a mandatory goal for all anesthesiologist doctors. During hepatic resection surgery, haemorrhage is related to the patient's prior conditions, to the technical difficulty presented by the resection, and also very associated with the anaesthesiologist's and surgeon's experience in these procedures [60].

Other strategies have been described in hepatectomies, in addition to the decrease of CVP. These can be used jointly or separately to inhibit haemorrhages.

The anaesthesiologist can continuously administer antifibrinolyctic drugs such as tranexamic acid, although this is not a widely spread practice. It is also possible to use normovolemic hemodilution during surgery with a double objective: to decrease CVP, and to have autologous and fresh blood for the end of the surgery. The latter method has proven to be safe and efficient, especially in live related donors [61]. At many institutions, the use of field blood recovery or cell saver is systematically included when the case calls for it [62].

In the last decade, many anaesthesiologists' adherence to blood administration procedure guidelines has resulted in the avoidance of unnecessary transfusions in patients undergoing high complexity surgeries.

These guidelines are based on scientific research which show that even with critical patients, a haemoglobin level of 7 g/dl does not increase surgical risk [63]. Hypothermia is another condition that anaesthesiologists know very well, and which they seek to prevent to maintain control of haemostasis.

Body temperature easily drops during hepatic resections, given the wide exposure of abdominal organs, cold fluid lavage, and ventilation with gases at room temperature. Control of hypothermia needs active work from the anaesthesiologist: use of thermal blankets, the administration of intravenous hot liquids, abdominal cavity lavage, and the heating of inspired gases, etc. During the hepatic resection surgery, it is necessary to maintain control of body temperature until the patient recovers consciousness during the immediate post-operative stage [64].

The recombinant factor VII, one of the most promising drugs in the field of haemostasis during the last decade, should be included among the possible therapies to be used in liver resections. In the case of coagulation alterations that lead to severe haemorrhage, factor VII will allow for control of the bleeding and sufficient time to make the necessary haemostasis corrections. Although it has been available for several years, its cost seems to be a limiting factor in is frequent use [65].

Finally, we could mention other techniques in the anaesthesia area which help towards preventing the increase of haemorrhage during hepatic surgery: [66, 67].

- Not using heparin, even at very low doses in the arterial line lavage liquids.
- During pre-anaesthesia assessment, we should consider if the administration of iron, erythropoietin/eritropoyetina, or vitamin K is necessary according to the patient's condition.
- Study all patients with Von Willebrand disease and prescribe desmopressin when necessary.
- Send the patient to the hemotherapy service to begin collection of autologous blood before surgery.

Surgery has also contributed, with sophisticated equipment to allow for bleeding-free hepatectomies. Those most used are ultrasonic scalpel, Argon beam, and haemostatic material with fibrin which can be placed on the liver surface to favour coagulation [66–68].

The angiography with arterial embolisation not only allows for the reduction of tumours before surgery but also helps decrease blood flow towards the anatomic sector where the operation is going to take place. It is an excellent and efficient technique to effectively mitigate intraoperative bleeding [69].

New surgical techniques have also been described to carry out small resections with little loss of tissue and a very low possibility of bleeding [70].

Another widely adopted method for preserving healthy tissue surrounding a malignant process or accessing tumours in difficult areas is radio frequency. It consists of using specially designed needles which are located within the metastasis which is destroyed through intense heat. Radio frequency also has the advantage of allowing the treatment of unresectable tumors through a mini invasive technique [71].

Ultrasound helps the placing of the needle when the use of radio frequency is decided upon [72].

Laparoscopic and robotic techniques have also been adopted to carry out hepatic resections, thus avoiding large incisions, hemorrhages, and a low amount of post-operative pain [73, 74].

Nowadays, hepatic resections at high surgical volume centres is a procedure which carries minimal risk of intraoperative bleeding [75].

Hepatic Injury due to Ischemia: Pre Conditioning

The use of hepatic fluid occlusion manoeuvres to diminish bleeding causes liver injury due to ischemia, and its consequences and prevention are studied by many authors, especially because the objective is to preserve the functions of the remaining liver so that the patient can have a swift and appropriate recovery [76].

These ischemia periods can be better tolerated by patients if preconditioning techniques are used.

Any strategy that protects the liver against ischemia is called hepatic preconditioning [77, 78].

Generally speaking, those who benefit the most are younger patients or those who suffer hepatic diseases and are more vulnerable in a surgery [78].

It has been proven in lab animals that hepatic protection strategies against ischemia have allowed for good organ performance even after a 75-min occlusion [79, 80].

One of the techniques to protect the liver against ischemia is to maintain the clamping of the hepatic hilum vessels for 10 min and then releasing them for another 10 min before the clamping. This scheme would produce intracellular biochemical changes that would preserve the ATP for a longer time in a prolonged ischemia period.

Other recommendations include the use of intermittent clamping, definitively discarding permanent ones. A greater amount of research is still needed to more thoroughly know which the most efficient pre-conditioning methods are [81].

In recent years, greater importance has been granted to interleukin 6 (IL 6) as a producer of hepatic injury. This cytokine could be a modulator of the death of the hepatocyte during severe and chronic diseases affecting the liver (Fig. 10.5).

Its action could be mediated by Toll-like receptors, which activate intracellular lines and influence the future destiny of these cells [82]. On the other hand and paradoxically, it is also possible to describe IL6 as a protector during hepatic failure [83].

That is to say, according to the conditions, the same lines that can produce apoptosis and hepatic failure could also counteract these signs and act protectively. In both situations, intracellular factor NF-kB appears to be the key towards determining the foundations of the death process or cellular proliferation. Currently, a significant amount of research seeks to describe the action of factor NF-kB both in animals and in humans during inflammation and ischemia [83, 84].

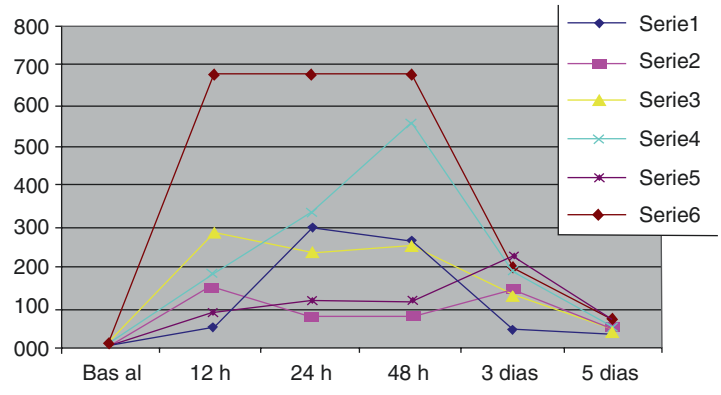

Fig. 10.5 Level reached by IL 6 after liver surgery with Pringle maneuver. Data from six patients treated at Hospital Italiano de Buenos Aires

Post-operative Analgesia and Fast Track Technique

The fast track concept includes different procedures within a multimodal programme to eliminate or diminish the effects of surgical stress on the patient. This technique which initially included almost as a sole objective the early extubation (within the first hours after surgery currently also requires an efficient treatment of post operative pain, perioperative fluid restriction, food and early mobilisation, etc.) [85].

There are programmes called ERAS (enhanced recovery after surgery) which encourage the study and development of techniques that allow for the increase of comfort in patients, the decrease of complications and costs of hospitalisation, thus also easing the medical and nursing staff work [86].

The analgesic technique to be chosen will depend on the patient's clinical condition and mainly on the level of coagulation at the time of administering it or withdrawing the catheters (Fig. 10.6).

Current discussion lies between two options: peridural thoracic analgesia and intrathecal opioids.

Peridural thoracic analgesia with catheter for the administration of local anaesthetics constitutes the higher analgesic standard in abdominal and thoracic surgeries, but in the case of a hepatic resection, the following conditioning elements should be noted: [87].

- In patients with cirrhosis or prior coagulation alterations, placing a large needle in the peridural space could ease the appearance of hematomas with the development of severe neurological injuries.
- Should the patient not have previous coagulation alterations, it is probable they will appear after the liver resection, even in patients with no cirrhosis and with previously normal lab tests. This seriously limits the removal of the catheter, which could extend up to 7 days. Some studies have recently shown that a moderate hepatic dysfunction would not appear to increase the possibility of hematomas above the average level. The causes of alternation of the coagulation profile during hepatic surgery post operative stage could be: intraoperative hemodilution, prolonged hepatic ischemia, or insufficient residual hepatic tissue.
- The removal of the peridural catheter should be preceded by coagulation tests that support the safety of the procedure. In the case of use of anticoagulants during the post-operative stage, they should follow the standards described in procedure guidelines for patients with regional anaesthesia and anti-clotting.

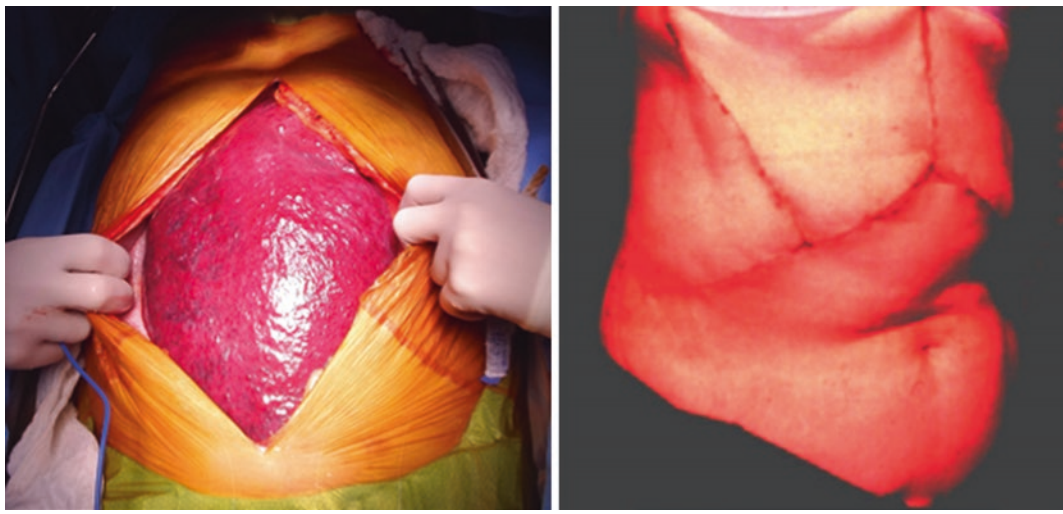

Fig. 10.6 Different incisions used in liver resections

- In addition to local anaesthetics, it is possible to administer low doses of peridural opioids to improve the quality of the analgesia.
- In large hepatic resections, lidocaine alters its metabolism and increases its concentration in blood, with the possibility of reaching toxic levels.
- Local anaesthetics are administered in low doses (ropivacaine 0.15–0.2%) or bupivacaine (0.125–0.150%) at 5–7 ml/h.
- Placing a peridural catheter before the surgery and the continuous administration of local anaesthetics can help diminish CVP during resection, given its light effect on the sympathetic tone.
- Recent studies have associated a great possibility of perioperative transfusion.
- When comparing the use of intravenous analgesia and peridural analgesia, it has been possible to observe a 7% reduction in the possibility of postoperative pulmonary complications with epidural analgesia, and an adequate pain management, though also a 26% increase in the use of colloids [86–89].

Epidural analgesia is prescribed jointly with general anaesthesia. Recently it had been associated with an increased use of blood transfusion and a longer hospital stay. It has a low level of complication, with relevant improvement in the patient's clinical condition in the long term [88–90].

The other analgesic technique also considered among the highest standards for the treatment of acute pain is intrethecal epidural analgesia with morphine. The intradural injection of opioids offers both advantages and disadvantages compared to epidural analgesia with local anaesthetics, which should be considered according to each patient.

Advantages:

- It grants quality analgesia for 24 h and a lower use of intravenous analgesic in the following 48 h.
- Only one injection is administered with a small needle, and therefore there is a lower possibility of hematomas and neurological injury in patients with hepatic dysfunction.
- There is no risk of hematoma resulting from the removal of the catheter in the post-operative period.
- It can be easily used in hospitals with little resources.
- It does not produce sustained hypotension.

Disadvantages: (compared to epidural analgesia with local anaesthetics)

- It produces greater sedation and requires greater re-injection of complementary pain killers.
- It presents typical opioid side-effects: immediate and later respiratory depression, urinary retention, pruritus, nausea, and vomiting [91].

The half-life of the subarachnoid morphine is 18–24 h, while the beginning of the effect is between 45 and 75 min. This leads to many anaesthesiologists choosing to administer a joint doses with fentanil (20–25 μg), since its effects comes within 5–10 min and its duration in not longer than 4 h.

The doses of subarachnoid morphine varies between 100 and 500 μg, but a useful dose could be related to weight, established between 2 and 3 μg/kg [92].

Among the central use coadjuvants along with intrathecal opioids, we should mention clonidine which with very low doses reduces acute pain and produces an adequate sedation. It provokes an increase in the sensitive block time and a decrease of the sympathetic tone, with light hypotension within 30 min of being administered [92, 93].

When analgesia after a liver surgery cannot be achieved through the use of a peridural or intrathecal technique, it will then depend on the intravenous administration of morphine, be it through the PCA (patient controlled analgesia) technique or the use of guided administrations according to the patient's degree of pain. In these cases, it is necessary to remember that the morphine's metabolism in hepatic resections could be altered [94].

In liver resections, the abrupt drop of the mass in the liver prevents the development of compen-

satory metabolic mechanisms, and thus the impossibility of reducing the concentration of morphine.

A greater plasma concentration of morphine show a higher risk of sedation, respiratory depression, and other side-effects when the same doses are administered in surgeries that do not involve a decrease of hepatic mass [94–97].

Ex-Situ, Ex-Vivo Hepatic Resection

Surgical teams with wide experience who also carry out hepatic transplants can take on surgeries involving great complexity that include patients with unresectable tumours with conventional techniques.

Ex-situ, ex-vivo surgery consists of removing the liver from the abdominal cavity, with the resection technique used in hepatic transplants to be able to resect the tumour on an adequate table. After the resection, the liver is once again implanted in its abdominal position with the corresponding arterial, venous, and biliary anastomosis.

The blood inside the liver is replaced with preservation liquid between 0 and 4°, which will allow for procedures lasting several hours without major problems when it is once again implanted [98].

Although morbimortality of this technique is higher than in conventional hepatic resections, it is also true that a higher percentage of patients survive, patients who would have no possibility of treatment without such surgery [98, 99].

During the ex-situ surgery, dissection and exeresis of the hepatic tissue does not imply any bleeding and, additionally, can be joined to large vessels that in the posterior implant could ease haemorrhage.

There are still few reports on the long-term results of this surgery, and the experiences described are varied and still incomplete [100].

Some conclusions could be added based on personal descriptions which include the following suggestions:

- Renal failure is one of the most frequent complications.
- The anaesthetic technique *SHOULD NOT* include the reduction of the CVP, since it is not necessary due to the vascular clamping and, additionally, because since it is a longer surgery it is more difficult to maintain hemodynamic stability. Hypovolemia and the clamping on the suprahepatic inferior vena cava are responsible for the I/R [101].

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy—ALPPS

This is a recently introduced surgical technique which has been developed to carry out large liver resections avoiding the development of hepatic insufficiency. This technique allows the inclusion in surgeries of patients who a few years ago could not be operated on because the remaining liver was too small.

It consists of two procedures generally carried out a few days apart. In the first one, the right portal vein is occluded which will allow for the progressive atrophy of that hepatic lobe, since it will not receive the usual blood flow, with the subsequent increase of the left liver [102].

In the second procedure, the right liver resection takes place which is generally more compromised, while the left extensive liver remains with enough functionality. Even partial resections can take place in this latter lobe if the growth has been significant. Thus, hepatic insufficiency is prevented.

In the first procedure, the conventional anaesthetic technique with CVP reduction will be used, with the objective of reducing the size of the liver, allowing the adequate work of the surgeon in a reduced space and decreasing bleeding. In the second procedure, it is not necessary to reduce the CVP; the liver is separated into two sectors, one of which (the right one) will finally be resected, but without a significant trans-section of the tissue. After the first surgery, the patient needs to remain in the intensive care unit until the possibility of hepatic insufficiency has passed.

The anaesthetic techniques, monitoring, and post-operative analgesia are carried out according to the criteria prescribed for general hepatic resections [103].

Final Considerations

It is clear that surgery continues to move forward, and that there are nowadays few patients who can be considered unresectable. In the last few decades, surgery, and anaesthesia have contributed with marvellous advancements which favour the concept of safety. Patients who previously suffered a surgery which left a physical and psychological imprint, and whose recovery would take several months, today are released a few days after surgery. The speed of change in current medicine brings us hope for the future. It is probable we will continue to be astounded by the progress made by medical science [104].

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Intraoperative Evaluation of Resectability

11

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Introduction

Up to now, liver surgery has been the standard treatment of colorectal liver metastases (CLM), provided that complete resection is possible [1–4]. Resection may benefit even patients with numerous colorectal liver metastases (CLM), achieving long-term survival [5–7]. Patients with multiple bilobar nodules are the most complex to treat because a large parenchyma sacrifice is often required, leading to the risk of postoperative liver failure [8]. To prevent this risk, in 2000 Adam et al. proposed two-stage hepatectomy (TSH) [9]. It schedules the cleaning of the less involved hepatic lobe during a first laparotomy, followed or not by the portal vein occlusion of the contralateral lobe in order to induce hypertrophy of the final future liver remnant (FLR), and then the resection of the most involved hemiliver. TSH is now a standardized procedure adopted worldwide, with good short- and long-term results [5, 10–15]. The major drawback of TSH is the drop-out risk: one-third to one-fourth of patients do not receive the second hepatectomy because of disease progression between the two stages [11]. More recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) have been proposed [16], again a staged operation like TSH; however, at the first step in addition to the cleaning of the left liver, parenchymal dissection is carried out, dividing the left lobe from the remnant liver or the two hemi-liver. This policy has allowed the relevant reduction of the drop-out, but the significant increment of the risk of postoperative mortality [17].

To overcome the drop-out risk of TSH, and the risk of mortality of ALPPS, one-stage hepatectomy (OSH) has been proposed, at least for those patients suitable for the first two procedures [16]. OSH schedules the simultaneous resection into a single procedure of all the bilobar lesions. In cases of bilobar superficial lesions, OSH is commonly adopted, but in cases of deep-located CLM, TSH is the preferred option. The authors reported the possibility to perform OSH even in presence of deep-located lesions thanks to the combination of thoraco-phreno-laparotomy, intraoperative ultrasound (IOUS) resection guidance, the detachment of metastases in contact with vessels, and the identification of communicating veins (CV) among hepatic veins to preserve an adequate outflow [18–21]. This strategy

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has minimized the need for parenchyma sacrifice and major hepatectomy [20, 22, 23]. Even if OSH prevents drop-out risks, some theoretical disadvantages have been raised: the technical complexity of the procedure, and the high rate of 0-mm margin (R1) resections (detachment of CLM from vascular structures). For that, the intraoperative evaluation of the tumor staging, the definition of the tumor–vessel relations, and the recognition of the presence of anatomical peculiarities, are fundamental steps together with the specific preparation of the operative field to allow the proper management of the patient in a OSH perspective.

Surgical Technique

The OSH approach scheduling the complete removal of all the multiple bilobar CLM in a single liver resection is based on the following main pillars.

1. The *incision*.
2. The *IOUS* [19].
3. The *liver mobilization*.
4. The *detachment of CLM* from intrahepatic vascular structures.
5. The *flow analysis*.

In this chapter we will get deep into these technical points, discussing the related consequences in terms of surgical strategy and resectability.

Incision

As a general principle, the surgical procedures herein described schedule the surgeon with left hand positioned over the resection area established by means of IOUS, driving together with the IOUS images the liver dissection, and hanging the liver for backflow bleeding control: in this perspective the incision is selected, using J-shaped laparotomy as the standard incision (Fig. 11.1). This last, which includes the removal of the xiphoid process, other than being propaedeutic for liver handling using the left hand (Fig. 11.2), also allows a vertical view of the hepato-caval confluence, both from above with the surgeon standing (Fig. 11.3), and from the right side with the surgeon seated

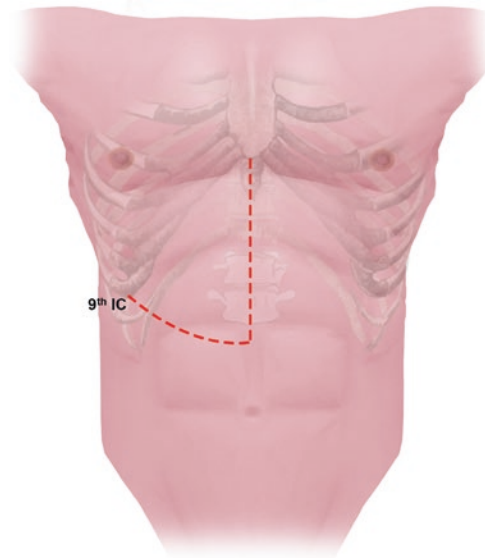

Fig. 11.1 J-shaped laparotomy. The incision starts from the xiphoid process on the midline to approximately 3–4 cm above the umbilicus. Then, it curves laterally towards the right hypocondrium until it reaches to the costal arch, at the level of the ninth intercostal space

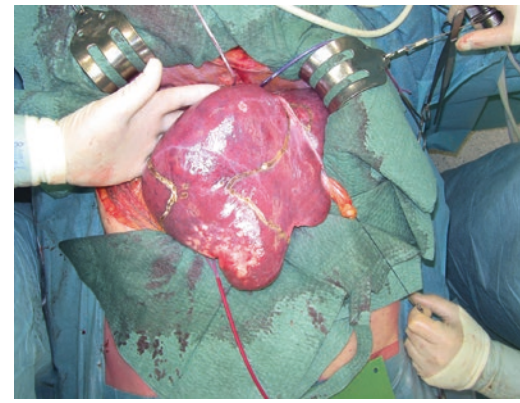

Fig. 11.2 Liver handling after a J-shaped laparotomy. This incision allows the surgeon's left hand to be positioned behind the liver at the posterior aspect of the defined dissection plane. Furthermore, it allows controlling the backflow bleeding by hanging the liver

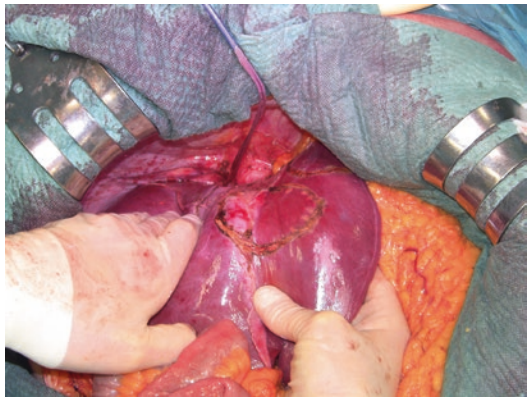

Fig. 11.3 Vertical view of the hepato-caval confluence achieved by means of the removal of the xiphoid process

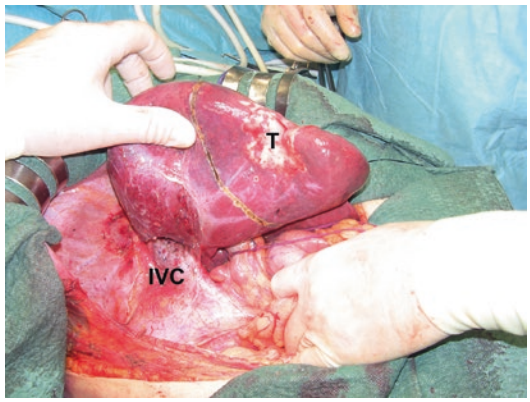

Fig. 11.4 Lateral view of the hepato-caval confluence with the surgeon seated: this perspective facilitates the mobilization of the right liver from the inferior vena cava (IVC). Tumor (T)

once approaching the hepato-caval plane (Fig. 11.4).

When the tumor is located in the para-caval portion of segment 1 or anyway at the hepato-caval confluence, and control of the hepatic veins at this level does not seem fully achievable with the abdominal incision only due to patient characteristics and/or the tumor features (position, relations and size), two solutions are possible, both featured by representing an extension of the J-shaped laparotomy, and both having the aim of extending the working space for the surgeon, especially at the mid–late phases of the dissection and in general when the major veins are approached.

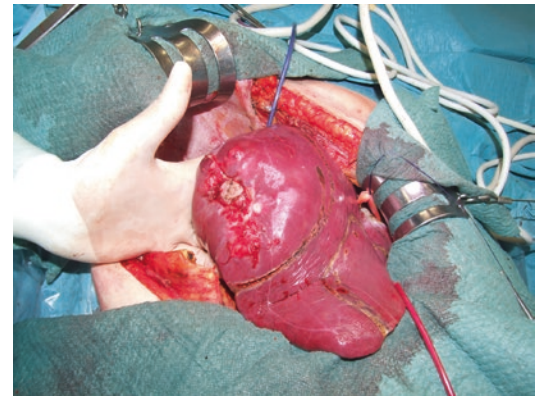

Fig. 11.5 J-shaped thoraco-phreno-laparotomy. The incision is a standard J-shaped laparotomy which continues along the ninth intercostal space up to mid-axillary line on the skin and the posterior axillary on the intercostal space. In this way, the space for the surgeon's left hand is increased, with a better control of the hepato-caval confluence

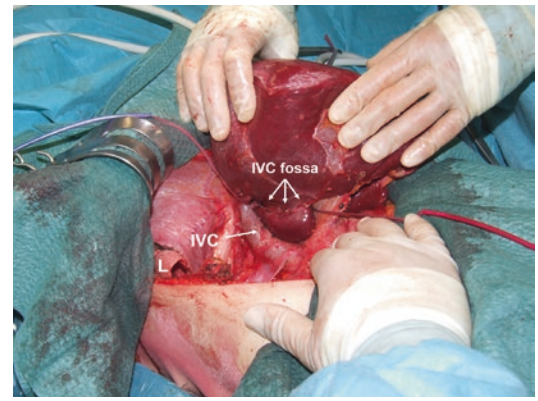

Fig. 11.6 Lateral view of the hepato-caval confluence after a J-shaped thoraco-phreno-laparotomy. The space for the surgeon's left hand is increased with a better view and control of the hepato-caval confluence. Right lung (*L*); inferior vena cava (*IVC*)

A J-shaped thoraco-phreno-laparotomy has the peculiarity of allowing the operator himself to have more space for left-hand positioning and the related liver handling (Fig. 11.5), and moreover opening a better view of the hepato-caval plane, which becomes in line with the visual plane of the operator (Fig. 11.6) [24], this being particularly useful for affording conservative resection of large tumor

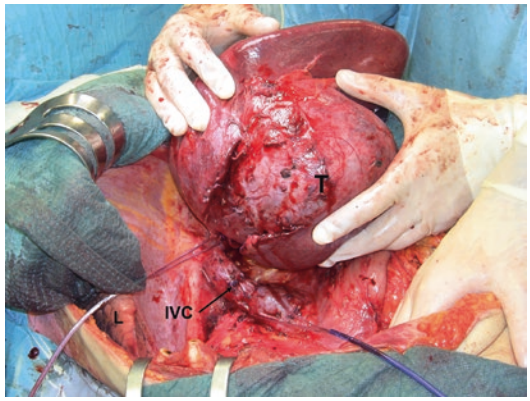

Fig. 11.7 J-shaped thoraco-phreno-laparotomy for a large tumor located in segment 1. The liver and the tumor (*T*) have been completely mobilized from the inferior vena cava (*IVC*)

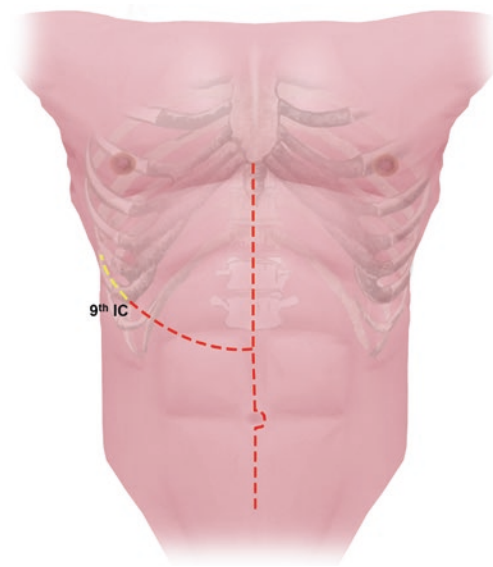

Fig. 11.8 Schematic representation of a J-shaped laparotomy (or thoraco-phreno-laparotomy in *yellow*) with a median extension to the lower abdomen

located in segment 1 (Fig. 11.7) [25]. It is worth stressing the fact that the need for opening the chest may not be evident during mobilization of the liver, but generally it appears crucial during the dissection, and more often at the end of it when the specimen is going to be detached from the hepatic veins, and more space for handling, particularly with the left hand, could be needed. Therefore, paradoxically, chest-opening is a maneuver more frequently carried out by expert surgeons rather than young fellows, since it is a decision taken taking advantage moreover of the background experience which leads the surgeon to foresee the potential difficulties of the resection, and to shift to a thoraco-phreno-laparotomic approach without hesitation.

A median extension to the lower abdomen is selected (Fig. 11.8), particularly in the event of existing median incision: this access facilitates the caudal tilting of the liver once mobilized, and like the previous incision a larger space for positioning the left hand and then for handling the liver. However, this access is not provided by a surgeon's visual plane being perpendicular to the hepato-caval space, and is probably linked to a higher risk of wound hernias.

IOUS Intraoperative Staging

In the case of CLM, the increment of the detection power of IOUS is still relevant. Indeed, in these patients the detection of any tiny nodule undiscovered preoperatively becomes crucial for attempting a reduction of the still high postoperative early recurrence rate [26]. Between 10 and 40% of patients who are carriers of colon cancer have not palpable CLM [27, 28]; as a consequence of that, IOUS exploration of the liver remains crucial, and contrast-enhanced intraoperative ultrasound (CE-IOUS) seems able to enhance its role in this sense. In a maximized parenchymal-sparing perspective, the relevance of an accurate staging is obvious for avoiding missing any tiny lesion, and otherwise resulting in a resection which would be radical but is in fact an R2 operation.

CE-IOUS in these conditions seems useful in a particular setting of patients carrying multiple CLM: those without a bright liver (steatotic) at IOUS [29], and presenting isoechoic CLM [30] (Fig. 11.9).

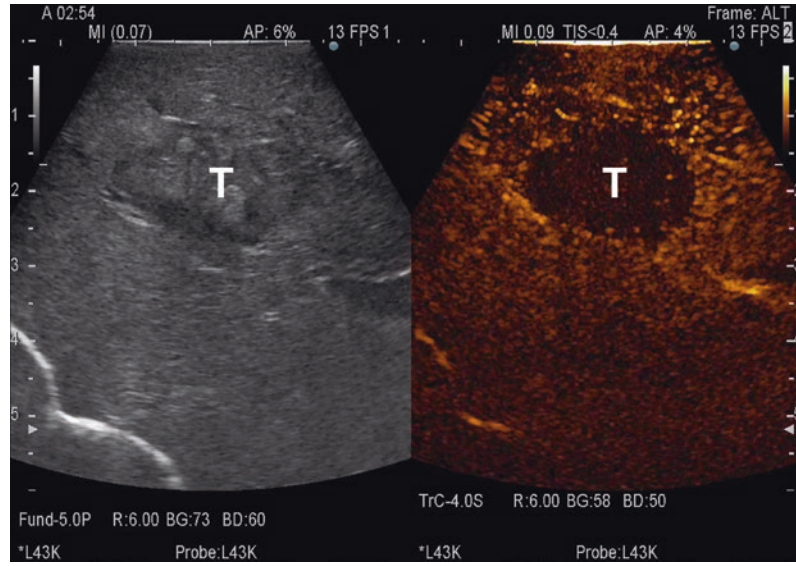

Fig. 11.9 Contrast-enhanced intraoperative ultrasound (CE-IOUS on the *right*) which is better revealing a isoechoic colorectal liver metastasis (*T*) compared with unenhanced IOUS (*left*)

New perspectives can be obtained by using liver-specific contrast agents, which allow prolonged exploration. In a preliminary experience CE-IOUS only showed new lesions in 2 out of 8 patients [31]. More recent studies have shown that the prolonged persistence of the black-hole effect may help also in detecting intraoperatively those metastatic foci which disappear after chemotherapy [32].

Mobilization

For right-sided segmentectomies or subsegmentectomies or sectionectomies, the bare area is dissected and the right hemiliver is mobilized till the surgeon's left hand is positioned behind the hemiliver, sustaining it, and is comfortably positioned over the posterior aspect of the drawn dissection plane (Fig. 11.10). This mobilization should be extensive enough to allow allocation of the surgeon's hand, minimizing the risk during the traction maneuvers of damaging the adjacent structures, and particularly any short hepatic vein which should be preventivly divided whenever at the edge of the dissection area: in the unfortunate event, their damaging could be the source of conspicuous bleeding from the inferior vena cava (IVC), which could even be massive because recognized late since it occurs back to the liver, and could be source of vessel fractures extended to the caval wall, meanwhile the surgeon is concentrated on dissecting the liver.

Therefore, a slight mobilization of the right hemiliver just dividing the triangular ligament and partially or completely the bare area will be accomplished for lesions located in segments 5, 6, 7 inferior and 8 ventral. Conversely, the right side of the retrohepatic IVC is reached for lesions located in the segments 7 and 8 dorsal. If the lesion is close to the hepatocaval confluence (last 4 cm), but not in contact with the hepatic veins, the retro-hepatic caval ligament is not divided, and only the space between the right hepatic vein (RHV) and the middle hepatic vein (MHV) is dissected allowing for finger-tip insertion and eventual compression. The caval confluence of the RHV is recognized following the trajectory of the right inferior phrenic vein, which flows near the RHV at this level and which is a constant landmark (Fig. 11.11) [33].

If the lesion is still right-sided but in contact with an hepatic vein at its caval confluence

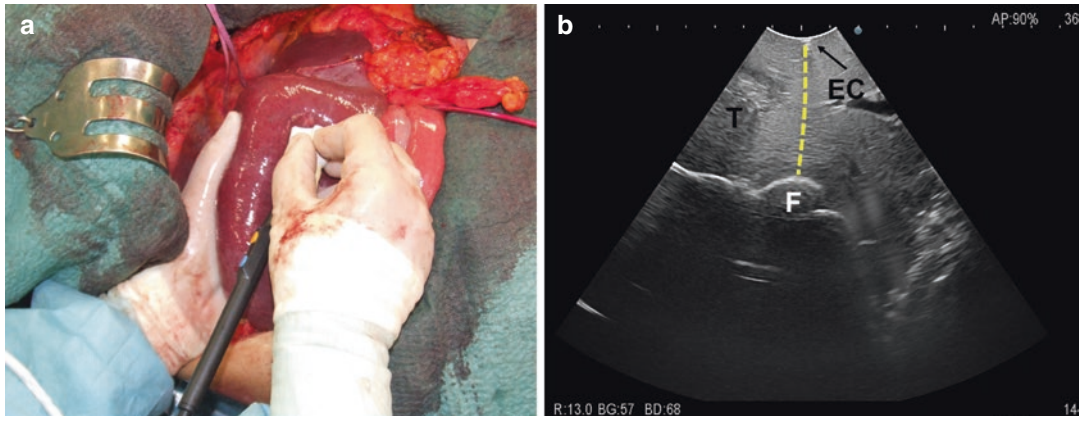

Fig. 11.10 Definition of the resection area. **a** The surgeon's left-hand fingertip and the probe act simultaneously to draw the optimal dissection plane to be followed. **b** The corresponding IOUS image in which the *yellow dashed line* indicates the ideal dissection plane that runs from the echoic shadow generated by the electrocautery interposed between the liver surface and the probe (EC) to the surgeon's fingertip (*F*); tumor (*T*)

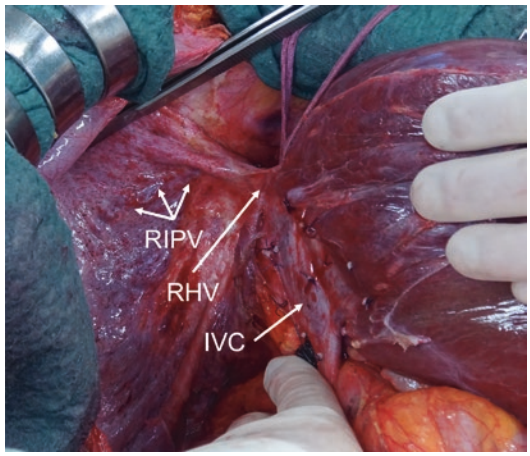

Fig. 11.11 Lateral view of the hepato-caval confluence after a J-shaped laparotomy. The right inferior phrenic vein (*RIPV*) represents a constant landmark for the caval confluence of the right hepatic vein (*RHV*) into the inferior vena cava (*IVC*)

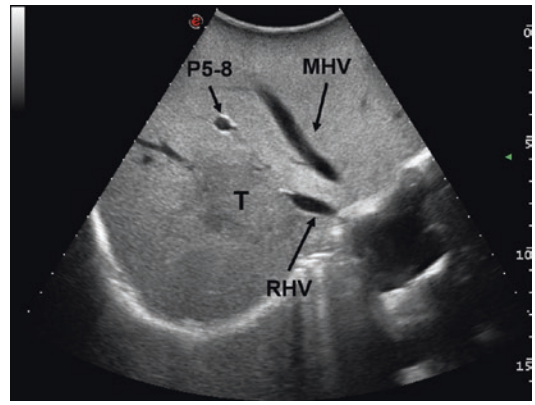

Fig. 11.12 IOUS image that shows a tumor (*T*) in contact with the right hepatic vein (*RHV*) at its confluence into the inferior vena cava (*IVC*). Middle hepatic vein (*MHV*); portal branch to the right anterior section (*P5–8*)

(Fig. 11.12), or is involving the para-caval portion of the segment 1 (Fig. 11.13), liver mobilization includes division of the retro-hepatic caval ligament and exposure of the retro-hepatic IVC until the area to be resected is under control of the surgeon's left hand (surgeon's finger tip being placed over the most distal portion of the planned dissection plane). This detachment proceeds unless control is obtained, even though this means reaching the complete detachment from the IVC (Fig. 11.14): in this case, once the mobilization of

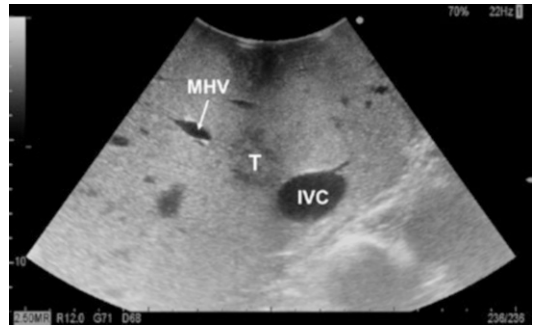

Fig. 11.13 IOUS image showing a tumor (*T*) involving the para-caval portion of the segment 1; middle hepatic vein (*MHV*); inferior vena cava (*IVC*)

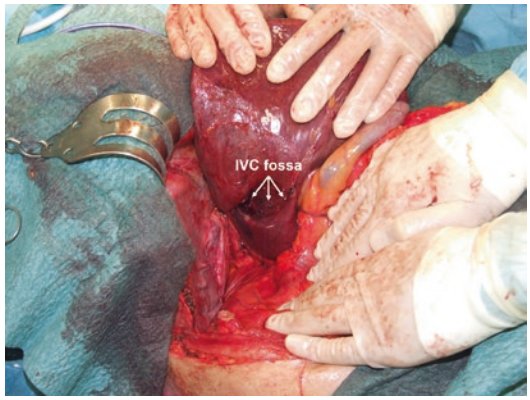

Fig. 11.14 Complete detachment of the liver from the inferior vena cava (*IVC*). The fossa where the IVC was laying is shown

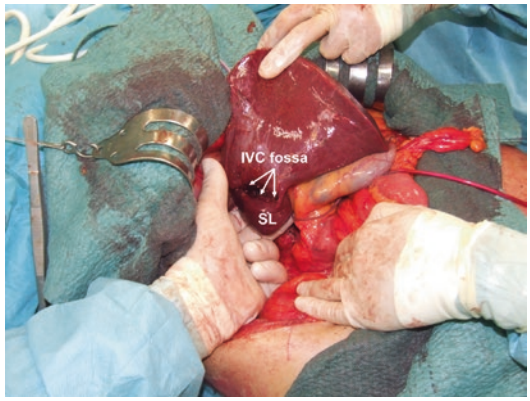

Fig. 11.15 The surgeon's left-hand fingertips are positioned at the edge between segments 2 and 1 where the Arantius' ligament runs, hooking the Spigelian lobe (*SL*)

the segment 1 is complete, and carried out through a right-sided approach, the left-hand fingertips are positioned at the edge between the segment 2 and 1 where the Arantius' ligament runs, somehow hooking the caudate lobe (Fig. 11.15).

For segment 2 and 3 segmentectomies or subsegmentectomies, the left triangular ligament and the left coronary ligament are divided, and the left lobe is handled with the surgeon's left hand.

For lesions located at the segment 4 superior at the hepato-caval junction, the mobilization combines the one described for lesions at the segments 7 inferior and 8 ventral and for those in the left lobe. For these lesions, once a relationship with the main trunk of the MHV is established, particular attention should be paid to the fact that MHV generally features a vertical confluence into the IVC (Fig. 11.16),

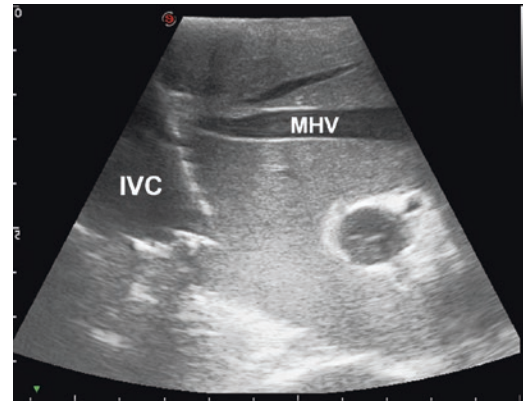

Fig. 11.16 IOUS image showing the perpendicular, and straight confluence of the middle hepatic vein (*MHV*) into the inferior vena cava (*IVC*)

which makes its length shorter than the others, and moreover, its central position makes its compression more difficult; for these reasons, the injury of this vein during the dissection could be source of massive bleeding, and therefore a preventive check of the control of the vein flow by finger compression, or vein encirclement itself, have always to be considered.

A particular trick which deserves to be mentioned is the use of IOUS to help mobilization once there are adhesions which may mask important structures to be recognized and preserved such as the hepatic hilum, the IVC, and the hepatic veins: just positioning the probe to check the position of these structures in relation to the dissection area (the surgeon's finger tips positioned in there would be helpful), and the distance between the latter and the structures themselves, helps to avoid them being damaged, with the severe consequences related with that.

Tumor–Vessel Detachment

The glissonian pedicle may be spared when in contact with an encapsulated hepatocellular carcinoma (HCC) or a CLM, with integrity of the vessel wall appreciable at IOUS without any sign of bile duct dilation (Fig. 11.17). In the presence of bile duct dilation, tumor thrombus, invasion of the vessel wall, and for CLM, contact wider than half of the pedicle circumference, the pedicle must be divided (Fig. 11.18). In these

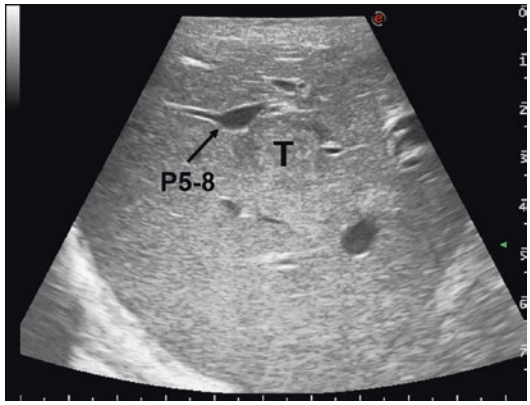

Fig. 11.17 IOUS image showing a CLM (*T*) in contact with the portal branch to the right anterior section (*P5–8*) without signs of infiltration (integrity of the vessel wall and no signs of bile duct dilation). The glissonian pedicle may be spared

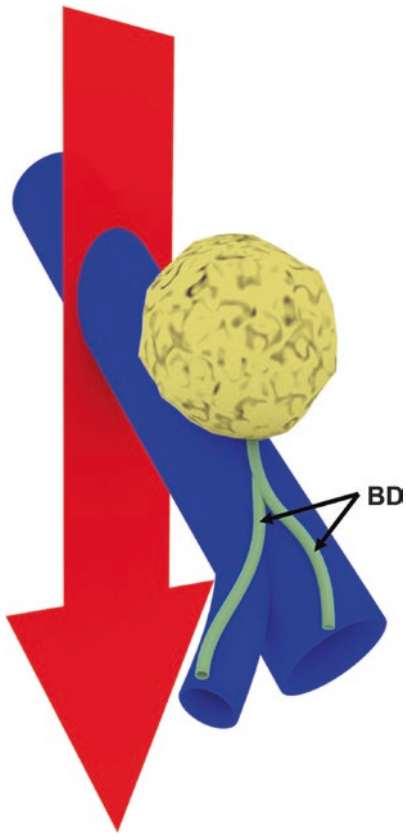

Fig. 11.18 In the presence of bile duct dilation (*BD*), the pedicle must be divided

conditions, extension of the hepatectomy is required for complete tumor clearance.

The hepatic vein may be spared when in contact with an encapsulated HCC with integrity of the vessel wall appreciable at IOUS (Fig. 11.19). Initially for the CLM, its contact was considered an indication for hepatic vein resection; more recently sparing of the hepatic vein is always attempted when the contact extension is less than two-thirds of the vein circumference at IOUS (Fig. 11.20).

Flow Analyses

In the presence of tumor thrombus, invasion of the vessel wall, and contact wider than two-thirds of the vein circumference in CLM, the hepatic vein must be divided (Fig. 11.21). In these conditions, extension of the hepatectomy is not compulsorily considered, even if the hepatic vein is invaded at its caval confluence (the last 4 cm). Indeed, an extension of the resection to the liver parenchyma theoretically drained by the hepatic vein to be resected is considered only if one of the following US signs is missing:

- Presence of accessory hepatic veins at IOUS as an inferior right hepatic vein (IRHV) (Fig. 11.22) [34] in the presence of an invasion at the caval confluence of the right hepatic vein.
- Color-flow IOUS (CF-IOUS) showing hepatopetal blood flow in the feeding portal branch, once the hepatic vein to be resected is clamped [35] by means of encirclement, or more simply by vein compression at its extrahepatic route using a fingertip [36]
- Communicating veins connecting adjacent hepatic veins (Fig. 11.23), these being more easily detectable using CF-IOUS to disclose their presence [19].

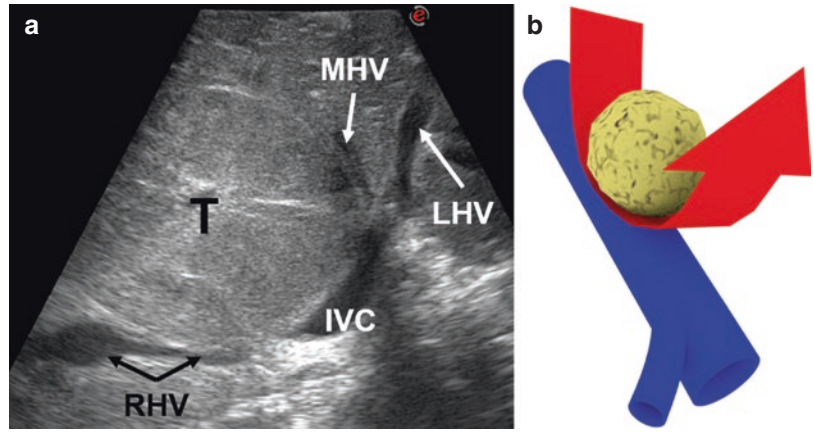

Fig. 11.19 **a** IOUS image showing an encapsulated HCC (*T*) in contact with the middle hepatic vein (*MHV*) and the right hepatic vein (*RHV*). **b** In this case, the hepatic veins could be spared

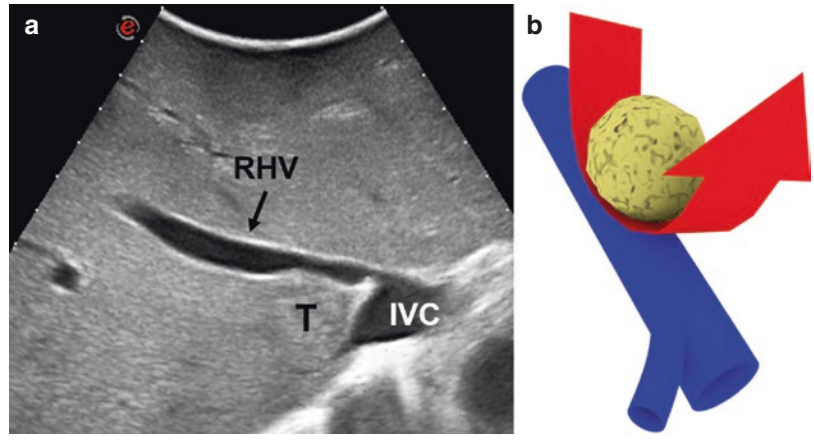

Fig. 11.20 **a** IOUS image showing a CLM (*T*) in contact with the right hepatic vein (*RHV*) at its confluence into the inferior vena cava (*IVC*). **b** In this case, the hepatic vein is spared

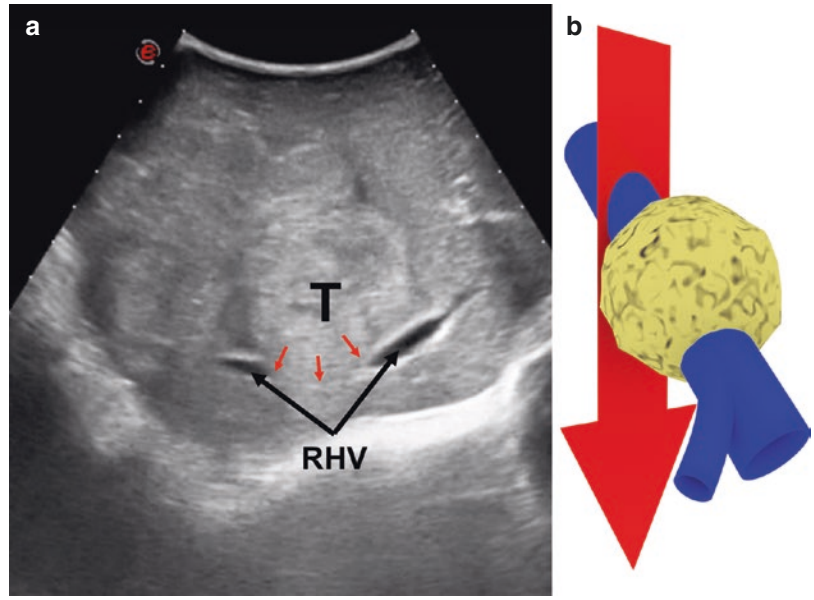

Fig. 11.21 **a** IOUS image showing a CLM (*T*) infiltrating (*red arrows*) the right hepatic vein (*RHV*). **b** In this case, the hepatic vein is resected

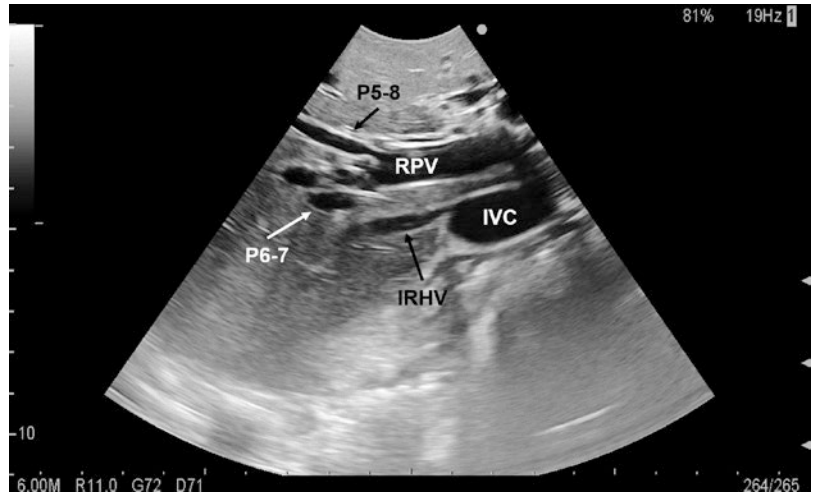

Fig. 11.22 IOUS image showing an inferior right hepatic vein (*IRHV*). This vein typically runs behind the right portal branch (*RPV*). Portal branch to the right anterior section (*P5–8*); portal branch to the right posterior section (*P6–7*); inferior vena cava (*IVC*)

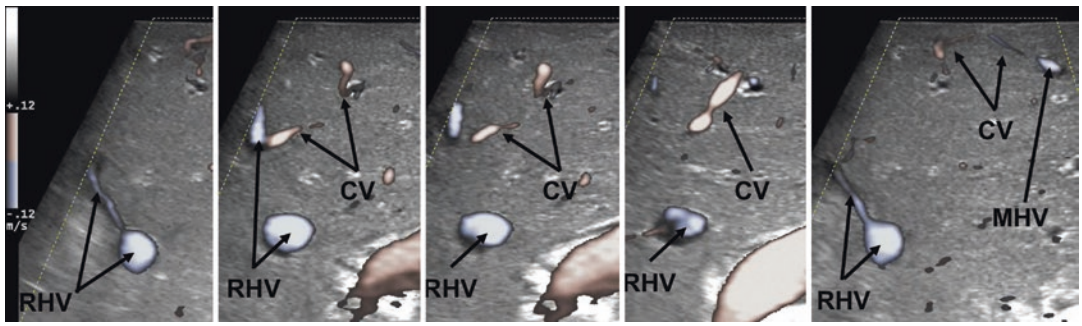

Fig. 11.23 CF-IOUS serial images showing the entire route of a communicating vein (*CV*) connecting the right hepatic vein (*RHV*) and the middle hepatic vein (*MHV*). The detection of these communicating veins represents a crucial step for the "radical but conservative" policy, aimed to minimize the rate of parenchymal sacrifice

New Operations

The aforementioned technical tricks assembled together have made it possible to devise new operation minimizing the rate of major hepatectomy in these patients. These new operations are herein listed.

Systematic Extended Right Posterior Sectionectomy

Systematic extended right posterior sectionectomy (SERPS) is a surgical technique that allows the systematic sparing of part of the right anterior section in the presence of tumors with the presentation shown in Fig. 11.24 [37].

Eligibility Criteria

Patients suitable for SERPS are those with tumors showing one of three conditions:

1. Invasion of the right hepatic vein (RHV) is evident within 4 cm of the hepatocaval confluence, with other lesions involving segment VI and eventually segment VII (Fig. 11.24a).
2. Invasion of the RHV within 4 cm of the hepatocaval confluence is evident, without other lesions involving segment VI, without an inferior RHV (IRHV), and with hepatofugal portal blood flow at CF-IOUS in the portal branch to segment VI (P6) when the RHV is clamped if not already occluded (Fig. 11.24b). In the event an IRHV is present, or, if not, when the flow direction in P6 remains hepatopetal,

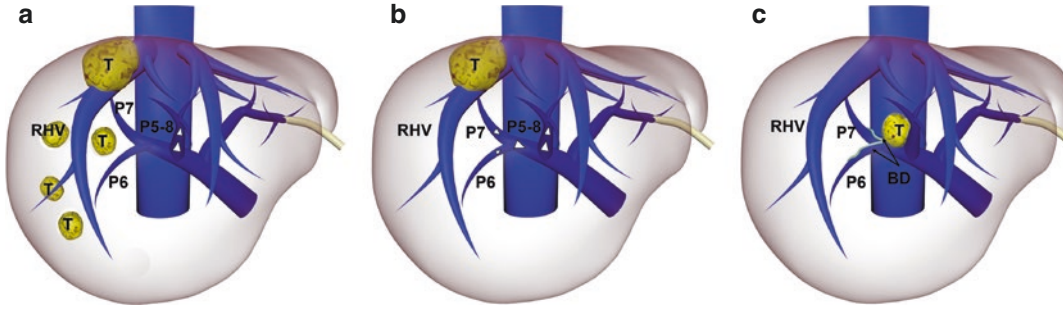

Fig. 11.24 Eligibility criteria for systematic extended right posterior sectionectomy (*SERPS*): in all cases, in CF-IOUS the hepatopetal blood flow must be evident in the portal branch to the right anterior section (*P5–8*) once the right hepatic vein (*RHV*) is clamped if not already occluded. **a** Presence of vascular invasion of the RHV at the hepatocaval confluence (within 4 cm), with tumors (*T*) also in segment 6. **b** Presence of vascular invasion of the RHV at the hepatocaval confluence, without any tumor in segment 6, but without accessory veins and with hepatofugal portal blood flow in the portal branch to segment 6 (*P6*) once the RHV clamped if not already occluded. **c** Presence of vascular invasion of the right posterior portal branch (*P6–7*) or anyway biliary dilation of the bile ducts draining segment 6 and segment 7 (*BD*), with T in contact also with P5–8 but without signs of infiltration

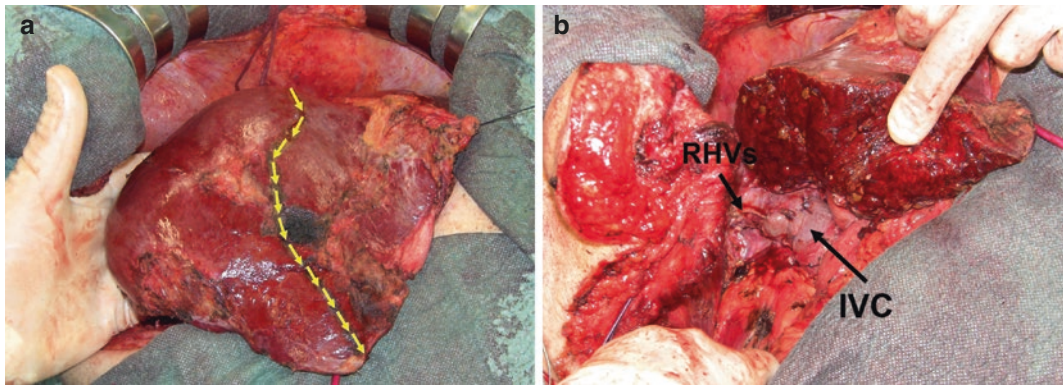

Fig. 11.25 Systematic extended right posterior sectionectomy (*SERPS*). **a** The dissection line (*yellow arrows*) is drawn. **b** The liver at the end of the resection, with the stump of the right hepatic vein (*RHVs*) which is evident; inferior vena cava (*IVC*)

resection of segments VII and VIII together with the RHV is carried out [34] rather than SERPS; therefore, SERPS is applied as an alternative to resection of segments VII and VIII in those patients who do not have proper outflow for segment VI once the RHV is divided.

3. Contact with the right anterior glissonian sheath and a relationship with the right posterior section is evident, with at least one of the following features: contact with the right posterior section determining proximal bile duct dilation, vessel wall invasion, or, for CLM, contact wider than half of the pedicle circumference (Fig. 11.24c, d).

Procedure

In the first two conditions, extension to the right anterior section is tailored to guarantee the complete removal of the tumor, and a dissection line is drawn on the left side of the RHV, which is also resected (Fig. 11.25); flow direction in the right anterior portal branch at CF-IOUS is estimated as previously described, once the RHV is clamped, if it is not occluded. The right anterior pedicle is not necessarily exposed on the liver cut surface. In the third condition, the extension of the resection into the right anterior section is tailored to preserve most of the parenchyma of segment VIII, the tract of the RHV at the hepatocaval confluence, and the left portion of segment V without division of the right anterior pedicle, which is exposed on the cut surface.

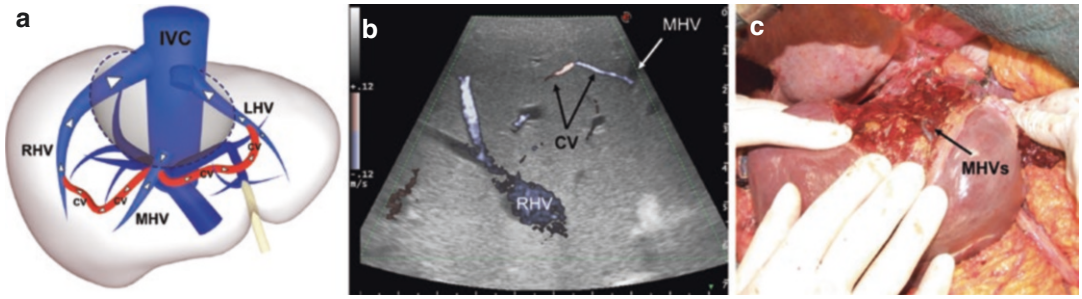

Fig. 11.26 Minimesohepatectomy. **a** Schematically it consists in a limited resection of segment 4 superior and 8 with the invaded tract of the middle hepatic vein (*MHV*). The presence of communicating veins (*CV*) between the MHV itself and one or both of the adjacent hepatic veins allows the blood to be drained by those veins (*white arrows*). **b** CF-IOUS showing communicating veins (*CV*) between the middle hepatic vein (*MHV*) and the left hepatic vein (*LHV*). **c** The liver at the end of the resection with the stump of the MHV (*MHVs*) exposed on the cut surface. Right hepatic vein (*RHV*); inferior vena cava (*IVC*)

Minimesohepatectomy

This procedure represents an alternative to the conventional mesohepatectomy in patients with tumors invading the MHV at its caval confluence; it consists of a limited resection, including the tract of the invaded vein without its reconstruction, sparing part of segment IV, and/or of the right anterior section, as shown in Fig. 11.26a and as described in the next section [23].

Eligibility Criteria

Patients suitable for minimesohepatectomy (MMH) are those with tumors having macroscopic signs of vascular invasion of MHV at hepatocaval confluence on preoperative imaging and IOUS.

Procedure

Mobilization of the right and left hemiliver is tailored based on the size of the lesion and its cranial extension toward the MHV caval confluence. As a general rule, mobilization of the liver to obtain the encirclement of the hepatic veins at caval confluence should be recommended. For planning an MMH (Fig. 11.26a), at least one of these three findings should be confirmed by means of CF-IOUS:

1. Detection on CF-IOUS without, and, if negative, with clamping of the MHV, of communicating veins between the MHV and RHV and/or LHV and/or IVC (Fig. 11.26b).
2. If no communicating veins are evident at CF-IOUS, reversal flow on CF-IOUS in the peripheral portion of the clamped MHV should be confirmed; this finding suggests the existence anyway of communicating veins with the adjacent hepatic veins, despite not found at their direct search.
3. Hepatopetal flow in residual portion of the central segments (IV, V, and VIII); this finding also suggests the existence anyway of communicating veins with the adjacent hepatic veins, despite them not found at direct search.

If none of these findings is confirmed, and especially if hepatofugal flow direction in portal branches to segments V and/or IV inferior is detected, hepatectomy should be extended to the area fed by those portal branches.

The posterior wall of the MHV, or of the tumor involving the paracaval portion, is used as a deep landmark for delimiting the resection area. A crucial point for proper performance of the MMH is, in the event a communicating vein is visualized, detecting and preserving the latter, on the contrary, keeping the dissection nearby the tumor to avoid division of communicating veins which anyway exists although not visualized.

Upper Transversal Hepatectomy (UTH)

For tumors involving more than one and up to all the hepatic veins at the hepato-caval confluence, major hepatectomy or vascular reconstruction, or even unresectabilty are considered. In 1987, Makuuchi et al. [34] reported that once the presence of a thick IRHV is evident at preoperative imaging or at IOUS,

resection of the tumor together with the RHV could be feasible without carrying out a formal right hepatectomy rather limiting the liver tissue removal to that of segments VII and VIII. That was the first paper showing how just the disclosure of an anatomical feature makes feasible surgical procedures otherwise unfeasible. Taking profit of the pioneering experience of Makuuchi, both SERPS and MMH have been released, and we have further proceeded with the herein-described UTH [20].

Eligibility Criteria

Tumor at caval confluence invading two of the hepatic veins at caval confluence in presence of IRHV and communicating veins, or just communicating veins. The tumor could lie over the hilar plate, with contact with but no invasion of the right and left portal branches and the segmental portal branches to segments IV inferior, V, and VI.

Procedure

UTH consists in the total or partial resection of the superior liver segments (II, III, IVsup, VII, VIII) including partially or completely segment I together with up to the three hepatic veins but preserving the inferior portion of the liver, preserving the communicating veins with or without accessory veins to guarantee the outflow of the inferior portion of the liver theoretically drained by the resected hepatic veins (Fig. 11.27).

The US study in these patients should precisely map the accessory veins, IRHV included, and the

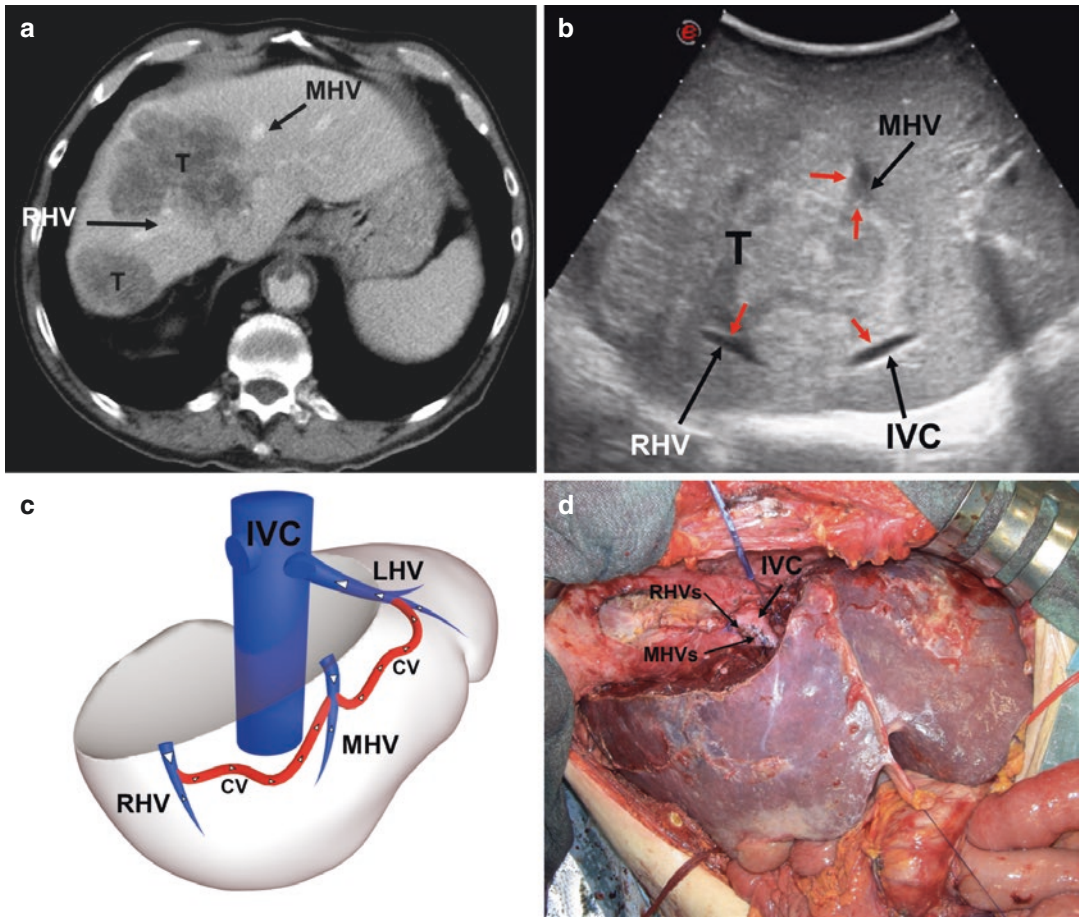

Fig. 11.27 Upper transversal hepatectomy. **a** Indications: pre-operative CT scan showing the right (*RHV*) and middle hepatic veins (*MHV*) affected by two large tumors (*T*). **b** IOUS image that confirms the vascular involvement (*red arrows*) of the MHV, the RHV, and the inferior vena cava (*IVC*) by the tumor. **c** Schema showing the vascular drainage (*white arrows*) at the end of the resection. The preservation of communicating veins between the RHV and the MHV and between the MHV and the LHV is a crucial point to perform this kind of procedure. **d** The liver at the end of the resection; the stumps of the RHV and MHV are shown (*RHVs*, *MHVs*)

communicating veins depicting their pattern is just connecting two adjacent HV or an HV and the IVC: in the latter circumstance, the short hepatic vein connected to the obstructed HV through the communicating vein has to be preserved. Inversely, in the absence of accessory veins flowing into the IVC, even in a similar tumor presentation, the caval plane can fully be freed (Fig. 11.28). Furthermore, adequate exposure and mobilization should allow positioning the left hand at the posterior aspect of the defined dissection plane. For all these reasons, a J-shaped thoraco-phreno-lapatorotic access is frequent in these circumstances. The direct view favored by this incision to the hepato-caval plane allows tailoring the adequate mobilization of the liver from the caval plane; in the event that an IRHV exists, this approach facilitates this mobilization without sectioning this vein root. The access, the mobilization, the in- and outflow mapping and the IOUS-guidance lead to the removal of a relatively small and almost completely diseased part of the liver, preserving the vast majority of the functioning liver parenchyma with adequate in and outflow. The existence and preservation of an IRHV and the communicating vein could make feasible the removal of all the superior segments and of the three HVs [21], sparing also segments IV inf, V and even III, compared with the preservation of just segment VI, as initially described by Makuuchi in 1987 [34].

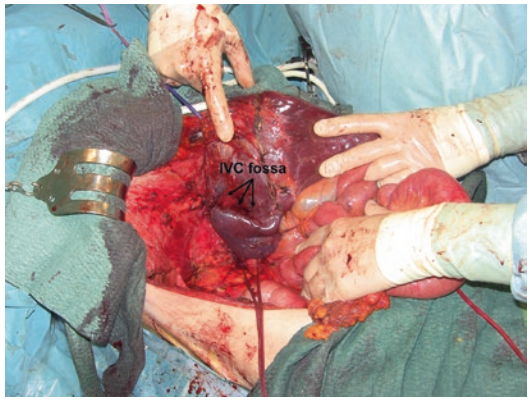

Fig. 11.28 Fully mobilization of the liver in the absence of accessory veins flowing into the inferior vena cava (*IVC*). The fossa where the IVC was laying is shown (*IVC fossa*)

Liver Tunnel

This procedure represents an extension of the MMH, including the total removal of segment I [38, 39].

Eligibility Criteria

Schematic representations of the procedure are shown in (Fig. 11.29). Patients eligible for this

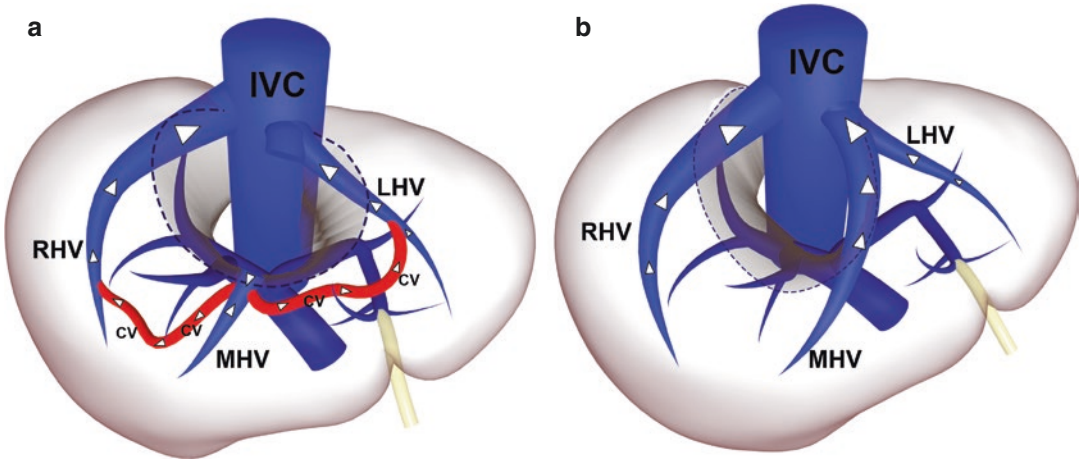

Fig. 11.29 "Liver Tunnel". This procedure represents an extension of the mini-mesohepatectomy, including the total removal of segment I. **a** Schema showing the vascular drainage (*white arrows*) at the end of the resection in case of resection of the middle hepatic vein (*MHV*). The presence of communicating veins (*CV*) between the MHV itself and one or both of the adjacent hepatic veins allows the blood to be drained by those veins. **b** Schema showing the vascular drainage at the end of the resection in case of preservation of the MHV. Inferior vena cava (*IVC*); right hepatic vein (*RHV*), left hepatic vein (*LHV*)

approach are those with tumoral involvement of segments VIII, IV superior and I, including the MHV at its caval confluence (within 4 cm), in presence of communicating veins between the MHV, the RHV, and/or the LHV; similarly, patients with tumors involving segments IV superior or VIII and segment I without invasion of the MHV are eligible too. It consists in a limited resection including or not the MHV [40].

Procedure

Once the anterior surface of the hepatocaval confluence is exposed. Complete mobilization of the liver has to be accomplished with full detachment of the retrohepatic IVC. Resection area is drawn under IOUS guidance. Dissection is started from the low-medial side of the drawn resection area, having the left hand positioned between the posterior surface of the liver and the IVC (Fig. 11.30): the surgeon's left hand fingertips grip the Arantius ligament shifting at IOUS almost on the same axis the MHV and the Arantius ligament itself. MHV resection is carried out according with the criteria described for the MMH procedure. Resection of the MHV or its tumoral detachment is accomplished first then the dissection proceeds towards the posterosuperior aspect of the left glissonian pedicle, then to the right and the dorsal portion of P5–8; finally, the RHV is exposed and following its route towards the IVC the resection is completed (Fig. 11.30c).

Conclusions

The terms "multiple bilobar" CLM includes a wide range of conditions, ranging from oligometastatic superficial deposits to numerous deep-located lesions. The authors suggest that OSH (pure surgical one-stage approach) is possible even for deep-located CLM [16]. This approach relies on: (1) the IOUS-guided detachment of CLM from glissonean pedicles and HVs whenever not infiltrated; (2) the HV resection and reconstruction when they are marginally infiltrated, and (3) an accurate flow analysis, including disclosure of CVs among HVs and of inflow direction after HV clamping, to preserve liver parenchyma despite main outflow resection [16, 21]. All these maneuvers require an adequate incision, e.g., a thoraco-phreno-laparotomy in most cases, and an extensive liver mobilization.

The main potential drawback of this policy is its oncological adequacy. Up to now, a negative surgical margin (≥1 mm) has been the standard for CLM. However, in multiple bilobar deep-located CLM a 0-mm margin is often mandatory to achieve resectability, which is the case in most presentations with tumor–vessel relations. The so called R1vasc, once the CLM is detached from the vessel to which it was in contact although without a clear infiltration, has shown in our experience local recurrence rates which are in line with those experienced removing CLM in the

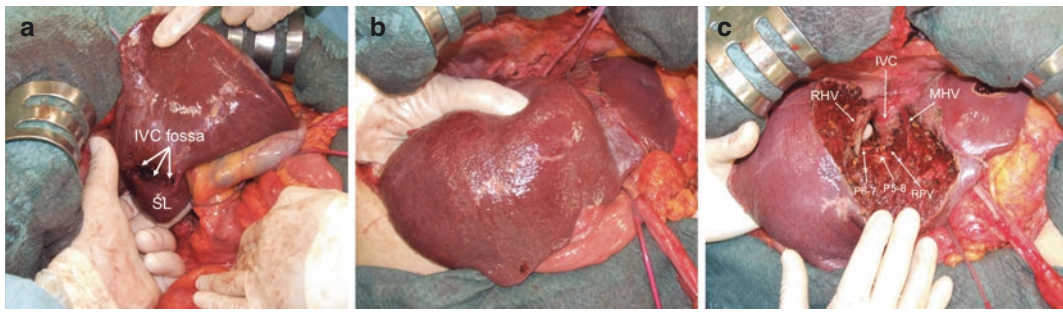

Fig. 11.30 Intraoperative pictures of a "liver tunnel". **a** Full mobilization of the liver with the surgeon's left-hand fingertips positioned at the edge between segments 2 and 1 where the Arantius' ligament runs, hooking the Spigelian lobe (*SL*). **b** The resection is carried out with the surgeon's left hand positioned between the posterior surface of the liver and the inferior vena cava (*IVC*). **c** The liver at the end of the resection. The right hepatic vein (*RHV*) and the middle hepatic vein (*MHV*) are exposed on the cut surface at their confluence in the IVC. Portal branch to the right anterior section (*P5–8*); portal branch to the right posterior section (*P6–7*); right portal vein (*RPV*)

parenchyma and leaving ≥1 mm of tumor-free resection margin [41]. Once confirmed in a large and multi-institutional series, these results are more than encouraging for several reasons:

1. they validate the intraoperative criteria herein described in confirming parenchyma-sparing resectability;
2. they provide more technical solutions;
3. they introduce the concept of a R1 oncologically suitable surgery once the 0-mm margin corresponds to the area of tumor vessel detachment (R1vasc).

In conclusion, the herein-described intraoperative criteria allows radical parenchyma-sparing surgery for multiple CLM, even when some of them show complex and deep located presentations. Thus, these criteria act as fundamental steps in determining the surgical strategy and then the resectability.

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Vascular Control in Major Hepatic Resections

12

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Introduction

After the first major hepatic resection, a left hepatic resection, carried out in 1888 by Carl Langenbuch [1], it took another 20 years before the first right hepatectomy was described by Walter Wendel in 1911 [2]. Three years before, in 1908, Hogarth Pringle provided the first description of a technique of vascular control, the portal triad clamping, nowadays known as the Pringle maneuver [3]. Liver surgery has progressed rapidly since then. Modern surgical concepts and techniques, together with advances in anesthesiological care, intensive care medicine, perioperative imaging, and interventional radiology, together with multimodal oncological concepts, have resulted in fundamental changes. Perioperative outcome has improved significantly, and even major hepatic resections can be performed with morbidity and mortality rates of less than 45% and 4% respectively in high-volume liver surgery centers [4]. Many liver surgeries performed routinely in specialized centers today were considered to be high-risk or non-resectable by most surgeons less than 1–2 decades ago.

Interestingly, operative blood loss remains the most important predictor of postoperative morbidity and mortality, and therefore vascular control remains one of the most important aspects in liver surgery [3, 4]. Bleeding control is achieved by vascular control and optimized and careful parenchymal transection during liver surgery, and these two concepts are cross-linked.

In this chapter, the standard and advanced techniques of vascular control will be described in detail—with main focus on colorectal cancer liver metastases surgery.

Anatomical Fundaments for Vascular Control in Liver Surgery

Thorough knowledge of liver anatomy is the basis of liver surgery. Vascular anatomy of the liver can be explained according to the conventional eight-segments scheme of Couinaud, which is an idealized scheme [5, 6]. The Couinaud scheme is ideally used as a common language to describe the location of lesions, and is based on the localization of the three hepatic veins and the level of the portal bifurcation. The branching of the portal vein defines a right and a left liver, and the three hepatic veins interdigitate with the two portal branches. In reality, liver vascular anatomy

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is much more complex than this idealized scheme. Modern liver surgeons need to be familiar with all anatomical details and variants, in order to perform complex hepatic resections. On the surgical level, understanding of the real branching of the hepatic vessels is necessary—which does not necessarily need to correspond to the theoretical or schematic segmentation [7]. Anatomical orientation in liver surgery is of major importance, as vascular control (resection of selectively devascularized parenchyma) and biliary control (bile ducts run as parts of the portal pedicle) help not only to avoid intraoperative blood loss, but also to avoid postoperative complications (bile leakage, hemorrhage, and infections) [7–9]. In addition, understanding the segmental anatomy is necessary for parenchymal sparing resections, which is especially important in colorectal liver metastases surgery. In many of these patients, two-stage or repeat surgeries take place, and due to chemotherapy-associated liver damage they often suffer from impaired hepatic function, which makes parenchymal sparing resections even more important [10–14].

Inflow–Outflow–Parenchyma

Each major liver resection needs to be planned according to the concept of inflow and outflow vascular control and residual parenchyma. Depending on the localization of the lesion, inflow (hepatic arteries, portal veins, bile ducts) and outflow control (hepatic veins) can be easily achieved, or in more complex cases only be obtained by total hepatic vascular exclusion in combination with ante-situm or ex-situ resection techniques [15]. Certain surgical techniques, such as the maneuver of the lowering of the hilar plate [16] for pedicle (inflow) control, or the Arantius' ligament approach [17] for outflow control of the left hepatic vein, are fundamentals of liver resection techniques. The remaining parenchyma, the so-called future liver remnant, needs to be large enough in size and functional capacity in order to avoid postoperative liver failure. Potential ischemic and ischemia reperfusion damage needs to be taken into account if extended hepatic resections are planned [8]. Parenchymal dissection should be adjusted to the underlying disease and localization of resection, and is also discussed elsewhere in this book [18, 19].

Following, the main strategies according to the inflow–outflow–parenchyma regime are listed:

- Anatomy-related segmental resections and selective vascular control/devascularization of resected areas before parenchymal transection.
- Parenchymal transection phase under low central venous pressure.
- Temporary inflow- and/or combined inflow- and outflow occlusion during the transection phase.

Types of Vascular Control

Occlusion of vascular inflow and/or outflow only makes sense during the actual phase of parenchymal transection. Vascular clamping is generally not used during the phase of mobilization of the liver. The methods of vascular control are summarized in Table 12.1. To minimize excessive blood loss during liver resections, various techniques of vascular control have been developed since the first description of a non-selective inflow occlusion by Pringle in 1908 [3]. Vascular control can be achieved by either inflow- or combined inflow- and outflow control. Both techniques can be either selective or non-selective. Inflow control can be combined and/or performed continuously or in an intermittent fashion, and all techniques of vascular control can be combined with ischemic pre-conditioning of the liver. Hepatic vascular occlusion can also be combined with cold-perfusion techniques and/or ex-situ or ante-situm resection techniques, especially for demanding central resections with involvement of the vena cava and/or hepatic veins. Various review articles and meta-analyses have analyzed the methods of vascular control/occlusion in detail, and randomized-controlled trials investigating the pros and cons of these techniques will be discussed in the next sections [20–24].

Table 12.1 Methods of vascular control in hepatic resections

Inflow control		In- and outflow control	
Non-selective	Selective	Non selective	Selective
Hepatic pedicle occlusion (Pringle maneuver)	Hemihepatic (right or left; hemi-Pringle) or segmental vascular occlusion	Total hepatic vascular exclusion	Selective hepatic vascular occlusion
–Continuous or intermittent			
–With or without ischemic preconditioning			

Portal Triad Clamping

The non-selective inflow occlusion via pedicle clamping is the classical form of vascular control during hepatic resections. The Pringle maneuver is the oldest form of vascular control [3] and also the fastest and easiest to perform, if immediate control of parenchymal bleeding is necessary. The hepatoduodenal ligament is freed from adhesions, in order to avoid injury to the inferior vena cava (IVC) or the duodenum when placing a vascular clamp. Afterwards, the hepatoduodenal ligament is encircled as a whole and a strong vessel loop is placed as a tourniquet, which is kept in place and can be closed permanently or intermittently during phases of parenchymal dissection. The tourniquet (or a vascular clamp) is tightened up to the point where the distal pulse of the hepatic artery disappears. If an aberrant left hepatic artery originates from the gastric artery, it will not be occluded by the pedicle clamping and needs to be occluded separately, if necessary. Pedicle clamping results in a modest cardiac index decrease (due to decreased venous return) and an increase in systemic vascular resistance and mean arterial pressure. In general, the Pringle maneuver is well tolerated, as caval flow is not impaired. After the lowering of the hilar plate maneuver, the pedicle clamping can also be performed separately for the left and right pedicle (Fig. 12.1) and also selectively for the right anterior or posterior pedicle (Fig. 12.2). The Pringle maneuver can be used continuously or intermittently, and also after a short phase of ischemic pre-conditioning to the liver. Numerous randomized controlled trials and meta-analyses have looked at the outcome and best implementation of the Pringle maneuver [25–27]. A recent meta-analysis including eight randomized controlled trials has investigated overall morbidity and mortality, cardiopulmonary and hepatic morbidity, blood loss, transfusion rates, and alanine aminotransferase (ALT) levels in patients undergoing liver resections with or without portal triad clamping. No differences between intermittent portal triad clamping and no

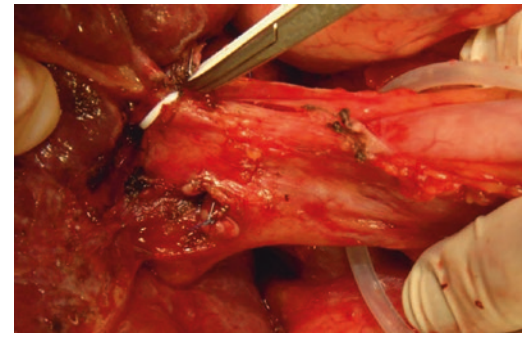

Fig. 12.1 Pringle maneuver. Shown in the figure is a selective Pringle maneuver of the left liver. The transparent loop encircles the portal triad, the white vessel loop is used for a selective left sided hemi-Pringle maneuver

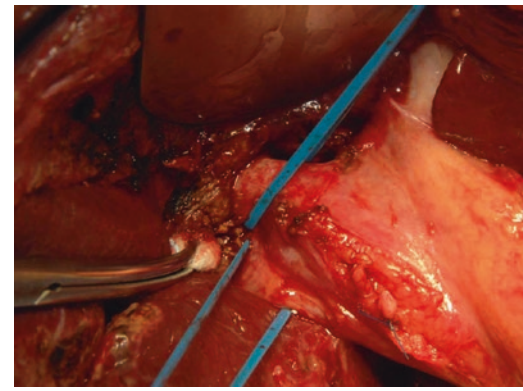

Fig. 12.2 Selective clamping of the right anterior and posterior pedicle. The two blue vessel loops encircle the right anterior and posterior pedicle respectively, and can both be selectively used for clamping and bleeding control

clamping were found with regard to all endpoints. In accordance with these findings, an analysis of patients receiving continuous portal triad clamping with- or without ischemic preconditioning did not reveal any differences with respect to the above mentioned endpoints, except for ALT levels, which were lower in the ischemic preconditioning group [26]. As a conclusion from these analyses, routine use of portal triad clamping cannot be recommended, as it does not alter the intraoperative blood loss or outcome (morbidity and mortality) after liver surgery. Nonetheless, it has its place in liver surgery for individual select cases and/or resection techniques. For example, routine use of the Pringle maneuver can be beneficial during parenchymal resection, using a stapler device, as mean resection time is less than 10 min. No ischemic injury to the liver will occur during this short time, and blood loss can be decreased [19]. With regard to clamping time, it appears safe to use total clamping times of up to 60–90 min, whereas intermittent reperfusion is probably helpful in avoiding ischemic reperfusion injury, at least for a clamping time of more than 20 min: An intermittent portal triad clamping of up to 60 min is probably also safe in patients with compensated cirrhosis, although cirrhosis is known to increase the sensitivity for ischemia reperfusion injury [28–33].

Total- and Selective Hepatic Vascular Exclusion

Total- and selective hepatic vascular exclusion should not be routinely recommended for liver resection procedures. Recent meta-analyses have shown no benefit of hepatic vascular exclusion for perioperative outcome in liver resections [26, 27]. In addition to liver inflow control using portal triad clamping, hepatic vascular exclusion has been proposed to further decrease hemorrhage in major hepatic resections originating from the hepatic veins. Total vascular occlusion for liver surgery combines portal triad clamping with supra- and infrahepatic clamping of the IVC. Selective vascular occlusion is a combination of portal triad clamping with selective hepatic venous clamping, which preserves caval flow and causes less hemodynamic instability. A recent meta-analysis including four randomized controlled trials has compared total- and selective hepatic vascular occlusion with conventional portal triad clamping for liver resections. No differences with regard to outcome, defined as morbidity and mortality, were observed between the portal triad clamping group and hepatic vascular occlusion. However, total hepatic vascular occlusion increased morbidity compared to portal triad clamping alone. Significant differences in reported blood loss were not observed, either [27]. In summary, hepatic vascular occlusion achieved by the above mentioned techniques should be reserved for extended central resections, such as resections involving the vena cava and/or main hepatic veins.

Selective or Total Hepatic Vascular Exclusion Combined with Cold Perfusion

Hypothermic ante-situm or ex-situ resections with total vascular exclusion can be the only possible options to resect central liver lesions with caval involvement [15]. Infiltration of the hepatocaval confluence has been considered a contraindication for liver resections, as achieving tumor-free margins in this area was regarded as technically impossible (Fig. 12.3a, b). However, several techniques, including ante-situm and ex-situ resection techniques, have been introduced to overcome this technical problem, and are discussed in detail elsewhere in this book. These techniques use a total vascular exclusion of the liver, combined with cold perfusion with organ preservation fluid, similar to the back-table preparation of liver transplantation as a common concept [15, 34, 35]. The hypothermic methods allow safer time frames for resection and better access, in comparison to total vascular occlusion without cold-perfusion resulting in warm ischemia and ischemia reperfusion injury, which is not well tolerated by the liver if it exceeds 60 min [36–39]. In general, these types of surgeries should only be

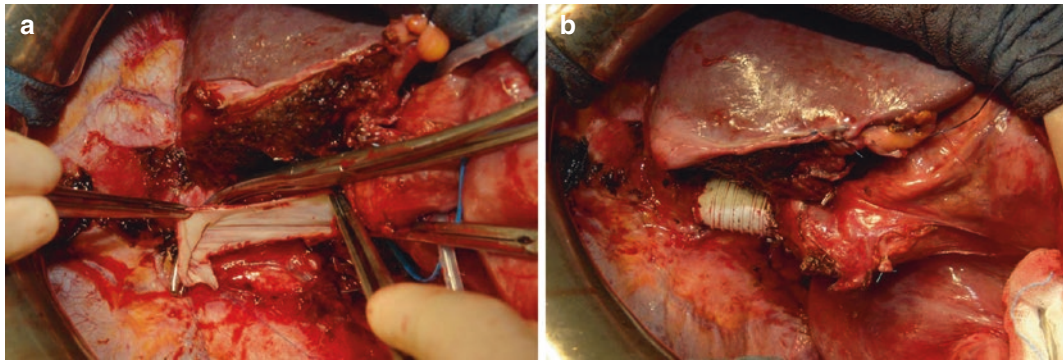

Fig. 12.3 Exclusion of the inferior vena cava. The inferior V. cava is clamped for resection of a central liver metastasis (**a**), and caval flow is reestablished using the implantation of a vascular prosthesis (**b**)

performed in experienced high-volume centers and for selected patients, as reported morbidity is high, with mortality rates reported between 9 and 33%, especially for ex-situ resections [15, 37]. It is noteworthy that 5-year survival rates after extended liver resections including caval resections have been reported as high as 33% [37, 40].

Infrahepatic Inferior Vena Cava Clamping

Bleeding from the hepatic venous system and the sinusoids during parenchymal dissection is directly related to the pressure within the sinusoids in the liver parenchyma. This pressure is directly related to the hepatic venous pressure, which in turn is dependent on the central venous pressure. While clamping the hepatic pedicle for bleeding control during parenchymal transection (Pringle maneuver), bleeding from the sinusoidal system will persist, as the hepatic venous system remains open and patent. A low central venous pressure (CVP) during parenchymal transection phase will result in a low hepatic venous pressure and subsequently less intraoperative bleeding. Achieving a low central venous pressure is not always possible by anesthesiological interventions (fluid restriction, reverse Trendelenburg position, etc.; also see next paragraph), and thus clamping of the IVC has been suggested and

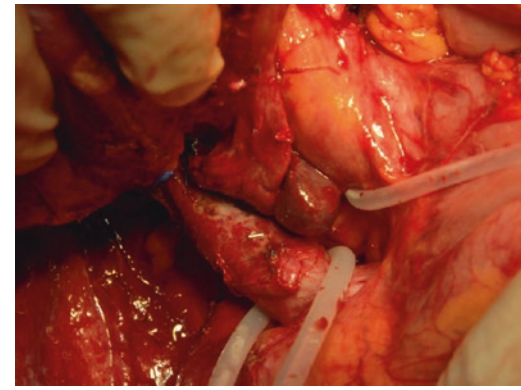

Fig. 12.4 Clamping of the inferior vena cava. Shown is the infrahepatic inferior vena cava which is encircled with a *blue and transparent* vessel loop and can be clamped in order to reduce central venous pressure. Also, the portal triad is encircled with a transparent loop in the same picture

evaluated as an alternative approach to reduce hepatic venous pressure and intraoperative bleeding during parenchymal transection (Fig. 12.4). A recent randomized controlled trial has evaluated the effectiveness and safety of IVC clamping for reduction of central venous pressure and bleeding control during elective hepatic resections. Patients were compared to the standard regime for lowering the CVP, namely anesthesiological means such as fluid restriction. IVC clamping resulted in reduced total intraoperative blood loss, mainly because it significantly lowered the blood loss during the parenchymal transection phase [41].

Mortality and morbidity rates were similar compared to the control group, while there was a significantly increased risk of pulmonary air embolism in the IVC clamping group. Due to hemodynamic instability, IVC clamping, as well as lowering the CVP with anesthesiological means, such as fluid restriction and/or reverse Trendelenburg position, is not possible in 10–20% of the patients [24, 41]. Close monitoring and interaction with the anesthesiological team is mandatory for both techniques.

Anesthesiological- and Pharmacological Interventions

The group of Jones et al. has shown that a central venous pressure of less than 5 cm H_2O during liver transection results in a significantly decreased blood loss and transfusion requirement in liver surgery [42]. Certain non-invasive techniques, such as peri- and intraoperative fluid restriction, can lower the CVP during elective liver surgery. CVP lowering increases the risk for air emboli, and experienced anesthesiological care is necessary in order to maintain the central venous pressure between 2 and 5 cm H_2O during the critical surgical phase. Additional options of lowering the central venous pressure, such as IVC clamping or table positioning (reverse Trendelenburg position), can be used and are discussed above [41].

Further anesthesiological and pharmacological methods to decrease the intraoperative blood loss have been evaluated intensely, such as preoperative haemodilution, autologous blood donation, and transfusion and the use of several drugs or anesthesiological regimes (volatile narcotics) in order to prevent ischemia reperfusion injury [22, 43–45]. At this point of time, these methods/techniques are clinically not important. Further trials are necessary for evaluation of these interventions, as there is no current evidence strong enough to support the routine use of any pharmacological or peri-operative intervention in order to reduce intraoperative blood loss during liver surgery.

Laparoscopic Surgery

In theory, most techniques of vascular control can technically be achieved using minimally invasive surgery. Currently, open surgery is considered to be the safest choice for major hepatic and extended resections. The general advantages of laparoscopic surgery have been widely evaluated in the past. These include smaller incisions, faster recovery, less pain, shorter in-hospital stay, less postoperative hernia, less wound infections, and less intraoperative blood loss (due to intra-abdominal pressure and higher magnification) [46–49]. Recently, the second international consensus conference for laparoscopic liver surgery has defined laparoscopic liver resections for minor resections as standard of care, while major laparoscopic liver resections were regarded as innovative procedures, which are still in the experimental phase [50]. Therefore, these procedures should only be performed at high-volume, specialized liver surgery centers, ideally as part of clinical trials.

Conclusion/Summary

- Intraoperative blood loss is one of the single-most important factors related to postoperative morbidity and mortality in liver surgery and should be minimized.
- Improved resection techniques and improved understanding of surgical liver anatomy have led to decreased blood loss during parenchymal resection in recent years.
- Using techniques of vascular clamping cannot be routinely recommended for every liver resection, as no changes in postoperative outcome are observed.
- In major hepatic resection, vascular control is often necessary, and appropriate techniques have to be used as required.
- Liver surgeons need to be competent in all techniques of vascular control.
- Techniques of vascular control can include the inflow or inflow- and outflow, and can be selective or non-selective (Table 12.1).

– Complex liver resections including the hepatocaval confluence may only be possible in combination of total hepatic vascular exclusion with cold perfusion of the liver (ex-situ or ante-situm resections).
– Pharmacological interventions to reduce intraoperative blood loss have not been proven to be effective so far.

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Two-Stage Liver Surgery

13

Katsunori Imai and René Adam

Although surgical resection is still the only treatment that can provide prolonged survival and a hope of cure for patients with colorectal liver metastases (CLM), nearly 80% of patients with CLM are thought not to be resectable at the time of diagnosis [1–3]. These patients were traditionally considered for palliative chemotherapy. Hence, to increase resectability for those patients is an issue of great importance.

In order to overcome the initial unresectability, considerable efforts have been made during the last two decades. The advent of more effective chemotherapy and developments of surgical procedure and perioperative management have expanded the pool of resectable patients with CLM, and a certain number of patients with initially unresectable CLM can be converted to resectable and have a chance of prolonged survival [4–9]. However, even with effective chemotherapy with or without targeted therapy, conversion rate is reported to be only 20% [9].

For patients with extensive bilateral multinodular CLM, a single hepatectomy, even with specific procedures such as portal vein embolization (PVE) and local ablation therapy is sometimes not sufficient to remove all the tumors, even after significant downsizing by chemotherapy. In 2000, our team reported the concept of two-stage hepatectomy (TSH), based on two sequential procedures to remove multiple bilateral tumors impossible to remove by a single hepatectomy, and using the liver regeneration obtained after the first procedure [10]. During the next decade, this procedure has evolved in combination with PVE and effective chemotherapy, and has been adopted by many specialized centers worldwide with promising short- and long-term outcomes. Herein, we describe the history, surgical technique, indication, drawbacks and outcomes of TSH for CLM.

Introduction and Development of TSH

The concept of TSH was first introduced by our team, in order to treat the patients with multiple bilateral unresectable metastases, since 1992 and published in 2000 [10]. Of note, the indication of this strategy was only bilateral, multinodular tumors which were unable to be resected by a single hepatectomy, even in combination with preoperative chemotherapy and with specific procedures such as PVE and local ablation therapy. This strategy aimed to remove all the intrahepatic tumors sequentially, by

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inducing hypertrophy of the future liver remnant (FLR) before second-stage hepatectomy, to avoid the risk of postoperative liver failure. In this first series, 6 of 13 patients who completed TSH received additional PVE to obtain more sufficient FLR hypertrophy [10]. Subsequently, the team of Strasbourg developed TSH, with routine use of PVE after first-stage and sequential right (or extended right) hepatectomy [11]. Since then, many specialized centers have adopted, developed, and modified this strategy.

Indication of TSH for CLM

Indication of TSH for CLM at Paul Brousse Hospital is summarized in Fig. 13.1. When the multinodular tumors are unilobar and thought to be unresectable because of small FLR (usually less than 30% or 40% when patients received prolonged chemotherapy), we perform PVE followed by one-stage hepatectomy (Fig. 13.1a). When the multinodular tumors are bilobar but the largest tumor size is ≤30 mm and the tumor number in the FLR ≤3, we generally perform standard one-stage hepatectomy with simultaneous local ablation therapy (Fig. 13.1b). When the multinodular tumors are bilobar, the largest tumor size is >30 mm, and/or the tumor number in the FLR >3, in the FLR, we consider TSH (Fig. 13.1c). In the literature, 3–29% of the patients with CLM who were submitted to surgery were planned for TSH (Table 13.1).

Concomitant Extrahepatic Disease

Previous studies reported the rate of concomitant extrahepatic disease to be ranged from 0 to 33% in patients who were planned for TSH (Table 13.2). At Paul Brousse Hospital, the presence of extrahepatic metastases is not considered a contraindication for hepatectomy if these are limited and resectable. When limited extrahepatic disease is located in the abdominal cavity (i.e. pedicular lymph node or peritoneal metastases), resection is performed at the time of first-stage hepatectomy. When extrahepatic

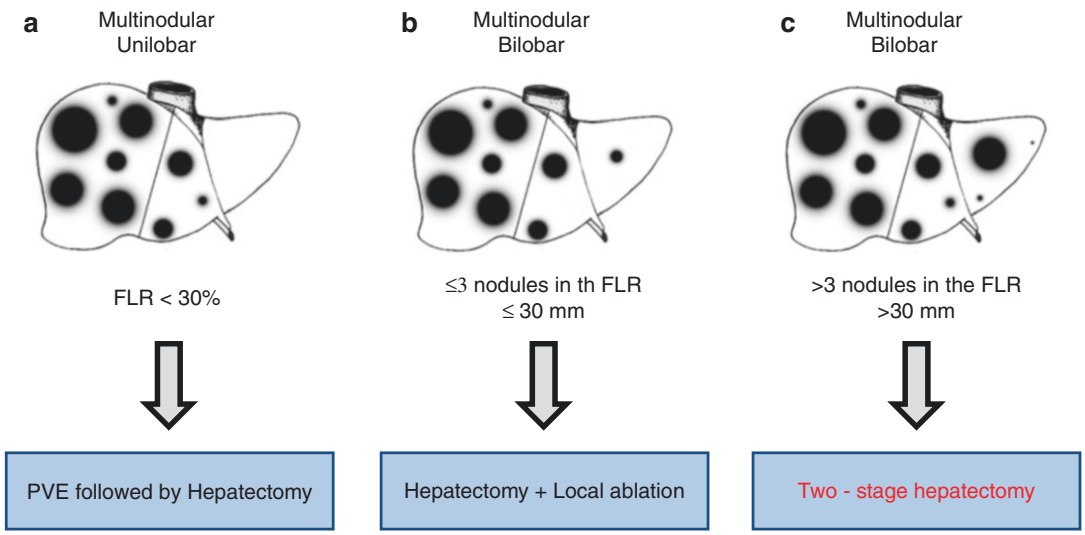

Fig. 13.1 Indication of two-stage hepatectomy for colorectal liver metastases at Paul Brousse Hospital. (**a**) When the multinodular tumors are distributed unilobar and thought to be unresectable because of small future liver remnant (FLR), portal vein embolization (PVE) followed by one-stage hepatectomy is performed. (**b**) When the multinodular tumors are distributed bilobar but the largest tumor size is ≤30 mm and the tumor number in the FLR ≤3, standard one-stage hepatectomy with simultaneous local ablation therapy is performed. (**c**) When the multinodular tumors are distributed bilobar, the largest tumor size is >30 mm and the tumor number in the FLR >3, two-stage hepatectomy (TSH) is performed

Table 13.1 Demographics of studies of two-stage hepatectomy for colorectal liver metastases in the literature

Study	Year	Country	Study periods	Total No. of surgically treated pts. for CLM	No. of pts. planned for TSH	Percentage of pts. planned for TSH (%)
Lygidakis et al.	2004	Greece	1991–2003	NR	62	NR
Garcea et al.	2004	UK	2001–2003	446	11	3
Pamecha et al.	2008	UK	1999–2005	280	14	5
Homayounfar et al.	2009	Germany	2005–2007	NR	24	NR
Tsai et al.	2010	USA	1994–2008	720	45	6
Karoui et al.	2010	France	2000–2008	NR	33	NR
Tsim et al.	2011	UK	2003–2006	131	38	29
Brouquet et al.	2011	USA	2002–2010	890	65	7
Narita et al.	2011	France	1996–2009	753	80	11
Stella et al.	2012	France	1995–2009	1042	56	5
Bowers et al.	2012	UK	2004–2010	NR	33	NR
Tanaka et al.	2012	Japan	2003–2011	232	24	10
Turrini et al.	2012	France	2000–2010	NR	48	NR
Muratore et al.	2012	Italy	1997–2009	653	47	7
Cardona et al.	2014	USA	2000–2009	1188	40	3
Giuliante et al.	2014	Italy	2002–2011	NR	130	NR
Faitot et al.	2015	France	2004–2010	NR	50	NR
Imai et al.	2015	France	2000–2012	845	125	15

When multiple publications were identified from the same institutions, only the most recent publication was included.
CLM colorectal liver metastases, *TSH* two-stage hepatectomy, *NR* not reported

Table 13.2 Perioperative features at first-stage hepatectomy

	Concomitant extrahepatic disease (%)	Preoperative chemotherapy (%)	Simultaneous resection of primary tumor (%)	Major resection (%)	Concomitant use of local ablation therapy (%)	Intraoperative PVE/PVL (%)	Morbidity (%)	Mortality (%)
Lygidakis et al.	NR	NR	100	0	100	100	11	0
Garcea et al.	0	100	0	28	0	NR	NR	0
Pamecha et al.	0	100	0	14	0	0	0	0
Homayounfar et al.	4	75	0	0	29.2	100	13	0
Tsai et al.	7	71	49	25	23	73	26	4
Karoui et al.	12	61	100	0	15	52	21	0
Tsim et al.	0	97	0	NR	0	0	11	0
Brouquet et al.	0	100	29	3	3	0	25	0
Narita et al.	14	84	31	0	32	4	14	0
Stella et al.	6	96	49	4	76	61	37	0
Bowers et al.	0	85	31	23	9	3	23	0
Tanaka et al.	33	100	NR	5	0	86	29	0
Turrini et al.	0	100	37	0	67	0	10	0
Muratore et al.	26	79	0	4	0	23	19	0
Cardona et al.	0	100	100	2	9	9	14	0
Giuliante et al.	26	87	55	3	4	52	17	0
Faitot et al.	10	90	NR	NR	38	88	18[a]	2
Imai et al.	26	98	30	2	10	76	14[a]	1

[a]Major complication (Clavien ≥ III)
PVE portal vein embolization, *PVL* portal vein ligation, *NR* not reported

disease is located outside the abdomen (such as lung metastasis), resection is usually performed 2–3 months after the second-stage hepatectomy, provided that the disease remains controlled by chemotherapy. In our recent study (2000–2012), concomitant extrahepatic disease was observed in 26% of the patients who were planned for TSH [12]. Among them, resection of concomitant extrahepatic disease was consequently achieved in 42%. Remaining concomitant extrahepatic disease was not resected mainly because of disease recurrence after second-stage hepatectomy or in cases of TSH failure. In our treatment strategy, the presence of extrahepatic disease was neither a predictive factor of TSH failure nor a prognostic factor of survival after TSH (unpublished data). What is crucial however, is to envisage resection of concomitant extrahepatic disease when the disease is controlled by chemotherapy.

Surgical Procedures of TSH

First-Stage Hepatectomy

At Paul Brousse Hospital, during the first-stage hepatectomy, either the most invaded hemiliver (usually the right) is resected, or, in most cases, the less-invaded liver lobe (FLR) is cleared of its metastases [10, 12, 13]. In the literature, limited hepatectomy (<3 segments) was mainly performed during first-stage hepatectomy (Fig. 13.2). Clearance is generally obtained by non-anatomical resection (Fig. 13.2a), and local ablation therapy such as cryotherapy and radiofrequency ablation (RFA), is only used in combination with hepatectomy for the treatment of unresectable tumors deeply located in the FLR with the purpose of sparing liver parenchyma of the FLR. Portal vein ligation (PVL)/PVE is routinely performed intraoperatively during the

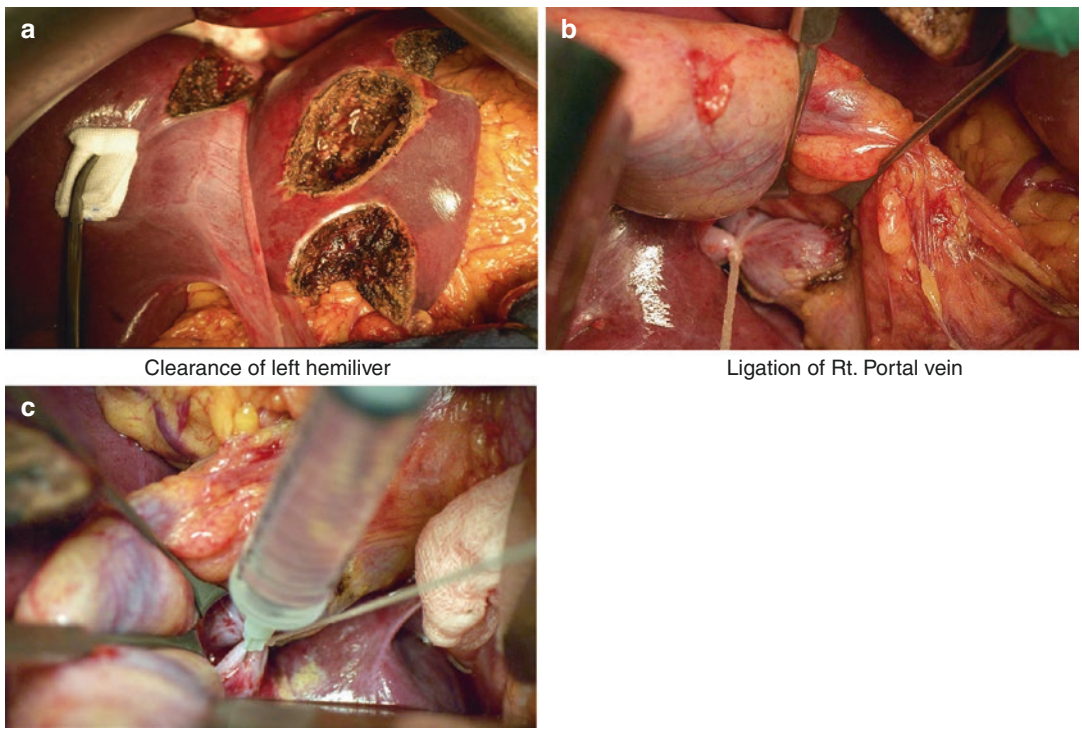

Fig. 13.2 Procedure of two-stage hepatectomy. (**a**) During the first-stage hepatectomy, in most cases, the less-invaded liver lobe is cleared of its metastases, usually by non-anatomical resection. (**b**) Ligation of right portal vein. (**c**) Embolization by dehydrated ethanol. For the safety of second-stage hepatectomy, portal vein ligation and embolization is routinely performed during first-stage hepatectomy

first-stage. Previous studies reported that stimulation of liver hypertrophy could also accelerate intrahepatic tumor progression after PVE [14–17]. From this aspect, what is essential during first-stage hepatectomy is that all tumors in the FLR should be removed to avoid tumor regrowth, leading to the failure to proceed to second-stage procedure.

Portal Vein Ligation/Embolization

At Paul Brousse Hospital, for the safety of second-stage hepatectomy, PVE using dehydrated ethanol in combination with ligation is routinely performed during first-stage hepatectomy (about 82%) (Fig. 13.2b, c) [12]. If PVL/PVE is not performed during first-stage, percutaneous PVE is added after first-stage (about 18%). The volume of FLR is evaluated by volumetric computed tomography (CT) analysis 4–6 weeks later. Whether PVL/PVE is performed during or after first-stage hepatectomy seems to depend on institutions (Tables 13.2 and 13.3).

Second-Stage Hepatectomy

Second-stage hepatectomy is performed when: (1) curative resection is possible, (2) the remaining disease is controlled by chemotherapy, and (3) the volume of FLR is thought to be sufficient. When the most invaded hemiliver is resected during first-stage, tumor clearance is performed from the remnant liver, usually by non-anatomical partial resection. When, in most cases, the less-invaded liver lobe is cleared of its metastases during first-stage, the tumor-bearing liver lobe is anatomically removed (usually lobectomy or extended lobectomy). In the literature, major hepatectomy (≥3 segments) was mainly performed during second-stage hepatectomy (76–97%) (Table 13.3).

Concomitant Use of Local Ablation Therapy

Local ablation therapy including cryotherapy and RFA is only used in combination with hepatectomy for the treatment of unresectable tumors

Table 13.3 Perioperative features at second-stage hepatectomy

	Interval duration (days)	Interval PVE (%)	Interval chemotherapy (%)	Major hepatectomy (≥3 segments) (%)	Concomitant use of local ablation therapy (%)	Morbidity (%)	Mortality (%)
Lygidakis et al.	40	0	100	77	0	11	3
Garcea et al.	150	NR	0	78	0	33	0
Pamecha et al.	210	35.7	100	73	0	27	0
Homayounfar et al.	42	0	0	73	11	58	5
Tsai et al.	135	4	62	80	17	26	6
Karoui et al.	111	15	76	92	4	32	4
Tsim et al.	NR	95	13	NR	0	33	0
Brouquet et al.	32	70	19	85	0	49	0
Narita et al.	92	92	31	95	8	54	0
Stella et al.	NR	0	84	92	12	49	0
Bowers et al.	84	72	15	59	7	56	4
Tanaka et al.	NR	0	52	76	0	38	0
Turrini et al.	72	100	29	91	59	20	6
Muratore et al.	114	56	53	94	0	44	0
Cardona et al.	150	60	86	83	30	60	0
Giuliante et al.	39	48	30	97	NR	35	4
Faitot et al.	NR	0	32	NR	NR	NR	NR
Imai et al.	96	16	74	93	6	33	3

PVE portal vein embilization

deeply located in the remnant liver, as described above. Recent systematic review reported that concomitant local ablation therapy such as cryotherapy, microwave or RFA, was performed in 17% (range, 0–67%) at first-stage and in 12% (range, 0–59%) at second-stage, respectively (Tables 13.2 and 13.3) [18]. At Paul Brousse Hospital, between 2000 and 2012, concomitant local ablation therapy was performed in 9.6% (12/125) at first-stage and in 6.2% (5/81) of patients at second-stage, respectively, and concomitant use of local ablation therapy did not influence the failure of TSH and the short-term outcome [12]. Furthermore, long-term outcome after TSH is also not affected by the concomitant use of local ablation therapy (unpublished data).

Primary Tumor Resection in Case of Synchronous Presentation

If the primary tumor is synchronous presented, its resection is performed at the time of first-stage hepatectomy or after second-stage hepatectomy. A Recent review reported that simultaneous resection of primary tumor was performed in a median proportion of 30% at first-stage hepatectomy [19]. However, whether or not the resection of primary tumor is performed during first-stage hepatectomy (when still in place) seems to depend on institutions (Table 13.2). In our recent study between 2000 and 2012, 46% of the patients who were planned for TSH had primary tumor in place at the moment of first-stage hepatectomy [12]. Among them, 66% underwent simultaneous colorectal resection during the first-stage, while 19% did so after the second-stage hepatectomy. Colorectal resection could not be performed on remaining 16% of the patients either because of failure of TSH or hepatic recurrence after second-stage hepatectomy. Previous studies reported that simultaneous resection of the primary tumor with first-stage hepatectomy did not affect the postoperative course [20, 21] and has the advantage to, reduce the number of procedures and optimize administration of chemotherapy [20].

Chemotherapy

Preoperative Chemotherapy

Preoperative chemotherapy is administered in almost all the cases before TSH in most institutions including ours (Table 13.2). We evaluated with CT, the response to chemotherapy after every four cycles of treatment, according to the Response Evaluation Criteria in Solid Tumors criteria [22]. In principal, hepatectomy is performed when the tumors are responding to chemotherapy (or at least in case of stable disease). In our recent update, disease progression during first-line chemotherapy and preoperative chemotherapy cycles >12 were the independent predictive factors of failure of TSH, together with carcinoembryonic antigen (CEA) >30 ng/mL and tumor size >40 mm. If we consider performing TSH for patients with extensive CLM, optimal first-line chemotherapy with short duration is crucial to prevent the failure of TSH [12].

Interval Chemotherapy

To decrease the drop-out rate from second-stage because of disease progression between the two stages, we generally recommend interval chemotherapy. Interval chemotherapy is delivered 3 weeks after first-stage hepatectomy using the same regimen as that used before first-stage hepatectomy. In our recent study, however, although nearly three fourth of the patients received interval chemotherapy, the interval chemotherapy failed to decrease the rate of TSH failure [12]. Another study also reported that interval chemotherapy could not decrease the failure rate of TSH [23]. We should also take into account the risk of liver injury by prolonged chemotherapy. To our knowledge, there is no study demonstrating the evidence of efficacy of interval chemotherapy for the feasibility or for survival. Thus the efficacy of interval chemotherapy is still uncertain and needs to be validated.

Postoperative Chemotherapy

At Paul Brousse Hospital, chemotherapy after second-stage hepatectomy is routinely recommended, if the patients' condition allows. Our previous study demonstrated that postoperative chemotherapy was an independent prognostic factor of survival after TSH [13]. However, recent update of our data failed to demonstrate the efficacy of postoperative chemotherapy on survival after TSH by multivariate analysis (only by univariate analysis, unpublished data). Therefore, the usefulness of routine postoperative chemotherapy (adjuvant setting) still needs to be demonstrated.

Drawbacks of TSH

The main drawback of TSH is obviously the failure to complete both two sequential procedures. Recent systematic review reported that failure rate of TSH ranges 0–36% (median, 23%), and the main reason of failure was disease progression between the two stages (56–100%, median, 100%) [19]. At Paul Brousse Hospital, between 2000 and 2012, 125 patients with initially unresectable, multiple, bilobar CLM were scheduled to undergo TSH. Among them, 44 patients could not proceed to second-stage (failure rate 35.2%). The reasons of failure of TSH were tumor progression in 39 patients (intrahepatic: 20, extrahepatic: 13, both: 6), insufficient volume of FLR in 3, poor general condition in 1, and postoperative mortality in 1 [12]. The overall survival (OS) after first-stage hepatectomy for patients who failed TSH was significantly lower than those who complete TSH (1, 3, 5-year OS rate: 66.3%, 14.0% and 0% vs. 95.0%, 69.0%, and 44.2%, $P < 0.0001$, Fig. 13.3) [12]. Therefore, to prevent the failure of TSH is crucial for patients who are planned for TSH, and this requires the prevention of disease progression after first-stage hepatectomy.

One possibility to prevent disease progression after first-stage is interval chemotherapy. However, there is little evidence supporting the routine use of interval chemotherapy in terms of preventing failure of TSH, as mentioned above. In addition, prolonged chemotherapy may lead to increase postoperative complications such as postoperative liver failure [24, 25]. Regarding interval chemotherapy, further large-scale study will be necessary.

In the literature, some predictive factors for failure of TSH have been reported (Table 13.4) [12, 26–30]. Recently, we identified four independent predictive factors for failure of TSH (Tumor progression on first line chemotherapy, number of chemotherapy cycles >12,

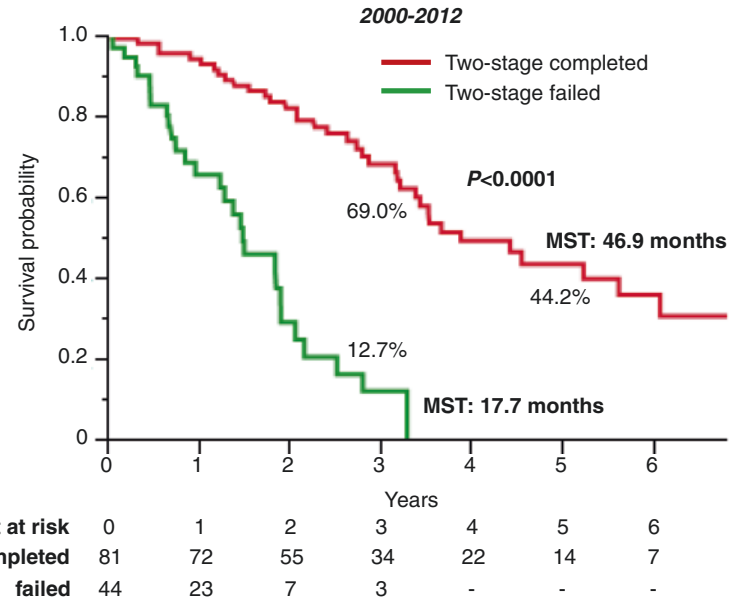

Fig. 13.3 Overall survival for patients who completed two-stage hepatectomy ($n = 91$) or failed ($n = 44$), between 2000 and 2012. *MST* mean survival time

Table 13.4 Reported predictive factors for failure of two-stage hepatectomy

Study	Year of publication	Country	No. of pts	Failure rate (%)	Predictive factors for failure of TSH	
					Univariate	Multivariate
Tsai et al.	2010	USA	45	22	• Higher tumor number • No preoperative chemo	• ND
Narita et al.	2011	France	76	20	• Age ≥ 70 • ≥3 tumors in the FLR • CEA > 200 (ng/mL) before PVE	• Age ≥ 70 • ≥3 tumors in the FLR
Turrini et al.	2012	France	42	19	• Combined resection of primary tumor • Interval chemotherapy	• Combined resection of primary tumor
Giuliante et al.	2014	Italy	126 (multicenter)	22	• Disease progression during chemo	• Disease progression during chemo
Faitot et al.	2015	France	50	24	• Male gender • Vascular invasion on primary • >5 tumors • Segment 1 metastases • Need for chemo change • Need for >3 curative treatments • Microscopic biliary invasion	• Nothing
Imai et al.	2015	France	125	35	• CEA > 30 (ng/mL) • Tumor size > 40 (mm) • No. of chemotherapy cycles > 12 • No. of chemotherapy lines > 1 • Disease progression during first-line chemo	• CEA > 30 (ng/mL) • Tumor size > 40 (mm) • No. of chemotherapy cycles > 12 • Disease progression during first-line chemo

TSH two-stage hepatectomy, *ND* not done, *FLR* future liver remnant, *CEA* carcinoembryonic antigen, *PVE* portal vein embolization

maximum tumor size >40 mm and CEA at hepatectomy >30 ng/mL), and a predictive model for failure of TSH was developed based on logistic model [12]. For patients without any risk factor, the probability of failure was 10.5%. The addition of each subsequent factor increased the risk to 43.5%, 72.7%, and 88.5% for one, two, three and four factors, respectively. Based on this predictive model, we can assess the probability of failure of TSH before surgery. This model can contribute to a better selection of patients who will be submitted to TSH.

Short-Term Outcome

In our first report in 2000, we reported that the mortality rates were 0% and 15% after first-stage and second-stage hepatectomy, respectively, and postoperative complication rates were 31% and 45%, respectively [10]. Through the process of surgical development of TSH procedure, our recent update (2000–2012) revealed that 90-day mortality rates were 0.8% and 2.5% after first-stage and second-stage hepatectomy, respectively (P = 0.97), and postoperative complication (Clavien ≥ III [31]) rates were 14.4% and 33.3%, respectively (P = 0.0015) [12]. One patient died of acute myocardial infarction 10 days after first-stage hepatectomy, and two patients died of postoperative liver failure after major hepatectomy (≥3 segments) during second-stage. In the literature, postoperative complications after first-stage occurred in 0–37% of patients, and the postoperative mortality was 0–4%, respectively (Table 13.2). On the contrary, postoperative complications after second-stage occurred in 11–60% of patients, and the postoperative mortality was 0–6%, respectively (Table 13.3). Although the complications are obviously more frequently observed after second-stage than after first-stage, these morbidity/mortality rates are thought to be almost equivalent, compared to one-stage hepatectomy. These findings suggest that TSH procedure is no longer an experimental surgery and can be performed with acceptable morbidity/mortality rates.

Long-Term Outcome

Previously reported 5-year OS rate after completion of TSH ranged from 32 to 64%, with median survival time of 24–44 months [12, 13, 23, 26–29, 32–36]. In our recent updated data between 1992 and 2012, 1116 consecutive patients underwent initial hepatectomy for CLM at our institution. Among them, 139 patients (12.4%) were scheduled to undergo TSH for extensive CLM (six patients who underwent ALPPS were excluded). Of these, 46 patients (33.1%) could not proceed to the second-stage mainly because of disease progression after first-stage hepatectomy. On an intention-to treat (ITT) basis, the OS for patients who were scheduled to undergo TSH was significantly lower than that of those who underwent standard one-stage hepatectomy (5-year OS: 31.8 vs. 47.1%, median 38.4 vs. 55.2 months, P = 0.0004) (Fig. 13.4a). However, among the patients who underwent liver-curative surgery (liver R0 or R1), the OS for patients who complete TSH compared similarly with that of those who underwent standard one-stage hepatectomy (5-year OS: 41.3 vs. 48.0%, median 44.3 vs. 56.6 months, P = 0.40) (Fig. 13.4b). These findings suggest that if both sequential procedures of TSH are completed, comparable long-term survival with standard one-stage hepatectomy can be expected.

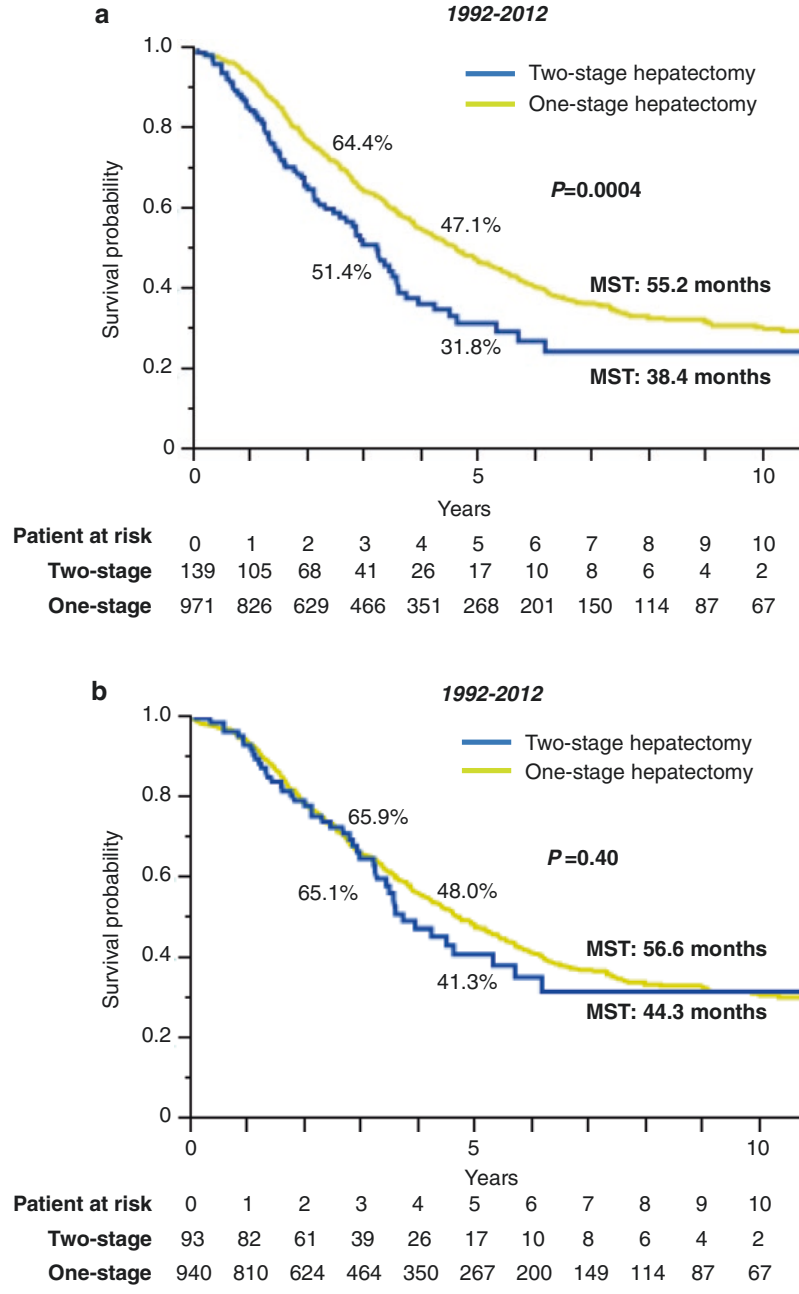

Fig. 13.4 (**a**) Overall survival for patients who were planned for two-stage hepatectomy ($n = 139$) and patients who underwent standard one-stage hepatectomy ($n = 971$), between 1992 and 2012 (intention-to-treat basis). (**b**) Overall survival for patients who completed two-stage hepatectomy ($n = 93$) and patients who underwent liver-curative one-stage hepatectomy ($n = 940$), between 1992 and 2012. *MST* mean survival time

Prognostic Factors of Survival After TSH

Previous studies reported several independent prognostic factors after TSH (Table 13.5). On an ITT basis (including the patients who failed to complete TSH), failure of TSH [30, 33] and major complications after first- or second-stage hepatectomy [33] were identified as independent prognostic factors of poor survival. On the contrary, among the patients who completed TSH, preoperative chemotherapy cycle ≥6 [27], tumor number ≥6 [13], presence of concomitant extrahepatic disease [13], and no postoperative chemotherapy

Table 13.5 Reported prognostic factors for survival after two-stage hepatectomy

Study	Year of publication	Country	No. of pts	5-year OS	Independent prognostic factors (multivariate)	Patients cohort
Wicherts et al.	2008	France	41	42	• Tumor number ≥ 6 • Concomitant extrahepatic disease • No postoperative chemotherapy	TSH completed cohort
Brouquet et al.	2011	USA	62	51	• Major complication after first- or second-stage • TSH failure	Whole cohort
Giuliante et al.	2014	Italy	102	32	• Chemotherapy cycle ≥ 6	TSH completed cohort
Failot et al.	2015	France	50	27 (3-year)	• TSH failure	Whole cohort

OS overall survival, *TSH* two-stage hepatectomy

[13] were reported as independent prognostic factors of poor survival after completion of TSH. The analyses of our data recently updated with the inclusion of 139 patients who were planned for TSH revealed that failure of TSH was the only independent prognostic factor in the whole cohort. Among the 93 patients who completed TSH, major complications (Clavien ≥ III) after second-stage and repeat surgery for recurrent disease were the independent prognostic factors of survival after TSH (unpublished data). It is obvious that the most important objective is to prevent the failure of TSH. In addition to that, however, keeping a low complication rate after second-stage (because complications after second-stage may lead to delay of postoperative chemotherapy or limitations of treatment options for recurrent disease) and aggressive repeat surgery for recurrence are thought to be crucial for long-term survival after TSH.

Future Perspective of TSH

Recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been reported as a novel form of TSH [37, 38]. ALPPS seems to offer two main advantages compared to 'conventional' TSH; rapid and higher volume increase of FLR and a shorter interval period between two procedures. As a result, the failure rate of ALPPS is almost 0 [39–44]. The higher feasibility of ALPPS may be able to overcome the drawback of "failure to complete two sequential procedures" in TSH. However, ALPPS is still in the process of evolution and the oncological outcome is still uncertain. For the treatment of extensive multiple bilobar CLM, it could be essential that the indications of TSH and ALPPS should be determined by considering the advantage and disadvantage of each procedure as well as their long term outcome.

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Two-Stage Liver Surgery with Portal Vein Occlusion

14

Michael Linecker, Henrik Petrowsky, and Pierre-Alain Clavien

Abbreviations

FLR	Future liver remnant
ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
PVL	Portal vein ligation
CLM	Colorectal liver metastases
PVE	Portal vein embolization
PVO	Portal vein occlusion
CRC	Colorectal Cancer
CT	Computed tomography
FDG-PET	Fluorodeoxyglucose positron electron tomography
MR	Magnetic resonance
BSA	Body surface area
TLV	Total liver volume
sFLR	Standardized future liver remnant
SFSS	Small-for-size syndrome
HIDA	Hepatobiliary iminodiacetic acid
5-FU	5-Fluoruracil
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
FOLFIRI	Folinic acid, fluorouracil, and irinotecan
FOLFOXIRI	Folinic acid, fluorouracil, oxaliplatin, and irinotecan
HAI	Hepatic aterial infusion
FUDR	Floxuridine
ISGLS	International Study Group of Liver Surgery
iPSC	Induced pluripotent stem cells

The Evolution of Staged Liver Surgery

The liver has the unique capability to restore its volume and functional capacity after major tissue loss within a short period of time. The ancient Greeks alreadydescribed this phenomenon in the myth of the fallen demigod Prometheus. According to this myth, an eagle devoured the chained Prometheus' liver every day. The liver re-gained its original size overnight, thereby trapping Prometheus in eternal pain [1]. The major challenges of the first liver resections in the second half of the nineteenth century were primarily bleeding problems rather than problems of insufficient liver volume. Technical advances including improved transection techniques and the introduction of the Pringle [2] maneuver, as well as the exact knowledge of hepatic anatomy [3], were the basis of modern liver surgery. However, solving these initial hurdles has led to a more extensive application of liver surgery, primarily

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for liver tumors, revealing insufficient regeneration of the remnant liver in some cases. The challenge of the small FLR evoked innovative surgical strategies, all relying on the liver's regenerative potential as initially described in the myth of Prometheus. This chapter addresses the concepts and variants of two-stage liver surgery with portal vein occlusion as an elementary tool enabling staged surgery.

Interestingly, the effect of portal vein occlusion had already been known for many years before the first anatomic liver resections [4], and the first reports on liver regeneration after major hepatectomy in humans appeared in the 1950s [5]. In 1920, Rous and Larimore [6] from Rockefeller Institute in New York recognized the importance of portal blood flow for liver volume maintenance in a rabbit model of portal vein occlusion. They performed ligation of the left portal vein (PVL) and observed atrophy of the ipsilateral liver and a corresponding hypertrophy of the contralateral liver. Within a few weeks, the grown portalized liver took over full liver function, and the deportalized liver steadily shrank to a fibrous tag [6].

Despite the early experimental discoveries, it took more than 70 years until the effect of unilateral disruption of portal flow entered into the clinical practice of liver surgery. Makuuchi et al. [7] pioneered the use of portal vein occlusion in liver surgery. He first described a series of 14 patients with hilar cholangiocarcinoma undergoing pre-operative portal vein embolization (PVE) to induce atrophy in the tumor-bearing lobe and parenchymal hypertrophy in the contralateral lobe (Figs. 14.1, and 14.2). This report was pioneering for all subsequent surgical strategies manipulating liver volume to increase resectability of hepatic tumors (Fig. 14.3).

Fig. 14.1 Masatoshi Makuuchi from the National Cancer Center in Tokyo

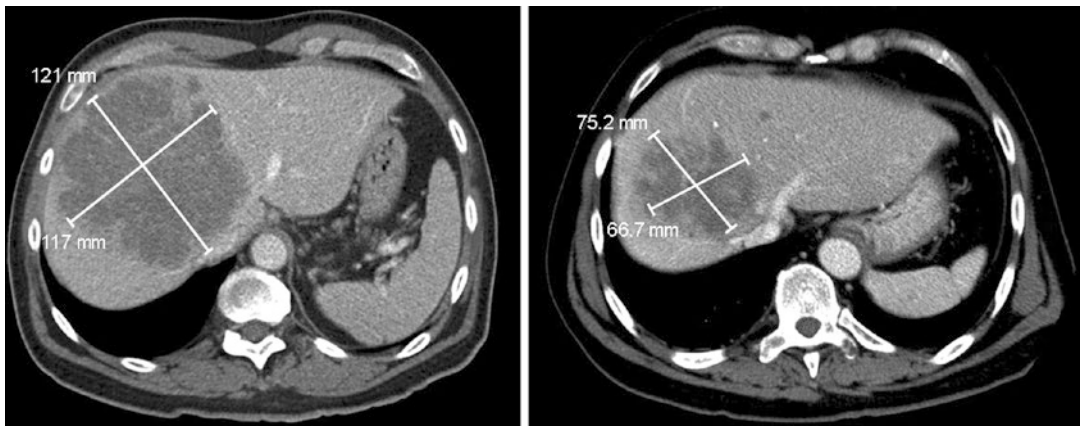

Fig. 14.2 Portal vein embolization: hypertrophy of the future liver remnant, atrophy of the tumor bearing lobe (colorectal liver metastases)

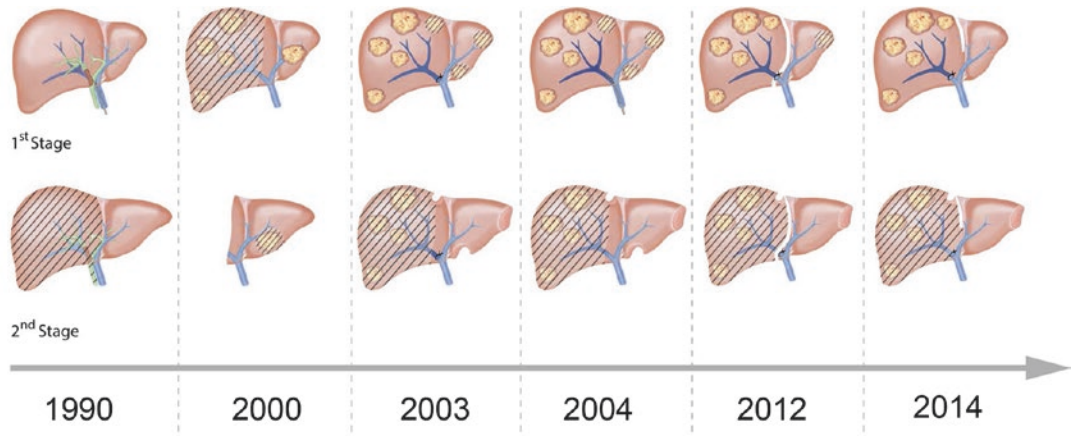

Fig. 14.3 Evolution of staged hepatectomies

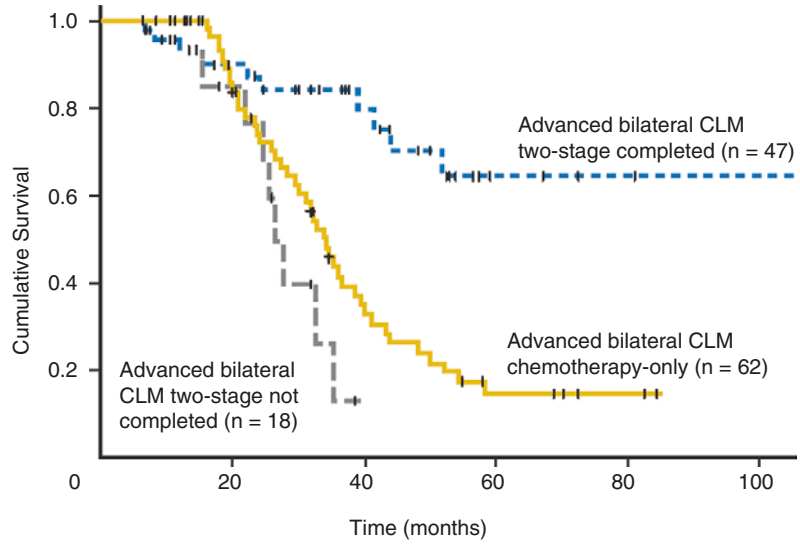

Fig. 14.4 Overall survival of patients undergoing a two stage hepatectomy (completed or not completed) and chemotherapy alone

Resection of hepatic metastases, especially colorectal liver metastases (CLM), was controversially discussed for a long time after its first description in 1940 by Cattell [8], due to a high peri-operative mortality and low 5-year survival rates. These figures have dramatically changed today. The currently largest series of two-stage hepatectomies for advanced bilateral CLM ($n = 890$) has been reported by Brouquet et al. in 2011. In this series, patients undergoing staged hepatectomy had a 5-year survival rate of 51% compared to 15% for patients receiving chemotherapy only [9] (Fig. 14.4).

The concept of two-stage hepatectomy for CLM, not necessarily with portal vein occlusion, was introduced by the Paul Brousse group from Paris in 2000 [10]. In a first stage, a maximum of metastases were removed. After a postoperative waiting interval of 2–14 months, enabling the liver to regenerate, the remaining tumors were resected. During this period, chemotherapy was frequently applied to reduce tumor growth. The authors reported a feasibility rate of 81% for both stages, with a median survival of 31 months from the second hepatectomy [10]. The next advancement of staged hepatectomy to achieve curative resection of bilobar CLM was reported by Jaeck et al. in 2004. This group described the non-anatomic removal of metastases of the left lobe (subsequently called "cleaning"), followed by PVE and later by right or extended right

hepatectomy after sufficient growth of the FLR [11]. In 76% of all patients enrolled, it was possible to achieve a second stage, resulting in a 3-year survival rate of 54%. Belghiti et al. [12] proposed portal vein ligation (PVL) as a surgical variant of portal vein occlusion (PVO), including simultaneous cleaning of the FLR in the same procedure (Figs. 14.5, 14.6, and 14.7), even in combination with resection of the primary tumor at the first stage. In this study, a total of 20 patients were included (12 patients with colorectal cancer and eight patients with neuroendocrine tumors). Finally, 15 of 20 patients (75%) were eligible for a definitive second-step operation due to absence of recurrent disease. This approach proved to be safe and feasible, as no major complications

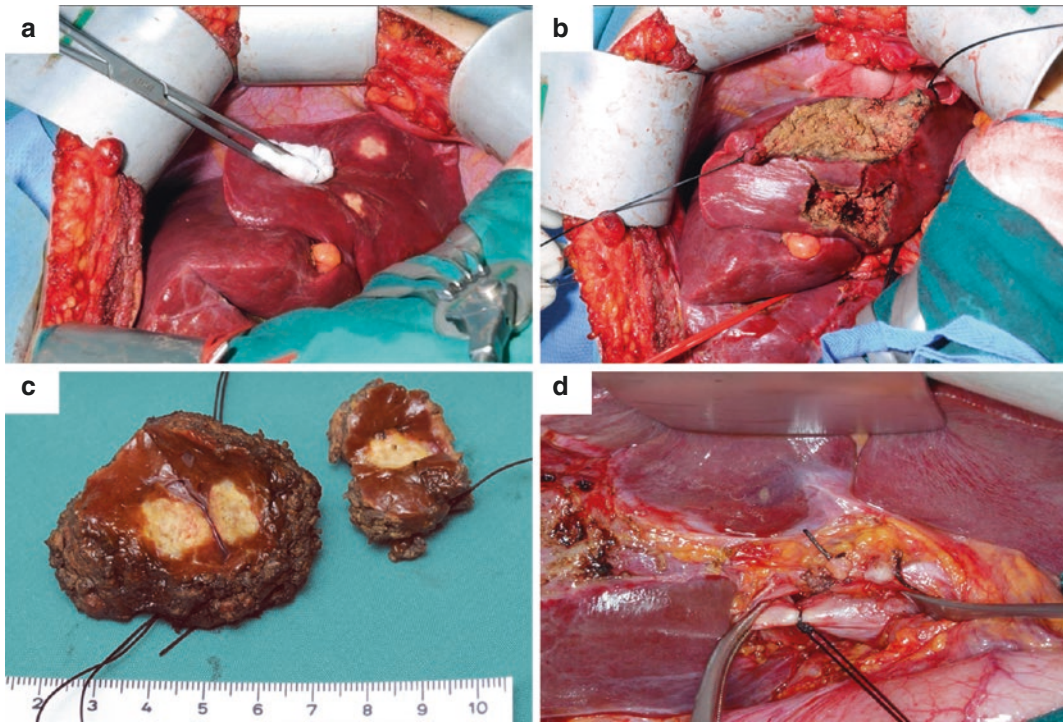

Fig. 14.5 First stage of a two-stage hepatectomy: "cleaning" of the future liver remnant (**a**–**c**) and portal vein ligation (**d**)

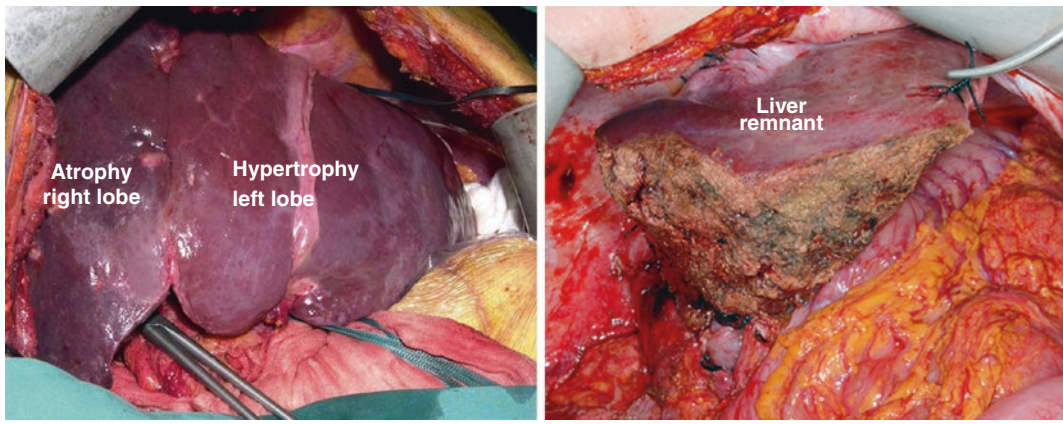

Fig. 14.6 Second stage of a two-stage hepatectomy: volume increase of the left lobe, atrophy of the right lobe

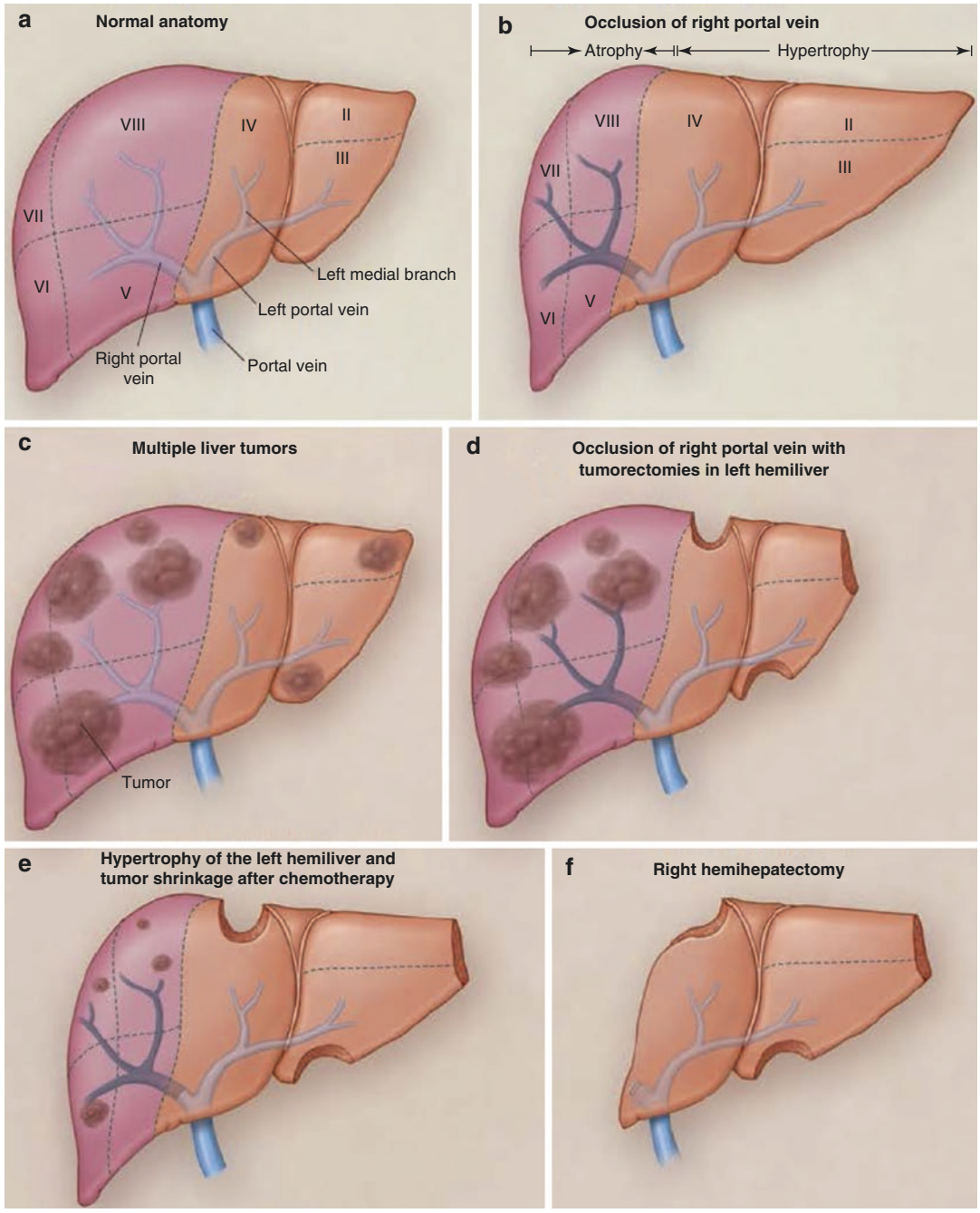

Fig. 14.7 Liver hypertophy induced by portal vein occlusion (**a**, **b**) and the concept of two-stage procedures (**c**–**f**)

were reported [12]. In another study of the Belghiti group, PVE and PVL were compared to assess liver hypertrophy in the setting of two-stage hepatectomies [13]. The degree of hypertrophy before second stage operation was measured by CT-based volumetry, revealing a comparative volume increase of 35% after PVE versus 38% after PVL.

Both types of portal vein occlusion (PVL and PVE) proved to be safe and efficient in a

multimodal setting, and were therefore implemented in multi-stage procedures as proposed by Clavien et al. [14, 15] (Fig. 14.7). However, a major drawback of this staged strategy is the waiting interval of liver hypertrophy between the two stages. Initially, non-selective PVE required a 2–14-month waiting time after stage 1 until resection could be completed [10]. This exposed the patients to a high risk of tumor progression. Both experimental and clinical data suggest increased tumor progression in the FLR after PVO [16, 17]. Today, the waiting period after PVE or PVL could be reduced to 4–6 weeks. Despite the significant reduction of the inter-stage interval time, a period of 1 month or longer might be too long to control tumor disease in patients with extensive bilobar tumor load who are planned to undergo curative resection in the second step. Therefore, efforts were undertaken to accelerate liver growth and shorten the time interval between the two stages. In 2012, Schnitzbauer and Schlitt [18] from Regensburg in Germany reported a preliminary series of patients with extensive hepatic tumor burden from primary and secondary liver tumors who underwent parenchymal in situ splitting and PVL. The initially used term "in-situ splitting" was derived from liver transplantation but was later replaced by the term "associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)", as proposed by de Santibañes and Clavien [15]. Intriguingly, the combination of PVL with parenchymal transection was able to reduce the median inter-stage waiting time to 9 days, with a median FLR increase of 74% [18]. Further developments of this procedure include the use of PVE in combination with parenchymal transection [19], ALPPS procedures with partial transection [20, 21], and laparoscopic [22] variants. In 2014, Robles et al. from the University of Murcia in Spain presented the first series replacing parenchymal transection by the application of a tourniquet [23]. They were able to show a median FLR increase of 61% within 7 days, which is in line with the classical ALPPS procedure.

When comparing two-stage hepatectomies with PVO with or without parenchymal partition, it becomes obvious that the regenerative boost in ALPPS is much stronger. However, the molecular mechanisms responsible for this phenomenon still remain unclear. A recently published experimental study using a mouse model for ALPPS suggests circulating factors in combination with PVL could mediate this unprecedented regeneration [24].

The development of various types of two-stage hepatectomies with PVO probably represents the most successful advances in hepatobiliary surgery during the past two decades. The clinical practice of these procedures has led to an expansion of resectability in patients who are otherwise not amenable for curative liver surgery.

Indications and Limitations

Despite the enormous advances in chemotherapy, complete surgical removal of CLM remains currently the best chance for long-term survival [9]. Most patients who are evaluated for a two-stage hepatectomy have already undergone systemic chemotherapy for colorectal cancer (CRC). Brouquet et al. [9] compared patients with objective response to first-line chemotherapy undergoing two-stage hepatectomy versus patients with chemotherapy alone. The results of this case-matched analysis were clearly in favor of the two-stage hepatectomy group, with a superior 5-year survival rate (51 vs. 15%). This observation emphazises that the removal of liver tumor mass appears crucial for long-term survival [9]. In the same line are data from a study demonstrating the beneficial impact of negative resection margins on both local recurrence and long-term survival [25]. Interestingly, the width of a negative surgical margin does affects neither risk nor site of recurrence nor survival. Even estimated margins <1 mm should not be used as exclusion criteria not to undertake curative resection in CLM [25]. Finally, the availability of a more effective chemotherapy regimen has increasingly led to scenarios where initially unresectable CLM can be converted into resectable disease. Therefore, downsizing chemotherapy is becoming an important strategy to achieve disease eradication. Adam et al. reported in their series that 16% of a total of 184 patients with initially unresectable CLM were successfully converted by chemotherapy to resectable disease [26].

Any oncologic surgery strongly relies on the selection of candidates for surgery. Traditionally, local resectability and the presence of extrahepatic disease have been considered as contraindications for liver surgery. This paradigm has changed in the last few years. Patients with extensive hepatic tumors and limited, curable extrahepatic disease, such as resectable lung metastases, may be eligible for two-stage hepatectomy. The pre-operative workup for two-stage hepatectomy essentially does not differ from the routine workup for other major hepatectomies, with a particular focus on *the extent of the systemic disease* and an exact picture of local liver and tumor anatomy (*extent of the tumor, involvement of major anatomic structures, and size of the FLR*). Based on these principles, the ability to achieve curative resections can be estimated quite accurately. Computed tomography (CT) scan is the standard imaging modality for the diagnosis of CLM in most institutions. Particularly when combined with fluorodeoxyglucose positron electron tomography (FDG-PET), this imaging modality has shown a high diagnostic accuracy [27] and should be used to rule out extrahepatic metastases. A mandatory element of the diagnostic workup for patients considered for two-stage hepatectomy is the determination of the tumor extent and the volume of the FLR. This is ideally done by three-dimensional CT or MR volumetry, allowing the measurement of segmental liver volumes. However, the measurement of the total liver volume (TLV) by this method is usually more inaccurate, since the subtraction of multiple tumors might lead to over- or underestimation. To exclude this problem, various formulas have been developed to estimate the TLV based on weight, height, and body surface area (BSA). One of the most frequently used formulas for Western adults is relying on the linear correlation between BSA and TLV: TLV (cm^3) = −794.41 + 1267.28 * BSA (m^2) [28]. The ratio between volumetrically measured FLR and calculated TLV is called standardized future liver remnant (sFLR). How much FLR volume is enough to maintain liver function is not clearly defined, and strongly depends on factors like parenchymal quality of the FLR. A survey among 133 international hepatobiliary centers [29] has revealed that the widely accepted minimal FLR for resection was 25% (range 15–40%) in case of normal liver parenchyma (Fig. 14.8). For patients with underlying liver disease, a more conservative FLR volume was suggested, which was up to 50% in cirrhotic patients (range 25–90%) [29] (Fig. 14.9). Underlying liver conditions including fibrosis, cirrhosis, steatosis, old liver, and

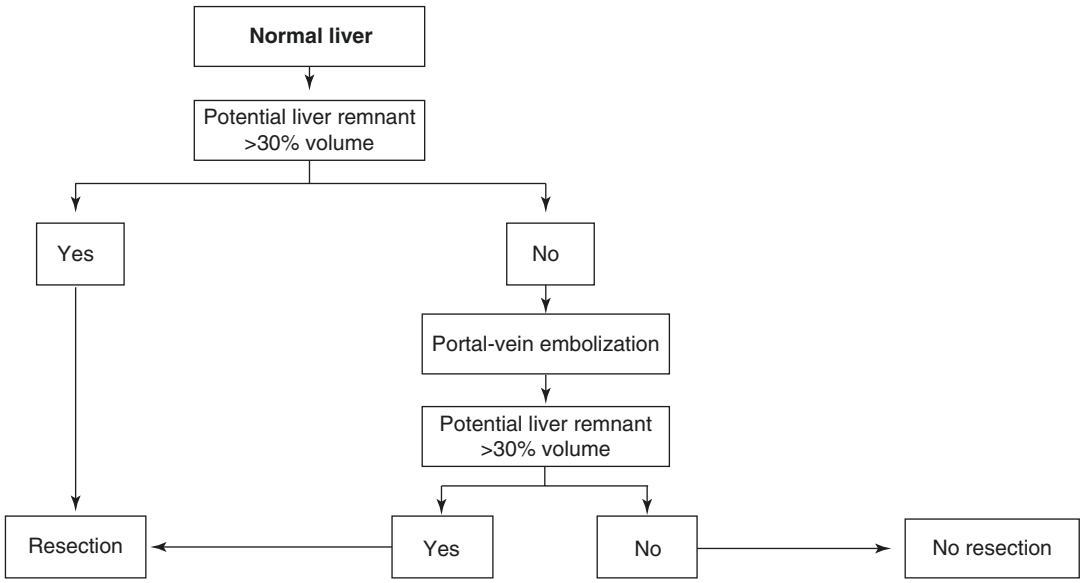

Fig. 14.8 Proposed algorithm for patients with normal liver parenchyma to undergo resection +/− portal-vein embolization

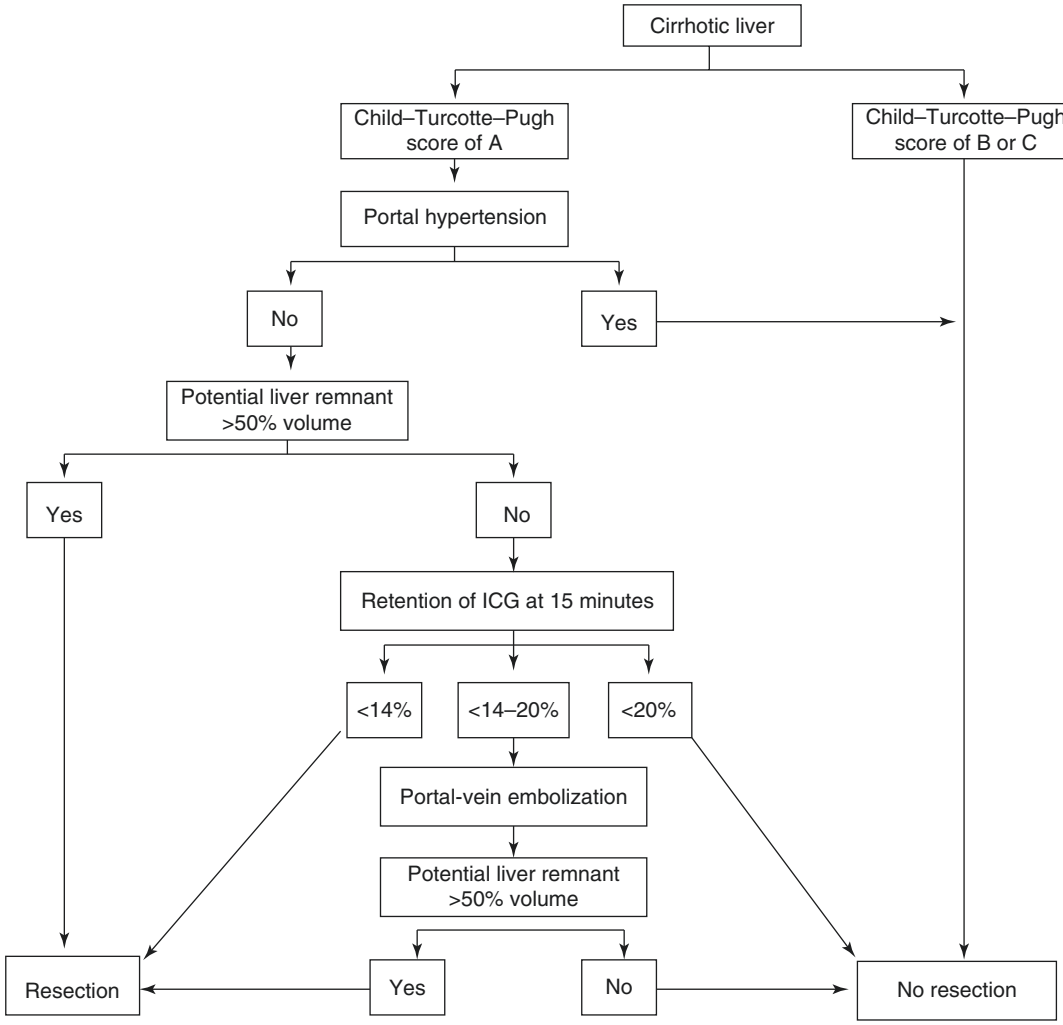

Fig. 14.9 Proposed algorithm for patients with diseased liver parenchyma to undergo resection +/− Portal-vein embolization

chemotherapy-associated liver disease are associated with impaired liver regeneration, and are risk factors for the development of the "small-for-size syndrome" (SFSS). In particular, intense chemotherapy in CLM influences postoperative morbidity and mortality. Irinotecan and 5-fluorouracil are known to cause chemotherapy-associated steatohepatits (CASH), whereas oxaliplatin may cause sinusoidal obstruction syndrome [30]. However, in most of the cases, patients are treated with different combinations, resulting in a mixture of these distinct syndromes. To address the functional quality, dynamic tests such as the indocyanine green (ICG) or Limax tests are important tools to provide information on the functional capacity of the liver. Ideally, a test can visualize the hepatic function of different topographic areas, which is very helpful to determine whether a staged approach is appropriate or when to proceed to the second stage. Recently, ^{99m}Tc-mebrofenin hepatobiliary iminodiacetic acid (HIDA) scan was shown to be a useful tool in visualizing regional functional differences in bile excretion as a measure of hepatic functional capacity [31].

The Three Elements of Two-Stage Hepatectomy

The rapid evolution of staged hepatectomies could be only achieved due to the concurrent development of an effective chemotherapeutic regimen and the advances in interventional radiological

procedures. In this setting of a multidisciplinary approach, the input of surgeons, hepatologists, oncologists, and interventional radiologists is absolutely essential. The concept of two-stage hepatectomy for CLM relies on three elements: portal vein occlusion, chemotherapy, and surgery, which are discussed in this section.

Portal Vein Occlusion (PVO)

The use of PVO, either PVE or PVL, to trigger hypertrophy of the contralateral liver is probably the most successful used concept in manipulating the liver volume. PVE is indicated in cases when the potential FLR is below the threshold of the minimal acceptable volume. Nowadays, PVE is mostly done by the percutaneous route using embolic materials including particles, coils, fibrin glue, gelatin sponge, or cyanoacrylate with ethiodized oil. Most surgeons consider a pre-operative waiting time of 4–6 weeks as enough to achieve adequate liver hypertrophy. After right PVE, a FLR volume increase of 30–80% can be expected within 4 weeks [32] (Fig. 14.10). Repeat imaging by CT or MR is usually performed at that time to assess the actual volume gain, and might be repeated if hypertrophy is not enough. In addition, PVE can be considered as a pre-operative stress test that assesses the capacity to regenerate [33]. Therefore, patients with failure of hypertrophy might not be eligible for a second stage. This becomes particularly important when the quality of liver parenchyma is impaired. Almost all candidates scheduled for two-stage hepatectomy have already received chemotherapy, which has potentially harming effects on liver parenchyma. The choice whether PVE or PVL is used depends on the presence of metastases in the FLR. In the scenario of bilobar CLM, PVL with simultaneous metastasectomies of the FLR is the preferred strategy of the first stage [14] (Fig. 14.3). The removal of all visible lesions in the FLR is necessary before exposing the liver to the desired

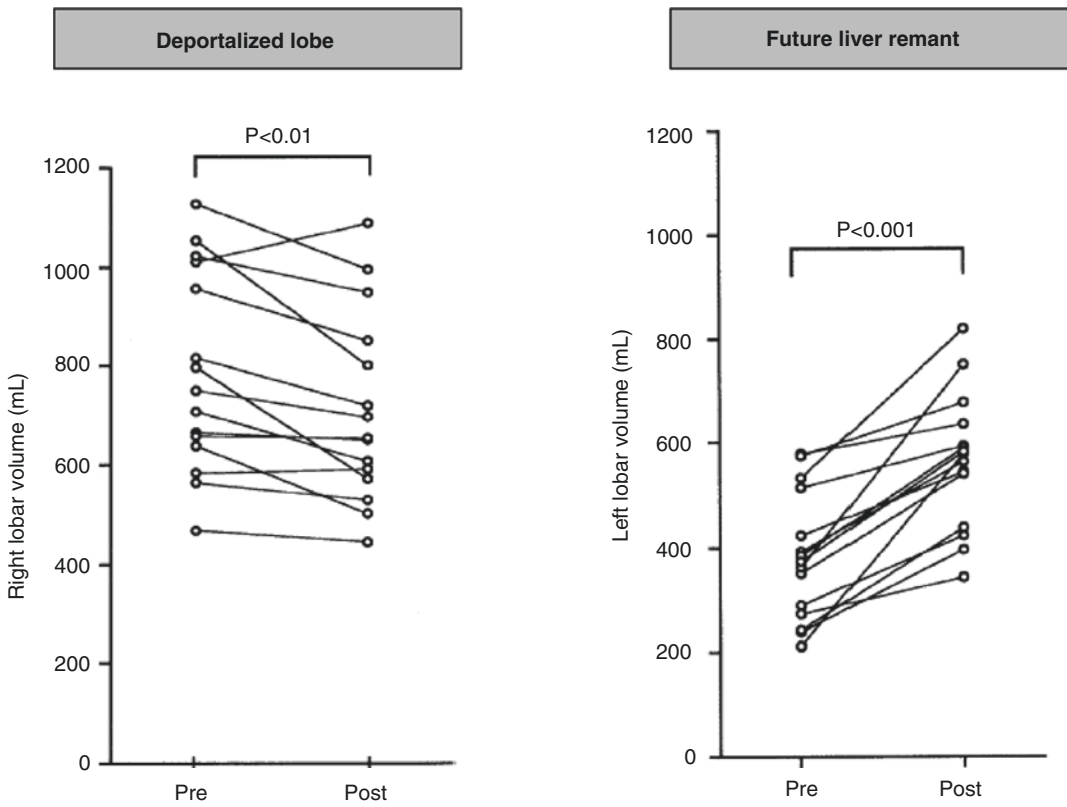

Fig. 14.10 Right Portal vein embolization: volumetric changes in 15 patients within 2–3 weeks before undergoing right trisectionectomy

regenerative stimulus induced by PVL. If cleaning of the FLR is not performed, it is very likely that tumor progression in the FLR will occur, as was shown in experimental models [17].

Chemotherapy (Systemic, Intra-arterial)

During the last decade, substantial progress has been made in shifting chemotherapy for CLM from a palliative to a potential curative setting in combination with staged liver surgery. Perioperative *systemic chemotherapy* is a crucial component of major [34] and staged liver surgery [9] which significantly improves disease-free and overall survival. Even patients with initially unresectable disease are now able to undergo effective downsizing chemotherapy with subsequent rescue surgery, offering them a chance of cure. Systemic chemotherapy has made significant advances during the past decades, starting with a purely 5-fluoruracil (5-FU) regimen to much more effective combinations such as FOLFOX (folinic acid, fluorouracil and oxaliplatin), FOLFIRI (folinic acid, fluorouracil and irinotecan) and FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin and irinotecan). In addition, specific "biological" therapy targeting vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptor (cetuximab and panitumumab) have been successfully introduced into clinical practice. In the past, chemotherapy has been discontinued before PVO to avoid any compromise of liver hypertrophy. However, it seems to become increasingly important to maintain systemic chemotherapy as "bridging chemotherapy" before the second stage to better control systemic disease. Clinical data suggest that chemotherapy neither impairs hypertrophy of the FLR after PVO nor increases postoperative morbidity [35].

Apart from systemic chemotherapy, *intra-arterial chemotherapy* (hepatic arterial infusion—HAI) was introduced to downsize extensive hepatic tumor load [36]. The rationale for the use of local chemotherapy via the hepatic artery is based on the fact that hepatic tumors are almost exclusively supplied by arterial branches [37]. Fluorouracil and floxuridine (FUDR) (the active metabolite of 5-FU) are continuously infused via implantable infusion pumps, resulting in a high drug concentration in liver metastases [38]. FUDR displays a high first-pass effect of around 95% resulting in low systemic toxicity. This pharmacokinetic profile makes the drug very useful for local tumor treatment. It has been demonstrated that the use of HAI increases the response rates of CLM [39] and leads to a higher resection rate of initially unresectable CLM compared to systemic chemotherapy [40]. Despite the improved hepatic progression-free survival after HAI treatment, extrahepatic progression-free survival is not improved in patients with unresectable CLM [41]. Therefore, HAI is a valuable therapy of downsizing CLM in unresectable situations, but needs to be supplemented with systemic chemotherapy to control systemic disease.

Surgery

Staged, margin-negative resection of extensive, bilobar CLM is the goal which can only be safely achieved in combination with strategically well-planned PVO and chemotherapy [14]. Typically, the first stage consists of PVO along with concomitant non-anatomic wedge resections of the FLR. The goal of this "cleaning" is the removal of small, isolated peripheral tumors in the FLR to prevent a potential accelerated tumor progression induced by PVO. For this reason, cleaning of the FLR is performed along with PVL in the majority of cases; however, PVE following a few days after FLR cleaning provides another option. After a waiting interval of 4–6 weeks, FLR size should have grown sufficiently to enable extended resection in a second stage with negative margins. Ideal candidates for this approach are patients with extensive tumor load in the right liver and segment 4, and single lesions in the left-lateral liver (segments II and III). In this situation, cleaning of segments II and III is performed with PVO of the right lobe (Fig. 14.5). After hypertrophy of the left lobe a right trisectionectomy can be performed with sufficient FLR size (Fig. 14.6).

How Far Can We Go? Failing Liver Regeneration and Small-for-Size Syndrome

The success of extended hepatic surgery primarily relies on an effective regeneration process of the FLR. The FLR size is important in predicting proper liver regeneration after major hepatectomy and is, therefore, the limiting factor of resectability in most cases. As mentioned before, there is a critical threshold where the FLR is unlikely to regenerate. Accepted figures are 25% for normal liver parenchyma and 40–50% for diseased liver. Quantifying functional capacity, a retention of ICG at 15 min (R15) should be less than 14% for safe resection [14]. Between 14 and 20%, a PVL should be attempted and patients with an R15 >20% should not undergo resection [14] (Fig. 14.9). In HIDA scan, a cutoff FLR uptake value of 2.69%/min/m^2 (^{99m}Tc-mebrofenin) has been proposed to identify patients with a significant risk for developing postoperative liver failure [31] (Fig. 14.11).

Proceeding with resection below these volumetric and functional thresholds can cause encephalopathy, coagulopathy, prolonged hyperbilirubinemia, and finally early postoperative death. This syndrome, mostly referred as "small-for-size syndrome" (SFSS) was adopted from liver transplantation. In liver transplantation,

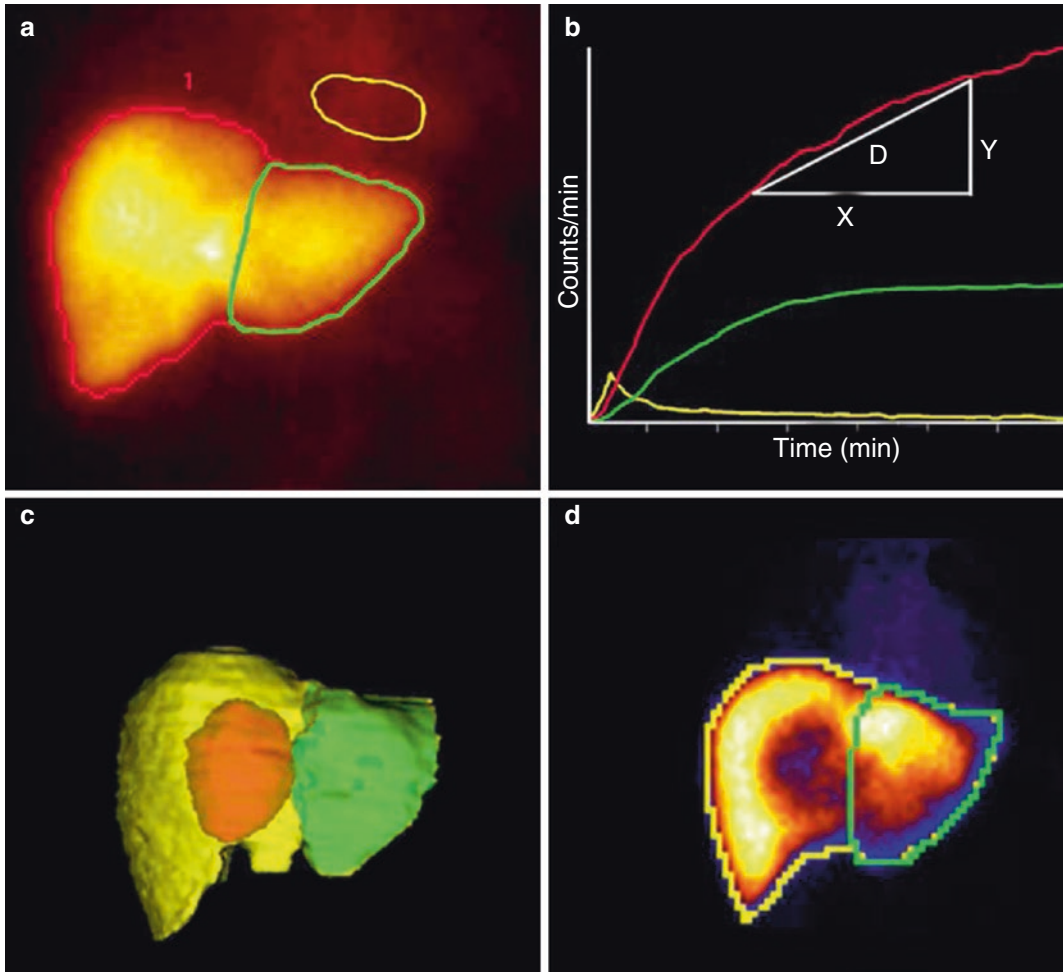

Fig. 14.11 HIDA scan 150-300 seconds after i.v. injection of ^{99m}Tc-mebrofenin (**a**) reveiling a blood pool corrected liver-uptake time-activity curve (**b**) of the whole liver and the FLR (*green*). Three-dimensional reconstructed CT images (**c**) are used to guide identification of the FLR on HIDA scan (**d**)

SFSS has been proposed to be defined as total serum bilirubin >100 µmol/l, INR > 2, and encephalopathy grade 3 or 4 with two of these features met on 3 consecutive days in the first postoperative week excluding technical, immunological, or infectious causes [42]. A simple approach to defining liver failure after extensive resection, named the "50–50 criteria" was proposed by Balzan et al. [43]. In this study, a prothrombin time <50% and serum bilirubin >50 µmol/l on postoperative day 5 (the "50-50 criteria") were an accurate predictor of more than 50% mortality rate after hepatectomy. In 2011, the International Study Group of Liver Surgery (ISGLS) has proposed a similar, easily applicable definition of post-hepatectomy liver failure, suggesting serum INR and bilirubin levels above the normal cut-off on or after postoperative day 5 [44]. In addition, Grade A requires no change of the clinical management, Grade B deviates from routine management without requiring invasive treatment and Grade C requires invasive treatment.

Therapeutic approaches to overcome the SFSS focus on the one hand on mitigating liver damage, and on the other hand on improving proliferation. However, such approaches are the focus of ongoing basic research. Therefore, prevention of SFSS by accurately choosing the appropriate two-stage strategy is absolutely essential. Assessment of liver volume by three-dimensional CT or MR along with dynamic liver function tests (ICG, Limax, HIDA, etc.) are helpful tools in decreasing the risk of SFSS.

Outlook

Major advances have been achieved for patients with unresectable liver tumors since the introduction of PVE by Makuuchi. Over the last decade, the criteria for resectability of CLM have undergone a paradigm shift from what is removed (number of metastases, size of metastases, extrahepatic disease) to what remains (adequate FLR, potential R0 resection). The two-stage hepatectomy has become an established part of a multidisciplinary approach including PVO and chemotherapy to achieve complete tumor removal, which is the most important factor to improve long-term survival.

Only fundamental mechanistic understanding of liver regeneration can help to further extend hepatic resections. Clinically applicable strategies overriding hepatic regenerative defects are highly wanted. In future, an ex-vivo growth of a fully functional partial liver might further push the limits of resectability. A major step in this direction was already performed by Takebe creating fully functional human three-dimensional liver buds from induced pluripotent stem cells (iPSCs) in vitro, which successfully rescued drug-induced liver failure in a mouse model [45].

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15 Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

Fernando A. Alvarez and Eduardo de Santibañes

Introduction

Approximately half of patients with colorectal cancer will develop liver metastases (CLM) during the course of their disease [1]. Liver resection is the treatment of choice to prolong survival and offer a chance of cure to these patients [1, 2]. However, resection is not always feasible due to tumor location, contact with major vascular elements, bilaterality, insufficient liver remnant, or patient comorbidities. Although not long ago the majority of patients with CLM (70–80%) were considered unsuitable for resection at diagnosis, nowadays a greater number of patients finally undergo surgery given the significant improvements in imaging modalities, surgical techniques, anesthesia, chemotherapy regimens, and the expansion of resectability criteria among surgeons [3]. The paradigm of resectability in modern liver surgery has shifted from being defined by what is resected, to being defined on the basis of what remains after resection. Those surgeons performing oncological liver surgery must balance two conflicting objectives that might jeopardize each other whenever extensive disease is present: (1) to achieve a complete tumor resection with curative intent (negative margins), and (2) to preserve as much liver parenchyma as possible to avoid liver failure. However, major hepatectomies are often required to achieve an R0 resection, and these are associated with substantial rates of morbidity and mortality [4]. Posthepatectomy liver failure (PHLF) is the main cause of death after major hepatectomy, and it is strictly related to the volume and quality of the future liver remnant (FLR) [5]. Several strategies have been developed in order to minimize the risk of PHLF and expand resectability. These strategies could be grouped into those that tend to reduce the tumor size (e.g., conversion chemotherapy, endovascular procedures) and those that tend to preserve or increase the amount of liver remnant (e.g., local ablation techniques, preoperative portal vein embolization, two-stage procedures). Portal vein occlusion of the tumor-bearing lobe has become the gold standard to induce hypertrophy of contralateral healthy parenchyma [6]. Right portal vein embolization (PVE) is best used before surgery when the FLR is tumor-free, while ligation (PVL) is usually applied as part of two-stage procedures for patients with bilobar disease who initially require tumor removal in the FLR. Yet, when using these classical approaches of portal vein occlusion, up to 40% of patients never arrive at tumor resection

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either because of insufficient hypertrophy or disease progression during the long intervals (6–12 weeks) usually required to achieve hypertrophy [7, 8]. Moreover, those patients who fail to complete the second stage have worse survival rates than those patients treated with chemotherapy alone [9].

Twelve years after the introduction of staged liver resections by Adam et al. [10] in 2000, Schnizbauer et al. [11] reported a technical innovation to this important concept that undoubtedly represented a major breakthrough in surgery. This new approach, so-called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), considerably accelerates FLR hypertrophy and drastically reduces the time interval between stages, therefore increasing resectability rates. As originally described, the technique consists in right PVL combined with in-situ splitting of liver parenchyma during the first stage, followed 7–10 days after by a second stage resecting the diseased hemi-liver. After being performed for the first time in 2007 by the German surgeon Hans Schlitt, this novel strategy gained rapid acceptance in Germany [12]. However, its spreading more recently worldwide has triggered different reactions in the surgical community, prompting the development of the International ALPPS Registry and the "1st ALPPS International Consensus Meeting" at Hamburg in February 2015 [13, 14]. So far, the ALPPS approach has been demonstrated to be feasible and safe in experienced hands, representing a promising option to be included in the multidisciplinary management of patients with locally advanced CLM [15, 16].

Patient Selection and Preoperative Evaluation

All patients with CLM have to be discussed at a multidisciplinary tumor board and considered eligible for surgery on a case-by-case basis. Despite the fact that ALPPS was originally proposed and currently applied for any type of liver tumor, the most frequent indication is CLM [11–16]. In addition, a recent multicenter analysis from the International ALPPS Registry on 202 patients indicated that patients with CLM are among those that most benefit from this approach, especially if they are younger than 60 years [17]. Preoperative staging should include a multislice computed tomographic (CT) scan of the abdomen and chest, as well as abdominal magnetic resonance imaging (MRI) for a better assessment in patients with small lesions, a fatty liver, or preoperative chemotherapy [18]. Positron emission tomography (PET) scan should be considered in cases of tumor recurrence in patients with a previous liver resection or suspected distant metastasis.

All the patients with marginally resectable or primarily non-resectable uni- or bilateral CLM could be considered eligible for ALPPS if an insufficient FLR in terms of volume and quality is present. On preoperative CT-scan or MRI-based volumetric planning, a FLR of less than 30% of total liver volume (TLV) in healthy livers, or less than 40% in patients with cholestasis, macrosteatosis, fibrosis, or long-course chemotherapy, is generally used to define FLR inadequacy [19]. The TLV could be calculated either by imaging-based volumetry or using the formula: $-794.41 + 1267.28 \times$ body surface area [20]. If preferred, a FLR to body weight ratio of less than 0.5% could also be used to determine an insufficient FLR volume in patients with normal liver, or 0.8% when abnormal liver parenchyma is present [11]. In order to get the best from this approach, it has been recently proposed to further restrict ALPPS to patients with an insufficient FLR and at least one of the following: (1) a tumor margin close to the FLR or its vascular pedicles, (2) bilobar disease with contraindication for PVE as single-stage strategy, (3) failure of PVE/PVL, (4) unexpected tumor extension during surgical exploration with a larger than

planned surgical resection, or (5) the need for a large hypertrophy (>65%) in an extremely small FLR [15]. The need to perform a major liver resection combined with the removal of the primary colorectal cancer could also be considered a potential indication to perform the procedure in order to provide a better liver functional reserve during the interval period between stages.

Unresectable liver metastases in the FLR or unresectable extrahepatic metastases, severe portal hypertension, high anesthesiological risk, medical contraindications to major hepatectomy, impossibility to achieve R0 margins, or unresectable primary tumor constitute contraindications to performing this procedure. Although age per se is not a contraindication, above the cutoff of 67 years old there is a significantly higher risk of poor perioperative outcomes [21]. If resectable extrahepatic disease is present, it should be treated either before or during ALPPS first stage, in order to avoid distant tumor stimulation from circulating growing factors during the interval period. From an oncological perspective, response to pre-operative systemic therapy in patients with dismal prognostic factors is a main consideration, as they are the most likely to benefit from a surgical approach. Therefore, associating a tailored surgical indication with a reasonable oncological indication should be a goal of liver surgeons when selecting candidates for ALPPS.

Surgical Technique

The ALPPS approach is a short-interval two-stage major hepatectomy. Briefly, as originally described the technique consists in right PVL combined with in-situ splitting of liver parenchyma during the first stage, followed by a completion surgery performed at surgeon discretion once FLR sufficiency has been assured, usually within 7–10 days (Fig. 15.1). In terms of the strategy itself, the current paradigm is basically represented by an aggressive prolonged first surgical procedure followed by a somehow shorter and less aggressive second procedure [11–17]. This philosophy has been adopted by most centers as the classical ALPPS technique. Some important aspects of the ALPPS technique, as well as the several proposed variations, will be summarized in this section.

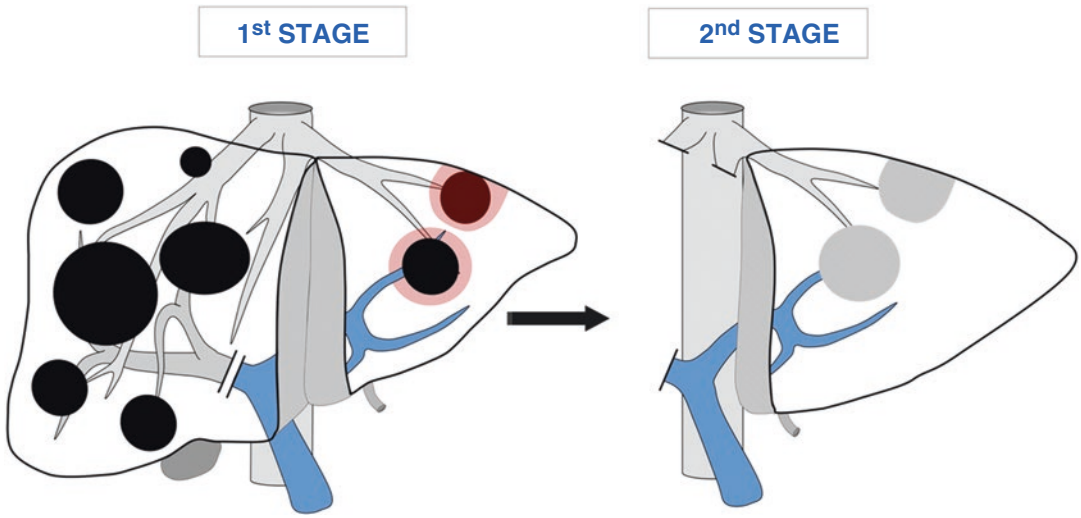

Fig. 15.1 Diagram summarizing both ALPPS stages. During first stage, right portal vein is ligated, the parenchyma is transected, and lesions in the future liver remnant are cleaned up

Classical Technique

First Stage

During first stage, the abdominal cavity is approached by a bilateral subcostal incision with midline extension, or a midline laparotomy when a simultaneous resection of the primary colorectal tumor is planned. Resecting the primary during the first stage is preferred, since an auxiliary liver is present during the interval period (Fig. 15.2). When a left colonic or rectal resection has to be performed, it is recommended to routinely perform fecal diversion in order to avoid the potentially catastrophic scenario of a symptomatic anastomotic leakage in these patients [22]. In order to define resectability, a detailed exploration of the abdominal cavity is carried out and a liver intraoperative Doppler ultrasound (IOUS) is performed to accurately assess the number, size, and location of all lesions. If bilateral lesions are present, a complete tumor resection (clean-up) of the FLR is performed, in order to induce hypertrophy in a non-tumor-bearing parenchyma [22]. Subsequently, the portal vein of the diseased hemi-liver is divided and either total (up to the inferior vena cava) or partial (up to the middle hepatic vein) parenchymal transection is carried out as for a future right trisectionectomy (Fig. 15.3). The anterior approach, with or without the "hanging maneuver", could also be applied to help liver transection and reduce tumor manipulation [22]. Partial transection has been demonstrated to offer equivalent FLR hypertrophy, while it has been associated with significantly lower morbidity than total transection (38.1% vs 88.9%; $P = 0.049$) [15] and zero mortality [23]. Total transection should therefore only be performed when a tumor is too close to the FLR boundaries in order to isolate the tumor and prevent FLR invasion [15]. The confirmation of complete deportalization of the diseased hemi-liver by IOUS is of paramount help to avoid technical failures related mainly to portal vein trifurcation. At the end of the procedure, it is advisable to perform whenever possible a trans-cystic hydraulic test and cholangiography in order to prevent postoperative biliary leaks, which have been reported at high rates in initial series (20–87%) and associated with increased morbidity and mortality (Fig. 15.4) [11, 24, 25]. Bile duct ligation should never be performed as it might lead to cholestasis, infection, and bile leaks with increased risk of mortality [25]. The identification of the diseased hemi-liver vasculobiliary structures with

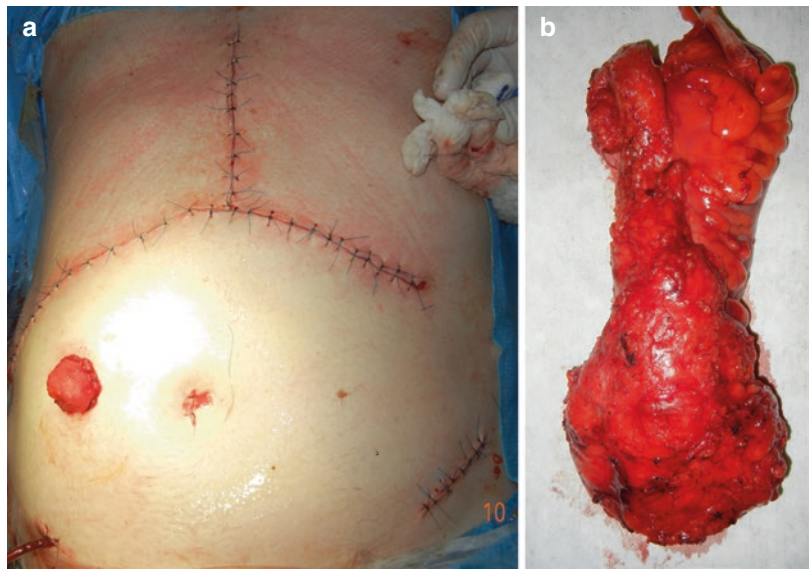

Fig. 15.2 Simultaneous resection during ALPPS first stage. (**a**) Abdominal incisions corresponding to a laparoscopic ultralow rectal resection with diverting ileostomy and open ALPPS. (**b**) Rectal specimen including an oncological total mesorectal excision

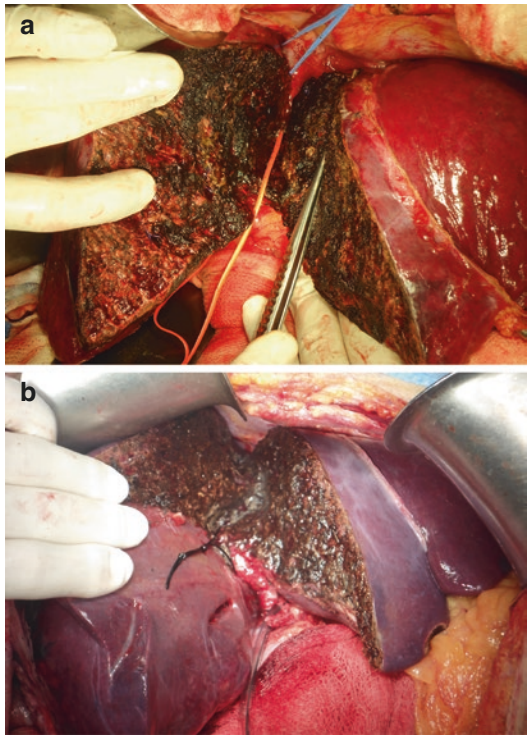

Fig. 15.3 Types of liver transection. (**a**) Total liver partition up to inferior vena cava. (**b**) Partial liver partition preserving the middle hepatic vein. The right vasculobiliary pedicle is marked either with a rounding silk or a vessel loop

strong silks or vessel loops is strongly recommended in order to facilitate their identification during the second stage [22]. Finally, with the aim of minimizing adhesions, some authors have proposed to place a plastic sheet or biological agent between both cut surfaces. However this is not mandatory and good results have been reported without the use of any material at the liver partition site.

Second Stage

The second stage should only be attempted if the patient is in good condition, once volumetric CT analysis and functional studies have demonstrated FLR sufficiency (Fig. 15.5). Abdominal exploration is performed carefully after releasing lax adhesions. The vasculobiliary structures of the diseased hemi-liver are recognized by identifying the silks or vessel loops around them. The resection of the tumor-bearing lobe is achieved using vascular staplers for all vasculobiliary structures and the remaining liver parenchyma if present (Fig. 15.6). Finally, it is strongly recommended to perform an intraoperative cholangiography and hydraulic test through the cystic duct in order to prevent postoperative bile leaks.

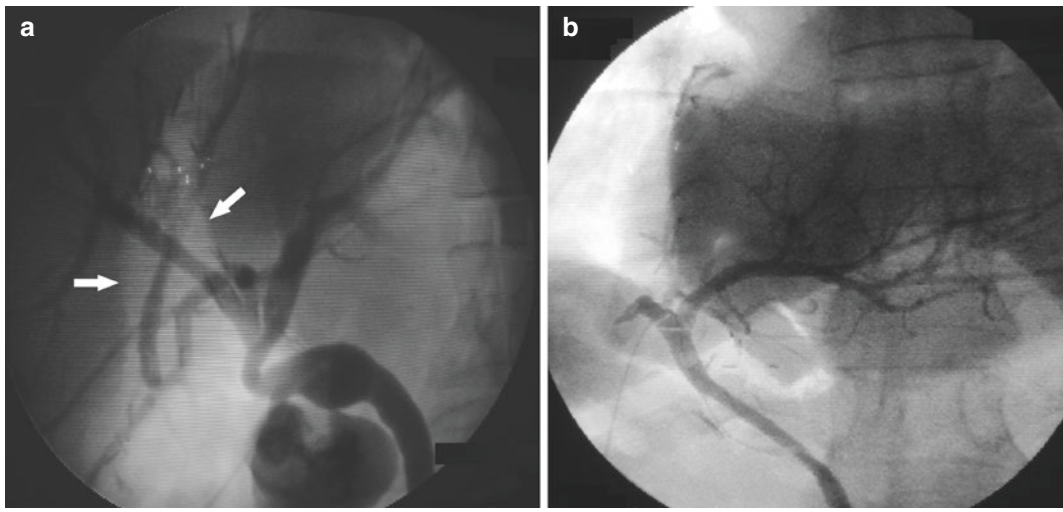

Fig. 15.4 Intraoperative cholangiography.(**a**) First-stage cholangiogram demonstrating an intact biliary tree and the absence of leaks in the partition groove (*white arrows*). (**b**) Second-stage transcistic cholangiogram after resecting the diseased hemi-liver

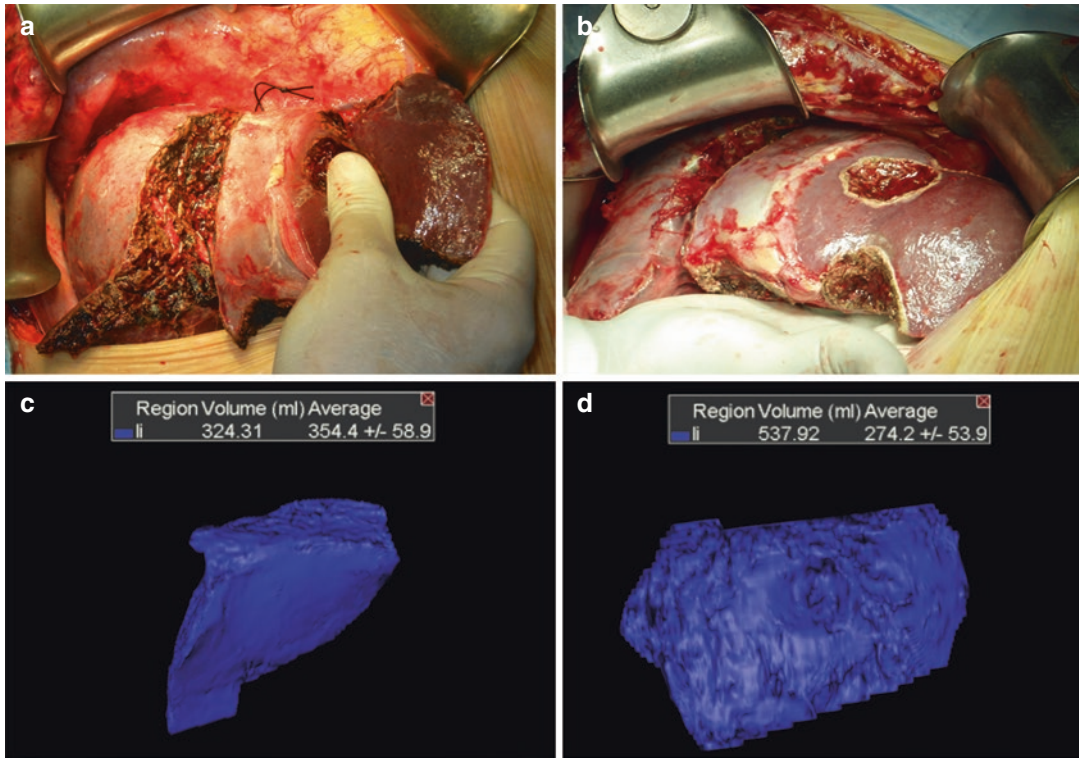

Fig. 15.5 Complete ALPPS strategy in a 57-year-old female with multiple bilateral colorectal liver metastases. (**a**) First stage showing partial parenchymal transection and multiple resections in the future liver remnant (FLR). (**b**) Hypertrophied FLR at completion surgery 7 days after first stage. (**c**) Preoperative CT-volumetry showing a FLR/total liver volume (TLV) ratio of 26.5%. (**d**) CT-volumetry 6 days after first stage showed a 67% FLR hypertrophy and a FLR/TLV ratio of 49%

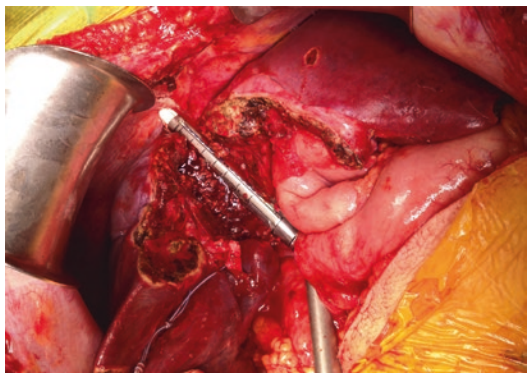

Fig. 15.6 A vascular stapler is being used to facilitate disease hemi-liver resection

Proposed Technical Variations

Many different technical variations of the ALPPS approach have been proposed. Even though the original technique as described by Schnizbauer et al. [11] consisted in a right trisectionectomy for patients with a tumor-free left lateral segment, Gauzolino and colleagues [26] later presented different technical variations of the ALPPS approach, including the "left ALPPS," the "right ALPPS," and the so-called "rescue ALPPS" in patients with failed PVE/PVL. An additional alternative was introduced by de Santibañes et al. [27], who preserved only segments 1 and 4 as FLR after performing a left lateral sectionectomy for extensive disease (Fig. 15.7). However, concerning FLR variants in ALPPS, the most important breakthrough was accomplished after demonstrating that monosegment remnants can be safely left behind when applying the ALPPS approach (Fig. 15.8) [15, 28]. This constitutes an important paradigm change in liver surgery, given that resectability has been traditionally defined as the complete tumor removal preserving at least two contiguous Couinaud's segments with intact vascular inflow, outflow, and biliary drainage.

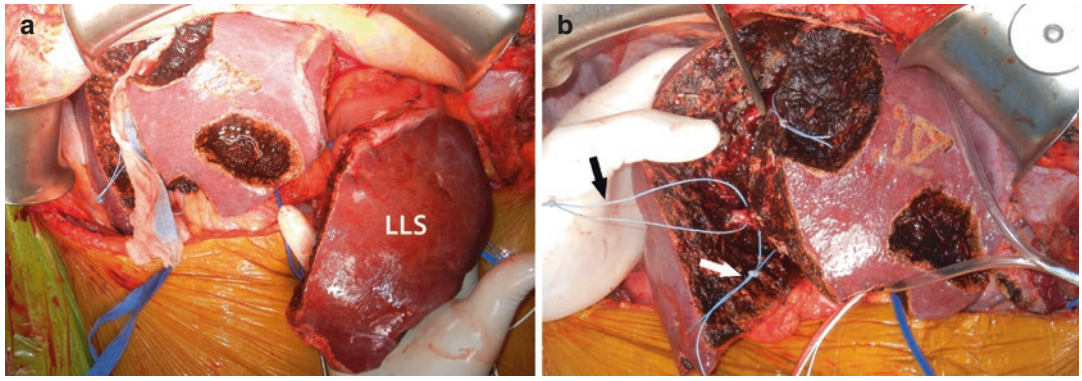

Fig. 15.7 ALPPS first stage preserving only segments 4 and 1 as future liver remnant. (**a**) The left lateral segment (LLS) is resected after atypical resections were performed in segment 4. (**b**) The liver partition is performed at the level of the Cantlie's line. The anterior (*black arrow*) and posterior (*white arrow*) right hepatic pedicles are encircled with *light blue* ties

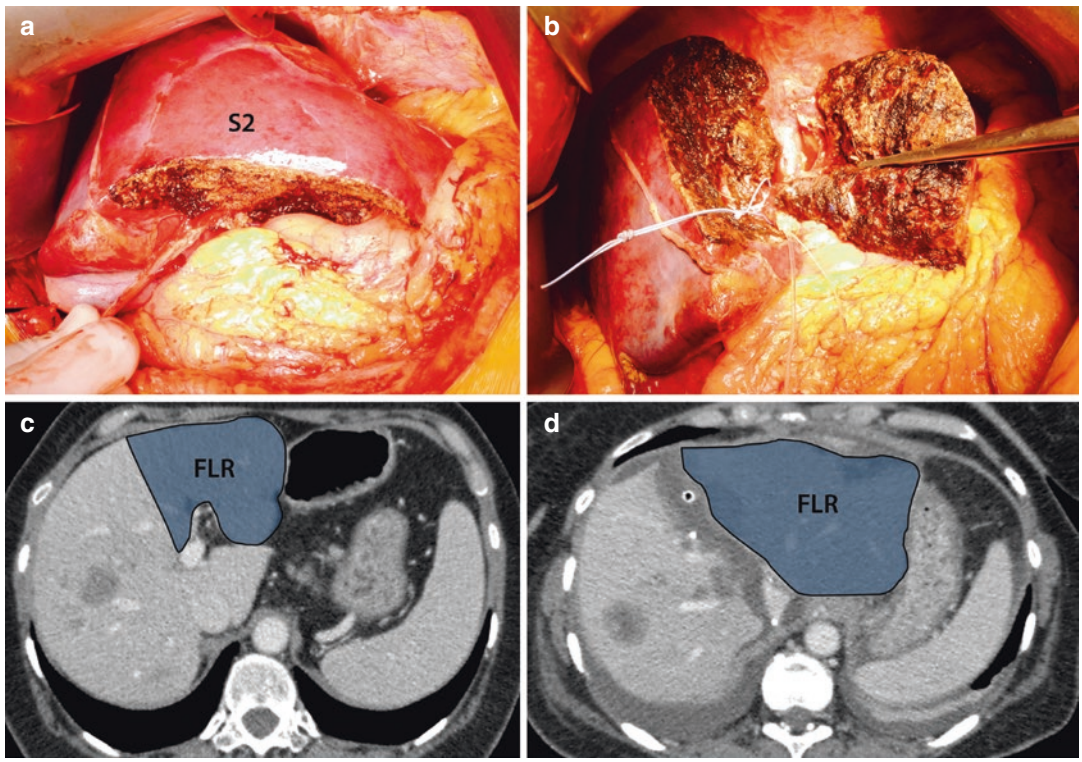

Fig. 15.8 Segment 2 monosegmental ALPPS in a 55-year-old woman with multiple bilateral liver metastases. (**a**) First-stage procedure showing complete the anatomical resection of segment 3 in the future liver remnant (FLR). (**b**) Total parenchymal transection up to the inferior vena cava. The right vasculobiliary pedicle is encircled with a *light blue* tie. (**c**) Preoperative CT-scan showing the FLR. (**d**) Postoperative CT-scan demonstrated a 170% hypertrophy of the FLR (segment 2) 6 days after first stage

Given that ALPPS has been associated in preliminary series with increased incidence of major complications and mortality [11, 24, 25], many different technical innovations and refinements have been introduced recently with the aim of improving both short- and long-term outcomes. With regards to liver partition modifications, Robles et al. [29] from Murcia, Spain, described the application of a tourniquet around a parenchymal groove of no more than 1 cm in

the transection line, and labeled this modification "ALTPS" (associating liver tourniquet and portal ligation for staged hepatectomy). Despite the attractiveness of the tourniquet, the 64% morbidity and 9% mortality in their series of 22 patients does not reflect a real improvement in terms of patient safety compared with most ALPPS series. More recently, other authors have proposed to replace parenchymal transection by using radiofrequency or microwave ablation (RALPP, LAPS) to create a virtual liver partition through a "necrotic groove" between both hemi-livers [30]. These approaches provided a similar hypertrophic profile than the standard ALPPS approach but with only minor complications, no mortality, and a high feasibility of being performed by laparoscopy. On the other hand, the application of PVE instead of PVL as method of portal vein occlusion, also known as "hybrid ALPPS", is undoubtedly one of the most promising innovations among the different ALPPS proposals. This was first described by Li et al. [31], who successfully performed a percutaneous PVE during the postoperative period in two patients with gallbladder carcinoma infiltrating the right portal vein. The fact of avoiding portal pedicle dissection during first stage is more in line with the "non-touch" oncological principle and facilitates second stage by generating fewer adhesions. Finally, based on the several proven benefits of laparoscopic over open surgery, different authors have demonstrated that pure laparoscopic ALPPS is feasible and safe, reaffirming that ALPPS candidates might also benefit from minimally invasive surgery [15, 32, 33]. Given the existence of many technical variants with different names, the founding members of the International ALPPS Registry have recently reported a "consensus" terminology in order to establish a common language to adequately compare and further develop different variants of the original ALPPS technique [34].

Hypertrophic Efficacy

The most impressive characteristic of the ALPPS approach is a very rapid and large FLR hypertrophy. Data from the ALPPS Registry in 202 patients indicated a FLR hypertrophy of 80% (range: 49–116%) within a median time interval of 7 days (range: 6–13 days) between surgery and volumetric CT-scan [17]. In a recent single-center series, 80% of patients treated with ALPPS achieved a sufficient hypertrophy in <10 days [15]. The hypertrophy seen in ALPPS is clearly superior to traditional strategies, especially for patients with initially very small FLR. A recent comparative study by Croome et al. [35] demonstrated that ALPPS was significantly superior to PVE in terms of both the degree of hypertrophy (84.3% vs 36%; $P < 0.001$) and the kinetic growth rate (32.7 cm^3/day vs 4.4 cm^3/day; $P < 0.001$). These results are in line with those of Schadde et al. [36], who demonstrated that kinetic growth rate was 11 times higher in ALPPS compared with PVE/PVL (34.8 cm^3/day vs 3 cm^3/day; $P = 0.001$).

The degree of hypertrophy after ALPPS is not unprecedented,; a similar phenomenon has been previously described, but in a totally different scenario. Nadalin et al. [37] observed that healthy liver donors who underwent a resection of 60% of liver volume exhibited a mean remnant liver hypertrophy of 88% within 10 days after surgery. More recently, a comparative study found similar or even greater kinetic growth rate in healthy liver donors compared with ALPPS [35]. Despite these experiences describing remarkable liver regeneration after partial hepatectomy, the rapid and large FLR hypertrophy observed with ALPPS is still impressive given that it is achieved in very ill patients with primarily non-resectable disease subjected to extended liver resections in a small-for-size setting, and with a remnant parenchyma of poor quality or even cirrhotic [11, 15, 17]. Furthermore, most patients treated with ALPPS undergo prolonged preoperative chemotherapy [11, 15, 17], which has been associated with less regenerative capacity, even in patients treated with the ALPPS approach [38]. On the other hand, the ALPPS has demonstrated to be an effective step-up alternative as a salvage procedure to induce further hypertrophy and allow resection in patients with CLM who fail to achieve a sufficient FLR after PVE or PVL [15, 39, 40]. Nowadays, this scenario has become an unquestionable indication for ALPPS.

It has been hypothesized that edema, liver congestion, or inflammation might explain macroscopic

FLR hypertrophy during ALPPS. However, there is already consistent evidence both in animals [41] and humans [11, 16, 42] indicating that there is true histological correlation through proliferative and architectural changes accompanying macroscopic hypertrophy during ALPPS. Despite the fact that the surgical interruption of bilateral cross-portal circulation appears to be the main catalyst of the enhanced liver hypertrophy observed in ALPPS, the exact regenerative kinetics behind the restoration of hepatovascular mass remains poorly understood, and is most likely multifactorial. This phenomenon could possibly be explained by the following mechanisms: (1) PVL creates a redistribution of portal blood flow and hepatotrophic factors to the FLR; (2) parenchymal partition impairs collateral circulation and causes a surgical trauma that might per se induce the systemic release of circulating proliferating factors that could be crucial for liver growth; (3) this new approach might also involve a preconditioning phenomenon for the FLR, where the diseased hemi-liver acts as a transitory auxiliary liver that assists the growing FLR in metabolic, synthetic, and detoxifying functions for the first and critical week after resection. Additionally, preliminary data indicates that portal flow modulation and portal pressure might also influence the hypertrophic phenomenon observed in ALPPS, where the arterialized auxiliary liver may play an alleviating hemodynamic role during the interval period that becomes less important once the FLR has recovered [15]. The restoration of the hepatovascular mass is a fascinating field in regenerative medicine. Certainly, the ALPPS is an innovative surgical model that will progressively give rise to more research and knowledge of the regulatory networks that control the regenerative mechanisms of the liver.

Interval Management and Timing of Second Stage

Patient management during the interval period between both surgical stages is key for the successful application of ALPPS. Morbidity and mortality during ALPPS have been associated in most series with inappropriate patient selection, unsuitable timing of the second stage, and errors in clinical judgment due to the lack of experience with the application of a new technique [11, 17, 24, 25]. The fact that mortality occurs more frequently after the second stage and PHLF remains an important cause of death [17, 43, 44], indicates that the criteria being used to judge FLR sufficiency before reoperation might not be adequate enough.

Given that remnant liver volume is a known predictor of PHLF [5, 6], most authors have defined FLR sufficiency during the interval period based in volume rather than function, simplifying postoperative functional assessment between the two stages to daily clinical evaluation and liver function blood tests. However, the results obtained from such functional evaluation could be misleading, as it provides total liver function assessment, which in this scenario includes that of the diseased hemi-liver that will be removed. Moreover, the fact that PHLF remains the most important cause of death in the ALPPS Registry indicates that the established volumetric criteria being used to judge FLR sufficiency before reoperation might not be sufficient, particularly when taking into account that these volume measurements are applied to a fast-growing parenchyma. Even though previous studies have observed proliferative and architectural changes at histological level accompanying macroscopic FLR hypertrophy in ALPPS, rapid volumetric increase may not be immediately corresponded by an equal increase in function, as recently suggested by histologic findings showing hepatocytes immaturity in nontumorous FLR parenchyma [45]. Even though there is agreement that the second stage should be postponed until a satisfactory function has been reached, the key question yet unanswered is how good the FLR function has to be in order to avoid PHLF. From the various more sophisticated liver functional studies available (HIDA test, galactose elimination capacity, the indocianine green test or the LiMAx test), hepatobiliary scintigraphy (HBS) is probably the most promising, given that it provides information on sectorial liver function [46]. This fact is particularly important in the case

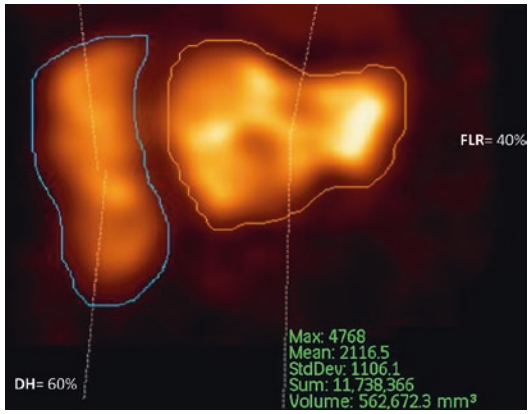

Fig. 15.9 Scintigraphic image during ALPPS interval period to assess sectorial liver function. The future liver remnant (FLR) represented 40% of overall liver function. *DH* diseased hemi-liver

of ALPPS, where the decision to perform the second procedure must be done taking into account the regional FLR functionality. In a previous study, we found that none of the patients with a FLR representing at least 30% of total liver function by HBS (%FLR-C) before the second stage developed PHLF (Fig. 15.9) [15]. However, a major drawback of the %FLR-C is that it does not take into account if the overall liver function is indeed good or not, which could lead to misinterpretations and errors in clinical judgment. This fact, along with the impossibility of using the 2.69%/min/m^2 FLR-function (FLR-F) cutoff proposed by the AMC group in Amsterdam [46], since it was not established using modern HBS assessment (Gmean and SPECT analysis), lead us to develop a new formula to measure FLR sectorial function during ALPPS interval. The Hospital Italiano de Buenos Aires Index (HIBA-*index*) is a dynamic measure that represents the proportion of radionuclide accumulating in the FLR during the phase between 150 and 350 s post-injection and is calculated using the area under the time-activity curves (AUC) with the following formula expressed as %:

$$\text{HIBA}-\text{index} = \frac{AUC\ \text{liver} - AUC\ \text{blood pool}}{AUC\ \text{field of view}} \times \frac{FLR\ \text{counts}}{\text{Total liver counts}}$$

Between 2011 and 2016, 20 out of 39 patients (51%) underwent HBS before completion of ALPPS second stage at the Hospital Italiano de Buenos Aires. After comparing the individual performance of three interstage FLR functional parameters (%FLR-C, FLR-F, and HIBA-index), a HIBA-index with a cutoff value of 15% was found to be the most accurate parameter to predict clinically significant PHLF after the second stage [47]. The predicted risk of PHLF in patients with a HIBA-index lower than 15% was 80%, whereas no patient with a HIBA-index higher than 15% developed PHLF. This practical cutoff value may become of paramount importance to avoid futile indication of ALPPS second stage, as current standard volumetric criteria have so far proved insufficient to adequately guide the safe timing of ALPPS stage 2.

In general, common sense indicates that second stage should be undertaken only if the patient is in good condition and functional and volumetric studies have demonstrated FLR sufficiency. Even though the feasibility of ALPPS to remove tumor in a short period of time is very high, the 1-week interval dogma has been penalized in several series with high complication rates and mortality. It is therefore important to remark that while ALPPS is a indeed a two-stage procedure, the second stage should be delayed or even abandoned in case of compromised clinical status, active complications, or abnormal liver function tests in order to avoid mortality. In cases where the patient is in good condition but FLR sufficiency has not been achieved, the patient can be discharged home and readmitted for second stage once FLR sufficiency has been certified during periodic outpatient evaluation [15].

Short and Long-Term Outcomes

Even after more than 5 years from the inaugural publications of the ALPPS approach, the available evidence in the existing literature remains low and mostly represented by retrospective studies including a limited number of patients, making the interpretation of outcome data difficult [48].

Postoperative Complications

The rapid worldwide adoption of ALPPS after being described in Germany has resulted in preliminary single-center and cooperative experiences showing high morbidity and mortality rates of this emerging method (Table 15.1), [24, 49–51]. A meta-analysis from Schadde et al. [48] including 295 patients with different tumor origins revealed a 90-day mortality of 11% and morbidity grade ≥IIIa of 44%. The relatively high morbidity and mortality rates reported with ALPPS could be explained, because it is composed essentially of two complex surgical procedures instead of only one, undergoing an obligatory "learning curve", and that is applied in borderline patients with high tumor burden and prolonged chemotherapy regimens. However, more recent data from the ALPPS Registry on 528 patients indicated more acceptable results, with an overall 90-day mortality of 8.9% [21]. When it comes to tumor origin, CLM has shown the highest safety profile, with a morbidity grade ≥IIIa of 29% and a 90-day mortality of 5% in 228 patients [44]. Moreover, a recent multicentric Scandinavian study as well as a single-center prospective study have both demonstrated that ALPPS can be performed with sufficient safety in specialized centers, reporting mortality rates of 2.8% and 6.6% respectively [15, 52]. In this later study, it must be remarked that mortality in the 19 patients with CLM was nil [15]. These results are

Table 15.1 Overview of ALPPS case series with more than ten patients including colorectal liver metastases (CLM)

Author	Year	Country	Case No. (total/CLM)	Hypertrophy (%)	Interval (day)	Feasibility (%)[a]	Hospital stay (day)	Morbidity (%)	Mortality (%)
Linecker et al. [21]	2016	Registry	528/364	70	10	98	20	40[b]	8.9
Røsok et al. [52]	2016	Scandinavia	36/25	67	7	100	17	11[b]	2.8
Serenari et al. [51]	2016	Italy[c]	50/21	63	10	96	–	54[b]	20
Truant et al. [40]	2015	France[c]	62/50	48.6	10.5	95.2	29.2	80.6	12.9
Alvarez et al. [15]	2015	Argentina	30/19	89.7	7	97	16	53	6.6
Petrowsky H et al. [23]	2015	Switzerland	24/16	61	10	100	–	33.3[b]	16.6
Lang et al. [58]	2015	Germany	16/9	99.3	9	100	30	81	12.5
Hernandez et al. [16]	2015	Canada	14/14	93	8	100	23	36	0
Ratti et al. [50]	2015	Italy[c]	12/12	47	8	100	24	83.3	8.3
Tanaka et al. [43]	2015	Japan	11/10	52.8	7	100	11	46	9
Schadde et al. [36]	2014	Multicenter	48/26	77	–	100	–	73	15
Nadalin et al. [24]	2014	Germany	15/5	87.2	13	100	–	66.7	28.7
Torres et al. [49]	2013	Brazil[c]	39/32	83	14.1	94.8	17.8	59	12.8
Schnitzbauer et al. [11]	2012	Germany[c]	25/14	74	9	100	–	64	12

[a]Completion of both stages
[b]Only major or severe complications reported
[c]Multicenter same country

in line with those of Hernandez-Alejandro et al. [16], who reported 36% morbidity and 0% mortality in 14 patients with CLM.

Even though morbidity rates are similar after stage 1 and 2, >90% of deaths occur after stage 2 [44]. Age, biliary tumors, operative time more than 5 h during stage 1 and the administration of red blood cell transfusions during either stage have been identified as significant risk factors for severe complications and 90-day mortality in ALPPS [17]. In addition, recent data from the International Registry indicate that patients who develop PHLF after stage 1 or have a MELD score ≥10 before stage-2 are at higher risk, with an adjusted odds of 90-day mortality of 3.9 (CI 1.4–10.9) and 4.9 (CI 1.9–12.7) respectively [44]. On the other hand, a recent prospective study at the Hospital Italiano de Buenos Aires found that total parenchymal transection was an independent risk factor of postoperative complications [15].

Proponents of PVE argue that the ALPPS has excessively high morbidity and mortality rates. However, the recently reported 84% morbidity and 10% mortality from 87 patients who underwent a major hepatectomy after PVE or PVL at the Beaujon Hospital in France for initially unresectable CLM does not seem to wholly support such asseveration [53]. Moreover, a recent publication aiming to compare a very selected series of PVE (78% as one-stage hepatectomy) with the ALPPS multicenter German experience, could not demonstrate a significant difference in overall morbidity and liver-related mortality between both methods [54]. Despite the efforts of comparing ALPPS with PVE, this does not seem completely accurate given that both strategies are to be used in different scenarios. CLM represents the main indication for ALPPS in most series, where up to 80% of the patients treated have bilateral disease [15]. Given the fact that PVE in a one-stage hepatectomy strategy should not be performed in this setting, it seems that the more reasonable and fair comparison of ALPPS is with other two-stage procedures rather than with PVE alone. Taking this into account, the results obtained from recent ALPPS series concerning only patients with CLM are better than initial ALPPS series, and compare favorably with most reported series of two-stage hepatectomies [15–17]. In a recent publication from the MD Anderson Group, among 65 patients who underwent a two-stage hepatectomy, they reported 49% morbidity and 6.4% mortality rates, considering only the second stage [9]. In the published experience at the Hôpital Paul Brousse with two-stage hepatectomies including 59 patients, a morbidity of 59% and mortality of 7% after the second stage was observed [8]. In addition, a cooperative experience including 45 patients from two major hepatobiliary centers reported an overall mortality of 8.8% (4% after the first stage and 5% after the second stage) [55]. As noted above, from the available data on the most important series of two-stage hepatectomies, the reported morbidity and mortality rates are similar to that obtained with the ALPPS approach in recent series. Finally, it should not be forgotten that the mortality of two-stage hepatectomy proposed by the Paul Brousse group dropped from a 15% in the inaugural series of the year 2000 to 7% in 2008 and to 4% in 2014 [8, 10, 56]. It is therefore likely that as with every new development, the outcomes of ALPPS will improve in the near future as a consequence of better patient selection and technical refinements as more experience is gained.

In order to increase ALPPS safety, current recommendations are based on the three pillars that determine outcomes: (1) *Patient selection*—the best candidates are patients younger than 70 years old with CLM; (2) *Operative technique*—partial parenchymal transection without sacrificing the middle hepatic vein, intraoperative cholangiography, and hydraulic test at both stages, avoidance of simultaneous pancreatic resections as well as fecal diversion in case of simultaneous left colonic or rectal resections are key rules; and (3) *Timing of second stage*—the 1-week interval dogma needs to be abandoned, and patients should be operated once volumetric and functional studies have demonstrated FLR sufficiency, but only if they are in good clinical condition, without complications, having normal

liver function tests and a MELD score <10, regardless of the number of days needed to achieve this status.

Oncological Results

Most ALPPS series to date reported only short-term outcomes. The promising short-term results obtained so far are difficult to interpret from the oncological point of view due to the heterogeneous group of patients with different underlying pathologies, variable use of chemotherapy, and technical variations applied.

In terms of tumor resectability, there is already strong evidence indicating that ALPPS has higher resectability rates compared with PVE or PVL in classical two-stage hepatectomy [15–17, 28, 48]. The first report from the International ALPPS Registry demonstrated that both ALPPS stages were completed in 98% (197/202) of patients [17]. This resectability rate is equivalent (97%) to that from meta-analytic data from six studies including 295 patients [48]. The R0 resection rate from this last study including the largest number of patients was 91% [48]. These results contrast with the recent systematic review from Lamb et al. [57] including 459 patients undergoing two-stage hepatectomy, where R0 resection was achieved in only 75% of the 76% of patients who finally arrived to the second stage. Moreover, a recent multicenter comparative experience demonstrated that ALPPS had a higher efficacy in terms of achieving complete tumor resection when compared with PVE/PVL (83% vs 66%; $P = 0.027$) [36]. Contrary to PVE/PVL, where up to 40% of patients might never arrive to the second stage, the ALPPS approach offers complete tumor resection to almost all patients treated. This dropout reduction can be explained because almost all patients achieve sufficient hypertrophy, the short interval makes tumor progression unlikely, and liver splitting prevents direct tumor infiltration of the future liver remnant.

With regard to oncological outcomes, probably the most important question still unanswered is whether the higher tumor resectability observed is latterly translated into improved overall (OS) and disease-free survivals (DFS). While the available evidence does not definitively answer this question, recent studies suggest that patients with CLM may have similar short-term oncological outcomes when compared with patients treated by traditional approaches [15–17, 36]. A recent comparative multicenter study showed that tumor recurrence occurred at a comparable rate in both groups at 12 months, with 54% in ALPPS and 52% in PVE/PVL [36]. The largest available data from the ALPPS registry in patients with CLM indicates so far a 1- and 2-year OS of 76% and 62% as well as a DFS of 59% and 41% respectively, with a median DFS of 14 months [17]. This median DFS is more than acceptable when compared to the 7.5 months of median DFS recently reported in the updated experience from the Hôpital Paul Brousse in two-stage liver resections [56]. Furthermore, the subgroup of CLM from the Registry with age ≤60 years exhibited the best OS, being 88% and 74% at 1- and 2-years respectively, with a median survival of 24 months. Even though only short-term follow up is available, this survival figures (on an intention-to-treat basis) are similar or even better than that in the few existing series of two-stage hepatectomies, provided that most reports analyzed only the survival of patients who arrived to the second stage [9, 56]. Moreover, the 64% 3-year OS in patients with CLM from the group leaded by Hans Schlitt [58] compares favorably with that of conventional staged approaches. At the Hospital Italiano we have treated 39 patients with the ALPPS approach; 26 of whom (67%) had CLM. In this specific subgroup, 96% of patients had received preoperative chemotherapy and 62% received more than six cycles. The disease-specific OS and DFS at 3 years in our series of CLM is 49% and 9% respectively. Such results are most likely related to an aggressive tumor biology, as demonstrated by the fact that more than 80% of our patients had a node + primary, synchronous presentation, and multiple bilateral disease all together.

Finally, when analyzing survival it must be taken into account that outcomes are directly

related to patient selection, and if we select for ALPPS those patients with extensive bilateral liver disease (probably not the ideal candidate but the "true" candidate), poor results should not be surprising. Therefore, current evidence does not allow any firm conclusion regarding the oncological superiority or inferiority of ALPPS compared with classical approaches, and randomized controlled trial data should be awaited to clarify this important aspect.

Benefits, Drawbacks, and Future Perspectives

Since the first formal reports in 2011, the ALPPS has gained rapid popularity and impressive worldwide impact [59], with over 900 patients currently enrolled in the worldwide registry [13, 21]. As demonstrated above, ALPPS has unique benefits over the established methods that prompt its inclusion among other treatment modalities for patients with locally advanced liver tumors: (1) aggressive FLR clean-up, with the possibility of leaving single liver segments as sufficient liver remnant, (2) unparalleled FLR hypertrophy, specially for patients with initially a very small FLR, (3) reduced interval, with less adhesions and easier definitive resection, (4) single hospitalization being possible in the majority of patients, with potential positive psychological, and financial impact, (5) higher resectability rates compared to classical approaches, and (6) rescue of unsuccessful PVE/PVL. In addition, there are other benefits of ALPPS that deserve to be commented despite they are shared with conventional two-stage resections: (a) abdominal exploration during first stage allows accurate staging, (b) the deportalized hemi-liver acts as a temporary auxiliary liver contributing to liver function during interval period, and (c) the hepatic mass reserve allows combined colorectal and major liver resections.

Despite the potential benefits of ALPPS, the surgical community is still debating its clinical application due to a relatively high morbidity and mortality in initial series as well as uncertain long-term oncological outcomes. This fact, together with the increased international interest, led to the "1st ALPPS International Consensus Meeting" at Hamburg in February 2015 [14]. In this meeting, everything seemed to indicate that ALPPS had arrived to stay as a valuable option for selected patients. However, in terms of safety, the quality of liver parenchyma and its function are clearly future directions to improve patient selection as well as timing of second stage, both important determining factors of outcomes. As an alternative way of improving outcomes, during the 1st International Consensus Meeting we proposed a new surgical paradigm for ALPPS. This proposal inverts the current paradigm, transforming the classical large first stage into a much less invasive procedure, and leaving the main surgical procedure for the second stage. The so-called "Mini-ALPPS" incorporates the combination of evidence-based facts such as partial parenchymal transection, intraoperative PVE, and "non-touch" oncological rules (strictly avoiding portal pedicle dissection and liver mobilization) with the aim of maximally reducing the surgical impact of ALPPS first stage to promote rapid patient recovery and facilitate second stage (Fig. 15.10), [60]. This new philosophy seems promising and could improve both safety and oncological outcomes.

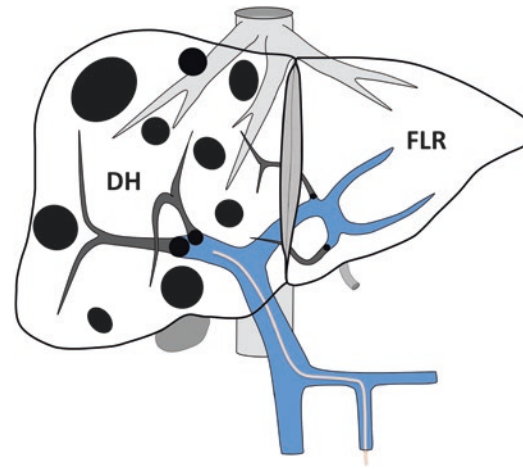

Fig. 15.10 Minimally aggressive ALPPS first stage. Intraoperative right portal vein embolization + segment 4 branches are applied through the inferior mesenteric vein replacing portal vein ligation. Additionally, minimal liver transection to an extent of about 2–3 cm deep is used instead of a larger partition. *FLR* future liver remnant, *DH* diseased hemi-liver

Conclusions

In summary, the ALPPS proposal represents a milestone in HPB surgery, as one of the ultimate advances to surgically induce fast liver hypertrophy. This short-interval two-stage strategy has been demonstrated to provide high rates of complete tumor resection in selected patients with otherwise unresectable CLM, where almost all patients eventually benefit from a curative resection. Recent evidence indicates that ALPPS can be performed with acceptable morbidity and mortality in experienced centers, comparable to conventional two-stage hepatectomies. Moreover, the high morbidity and mortality rates published in multicentric reports will most probably improve in the near future as a consequence of learning curve, technical improvements, and better patient selection. Although there are patients who may be treated with either PVE, classical two-stage hepatectomy or ALPPS, there are patients who do not have another option or might mostly benefit from ALPPS instead of other strategies. Such patients have failure of PVE/PVL or extensive bilateral disease where an extremely small FLR might result as consequence of tumor clean-up, especially if there is tumor close to FLR boundaries. It seems that ALPPS will never replace PVE for patients with a tumor-free FLR, but it might become a good option in certain cases with bilateral disease if future evidence demonstrates better or equal long-term outcomes compared with classical two-stage liver resections. Given the increasing evidence supporting the use of HBS to quantify sectorial liver function, we encourage the routine use of this complementary non-invasive low-cost exam to facilitate decision-making regarding the timing of the second stage. The ALPPS is a challenging surgical innovation that should be performed only at high-volume specialized centers, on patients selected by a multidisciplinary team, and included in the International ALPPS Registry.

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Parenchymal-Sparing Liver Resections

16

Alessandro Ferrero, Roberto Lo Tesoriere, Serena Langella, and Nadia Russolillo

Introduction

Resection is the established gold-standard treatment of colorectal liver metastases (CLM). The surgical management of CLM has changed dramatically during the past three decades. Historically, major hepatectomy represented the treatment of choice in patients with CLM. This paradigm has changed with the diffusion of the parenchymal-sparing liver resections (PSLR). This approach preserves healthy functional liver parenchyma without compromising principles of oncological surgery [1]. The PSLR was initially proposed only in patients with single and subglissonian CLM, and subsequently extended to patients with deep and multiple CLM, thanks to the development and widespread use of intraoperative liver ultrasound (IOUS) (Fig. 16.1). As a direct consequence, all the main series in literature have reported a dramatic increase of the number of segmentectomies and wedge resections as alternatives to major liver resections.

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Surgical Principles of Parenchymal-Sparing Liver Resection

An independent association of the number of resected segments with postoperative complications and mortality rate is clearly described. The main series focusing on trends in perioperative outcomes after liver resection over the decades have shown a significant reduction of mortality rate. Nevertheless, despite better patient selection and perioperative management, the rate of postoperative mortality after major or extended resection did not change over the years. Therefore, we can suppose that much of the decrease in mortality was probably related to the intensely diffusion of PSLR. A recent study on 3875 patients with CLM treated from 1993 to 2012 at Memorial Sloan Kettering [2] reported a significant decrease of the median number of resected segments over the years (from 4 to 2), with a simultaneous decreased mortality rate from 5.2 to 1.6%. Interestingly, these results were not confirmed in the subgroup of patients treated with major liver resections. Many authors reported that PSLR was also associated to a significant reduction of postoperative morbidity. In particular, Gold et al. [3] showed at multivariate analysis that the rates of liver-related complications were strictly correlated to the number of resected segments.

In fact, postoperative liver function is well preserved in PSLR with postoperative serum bilirubin level significantly lower and prothrombin time significantly higher with respect

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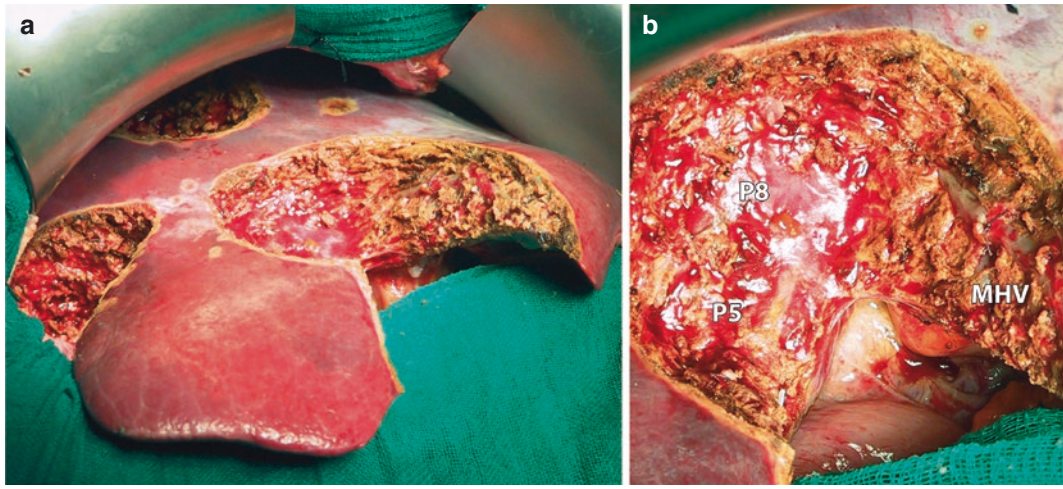


Fig. 16.1 Multiple atypical resections for colorectal liver metastases (CLM) synchronous to colon cancer. (**a**) Sg8 wedge resection, Sg6 wedge resection, and Sg5 subsegmentectomy. (**b**) Detail of Sg5 subsegmentectomy. The Sg5 spared pedicle (*P5*) and Sg8 pedicle (*P8*) are exposed on the right side of the cut surface. Middle hepatic vein (*MHV*) is exposed on the left side of the cut surface

to patients who received major resection [4]. These results concerning liver function are even more interesting if we consider the adverse effects of neoadjuvant chemotherapy on liver parenchyma. It's important to note that the main cause of death after liver resection is still liver failure. So it is crucial to prevent this complication for which no efficient therapies are available. Finally, Kingham et al. [2] reported lower estimated blood loss and transfusion rate, as fewer segments were resected. These data are important given the negative impact of both these factors on long-term results.

Oncological Principles of Parenchymal Sparing Liver Resection

The development of PSLR is based on the assumption that it meets the principles of oncological surgery. Per definition, PSLR is more likely to be associated with smaller margins. It is known that intrahepatic micrometastases via portal branch are uncommon in case of colorectal liver metastases, as reported by the histopathological study performed by Yamamoto et al. [5]. In addition, we previously reported [6] that the width of a negative surgical margin does not affect the risk of local recurrence or survival. A recent propensity score-matched analysis of nearly 3000 CLM hepatectomies validates these data [7]. In confirmation of oncological suitability of PSLR, many studies reported similar disease-free survival and liver recurrence rate in patients treated with or without conservative liver resection. One advantage of leaving the maximal amount of liver parenchyma is to enhance the possibility of repeat hepatectomy in case of liver recurrence. From 60 to 70% of patients undergoing liver resection for CLM will develop recurrence of the disease [8]. Of these, one third will have isolated liver recurrence. It has been demonstrated that patients who undergo a second or a third liver resection for recurrent liver metastases may have long survival. According to this notion, some studies reported better overall survival for patients treated with PSLR compared with major resections, due to a higher likelihood of undergoing salvage hepatectomy for recurrence. One can argue that the majority of these reports compared heterogeneous groups of patients without matching tumor number or size, which makes the interpretation

of the data difficult. Nevertheless, Mise et al. [9] recently compared long-term results of patients with a single CLM less than 3 cm treated with (156 patients) or without (144 patients) PSLR. In this cohort of patients with uniform tumor characteristics, the authors confirmed better overall survival (72.4% vs 47.2%, $p = 0.047$) and higher redo-resection rate (68% vs 24%, $p < 0.01$) in PSLR group.

Ultrasound Guidance to Parenchymal-Sparing Liver Resections

IOUS has a key role in modern hepatic surgery not only to better stage the disease, but above all as guidance to resection [10]. The extensive use of IOUS allows to maximize the parenchymal sparing of healthy liver tissue. In fact, conservative liver resections in case of metastases deeply located can result in thin surgical margins, with the risk of exposing the tumor during the parenchymal transection. IOUS reduces this risk, as it makes it possible to precisely identify the site and the number of lesions, showing the relationships between the metastasis and the main vascular structures that can be followed in real time. Furthermore, IOUS permits to check the correct plane during parenchymal transection.

PSLR is a philosophy rather than a surgical technique that encompasses a wide range (countless actually) of liver resections, ranging from small non-anatomical wedge resection, to complex atypical non-anatomical resections (Fig. 16.2), to segmentectomies or subsegmentectomies. The crucial feature according to which type of resection is more appropriate is the need to sacrifice liver vessels, both glissonian pedicles and hepatic veins. Therefore, it is clear that a meticulous IOUS exploration of the liver is the necessary prerequisite for modern liver surgery. It is very important to be methodical in the IOUS exploration, in order to perform a complete and accurate examination. We recommend performing two standardized explorations. The first scan is for liver anatomy assessment, and is performed in a systematic manner, i.e., starting from the hepato-caval confluence and hepatic veins, than moving to portal bifurcation, left and right segmental pedicles till the third order of division. The second systematic exploration is for IOUS staging. The surgeon explores the parenchyma looking for new lesions, and precisely locates the metastases in the three-dimensional map of liver

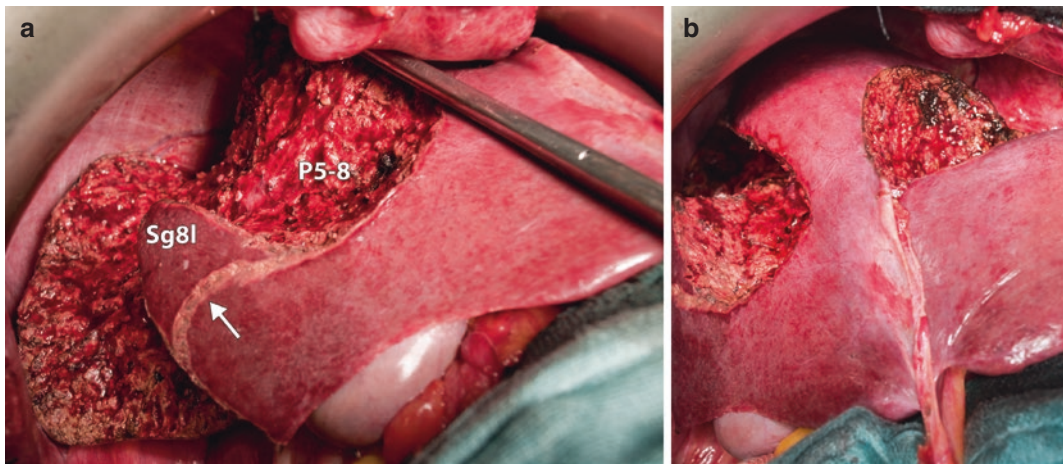


Fig. 16.2 Liver resection for multiple colorectal liver metastases (CLM). (**a**) Thirteen CLM have been resected with one wide resection of Sg5-6-7-8-4. While on resection, the lateral part of Sg8 (*Sg8l*) has been further spared (*arrow*: former section line including the whole Sg8). Anterior portal branch (*P5–8*) is exposed on the cut surface. (**b**) Resection of Sg3-4a for one additional CLM

vascular structure he just explored. During this step, the tumor vascular relationships are carefully assessed. IOUS makes it possible to measure the distance between a metastatic nodule and a vessel or, in the case of adhesion to the vessel, to define the longitudinal and circumferential extent of the contact. Vessels in contact with metastases have to be deeply explored for signs of infiltration such as tumor thrombi, or direct infiltration with endoluminal growth. Other indirect signs of infiltration such as uneven vessel wall profile, disappearance of the hyperechoic venous wall (Fig. 16.3), or biliary dilatation around glissonian pedicles (Fig. 16.4) can be identified. According to all these elements, the surgeon will decide which vessel to spare and which to cut, thus planning the extent of the resection. If vascular infiltration is suspected, the vessel should be ligated and sectioned in order to allow radical resection. Otherwise, the lesion can be dissected from the vessel, even if a thin surgical margin is obtained. However, in the case of infiltration of hepatic veins, when accessory veins or communicating veins are present, it may not be necessary to remove all of the liver parenchyma drained by that vein. In this setting, knowledge of the liver inflow and outflow by IOUS is fundamental for determining the feasibility of surgery. In fact, a third exploration is needed. It is the real IOUS guidance to whatever resection. As opposed to the first two, this exploration is focused on the lesion to be removed, and is performed after appropriate liver mobilization that can be minimal or extensive, with the liver lifted by the left hand of the surgeon. Relationships between tumor and surrounding vessels are

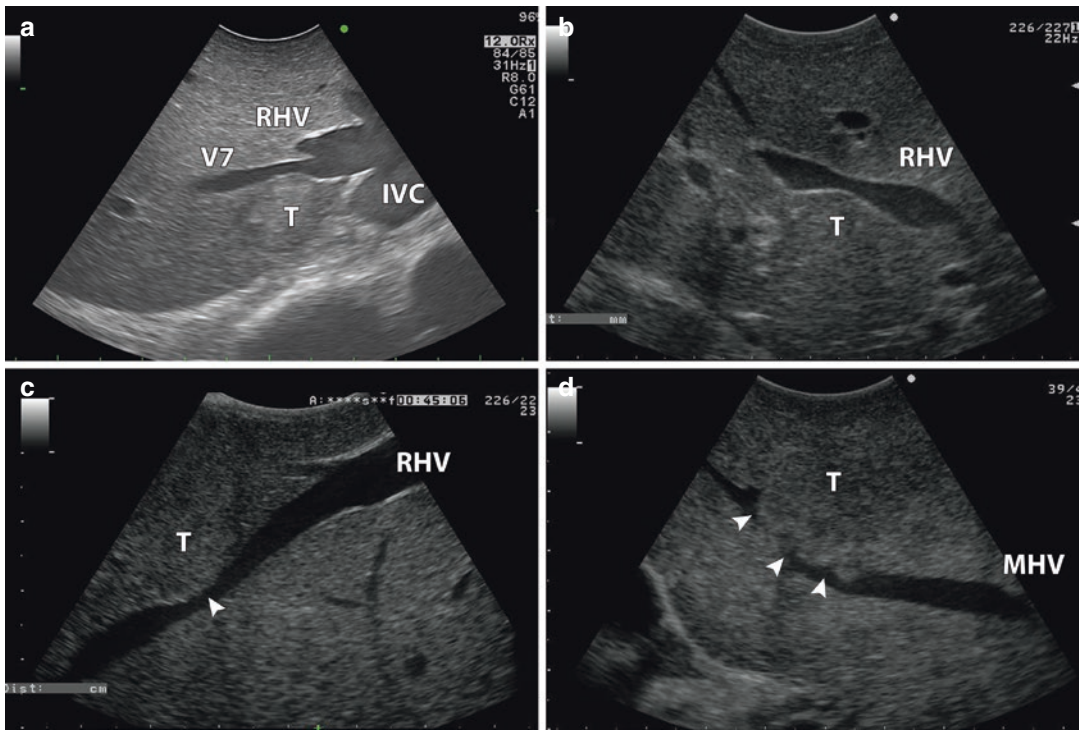


Fig. 16.3 Intraoperative evaluation of colorectal liver metastases (CLM) relationships with hepatic veins. (**a**) Hyperechoic CLM (*T*) in contact with a branch of right hepatic vein (*RHV*) draining Sg7 (*V7*) near the confluence with the inferior vena cava (*IVC*). The continuity of the hyperechoic rim of the vein indicates the integrity of the venous wall. (**b**) CLM (*T*) in contact with RHV. The isoechoic lesion can be identified barely by the distorted profile of the RHV. There is no interruption of the vein wall. (**c**) Isoechoic CLM (*T*) in contact with RHV with interruption of the venous wall (*arrowhead*). (**d**) Hypoechoic CLM (*T*) infiltrating middle hepatic vein (*MHV*). The venous wall is interrupted and grossly irregular in the site of infiltration (*arrowheads*).

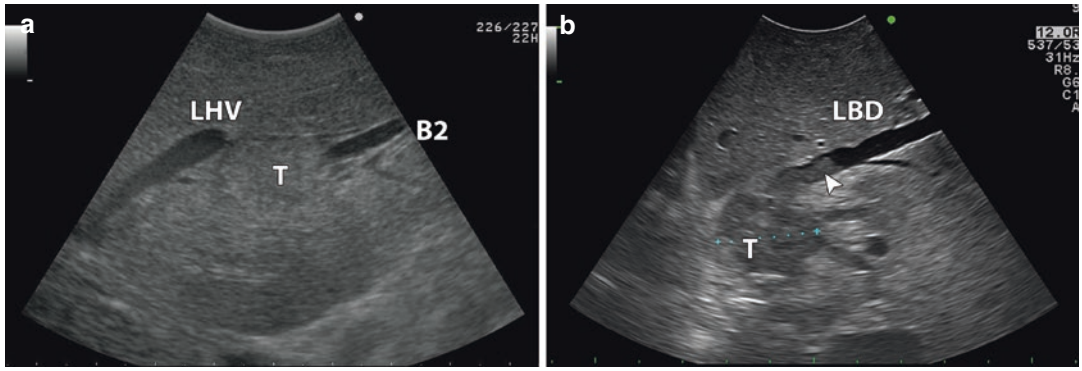


Fig. 16.4 Intraoperative evaluation of colorectal liver metastases (CLM) relationships with glissonian pedicles. (**a**) CLM (*T*) in contact with left hepatic vein (*LHV*) infiltrating Sg2 pedicle. The infiltration is indirectly revealed by the Sg2 bile duct (*B2*) dilatation. (**b**) Recurrent CLM (*T*) in Sg4-Sg1 in a patient previously undergone right hepatectomy. The tumor infiltrates the left bile duct (*LBD*). The duct is dilated with a tumor thrombus (*arrowhead*) spreading proximally

explored again in order to visualize and draw on the liver surface with cautery hepatic veins, portal pedicles and their branches, directly involved or just surrounding the lesion (Fig. 16.5). Vessel can be scanned in the longitudinal plane and the brief impression on the glissonian capsule left by of the probe mildly pressed can be marked with cautery. When the vessel is cross-scanned, it can be targeted with the artifact of the tip of the electrocautery slipped beneath the US probe and then properly marked. A series of cross-section marks can be joined to draw the longitudinal axis of the vessel. After the map of the area has been traced, the lines of transection are drawn accordingly. During parenchymal transection, IOUS allows monitoring of the correct surgical plane in order to maintain an adequate surgical margin and avoid lesions to major vascular structures. Finally, IOUS can be used to assess the correct drainage of remnant liver. Inflow and outflow are evaluated to detect ischemic or congestive areas. At the end of the operation, the raw cut surface of the liver can be visualized by IOUS, allowing the detection of any remaining lesion. The specimen itself can be explored outside the operative field to check the lesions and the surgical margin.

Resections of small, superficial metastases often do not require pedicle dissection or ligation. Nevertheless, the importance of IOUS should not be underestimated. In the first place, to ascertain the distance of vessels and that indeed none has to be ligated. Then, IOUS helps to choose the proper distance between the section line and the metastasis projection (Fig. 16.6). It is in fact important to allow an adequate distance, not only to get a negative margin in the lateral aspect but especially in the deep plane. The transection route has to reach the deepest point beneath the lesion with an even angle and adequate margin. Beginning the transection too close to the lesion would require an almost vertical route that would make the resection difficult and unsafe. In fact, it is not uncommon to achieve a positive margin for "easy" resection. Besides, limited resections does not always mean easy resections. Multiple bilobar atypical resections, possibly associated with segmentectomies or subsegmentectomies, are often lengthy and demanding procedures inconceivable without IOUS planning and constant guidance (Fig. 16.7). When a glissonian pedicle is involved and cannot be spared, it can be checked by IOUS, precisely targeted and ligated in the dissection, even though in many cases the extent of the resection is decided upon the involvement of hepatic veins, whose ligation could impair the outflow of (theoretically) a whole liver sector. When IOUS shows no sign of infiltration or limited contact, lesions can be detached during dissection, thus sparing the vessel involved. IOUS guidance makes it possible to reach the proper vein with a correct angle and to guide the dissection exposing the spared hepatic

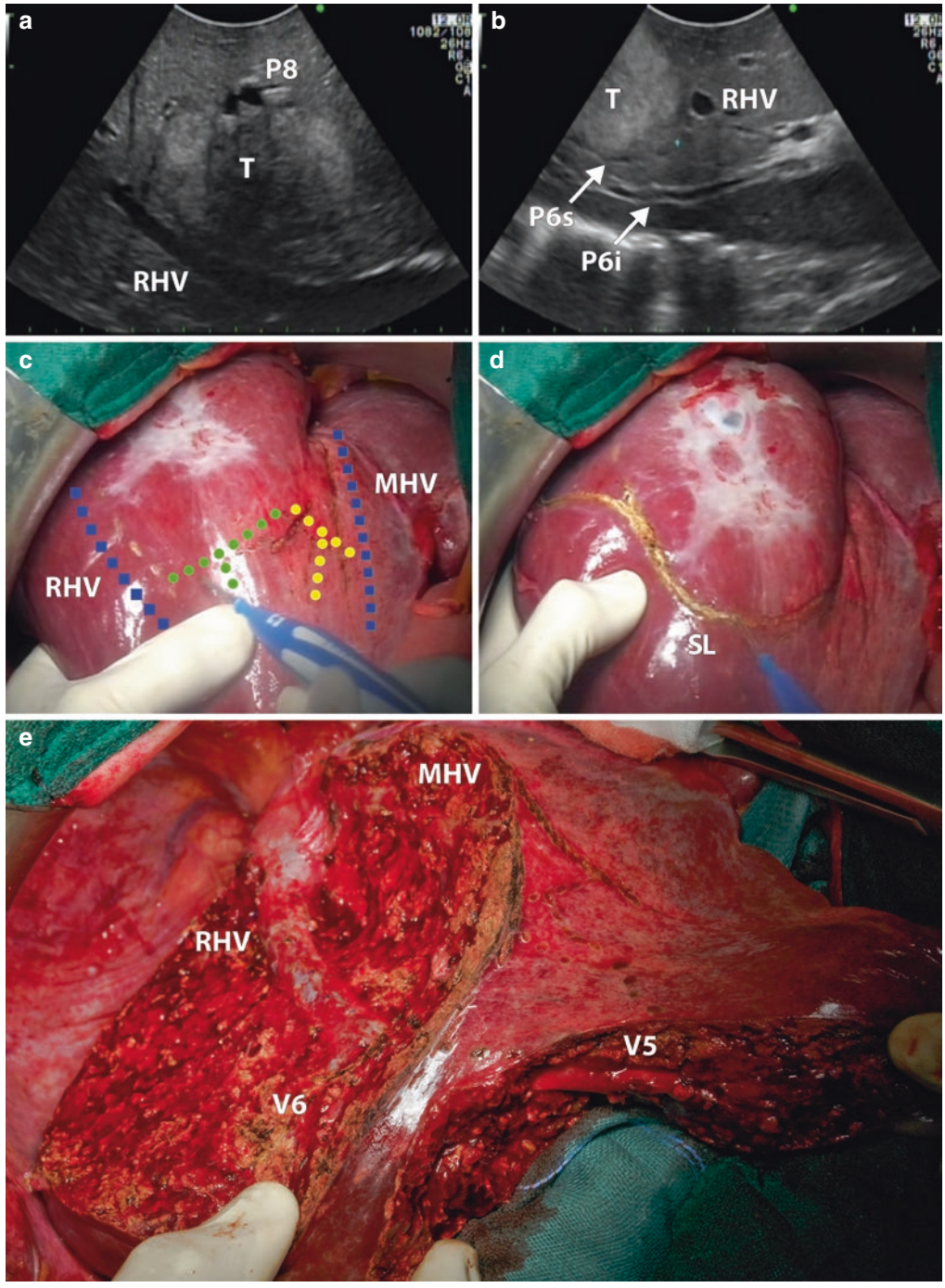


Fig. 16.5 IOUS guidance to liver resection for colorectal liver metastases (CLM). (**a**) IOUS shows a hyperechoic CLM (*T*) in Sg8, in contact with right hepatic vein (*RHV*) without sign of infiltration, adherent to Sg8 pedicle (*P8*). (**b**) A second lesion (*T*) in Sg6, in tight contact with the superior Sg6 pedicle (*P6s*), while the Sg6 inferior pedicle (*P6i*) is free. (**c**) All the anatomical landmarks surrounding the lesion to be resected are marked on the liver surface. *Blue dotted lines*: RHV and middle hepatic vein (MHV); *yellow dotted line*: anterior portal branch dividing in Sg8 and Sg5 pedicle; *green dotted line*: posterior portal branch with Sg6 portal branch origin. (**d**) Section line (*SL*) is drawn on liver surface according to the landmarks. It runs along the hepatic veins projection and across Sg8 pedicle mark. (**e**) Sg8 and Sg6 superior resection. RHV and MHV are spared and exposed on the cut surface of Sg8 segmentectomy. A venous branch draining Sg6 (*V6*) in the RHV has been ligated, while a venous branch draining Sg5 (*V5*) has been spared and exposed on the cut surface

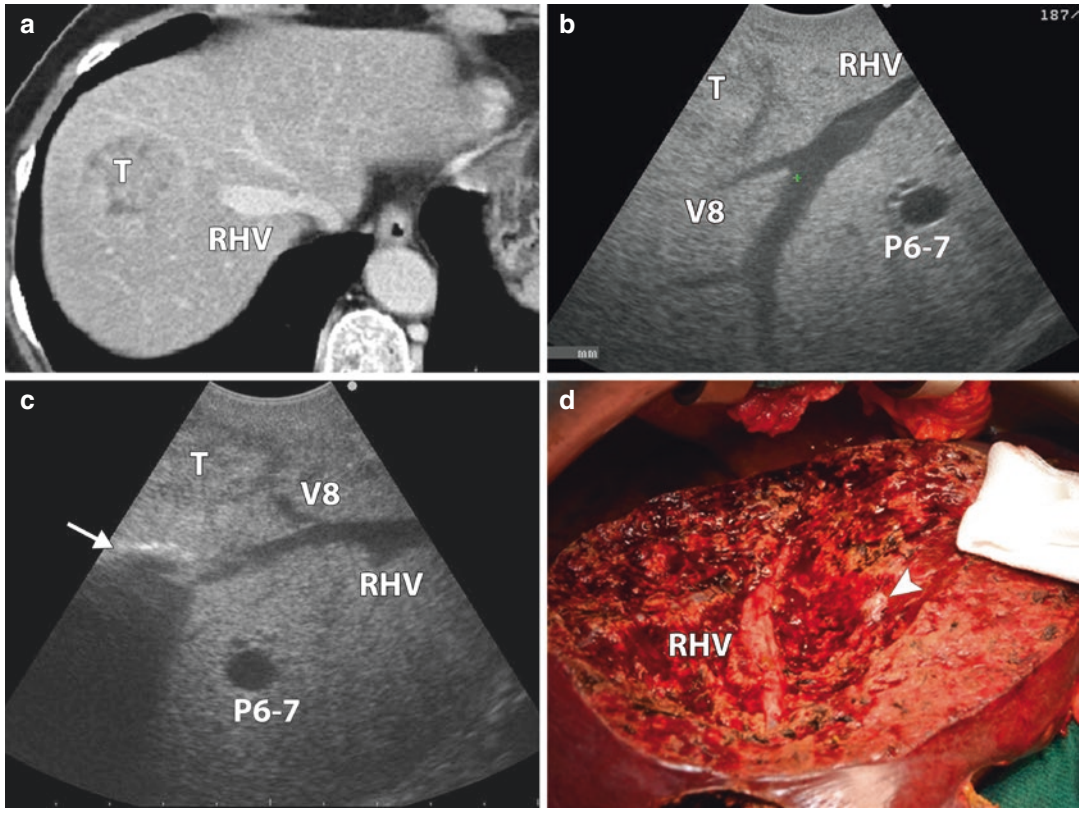


Fig. 16.6 (**a**) CT scan showing a colorectal liver metastases (*T*) in Sg8 close to right hepatic vein (*RHV*). (**b**) IOUS: the lesion has no relationships with RHV but is in contact with a venous branch draining Sg8 (*V8*). Beneath RHV right posterior glissonean pedicle (*P6-7*) can be visualized. (**c**) IOUS real-time monitoring of the surgical plane. The hyperechoic artifact of the section plane (*arrow*) has reached RHV, which will be followed to the caval confluence while V8 will be cut. (**d**) Atypical Sg8 resection completed. RHV has been spared and exposed on the cut surface. *Arrowhead*: stump of Sg8 pedicle

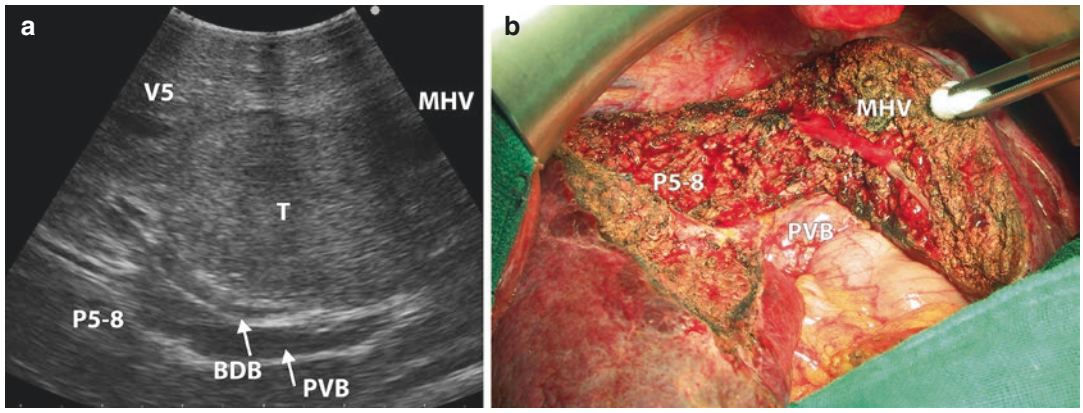


Fig. 16.7 (**a**) IOUS showing a 3.5 cm colorectal liver metastases (*T*) in Sg5-8 in contact with the bile duct bifurcation (*BDB*). *MHV*: middle hepatic vein. *V5*: hepatic vein draining Sg5. *P5-8*: right anterior portal branch. *PVB:* portal vein bifurcation. (**b**) Resection of ventral portion of Sg8 extended to Sg5. MHV, PVB and P5-8 are exposed on the cut surface

vein (Fig. 16.8). In case of focal infiltration, hepatic veins can be partially resected en bloc with the tumor, and reconstructed with direct suture or with a patch (Fig. 16.9). Cases with multiple lesions, with various glissonian and hepatic vein involvements, can often still be treated with limited (meaning non-formal major hepatectomies) resections, unachievable without IOUS guidance (Fig. 16.10). Concerning CLM, an anatomic segmentectomy is required when a glissonian pedicle has to be sacrificed. In that case, the whole segment fed by the pedicle has to be removed in order not to

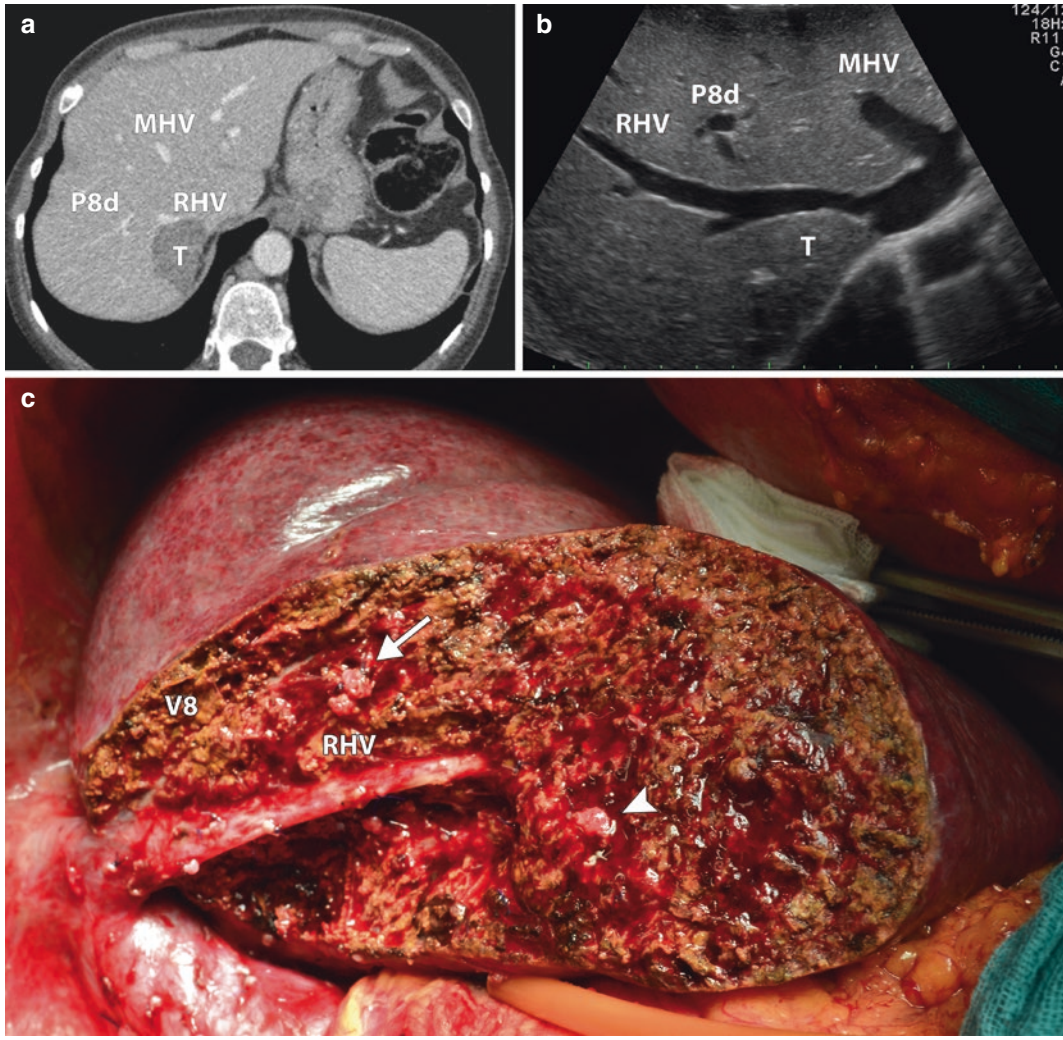


Fig. 16.8 Synchronous CLM in Sg7 involving the paracaval portion of Sg1. (**a**) CT scan showing the metastasis (*T*) in contact with right hepatic vein (*RHV*). *MHV*: middle hepatic vein, *P8d*: Sg8 dorsal pedicle. (**b**) *IOUS*: isoechoic lesion (*T*) in contact with RHV without interruption of the hyperechoic venous wall. (**c**) Sg7 segmentectomy extended to Sg8d and paracaval portion of Sg1. RHV and a hepatic vein draining Sg8 (*V8*) are exposed on the cut surface. The stumps of Sg8d (*arrow*) and Sg7 pedicles (*arrowhead*) are visible on the cut surface

Fig. 16.10 Multiple liver resections for colorectal liver metastases (CLM). (**a**) IOUS showing a hyperechoic lesion (*T*) between Sg8 and the paracaval portion of Sg1. *RHV*: right hepatic vein, *MHV*: middle hepatic vein, *IVC*: inferior vena cava. (**b**) Subsegmentectomy of ventral portion of Sg8 extended to the paracaval portion of Sg1. MHV and anterior portal branch (*P5-8*) are exposed on the cut surface. *Arrowhead*: stump of Sg8 ventral pedicle. (**c**) IOUS of a hyperechoic lesion (*T*) adherent to Sg7 pedicle (*P7*). (**d**) Subsegmentectomy of Sg7. *RHV* and a middle right hepatic vein (*MRHV*) are exposed on the cut surface

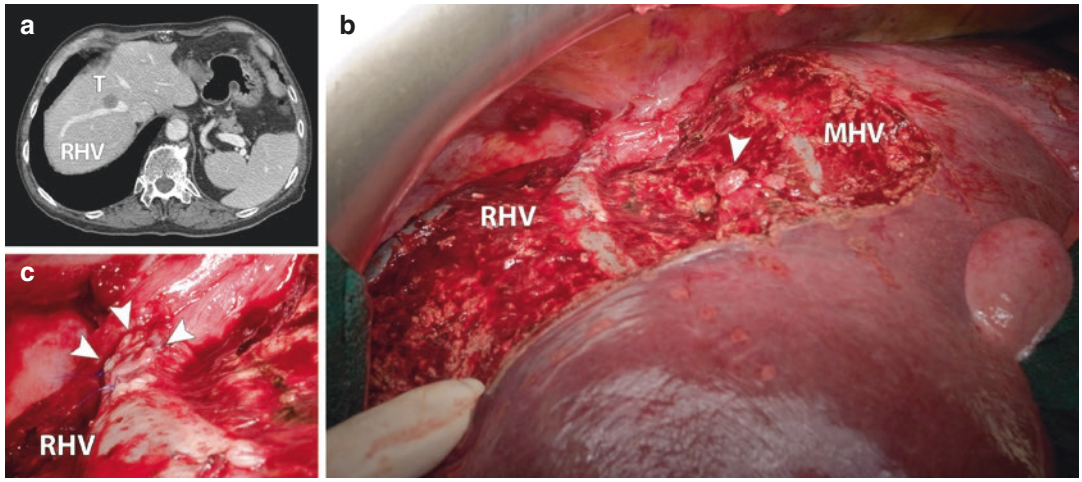
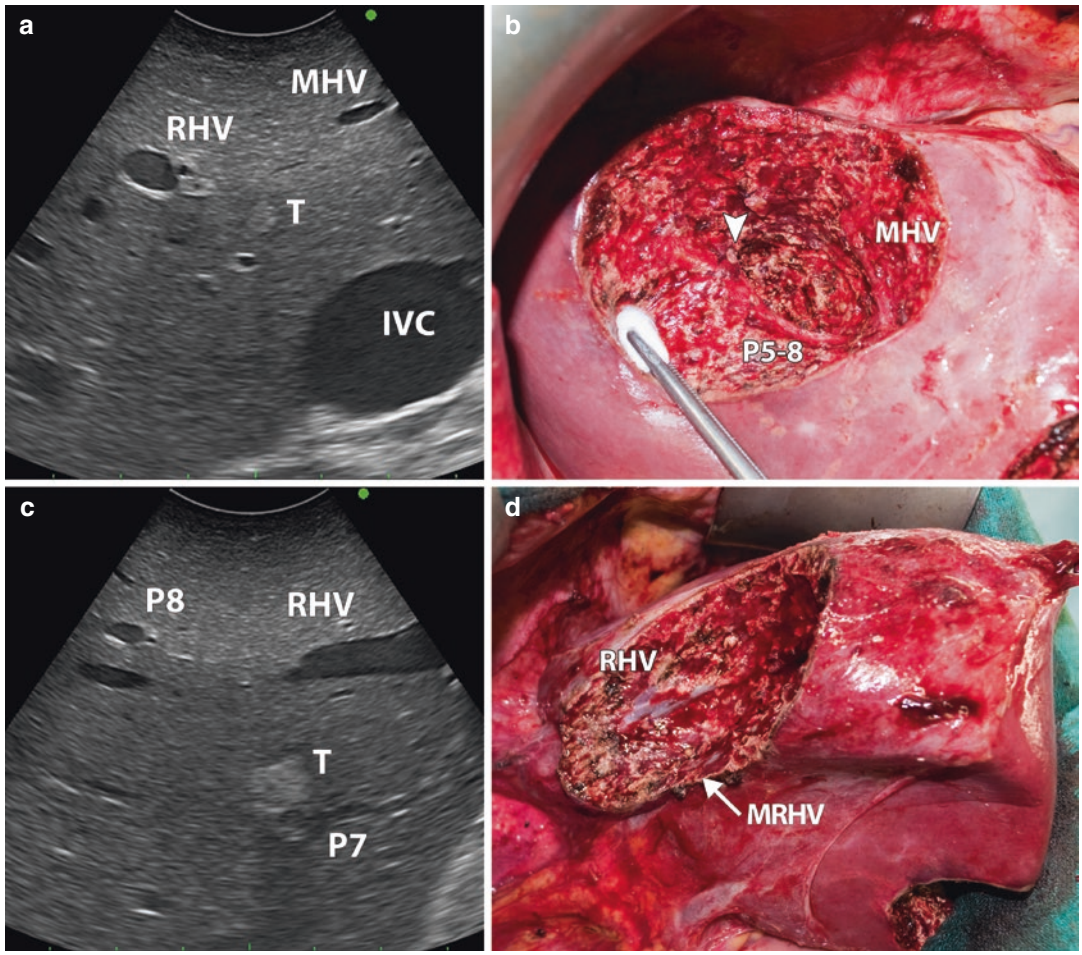


Fig. 16.9 Segmentectomy Sg8 for a colorectal liver metastases with focal infiltration of right hepatic vein (*RHV*). (**a**) CT scan showing a metastasis (*T*) in contact with RHV. (**b**) Segmentectomy Sg8 with resection of the anterior wall of the RHV. All the anatomic boundaries are visible on the cut surface: RHV, middle hepatic vein (*MHV*) and Sg8 pedicle stump (*arrowhead*). (**c**) Detail of the RHV reconstruction with a peritoneum patch (*arrowheads*)



leave ischemic parenchyma. The sacrifice of a hepatic vein can also require the resection of the drained segments. The difficulty of segmentectomies relies on the lack of landmarks on the liver surface to guide resection. Over the years, many methods have been proposed for liver segment identification. The first procedure was described by Makuuchi et al. [11] for anatomic resection for hepatocellular carcinoma, and consists of the puncture of the portal branch involved and injection of indigo carmine. As a result, the stained area becomes visible on the liver surface and can be marked by electrocautery. Although the dye staining is the most accurate method of segmental or subsegmental identification, it is not easily reproducible, and if a wrong pedicle is punctured, a mistaken area is stained, making it very difficult to identify the right segment once more. To apply the precision of staining in a reversible fashion, Torzilli et al. [12] proposed the compression of the portal branch technique. It consists in the IOUS identification of the feeding portal branch of the concerned segment. The branch is compressed between the IOUS probe and the finger, inducing a transient ischemia of the distal parenchyma. The area can then be marked by electrocautery. Another technique proposed by Machado et al. [13], first for left segments and then extended to almost all segments, is the intrahepatic glissonian approach. This technique requires small liver incisions according to anatomic landmarks such as the Arantius' and round ligaments to isolate second- or third-order pedicles. After the ligation, transection can follow the ischemic line on the liver surface. Several segmentectomies can be safely performed with extrahepatic pedicle control, such as left liver segmentectomies (Sg2 and Sg3) or subsegmentectomies (Sg4a and Sg4b), as well as right sectorectomies: Sg6–7 and Sg5–8 (Fig. 16.11). The inferior pedicles

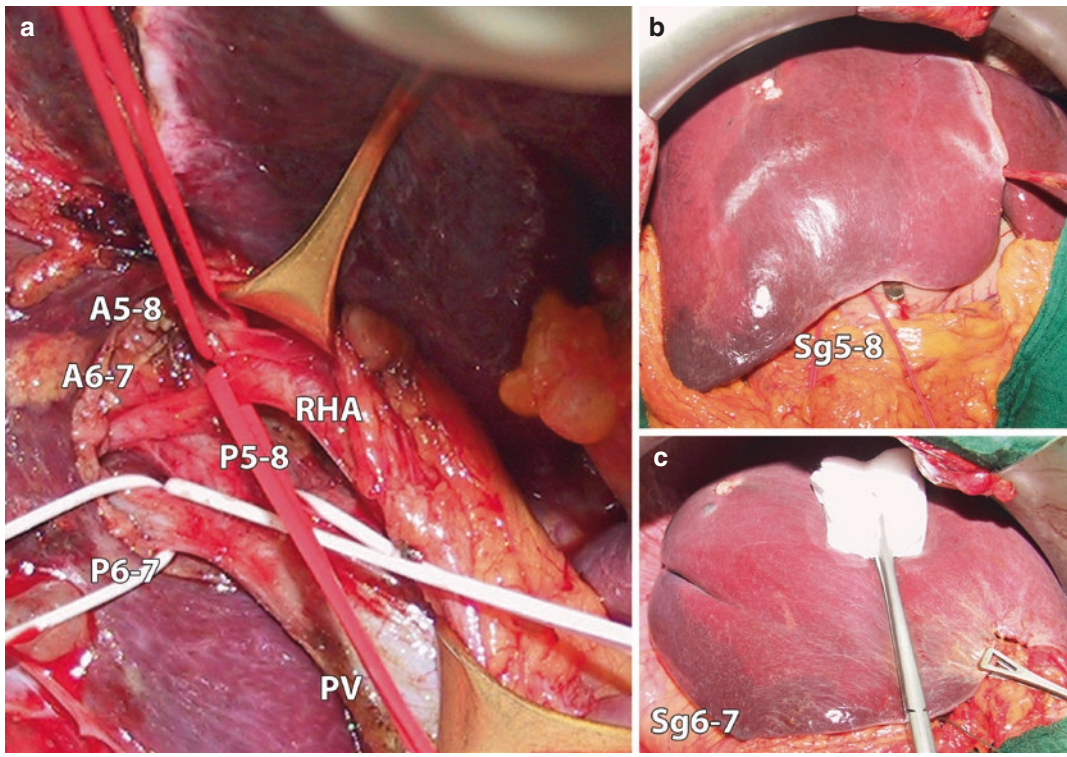


Fig. 16.11 Bisegmentectomies with extrahepatic glissonian pedicle control. (**a**) Dissection of the right margin of the porta hepatis allows the isolation of the right hepatic artery (*RHA*) and its right second order branches for anterior (*A5-8*) and posterior (*A6-7*) sectors as well as the portal vein (*PV*) and the anterior (*P5-8*) and posterior (*P6-7*) branch. (**b**) Ligation of the right anterior artery and portal branch produces the ischemic demarcation of the right anterior sector (*Sg5-8*). (**c**) Ligation of the right posterior artery and portal branch produces the ischemic demarcation of the right posterior sector (*Sg6-7*)

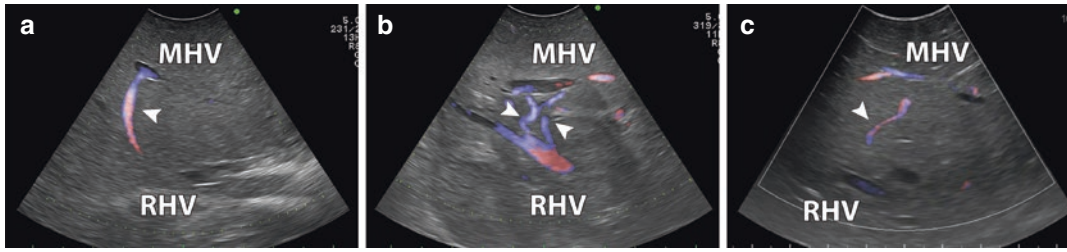


Fig. 16.12 Three cases of IOUS demonstration of communicating veins (*arrowheads*) between middle hepatic vein (*MHV*) and right hepatic vein (*RHV*)

of Sg4 can be dissected on the right side on the round ligament and ligated. The discoloration on the glissonian surface then drives the resection. In the same way, the pedicle of Sg2 and 3 can be managed on the left side of the ligament. The dissection of the right side of the hilum allows the identification of the portal branch and artery of the posterolateral and anteromedial sector. Their correct identification can be ascertained by temporary clamping and with IOUS with color Doppler showing no inflow in the proper segments. After the ligation, the ischemic line guides the transection. Nonetheless, continuous IOUS control of the transection is helpful. Concerning mono segmentectomies or subsegmentectomies, a pure IOUS-guided resection is feasible with a technique not different (and sometimes easier) from a large atypical resection. The lateral landmarks of a liver segment (course of the proper hepatic veins) are visualized and marked, as well as the glissonian pedicle. The parenchymal transection is carried out and the glissonian pedicle is reached under IOUS control. Its proper identification before ligation can be confirmed by the hooking technique [14]. The ligation of the pedicle causes an ischemic demarcation line that together with the anatomical IOUS landmarks allows the achievement of the resection. Tumor infiltration of a hepatic vein close to the caval confluence has for years entailed a major hepatectomy, namely a right hepatectomy in case of right hepatic vein infiltration and central hepatectomy for middle hepatic vein involvement. This is no longer acceptable in many cases; in fact there are several settings that allows the blood outflow from the territory of a closed hepatic vein. The first instance is the presence of an accessory hepatic vein clearly demonstrated at the preoperative workup and confirmed at IOUS. The most typical case, as first described by Makuuchi et al. in 1987 [15], is the bisegmentectomy of segment 7–8 with ligation of the right hepatic vein, thanks to the presence of a right inferior hepatic vein providing blood drainage of segment 6. Similarly, when the ligation of hepatic vein is required, it is always necessary to rule out the presence of vicarious accessory branches of the adjacent hepatic veins, such as branches of the middle hepatic vein draining Sg6 or branches of the left hepatic vein draining Sg4. In other cases, neither accessory vein nor communicating veins between adjacent sectors can be demonstrated preoperatively. Nevertheless, communicating veins can be identified intraoperatively thanks to color Doppler, especially through the latest high-resolution ultrasound colour flow modes that allow the identification of low flow vessels (Fig. 16.12). During the operation, as part of the anatomical exploration, color Doppler is used to check for the presence of communicating veins between the hepatic vein to be resected and the adjacent hepatic vein. If no communicating veins can be identified, a second exploration is performed after liver mobilization, dissection, and clamping of the hepatic vein that will eventually be resected. This maneuver can allow the perfusion of small communicating veins that are almost void in native state. Another method for ascertaining vicarious drainage was described by Sano et al. [16]. This method does not rely on morphological examination (i.e., the actual visualization of communicating veins) rather than on functional observation. After clamping of proper hepatic vein, the flow in the portal branch in the veno-occlusive area is evaluated with color Doppler. In the presence of an adequate outflow through the adjacent hepatic vein, portal flow remains hepatopetal thanks to intrahepatic venous anastomoses. In contrast, if the

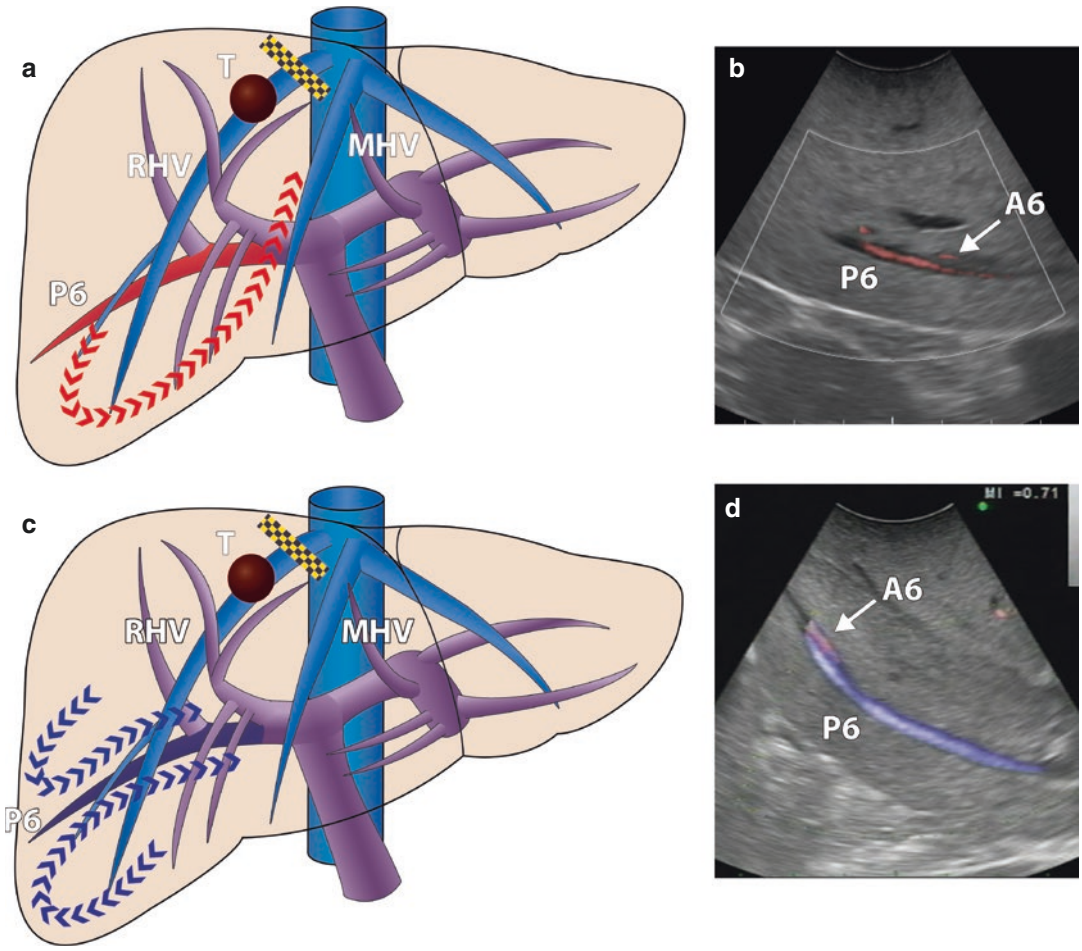


Fig. 16.13 Schematic representation of a colorectal liver metastases (*T*) infiltrating right hepatic vein (*RHV*). (**a**) Clamping of the RHV to be resected. Portal flow in the veno-occlusive segment (*P6*) remains hepatopetal thanks to the outflow through the middle hepatic vein (*MHV*). (**b**) IOUS sampling of Sg6 portal pedicle (*P6*) flow after RHV clamping. Blood flow in P6 remains hepatopetal and consistent with the flow direction in Sg6 artery (*A6*). Sg6 can be spared after RHV ligation. (**c**) Without an adequate outflow trough MHV, portal flows in the veno-occlusive segment (*P6*) inverts direction from hepatopetal to hepatofugal. (**d**) IOUS after RHV clamping shows hepatofugal flow in P6, contrary to the flow direction in Sg6 artery (*A6*). Sg6 cannot be spared after RHV ligation

veno-occlusive area is congested, hepatic venous blood is regurgitated to the portal vein through the sinusoid, thus inverting the direction from hepatopetal to hepatofugal (Fig. 16.13). In this area, portal branches become draining veins, and the occluded area is supplied with arterial blood alone. This supply, especially in an engorged segment, could not be adequate and the parenchyma can become ischemic and eventually necrotic. Therefore it is advisable to resect that segment. We recommend checking the direction of the portal flow even in the presence of accessory or communicating veins. This technique allows operations such as the bisegmentectomy Sg7–8 without right inferior hepatic vein, which we first described in 2006; the bisegmentectomy Sg6–7 with RHV ligation, central resection with ligation of MHV sparing segment 5 and 4b.

Laparoscopic Liver Resection

Over the last decade, laparoscopic hepatectomy has been increasingly performed throughout the world thanks to the evolution of technology and improved surgeons' experience [17]. Nevertheless,

the oncological safety of laparoscopic liver resections (LLR) is still a matter of debate. With regard to CLM, although there were initial concerns about the oncologic adequacy of the laparoscopic approach, it has been reported that LLR can achieve outcomes comparable to those of open resection. The oncological controversies are mainly related to the risk of surgical resection margin infiltration due to laparoscopic technical limitations. In fact, the technique of LLR differs from the open approach because the angle of parenchymal transection is caudal-to-cranial, liver exposure and mobilization are limited, and transection technique is still not standardized. Reported R1 rate after LLR for colorectal metastases ranges from 3.6 to 12.3% [18, 19]. This variability is related to different surgical policy and to the heterogeneity of R0 definition. Moreover, some authors have advocated an increased risk of R1 resection for lesions localized in the postero-superior segments [18]. Currently, a randomized trial on short- and long-term outcomes of laparoscopic vs open liver resection is ongoing in Norway [20]. Thus, the results coming from the study will add some answers to this issue. However, LLR presents some inherent limitations. The lack of tactile sensation impairs the planning of the operation and increases the difficulty of determining the direction of dissection. These great disadvantages cannot completely be compensated by an accurate preoperative investigation of the anatomy by imaging findings. On the other hand, LLR has to offer the same performance of open surgery, even in the setting of PSLR. Segmentectomies and non-anatomical wedge resections are often more challenging than major hepatectomies, where the resection line is indicated by the demarcation consequential to the extraparenchymal control of the hepatic inflow. Nonetheless, LLR has to guarantee the minimum healthy parenchyma to be removed. Ultrasound is the only tool that can overcome these limitations, allowing the surgeon to see beyond the surface. Laparoscopic ultrasound (LUS) use was first reported in 1981 by Fukuda et al. [21]. Despite early introduction, it has been poorly developed and studied. Although LUS is reported to increase surgical safety [22], it is currently far from being routinely used [23]. The reliability of LUS for staging liver diseases has been demonstrated by its performances similar to those of open IOUS [24]. Furthermore, it has to provide real-time guidance during surgery, providing indispensable tool for laparoscopic PSLR. During the first step of the operation, relationships between tumor and intrahepatic vasculobiliary pedicles can be precisely visualized, and resection lines are designed on the liver surface with monopolar coagulation. During transection, the resection plane is repeatedly checked by LUS to maintain a safe margin, providing the surgeon with immediate feedback of possible necessary changes. Any glissonian pedicle or vein encountered during liver transection can be checked and recognized by LUS before ligature and section. Color-Doppler US allows the user to visualize blood flow and assess flow in and near the area of interest providing real-time feedback during the hepatectomy. LUS has some drawbacks and limitations. Hand–eye coordination of the probe visualized through the video laparoscope can be difficult. Orientation and the following image interpretation can be complicated. Furthermore, the field of view is limited due to transducer size. Some US-specific drawbacks add to the difficulties of interpretation, such as shadowing, multiple reflections, variable contrast depending on liver parenchyma status, and the fact that image quality may also be somewhat operator-dependent. Nevertheless, despite these difficulties, LUS remains an indispensable tool for surgeons dealing with LLR. The technique of anatomical LLR with the use of LUS to identify the longitudinal (hepatic veins) and horizontal (portal pedicle bifurcation) boundaries of resection has been described [25, 26]. We recently reported [27] our technique of LUS-guided liver resection, which reproduces in the setting of minimally invasive liver surgery the technique adopted in open surgery. This technique, developed in order to perform PSLR, be they anatomical segmentectomies, subsegmentectomies, or non-anatomical wedge resections, is based on the identification and actual sketching on the liver surface of the anatomical elements of the segment or segments involved, the feeding portal pedicles, and the hepatic veins (Fig. 16.14). This map is the basis for planning the resection. The lines of the resec-

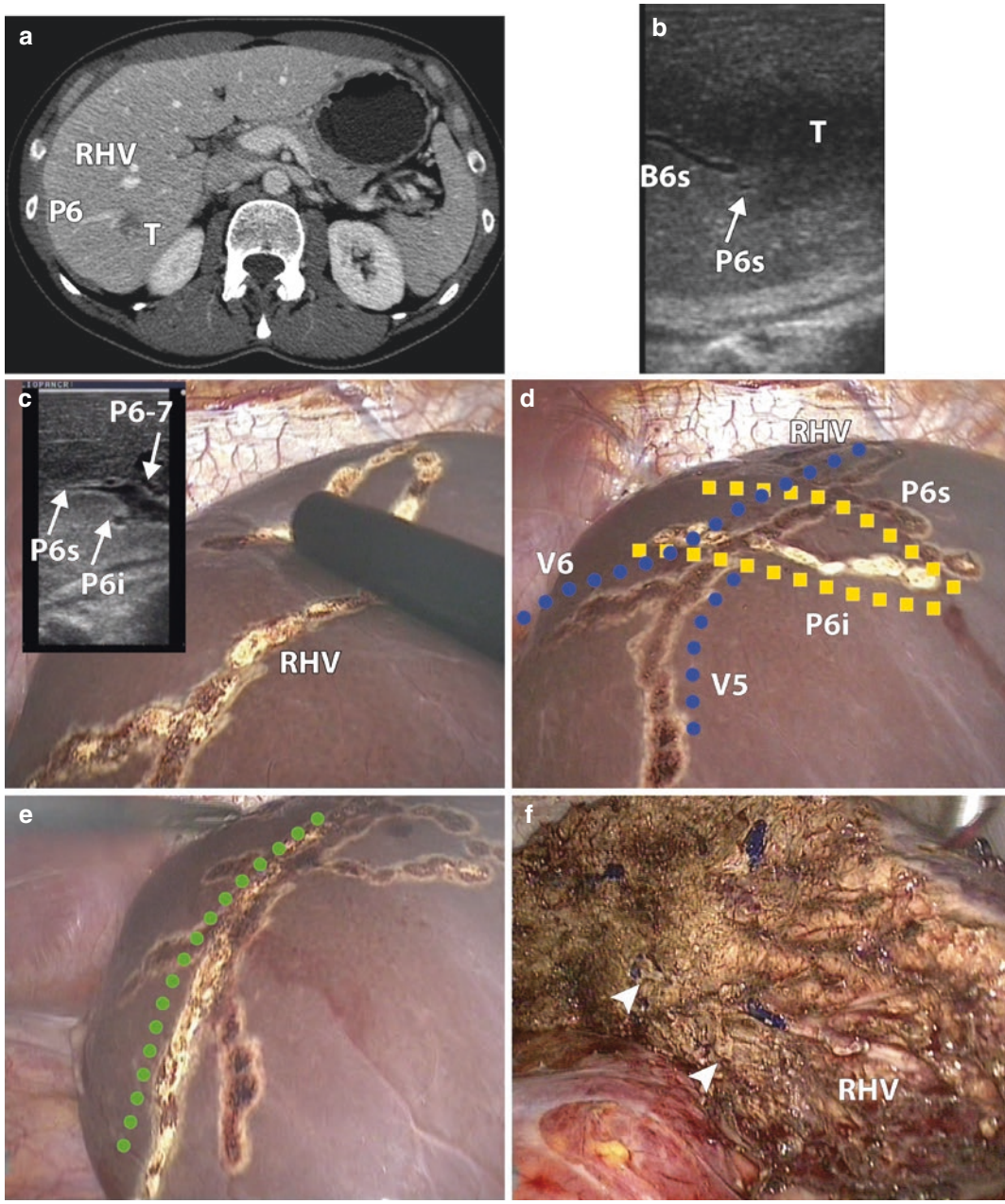


Fig. 16.14 Laparoscopic ultrasound (LUS) guidance to resection. (**a**) CT scan of a colorectal liver metastases (*T*) in Sg6, in contact with a Sg6 portal branch (*P6*). *RHV*; right hepatic vein. (**b**) LUS showing an hypoechoic metastasis in contact with Sg6 superior pedicle (*P6s*) with dilatation of the corresponding bile duct (*B6s*). (**c**) LUS identification of Sg6 superior (*P6s*) and inferior (*P6i*) pedicles at the origin from the posterior portal branch (*P6-7*). RHV has already been marked on liver surface. (**d**) All the landmarks required for a Sg6 resection are marked on liver surface. RHV (*blue dotted line*) with a branch draining Sg6 (*V6*) and one draining Sg5 (*V5*); Sg6 superior (*P6s*) and inferior (*P6i*) pedicles (*yellow dotted line*). (**e**) The section line (*green dotted line*) is marked on the liver surface. The line runs across P6i and P6s that will be cut and along RHV that will be spared. In particular the section line runs between Sg6 (*V6*) and Sg5 (*V5*) branches of RHV. V6 will be cut and V5 will be spared. (**f**) Cut surface at the end of the Sg6 resection. RHV is exposed on the cut surface. *Arrowheads*: Sg6 superior and inferior pedicle stumps

tion planes are drawn parallel to the lines of vessel to be spared and across the ones to be interrupted. This way, during the transection, the surgeon can anticipate which vessel he is about to come across, thus minimizing the risk of bleeding and increasing the safety of the procedure. Moreover, the surgeon is always aware how to manage (divide or spare) the vascular structures encountered, hence minimizing the risk of remnant liver ischemia. When the parenchymal section is performed according to the section lines, a vessel is isolated just at the point where it has to be divided. Thus, an accurate LUS can allow hepatic segment identification without the dye-staining technique [11], which is technically demanding and even more difficult during laparoscopy.

Conclusion

Parenchymal-sparing liver resections are supported by pathological, oncological, and technical reasons. This strategy reduces postoperative mortality and morbidity rates, better preserves postoperative liver function, thus decreasing the risk of liver dysfunction, offers similar survival results, and increases the opportunity to re-resection in case of recurrence. Only the intensive use of IOUS makes it possible to perform parenchymal-sparing liver resections.

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Combined Vascular Resections

17

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Introduction

The indications for hepatic resection for colorectal liver metastasis (CLM) have been increasing along with advances in surgical techniques, perioperative management, and chemotherapy regimens. The addition of novel molecular target agents to conventional chemotherapy regimens has strengthened the anti-tumor effects [1, 2]. Accordingly, more and more patients with CLM who otherwise would have no chance of undergoing radical surgery are becoming candidates for curative hepatic resection after having received effective chemotherapy, a treatment strategy known as "conversion chemotherapy." Even after successful conversion chemotherapy, a radical hepatic resection may be possible only when a combined hepatic vascular resection can be achieved.

Unlike hepatocellular carcinoma, which is another disease that is commonly treated with hepatic resection, CLM usually grows in an infiltrative fashion, rather than in an expanding fashion. In surgery for hepatocellular carcinoma, the tumor can be detached from the vasculature, which is adjacent to the tumor in most cases. CLM tumors usually adhere to the adjacent vasculature and are difficult to dissect; even if the tumors can be detached from the vasculature, the macroscopic surgical margin at the corresponding site is likely to be positive for cancer cells. When the tumor appears to abut on the portal triad or the hepatic veins, the resection of the vasculature and the hepatic parenchyma fed by involved vasculature is preferred. However, such procedures frequently require the resection of a large volume of hepatic parenchyma, and may be impossible in patients with multiple tumors or when the hepatic functional reserve is impaired because of lengthened systemic chemotherapy [3]. In such cases, a combined vascular resection with or without reconstruction may be proposed as an alternative to secure the hepatic functional remnant. Hepatic vascular resection is also considered when local ablation therapy, such as radiofrequency ablation, has been used to treat a CLM tumor. CLM tumors with previous radiofrequency ablation therapy reportedly tend to require a more expanded hepatic resection than would have been considered necessary before ablation therapy; the complete resection of these tumors sometimes necessitates a combined resection of the hepatic vein, portal triad, and inferior vena cava [4].

Combined vascular resection is technically challenging, and should be performed by experienced surgeons to secure the safety of patients. Several techniques can be used to avoid

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unexpected trouble. In this chapter, technical issues for performing combined vascular resections during hepatic resections in patients with CLM are described in separate sections as follows: portal triad resections, hepatic vein resections, and inferior vena cava resections.

Portal Triad Resections

If a tumor invaded to the peripheral portal triad, namely third-order portal branches or further, the portal triad is usually sacrificed. The portal triad is composed of firm and thick connective tissue surrounding a thin portal vein, hepatic artery, and bile duct; consequently, the separation and reconstruction of each vessel is nearly impossible. Anatomic hepatic resection is necessary to prevent adverse effect caused by hepatic ischemia, and the liver volume fed by the portal triad adjoining a tumor should be calculated preoperatively (Fig. 17.1a). It should be kept in mind that an anatomic hepatic resection for CLM has not been confirmed to prevent recurrence caused by intrahepatic metastasis, as in hepatocellular carcinoma. Hence, a non-anatomical limited resection should be chosen when a sufficient distance is recognized between the tumor and the portal triad. Before performing an anatomical hepatic resection, a volumetric analysis based on preoperative CT scan images is necessary to prevent postoperative liver failure by assessing the future hepatic functional reserve (Fig. 17.1b).

When the main trunk of the portal vein or its first-order branch seems to abut the tumor, a hemi-hepatectomy, i.e., a right or left hepatectomy, should be considered, and the combined resection of the wall of the main portal vein may be required. In such cases, the combined resection and the following choledocho-jejunostomy may be also required, although much less frequently, and the indication should be limited from the oncological standpoint [5]. Indeed, the management of the portal vein, hepatic artery, and bile duct when a CLM tumor is located near the hepatic hilum, is almost the same as that in hilar bile duct carcinoma. When the tumor does not invade the whole circumference of the portal vein, a wedge resection of the wall is suitable (Fig. 17.2a). A primary closure may be enough to secure intrahepatic portal flow for a small defect of the venous wall (Fig. 17.2b); otherwise a patch

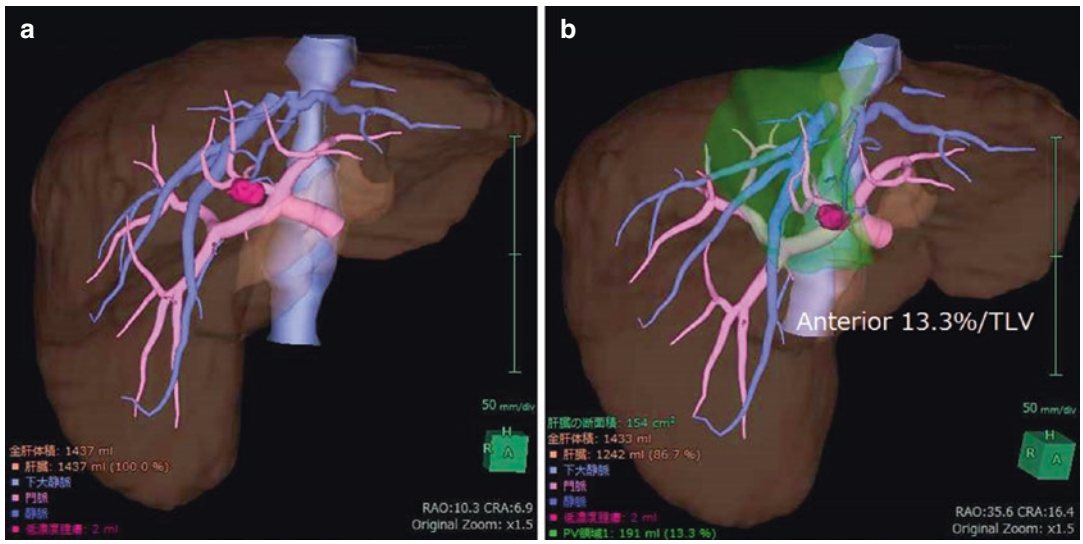

Fig. 17.1 A 60-year-old man presented with a liver metastasis adjoining the right anterior branch of the portal triad. The indocyanine retention rate at 15 min was 8.5%, which indicated normal liver functional reserve. (**a**) A simulation 3D-image demonstrating the relationship between the tumor and the portal triad. (**b**) A simulation 3D-image of the right anterior sectionectomy supposed that 13.3% of the total liver parenchyma would be resected

repair is indicated (Figs. 17.2c and 17.3). The suture direction in a primary closure should be vertical, rather than longitudinal, to the portal axis in order to prevent stenosis of the portal vein (Fig. 17.2b). When the tumor invades the whole circumference or the area in contact with the tumor is relatively large, a segmental resection of the portal vein followed by either direct end-to-end anastomosis or interposed reconstruction using a tubular graft may be indicated (Fig. 17.2d).

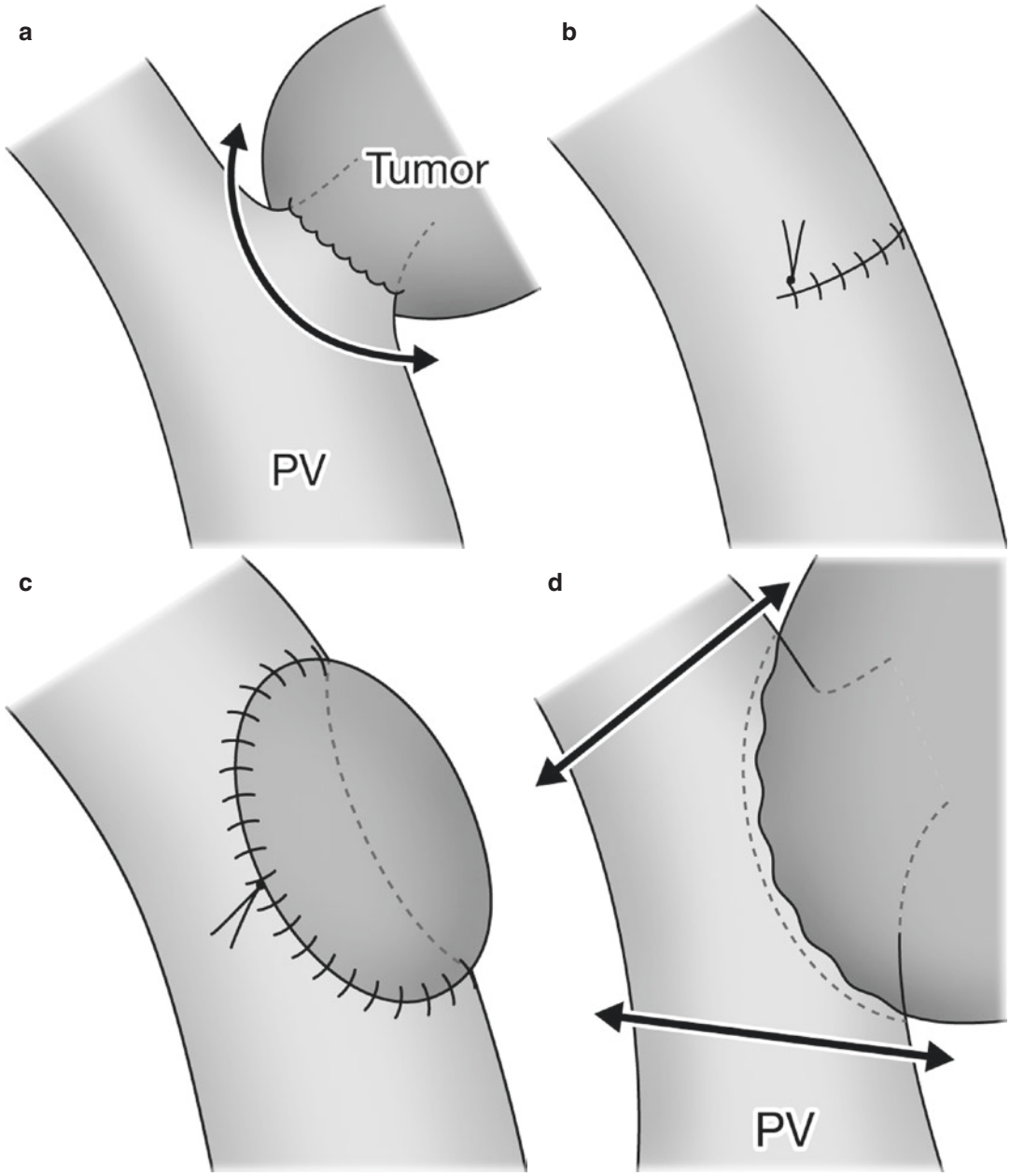

Fig. 17.2 The schematic views indicating the reconstruction methods of portal vein. (**a**) A wedge resection is indicated when a tumor invades the portal vein on a narrow area. (**b**) Primary closure of the defect of the portal vein. The suture line should be vertical against the long axis of the portal vein. (**c**) A patch repair should be performed when the defect of the portal vein is large. (**d**) A circumferential segmental resection is indicated when a tumor invades the portal vein a large area. (**e**) An end-to-end anastomosis after segmental resection followed by "growth factor" to prevent stenosis

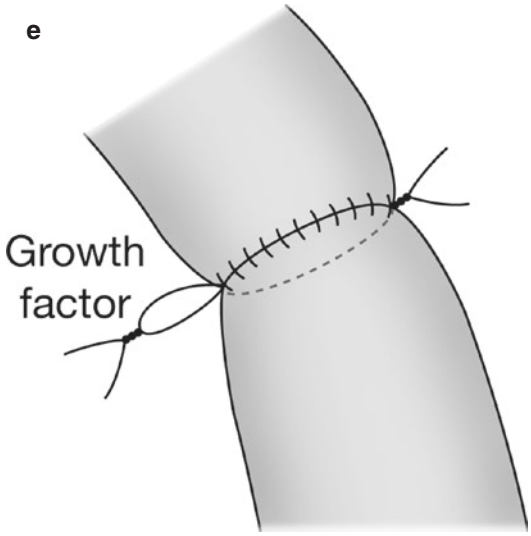

Fig. 17.2 (continued)

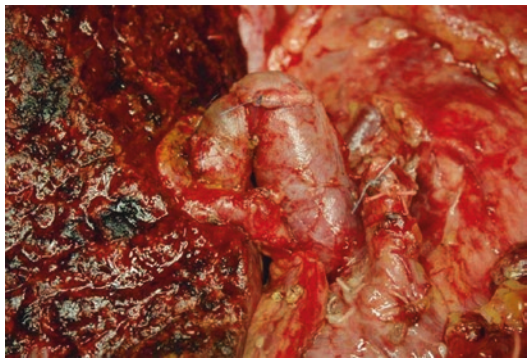

Fig. 17.3 A 63-year-old man with colorectal liver metastasis invading hepatic hilum underwent left hepatectomy. Combined portal venous and extrahepatic bile duct resections followed by reconstruction were accompanied. A patch graft using cryo-preserved allograft of portal vein was used

Compared with the caval flow, portal flow is more sensitive to the area of the anastomotic lumen, and meticulous care should be devoted to prevent stenosis during the suture. For example, the suturing thread should be pulled gently, and some surgeons prefer to make so-called "growth factor" finishing anastomosis (Fig. 17.2e).

When a CLM tumor is located near the hepatic hilum, as in hilar bile duct carcinoma, the reconstruction of the hepatic artery as well as portal vein is sometimes required. It is usually accompanied with hemi-hepatectomy, and the hepatic arterial reconstruction is required when a tumor invades the hepatic arterial branch feeding the hepatic remnant. Radical surgery is contraindicated when the hepatic artery which is subject to reconstruction cannot be encircled at the distal side of the tumor, which should first be confirmed after the laparotomy. Arterial reconstruction may be performed in direct end-to-end anastomosis between the stumps of the hepatic arteries; otherwise, an arterial pedicle graft must be prepared using, for example, the right gastroepiploic artery, the gastroduodenal artery, the middle colic artery, and the left gastric artery.

Hepatic Vein Resections

When the wall of the major hepatic vein abuts a CLM tumor, the surgeons must preoperatively decide whether to sacrifice or to reconstruct the vein taking the impact of hepatic congestion into consideration, as described in the following paragraph. When hepatic venous reconstruction is needed, the method of reconstruction should be chosen from among primary suture repair, patch reconstruction, and interposed graft reconstruction. Because of the small diameters of the hepatic veins, a wedge resection followed by simple primary closure is difficult or, if possible, may cause hepatic congestion. Therefore, a patch reconstruction following a wedge resection and a circumferential segmental resection, followed by a reconstruction using an interposed graft (Fig. 17.4) are frequently adopted. Few reports have assessed the long-term survival of CLM patients undergoing a combined hepatic venous resection. Aoki et al. reported a median survival time of 26 months, which is not favorable but not hopeless, after the combined resection of the hepatic venous confluence in the seven patients [6]. Saiura et al. analyzed 16 patients with hepatic venous reconstruction, in whom a total of 18 hepatic veins were reconstructed, and reported a much better prognosis, that is, a 5-year overall survival rate of 76% [7].

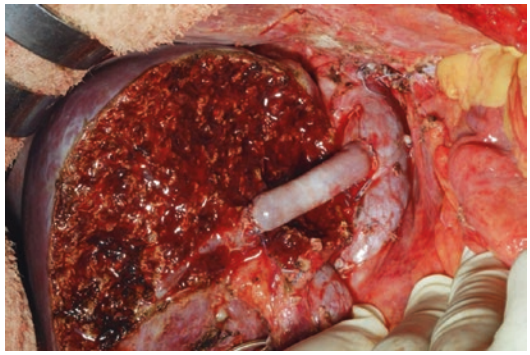

Fig. 17.4 A 68-year-old patient with colorectal liver metastasis underwent an extended left hepatectomy with combined resection and reconstruction of the middle hepatic vein. Because the middle hepatic vein was cut at its root and at the periphery, a tubal cryo-preserved allograft of the portal vein was interposed between the peripheral cut-end of middle hepatic vein and the vena cava. The graft has been worked for one and a half years

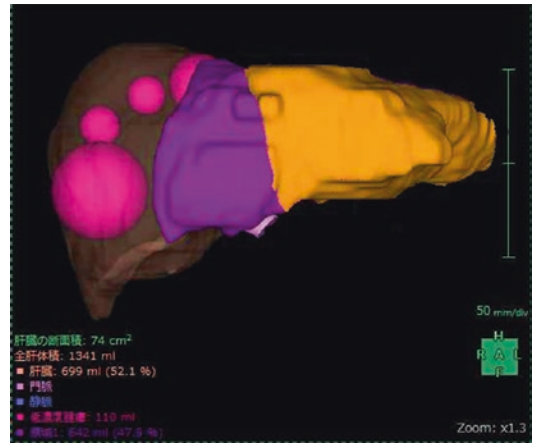

Fig. 17.5 A 49-year-old patient who had undergone a resection of sigmoid colon carcinoma presented with liver metastases, one of which adjoined the middle hepatic vein. A simulation using computer software was performed as the middle hepatic would be sacrificed, supposing that 47.9% of the total liver parenchyma was to be resected in right hepatectomy and an additional 18.7% of the total liver parenchyma was to be congested within the future hepatic remnant. Thus, 29.2% of the total liver parenchyma would be the future non-congested hepatic remnant, showing the procedure would be acceptable considering that the indocyanine retention rate at 15 min was 8.8%

Resection of the major hepatic vein or its main tributary may cause congestion of the corresponding drained volume of the liver [8]. This congestive state had been merely a concern until graft necrosis and intractable massive ascites after liver transplantation was related to hepatic outflow block, namely in the late 1990s [9–11]. Recently developed computer software simulating hepatic resection by incorporating contrast-enhanced CT images into 3D-images has enabled the hepatic volume drained by a certain venous tributary to be calculated (Fig. 17.5). However, the proportion of the hepatic functional reserve that is impaired by venous congestion remains to be resolved. To secure patient safety, the hepatic functional reserve of the congested volume may be supposed to be zero; however, Sano et al. revealed that the portal vein may exhibit regurgitation after the occlusion of the hepatic vein, to partly substitute the drainage effects [8]. A clinical study comparing the uptake of liver-specific contrast agent during magnetic resonance imaging suggested an unimpaired hepatic functional reserve of approximately 65% in the congested hepatic area [12], while another study comparing the uptake of indocyanine green using fluorescence imaging suggested a reserve of approximately 40% [13]. As the results of the two reports differed and the validities of their methodologies have not been established, further investigation of this issue is needed. Nonetheless, it is important to note that the congestive area may have reduced, but not necessarily obliterated, hepatic functional reserve.

At the University of Tokyo, reconstruction of the major hepatic vein is planned based on the following criteria: a calculated non-congested hepatic remnant of less than 40% of the total liver volume when the ICG retention rate at 15 min is 10% or less, and a calculated non-congested hepatic remnant of less than 50% of the total liver volume when the ICG retention rate at 15 min is 10–20%. Indeed, these criteria are so conservative that the functional reserve of the congested part is supposed to be zero; Mise et al. reported postoperative complications of Clavien–Dindo grade 3 or more in only 2% of patients, with no perioperative mortality [14]. Another notable issue when considering venous reconstruction is the presence of an innate anastomosis between the peripheries of the two major hepatic veins,

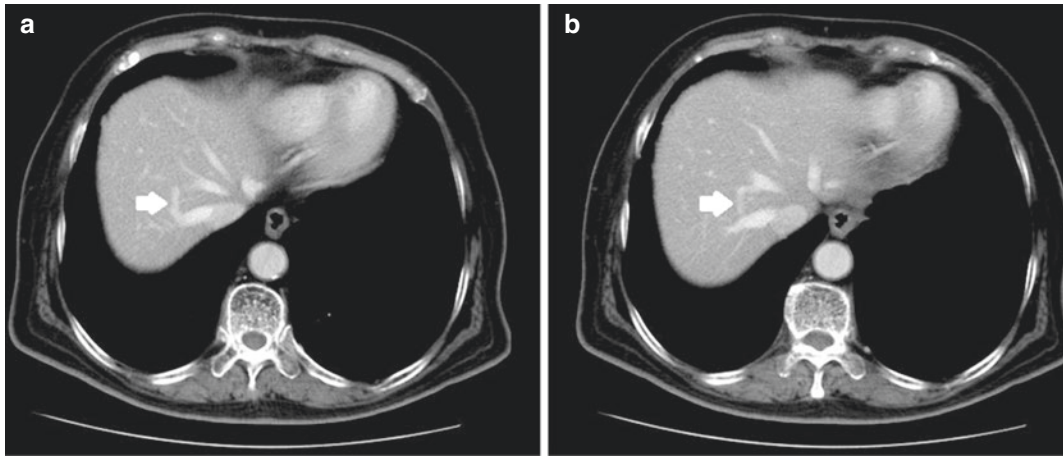

Fig. 17.6 Preoperative contrast-enhanced computed tomography images (**a**, **b**, continuous) demonstrating the anastomosis between the right and middle hepatic vein (*arrows*)

with which one of them may be sacrificed because of collateral drainage [8, 15]. Such hepatic venous anastomoses may be recognized in preoperative imaging studies in some patients (Fig. 17.6), and may be recognized only after laparotomy using intraoperative ultrasound.

Vena Cava Resections

Until recently, a CLM tumor involving the vena cava was considered to be a contraindication for resection because of concerns over intraoperative massive bleeding and air embolism; furthermore, the patient survival after surgery was relatively poor (around 12 months), in patients without resections based on such consideration [6]. Thanks to experience performing liver transplantation, many techniques and materials for caval grafts have been reported. The use of bovine pericardium for a patch graft following a wedge resection, and the use of Gore-Tex®, Dacron® tubes, or polytetrafluoroethylene (PTFE) graft tubes for interposition following a segmental resection, have been reported in a case series [16, 17]. The use of cryo-preserved venous allografts, which has only been reported for pancreatic surgery [18] but is useful because of the quick access and availability of many sizes and shapes, is another graft option.

Total vascular exclusion, first reported for the resection of HCC tumors [19], is useful during parenchymal transection to prevent massive bleeding because the caval venous pressure is increased due to an obstruction by the tumor. Total vascular exclusion can also be applied during the cross-clamping of the vena cava for the combined resection and reconstruction of the vena cava. If the systemic blood flow of the patient cannot tolerate total vascular exclusion, the veno-venous bypass technique should be adopted, with the conditional accompaniment of hypothermic perfusion using hepatic preserving liquid [16]. A report has advocated the use of wedge resection with primary closure without a patch graft when the defect is both less than 60° in circumference and has a longitudinal diameter of less than 2 cm [16]. This technique brings the following advantages; the mainstream of the vena cava remains because of side-clamping during reconstruction, the blood loss is minimal during reconstruction, and the danger of post-suture stenosis of the vena cava may be minimal. In cases with extensive tumor invasion to the vena cava, cross-clamping of the vena cava at both sides of invasion is necessary. When the invaded area of the vena cava is relatively large, a wedge resection followed by the repair using a patch graft or a circumferential segmental resection, followed by reconstruction using an interposed

tube graft, may be performed. It is sometimes experienced that the patients survive after a gradually completing stenosis of IVC, perhaps because of the formation of a compensatory venous collateral that drains the lower extremities and pelvic organs. Meanwhile, the short-term prognosis of patients may be poor after the circumcision of the IVC without reconstruction, which would be limited to such cases where an attempt at primary repair results in failure [20].

Several kinds of morbidity are specific to vena cava resections and reconstructions. Some patients develop severe edema of the lower extremities and others, though rare, develop renal dysfunction. Among the 15 patients who underwent caudate lobe resection with vena cava resection, three patients died, and the cause of death was either intraoperative or postoperative hemorrhage in all of them [20]. In the same report, combined resection of the vena cava were reported to be dangerous when the tumor invaded at the confluence of the major hepatic veins.

In a single institutional experience of more than 2,000 hepatic resections for CLM, the vena cava was concomitantly performed in 1.6% of the total cases, and a 5-year overall survival rate of 20% was reported [16]. Hashimoto et al. retrospectively assessed the preoperative findings that predicted a need for vena cava resection, analyzing 162 patients with tumors attached to the vena cava [21]. Twenty-two percent of the patients with adenocarcinoma lesions required combined resections of the vena cava, resulting in an overall 5-year survival rate of 33%, whereas none of the patients with hepatocellular carcinoma lesions ultimately required vena cava resection. A multivariate analysis revealed two independent predictors of vena cava resection: a vena cava circumference attached to the tumor of more than one fourth, and a peak-like deformity of the vena cava toward the tumor.

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Ex-Vivo Liver Surgery

18

G. Felix Broelsch, John F. Renz Jr.,
Eugen Malamutmann, and Christoph E. Broelsch

Introduction

Hepatic resection has evolved as a curative procedure to treat secondary liver metastases from primary colorectal cancer. Standard guidelines have been the subject of consensus conferences for specific treatment of this entity [1, 2]. In essence, the combination with chemotherapy and subsequent resections of metastases, including extended partial hepatectomies, has become the most effective treatment for this setting.

Since the first reports of the benefit of partial hepatic resections for colorectal metastases [3–6], the extent of hepatic resection has extended beyond trisegmentectomies and multiple sectionectomies, as well as two-stage procedures following portal vein embolisation and recently liver transection with portal vein ligation for rapid growth of the future remnant in two-stage liver resection (ALPPS) [7–9].

While ALPPS addresses the concern of insufficient hepatic mass upon completion of the hepatectomy, traditional resection techniques are inadequate to address tumors invading the inferior vena cava (IVC), hepatic vein(s)–IVC junction, or extensive hilar disease that requires complex vascular reconstructions. These limitations have spurred a series of technical advances to address these challenges. The earliest attempt to advance resectability was total vascular exclusion (TVE), proposed by Heaney et al. [10] and modified by Huguet et al. [11], where the liver is excluded from circulation by simultaneous clamping of the hilum, infra-hepatic IVC, and supra-hepatic IVC. This technique provided a bloodless field to facilitate larger resections, but does not enhance the application to tumors invading the IVC or hepatic vein–IVC junction tumors. Furthermore, the organ is injured by warm ischemia. In general, TVE limited to less than 60 min is well tolerated; however, the impact of previous chemotherapy upon the liver's ability to tolerate TVE has not been well studied, and may significantly lower the capacity to tolerate warm ischemia.

To increase tolerance of TVE and reduce warm ischemic injury, Azoulay et al. proposed the continuous infusion of 4 °C preservation solution while TVE was applied [12]. Hypothermic TVE is performed by cannulating

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the portal vein proximal to the hilar occlusion clamp and draining cold preservation solution through a venotomy. Hannoun et al. demonstrated that hypothermic TVE could be applied to normal as well as diseased livers for as long as 4 h, and that it facilitated bloodless parenchymal transection [13]. While hypothermic TVE increased the resectability of advanced tumors, it did not address the technical limitations of the technique [14] to certain geographic areas of the liver.

For large tumors located on the dorsum of the liver involving the IVC, IVC–hepatic vein junction, or a potentially complex vascular reconstruction within the hilum, greater anatomic access was required than that afforded by hypothermic TVE. In 1988, Pichlmayr reported the first performance of an ex-situ operation on the liver, and postulated a potentially new operative procedure [15]. It was hallmarked as a new possibility in liver surgery deriving from experience in reduced-organ [16–18] and split-liver transplantation [19, 20].

The initial series of 11 patients was reported by Pichlmayr et al. in 1990 [21], and was later updated to include 24 patients in 2000 [22]. He asserted ex-vivo hepatectomy with autotransplantation (EVAT) could achieve the following aims: (a) to increase the resectability rate in patients with advanced tumors, (b) to improve the radicality of tumor resections, (c) to avoid the need for liver grafting, and (d) in theory, to allow oncological methods to be used extracorporeally. EVAT achieves all of the above in a bloodless field that permits complex vascular reconstructions with fewer time constraints; however, satisfactory performance of EVAT demands technical excellence, precise patient selection, and considerable institutional strength in anesthesia, critical care, medical subspecialties, nursing, and rehabilitation. Thus, its utilization has been limited to centers with considerable strength in hepatobiliary surgery, split-liver, and living-donor liver transplantation. This manuscript summarizes the current literature on EVAT and explores patient selection, technical considerations, and outcomes over the past three decades of EVAT.

Patient Selection

Patient selection is central to satisfactory outcomes from EVAT. To date, most series indicate the principal indications are metastatic colorectal carcinoma [22, 23] and primary cholangiocarcinoma [21, 24]. Less frequent indications include: leiomyosarcoma [15, 25], gastrointestinal stromal tumors [26] and hepatic adenocarcinoma [27]. EVAT has also been used in a novel way to avoid orthotopic liver transplantation in the treatment of hepatic alveolar echinococcosis [28, 29].

When approaching a potential candidate for EVAT, our pre-operative evaluation focuses on three central themes: physiologic assessment to withstand a demanding surgical procedure, demonstrated tumor control, and technical appropriateness. The evaluation parallels that for orthotopic liver transplantation as outlined by Diaz et al. [30]. Particular attention is focused on cardiac performance as determined by a dobutamine stress echocardiography and right ventricular function, as this may be compromised in severe ischemia/reperfusion injury [31]. Estimation of sufficient physiologic reserve, adequate nutrition, and recognition of sarcopenia are essential. Pre-operative jaundice that is not relieved by percutaneous transhepatic biliary drainage or endoscopic stenting indicates hepatic injury, and strongly correlates with post-operative morbidity and mortality from liver failure. We and others advocate refraining from EVAT in this setting [21, 22, 25, 29, 32].

When indicated, neoadjuvant chemotherapy to control disease and potentially reduce tumor load is recommended. An observation period where the candidate is receiving neoadjuvant chemotherapy serves to exclude rapidly progressive disease and confirm the absence of radiologic disease in the planned hepatic remnant. Tumor response and exclusion of metastasis can be assessed by sequential computed tomography, magnetic resonance imaging, or positron emission tomography as indicated. The authors have found endoscopic ultrasound especially useful in sampling portal hilar, hepatocaval, and celiac adenopathy to exclude extra-hepatic disease. Observation periods while receiving

chemotherapy of approximately 6 months are conducive to surgical planning and prevention of early recurrence within the hepatic remnant or newly diagnosed metastatic disease. In our experience, an observational period of neoadjuvant chemotherapy results in attrition of approximately one-third of patients originally identified as potential EVAT candidates.

The third consideration is technical appropriateness. EVAT is optimally reserved for specific anatomic indications that include: IVC invasion involving >50% of caval diameter or extending >3 cm along the IVC, multiple hepatic vein involvement requiring venous outflow reconstruction, IVC–hepatic vein junction invasion, or hilar involvement requiring complex vascular reconstruction [15, 21–24] (Fig. 18.1).

The confirmation of these relationships often requires three-dimensional image analysis. CT or MRI IVC invasion of <50% diameter or <3 cm in length is amenable to direct repair, or patch repair using either saphenous vein (autogenous or cryopreserved), bovine pericardium, or prosthetic material [14, 22, 23]. For IVC–hepatic vein junction tumors, we agree with Hemming in advocating EVAT versus modified TVE in order to provide a surgical field most conducive to complete tumor extirpation with acceptable parenchymal margins [24]. Complex vascular reconstructions, whether hepatic venous outflow or hilar, are facilitated by EVAT, as the reconstructions and parenchymal transection can be performed under cold preservation with minimal time constraints. Furthermore, the recipient remains hemodynamically stable through veno-venous bypass or decompressive shunting without the physiologic challenge of sustained volume loading or hypothermia that occurs with a prolonged performance of TVE.

Autograft volume assessment is performed utilizing three-dimensional image reconstructions. A future liver remnant (FLR) above 40% of predicted is ideal for hepatic parenchyma exposed to chemotherapy. A lower threshold of 25–30% is possible when the operative recipient is young and has not been exposed to chemotherapy [24, 29]. Estimation of FLR in EVAT does not typically require the degree of consideration given to larger in-situ hepatectomies. EVAT usually involves vast, bulky tumors that stimulate significant hypertrophy in the future liver remnant. When analyzing outcomes data, mortality secondary to early liver failure has steadily declined since the introduction of EVAT.

We routinely apply portal vein embolization (PVE) approximately 3–4 weeks before EVAT as a mechanism of graft conditioning. PVE not only optimizes the FLR, but hepatic regeneration secondary to PVE may stimulate growth of occult neoplasms within the planned remnant (Fig. 18.2).

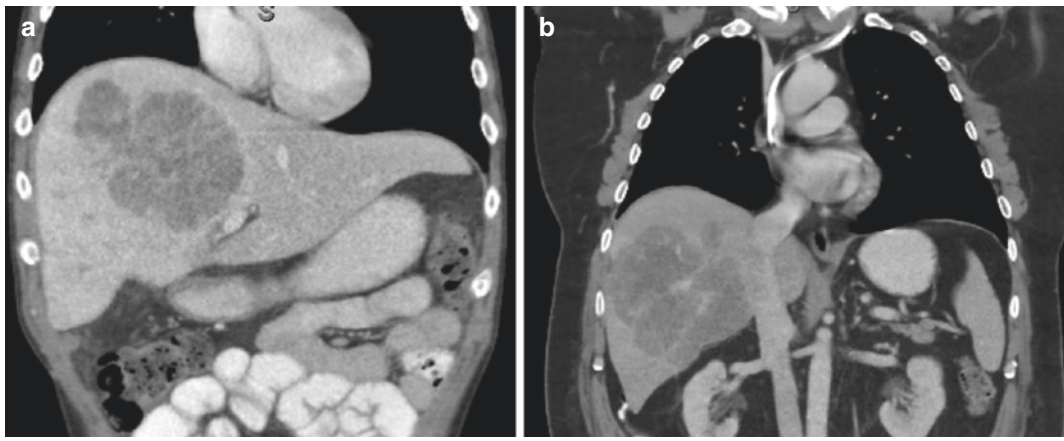

Fig. 18.1 Computerized tomography of a large cholangiocarcinoma of the right lobe invading the takeoff of the left portal vein (**a**) and inferior vena cava (**b**)

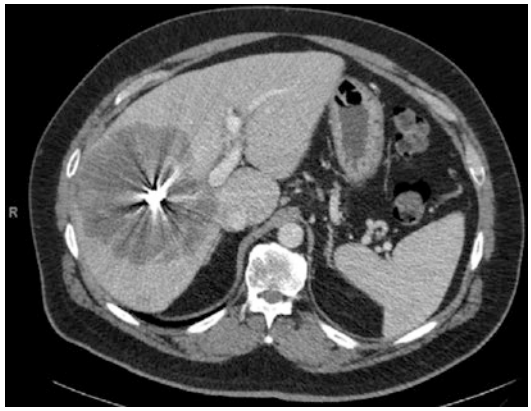

Fig. 18.2 Portal vein embolization of a large cholangiocarcinoma of the right hepatic lobe with invasion of the inferior vena cava

Thus, we employ PVE as an attempt to avert early disease recurrence secondary to occult micrometastatic disease in the remnant, and also as a final screen for resectability. Two to 3 weeks after PVE and within 2 weeks of planned EVAT, the patient receives their final cross-sectional imaging prior to surgery to confirm volumetry and exclude radiographic disease in the remnant. Our experience with increasing FLR from PVE when planning EVAT has been variable, but the improvement of FLR by as much as 30% has been reported [24].

Operative Technique

Successful performance of EVAT integrates hepatobiliary surgery, partial-allografting in transplantation, pre-operative three-dimensional reconstruction imaging, volumetry, and advanced intraoperative imaging techniques. Pre-operative planning includes anesthesia, nursing, blood-bank/laboratories, and intensive care unit personnel [21]. Two complete surgical teams will be required during the period of ex-vivo hepatectomy to minimize the period of cold storage: one team to work in infusion of the allograft with preservation solution, resection of the tumor, and remnant preparation for implantation, and another team to recreate the IVC, perform a portacaval shunt, and prepare the arterial inflow.

The procedure begins with a diagnostic laparoscopy with intraoperative ultrasound to verify the anatomic relationships and exclude metastatic disease or radiologically occult disease in the anticipated hepatic remnant. Laparoscopic examination of hilar nodes is included with biopsy of any suspicious adenopathy. Upon completion of the diagnostic laparoscopy, a supraumbilical midline incision with bilateral subcostal extension is performed to include the previous laparoscopy port sites. The retractors are positioned and the liver mobilized as performed for OLT.

The type and extend of veno-venous bypass (VVB) is optional; however, VVB of the systemic and portal circulations must be immediately available should volume loading be insufficient to maintain cardiac output, occurrence of a cardiac arrythmia, rapidly increasing splenomegaly, or mesenteric congestion.

Upon complete mobilization of the liver and establishment of VVB, as desired, total vascular exclusion is performed and the liver is explanted. The principal surgical team remains with the liver to immediately initiate cold preservation through infusion of 2 l of HTK via the portal vein, 1 l via the artery, and 300 cm^3 via the bile duct. We prefer to flush only the potential remnant.

Upon completion of organ flush, the dissection is performed in cold preservation. Parenchymal transection is at the discretion of the surgeon but has been described utilizing clamp–crush, sharp dissection, and the Cavitron ultrasonic dissector. Vascular structures are sharply dissected in preparation for reconstruction. Vascular reconstructions may involve vessels salvaged from the explant specimen when necessary. Upon completion of parenchymal transection, oversew of biliary and vascular structures, and any vascular reconstructions, the remnant is again flushed with 1 liter of HTK in the portal vein, 500 cm^3 in the hepatic artery and 50 cm^3 gently flushed in the bile duct immediately prior to implantation.

With an EVAT, surgery on the liver can be extended between 3 and 5 h, while vascular exclusions alone mostly remain between 30 and

35 min. In the majority of reported cases for extreme surgery, the exclusion period of up to 55 min sufficed to perform vascular reconstructions required to obtain an R0 resection.

Major reports of the success of extended partial hepatectomies for metastatic diseases fostered a surge of procedures using isolated liver perfusion for prevention of hepatic ischemia to extend the time for operating on the liver.

The vast majority of procedures, however, avoided the ex-vivo approach and instead reported vascular exclusion with hypothermic perfusion, in-situ or ante-situm operations with a hypothermic protection of the liver while an extracorporeal bypass was introduced [23, 33, 34].

The last report of a series of ex-vivo liver resections and autotransplantation was published by Wen et al. [29] including 15 patients with end-stage alveolar echinococcosis (benign disease). The indication was highly selective, arguing that their procedure requires no organ donor nor immunosuppression. They performed temporary IVC interposition and portosystemic shunting for hemodynamic stability. The postoperative complications were minimal, with only one death due to liver failure and 20% requiring postoperative reintervention. Hence, the peculiarity of a unilocular located tumor, obstructing the portal vein entrance, works like an artificial portal vein occlusion, thus leading to a regenerative growth of the remnant liver. The volume of the reimplanted livers, not affected by chemotherapy or other toxic agents, all remained satisfactory.

Another successful ex-situ operation was reported by Hanoun et al. [15], but the one patient with metastatic disease developed recurrence after 11 months.

Chui et al. [33] reports a single case of hilar cholangiocarcinoma, and there are other reports of technically successful operations, but the results reported for the treatment of malignancies do not yet warrant a broader application.

The only report with long-term experience after ex-situ liver surgery derives again from the Hannover group, published in 2000 after the untimely demise of Rudolf Pichlmayr in 1997 [22]. In 22 patients, ex-vivo partial hepatectomies were performed with ten patients presenting with metastatic disease from primary colorectal cancer.

Six patients could be followed up for up to 2 years and 7 months, ultimately dying from the recurrent disease with the majority having a lesser survival time (Table 18.1).

Including other metastatic and primary malignant diseases, only seven patients survived more than 18 months. The intraoperative mortality for

Table 18.1 Results of the two major reports of EVAT for malignancies

Author	N	Hospitalization (days)	Survival time (months)	Cause of death
Oldhafer [22]	10			
	1	14	13	Tumor recurrence
	2	44	0	Liver failure
	3	56	21	Tumor recurrence
	4	60	2	Intracerebral bleeding
	5	60	2	Sepsis
	6	24	15	Tumor recurrence
	7	27	31	Tumor recurrence
	8	61	36	Tumor recurrence
	9	14	0	Pneumonia
	10	42	0	Sepsis
Lodge [23]	4			
	1	42	30	Tumor recurrence
	2	15	0.5	Liver failure
	3	9	NA	Tumor recurrence
	4	10	NA	Tumor recurrence

primary Klatskin tumors was three out of four patients, demonstrating, that the courageous attempt for a curative resection failed. By looking closely into the results of two other relevant publications, it becomes evident that the price for a possible extended life span included a long hospital stay up to 61 days, eventually dying from recurrence after 36 months [23, 35, 36].

In total, a few articles have been identified up to 2016 in comparison to multiple hundreds of articles referring to in-situ partial hepatectomies using vascular exclusions, in-vivo perfusion applying porto-venous shunting as well as rare ante-situm procedures to allow for extended vascular reconstructions around the vena cava and the hepatic venous confluence.

The hypothesis of the ex-vivo approach calls for an extended hepatic resection requiring vascular reconstructions while the patient remains either on a veno-venous bypass or an in-situ porto-caval anastomosis being performed along with a vena cava interposition graft [35]. The entire liver has to be severed from its attachments, and five anastomoses are required for reimplantation, just as with an allograft. Technically, all this can be accomplished by experienced hands. Normal liver, preserved with appropriate solutions should tolerate this manipulation. However, since surgical interventions are aiming at removal of all cancerous tissue, particularly in the liver with a multilocular metastatic disease, anatomical lines have to be transgressed, causing necrotic areas, bile leaks, and eventually sepsis or liver failure. There is no doubt that advances in surgical techniques over the last decades converted the once untouchable organ into a special task, manipulatable along its well-known anatomical entities as long as inflow, drainage, and outflow are adequately restored. Seemingly, there are no limits because of the organ's capacity to regenerate.

Nevertheless, other factors such as underlying cancerous diseases have to be taken into account for improving the patients prognosis and even cure. The initial intention by the Pichlmayr group in 1988 was to open a new perspective for surgery for an otherwise inoperable situation, and their procedure has been classified as an "extreme salvage procedure after the failure of conventional treatments". The ethical justification then derived from severe, disabling symptoms of the patients, lack of alternative treatments at that time, including scarcity of organ donors for a rescue transplant, the competence of the surgical team deriving from experimental experiences, and a fully informed consent of the patients.

The planning of these extended resections today include CT, MRI, and 3D imaging techniques, as has become standard preoperative assessment for any major hepatic surgery. Thus, for the last decade these preoperative procedures have made possible more accurate diagnoses and operative planning [37]. Colorectal metastases are often multilocular, and the exact location, including the vascular segmental anatomy and calculation of any remnant liver segment volume, is pivotal for the surgical approach to be chosen. Currently, there is accumulated experience with 3D imaging-guided liver surgery to avoid the removal of the entire liver deliberately out of its natural location to perform bench procedures. With in-situ protection, there is definitely up to 1 h to dissect parenchyma and reconstruct vascular structures in a anicteric, normal liver. Simultaneously, oncological principles have to apply, which are well known and unfavorable for a colorectal metastatic disease, but vary for primary liver tumors or metastases from neuroendocrine tumors.

Since EVAT operations do not require a regular or a rescue transplant out of a limited donor organ pool, the place for such a treatment of metastatic diseases, avoiding immunosuppression but continuation of chemotherapy, still needs to be determined. In countries without access to cadaveric donor organs, the procedure is still appealing and, in extreme situations, performed, with a live donor prepared. Assuming that live donors are readily available in Asian countries, the question remains: where to stop definitely treating colorectal metastases surgically or in combination with oncological protocols? With the data published thus far, a potential ethical problem for the performance of such a procedure will arise. In Western countries, however, the resources required for such unvalidated

procedures are hard to cover for any DRG (disease-related group) through insurances or hospital allowances.

In this context, benign diseases or primary solitary liver tumors such as HCC or even cholangiocellular carcinomas are different from colorectal metastases, considering their prognostic factors and alternative treatments.

Thus, there may remain indications of ex-vivo procedures for benign tumors such as adenomas or parasitic diseases such as alveolar echinococcosis. However, even for those benign indications such as alveolar echinococcus (AE), surgeons argue [38] that residual or recurrent parasitic lesions in patients with a liver disease considered lethal at short term have been allowed to survive for more than 20 years. The slow growth of *E. multilocularis* and the simultaneous stimulation of hepatic regeneration by metacestodes of *E. multilocularis* through the mitogen-activated protein kinase system (MAPK) provide a rational explanation for the clinical observation of hepatomegaly and a well-functioning remnant liver lobe even after major hepatic resection [29]. Primary transplants or rescue transplants for AE have shown a detrimental effect of immunosuppression on residual disease unknown before surgery.

The experience of ex-vivo surgery of the liver thus far has not established itself as an accepted procedure for malignant primary or metastatic diseases.

However, the procedure is there; finding the appropriate indication will be a task for the future. In combination with other treatment modalities a resurrection is not excluded. “Diseases desperate grown by desperate appliance are relieved—or not at all” (Shakespeare—Hamlet).

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The Role of Laparoscopy in Advanced Liver Disease

19

Juan Pekolj and Martín Palavecino

Introduction

For several years, diagnostic and staging laparoscopy were the only laparoscopic procedures performed for liver tumors. The limitations to the use of this approach were the lack of conviction, difficulties with the parenchymal transection, and the elevated risk of intraoperative bleedings [1]. The development of new technological devices, the improvement of surgeons' skills, and other technical advances made it possible to increase the number of liver surgery units routinely performing both minor and major laparoscopic liver resections (LLRs) for the management of colorectal liver metastasis (CLM) [2].

For the management of CLM, laparoscopy can be used in three different situations: staging and/or determination of resectability, tumor ablation, and liver resections [1].

Staging

The objective of staging laparoscopy is to avoid an unnecessary non-therapeutic laparotomy. In general, the intraoperative finding of peritoneal carcinomatosis contraindicates laparotomy and liver resection, but cytoreductive surgery and hyperthermic intraperitoneal chemotherapy could be offered in specialized centers to selected cases with limited hepatic (<3 nodules) and peritoneal disease [3]. With regard to tumor staging of the liver, intraoperative assessment with laparoscopic ultrasound (LUS) increases the accuracy of laparoscopy (Fig. 19.1). Recent evidence indicates that LUS is a reliable tool for staging liver tumors, with a performance similar to that of open intraoperative ultrasound in detecting

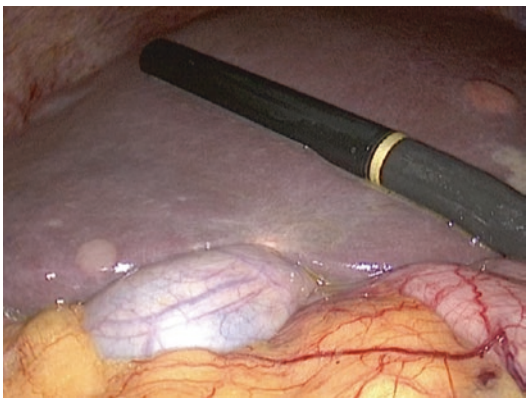

Fig. 19.1 Intraoperative view of laparoscopic ultrasound evaluation in a case of multiple bilateral metastases

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new nodules [4]. However, due to the improvement of diagnostic imaging (CT-scan, MRI, PET-scan), this situation is rare. The finding of a greater number of metastases, contralateral metastases, and/or porta hepatis lymph nodes change the strategy, but they are not always causes to abort a liver resection. Even though in some initial series laparoscopy precluded liver resection in up to 38% of patients bearing CLM, the benefits of laparoscopic staging have decreased in more recent years due to the expansion of resectability criteria and modern imaging modalities. From 274 patients who underwent an attempted open hepatectomy at the Liverpool hepatobiliary center between 2008 and 2012, only 12 (4.4%) were found to have irresectable disease at laparotomy [5]. Therefore, nowadays the vast majority of patients with potentially resectable CLM do not benefit from laparoscopy. For this reason, staging laparoscopy should not be used routinely, and only patients at high risk of occult unresectable disease should be selected for this approach. The Clinical Risk Score proposed by the Memorial Sloan Kettering Cancer Center could be used for this purpose, where 42% of patients with score >2 can be spared an unnecessary laparotomy [6]. In summary, the indication of staging laparoscopy should be analyzed case-by-case in a multidisciplinary fashion.

Tumor Ablation

The LUS can be used as a guidance method to perform radiofrequency ablation (RFA) or microwave ablation of liver metastases. The main advantage of this approach over the percutaneous approach is the possibility of treating tumors in challenging locations, such as those in close proximity to adjacent organs (contact with the colon, duodenum, stomach, and kidneys) or located in the dome of the right hemiliver. A more accurate ablation needle placement explains the lower recurrence rate when compared with the percutaneous approach. However, this approach has very selected indications, mainly in cases where liver resections are contraindicated. Tumor size is the main limitation for this local treatment modality, with proved lower efficacy for lesions larger than 3 cm [7].

Laparoscopic Liver Resections (LLRs)

A steady and sustainable global diffusion of LLRs has occurred since the first international consensus conference in 2008 [1]. Despite the number of publications having increased in the last years, the level of evidence is still low and based on retrospective comparative series. Prospective randomized trials have not been published yet. Patients with CLM represent the main indication for LLRs in Western countries, in contrast with hepatocellular carcinoma in Eastern countries [8]. In our own series of 109 LLRs, 44% of the cases were CLM [9].

At the First International Consensus Conference on laparoscopic liver surgery held in Louisville (USA) in 2008, indications for LLRs were well defined [1]. During the Second Consensus Conference in Morioka (Japan) in October 2014, indications were extended regardless of the type, number, and localization of the metastases [8]. At the beginning, the ideal cases were those with small metastatic lesions in the anterior segments of the liver (II, III, IVB, V, VI) (Fig. 19.2). In recent years, indications progressed to the "deep, posterior, or complex" segments (I, IVA, VII y VIII). The LLRs in this last group are considered major liver resections not due to the amount of parenchyma resected nor the risk of postoperative liver failure, but due to their anatomical relationship with main vascular structures and the risk of intraoperative severe hemorrhagic complications [10]. The laparoscopic approach of liver resections has some technical advantages over open surgery: excellent visibility of vascular pedicles, the magnification provides an optimal view of the parenchymal transection, and the pneumoperitoneum pressure reduces bleedings from the hepatic veins [2, 8, 11] (Fig. 19.3). The applicability of the laparoscopic approach for liver resections is variable and related mainly to the type of patients managed at each center, the expertise of the team, and the

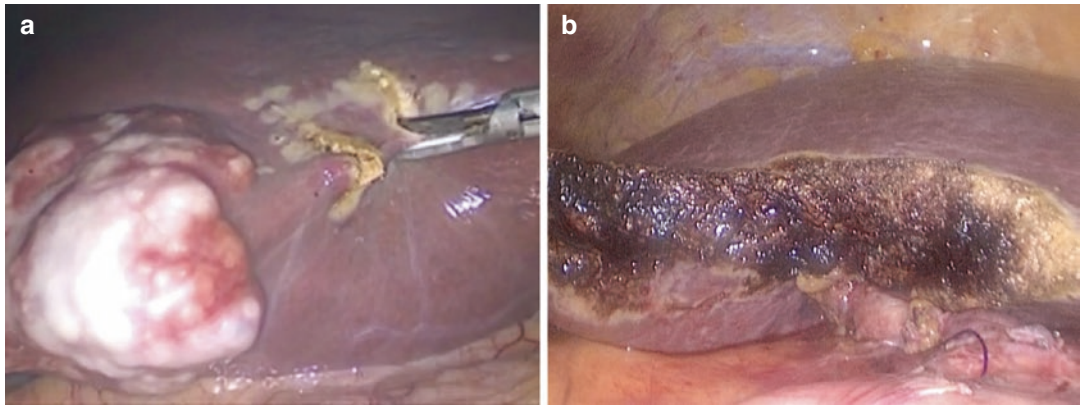

Fig. 19.2 (**a**) Colorectal cancer metastases in segment 5 of the liver. (**b**) Transection line after laparoscopic resection

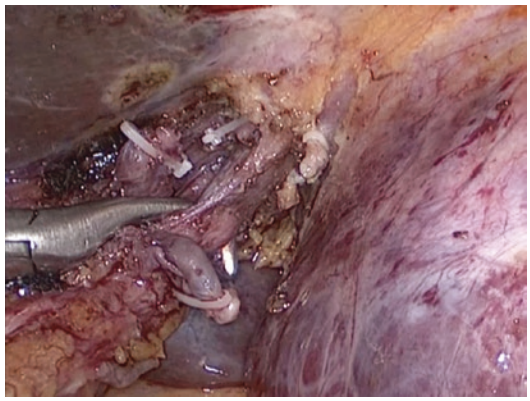

Fig. 19.3 Left hepatic pedicle. Arterial branches were clipped and transected. Left portal branch is mobilized with right angle forceps

confidence with the approach. As an example, the rate of LLRs was 19% in the Henri Mondor Hospital series of 2009, 46.5% at the Institut Mutualiste Montsouris in 2006, and passed from 10 to 80% of all liver resections at the Northwestern University of Chicago between 2001 and 2006 [12–14]. In our own series, the applicability was initially 5.2% and it increased to 20% during 2014 [9].

For LLRs, four different techniques can be used: totally laparoscopic, hand-assisted, hybrid, and robotic-assisted techniques.

- In the totally laparoscopic technique, all the procedure is done by laparoscopy and an abdominal incision (for example a Pfannestield incision) is performed at the end of the procedure only to remove the specimen [1, 8].
- In the hand-assisted technique, a hand is introduced in the abdomen through a special device that prevents losing pneumoperitoneum. This approach is useful at the beginning of the experience and in cases with tumors located in posterior segments of the liver [1, 8].
- In the hybrid technique, part of the procedure (i.e., pedicle dissection) is carried out by laparoscopy, and after that a limited abdominal incision is performed to complete the surgery (i.e., parenchymal transection and specimen removal). This approach is helpful at the beginning of the experience with major LLRs [1, 8].
- In robotic-assisted LLR, the robot technology is used in some technical steps of the procedure. The advantages of the robot are safe dissection of the pedicle, and ergonomic benefits for the surgeon. However, it has not shown any clinical advantages when compared to classical LLRs. High costs related to the robotic technology are still an issue to be discussed [2, 8].

Surgical Technique

The technique depends on each surgical group. The laparoscopic devices should be placed following the principles of laparoscopic surgery, thus the surgeon standing in front of the site of the lesion to be resected. Some surgeons prefer to stay between the legs of the patients

("French position"). For right LLRs, intermediate left later decubitus is recommended. For all the other LLRs, the patient should be positioned in supine decubitus. The trocar placement sites rely on the location of the tumors (Fig. 19.4). Reverse Trendelenburg's position, near-zero central venous pressure (CVP), and increased pneumoperitoneum pressure (16 mmHg) are recommended for LLRs [2, 11–13, 15, 16].

Nowadays, it is possible to perform almost all types of minor and major LLRs (according to the expertise of the surgical team), for example: staged liver resections, simultaneous colorrectal and liver resections, and ALPPS [2, 11–13, 15–17]. In Fig. 19.5, a step-by-step evolution in the complexity of LLRs is represented.

The transection of the liver parenchyma is still a topic of discussion and is the most challenging step in LLRs, mainly in the case of major resections. There are basically two ways to transect liver: sharp dissection with an ultrasonic dissector (CUSA®) combined with bipolar energy devices, or energy sealant devices (Ligasure®, Ultracision®) combined with vascular staplers. The main purpose of the devices designed for this procedure is to avoid bleeding. In our institution, the preferred strategy is the use of energy devices (Ultracision®) combined with vascular staplers (Figs. 19.6, 19.7, 19.8, and 19.9). The principal disadvantages to this technique are higher costs and a less refined anatomical dissection. The use of ultrasonic dissector (CUSA®) combined with

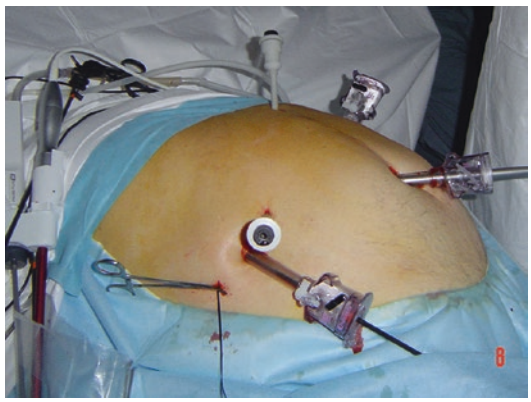

Fig. 19.4 Trocar placement for right liver resection. The forceps is clamping the tourniquet for percutaneous Pringle maneuver

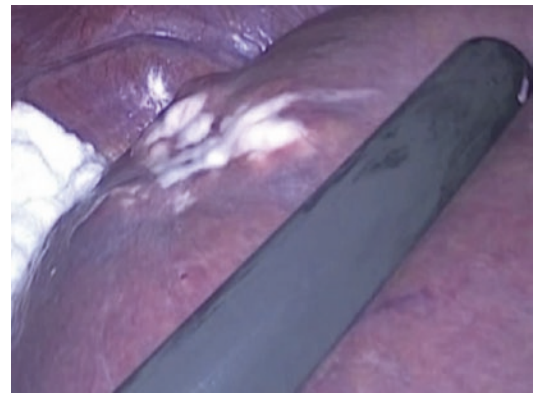

Fig. 19.6 Delimitation of surgical margin with laparoscopic ultrasound in a non-anatomic liver resection

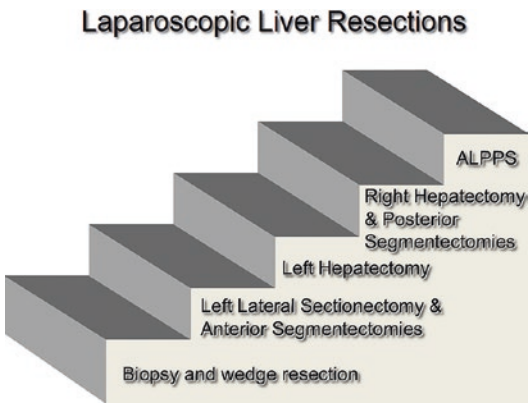

Fig. 19.5 A step-by-step evolution in the complexity of LLRs

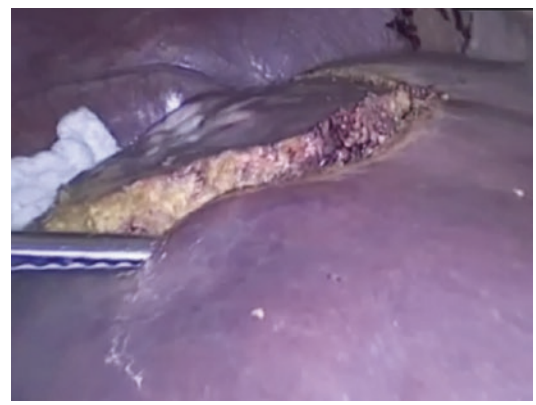

Fig. 19.7 Transection line in a non-anatomic liver resection

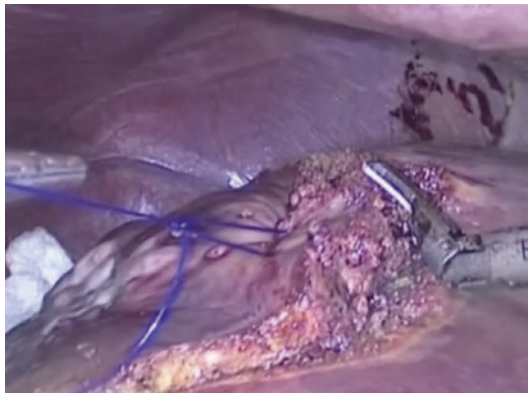

Fig. 19.8 Transection of liver parenchyma whit a sealant device (Ultracision)

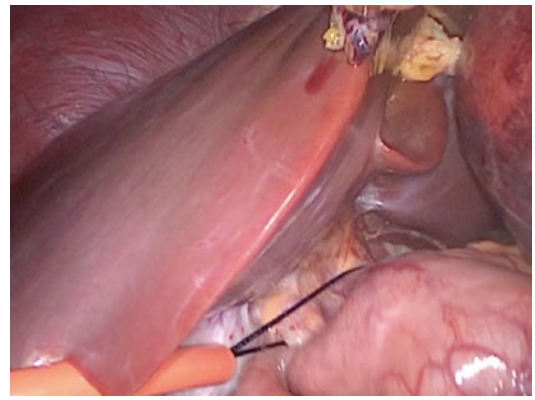

Fig. 19.10 Intraoperative view of the tourniquet around the porta hepatis for the Pringle's maneuver

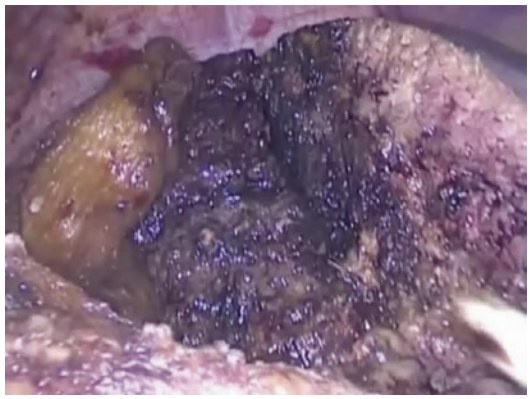

Fig. 19.9 Final view of the operative field with free margins

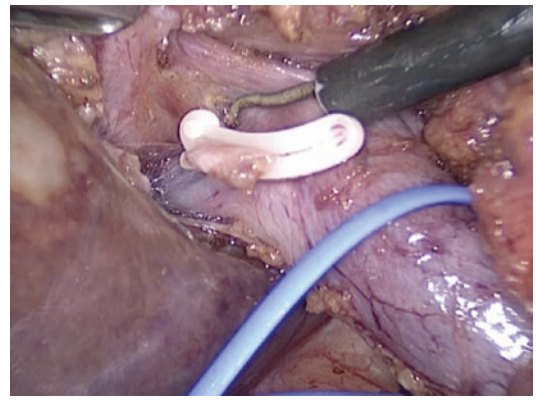

Fig. 19.11 Operative view of the branches of right portal vein (trifurcation). The main trunk of portal vein is encircled with a *blue* vessel loop

bipolar energy is the other possible technique, and it is employed mainly in France and Asia. The principal disadvantage of this approach is a longer operative time [16]. In order to reduce blood loss, the vascular pedicle of the liver can be clamped as it is done in open surgery. Intermittent clamping (Pringle maneuver) is employed more frequently at the beginning of the experience [2, 8, 12] (Fig. 19.10). When performing anatomic major liver resections, the right or left vasculobiliary elements are dissected and individually controlled using either vascular staplers (white cartridge) or locking ligation systems such as Hem-o-lok clips (Figs. 19.11 and 19.12). The control and transection of the hepatic veins is one of the most challenging steps of the procedure, due to the possibility of gas embolism and

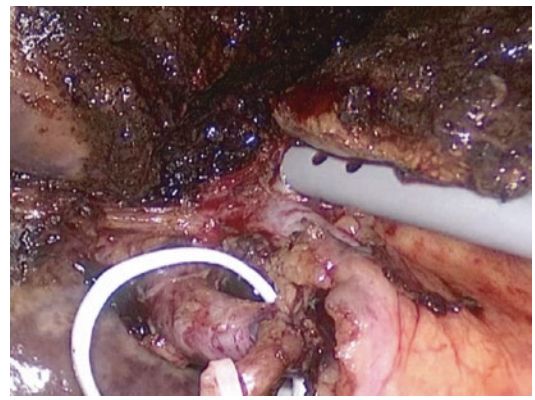

Fig. 19.12 Operative view of the right branch of hepatic artery (*white* vessel loop) and the common hepatic duct and right hepatic duct

Fig. 19.13 Transection of the right hepatic vein with a laparoscopic vascular stapler

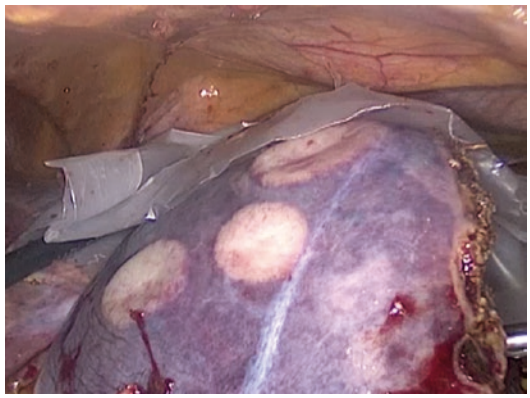

Fig. 19.14 Placement of the surgical specimen in a plastic bag to be removed through an auxiliary incision

massive bleeding. Vascular staplers (white cartridge) are usually employed by most surgeons [2, 8, 12, 16] (Fig. 19.13).

At the end of the procedure, the specimen is removed in a plastic bag using different abdominal incisions (Fig. 19.14). Frequently, the extension of the umbilical trocar incision is enough to remove small specimens. In major LLRs, a transverse suprapubic incision (Pfannestield incision) is recommended.

From a technical point of view, one of the initial concerns was how to reproduce the wide mobilization of the liver required for major LLRs in a limited abdominal space, as is the case of the laparoscopic approach. To solve this problem, the concepts of the "anterior approach" for open liver resections were applied [11]:

- 1st control of portal pedicle,
- 2nd transection of the liver parenchyma,
- 3rd control and transection of hepatic veins,
- 4th mobilization by transecting the different liver ligaments,
- 5th removal of the specimen.

Results

At the beginning of the experience with the laparoscopic approach to treat liver tumors, the three main concerns were: the possibility of tumoral seeding at the port insertion sites, local recurrence due to an inadequate margin, and a poor short- and long-term oncologic result. There are several publications showing that the oncologic results are at least equivalent to open resections, with no increased rate of port insertion sites recurrence. In 37 different studies, the evaluation of surgical margins was similar to open surgery, in five studies the margins were better in the laparoscopic approach, and it was worse in only one. The employment of laparoscopic ultrasound is helpful to guide LLRs, and has been associated in several series with a higher rate of tumor-free margins [13, 18, 19]. In some series, oncologic results were even better in the laparoscopic approach than in the open fashion. A lower level of postoperative immunodeppression was considered a possible cause for these better results.

One of the first published series that highlighted comparable 5-year oncological outcomes of patients with CLM between the open and the laparoscopic approach was that from the Paul Brousse and the Institut Mutualiste Montsouris groups in Paris, France [18]. This study compared oncological outcomes from two highly specialized centers, including 60 patients in each group matched for clinical and oncological characteristics. The oncological results of this series are summarized in Table 19.1 [18]. In a larger series reported by Nguyen et al. [19], 109 patients underwent LLR for CLM. The 1-, 3-, and 5-year overall survival rates were 88%, 69%, and 50% respectively; while the 1-, 3-, and 5-year disease-free survival rates were 65%, 43%, and 43% respectively. More recently, two propensity

Table 19.1 Oncologic results comparing open and laparoscopic liver resections [18]

	Overall survival			Disease-free survival		
	1 year	2 years	3 years	1 year	2 years	3 years
Laparoscopic liver resections (%)	97	82	64	70	47	35
Open liver resections (%)	97	70	56	70	40	27

score-based analysis showed that LLRs for CLM may provide R0 resection rates and long-term survival profiles comparable to those for open surgery [20, 21].

Cosmetic benefits, low postoperative pain, less necessity of pain treatment medication, short hospital stay, and a prompt recovery to daily activities are the well-known benefits of every minimally invasive surgical procedure [1, 8, 22, 23]. Related to LLRs, several meta-analyses and have showed a lower level of bleeding, a lower blood transfusion rate, and a shorter length of stay compared to the open approach [22–24]. Fewer postoperative adhesions is another advantage of the laparoscopic approach, which is especially important considering that many of these patients will need repeated resections to treat recurrent disease. The global rate of postoperative complications is also lower than in open surgery [20, 21].

The main causes for conversion to open liver resections are intraoperative bleeding, technical difficulties in continuing with the procedure, and concerns to obtain a free margin [20, 21]. Even though the operative time at the beginning of the experience was longer than in open surgery, the operative time decreased after the learning curve period and now it is similar to open surgery. In a recent evaluation of 75 publications comparing the two approaches, the operative time was longer in laparoscopic than in open approach in only 15 of them [20, 21]. Patient selection and surgeon expertise are paramount to obtain satisfactory results. Judgment needs to be carefully used when selecting the appropriate candidate to perform a LLR. Given the increasing amount of evidence supporting the use of the laparoscopic approach to treat patients with CLM, nowadays every liver surgery referral center should have within the team an experienced surgeon able to safely perform LLRs.

Conclusions

In selected cases and performed by trained surgeons, LLR is a safe and feasible treatment for patients with CLM. This approach provides less morbidity and shorter hospital stay than open liver resections, without compromising oncological outcomes.

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Liver Transplantation for Unresectable Disease

20

Pål-Dag Line, Morten Hagness, Jon Magnus Solheim, Aksel Foss, and Svein Dueland

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women [1], and about 50% of the patients will develop liver metastases. The treatment for patients with colorectal liver metastases (CLM) is multimodal, including liver resection, chemotherapy, targeted therapies (monoclonal antibodies), interventional radiology, and radiotherapy.

Untreated nonresectable CLM has a dismal prognosis, but during the last decade modern chemotherapy has increased overall survival from 12 to more than 24 months after start of first-line chemotherapy. Oncological treatment alone is not curative, and 5-year overall survival after start of first-line chemotherapy is currently at best 12% [2], after start of second-line chemotherapy the overall survival is in the range of 10–12 months [3], and about 6–8 months after start of third line [4].

Liver resection is the only potential curative treatment option, but among patients with disease limited to the liver, only 10–30% become surgically resectable [5]. In a recent comprehensive meta-analysis based on 116 peer-reviewed papers published between 1999 and 2010, 86 studies reported a median 5-year overall survival of 38% (range 16–74%) [5]. Nevertheless, the majority of these patients develop recurrence. A plateau in the disease-specific survival curves at between 12 and 36% have consistently been reported at 10 years post liver resection [6, 7]. This clearly indicates that the surgical removal of liver metastases is potentially curative.

The main limiting factors in liver resection surgery are the volume and quality of the future remnant liver, as well as the proximity of metastatic tumors to vital vascular structures. The criteria for resectability has evolved from emphasis on formal resections toward a more aggressive approach

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where providing a sufficient liver remnant (usually about 30% in normal liver tissue) is the key element [8]. Operability of hepatic metastases is a moving target, and numerous improvements have lead to increased resectability rates. Liver surgery has undergone tremendous changes during the last two decades, and has been profoundly influenced by the technical progress of liver transplantation surgery. This has facilitated development of maneuvers for control of hepatic inflow and outflow, and novel preservation techniques to improve the hepatic tolerance to ischemia. This enables more advanced hepatic surgeries to be performed. Other techniques such as staged resections, portal vein embolization, and the recently developed associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure to induce liver regeneration are valuable tools in avoiding insufficient remnant liver mass after surgery [8–11]. The results following resection have been improved further by modern chemotherapy, and this can also be used to downstage patients in a conversion therapeutic approach so that a larger cohort of patients become resectable [12]; but despite all the advances in oncological and surgical development, about 75% of the patients with CLM still remain unresectable.

Liver transplantation inherently involves removal of the whole liver, and can be regarded as the ultimate R0 resection. Since liver resection can cure a significant proportion of the patients, it is conceptually attractive to explore liver transplantation as a treatment modality for unresectable CLM.

Liver Transplantation for Tumors: Historical Perspective

Cancer constitutes 14% of primary diseases leading to liver transplantation in Europe, with hepatocellular carcinoma (HCC) being the most common indication. Initially, the results after transplantation for HCC were dismal, with high recurrence rates, but after the publication of the now universally accepted Milan criteria for proper patient selection, the survival rates are in line with transplantation for benign indications [13, 14]. For unresectable hilar cholangiocarcinoma, careful patient selection in a protocol with pre-transplant staging laparotomy and neo-adjuvant chemoradiation therapy followed by liver transplantation has rendered excellent results, with overall survival rates of about 70% [15, 16]. The most common secondary tumors that might be treated by liver transplantation are metastases from well-differentiated neuroendocrine tumors (Ki-67 fraction of 2–5%) where carefully selected cases are considered an established indication for liver transplantation [17].

In the early phase of liver transplantation, CLM were not an uncommon indication. In two of the first seven liver transplantations performed in 1963 and 1964, the indication was colorectal liver metastases [18]. The majority of liver transplantation procedures for CLM were performed before 1995. In the European Liver Transplant Registry (ELTR), 50 cases were reported from 1968 to 1995. Based on ELTR data, the 1- and 5-year survival prior to 1995 was 62% and 18% respectively [19]. Twenty-four of the procedures were performed as part of a program in Vienna that lasted from 1984 until 1994; the remainder were done as sporadic procedures at several centers. The Vienna group reported 30-day perioperative mortality of 30% in the initial parts of the series, which included the learning phase of liver transplantation. In 44% of the cases, graft loss was not related to tumor recurrence [20]. They soon restricted the procedure to patients with histologically lymph node negative primary tumor (pN0), which improved the results. However, the program was abandoned in 1994 due to a high rate of recurrence and decline in available donor livers. A subgroup of three pN0 patients that were without genetically detectable micrometastases in lymph nodes achieved long-term survival, one more than 22 years after liver transplantation [21]. Further case reports with recurrence-free survival after 5 and 10 years exists in the literature [22, 23]. These historical cases demonstrate that long-term survival is possible after liver transplantation for CLM.

Liver Transplantation for Nonresectable CLM in Norway: The SECA Study

Norway has had a low prevalence of hepatitis C compared with many other countries, and the most common indication for liver transplantation has been primary sclerosing cholangitis. The donation

rate has been consistently high compared to the incidence of liver disease, resulting in waiting times of about 3–4 weeks. This epidemiological situation made it possible to explore new indications for liver transplantation, including malignancies. In the early part of the millennium, CLM were considered a contraindication for liver transplantation [24]. The results of liver transplantation for CLM prior to 1995 in The European Liver Transplant Registry (ELTR) showed 5-year survival of only 18%. However, the overall survival probability after liver transplantation in general has improved with 20–30% since then. Furthermore, significant advancements in oncological treatment and imaging techniques have improved the prognosis and selection of CLM patients for liver surgery. In addition, the introduction of the mammalian target of rapamycin (mTOR) inhibitors provided the possibility of giving immunosuppressive treatment combined with antineoplastic effect. On this background, we hypothesized that a 5-year overall survival after liver transplantation for CLM of 50% was attainable [25].

The SECA study was a pilot study for nonresectable CLM that was initiated at Oslo University Hospital in 2006. Twenty-four patients were screened, but three patients were found to have liver hilar lymph node-positive disease at exploratory laparotomy. Thus, 21 patients underwent liver transplantation in the study. The 5-year overall survival was 60% (95% CI: 34–85%). Median follow-up at the time of publication (2013) was 27 months (range 8–60 months). Six of 21 patients died due to disseminated cancer after median 26 months (range 6–41 months). The disease-free survival was 35% at 1 year, and 19 of the 21 patients experienced recurrences (Fig. 20.1). In the majority of the patients, however, the recurrence was evident as small (<1 cm) lung metastases, and a significant proportion of these were accessible for surgery. At follow-up, 33% of the patients had no evidence of disease [26].

The initial study protocol was quite strict with regard to extent of disease and response to chemotherapy; but after 11 months without included patients, a protocol amendment with wider inclusion criteria was approved. These consisted broadly of minimum 6 weeks of chemotherapy, good performance status (ECOG 0–1), and absence of extra-hepatic disease. Thus, the

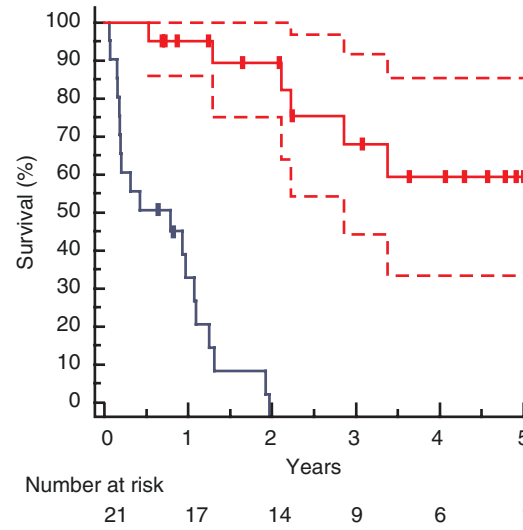

Fig. 20.1 Overall survival after liver transplantation for nonresectable CLM. The Kaplan–Meier (KM) plot shows overall survival from the time of liver transplantation (*red line*). *Stapled lines* show 95% CI for the KM plot. *Blue line* shows DFS. All deaths were due to the underlying cancer disease. No patients were lost to follow-up (From Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800–806)

principal selection criterion was *unresectability of metastases* assessed at the multidisciplinary conference in our institution. Accordingly, the study population ended up being very heterogeneous with regard to T and N stage, CEA levels, previous exposure, and response to oncological treatment. At the time of liver transplantation, 16 patients had progressed on first or later lines of chemotherapy, six patients had progressed on all standard lines of chemotherapy, and 38% of the patients had received second-line chemotherapy. The hepatic tumor load was extensive; median number of metastatic lesions was eight (range 4–40 metastases), and median diameter of the largest lesion was 4.5 cm (range 2.8–13.0 cm) [26].

In liver resection surgery for CLM, there is a strong relationship between postoperative survival and clinical scoring systems [27]. Since hepatic resection for CLM is routinely performed in resectable patients, these clinical scoring systems are not used in the decision-making on whether to perform hepatic resection or not in single cases.

The selection of patients to liver transplantation for CLM is, however, highly important due to the scarcity of donor livers. Outcome for a new

indication should in general be comparable or better than outcome for established transplant indications. The heterogeneity of the SECA population made it likely that the prognostic profiles of the patients were highly diverse.

The two patients demonstrating the shortest survival in the material had tumor breaching the liver capsule, and cancer infiltration of diaphragm were found after vital structures were divided and transplantation unavoidable [26]. In hindsight, these cases would not have been transplanted with our current knowledge. By analyzing preoperative status and outcome following liver transplantation, four factors were found to be significantly associated with decreased survival:

- Maximal hepatic tumor diameter above 5.5 cm
- Time from primary cancer surgery less than 2 years
- Carcinoembryonic antigen (CEA) of more than 80 µg/l
- Progressive disease at time of liver transplantation.

These are established clinical prognostic factors known from studies on liver resection, and are included in clinical scoring systems. Five of the six deceased patients had all of these factors present (Fig. 20.2). Very cautious interpretation of these findings is stressed because of the small study population, but the results indicate a

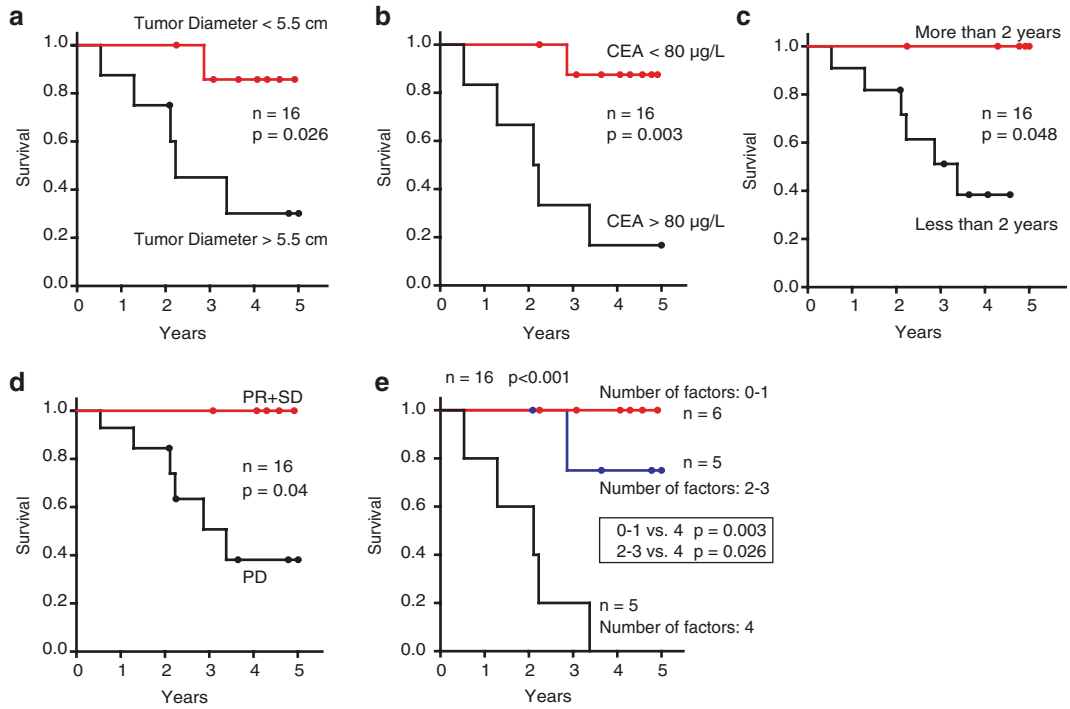

Fig. 20.2 Preoperative factors affecting survival. The 16 first patients in the study who had observational time of more than 2 years or who died within this period were analyzed. Median observational time was 50 months (range, 25–60 months). (**a**) Kaplan–Meier (KM) plots for patients with maximum tumor diameter above and below the median diameter of 5.5 cm. (**b**) KM plots with CEA levels before transplantation above and below 80 µg/L. (**c**) KM plots for patients with time from primary surgery to liver transplantation more than 2 years and less than 2 years. (**d**) The number of patients who had progressive disease (PD) on chemotherapy at the time of liver transplantation was plotted against the number of patients with stable disease (SD) or that had partial response to chemotherapy (PR). The factors displayed in panels **a**–**d** present in each patient was summed up, giving factors from 0 to 4. The number of factors for each patient was significantly associated with survival ($P < 0.001$, Cox regression). **e** KM plots for three groups of patients, those having 0–1 factors, those having 2–3 factors, or those having all four factors. Log–rank method is used for the calculation of P values in all panels (From Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800–806)

possible potential for selecting patients based on established clinical parameters, and by this further improving outcome [26]. Since the first report in 2013, the SECA data has matured with more than 2 years. At median follow-up of 65 months (range 19–85 months) post liver transplantation, the four prognostic factors were still significantly associated with survival, and if the five patients with all four factors present are excluded, the survival at 6 and 7 years was 60% [26, 28].

All patients in the SECA study who were observed for more than 11 months experienced recurrence of disease. The median time to recurrence was 6 months (range 2–24 months); 17 patients experienced lung metastases, and seven patients recurred in the liver graft. At the end of follow-up, seven patients were alive with no evidence of disease, eight patients were alive with recurrence, and six patients were deceased.

The initial recurrence pattern was: 68% lung metastases, 11% liver and lung metastases, 11% lymph node metastases, 5% liver and ovarian metastasis, and 5% experienced local recurrence of rectal tumor as first recurrence [29]. No patient had metastases to the new liver only as first site, and liver metastases developed exclusively as part of disseminated disease. At end of follow-up, six of the seven patients that developed liver metastases were dead. Median time from diagnosis of liver metastases to death was 14 months (range 4–21 months). In contrast, all the 12 patients with recurrences that did not include the liver were alive at end of follow-up, and patients with pulmonary first-site recurrence had a 5-year overall survival of 72% [29]. One might speculate to what extent the pulmonary metastases are true recurrences, or represents selection failures in the sense that they were present at the time of transplant. In order to address this question, reassessment of CT scans by one experienced radiologist was performed. Tracing back from evident metastases in all the 17 patients with pulmonary manifestations, it became evident that seven of them had pulmonary metastases appearing as small nodules at time of liver transplantation. Four of them had pulmonary deposits on earlier CT scans as well (2, 2, 3, and 12 months prior to liver transplantation respectively). The survival analysis showed that the presence of these metastases at the time of liver transplantation did not have negative impact on survival. An interesting clinical observation regarding lung metastases were that they proved to be very slow-growing. Thus, they were observed over extended periods in most patients, and treated surgically, or by radiofrequency ablation whenever possible. For lung surgery, a nodule size of about 15 mm was chosen to ensure that the metastases should be readily identifiable at surgery.

The SECA study was an uncontrolled pilot study; thus the results, although very favorable for nonresectable liver metastases, could not be easily compared to standard treatment. In order to evaluate a survival comparison between transplantation and a modern chemotherapy study, data from a similar cohort of patients included in the NORDIC-VII study were obtained [30]. The NORDIC-VII study was a three-arm, multicenter Phase III trial, on Nordic FLOX and two different regimens containing cetuximab and FLOX, as first-line treatment of metastatic CRC [31]. Patients that had nonresectable CLM, no extrahepatic disease, no BRAF mutation, and similar age were extracted from the NORDIC-VII database. The study population characteristics ended up comparable to the SECA population; however, 5-year overall survival was 9% after start of first-line chemotherapy (n = 47), significantly lower than the 5-year overall survival in the SECA study [30] (Fig. 20.3).

Several patients in the SECA study had unfortunate tumor characteristics (Fig. 20.4). Six of the patients had progressive disease on all standard lines of chemotherapy; three after three lines of chemotherapy, and three with mutation of *Kras* after second line of chemotherapy. For these patients, the median overall survival was 41 months and 5-year overall survival was 41%. In the Nordic-VII study, the median overall survival for a similar cohort was significantly shorter, 5.6 months, and all patients were dead before 2 years [32].

In comparison, the only drug that has demonstrated prolonged survival in treatment of metastatic CRC after progression on all lines of chemotherapy is regorafenib. In a multicenter trial with this drug, the median survival was enhanced from 5.0 (placebo) to 6.4 months [33].

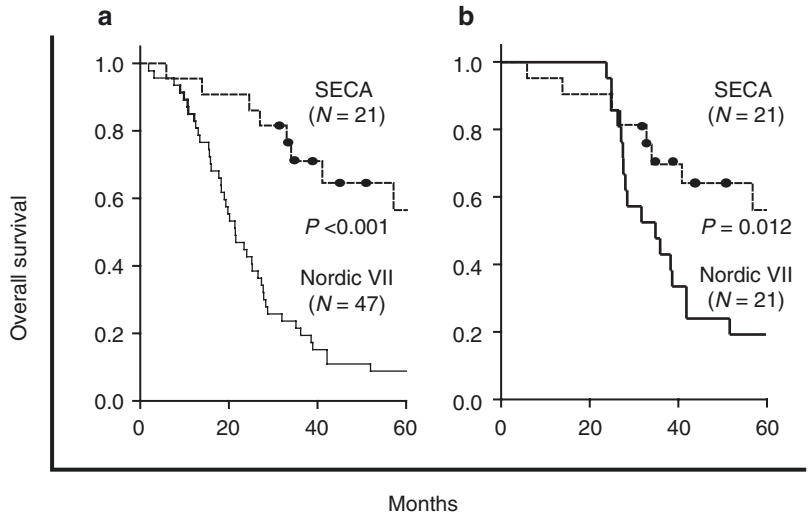

Fig. 20.3 Kaplan–Meier OS curve for patients included in the liver transplantation group (SECA study, *hatched line*) and the chemotherapy group (NORDIC VII study, *solid line*). (**a**) All SECA patients (n = 21) versus all NORDIC VII patients (n = 47). (**b**) All SECA patients (n = 21) versus the NORDIC VII patients with the longest OS (n = 21) (From Dueland S, Guren T, Hagness M, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg. 2015;261(5):956–960)

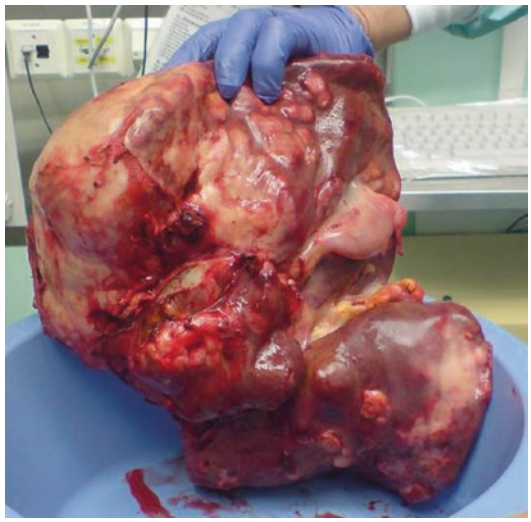

Fig. 20.4 The explanted liver of a SECA study patient; female weighing 60 kg with a liver of 4.7 kg. She had progressed on all three lines of chemotherapy and the tumor had infiltrated the diaphragm. The patients had 5 l of ascites drained at a local hospital the day before liver transplantation. She had the shortest overall survival in the SECA study, only 6 months

In addition, the comparison with the matched group of CLM only in the NORDIC-VIII study strengthens the impression that liver transplantation for nonresectable CLM is superior to chemotherapy alone.

Thus, the results clearly suggest that liver transplantation for CLM can be indicated in properly selected patients. However, this is the only study currently reported on the subject, the sample size was small and the frequency of recurrences almost universal, and the data need to mature further to evaluate the true long-term results [34]. Thus, the role of liver transplantation for CLM is not sufficiently clarified, and should still be subject to scientific prospective studies.

Further Developments

In order to develop liver transplantation for CLM into routine practice, it is necessary to establish the boundaries between liver

transplantation and chemotherapy, between liver transplantation and liver resection, and between liver transplantation for CLM and established indications for liver transplantation. This involves identification of patient groups likely to benefit from liver transplantation, and development of patient selection strategies. Graft availability is the main limiting factor for wide application of this treatment modality. The probable expansion of available donor livers after the introduction of new eradicating drugs for hepatitis C is a factor to consider in this context. Also, the results from the SECA study already exceed the results from some of the current indications for liver transplantation. It is notable that 5–10% of liver transplantations performed are retransplantations, after which 5-year OS reaches around 50% [35], a figure that is achievable in crudely selected CLM patients.

Patient Selection

Optimally, what one is looking for when selecting patients to liver transplantation for CLM is cases with unresectable disease due to unfortunate anatomy and not because of unfortunate biology.

Based on our current results and the knowledge from the vast amount of studies in liver resection, it seems reasonable to suggest that the majority of the following clinical criteria should be considered in future studies:

- Response to chemotherapy
- Time interval from surgery of the primary tumor of >12 months
- CEA levels at the time of transplantation
- Size of the hepatic tumors
- N0 status of the primary tumor

Currently, a SECA 2 trial, acting as a follow-up to our initial study and based on the above-mentioned criteria, is ongoing in Oslo.

Can the Access to Liver Grafts to CLM Patients Be Improved?

Only a small number of patients with CLM can realistically be offered transplantation, and this should be as part of prospective studies. One way to expand the number of available liver grafts could be an increased use of split-liver donor transplantation. Classical split-liver transplantation with an extended right graft (segment 1 + 4–8) for adults and segment 2 + 3 to a pediatric recipient has been shown to be an excellent option for expanding the donor pool, and provides good-quality liver grafts [36]. Segment 2 + 3 is, however, almost never sufficient for normal-sized adults [37]; thus, the net gain in grafts available for liver transplantation is very modest using this approach. An extended right lobe graft containing segments 4–8 has an outcome comparable to that of a full-sized liver graft, whereas insufficient size of a partial graft will result in postoperative liver failure due to inability to meet metabolic demands. Furthermore, a small liver volume can lead to development of the small-for-size syndrome (SFSS), characterized by sinusoidal disruption and hemorrhage, and elevated portal pressure and portal hyperperfusion [38, 39]. In liver transplantation, a graft to body–weight ratio (GBWR) of >0.8 is generally considered safe in terms of both metabolic needs and avoidance of SFSS, given an acceptable graft quality. Below this level, the risk of graft failure due to SFSS is greatly increased. However, a GBWR of less than 0.8 might be tolerated if the damaging effects of elevated portal pressure is attenuated by means of a temporary portocaval shunt [39]. The tolerable portal pressure limit seems to be at about 20 mmHg and below in liver transplantation. A similar strong association between elevated portal vein pressure values above 22 mmHg and postoperative liver dysfunction after liver resection has been reported [40].

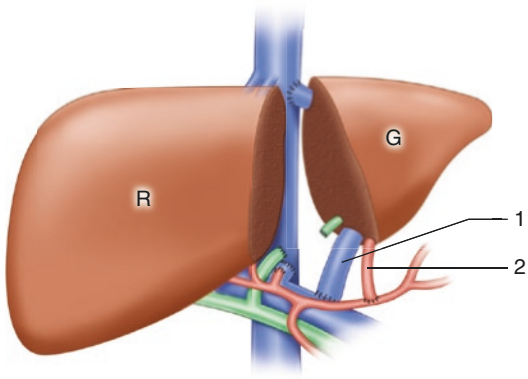

Fig. 20.5 Schematic overview over the operative field in the RAPID procedure following first stage resection of segments 1–3 leaving an extended right liver remnant (*R*) and the transplanted segment 2–3 graft (*G*). Note the mode of vascular anastomosis with end-to side anastomosis of the graft portal vein (1) and graft hepatic artery (2) to the main portal trunk and common hepatic artery respectively (From Line P-D, Hagness M, Berstad A, Foss A, Dueland S. A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: The RAPID concept. Ann Surg. 2015;262(1):e5–9)

Recently, we have developed a novel approach called the RAPID procedure (resection and partial liver segment 2/3 transplantation with delayed total hepatectomy) [41]. Briefly, the protocol entails transplantation of an auxiliary segment 2 + 3 donor liver graft into a CLM recipient directly following resection of segments I–III (Fig. 20.5). The liver graft is subjected to portal inflow modulation in an ALPPS-like approach, but the nature of portal inflow modulation is guided by measurement of portal vein pressure in order to avoid SFSS. In short, the portal vein pressure is monitored after revascularization and during clamping of the right portal vein branch to the native liver remnant. If the pressure remains stable below 20 mmHg, the portal vein to the right remnant liver is ligated. If the pressure is >20 mmHg during clamping, the splenic artery is ligated. If this does not alleviate graft portal hypertension, a banding of the portal vein to the right liver remnant is performed to attain stable portal pressure of less than 20 mmHg. Ultimately, a portocaval shunt may be constructed using the right portal vein in an end-to-side fashion to the cava if the above-mentioned techniques fail. Graft size is followed by CT volumetry on a weekly basis, and regarded as sufficient when the donor graft has obtained a size approaching 0.8% of body weight of the recipient, or 35–40% of recipient standard liver volume (whichever occurs first) (Fig. 20.6). The primary goal is to allow second-stage hepatectomy after less than 4 weeks. The RAPID trial is an ongoing study, and the experience is favorable but strictly limited at the present time [41]. It is, nevertheless, a very radical approach to therapy for CLM and not without controversy [42]. The clinical value of the RAPID concept is that, if proven to be safe and clinically feasible, it would be a valuable strategy to meet one of the main obstacles in liver transplantation for CLM, by enabling transplantation of small segment 2–3 grafts in adult patients with liver tumors. This would represent a highly needed expansion of the donor pool without significant negative impact to the other patients on the waiting list for liver transplantation. There are, however, a number of caveats that need to be clarified before any conclusion can be made. The oncological aspects of the RAPID procedure cannot be evaluated long term in the current protocol, and the effects of the treatment must be interpreted with care given the short observation period. It is theoretically possible that the combination of a two-staged procedure, a strong regeneration signal during 2–3 weeks, and concomitant immunosuppression could adversely affect growth of the remaining liver metastases and dissemination of the disease. Of concern is also the fact that the immunosuppression could promote tumor growth and spread until the time of the second-stage hepatectomy. In our previous SECA study, we did, however, demonstrate that patients who develop relapse on immunosuppression have 5-year OS of 53% from time of relapse, compared to about 0% in patients receiving palliative chemotherapy [30]. This may suggest that the immunosuppressive regimen used does not accelerate the progression of malignant

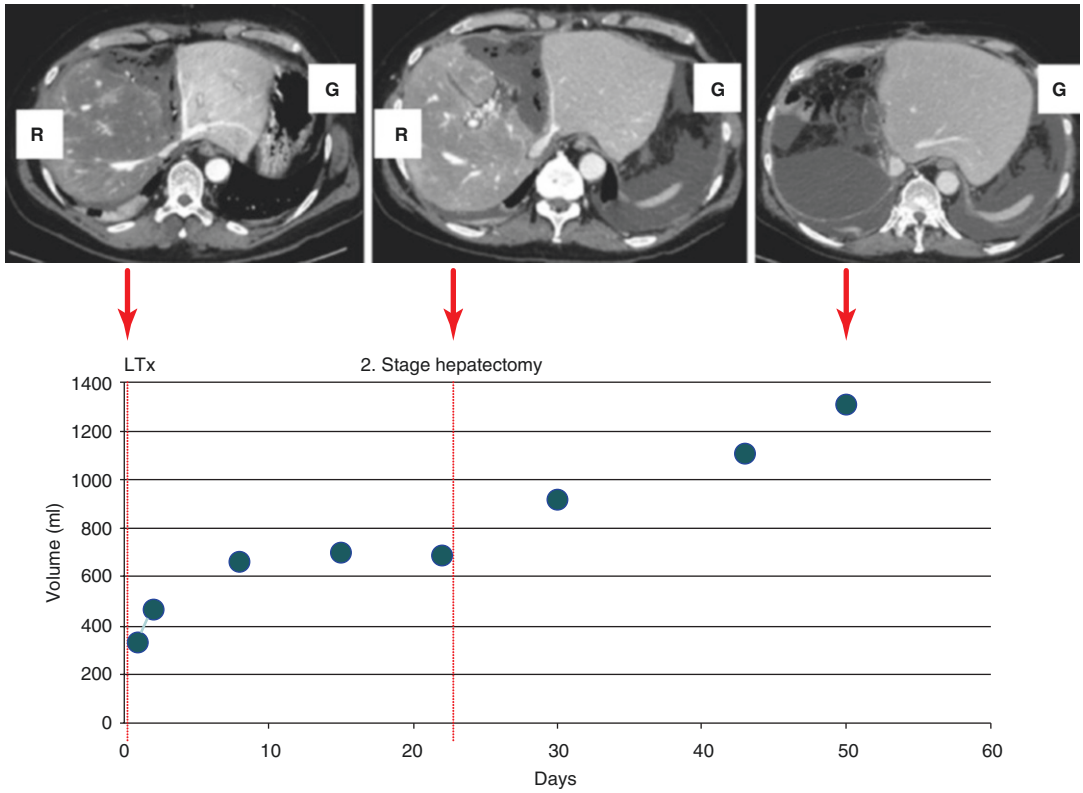

Fig. 20.6 Example of CT volumetry of the transplanted graft and corresponding representative CT images at days 1, 21 and 50 in a patient treated in the RAPID protocol. Right liver remnant removed at day 22 after transplantation (*R*: liver remnant, *G*: graft) (From Line P-D, Hagness M, Berstad A, Foss A, Dueland S. A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: the RAPID concept. Ann Surg. 2015;262(1):e5–9)

disease to a clinically apparent or relevant level. If the above-mentioned theoretical disadvantages prove to be of minor significance or can be managed by additional interventions, the RAPID approach could be an alternative strategy to increase graft availability for selected patients with technically nonresectable liver tumors. Another important aspect is that, given a successful development of the RAPID concept, the prospect of living donation of segment 2–3 grafts to this cohort of patients might be conceivable, since the risk of segment 2–3 donation is very much lower and vastly different to donation of a right or left liver lobe [43]. At this stage, it is very important to evaluate this new innovation in a scientifically controlled and staged manner, according to the principles outlined by Barkun and coworkers [44], before it is applied outside the concepts of the current protocol (Clinicaltrials.gov—study number NCT02215889).

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Part IV

Management of Concomitant Extrahepatic Disease

Lung Metastases

21

Sergi Call, Ramon Rami-Porta, Raul Embun, and Paul Van Schil

Introduction

Pulmonary metastasectomy is the most frequently performed major thoracic procedure after lung resection for cancer. A survey reported in 2008 by the European Society of Thoracic Surgeons (ESTS) Pulmonary Metastasectomy Working Group (PMWG) showed that pulmonary metastasectomy is commonly performed, but that there was a wide range of practices concerning the appropriate extent and limitations of surgical resection [1]. Although there is no randomized clinical trial comparing resection with medical oncological management in patients with lung metastases from colorectal cancer (CRC), there is substantial evidence based on prospective and retrospective series demonstrating that resection of colorectal pulmonary metastases can be performed safely with a low mortality rate [2], and offering an average 5-year overall survival rate of 48% (range 41.1–56%) [3]. The criteria for patient selection are variable, and several risk factors for impaired outcome have been identified to guide the selection of suitable candidates for surgery [4]. The role of induction or adjuvant chemotherapy has not been established. For this reason, every patient with lung metastases from CRC should be discussed within a multidisciplinary board including oncologists and thoracic surgeons to determine optimal, individualized treatment.

Historical Note

In 1882, Weinlechner performed the first pulmonary metastasectomy at the same time of the resection of a chest-wall sarcoma [5]. In 1927, Divis [6] reported the first isolated pulmonary metastasectomy planned in a separate procedure. Twenty years later, Alexander and Haight

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published the first case series of 24 patients with sarcomas and carcinomas [7]. It is important to highlight that this series included the first report of metachronous metastases resection, with the patient remaining free of disease 14 years after her second metastasectomy. The same authors described the following criteria for resection [7]: (1) the primary site of disease should be controlled or controllable, (2) absence of extrapulmonary metastases, and (3) good status of the patient to tolerate the resection. From this time to the mid-1960s, resection of lung metastases was performed infrequently and only in highly selected patients [8].

In 1971, Martini et al. [9] from the Memorial Sloan Kettering Cancer Center reported the strongest evidence supporting the efficacy of metastasectomy, based on a series of 22 patients who underwent pulmonary metastasectomy with removal of all palpable disease, with a 5-year survival rate of 32% and 20-year survival rate of 18%. Years later, the experience accumulated from these major thoracic surgical centres [10, 11] promoted a more liberal indication for this type of surgery.

In 1980, Aberg et al. [12] complained that despite >2500 patients worldwide who had undergone surgery for metastases, no comparison between a surgical group and a non-surgical control group had been published. Seventy surgically treated patients were compared with a small group of 12 patients who met the criteria for metastasectomy, but who had not undergone resection. Aberg et al. found that three were alive at 5 years. These authors stated that certain factors had to be considered when evaluating patients for pulmonary metastasectomy [12].

The International Registry of Lung Metastases (IRLM) was launched in 1990 with clear objectives: set up a common database through the major centres of thoracic surgery in Europe and the United States of America to facilitate the exchange of information; perform a more homogeneous evaluation of the results for the various primary tumors; define prognostic factors; and propose a system of stage grouping [13]. This cooperative multicenter clinical study accrued 5206 patients with lung metastasectomy, and the main conclusion was that complete resection, short disease-free interval, and single lesions were favourable factors for long-term survival [13]. Since the publication of the results of the IRLM, pulmonary metastasectomy has become the most frequent procedure performed in thoracic surgery departments after lung cancer operations.

Rationale for Resection of Pulmonary Metastases

There are no randomized trials evaluating the real benefit and effectiveness of pulmonary metastasectomy. At the time of compiling this chapter, the first randomized trial to investigate the real impact of surgery on patients with lung metastases still is in progress [14]. Awaiting the results of this randomized trial, the rationale for resection of pulmonary metastases is based on the results of retrospective series.

Focusing on CRC lung metastases, Pfannschmidt and colleagues [4] reviewed 20 relevant series reporting the outcome of surgical resection with curative intent published between 1995 and December 2006. Global results indicated that postoperative mortality after lung metastasectomy was commonly low (0–2.5%), with many authors reporting no mortality at all. Five-year survival rates ranged from 41.1% to 56%. Riquet et al. [15] observed that those encouraging results were also persisting over time (5- and 10-year survival being 41% and 27% respectively). Such results are also supported by a recent study conducted by Tampellini et al. in which the outcomes of CRC patients with lung metastases submitted to metastasectomy were compared with those patients who were not operated [16]. They reported remarkably longer progression-free survival (PFS) and overall survival (OS) in patients submitted to resection with radical intent of their pulmonary metastases than in those who received chemotherapy alone [15]: median PFS of 26.2 months (95% CI, 9.6–11.4 months) versus 10.5 months (95% CI, 9.6–11.4 months) respectively; median OS of 72.4 months (95% CI, 40.7–104.1 months) versus 31.5 months (95% CI, 28.8–34.2 months) respectively.

Criteria for Pulmonary Metastasectomy

Indications for lung metastasectomy in CRC patients are currently based upon guidelines established by The National Comprehensive Cancer Network (NCCN). All metastatic patients should be carefully evaluated with adequate imaging before surgery, and the following criteria should be met [17]:

1. Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.
2. The primary tumor must have been resected for cure (R0).
3. Patients with resectable synchronous metastases can be resected synchronously or using a staged approach in which the primary tumor is resected first.
4. Resectable extrapulmonary metastases do not preclude resection
5. Re-resection can be considered in selected patients
6. External beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial, and should not be used indiscriminately in patients who are potentially surgically resectable.

Imaging Requirements

Imaging techniques play the most important role in patient selection for lung metastasectomy and surgical resection planning. In determining the specific imaging modality that should be performed, several factors should be considered [18]: (1) the biological behaviour of the tumor, (2) the sensitivity and specificity of the imaging modality, (3) radiation dose, and (4) cost-effectiveness.

There have been improvements in CT imaging quality and scan time, as well as advances in the field of nuclear medicine and MRI. Compared with chest radiography, CT is much more sensitive for detecting lung nodules because of its lack of superimposition and its high-contrast resolution. According to current clinical guidelines, a contrast-enhanced CT of the chest, abdomen, and pelvis, to estimate the stage of the colorectal cancer, should be routinely performed [17].

In patients being evaluated for possible lung metastasectomy, a minimum standard should include a helical CT with 3–5 mm reconstruction interval [19]. Whenever possible, imaging view by scrolling on a digital monitor is preferred over static images on cut films, since it improves by approximately 10% the detection of small lung nodules (<5 mm) [20]. Other abnormalities, such as lymph nodes, pleural involvement, chest wall lesions, endobronchial lesions, intravascular invasion, or incidental findings in the upper abdomen, may also be revealed or better understood by CT scan.

There has been widespread use of PET/CT to evaluate patients with metastatic lung disease. However, the high false-negative rate of PET/CT determining the nature of small lung nodules should be taken into account, even more so when dealing with patients suspicious of suffering from metastatic disease. Therefore, ruling out extrathoracic disease is the main role of PET/CT in the workup of lung metastasectomy [21, 22].

Factors Influencing Outcome After Lung Metastasectomy in Colorectal Cancer

The report by McCormack et al. in 1979 is considered the first series assessing the potential prognostic factors after lung metastasectomy from colorectal cancer [23]. This series of 35 patients, which included a noteworthy high proportion of patients who underwent a lobectomy (18/35), concluded in their limited statistical analysis the importance of the primary tumor stage according to the Dukes' classification.

Throughout the 1980s and the first half of the 1990s, several reports, most of them based on small series from one institution, were published. However, since Pastorino et al. published the results of the IRLM in 1997, based on 5206 patients with different primary tumors, the literature about the role of lung metastasectomy has

experienced a sharp rise, mainly in the case of CRC [13, 24]. Most current series lack a control group of non-operated patients, and their main purpose has been to determine factors influencing global survival. Some of the reports comprising a denominator of non-surgical cases are derived from nationwide or multi-institutional cohort studies [16, 25–27].

Virtually all published reports derive from retrospective series covering long recruiting periods. In this regard, a remarkable exception is the study from the Spanish Colorectal Metastasectomy Registry of the Spanish Society of Pneumology and Thoracic Surgery (GECMP-CCR-SEPAR) which represents the largest prospective series recruited in the shortest time frame (2 years) [28]. Their results on prognostic factors and survival models, based on 543 patients from 32 thoracic surgery departments, are to be published soon.

Although there is no randomized clinical trial confirming the supposed benefit of lung metastasectomy, those in favor of a surgical approach argue a better survival rate after complete resection of lung disease compared with that after incomplete resection. In fact, even though many risk factors have been assessed, the only one unanimously seen as an absolute contraindication to surgery is the inability to obtain a complete resection. However, this paramount assumption has hardly ever been addressed in series of colorectal cancer patients, since most of these series consider the complete removal of all lung disease as a fixed inclusion criterion [4].

Almost all reports deal with clinical prognostic factors. Among them, the number and laterality of lung metastases, the disease-free interval (DFI), the carcinoembryonic antigen (CEA) level, the size of the largest lung lesion, the involvement of thoracic lymph nodes, the iteration of lung metastasectomies, and the coexistence and/or history of liver metastases are the variables worked on more frequently. Other clinical factors less often referred to are the histological type, stage, and location of the primary tumor. Although the conclusions of the published series often differ from each other, the clinical features that have most commonly emerged as determinant risk factors in multivariate analyses are: multiple lung metastases, CEA > 5 ng/ml, shorter DFI (cut-off values 12, 24, or 36 months) and thoracic lymph node involvement (intrapulmonary, hilar and mediastinal) [29–40] (Table 21.1).

Although a few systematic reviews about prognostic factors after lung metastasectomy have been reported [4, 24], the only meta-analysis was published by Gonzalez et al. [3]. This meta-analysis, based on 25 series (2925 patients)

Table 21.1 Results from the largest series of lung metastasectomy of colorectal cancer

Year	Author	Ref.	*n*	Period	5-Year survival	Risk factors[a]
2002	Saito	29	165	1990–2000	40	CEA, N+
2003	Pfannschmidt	30	167	1985–2000	32	CEA, number, N+
2007	Welter	31	175	1993–2003	39	Number, N+
2009	Onaitis	32	378	1998–2007	56	Number, DFI, age, gender
2012	Blackmon	33	229	2000–2010	55	Gender, age, number
2012	Hamaji	34	518	1985–2009	47	N+
2013	Hirosawa	35	266	1991–2003	56	Stage CRC, number, Laterality, CEA, DFI
2013	Iida	36	1030	1990–2008	53	Number, CEA, size, CEA, R0
2013	Salah[b]	37	927	1983–2008	53	CEA, DFI, number
2014	Bolukbas	38	165	1999–2009	54	Location CRC, stage CRC, number
2014	Renaud	39	320	1992–2011	Non stated	N+, liver metastases
2014	Zampino	40	199	1998–2008	43	R0, CEA, number, N+

n number of patients, *CRC* colorectal cancer, *Number* number of lung metastases, *N+* lymph node involvement, *R0* complete resection of the lung metastases, *Size* diameter of the largest lung metastasis

[a]Risk factors in multivariate analysis

[b]Pooled analysis from eight retrospective series

published between 2000 and 2011, concluded the importance of the four risk factors previously referred to. Their resulting hazard ratios (HR) were: (1) shorter DFI, HR = 1.59 (95% CI 1.27–1.98), (2) multiple lung metastases, HR = 2.04 (95% CI 1.72–2.41), (3) positive hilar and/or mediastinal lymph nodes, HR = 1.65 (95% CI 1.35–2.02), and (4) elevated pre-resection CEA, HR = 1.91 (95% CI 1.57–2.32). Nevertheless, a history of resected liver metastases was the only factor analyzed that was not shown as significant in this meta-analysis, HR = 1.22 (95% CI 0.91–1.64).

Over the last decade, different molecular prognostic factors have been reported. The one most often assessed has been the presence of K-RAS mutations, which has been linked to a higher incidence of lung metastases and a shorter disease-free survival after metastasectomy [41–43].

Other risk factors frequently referred to in literature are those related to the different therapeutic choices. A number of them include: extent of lung resection and lymph node dissection, type of thoracic surgical approach, and induction or adjuvant chemotherapy with respect to lung metastasectomy. All these risk factors are discussed in other sections in this chapter.

Surgical Aspects of Pulmonary Metastasectomy

The term pulmonary metastasectomy refers to surgical excision of malignant lesion(s) of the lung of extrapulmonary origin. In current practice, limited resections to preserve lung parenchyma are the preferred method to perform metastasectomy because this type of surgery may be performed more than once.

Surgical Approach

The type of surgical approach used in pulmonary metastases is highly variable. The choice of approach varies between thoracic surgery departments and between countries. This fact was noticed in the survey of the European Society of Thoracic Surgeons undertaken in 2006 [1]. The survey showed that palpation of the lung was regarded as mandatory by 65% of responders, but the use of videothoracoscopic surgery (without complete palpation) was acceptable to 60%.

Debate in the surgical literature exists over whether pulmonary metastases should be removed by a thoracoscopic approach or by thoracotomy, due to the high rate of non-imaged metastases. Cerfolio et al. found that 52 (34%) of 152 patients had non-imaged pulmonary nodules detected by palpation; almost half of these nodules were malignant [44]. Eckardt prospectively evaluated 37 patients who underwent video-assisted thoracoscopic surgery (VATS), followed by thoracotomy, in whom 29 additional nodules of a total of 84 were resected (35% non-imaged nodules). Of non-imaged resected nodules, eight (28%) were malignant [45].

Recently, the European Metastasectomy Working Group made a systematic review on this issue [46]. They reviewed seven studies providing outcome data comparing VATS with thoracotomy, with no survival difference between groups in six studies; in one of them, they found lower recurrence-free survival at 5 years in patients having open surgery (21%) rather than videothoracoscopic surgery (34%). These authors admitted to disagreement within the working group, but still concluded lung palpation was necessary [46].

With regard to the choice of approach for bilateral disease based on the ESTS survey [1], two out of three surgeons preferred bilateral staged thoracotomy, followed by sternotomy, bilateral sequential thoracotomy (one stage), bilateral staged thoracoscopy, bilateral thoracoscopy (one stage), and finally clamshell incision. In the 1980s and 1990s, several authors published their results in the use of sternotomy for pulmonary metastasectomy, reporting higher accuracy for detecting unsuspected metastases and lower morbidity [47–50]. The utility of a bilateral approach to discover unsuspected disease may progressively diminish in importance as imaging improves [46].

Type of Resection

In current practice, pulmonary metastasectomy may be performed more than once; therefore, conservative resections are recommended. Preservation of as much functioning lung parenchyma as possible is an agreed principle, while removing a centimeter of the surrounding pulmonary tissue to ensure free resection margins [51]. For nodules located peripherally, stapled wedge resection is generally the preferred treatment (Fig. 21.1) but for large or central lesions, segmental resections, lobectomy, or occasionally, pneumonectomy may be required [51, 52]. In patients in whom the planned resection is deemed to be complete, extended resections beyond lung parenchyma, including the chest wall, the azygos vein, the diaphragm, the pulmonary vessels, and larger lung resections, such as sleeve lobectomies and pneumonectomies, are associated with 5- and 10-year survival rates of 42% and 36% respectively [53].

For those patients with a low cardiopulmonary reserve, cautery resection, or laser resection have been proposed as an alternative to save as much surrounding lung as possible.

Cautery resection or precision resection was described by Perelman [54]. This technique allows excising deep-seated lesions or nodules located on the broad surface by coring them out of the parenchyma using cautery (Fig. 21.2). This technique is useful for those cases with multiples

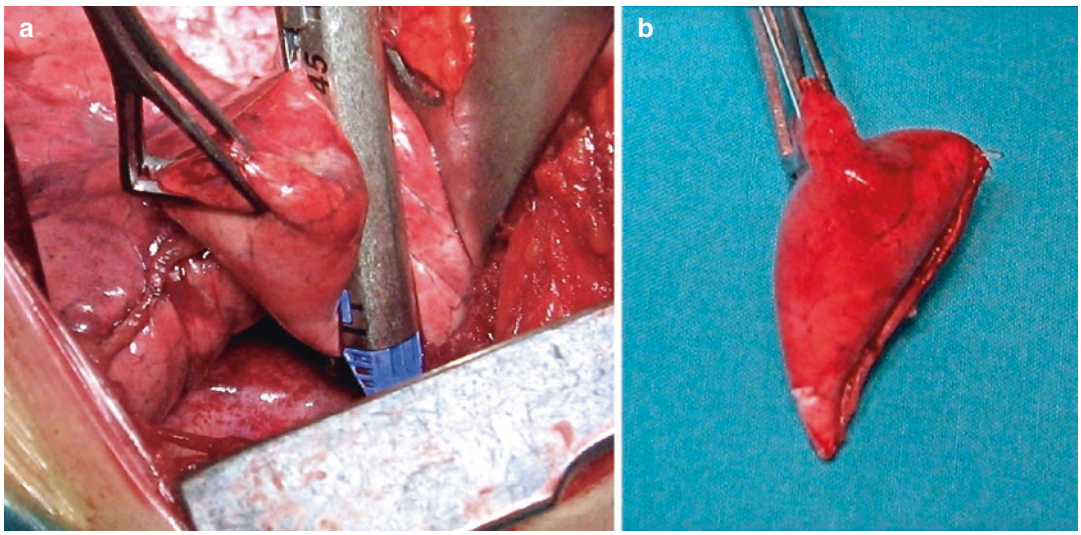

Fig. 21.1 (**a**) Open wedge resection of the lung using a stapler. (**b**) The stapled line on the specimen is useful for the assessment of the margin by the pathologist

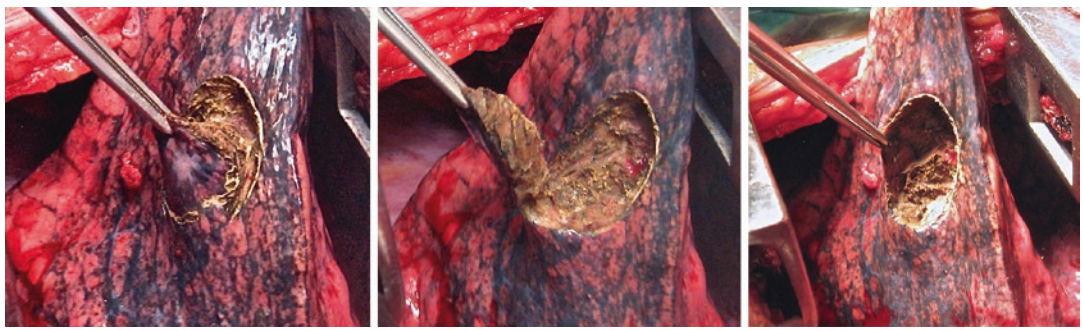

Fig. 21.2 Cautery resection or precision resection of the lung. Once the suspected lesion is located by palpation, pulmonary resection is started. An extra oncologic safety margin is achieved by the zone of coagulation necrosis, which reaches several millimeters deep into normal lung tissue

metastases or in patients who are not considered good candidates for anatomic resection.

Laser resection uses the same principles of cautery resection with the following major advantages: it permits limited excision of deep-seated lesions sparing lung tissue as much as possible, there is minimal deformity or damage to the adjacent lung tissue, and for lesions located near a major bronchus or vessel a maximum margin of tissue around the lesion can be taken without injury to these adjacent structures [51]. In 2006, Rolle et al. [55], the group that has dedicated more efforts to the development of this technique, published their results on 328 patients with a 5-year survival rate of 41% following laser resection of a mean of eight metastases per patient (range 1–124). They recommended laser resection even in patients with more than 20 metastases, because a 5-year survival rate of 26% was observed [55].

With regard to the extent of resection, Migliore et al. reviewed seven reports addressing pneumonectomy for metastatic disease, five of whom reported completion pneumonectomy [56]. Operative mortality rates ranged between 0% and 11% (19% in one study with R1 resections) and 5-year survival rates ranged between 10% and 41%. Seven studies reviewed the issue of repeat metastasectomy with 5-year survival rates ranging from 19% to 53.8%. Thirty percent to 40% 5-year survival rates are reported after a third or fourth thoracotomy. Resectability was an independent prognostic factor for survival after each subsequent thoracotomy, but the chance of being resectable decreases after each thoracotomy, as does the chance for permanent control. After patients are determined to be unresectable, median survival was 8 months (19% 2-year survival rate) [56].

Postoperative complications are rare, occurring in between 0% and 22% of patients [4], and the most common are respiratory (pneumonia and acute respiratory syndrome), cardiovascular (arrhythmias), and those related to surgical technique (air leaks) [2]. Postoperative mortality rates range between 0% and 2.5% [4], and are lower for sublobar and lobar resections than for pneumonectomy. Reported causes of death are pulmonary embolism, pneumonia, respiratory failure, and cardiac failure [2, 4].

The Role of Lymph Node Dissection

The role of lymph node assessment in pulmonary metastasectomy has not been well defined, and thus it is not a common practice in most thoracic surgery departments around the world. The results of the survey of the European Society of Thoracic Surgeons with regard to lymph node assessment at the time of pulmonary metastasectomy showed that 55.5% of the responding surgeons performed mediastinal lymph nodal sampling, while 13% performed a complete mediastinal lymphadenectomy. One surgeon out of three (32.2%) performed no lymph node biopsy whatsoever [1].

Regarding the prevalence of lymph node involvement, Garcia-Yuste et al. [57] analyzed six studies, finding a prevalence ranging from 14 to 32%, giving a weighted average of 22%. Tumors were of varied types but colorectal carcinoma was well represented.

Regarding the impact on survival, the meta-analysis published by Gonzalez et al. in 2013 [3], found that involvement of the hilar and/or mediastinal lymph nodes was associated with a clear increased risk of death, HR = 1.65 (95% CI 1.35–2.02). Recently, the Spanish Colorectal Metastasectomy Registry of the Spanish Society of Pneumology and Thoracic Surgery has examined the impact on survival depending on the pathological nodal status based on data from 522 patients collected prospectively from 2008 to 2010 [58]. For this purpose, a systematic nodal dissection or nodal sampling was required to certify pathological absence of lymph node metastases, or the pathological lymph node status was coded as uncertain. The 3- and 5-year disease-specific survival rates of patients with lymph node metastases and uncertain lymph node status were clearly independent, with a worse survival in comparison with the survival of patients with no lymph node metastases; presence of lymph node metastases was 50.5% (95% CI 29.6–71.4)/24.8% (95% CI 3.6–46) respectively; uncertain lymph node status, 69% (CI 64–74.4)/44% (CI 35–53) respectively; and absence of lymph node metastases: 73.5% (95% CI 65–82)/58.3% (95% CI 41.6–75.1) respectively. With these results, the Spanish group concludes that the presence of lymph

node metastases remains an important prognostic factor, and hypothesizes that the missed lymph node metastases in patients with uncertain lymph node status can impair survival because of misclassification of risk [58]. Awaiting a future randomized trial to answer the precise impact of surgery in lung metastases from CRC, the current findings in the literature suggest that intraoperative nodal assessment should be performed in metastasectomies, at least to determine the individual postoperative prognosis.

The Role of Chemotherapy

In many surgical series, it has been demonstrated that complete resection of lung metastases yields the longest overall and disease-free survival, but this can only be obtained in a minority of patients presenting with lung metastases. Generally, in the case of resectable lung metastases 5-year survival rates of 30–40% may be obtained [13]. However, a substantial number of patients will develop recurrent disease inside the chest, demonstrating that micrometastases that go undetected at the initial procedure will determine long-term outcome.

Systemic Chemotherapy

Despite more refined and extensive resection techniques, enhanced selection of patients, and evolving multidisciplinary treatment options, only a small proportion of patients with isolated pulmonary metastases undergo resection. Systemic chemotherapy has become an important treatment modality for metastatic colorectal cancer. For advanced disease, combination chemotherapy consisting of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX), or 5-FU, leucovorin, and irinotecan (FOLFIRI) is most widely used, with median overall survival ranging between 14.7 and 20.0 months [59–61]. By addition of cetuximab in selected patients, median overall survival time increases to 23.5 months [61].

In the case of liver metastases that are considered for surgical resection, perioperative combination chemotherapy with the FOLFOX regimen is recommended [59]. However, the optimal treatment schedule has not been determined yet.

In patients undergoing pulmonary metastasectomy, the role of induction or adjuvant chemotherapy has not been established, and no convincing evidence is currently available supporting its use in daily practice. For this reason, every patient with lung metastases from colorectal cancer should be discussed within a multidisciplinary board including a thoracic oncologist and surgeon to determine optimal, individualized treatment.

Loco-Regional Therapy

As already shown in the large retrospective database of Pastorino et al., most patients who underwent macroscopic complete resection of pulmonary metastases from colorectal cancer or sarcoma will develop single or multiple recurrent disease inside the chest [13].

The dose of intravenously administered chemotherapy is limited by systemic toxicity. Regional drug delivery systems may enhance drug uptake in lung tissue and minimize systemic side-effects and toxicity [62, 63]. Several techniques are able to administer a high dose of loco-regional chemotherapy very efficiently, of which isolated lung perfusion, selective pulmonary artery perfusion, and chemoembolization are the most thoroughly investigated.

Chemoembolization

Chemoembolization with degradable starch microspheres loaded with carboplatin has been studied in an animal model by Schneider et al. [64, 65]. The use of degradable microspheres allows for higher concentrations in the lung parenchyma during the degradation phase of the treatment. Vogl et al. used chemoembolization with palliative intention in 52 patients with unresectable lung metastases [66]. The tumor-feeding pulmonary arteries were selectively injected with lipiodol, mitomycin C, and microspheres under

guidance of a pulmonary artery balloon catheter. Patients received repetitive treatment ranging from two to ten sessions. Treatment was well tolerated, without any major side-effects or complications. Partial response was noted in 16 cases, stable disease in 11 and progressive in 25 cases.

Isolated Lung Perfusion

Preclinical studies by Weksler et al. in rodents with a model of experimental pulmonary metastases from a methylcholanthrene-induced syngeneic sarcoma have shown that chemotherapy may be regionally delivered to the lung parenchyma in significantly higher concentrations than by systemic injection [67, 68]. Minimal to no systemic toxicity was noted. Experimental studies with different chemotherapeutic agents are summarized in Table 21.2. So far, in animal models only melphalan has shown to be effective against pulmonary metastases from both sarcoma and adenocarcinoma tumors [77, 79].

Equally, initial clinical studies of lung perfusion by Pass and Johnston have demonstrated higher drug concentrations in pulmonary tissue, although clinical tumor response has been limited [80, 81]. Clinical phase I and II studies of isolated lung perfusion performed since 1995 are listed in Table 21.3.

Ratto et al. introduced the concept of combining resection of lung metastases with isolated lung perfusion as additional or adjuvant treatment, in order to reduce the local recurrence rate in the operated lung [82]. In a series of six patients, platinum was administered in the perfusion circuit, which was found to be feasible and safe. Hendriks et al. reported a phase I trial of melphalan in combination with pulmonary metastasectomy [85]. This trial was followed by an extension trial reported by Grootenboers et al., who concluded that the maximum tolerated dose was 45 mg of melphalan at a perfusion temperature of 37 °C [87]. The long-term follow-up of these two trials comprising a total of 23 patients was reported by den Hengst et al. showing that isolated lung perfusion with melphalan has no long-term negative effect on pulmonary function, and no long-term pulmonary toxicity [86]. So far, only one phase II study of isolated lung perfusion has been published. In this multicenter trial, reported by den Hengst et al., lung perfusion with melphalan was combined with pulmonary metastasectomy including lung metastases from osteosarcoma, soft-tissue sarcoma and colorectal carcinoma [88]. A dose of 45 mg of melphalan was given at a perfusion temperature of 37 °C; perfusion time was 30 min, followed by a 5 min wash-out. In total 50 patients were included, of whom 30 had colorectal carcinoma as primary tumor. Twelve patients had staged bilateral perfusions. There was no perioperative mortality and acceptable short-term morbidity. After a median follow-up of 24 months,

Table 21.2 Experimental studies of isolated lung perfusion

Drug	Ref.	Animal model	Effect-comment
Doxorubicin	[69]	Rat	Effective against sarcoma mets
Doxorubicin + BSO	[70]	Rat	More effective than doxorubicin alone
FUDR	[71]	Rat	Effective against carcinoma mets
TNF-α	[72]	Rat	Effective against sarcoma mets
Cisplatin	[73]	Pig	High lung levels obtained
Cisplatin + digitonin	[74]	Rat	Enhanced uptake in lung tissue
Paclitaxel	[75]	Sheep	High lung levels obtained
Melphalan	[76]	Rat	Effective against carcinoma mets
		Pig	Safe pharmacokinetic profile
Melphalan + TNF-α	[77]	Rat	No additional effect of TNF-α
Melphalan + gemcitabine	[78]	Rat	Most effective combination in carcinoma mets

BSO buthionine sulfoximine, *FUDR* 5-fluorodeoxyuridine, *mets* metastases, *Ref.* reference, *TNF-α* tumor necrosis factor alpha

Table 21.3 Clinical studies of isolated lung perfusion performed since 1995 (all phase I studies except for den Hengst [89], which is a phase II study)

Year	Author	Ref.	Drug	*N*	Lung temp (°C)	Perfusion time (min)	Resectable metastases	MTD
1995	Johnston	[81]	Doxorubicin/cisplatin	8	NA	45–60	No	NA
1996	Pass	[80]	TNF-α + γ-interferon	15	38–39.5	90	No	6 mg
1996	Ratto	[82]	Cisplatin	6	37	60	Yes	200 mg/m^{2a}
2000	Burt	[83]	Doxorubicin	8	37	20	No	40 mg/m^2
2002	Putnam	[63]	Doxorubicin	16	37	NA	No	60 mg/m^2
2002	Schröder	[84]	Cisplatin	4	41	21–40	Both	70 mg/m^{2a}
2004	Hendriks	[85]	Melphalan	16[c]	37, 42	30	Yes	45 mg–42 °C[b]
2014	den Hengst	[86]	Melphalan	50	37	30	Yes	45 mg

MTD maximum tolerated dose, *N* number of patients, *min* minutes, *NA* not available, *Ref.* reference, *TNF-α* tumor necrosis factor alpha

[a]fixed dose

[b]in an extension trial [80] safe MTD was found to be 45 mg at 37 °C

[c]21 procedures (five bilateral)

18 patients died (two of unrelated causes) and 30 patients had recurrent disease. The 3-year overall survival and disease-free survival rates were 57 ± 9% and 36 ± 8% respectively. This trial showed an intrapulmonary recurrence rate in the operated lung of 23%, which is lower than the 48–66%, reported by Pastorino et al. [13]. This finding indicates that isolated lung perfusion may be a valuable tool in the future in combined modality treatment of lung metastases. Less invasive techniques such as selective pulmonary perfusion with blood flow occlusion by way of a pulmonary artery catheter are currently being explored, but as yet no clinical studies have been described [89–92].

Conclusion

Pulmonary metastasectomy is associated with prolonged survival, especially in patients with single metastasis, absence of nodal involvement, long disease-free interval, and low preoperative levels of CEA. Whether this favourable prognostic effect is due to the resection itself or to the selection of patients is unknown, and prospective clinical trials are needed to answer this question. In the meantime, in view of the results and the few postoperative complications of the procedure, complete lung metastasectomy should be considered part of the multidisciplinary treatment of selected patients with advanced colorectal cancer.

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Nodal Involvement

22

Masato Narita, Iwao Ikai, Pascal Fuchshuber, Philippe Bachellier, and Daniel Jaeck

Introduction

Involvement of perihepatic lymph nodes (LN) does occur in patients with colorectal liver metastases (CLM), and is thought to originate from the liver metastases rather than the primary tumor [1, 2]. Most surgeons consider the presence of hepatic pedicle lymph node (HPLN) involvement (i.e., LN at the sites of hepato-duodenal ligament, retropancreatic area, common hepatic artery area, and coeliac axis area), and supradiaphragmatic, mediastinal, and para-aortic LN involvement as a contraindication for liver resection in patients with CLM. It has been regarded as equivalent to extrahepatic disease, essentially removing the chance of a curative liver resection. However, improvement of surgical procedures and recent developments of new chemotherapy regimens have led to reports of improved outcomes even in patients with HPLN involvement [3]. This book chapter presents a detailed description of hepatic lymph anatomy and distribution, the frequency and the clinical impact of HPLN involvement, and our surgical technique of en-bloc lymphadenectomy of HPLN. Its aim is to define the current clinical practice recommendations for patients with CLM and HPLN involvement based on the available evidence.

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Anatomy

Hepatic Lymph

The liver produces 25–50% of the entire lymphatic volume draining into the thoracic duct [4]. The hepatic lymphatic fluid originates from the hepatic sinusoids, and drains into each hepatic lymphatic vessel. The hepatic lymphatic vessels are divided into three categories depending on their location; portal, sublobular, and superficial lymphatic vessels [5]. At least 80%

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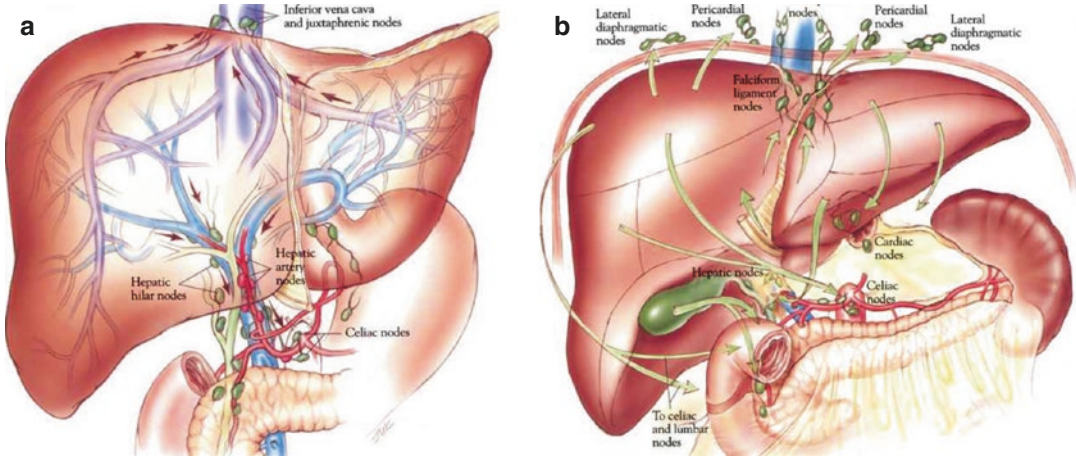


Fig. 22.1 Schema of lymphatic drainage of the liver. Sublobular and portal lymphatic pathway (**a**) and superficial pathways (**b**) (Source: 'Patterns of spread of disease from the liver', Figs. 9 and 10; Meyers et al. Reprinted with the kind permission of Springer Science + Business Media, LLC) [31]

of hepatic lymphatic fluid drains toward the "porta hepatis" (i.e., transverse fissure of the liver), subsequently draining through lymphatic vessels in the hepatic pedicle (Fig. 22.1a). The remaining lymphatic fluid drains into either sublobular or superficial lymphatic vessels [5]. Sublobular lymphatic vessels drain into the inferior vena cava (Fig. 22.1a). The superficial lymphatic vessels form a complex capillary network under the liver capsule and drain into regional LN including supradiaphragmatic, mediastinal, and lesser omental LN (Fig. 22.1b) [6, 7].

Drainage of Portal Lymphatic Vessels

According to cadaver studies of gallbladder lymphatics, the lymphatic drainage of the hepatic pedicle can be divided into three pathways: (1) the cholecysto-retropancreatic pathway (right descending pathway), (2) the cholecysto-celiac pathway (left oblique pathway), and (3) The cholecysto-mesenteric pathway (mesenteric pathway) [8, 9]. These three pathways converge with the para-aortic lymph nodes (PALN) near the left renal vein. The lymphatic vessels of the right descending pathway (to the right of the hepatoduodenal ligament) first drain into the cystic node and through several lymphatic vessels eventually into the epiploic foramen LN (foramen of Winslow), located to the right of the common hepatic duct (Fig. 22.2a). The epiploic foramen LN drains into the superior retropancreaticoduodenal (Rouvière) LN and from there either directly or via posterior pancreaticoduodenal LNs into the PALN at the level of the left renal vein (Fig. 22.2a). The lymphatic vessels of the left oblique pathway run along the cystic artery and hepatic artery to reach the nodes around the celiac trunk via the common hepatic artery (CHA) LN (Fig. 22.2b). The mesenteric pathway is composed of many thin lymph vessels originating from the porta hepatis and the gallbladder neck. These lymph vessels drain into the "principal portal node", located in front of the portal vein and at the confluence between portal vein and splenic vein. From this node, lymphatic vessels connect into LN surrounding the superior mesenteric artery (Fig. 22.2c). Several reports have argued that the right descending pathway is the dominant lymphatic pathway [10, 11].

In summary, the vast majority of hepatic lymphatic drainage is directed towards the HPLN.

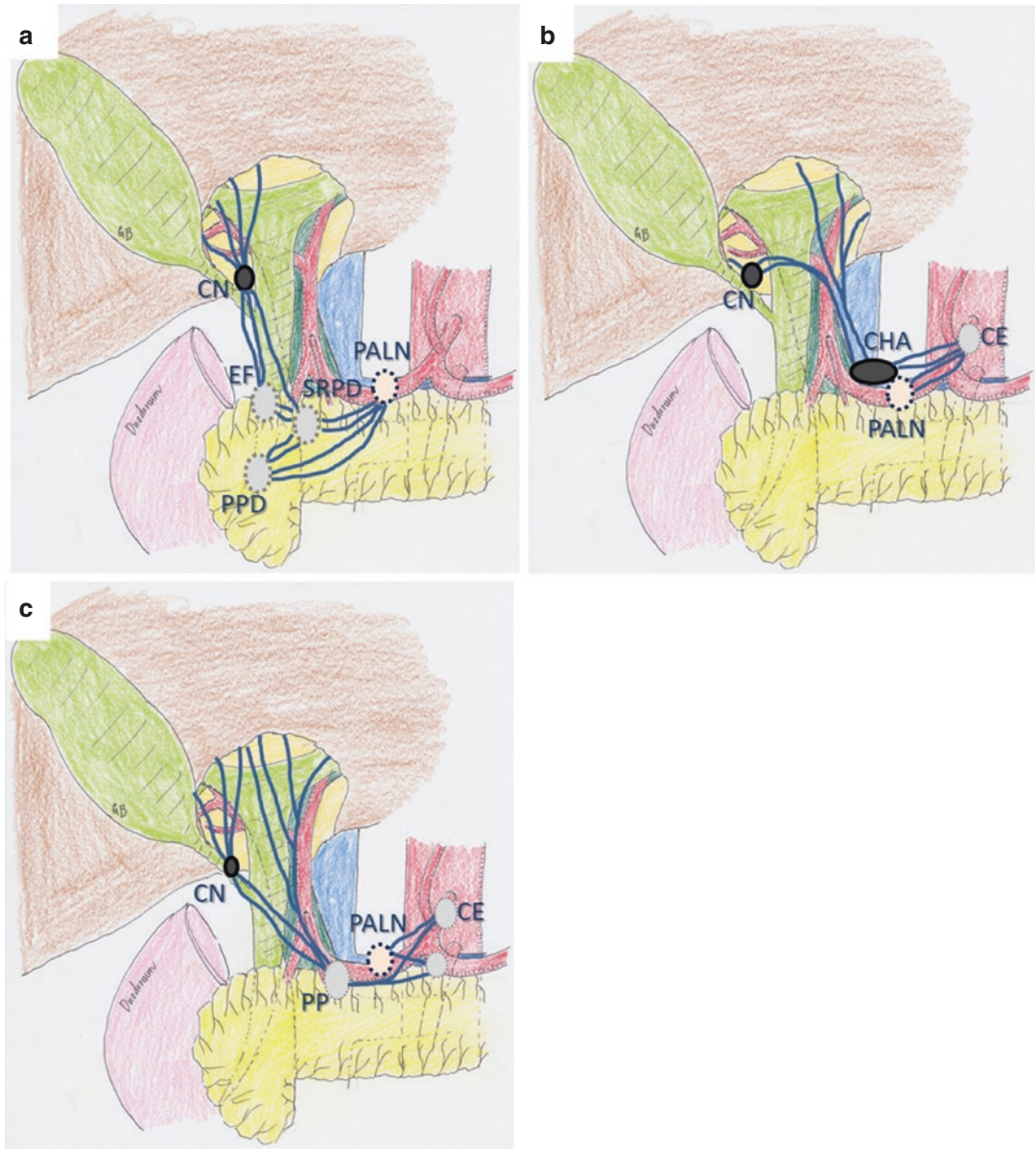


Fig. 22.2 Schema of lymphatic vessels draining through hepatoduodenal ligament. (**a**) Right descending pathway; *CN*, cystic node; *EF*, epiploic foramen LN; *SRPD*, superior retro-pancreaticoduodenal LN; *PPD*, posterior pancreaticoduodenal LN; *PALN*, para-aortic LN. (**b**) Left oblique pathway; *CN*, cystic node; *CHA*, common hepatic artery LN; *CE*, celiac trunk LN; *PALN*, para-aortic LN. (**c**) Mesenteric pathway; *CN*, cystic node; *PP*, principal portal node; *CE*, celiac LN; *PALN*, para-aortic LN

Frequency and Pre- and Intra-Operative Assessment of HPLN Involvement

The frequency of involvement of distant LN such as para-aortic, supradiaphragmatic and mediastitinal LN in patients with CLM is not well known. This is not surprising as lymph node dissection is rarely indicated and remains technically difficult. Interestingly the frequency of mediastinal LN involvement in colorectal cancer patients with lung metastasis was reported to be 12–33% [12, 13].

The analysis of HPLN involvement is further complicated by the fact that LN involvement can be either microsocpic or macroscopic. Studies looking only at macroscopic LN involvement, mostly by using the technique of "cherry picking", do not take into account the number of microscopically involved LNs and therefore may grossly underestimate the frequency of HPLN involvement. A few studies on the frequency of HPLN involvement are reliable, as they use systematic lymph node dissection in consecutive patients with microscopic analysis [14, 15]. The study from Beaujon Hospital [15] analyzed 76 patients who underwent systematic HPLN dissection simultaneously with CLM resection. Macroscopic palpable LN involvement (1 cm in a diameter and/or firm on palpation) was suspected in 23 patients during surgery. Of these, only ten patients had microscopically proven metastatic disease in the LN, and five patients who had microscopically node-positive disease were misdiagnosed as node-negative disease during surgery. In a series of 114 patients undergoing CLM resection reported by Elias et al. [14], 22 patients had microscopic HPLN involvement on final pathology, but only eight patients (40%) were suspected to have positive nodal disease intraoperatively.

Table 22.1 Incidence of HPLN involvement in patients undergoing curative hepatic resection for CLM

Authors	Year	Number of patients	Patients with nodal involvement
Nakamura [27]	1999	79	7 (8.9%)
Jaeck [16]	2002	160	17 (11%)
Elias [14]	2003	114	22 (19%)
Laurent [28]	2004	156	23 (15%)
Viana [29]	2009	28	5 (17.9%)
Rau [15]	2012	76	15 (20%)

Therefore, the sensitivity and positive predictive value (PPV) of intraoperative diagnosis was quite low (67% and 43% respectively) [15]. In this context, frozen section analysis of macroscopically suspected LN would have less value. Current evidence suggests that accurate diagnosis of HPLN and other perihepatic LN involvement in patients with CLM during surgery is very difficult to obtain.

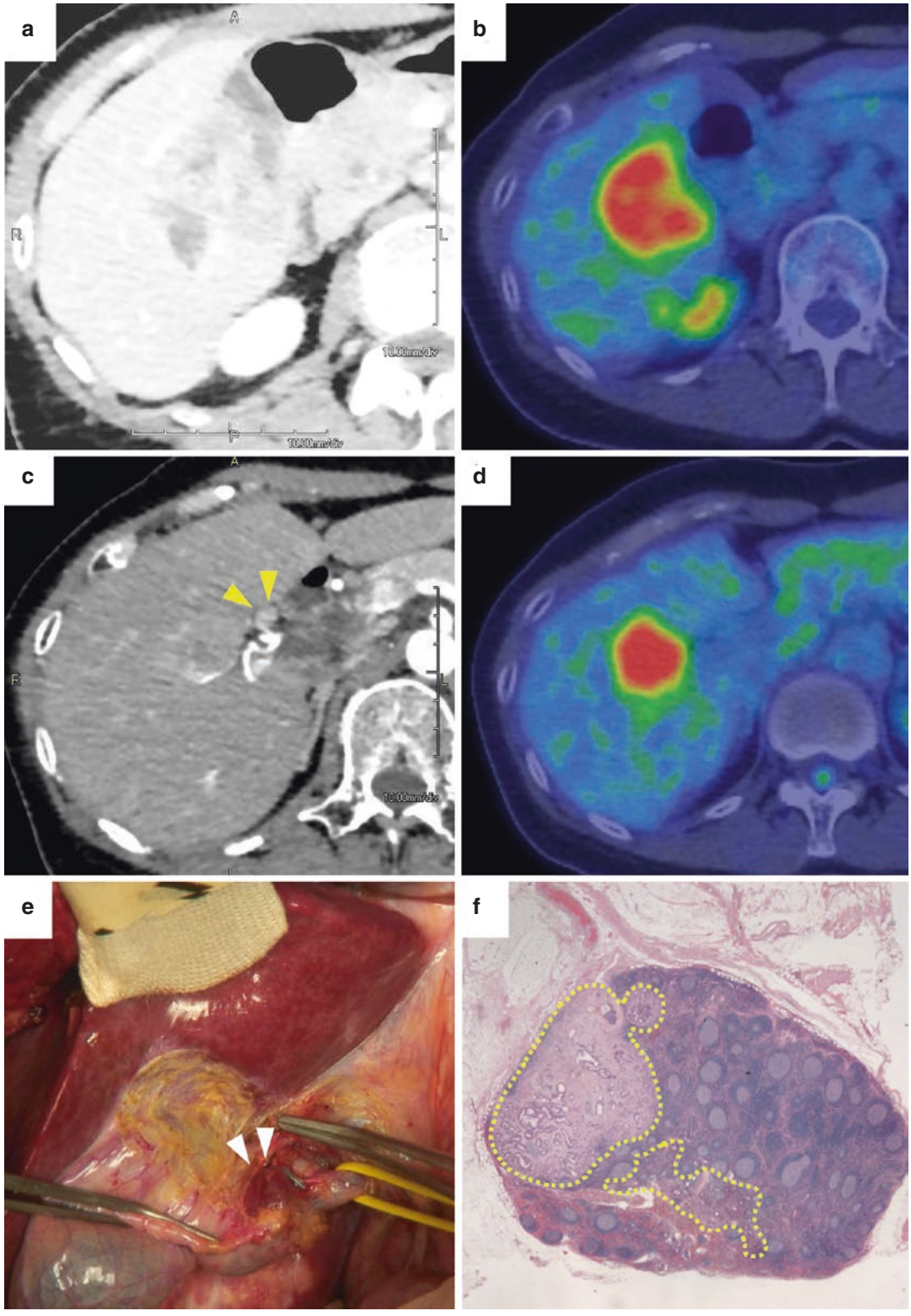
Studies using postoperative results of LN involvement after systematic HPLN dissection in patients with CLM report a frequency of 8.9–20% (Table 22.1). Elias et al. [14] studied the pattern of LN involvement in patients with CLM according to the anatomic location of respective LN basins. They divided LN specimens into six groups: (1) antero-superior LN in the hepatic pedicle, (2) antero-inferior LN in the hepatic pedicle, (3) postero-superior LN in the hepatic pedicle, (4) postero-inferior LN in the hepatic pedicle, (5) common hepatic artery LN, and (6) celiac LN. They showed that the most frequently invaded group of LNs was the common hepatic artery LN basin, and that the positive LN location was highly variable even in patients with a single CLM. This result suggests the possibility of "skip metastasis" and a random pattern of LN involvement in CLM patients.

The ability to predict the presence of HPLN involvement in patients with CLM was

evaluated by Jaeck et al. [16]. In this study the clinicopathological variables associated with HPLN involvement in 160 patients undergoing systematic HPLN dissection during liver resection for CLM were reviewed. Five relevant clinico-pathological factors were extracted by univariate analysis; (1) the presence of more than three CLM, (2) CLM located in segment 4 and / or segment 5, (3) synchronous CLM, (4) the presence of a resectable peritoneal deposit, and (5) poorly differentiated histology of CLM. In a similar study Elias et al. [17] evaluated 100 patients who underwent systematic HPLN dissection concomitantly with liver resection for CLM. They found that HPLN involvement was significantly correlated with (1) more than three metastases, (2) a greater than 15% tumor burden relative to total liver volume, and (3) a CEA level > 118 ng/L. In contrast, a study from the group at Beaujon Hospital with 76 patients who underwent systematic HPLN dissection simultaneously with liver resection for CLM (multiple CLM, 74%; bilobar CLM, 49%) did not find any correlation between HPLN involvement and any clinicopathological variables [15]. Based on these studies, it is reasonable to expect a higher chance of HPLN involvement in patients with higher tumor burden, multiple CLM, poor histology, and presence of extrahepatic disease.

Although very desirable, preoperative prediction of HPLN or other perihepatic LN involvement in patients with CLM remains very difficult. Current state-of-the-art imaging modalities such as 64-slice multi-detector computed tomography (MDCT), MRI, and PET scans lack sufficient diagnostic accuracy to be relied upon in clinical practice. The report from Beaujon Hospital team evaluated the ability of preoperative CT imaging to detect HPLN involvement compared to intraoperative assessment [15]. They defined preoperative LN involvement as greater than 1 cm in the short axis diameter, round-shaped, irregular contoured and/or heterogeneous LN in CT appearance. Of 15 patients with pathological proven LN involvement, only five patients fulfilled the preoperative imaging criteria for positive LN disease, resulting in a low sensitivity and positive predictive value (PPV) of 33% and 56% respectively. Positron emission tomography (PET) scan appears to be more accurate than CT for detection of HPLN involvement. A study from Memorial Sloan Kettering Cancer Center (MSKCC) evaluated 100 patients with metastatic hepatic malignancies who underwent liver resection and HPLN sampling [18]. In their study, CT scan had a high negative predictive value (NPV) of 95% and a low PPV of 39%, compared to PET scan with a NPV of 88% and a PPV of 100%. In patients demonstrating both a negative CT and PET scan, HPLN involvement was very unlikely (only one patient; 2.1%). However, systemic HPLN dissection was not performed, which limits the ability to assess the true denominator for occult metastases in this study and therefore prevents a true meaningful comparison of preoperative imaging and postoperative pathologic results. Although PET has a reasonable specificity for the presence of colorectal cancer and CLM (87%), it was found to be unreliable to detect LN metastases with a small tumor burden, leading to an overall low sensitivity of 37% for primary LN staging [19]. The authors experienced a CLM patient with HPLN involvement with a small tumor burden in whom both CT and PET scan were negative (Fig. 22.3a–f).

In conclusion, current imaging modalities cannot predict the presence of perihepatic LN involvement in patients with CLM with sufficient accuracy to be clinically valuable.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Prognosis of CLM Patients with Metastatic HPLN and Distant LN, Particularly Para-Aortic LN (PALN)

There have been few reports about the prognosis in patients with CLM and distant LN involvement. Two large studies analyzed the prognosis of CLM patients with resectable extrahepatic disease (EHD). An international multi-institutional database evaluated 1,629 patients with CLM who underwent resection for CLM [20]. Of these 1,629 patients, 171 (10.4%) had resectable EHD, and all malignant foci including CLM were removed. The common EHD sites were the lung ($n = 62$), HPLN ($n = 41$) and peritoneum ($n = 25$). PALN involvement was observed in 14 patients. The median survival and 5-year actual overall survival in patients without EHD who underwent CLM resection ($n = 1{,}458$) were 77 months and 57%, respectively, while the median overall survival was 39 months and 5-year overall survival rate was 26% in patients with successful resection of EHD. The prognosis of patients with HPLN involvement (median, 29 months; 5-year, 27%) was comparable to that of patients with lung metastasis (median, 46 months; 5-year, 33%) and peritoneal carcinomatosis (median, 32 months; 5-year, 26%). Patients with PALN involvement had a particularly poor survival (median, 13 months; 5-year, 7%). A second single institutional study evaluated 1,369 patients with CLM who underwent hepatic resection [21]. Of these, 127 (9%) underwent concomitant resection of EHD. The most common EHD site was the lung ($n = 34$) followed by HPLN ($n = 27$). Nine patients had ovarian metastasis. PALN and mediastinal LN involvement were observed in five patients and one patient respectively. The median and 5-year survival rate in 1,242 patients without EHD were 55 months and 49% respectively, compared to 36 months median survival and 26% 5-year survival in patients with EHD. Patients with HPLN involvement had poor survival (median, 26 months; 5-year, 12%), compared to 45 months median survival and 28% 5-year survival for patients with lung metastasis and 82 months median survival and 51% 5-year survival for patients with ovarian metastasis. The worst survival was seen in the five patients with PALN (median, 16 months). All five patients relapsed, and three of five patients died within 16 months of surgery.

Based on these results, concomitant resection of PALN may make little contribution to long-term survival, and patients found to have positive PALN probably should not undergo surgical resection upfront. Operation for those patients must be considered as palliative resections.

The prognosis of patients with HPLN involvement is not much better, based on the currently available evidence. A systematic review by Rodgers and McCall, published in 2000, reports the results of 15 English-language studies on the prognosis of patients who underwent concomitant CLM and HPLN resection [22]. Of 145 node-positive patients identified in this review, only five patients (3.4%) reached the 5-year survival point. The authors concluded that HPLN involvement constitutes a relative contraindication for CLM resection, similarly to other EHD. The ultimate success of operations in this context depends on the development of more effective multimodality treatment and chemotherapy regimen.

With the advent of modern multidrug chemotherapy for CLM and a better understanding of the location of HPLN metastases, recent data on

Fig. 22.3 Clinical images of a 54-year-old female with metachronous solitary CLM and HPLN involvement in whom both CT and PET scans were negative. Preoperative CT scan indicates a 5.5 cm solitary CLM in the right hemi-liver (**a**), and fused PET/CT depicts a 2-[18F] fluoro-2-deoxy -D-glucose accumulation in the CLM (**b**). Preoperative CT scan; arrows indicate small HPLN of 7 mm in diameter located adjacent to the gallbladder (**c**). Fused PET/CT is negative for this small LN (**d**). **e** Intraoperative photography. *Arrows* indicate intraoperative gross appearance of LN. The LN was less than 1 cm in size and soft to palpation, suggesting a negative LN. It was removed with the gallbladder (**f**) and microscopic images (200×) revealed metastatic foci within the lymphatic tissues highlighted by the *dotted lines*

the prognostic implications of HPLN involvement on overall survival seems to indicate an improvement in outcome and patient selection. Two recent studies reported 5-year survival rates of more than 20% in patients with HPLN involvement [14, 20]. The study by Jaeck et al. from Strasbourg reported on 160 patients who underwent HPLN dissection simultaneously with curative liver resection for CLM [16]. They divided HPLN into two groups according to their specific anatomic location: area 1 = LN located at both hepatoduodenal ligament and retropancreaticoduodenal area, and area 2 = LN located at the site of the common hepatic artery and celiac axis. Of the160 patients analyzed, 17 had HPLN involvement. HPLN involvement limited to area 1 was found in eight patients, and HPLN involvement in area 2 was found in nine patients. No patient with area 2 involvement survived longer than 1 year after liver resection (3-year survival, 0%), whereas two of eight patients with area 1 involvement survived more than 3 years after surgery (3-year survival, 38%). Cognizant of the limitations for the small numbers, the authors concluded that currently liver resection for CLM in patients with area 2 HPLN involvement is definitively not justified. In a follow-up study, the same group analyzed 45 patients with HPLN involvement who underwent liver resection and concomitant dissection of HPLN [3]. HPLN involvement limited to area 1 or 2 was found in 17 and 18 patients respectively. Involvement of both areas was found in ten patients. The median survival and 5-year survival rate for all patients were 20.9 months and 17.3% respectively. There was no statistical difference of overall survival among the three groups of patients. On multivariate analysis, (1) serum CEA level $\geq$ 200 μg/L before liver resection, (2) R1 or R2 resection, (3) ratio of involved/resected HPLN = 1, and 4) absence of adjuvant chemotherapy were independent factors associated with poor overall survival. The 5-year survival rate in patients without any independent risk factor was 39.1%, whereas none of the patients with two or more risk factors reached the 2-year survival mark. These studies demonstrate that the ability to potentially select patients with favorable prognostic factors and the availability of multidrug effective chemotherapy may change the role of surgery in patients with perihepatic and, particularly HPLN involvement. The use of effective perioperative chemotherapy, as Rodgers and McCall had already noted, may be the most important factor to achieve acceptable survival rates after surgical resection in these patients.

Surgical Technique of HPLN Dissection

There is no evidence that systemic routine en-bloc lymphadenectomy in patients undergoing CLM resection has prognostic value. Routine lymph node resection is not recommended in patients with CLM, since the majority of patients (>80%) are node-negative and the procedure fraught with potential complications, including ischemic bile duct stricture, pancreatic fistula, and lymphorrhea [23, 24]. On the other hand, en-bloc lymphadenectomy of HPLN might carry a benefit in selected patients who have enlarged HPLN on surgical exploration or on preoperative imaging, as enlarging HPLN can lead to obstructive jaundice, and determining the presence of metastatic disease has important prognostic value. Selected patients with long-term disease control after resection and adjuvant chemotherapy who develop metachronous disease in the HPLN following curative resection for CLM may also benefit from this procedure. It is important to rule out EHD in these patients prior to embarking on a possible regional lymphadenectomy.

Our technique of a standardized en-bloc lymphadenectomy of HPLN is described using a case of a 65-year-old male with intrahepatic cholangiocarcinoma. This patient underwent en-bloc lymphadenectomy of HPLN concurrent with central hepatectomy in National Hospital Organization, Kyoto Medical Center.

We prefer a bilateral subcostal incision with upper midline extension. After dissection and division of the round and falciform ligaments and generous Kocher's maneuver, the assistant subsequently retracts the duodenum anteriorly to expose the retropancreatic area (Fig. 22.4a).

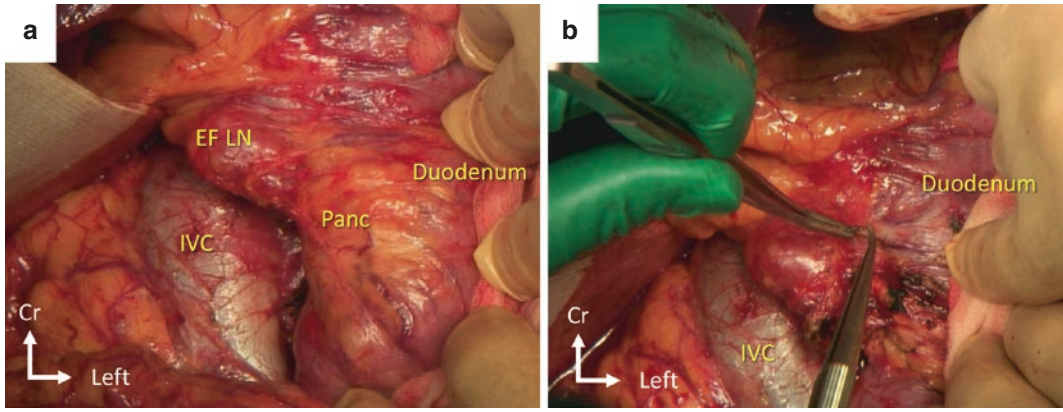


Fig. 22.4 Intraoperative photographs of en-bloc lymphadenectomy of HPLN. (**a**) Preparation for retropancreatic LN dissection. *EF LN*, epiploic lymph node; *IVC*, inferior vena cava; *Panc*, pancreas. (**b**) Retropancreatic LN dissection is performed using pinch–burn–cut technique. *IVC*, inferior vena cava. (**c**) Right gastric artery is ligated and divided. *GB*, gallbladder. (**d**) Common hepatic artery (CHA) LN is retrieved up to the origin of left gastric and splenic arteries. *GDA*, gastroduodenal artery; *Panc*, pancreas. (**e**) *Arrowhead* indicates the origin of the right gastric artery, which arises from proper hepatic artery. *Arrow* indicates the stump of left gastric vein. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *Panc*, pancreas; *PHA*, proper hepatic artery. (**f**) Complete dissection of the anterior border of the common hepatic artery (CHA) up to the origin of left gastric and splenic arteries. *GDA*, gastroduodenal artery; *Panc*, pancreas; *PHA*, proper hepatic artery; *CA*, celiac axis; *LGA*, left gastric artery. (**g**) The right side of celiac axis LN is dissected using ultrasonic scalpel. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *PHA*, proper hepatic artery; *CA*, celiac axis; *LGA*, left gastric artery. (**h**) *Arrowheads* indicate left gastric vein which is ligated at the bifurcation of portal vein. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *Panc*, pancreas; *PHA*, proper hepatic artery; *CA*, celiac axis; *LGA*, left gastric artery. *PV*, portal vein. (**i**) The *dotted lines* indicate the LNs of the left oblique pathway, which are separated from the left side and retracted to the patient's right. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *CA*, celiac axis; *LGA*, left gastric artery. *PV*, portal vein. (**j**) LNs are dissected from the anterior border of portal vein using electrosurgical instrument. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *CA*, celiac axis; *LGA*, left gastric artery. *PV*, portal vein. (**k**) The anterior border of the hepatoduodenal ligament is opened and left and middle hepatic arteries exposed. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *PHA*, proper hepatic artery; *MHA*, middle hepatic artery; *LHA*, left hepatic artery. (**l**) LN dissection of left oblique pathway is completed. Traction of the PHA anterolaterally facilitates LN dissection of the posterior border of the hepatic arteries. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *PHA*, proper hepatic artery; *LHA*, left hepatic artery; *PV*, portal vein; *LN*, lymph node. (**m**) *Arrowheads* indicate "3 o'clock" artery of CBD. During dissection, care should be applied to preserve these vessels. *GDA*, gastroduodenal artery; *PHA*, proper hepatic artery; *CBD*, common bile duct; *EF LN*, epiploic lymph node. (**n**) *Arrowheads* indicate a replaced right hepatic artery arising from the superior mesenteric artery. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *MHA*, middle hepatic artery; *LHA*, left hepatic artery. *PV*, portal vein; *CBD*, common bile duct; *Panc*, pancreas. (**o**) *Arrowheads* indicate small arterial collaterals arising from a replaced hepatic artery. These small collaterals should be identified and ligated. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *MHA*, middle hepatic artery; *LHA*, left hepatic artery. *PV*, portal vein; *CBD*, common bile duct; *Panc*, pancreas. (**p**) *Arrowheads* indicate the biliary stent inserted to perform intraoperative cholangiography. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *MHA*, middle hepatic artery; *LHA*, left hepatic artery. *PV*, portal vein; *CBD*, common bile duct; *Panc*, pancreas. (**q**) *Arrowheads* indicate the posterior branch of the right hepatic artery. *Arrows* indicate the biliary stent inserted into the CBD via the cystic duct. *CHD*, common hepatic duct, *RHA*, right hepatic artery. (**r**) The area highlighted by the *dotted lines* indicates the right descending pathway LN, which is dissected from the hepatoduodenal ligament by a cranial–caudal approach. *CHA*, common hepatic artery; *GDA*, gastroduodenal artery; *LHA*, left hepatic artery. *PV*, portal vein; *CHD*, common hepatic duct; *Panc*, pancreas; *RHA*, right hepatic artery; *LN*, lymph node. (**s**) *Arrowheads* indicate the lymphatic vessels, which should be ligated before division. *PV*, portal vein; *CBD*, common bile duct; *Panc*, pancreas; *RHA*, right hepatic artery; *LN*, lymph node. (**t**) The area highlighted by the *dotted lines* indicates the retrieved LN, which are connected to the PALN located at the inferior border of left renal vein. The forceps grasps a part of PALN which has been divided. *GDA*, gastroduodenal artery; *PV*, portal vein; *CHD*, common hepatic duct; *Panc*, pancreas; *RHA*, right hepatic artery; *LN*, lymph node; *LRV*, left renal vein; *PALN*, para-aortic lymph node; *IVC*, inferior vena cava. (**u**) Completed lymphadenectomy. En-bloc lymphadenectomy of the HPLNs concurrent with central hepatectomy was completed. No blood transfusion was required. *GDA*, gastroduodenal artery; *PV*, portal vein; *CHD*, common hepatic duct; *Panc*, pancreas; *RHA*, right hepatic artery

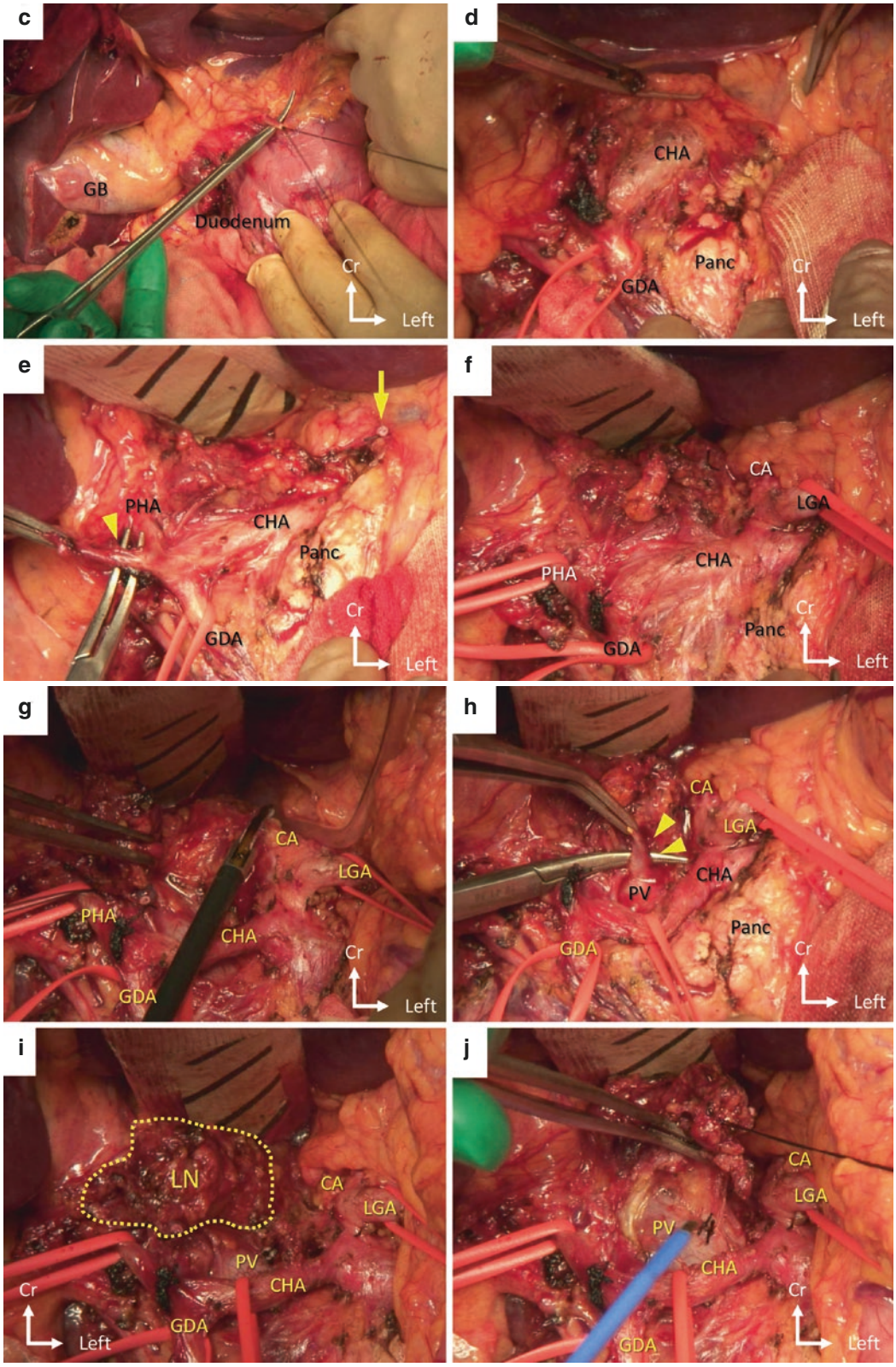
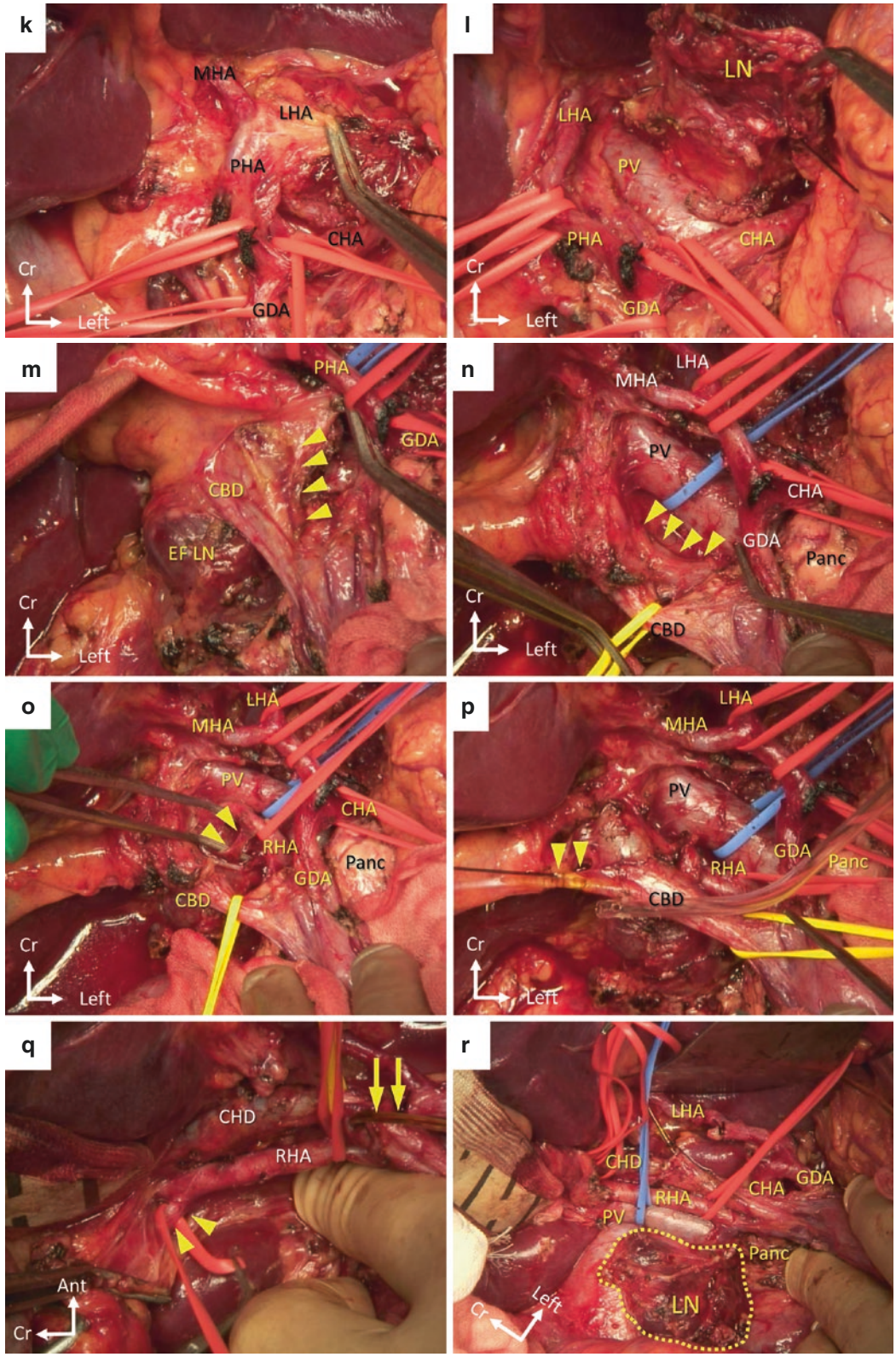


Fig. 22.4 (continued)



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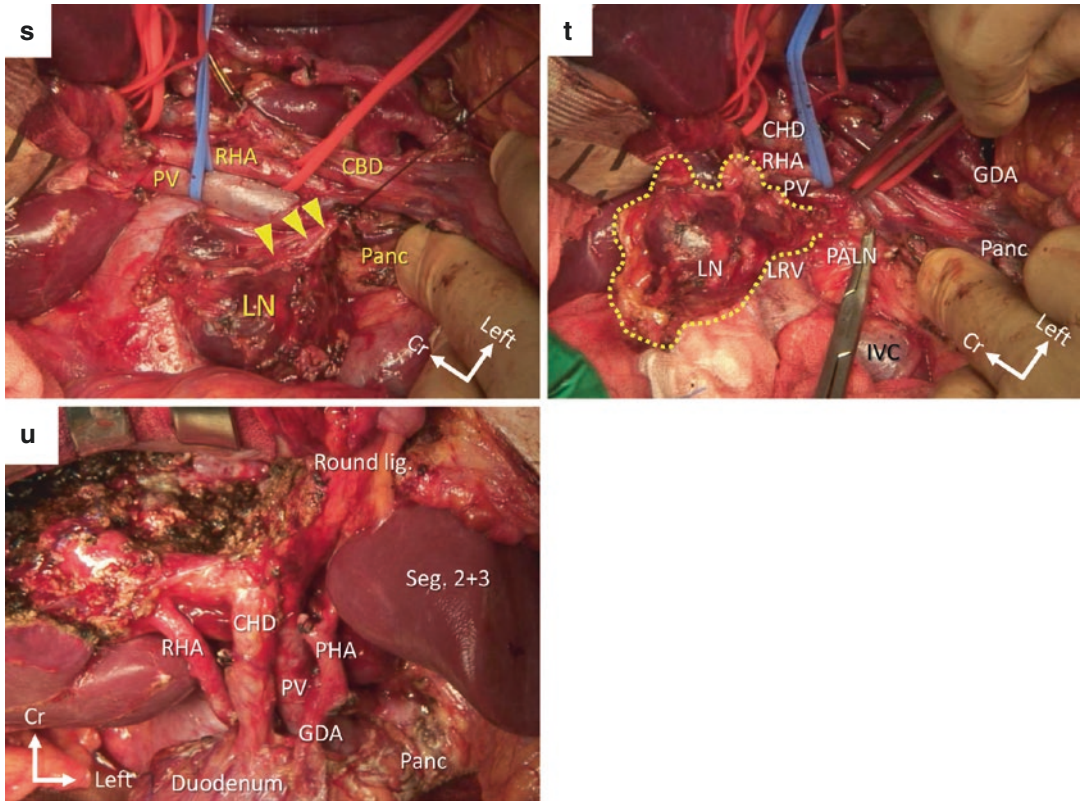

Fig. 22.4 (continued)

The lymphadenectomy of the retropancreatic area is begun by harvesting the posterior pancreaticoduodenal and superior retropancreaticoduodenal LNs using the pinch–burn–cut technique (Fig. 22.4b) [25]. The peritoneal envelope of the hepatoduodenal ligament is transected at the upper border of the pancreatic head. Supraduodenal vessels should be preserved to maintain blood supply to the bile duct. The right gastric artery is ligated and divided (Fig. 22.4c), and the lesser omentum opened. The gastroduodenal artery is dissected and encircled with vascular tape. This exposes the lymphatic nodal tissue in front of the hepatic artery, which is cleared anterior and superior to the common hepatic artery (CHA) and up to the origin of the left gastric and splenic arteries (Fig. 22.4d and f). Care is taken not to injure the left gastric vein. If necessary, the vein can be ligated and divided to expose the posterior aspect of CHA (Fig. 22.4e). The LNs to the right of the celiac axis are dissected (Fig. 22.4g). Then CHA is encircled with vessel tape, and lymphadenectomy along its posterior surface is performed. The anterior surface of portal vein is exposed and the left gastric vein is ligated and divided (Fig. 22.4h). The celiac and CHA LN are completely separated from the left side and retracted to the patient's right (Fig. 22.4i). LNs are subsequently dissected from the anterior surface of the portal vein (Fig. 22.4j). The anterior surface of the left and middle hepatic arteries are exposed and circumferentially dissected using vessel tape (Fig. 22.4k). Anterolateral traction of these vessels allows clearance of the lymphatic tissue posterior to the proper and left hepatic arteries and to the left side of the portal vein (Fig. 22.3l). Lymphadenectomy on the right descending pathway is begun by dissecting the connective tissues around the common bile duct (CBD). The CBD is supplied via two main arteries running at the left and right border of the bile duct, the "3

Table 22.2 Review of publications describing prognostic implications of HPLN involvement on overall survival

Authors	Year	Number of patients	Patients with nodal involvement	5-year overall survival rate	
				HPLN (+)	HPLN (−)
Jaeck [16]	2002	160	17 (11%)	0	47%
Elias [14]	2003	385	12 (3%)	27%	NR
Laurent [28]	2004	156	23 (15%)	5%	43%
Adam [30]	2008	763	47 (6%)	18%	53%
Carpizo [21]	2009	1369	27 (2%)	12%	49%
Oussoultzoglou [3]	2009	45	45 (100%)	17.3%	NR
Pulitano [20]	2012	1629	41 (3%)	27%	57%

HPLN hepatic pedicle lymph node; *NR* not reported

o'clock" and "9 o'clock" arteries, which variably arise from the retroportal, retroduodenal or gastroduodenal arteries and communicate with the right or less often with the left hepatic artery [26]. Therefore, dissection should be done with caution to avoid injury to these vessels (Fig. 22.4m). The CBD is subsequently encircled and retracted laterally to facilitate identification of a replaced right hepatic artery (Fig. 22.4n). The dissection is carried out between the right hepatic artery and CBD. Small arterial collaterals should be identified and ligated in order to avoid subadventitial hemorrhage (Fig. 22.4o). After identification of the cystic duct, a biliary stent is inserted into the CBD through the cystic duct to perform intraoperative cholangiography (Fig. 22.4p). Lymphadenectomy is continued by harvesting the cystic node and dissecting the "porta hepatica". This procedure allows exposure of the anterior border of the common hepatic duct and right hepatic artery. The dissection is continued until the posterior branch of right hepatic artery is identified and encircled with vascular tape (Fig. 22.4q). The LNs along the posterior border of the hepatoduodenal ligament are retrieved by exposing the posterior border of the right hepatic artery and portal vein. The dissection is continued inferiorly to the epiploic foramen LNs which are harvested. Dissection is carried on to the upper and posterior border of the head of the pancreas, harvesting any encountered LNs (Fig. 22.4r). All visible lymphatic vessels should be ligated to prevent postoperative lymphorrhea (Fig. 22.4s). En-bloc lymphadenectomy of HPLN ultimately ends by division of the connection to the PALN (Fig. 22.4u). After completion of the procedure, the hepatoduodenal ligament is completely devoid of lymphatic tissue and LNs. Between April 2012 and May 2015, we performed 14 en-bloc lymphadenectomies of the HPLN, with a mean number of 13 LNs retrieved per patient (range, 3–22). All patients had biliary tract cancer including gallbladder cancer and intrahepatic cholangiocarcinoma and underwent en-bloc lymphadenectomy concurrent with liver resection without biliary reconstruction. There was no mortality and no specific postoperative complication related to the LN dissection. Overall morbidity rate was 7.1% (n = 1), including an organ/space surgical site infection requiring antibiotic therapy.

Safe and successful en-bloc lymphadenectomy of HPLN can be achieved by paying attention to the following steps: avoid injury (1) to the small arterial collaterals during the LN dissection adjacent to the named arteries to avoid subadventitial hemorrhage leading to arterial thrombosis, (2) to the pancreas to prevent pancreatic fistula, and (3) to the supraduodenal vessels and the "3 o'clock" and "9 o'clock" arteries during the common bile duct dissection to prevent ischemic bile duct strictures. All the visible lymphatic vessels should be ligated in order to prevent postoperative lymphorrhea. The maintenance of an appropriate dissecting plane between LN and the structures of hepatic pedicles is of upmost importance to achieve safe en-bloc lymphadenectomy.

Conclusions

In patients with CLM, HPLN involvement has been one of the most powerful prognostic factors associated with poor survival after

liver resection. Patients with primary colorectal cancer who have regional LN involvement can achieve long-term survival by means of regional lymphadenectomy concomitant with resection of the primary tumor, while surgical resection alone has not improved prognosis of patients with CLM who have HPLN involvement. The biologic relevance of lymphatic invasion in patients with CLM can be viewed as equivalent to systemic disease. Therefore, if metastatic disease is suspected or proven in HPLN, surgical resection should only be entertained in the context of a multimodality treatment algorithm. Despite advances in imaging modalities, it remains very difficult to identify HPLN involvement preoperatively in those 20% of patients having metastatic HPLN disease. The prognostic and therapeutic implications of systematic routine en-bloc lymphadenectomy of HPLN remain unclear and need further investigation. With improved systemic treatment options, surgical removal of involved HPLN nodes may translate into a survival advantage in selected patients with PET-positive nodes and after curative resection with long-term response to chemotherapy, but at this time cannot be viewed as standard of care.

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Peritoneal Metastases

23

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Introduction

Mechanisms

In addition to hematogenous and lymphatic dissemination, colorectal tumor cells can spread directly into the peritoneum via the transcoelomic route and cause peritoneal metastases (PM). The process of metastasis in general comprises different phases: first, tumor cells detach from the primary tumor, second, they migrate to the distant site, and third they adapt to the new microenvironment, i.e., niche, and grow out [1]. Relatively little is known about the biology of peritoneal spread of CRC. The development of PM involves several steps, including: detachment of malignant cells, anoikis evasion, and attachment to and invasion of the peritoneal surface ultimately ending in a colonization phase in which the malignant cells thrive in the newly formed niche. The niche in question, the peritoneum, is made up of a single layer of mesothelial cells on a basement membrane supported by a connective tissue or stroma compartment, also referred to as the submesothelium, which forms the niche for PM [2, 3]. With regard to the mechanisms implicated in the peritoneal dissemination, de Cuba et al. [4] have pointed out interesting candidate biomarkers for possible clinical application, which all require extensive further validation prior to clinical application.

Incidence

Occurring either synchronously or metachronously to the primary tumor, PM are diagnosed in 8–20% of the patients with CRC [5, 6]. In a recent Swedish registry, which analysed 11,124 patients with CRC treated between 1995 and 2007, PM was diagnosed in 8.3% [7]. In another recent analysis of 5671 patients operated on for CRC [8], and followed up at least 5 years, 1042 (18%) developed metastases, which were located in the peritoneum in 197 patients (19%), and PM were isolated, without any other metastatic localization in more than 40%; it is important to underline this, as in these patients, a potential curative treatment has to be discussed. Finally, 14% of the patients included in the cohort developed PM.

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Diagnosis

On a clinical basis, no symptoms are fully specific to PM, which is, in addition to that, usually symptomatic at a very advanced stage [9, 10]. The main signs which in combination with the possibly associated symptoms of the primary tumor can lead to suspicion are the presence of an ascites, occurring in 28–30% of patients with synchronous PM, and/or an associated small bowel obstruction, which concerns 8–20% of patients at the time of diagnosis [5, 6]. In most patients with CRC, PM are diagnosed at laparotomy done for resection of the primary cancer. Indeed, the accuracy of imaging is quite disappointing in the diagnosis of PM.

Although regular follow-up and serial imaging is the rule in patients with resected primary tumors, early diagnosis of small-volume PM is rarely possible: there are certainly no symptoms or signs for small volume progression on imaging.

Computed tomography remains the standard for the diagnosis of PM, although its sensitivity is moderate, ranging from 23 to 76% [11–13].

Intravenous injection of contrast media and multiplanar reconstructions (especially in the coronal plan) are mandatory, making it possible to distinguish PM from small bowel loops. A recent report also suggests that preoperative evaluation of the small bowel could be done with high sensitivity (92%) and specificity (96%) using CT-enteroclysis [14], but this has to be confirmed.

The main obstacles for the detection of PM are related to their size (<5 mm) and specific locations such as mesentery and small bowel surface. Many other factors influence the sensitivity of CT in PM diagnosis: in particular, the aspect of the peritoneal lesions (nodular or beach) and the experience of the radiologist [13].

Positron emission tomography (PET) with 18fluoro-deoxyglucose (18FDG) is equally sensitive for the positive diagnosis of PM, ranging from 57 to 86.4% [15, 16] and seems quite superior for the detection of PM located in the mesentery and the small bowel surface [17]. However, the specificity of PET FDG is lower, allowing confusing images to be interpreted as metastatic, such as lymphadenopathy, digestive physiological uptake, ureters, post-surgical aspects, and abscess. Cystic and mucinous tumor deposits also show no uptake in PET FDG, but this exam is nevertheless useful for characterizing a specific image detected on CT or searching for an extra-peritoneal disease [18].

PM detection with magnetic resonance imaging (MRI) is still being evaluated but is promising, especially with the use of diffusion-weighted sequences. Diffusion suppresses fluid hyper signals and consequently allows a better detectability of tumoral implants. Standard T2-weighted sequence also easily depicts mucinous deposits [19–22]. However, a strict protocol and an experienced radiologist are required.

Thus, with the globally low sensitivity of actual imaging tools, the diagnosis is usually made at an advanced stage. Preoperative radiological aspects can arouse suspicion of a synchronous PM: ovarian metastases, peritoneal thickenings around the liver or the spleen, a peritoneal enhancement, either smooth or nodular, an omental involvement such as soft-tissue permeation of fat, enhancing nodules or omental cake, ascites, ureteral dilatation without detectable obstacle, a small-bowel involvement with wall-thickening and bowel distortion, (Fig. 23.1) [18, 23]. It is important to note that some factors of developing PM had been identified and may help to diagnose earlier PM on imaging exams, or to propose new therapeutics in these patients (see below).

Nevertheless, all of these imaging modalities strongly underestimate the real extent of the peritoneal disease [24]. In addition, because radiologic tests lack sensitivity for PM, when peritoneal extension is discovered during surgery, it is mandatory to precisely describe the locations, number, and sizes of the peritoneal implants, to estimate the possibility of complete resection.

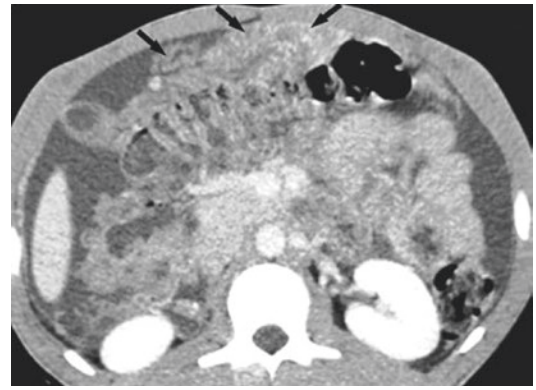

Fig. 23.1 Diagnosis of PM on computed tomography. View of an omental involvement such as enhancing nodules or omental cake

Patients at Risk

Numerous studies have retrospectively reported on factors linked to the primary CRC that exert an influence on the onset of recurrences in general, but only very few have focused on peritoneal recurrences [4, 25–29]. Nevertheless, multiple factors have been identified that give rise to a high risk of developing PM. A predictive score of metachronous PM has been established, after follow up of 8044 patients, with a maximal incidence of 60.7% when all the risks factors are present [7]. In a recent review of the literature including studies published between 1940 and 2011, Honoré et al. [30] selected 16 clinical studies, three prospective and 13 retrospective, which analyzed the risk of PM after resection of CRC. The low quality of the methodology of these studies has to be underlined. Nevertheless, risk factors of developing PM were: synchronous PM resected with the primary tumor, history of ovarian metastases, perforated tumor, serosal and/or adjacent organ invasion, histological mucinous subtype, positive peritoneal cytology, with a reported incidence of peritoneal relapse ranging from 8 to 75%. In these patients identified at high risk of developing PM (localized PM resected, ovarian metastasis, perforated tumor), new treatment protocols have been evaluated and will discuss below.

Complete Cytoreductive Surgery Plus HIPEC—Objectives and Results

For the last two decades, prognosis of PM arising from CRC has nevertheless been widely improved, and modern systemic chemotherapies actually enable a median survival of 12.7 to 24 months [31, 32]. However, prognosis of stage IV patients unable to undergo surgery and treated with systemic chemotherapy (5-FU plus oxaliplatin or plus irinotecan) was worst in case of PM associated to other metastatic sites, with a median survival 12.7 months, compared to 17.6 months when patients had no PM [21]. The worst prognosis of the patients with PM from CRC, and their lower benefit from recent improvement in contemporary systemic chemotherapy, leading to only limited survival benefit, were confirmed in a large cohort study of 2406 patients [26].

Beside the improvements in these drugs, the development of a new therapeutic concept which combines a complete cytoreductive surgery (CCRS) of the visible peritoneal tumorous deposits followed by hyperthermic intraperitoneal chemotherapy (HIPEC) was able to improve the median survival up to 63 months [32–34]. This major survival benefit could only be achieved in a selected population of patients.

Principles and Objectives

The combination of maximal cytoreductive surgery with HIPEC to treat peritoneal cancer was first described by Spratt in 1980 [35], but the main initiator of this combined treatment for peritoneal disease was Sugarbaker [36, 37]. The purpose of surgery is to treat all the macroscopic, i.e., visible disease, and immediately after resection, the purpose of HIPEC is to treat the remaining microscopic i.e., non-visible residual disease. It is essential that surgery resects all the tumor implants exceeding 1 mm, as the drug penetration in the tissue and in the tumoral deposits is small, less than 1 to 2 mm [38, 39]. HIPEC must be performed immediately after surgery, to avoid peritoneal adhesions in which cancer cells may be trapped and which could constitute a tumor sanctuary [40, 41]. In fact, the exact effect of HIPEC alone in this package is currently unknown in human beings. In an experimental study, animals treated with HIPEC survived longer than those treated with intraperitoneal chemotherapy alone or exclusively with intraperitoneal hyperthermia [42]. This was confirmed in another experimental study, with a reduced tumor load in rats which received intraperitoneal chemotherapy combined to hyperthermia, compared to those which had either chemotherapy or hyperthermia alone [43]. With regard to the potential beneficial effect on survival of HIPEC, until now, only one randomized study has been conducted, a multicentric French trial (NCT00769405), which compared CCRS plus HIPEC to CCRS without HIPEC. This trial has

just closed for inclusion, and final results on overall survival should be available in 2017. Two retrospective [44, 45] and one prospective [46] studies have reported survivals of patients who had a complete resection of the PM without intraperitoneal treatment; the 5-year overall survival ranged from 24 to 36%, but their non-randomized manner and their small effect make conclusions difficult to do.

Surgical Technique

A complete exploration of the entire abdominal cavity has to be done, with a meticulous exploration and palpation of all the peritoneal surfaces, and all the previous dissected planes have to be reopened, as tumor cells could be trapped inside these cicatricle planes. Searching extraperitoneal metastases (liver, retroperitoneal lymph nodes) has also to be performed during the exploration. At the end of the exploration, the extent of the PM is scored using the peritoneal cancer index (PCI) described by Jacquet et Sugarbaker [47] (Fig. 23.2). Succinctly, the abdomen is divided into 13 areas (nine abdominal regions and four small-bowel sections), and a score is attributed for each region according to the size of the peritoneal implants (score from 0 to 3). At this time, the surgeon has to decide if the complete resection of all the peritoneal disease can be performed, taking into account the value of the PCI, the amount of the visceral resections, the risk of postoperative complications, and the expected quality of life after surgery. With regard to the surgical technique, all the visible peritoneal deposits have to be resected, even if they look like granulomatous nodules; indeed, macroscopic differentiation between benign inflammatory nodules and tumoral nodules might be difficult to do. Digestive anastomoses are usually performed after HIPEC in the open technique (see below), and before HIPEC in the closed technique. Ostomies are usually done to protect colorectal anastomosis.

Hyperthermic Intraperitoneal Chemotherapy

HIPEC techniques are heterogeneous but their elaboration is highly complex. The combination of drugs can be modified, as can their concentration, but also the composition as well as the volume of the perfusion, the duration, and the temperature. A high number of combinations of these six parameters are possible, and it is not possible to test all of them [48]. Each modification of one of these parameters implies

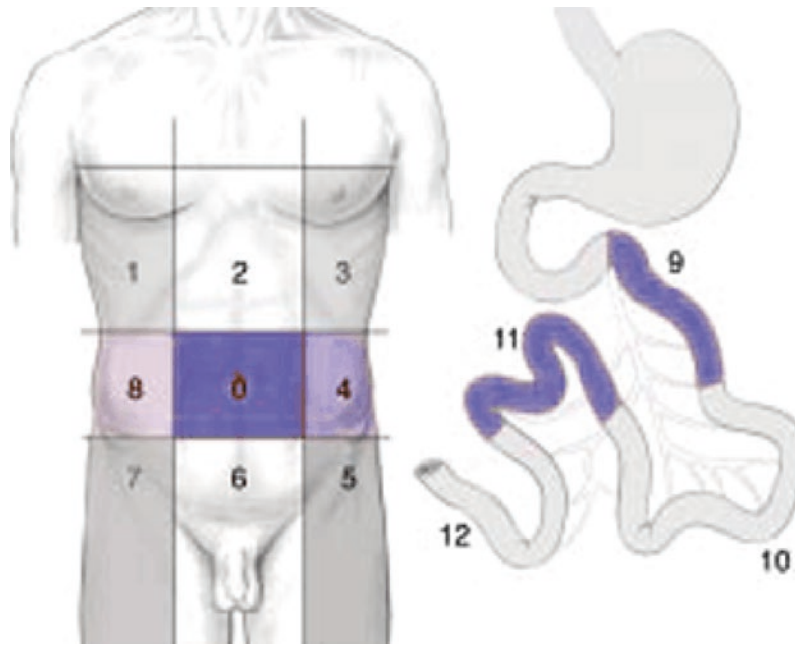

Fig. 23.2 Peritoneal cancer index (PCI). The abdomen is divided in 13 areas (9 abdominal regions and 4 small bowel sections), and a score is attributed for each region according to the size of the peritoneal implants (score from 0 to 3)

conducting a new pharmacokinetic study. In a recent experimental study which compared the open to the closed technique, using intraperitoneal oxaliplatin at a temperature of 42 °C, the open technique had far higher systemic absorption and abdominal tissue penetration of oxaliplatin than the closed technique; the closed technique achieved a higher temperature in the diaphragmatic regions, while the open technique was more effective in the other areas. Nevertheless, intraperitoneal hyperthermia could be achieved with both techniques [49]. After all, it is very important for the surgeon to obtain a high and homogeneous temperature throughout the abdominal cavity, to choose "his" technique and to routinely perform this technique, leading to an analysis of homogenous data, as no prospective comparison of open and closed techniques of HIPEC in terms of survival, morbidity, or pharmacokinetics as ever been reported [50].

Schematically, there are two main trends worldwide for HIPEC: one uses mitomycin C over 60–90 min at 41 °C with a closed-abdomen technique, and the other uses oxaliplatin (460 mg/m^2 of oxaliplatin in 2 L/m^2 of iso-osmotic 5% dextrose) over 30 min (strictly 30 min as soon as the minimal temperature of 42 °C had been reached throughout the abdominal cavity, plus 5 to 8 min before to heat the infusate from 38° to 42 °C), at a homogeneous temperature of 43 °C (range: 42–44 °C) with an opened-abdomen technique [51] (Fig. 23.3). A bidirectional (intraperitoneal + systemic) intraoperative chemotherapy which combines intraperitoneal oxaliplatin preceded by an intravenous infusion of 5-FU (400 mg/m^2) with leucovorin (20 mg/m^2) is now mostly used for PM from CRC [52, 53].

Short-Term Results

Specialized centers have now reached technical maturity, leading to an incidence of adverse events comparable with those for other established surgical procedures. Reported mortality is now below 5%, and severe morbidity (grade 3–4) is approximately 30%. These acceptable operative results can be obtained in experienced centers, and in selected patients [54–65].

Many predictors of postoperative complications have been described, including the operation length [53, 60], the age [61], the number of visceral resections [53], the stoma formation [62], the dose of chemotherapeutic agent [63], and recurrent cancer [59]. But the most widely known factor is the extent of the peritoneal disease measured with the PCI, with an increased risk of grade IV morbidity when the PCI is greater than 12 [58–60]. In the study reported by Saxena et al. [58], an extensive disease involvement in the left hemidiaphragm was the only significant predictor of severe morbidity on multivariate analysis, probably because this procedure results in respiratory complications, and in a higher risk of pancreatic leak, bleeding, intra-abdominal abscess, due to the dissection of the hilum of the spleen.

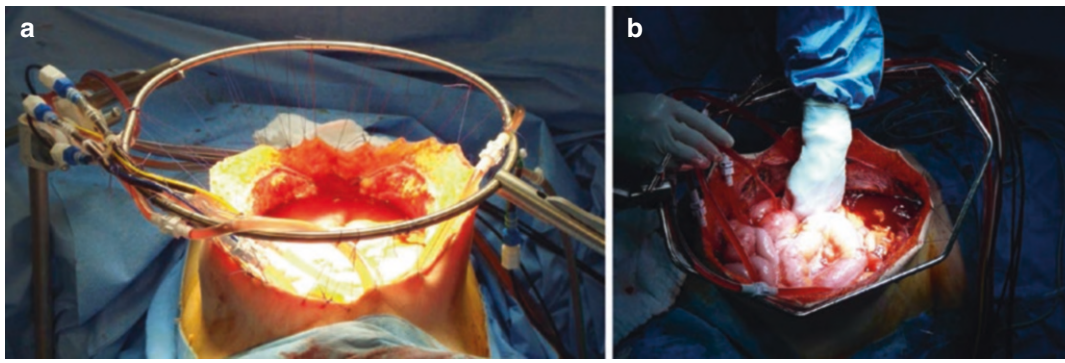

Fig. 23.3 HIPEC: Open technique. Pictures corresponding to operative view of the opened-abdomen technique over 30 min at a homogeneous temperature of 43 °C (range: 42–44 °C)

Long-Term Results

The benefit of the cytoreductive surgery combined with HIPEC above systemic chemotherapy (5-FU leucovorin) has been confirmed in a phase 3 randomized study [33, 34], with a significant improvement of the median overall survival from 12.6 to 22.2 months ($p = 0.028$). Moreover, these results were obtained despite the fact that half of the patients in the experimental arm were ultimately not good candidates for HIPEC because their PM could not be completely surgically resected. A more recent retrospective study compared similar patients with resectable PM treated either with CCRS and HIPEC or with standard systemic chemotherapy (FOLFOX, or FOLFIRI). Again, the median survival was significantly increased in patients who underwent CCRS plus HIPEC, from 24 to 63 months ($p < 0.05$) (Fig. 23.4) [32]. Thus, the results of experienced centers concerning patients who underwent CCRS plus HIPEC are consistent with an overall 5-year survival rate close to 40% [34, 55, 66]. In a large review of the literature [67], the median overall survival after CCRS (R0/R1) plus HIPEC varied between 28 and 62.7 months. Finally, definitive cure of PM with HIPEC is possible. The authors recently followed up those of their patients who had had no recurrence more than 5 years after their last treatment. Among 107 patients treated between 1995 and 2005, 16% were definitely cured [68]. This rate of cure was comparable to that reported after resection of colorectal liver metastases [69, 70], suggesting that prognosis of selected patients who underwent CCRS plus HIPEC could benefit from this aggressive treatment, as well as patients operating on liver metastases. This was confirmed in a recent study, with a 5-year overall survival rate not statistically different between patients operated on liver metastases from CRC and those who had CCRS plus HIPEC (respectively, 38.5% and 36.5%) [71].

Prognostic Factors

Completeness of Resection

As mentioned above, one key prognostic factor is the completeness of cytoreduction. Indeed, the median survival is about 12 months for patients in whom macroscopically complete resection of PC is not possible [33, 72, 73]. This survival is comparable to that obtained with palliative systemic chemotherapy alone [6, 31], while systemic chemotherapy bears significantly lower morbidity and mortality risks. Resection is scored according to the completeness of cytoreductive surgery (CCS score ranging from 0 to 3). All the studies have the same conclusions: an incomplete resection, leaving tumor deposits greater than 2 mm, does not provide prolonged survival even

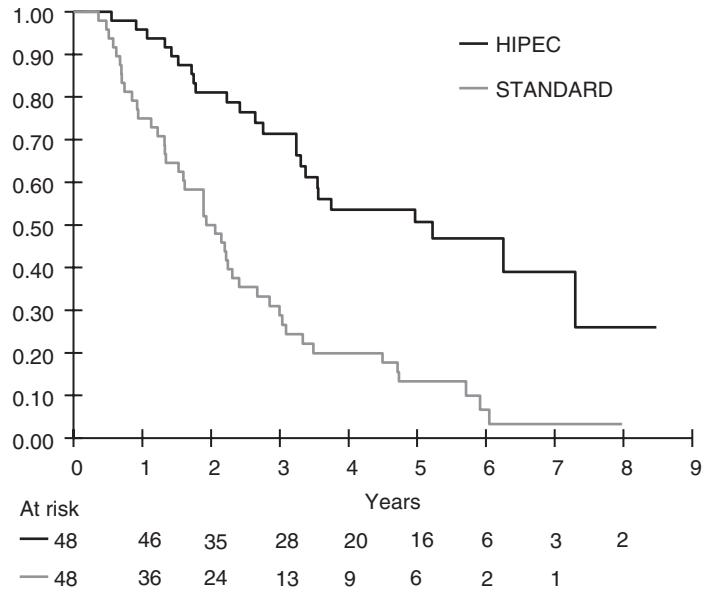

Fig. 23.4 Overall survivals: comparison between patients treated with curative intent (CCRS plus HIPEC) and those treated with modern systemic chemotherapy. Survivals reported in a retrospective study which compared similar patients with resectable PM treated either with CCRS and HIPEC or with standard systemic chemotherapy (Folfox, or Folfiri). The median survival was significantly increased in patients who underwent CCRS plus HIPEC, from 24 to 63 months ($p < 0.05$) [32]

if HIPEC is performed [33, 54, 74]. In the French registry, there was no 5-year survivor in cases of remnant tumor deposits greater than 2 mm.

Extent of Peritoneal Disease

Another major prognostic factor is the extent of PM, which is intimately associated with the completeness of resection. Different scores evaluate peritoneal extension, the most common being the PCI (see above), which can only be accurately determined at laparotomy. Among 523 patients reported in the French registry [54], 5-year overall survival was directly correlated with the PCI, ranging from 44% with a very low PCI (less than 6) to 7% with the highest PCI (more than 19); and a PCI exceeding 20 appeared as one of the main prognostic factors for survival in the multivariate analysis. The main impact of the PCI has been underlined in many studies, and some tried to define a cut-off above which CCRS and HIPEC could not be effective. Thus, a PCI above 16 [75] or 20 [66] has been demonstrated to have a negative prognostic impact. Recently, a group of patients judged amenable to CCRS, but in whom CCRS plus HIPEC could not be performed during laparotomy (they received palliative systemic chemotherapy), was compared to a group of patients who underwent CCRS and HIPEC, with the aim of determining a threshold value beyond which CCRS plus HIPEC may not offer survival benefit compared to systemic chemotherapy. After a median follow-up of 60 months (47–74), 3-year overall survival was 52% [95% CI 43–61] in the curative group compared to 7% [95% CI 2–25] in the palliative group. Comparison of survivals for each PCI (comprised between 5 and 36) showed that OS did not differ significantly between the two groups of patients when the PCI was greater than 17 (HR = 0.64 [0.38–1.09]) (Fig. 23.5) [76].

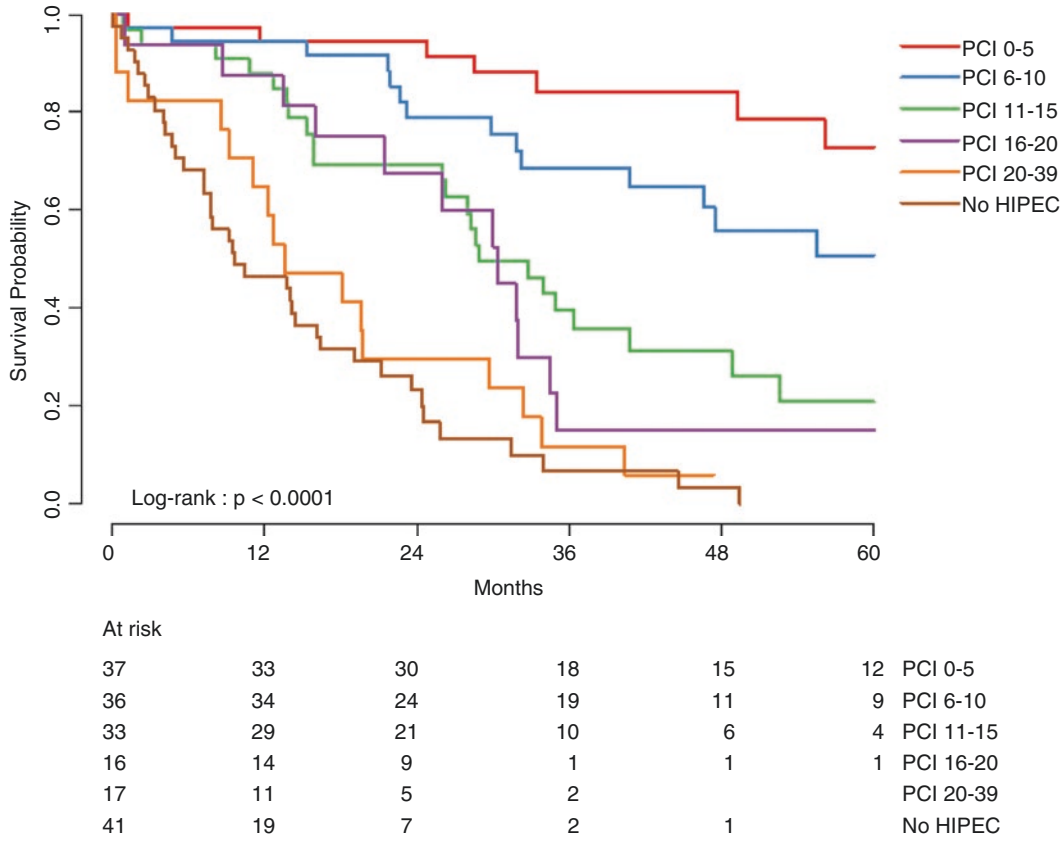

Fig. 23.5 Overall survivals: comparison between patients treated with curative intent (CCRS plus HIPEC) and those whom CCRS plus HIPEC could not be performed during laparotomy (they received palliative systemic chemotherapy), according to the peritoneal extension (PCI). After a median follow-up of 60 months [47–74], 3-year overall survival was 52% [95% CI 43–61] in the curative group compared to 7% [95% CI 2–25] in the palliative group [76]

Others Prognostic Factors

Through multivariate analysis by various studies, others prognostic factors have been identified: the presence of positive lymph nodes, the absence of delivery of adjuvant chemotherapy, the progression under chemotherapy and the presence of liver metastases [32, 54, 66, 77]. Also, the presence of synchronous liver metastases decreases survival in patients operated on PM; however, when the extent of peritoneal disease is limited and when the number of liver metastases is not greater than three, complete resection of both types of disease results in interesting prolonged survival [78].

Histological Findings and Response to Systemic Preoperative Chemotherapy

Response to systemic preoperative chemotherapy is still difficult to appreciate, mainly due to the lack of target lesions on imaging. Therefore, appraisal of histological findings to evaluate response to systemic chemotherapy appears to be attractive. In a recent retrospective study, a review was performed of 115 patients who underwent preoperative irinotecan- or oxaliplatin-based chemotherapy before complete CRS alone or combined with hyperthermic intraperitoneal chemotherapy (HIPEC) [79]. The pathological response was defined as the mean percentage of cancer cells remaining within all specimens. A complete pathological response (no residual cancer cells in all specimens) was observed in nearly 10% of the patients, and 20% of the patients had a major response (1–49% residual cancer cells); the remainder had minor or no responses. Pathological response was the only independent predictor of survival ($p = 0.01$; major response: hazard ratio [HR] = 4.91; minor response: HR = 13.46), using multivariate analysis. The authors did not identify any significant predictor of pathological response. This study confirms that pathological response can be obtained in PM, but rates of major and complete responses appear to be lower than those observed after systemic chemotherapy for liver metastases from CRC.

Indications

The selection of patients is made roughly on clinical parameters and intra-operative findings. Indications are based on absolute and relative contraindications. An absolute contraindication for CCRS plus HIPEC is a poor general status, the presence of extraperitoneal metastases (except for three easily resectable liver metastases) and huge and diffuse PC. Relative contraindications are: a subocclusive syndrome due to more than one digestive stenosis, peritoneal disease progressing under systemic chemotherapy, and the presence of more than three resectable liver metastases (LM are not contraindicated if there are <4 and they are easily resectable) [78, 80].

In summary, eligibility criteria for CCRS and HIPEC are as follows: a good general status and age below 65–70 years, no extra-abdominal disease, no occlusive disorders, and no bulky clinical or radiological PM.

Perspectives

Standardization of the Procedures

The HIPEC procedure will have to be gradually standardized in the future in terms of the drugs, their concentration, the temperature of the perfusate, the duration, and the use of open or closed procedures. In theory, a randomized trial would be required for each modified parameter, but 100 or so different combinations would need to be tested. It is clear that multiple trials will not be conducted.

New Drugs, New Combinations

In the future, optimizing the long-term results, and reducing the morbidity of the procedure could pass by the use of new drugs intraperitoneally, new combinations either intraperitoneally or bidirectionally (IP and IV). In addition, the concept of personalized approach for cancer treatment could also be applied in the future to the

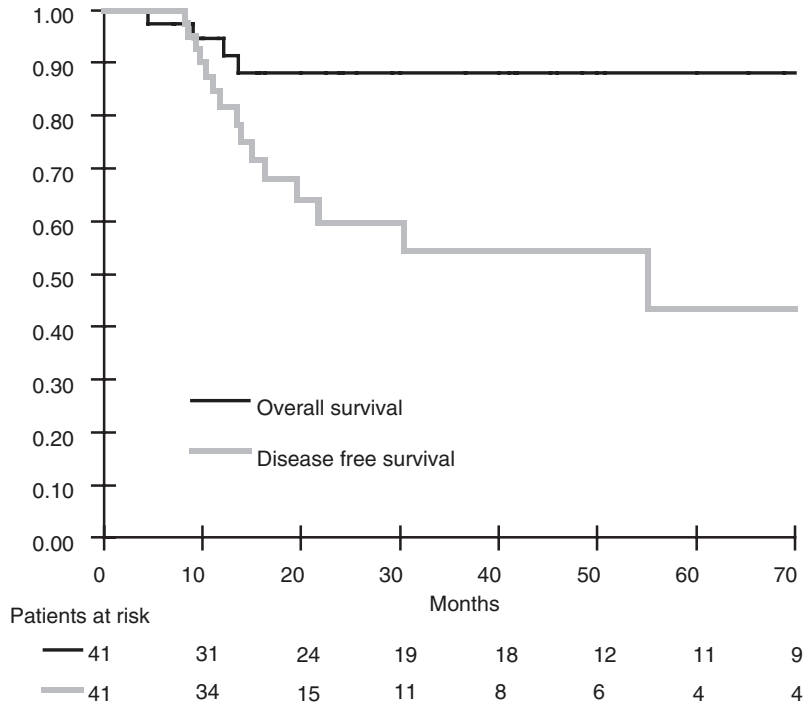

Fig. 23.6 Overall and disease-free survivals after systematic 2nd look surgery in patients at high risk of developing PM. After a median follow up of 30 [9–109] months, overall survival and disease free at 5 years were 90% and 44% [82]

treatment of PM. Better knowledge of the tumor biology at the individual scale may help to refine indications or to select drug among patients treated for PM. It is also possible that targeted therapies which have led to great advances in the colorectal liver metastases field may be used in the local treatment of PM. Their efficiency on peritoneal lesions has to be evaluated in patients with initially unresectable disease.

To Treat earlier

As the extent of the disease (PCI) and the completeness of resection are the main linked prognostic factors, survivals are far better in patient with low PCI. Because the early diagnosis of PM are unusual with current imaging, a new policy consisting in a systematic second look surgery in patients at high risk of developing PM has been evaluated [81, 82]. In patients without evidence of recurrence (clinical, radiological, or biological), a PC was discovered and resected during the second-look surgery in 55 per cent of the patients. The mean peritoneal cancer index was low (8 ± 6), and peritoneal deposits were resectable in all of the patients. After a median follow up of 30 [9–109] months, overall survival and disease-free figures at 5 years were 90% and 44% (Fig. 23.6). Therefore, this strategy is currently being tested in a randomized phase 3 study (NCT01226394) which has just been closed for inclusion. In this study, after 6 months of adjuvant systemic chemotherapy following resection of the primary, patients at high risk of peritoneal recurrence without any sign of recurrence were randomized in two arms: the standard arm which consists in monitoring every 3 months the first 2 years and then every 6 months the 3 years later, and the experimental arm which consist in a systematic second-look surgery followed by HIPEC.

Conclusion

In conclusion, complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy can provide long-term survival in patients with peritoneal metastases from colorectal cancer, in selected patients, with an acceptable morbidity and mortality in experienced centers. Different ways will allow to further

improve the prognosis, and currently one that seems most promising is to treat PM at the earliest opportunity, by performing a systematic second-look surgery in patients at high risk for peritoneal recurrence.

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Adjacent Organs Invasion: Multivisceral Resections

24

Martin de Santibañes

Introduction

Colorectal liver metastases are present in one third of patients at the time of diagnosis of the primary tumor (synchronous presentation), and 10–20% of patients are diagnosed with a colon cancer that directly invades or is adherent to adjacent organs [1]. This scenario is defined as a locally advanced colorectal tumor. Multivisceral resections associated with liver surgery are uncommon procedures that demand extensive surgical skills in visceral and liver surgery. Over the past three decades, there has been considerable improvement in surgical techniques and factors closely related to surgical treatment, making this kind of high complex procedures feasible. However, evidence concerning the feasibility, short- and long-term outcomes of combined liver and multivisceral resections (CLMVR) procedures are very limited.

Surgical Indications

Combined liver and multivisceral resections can arise in the case of an en-bloc resection of tumors that have directly infiltrated other organs, or in the circumstance of simultaneous resections of primary tumors along with distinct sites of metastatic extent [2]. When liver metastases are detected at the same time as the primary tumor, the surgical strategy remains debatable. Current studies suggest that simultaneous resections can be performed safely with outcomes comparable to or even better than staged procedures [3]. However, these reports did not include multivisceral resections in their analysis. Peritoneal carcinomatosis (PC) of colorectal origin was previously reflected as a terminal condition, and consequently treated with palliation. Recently, the introduction of an aggressive approach, combining complete cytoreductive surgery with multivisceral resections and intraperitoneal chemotherapy, has led to a major improvement in long-term survival. Moreover, a recent case–control study seems to confirm that prolonged survival can be achieved in highly selected patients operated on for limited PC and fewer than three liver metastases [4].

Patient Work-Up

Due to a lack of scientific evidence for CLMVR, patients must be highly selected and indications must be discussed in a multidisciplinary council.

The stratification of preoperative risk variables in major abdominal surgery can increase patient assortment and postoperative consequences.

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Patient age (≥75), ASA score (>3) and other comorbidities (cardiac and pulmonary diseases) can predict prolonged length of stay, major complications, and 30-day mortality [5, 6]. Obesity and diabetes are known related factors associated with adverse outcomes after liver resection. Due to a high tumor burden, patients undergoing a CLMVR received preoperative chemotherapy therapies, which have been associated with steatosis, sinusoidal injuries, and steatohepatitis. These histopathologic alterations in the liver parenchyma were related with higher morbidity and mortality [7].

Radiological Assessment

The impact of modern imaging modalities is manifested in a significant improvement in the patients' selection and stratification. Patients planned for a CLMVR should undergo an extensive radiologic evaluation with multidetector computed tomography (MDCT), and/or state-of-the art magnetic resonance imaging (MR) of the chest, abdomen, and pelvis to define local extent of the disease and assessment of liver metastases (Fig. 24.1a, b). Both methods can be used to determine the volume of the future liver remnant in the situation that a major hepatectomy is planned.

Diffusion-weighted imaging (DWI) is another functional imaging tool for liver tissue characterization and pretreatment response estimation in colorectal metastases. From the DWI-MR images an apparent diffusion coefficient (ADC) can be calculated. The ADC is inversely associated to the cell density, because cellular membranes inhibit water movement. It has been shown that ADC increased within days after chemotherapy [8]. Remarkably, the DWI sequence does not demand the administration of intravenous contrast material.

The diagnostic benefits of positron emission tomography (PET) scan have also been confirmed in patients with colorectal cancer with metastatic disease to the liver and extrahepatic sites, such as lymph nodes, soft tissues, and bones [9] (Fig. 24.1c). However, the main limitation in using PET-CT is its restricted accessibility and high cost. Its use can be justified in the case that the tumor extension was not clearly definable on MDCT or Magnetic Resonance (MR).

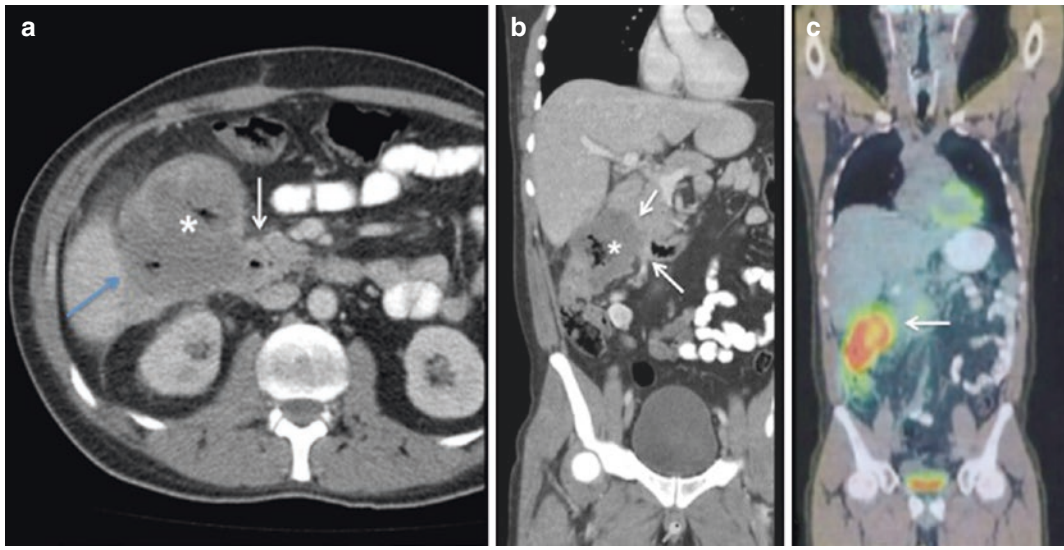

Fig. 24.1 Abdominal and pelvic multidetector computed tomography (MDCT) in a patient with a large colonic tumor (*asterisk*), which involves duodenum and pancreas (*white arrow*) and segment VI of the liver (*blue arrow*) (**a** and **b**). Whole-body positron emission tomography shows a focus of intense FDG uptake in the liver and right flexure of the colon (*white arrow*) (**c**)

Operative Procedure

Definitions

A CLMVR can be defined as a liver resection plus the resection of at least two other organs that are not routinely removed during the surgical procedure [10]. Others define a multivisceral as en-bloc removal of any organ or structure to which the primary tumor was adherent [11].

Preoperative Care

To reduce intestinal content, mechanical bowel preparation with an oral phosphate solution is recommend.

Surgical Aspects

Multivisceral resection for locally advanced colorectal cancer offers the chance of long-term cure [11]. However, few reports have discussed the benefit of these complex procedures in association with hepatic resections. Current literature emphasizes the importance of achieving a R0 resection in colorectal cancer surgery. A recent systematic review, found that R0 resection is a strong predictor of outcomes following multivisceral resections. Partial resection is a poor prognostic element for survival, so that even palliation surgery is not a good surgical indication for multivisceral resections, given the morbidity associated with these procedures.

Timing of hepatic resection has been reported to be a significant prognostic factor. Some studies have shown that simultaneous colon and liver resection was a significant poor prognostic factor, associated with high morbidity and mortality. However, since the advances in anesthetic techniques and the improvement in surgical skills, as well as the progress in postoperative care, simultaneous resections can be performed safely with comparable or even better outcomes than staged procedures [3].

Usually, MVR is undertaken prior to liver resection to ensure a R0 margin resection (Fig. 24.2). It's important to perform routinely intraoperative liver ultrasound to confirm lesions diagnosed preoperatively or to detect new lesions and establish the relationship between the tumor and major intrahepatic vessels and bile duct. Before parenchymal transection, central venous pressure must kept at <5 cm H_2O to decrease blood loss. The Pringle maneuver can be applied in cases where bleeding was encountered during the parenchymal transection despite a low central vein pressure.

In the case of PC, tumor extent is typically scored during the intraoperative procedure according to the Sugarbaker peritoneal cancer

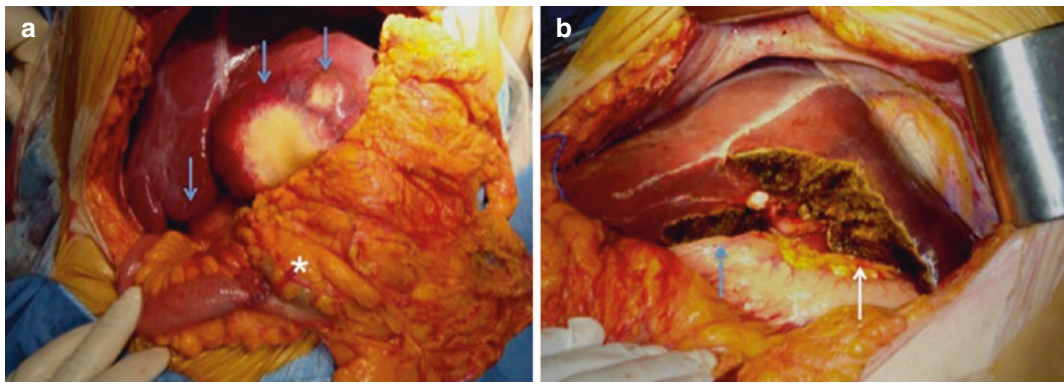

Fig. 24.2 Colorectal liver metastases in segments III and IV (*blue arrows*). **(a)** The *asterisk* shows a tumor involving ileum, right colon, and the great omentum. The *white arrow* shows the resection of segment III and atypical resection of segment IV (*blue arrow*). **(b)** The colonic tumor was removed with an extended right colectomy, atypical gastrectomy, and the resection of the great omentum

index (PCI) [12]. Cytoreductive surgery should be performed with peritonectomy procedures, as described by Sugarbaker in diseased regions of the abdomen and pelvis [13]. Usually, cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) is used to treat macroscopic and microscopic disease. Maggiori et al. [4], suggested that patients with a PCI of less than 12 and one or two easily resectable liver metastases should be subjected to a complete surgical resection followed by hyperthermic intraperitoneal chemotherapy.

Short-Term and Long-Term Outcomes

Govindarajan et al. [14] identified 8380 patients who underwent surgical resection for locally advanced adherent colorectal cancer, of whom only 33.3% were managed with MVR, despite improved survival with these types of procedures. Several large population-based studies have demonstrated that increasing hospital and surgeon volumes result in fewer postoperative complications and lower mortality in high-complexity surgical procedures [15]. While CLMVR in colorectal cancer is associated with a significant morbidity rate, perioperative mortality is comparable with previously published data on mortality following MVR in hepatobiliary malignancies, advanced gastric cancer, and neuroendocrine tumors [2, 10, 16–18].

The most common complications are: wound infection, bowel obstruction or ileus, urinary complications, intra-abdominal abscess, anastomotic leak, eventration or dehiscence, intestinal fistula, bleeding, urinary fistula, biliary fistula, and posthepatectomy liver failure. Other complications include leg weakness, medical complications including cardiac and pulmonary morbidity, and venous thromboembolism [10, 16]. A recent study recognized extended multivisceral resection of two or more additional organ, and long operative time, as independent risk factors for intra-abdominal complications or need for relaparotomy in patients with pancreatic malignancies [19]. Another study showed that the resection involving more than four organs was found to be a statistically significant risk factor for developing major complications [10].

Patients undergoing synchronous resections seem to have poor survival outcome compared with those with metachronous metastases [20]. If we add that this population of patients probably presents a greater tumor burden, it is predictable that oncological limitations may occur during follow-up, because of recurrence or tumor progression. Recently de Santibañes et al. [10] published a series of 21 patients with CLMVR, including nine patients with colorectal cancer. Three-year overall survival was 33%, with a median of 9 months of disease-free survival. Therefore, patients should be selected according to predictable operative hazards, based on their co-morbidity and the procedure-related complication rate, and on oncological risk factors and/or the anticipated time to recurrence [21, 22].

Patients with PC and liver metastases from colorectal cancer have a significantly reduced overall survival and disease-free survival compared to patients with PC alone. Recently, Maggiori et al. [4] in their study described three groups with a long-term prognosis: (1) patients with a "good prognosis," namely, patients with a low PCI (<12) and no liver metastases, with an associated overall survival of 76 months, (2) patients with an "intermediate prognosis," that is, patients with a low PCI (<12) and one or two LMs, with an associated OS of 40 months, and (3) patients with an "impaired prognosis," that is, both patients with a high PCI (≥12) and patients with three LMs or more, with an associated survival dropping to 27 months. This study concluded that patients with a PCI of less than 12 and one or two easily resectable liver metastases should have a complete surgical resection followed by HIPEC.

In conclusion, patients who qualify for CLMVR should be well selected, considering their preoperative comorbidities, and these procedures should be done in high-volume centers. Despite an increased morbidity rate, short- and long-term survival is comparable to standard resections.

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Part V

Miscellany

Postoperative Complications and Their Management

25

Juan Pekolj, Martín Palavecino, and Victoria Ardiles

Introduction

Hepatic resections (HRs) have been increasingly used for the treatment of both, benign and malignant tumors of the liver. In the last two decades, the results of HR have significantly improved. This improvement was possible because of the development of new anesthetic techniques, a better postoperative care, a better patient selection, the development of new technological devices and the specialization of hepatobiliary surgery units. The accurate knowledge of anatomy of the liver, the development of parenchymal sparing surgical techniques and the intraoperative bleeding control have been important factors for the improvement of surgical results [1].

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The low mortality in specialized unit has extended indication for HRs, allowing surgeons to perform extreme procedures in patients considered unresectable 20 years ago. Among these extreme procedures, HR with associated vascular resection and reconstruction, ex vivo surgeries and other organs simultaneous resection can be mentioned.

The incidence of complications and perioperative mortality varies, in several publications, between 15–45% and 0–25% respectively. Factors that conditioned these results are experience of the surgical team, type of tumor (benign vs. malignant), the moment of indication (elective, urgency, emergency resection), extent of resection, parenchymal quality of the future liver remnant (steatosis, steatohepatitis, fibrosis, cirrhosis, post-chemotherapy changes) and patient selection (comorbidities). The different criteria utilized to define complications, the inclusion (or not) of mild complications (Dindo-Clavien's Grade 1 and 2) explain the variability on the results and the differences in morbidity rates in the literature [1–8].

Reoperations to solve postoperative complications vary between 3 and 19%. The most frequent cause of reoperations is postoperative bleeding and intra-abdominal collections.

Different factors have been associated with the development of postoperative complications. In a series published by the Memorial Sloan-Kettering Cancer Center in New York, on 1803

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consecutive patients, the conditioning factors for complications were: blood loss, number of resected segments, preoperative hypoalbuminemia, high serum creatinine level, associated biliary procedures, associated vascular procedures, males and associated comorbidities. The first two factors were also independent predictors of mortality; together with preoperative hyperbilirubinemia, thrombocytopenia, complex resections and age [8].

In this chapter, only local specific postoperative complications related to HR will be described (general complications and other complications common to other surgeries will no be mentioned).

Post HR Liver Insufficiency

With the development of liver surgery, attempting to achieve negative margins and to improve perioperative survival, indications for HR have been extended. Among these indications, extended HRs, HRs in cirrhotic livers, resections in post-chemotherapy damaged livers, re-resections and two-staged liver resections are the most challenging procedures. A small future liver remnant (FLR) and those patients with an impaired liver function, the risk of a post-hepatectomy liver insufficiency is high. In fact, liver insufficiency is the result of an insufficient liver remnant (in volume and quality) to maintain patient's physiological needs.

Despite of the development liver functional tests, the volumetry assessment guided by radiological imaging and the use of portal vein embolization, post-HR liver insufficiency is the main cause of mortality related with the procedure.

Liver insufficiency is usually self-limited until definitive hepatic regeneration is reached. However, persistent insufficiency decreases protein synthesis and it generates immunological problems (through Kupffer's cells). These factors increase infectious complications, anastomotic dehiscence conditioning impairment of patient's clinical status and worsening of liver insufficiency. In more severe cases, patients could dead after multi-organic failure and sepsis.

Definition

According to different series, liver insufficiency varies between 1.2% and 32%. The variations depend on differences among patients, the procedures and the criteria used to define this condition.

In 2008, the International Study Group of Liver Surgery (ISGLS) organized a Consensus Conference to define a unified definition of post-HR liver insufficiency. The group revised more than 50 different criteria utilized in different papers [2].

Based on the fact that liver insufficiency is transient and it usually solves at postoperative day 5, the ISGLS proposed a new definition.

Liver insufficiency is defined as an acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, liver insufficiency is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out [2].

Hepatic insufficiency severity varies from a transient laboratory test alteration up to a sever condition that could lead the patient to death. For this reason, the new definition defines different grades of post-HR liver insufficiency (Table 25.1).

Table 25.1 Grades of post-hepatectomy liver failure (Consensus of the International Study Group for Liver Surgery, ISGLS) [2]

A	Deterioration in liver function tests with no modifications needed in the clinical management of the patient
B	Deviation from expected post-operative course without requirement for invasive procedures
C	Multi-system failure requiring invasive procedures

Table 25.2 criteria used to assign a post-hepatectomy liver failure grade according to the consensus of the international study group for liver surgery (ISGLS)

	Grade A criteria	Grade B criteria	Grade C criteria
Specific treatment	• No requirement	• Fresh frozen plasma • Albumin • Diuretics • Non-invasive ventilation • Intermediate or Intensive Care Unit	• Intensive Care Unit • Vasoactive drugs • Glucose infusion • Hemodialysis • Invasive ventilation • Extracorporeal liver support • Salvage hepatectomy/liver transplantation
Liver function	• Normal prothrombin activity (INR < 1.5) • No neurological symptoms	• Abnormal prothrombin activity (RIN ≥ 1.5–2) • Mild—moderate neurological symptoms (confusion)	• Abnormal prothrombin activity (RIN ≥ 2) • Severe neurological symptoms • Hepatic encephalopathy
Renal function	• Adequate diuresis (> 0.5 mL/kg/h) • BUN < 150 mg/dL • No symptoms	• Inadequate diuresis (≤ 0.5 mL/kg/h) • BUN < 150 mg/dL • No symptoms	• Renal failure, no response to diuretics • BUN > 150 mg/dL • Uremic syndrome symptoms
Lung function	• Arterial 0_2 saturation > 90% • 0_2 supplementation if needed	• Arterial 0_2 saturation < 90% despite 0_2 supplementation	• Refractory severe hypoxemia • Arterial 0_2 saturation ≤ 85% despite high fraction of inspired oxygen support
Additional assessment	• No requirement	• Abdominal US/CT Scan • Thorax Rx • Sputum, blood, urine culture • Brain CT Scan	• Abdominal US/CT Scan • Thorax Rx/CT Scan • Sputum, blood, urine culture • Brain CT Scan • Intracranial pressure monitor

The grade of liver insufficiency is classified according to the worst patient's condition (Table 25.2) [2].

Prevention

In Table 25.3, different measures that need to be taken into account to prevent the risk of post-HR liver insufficiency are described.

One important factor is the pre-existence of liver parenchyma diseases, which could limit the extension of HRs and the patient's possibility to tolerate an HR. The presence of cirrhosis, fibrosis, steatosis and/or chemotherapy associated hepatic toxicity are factors that the surgeon has to assess prior to surgery. These different conditions determine an impaired hepatic functional reserve and a minor hepatic regeneration rate; with an increased morbidity, mortality and post-HR liver insufficiency rate.

In cirrhotic patients, the Child Pugh's classification is important to determine liver function

Table 25.3 main issues to be taken into account to prevent the risk of post-hepatectomy liver failure

Patient selection	• Assessment of prior hepatopathies
	• Classification of cirrhosis (if present)
	• Functional tests
Procedure selection	• Parenchymal sparing resections
	• In extreme cases, consider alterative treatments (chemoembolization, thermoablation, etc.)
Preoperative preparation	• Laboratory test
	• Future liver remnant volumetry
	• Manipulation of the insufficient future liver remnant
	• Clinical conditions improvement: selective preoperative biliary drainage, nutritional support.
Surgical technique	• Intraoperative bleeding control
	• Parenchymal sparing resections/two-stage resection.

and to select and categorize patients. In Child Pugh A patients, HR can be performed and a 50% of the total liver parenchyma can be resected; in Child B patients up to a 25% and in Child C HR is contraindicated and other procedures should be considered (Transarterial chemoembolization [TACE], portal vein embolization [PVE], radiofrequency ablation [RFA]) [6].

The Model for End-stage Liver Disease (MELD) score is a mathematical model described initially to evaluate the short-term results of the Transjugular Intrahepatic Portal Shunt (TIPS) placement. Posteriorly, the MELD score was used to determine priority for patients on the waiting list for liver transplantation. Most recently, the MELD is also used as a prognostic factor to develop post-HR liver insufficiency. Different series showed that, in the preoperative assessment of cirrhotic patient undergoing an HR, a high MELD score presented higher risk to develop liver insufficiency (using a cut off of nine points: liver insufficiency 0% vs. 29%, and using 11 points: 0% vs. 37.5%). It has also been showed that and initial MELD >11 points prior to HR, with an increasing value between the 3rd and 5th postoperative day, is an independent factor for the development of post-HR liver insufficiency.

There are different tests to globally assess the liver function (indocyanine green clearance test, Limax test, MEGX, etc.) that allow stratifying patient's risk for liver insufficiency. However, they are not available worldwide; in this case patient's clinical history, symptoms, laboratory tests and imaging should be carefully evaluated prior to HR.

In all patients undergoing HRs, a volumetry of the Future Liver Remnant (FLR) should be carried out. The FLR volume has to be assessed according to patient's weight or body surface area and the Total Liver Volume (TLV). CT-scan and MR can be used to precisely determine the FLR volume. The total liver volume can be also calculated with the same studies or using any of the available formula, such as:

$$TLV\left(cm^3\right) = 706 \times \text{body surface area}\left(\text{m}^2\right) = 2.4$$

The most important ratio is between the FLR and the TLV (FLR/TLV) and patient's weight (FLR/weight). It is recommended to preserve a 25% of the TLV in patients with normal livers, >30% in patients with diseased livers (steatosis, chemotoxicity, etc.) and >40% in cirrhotic patients.

The accepted ratio between FLR/weight is 0.8. This ratio is widely used in living related donor liver transplantation. The advantage of this ratio is that is independent from the resected volume. It is also useful to preoperatively determine, in those patients who will undergo an extended HR, who will need a procedure to increase or to preserve the FLR.

In those cases in which the pre- or intraoperative assessment determines an insufficient FLR, portal vein occlusion (either by ligation or PVE) should be indicated. With these techniques, a degree of hypertrophy of 10–40% in 4–8 weeks is achieved and HR can be safely performed afterwards. However, a group of patients cannot be resected using these strategies due to an insufficient hypertrophy or due to an accelerated tumor growth. For this reason, it is important to rule out (before PVE) the presence of tumor in the FLR.

There is a new surgical strategy to increase the FLR volume (reducing the post HR liver insufficiency) denominated Associated Liver Partition and Portal vein occlusion for Staged hepatectomy (ALPPS). This two-staged surgery consists in a first procedure where the tumors from the FLR are removed, the hepatic transection is performed and the portal vein is occluded; and a second procedure where the HR is performed, usually 7–10 days after the first one. With this new strategy, a faster and greater FLR hypertrophy is achieved (up to a 200% in 7–10 days). When the ALPPS procedure is carried out, the number of R0 patients is higher than simple portal occlusion (in an intention to treat analysis). Another advantage is that in ALPPS, due to the possibility to resect the nodules in the FLR, patients with bilobar and multiple tumors are amenable to undergo surgery. However, as ALPPS is a new procedure, further studies on oncological long-term outcomes are needed.

When a HR is performed, the surgeon should try to do non-anatomical resections and to spare as much parenchyma as possible (local and multiple resections vs. extended resections). During resection, Pringle's maneuver and low central venous pressure (<5 cm H_2O) are necessary to decrease the blood loss.

There is no consensus on the algorithm to treat patients with obstructive jaundice in proximal biliary tumors that will need a HR. There is no evidence whether the patient should be percutaneously drained or not (prior to surgery). Patients with cholangitis, coagulopathy, malnutrition, or patients who will undergo PVE, percutaneous transhepatic biliary drainage (PTBD) is mandatory. However, there is no evidence to routinely perform a PTBD based only in bilirubin levels [5].

Treatment

Hepatic insufficiency has no specific treatment. The aim is to correct metabolic alterations (acidosis, hypoglycemia), coagulopathy and hypoalbuminemia; encephalopathy has to be treated and infections should be prevented and eventually treated. These symptoms need to be treated in order to let the liver to regenerate. Extracorporeal hepatic support is possible, but indications are still limited and controversial.

Bile Leaks

Despite the advances in liver surgery, bile leaks are still a major cause of postoperative morbidity. Bile leaks increase hospital stay; require abdominal drains for long periods of time and additional diagnostic imaging and/or therapeutic interventional procedures. In more severe cases, bile leaks could cause patient's death [4, 7].

The incidence of bile leaks after HRs with no biliary reconstruction ranges from 3.6 to 12% and with biliary reconstruction between 0.4 and 8%. Usually, bile leaks are minor (a small amount of bile leakage, or an amount that decreased daily), self-limited and are related to small ducts in the cut surface. If the amount of bile leakage is high and/or persistent, an injury of the main bile duct (or a dehiscence of a biliodigestive anastomosis) has to be suspected.

The variation among different reported series on post HR bile leaks was due to the lack of consensus on a definition. In fact, in most of the series an arbitrary cut-off (of the bile leak volume and the fluid's bilirubin concentration) was defined. In 2011, the International Study Group of Liver Surgery (ISGLS) published a consensus establishing a definition for post HR bile leak. They define a bile leakage as fluid with an elevated bilirubin level in the abdominal drain or intra-abdominal fluid on or after post-operative day 3 or the need for radiological intervention (i.e. interventional drainage) owing to biliary collections or re-laparotomy due to biliary peritonitis. The elevated bilirubin level in the drain or intraabdominal fluid is defined as a bilirubin concentration at least three times higher than the serum bilirubin level measured at the same time. The ISGLS also proposed 3 grades of severity, based on the therapeutical management of this group of patients (Table 25.4) [4].

HRs with high risk of bile leakages are right anterior sectionectomies, caudate segmentectomies and central resections (segments 4 and 5).

Table 25.4 Definition and grades of bile leakage (Consensus of the International Study Group for Liver Surgery, ISGLS)

Definition	Fluid with increased bilirubin concentration (at least 3 times greater than the serum bilirubin concentration) in the abdominal drain or in the intra-abdominal fluid on or after postoperative day 3.
Grade	
A	Bile leakage requiring no or little change in patients´ clinical management
B	Bile leakage requiring a change in patients´ clinical management (diagnostic or interventional procedures) but manageable without relaparotomy, or a Grade A bile leakage lasting for >1 week.
C	Bile leakage requiring relaparotomy.

This risk is due to the small ducts of the caudate segment and the anatomical variations of the posterior right section ducts (specially those ducts emerging from the left hepatic duct). In HRs of the right lobe, leakages can be persistent, probably because of the negative pressure generated by diaphragm's movements.

Treatment

Treatment depends on leakage's volume, clinical presentation and patient's performance status. In those patients with abdominal drain in place, asymptomatic, low volume leak with no associated fluid collections, leakage usually solves spontaneously.

However, even if the drain is in place, fluid collections may appear. For this reason, abdominal ultrasound or CT Scan are mandatory. If there is any modification on the normal postoperative course, the algorithm proposed in Fig. 25.1 is suggested.

In those cases with no abdominal drains (or if the leakage appears after the drain removal) the patient will develop a biloma or a choleperitoneum. A delay on the treatment will condition a deterioration of the patient and septic complications.

The initial procedure to treat bilomas is percutaneous drainage. If biliary hypertension is not present, probably the leakage will close spontaneously. In those cases were the leakage persists, a fistulography might be useful to determine the cause of the persistence. If an obstruction is demonstrated (lithiasis or stenosis), an ERCP is mandatory. Percutaneous biliary drainage is an

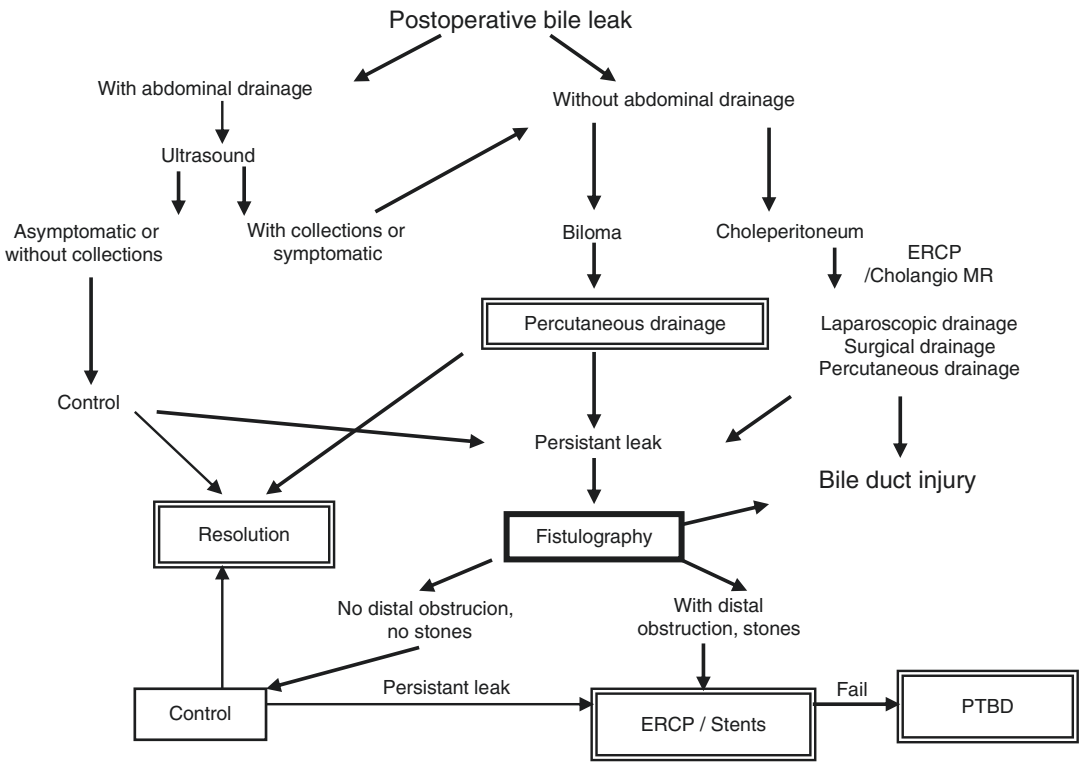

Fig. 25.1 Algorithm for the management of postoperactive bile leak

excellent procedure for biliary leakages when ERCP is contraindicated or when ERCP previously failed; sometimes is the only measure to close the biliary leakage.

In choleperitoneum, endoscopic diagnosis and treatment might be useful. In selected cases, a magnetic resonance cholangiography (MRCP) or an intraoperative cholangiography could be performed (cystic duct leakage, bile duct injury).

The choleperitoneum can be drained either by laparoscopy, laparotomy or through a percutaneous drainage. The laparoscopic approach allows to perform a complete peritoneal exploration, irrigation and aspiration. Laparoscopy provides the advantage of this approach, avoiding abdominal wall complications (usually present in the open approach). A cholangiography can also be repeated or carried out for the first time (if it was not performed during the first surgery). The cause of the leakage can be repaired, such as cystic duct fistulae, aberrant ducts, small and partial bile duct injuries. The difficulties of the laparoscopic approach are the limitation to solve complex bile duct injuries and the learning curve for laparoscopic reinterventions.

Percutaneous drainages consist in the placement multiple catheters in predominant bile collections. The advantages are those of the minimally invasive approach; the disadvantages are the requirement of multiple catheters, the potential risk of an unadequate drainage of an abdominal section and the need of periodically reevaluation by images such as a CT-Scan.

The advantage of the laparotomic drainage is that complex bile duct injuries can be solved; the disadvantages are abdominal wall complications and a longer postoperative recovery.

Fistulography generally shows the dimension of the leakage. If a major bile duct is injures, the leakage is uncontrolable and an early (endoscopic or percutaneous) decompression has to be carried out. Reoperations are excepcionally needed and they should be early performed to avoid firm adhesions and abscesses that could condition difficulties in the identification of the biliary injury and/or leakage. Reoperatios are usually associated in increased mortality.

Endoscopic decompression in ineffective in bile leakages not communicated with the mail biliary tree.

Prevention

Ligature and primary closure with separated stitches or running sutures of small ducts, the use of intraoperative hydraulic tests or the injection of dyes should be done when there are concern or risk of postoperative bile leaks.

Intraoperative tests such as instillation of isotonic solutions, air or methylene blue and intraoperative cholangiography through the cystic duct are useful to demonstrate leakages of small ducts connected with the main biliary tree. It is ineffective to diagnose leakages in ducts not connected to the biliary ducts (in no anatomical resections or intrahepatic biliary anatomical variations).

Hemorrhage

Despite of the development of hepatic surgery, post resection hemorrhage is an important cause of morbi-mortality. Also, several studies demonstrate that the need of postoperative transfusions impacts on oncological outcomes.

According to different series, the incidence of post-HR hemorrhage varies between 1 and 10%. This variation is due to the lack of a standard definition of hemorrhage. For this reason, the International Study Group of Liver Surgery (ISGLS) published a consensus on this topic. This paper states a new definition and categorizes degrees of severity of post-HR hemorrhage (Tables 25.5 and 25.6) [3].

The two most common causes of hemorrhage are: (1) bleding of the HR's surface and (2) coagulopathies.

Table 25.5 Definition and grade of post-hepatectomy hemorrhage (Consensus of the International Study Group for Liver Surgery, ISGLS)

Definition	• A drop of hemoglobin level > 3 g/dL after the end of surgery compared to postoperative baseline level and/or any postoperative transfusion of PRBC for a falling hemoglobin and/or the need for invasive re-intervention (e.g. embolization of re-laparotomy) to stop bleeding. • To diagnose hemorrhage, frank blood via the abdominal drain should be obtained (e.g. hemoglobin level in drain fluid > 3 g/dL) or detection of an intra-abdominal hematoma or active hemorrhage by abdominal imaging (ultrasound, CT Scan, angiography). Patients who are transfused immediately postoperatively for intra-operative blood loss by a maximum of two units of PRBCs (i.e. who do not have evidence of active hemorrhage) are not diagnosed with post-hepatectomy hemorrhage.
Grade	
A	Hemorrhage requiring transfusion of up to 2 units of PRBCs
B	Hemorrhage requiring transfusion of > 2 units of PRBCs but manageable without invasive intervention
C	Hemorrhage requiring radiological interventional treatment (e.g. embolization) or re-laparotomy

PRBC, packed red blood cells

Bleeding of the HR's Surface

The lack of vascular control or the late utilization of it, together with a deficient anesthetic technique can lead to hemorrhages. Excessive blood in the operative field impairs visualization and adequate control and ligation of vascular and biliary structures leading to an increased rate of biliary leakages and postoperative hemorrhages. To avoid this situation, a exhaustive control and ligation of all vascular structures must be performed. Hemostatic stitches generate regional ischemia, necrosis and infection, for this reason and if it is possible, they should be avoided. Other cause of hemorrhage is a sudden increase in central venous pressure. This kind of bleeding occurs within the first 48 h after HR and it is usually diagnosed by the abdominal drainages. If the bleeding is persistent, reintervention is mandatory for a correct hemostasia. It is important to control bleeding and to perform a correct hemostasia before finishing surgery.

Coagulopathies

These can be secondary to: (1) improved function of the FLR due to prolonged ischemia or prior

Table 25.6 Common clinical characteristics of patients with different severity grades of post-hepatectomy hemorrhage (Consensus of the International Study Group for Liver Surgery, ISGLS)

	Grade A	Grade B	Grade C
Clinical condition	• Not impaired	• Impaired	• Life-threatening
Symptoms	• No	• May have hypotension and tachycardia	• May have hemodynamic instability (severe hypotension and tachycardia). Potential hypovolemic shock with organ dysfunction/failure.
Adequate response to transfusion of PRBCs	• Yes	• Yes/no	• No
Need for diagnostic assessment	• No	• Yes	• Yes
Radiological evaluation	• Possible free intra-abdominal fluid/hematoma	• Free intra-abdominal fluid/hematoma. • May have active bleeding on angiography.	• Free intra-abdominal fluid/hematoma. • Active bleeding on angiography.
Hospital Stay	• Commonly not prolonged	• Commonly prolonged	• Prolonged
Specific treatment	• Discontinuation of anticoagulants. • Intravenous fluid therapy. • Transfusion of ≤ units of PRBCs	• Discontinuation of anticoagulants. • Intravenous fluid therapy. • Transfusion of > 2 units of PRBCs.	• Discontinuation of anticoagulants. • Intravenous fluid therapy. • Transfusion of PRBCs. • Vasopressor therapy. • Embolization and/or re-laparotomy.

PRBC, packed red blood cells

hepatic dysfunction (e.g. cirrhosis); (2) intraoperative hemorrhage or massive blood transfusions; (3) hypothermia during surgery; (4) heparine overdose after arterial or portal catheterization; (5) coagulation factors and platelets consumption due to hematomas or local infections; (6) cardiopulmonary bypass with extracorporeal circulation pump.

Prevention

It has been already commented the importance of an adequate FLR (volume and function). Is mandatory to assess the FLR in preoperatively. An correct anesthetic technique and the use of vascular intermittent clamping (Pringle's Maneuver) decrease intraoperative bleeding and blood transfusions. The absence of bleed in the operative field allows a correct visualization and a selective ligature of vascular and biliary structures, preventing biliary leakages and hemorrhages. It is important to preserve patient's temperature to prevent hypothermia, especially in prolonged procedures (due to constant fluid reposition and frequent abdominal perfusion). Hypothermia can be prevented by the use of external healing devices and the perfusion using normothermic fluids. The development of modern liver surgery also decreased the use of extracorporeal circulation pump for HRs. The correct management of coagulopathies is based on an adequate preoperative diagnosis and reposition of coagulation factors using cryoprecipitates, platelets, red blood cells and fresh frozen plasma transfusion.

Abdominal Collections

Abdominal collections are the most frequent postoperative complication in all abdominal surgeries. The incidence rate varies between 5.8 and 28% according to different series [7, 8]. The presence of a residual cavity with blood and/or bile after HRs and a relatively ischemic parenchyma, create an ideal environment for the development of a collection and infection. Most of the cases are successfully solved by a percutaneous drainage. Laparoscopic and laparotomic approaches are limited for those cases where the percutaneous drainage failed or when necrotic hepatic parenchyma is present.

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Improving Quality of Life in Patients with Unresectable Disease

26

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Introduction

Colorectal is one of the most frequently diagnosed cancers, with high incidence and mortality; 70% of patients develop liver metastasis. Without treatment, the median survival in this population is 6–12 months. Although surgical resection is the gold standard for colorectal liver metastasis (CLM) treatment, achieving cure or enhancing survival is currently possible in many patients; others are not surgical candidates because of insufficient residual liver tissue, extrahepatic disease, anatomic constraints of the tumor, or medical comorbidities [1]. For this group, palliative therapy remains the only option: it permits local symptom control and prolonged survival in some cases. As established methods are continuously improved, new palliative therapies are tested in clinical trials and subsequently introduced into clinical practice. The present review provides an overview of current CLM treatment, with or without resection. This chapter gives the basis for an interdisciplinary and integrative approach [1, 2].

Palliative care (PC): It is a type of care that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of avoidable suffering (WHO). It is made up of actions in the physical, psychological, social, and spiritual fields which promote well-being and meaningful life experiences during the course of the illness [3].

We will describe two ways of providing PC:

1. **Primary PC or palliative approach**: this is the PC standard that must be provided by all the reference teams, such as surgery, internal medicine, oncology, etc., within their ordinary duties of patient care. In surgery in particular, this includes highly-specialized surgical procedures of palliative intervention.
2. **Palliative care as specialty**: this is the standard of care provided by a trained interdisciplinary team in order to solve problems which are persistent or complex from the perspective of symptoms or are of a psycho-socio-existential nature. Thus, it is proposed that patients who cannot be alleviated by the intervening base team are referred to specialized PC teams [4, 5]. A PC intervention can be performed at *any time during the course of the cancer progression*. A distinction must be made between *Early PC* and *PC at the end-of-life stage*. The concept of continuous or integrated PC during all the course of the cancer does not restrict the application of this outlook exclusively for the end-of-life stage [2, 4–6].

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PC is an addition and a complement to curative or palliative interventions by the specialties which treat the base pathology. Therefore, even if PC has developed mainly in patients with advanced cancer, every situation with a high level of suffering, in any dimension, may be assisted with an approach focused on care, which may complement specific treatment of pathologies such as surgery or oncology-specific treatment.

PC team: the comprehensive assistance of patients and their families requires a multidimensional, interdisciplinary approach. The team can be made up of specialists in different areas: doctors, nurses, psychologists, social workers, occupational therapists, spiritual advisors, and volunteers, among others.

Teamwork: this is a challenge, requiring fluent interaction and dialogue, speaking a common language, and keeping all the different specialties in a symmetrical relationship. Individual responsibility, a proactive attitude, and respect for one another are of paramount importance.

A PC team relates and integrates to other teams assisting the patient (surgery, oncology, radiotherapy, anesthesiology, and others) [2].

The benefits of this type of work can be described both at the level of assistance to patients and families and at the level of the members of the teams. In connection to this last point, we can highlight emotional support, prevention of burnout syndrome, reciprocal training, and the opportunity of sharing experiences and hard decisions [6, 7].

In order to achieve better results, it is key to work in relationships of cooperation, coordination, and flexibility among the different professionals that compose the team that provides care (primary doctor, hospital and home teams, etc.). The primary doctor and/or specialty consultant has a pivotal role, and specialized PC teams ideally act as support. An interdisciplinary approach is required to provide PC, but specialized teams made up of all the professions will not be required for each patient.

The team's structures must be adapted to the needs of the population, its culture, and its healthcare system, so that there are hospital support care teams, outpatient care teams, hospitalization units, hospices, home-based care teams, and day centers.

It is crucial that different levels of care and different structures of PC work seamlessly in order to adequately respond to each situation.

Interaction Between Surgery and Palliative Care in the Case of Planning a CLM Resection

This book shows that the limited possibilities available for the treatment of unresectable colorectal metastases are no longer the rule. Therefore, to provide optimal outcomes for patients with CLM, it is imperative to consider all treatment options available based on each patient's comorbidities and tumor extent and available technical and professional resources [8–11].

When the teams of surgery and PC collaborate, these are the fundamental questions they need to pose:

- What is the support PC can provide to oncological surgery? What support can oncological surgery provide to PC?
- Which are the benefits to be expected from their interaction?

Thus, it is possible to plan strategies, adapt them to the needs of each patient, the team that provides him care, and his affective environment. These strategies should deal with:

- Pain management and control of other symptoms (anorexia, nausea, itching, etc.).
- Psycho-socio-spiritual support
- Joint deliberation for decision-making, recognizing that each case is unique regarding: communication with patient and family, tests or procedures that can be diagnostic or therapeutic, and type of follow-up chosen (surgery with PC support, surgery and PC, PC with surgery support, or PC exclusively).
- Help in practical issues to set up care: in an institution or planning the release.

- Assessment and reciprocal inter-professional support for the follow-up of complex cases.
- Assessment of palliative surgical treatment, even in patients with advanced illnesses who are initially referred exclusively to PC, in order to avoid their under-treatment due to their being palliative patients.

Even if the word, applied to surgery, has historically had a connotation frequently associated to therapeutic failure, surgeons have a lot to offer for symptom control and the improvement of quality of life for patients with advanced illnesses.

PC during surgical care is, most of the times, more about rediscovery and relabeling and not of learning new ideas. Palliative surgery makes up a significant share of a surgeon's professional practice. Despite it being less common that surgeons receive formal training in PC, many recognize the palliative nature of a great part of their daily work.

Decision-Making and Communication

Decision-making in the context of an oncological patient with CLM should not differ from others: a joint discussion between patient, family and team about the recommended interventions, respecting the patient's wish once his competence is ascertained [12, 13].

Every decision-making process entails truly informed consent, one which is autonomous and competent on the part of the patient, and also an instance of joint discussion with the attending team.

Nevertheless, in the context of a patient with CLM diagnosis, be it potentially resectable or not, we must acknowledge that there are unique aspects for decision-making: these involve ethical, clinical, and communication aspects. Truthful information on diagnosis and prognosis is essential for a proper decision-making process to take place. There are two situations that can make therapeutic dialogue and deliberation harder: reluctance to communicate truthfully and violent truth [14].

Reluctance to talk about diagnosis and possible prognosis is something that can affect both healthcare professionals and patients, and even the patient's relatives in some cultural contexts. If communication is ambiguous, or one is afraid to face reality, any analysis could turn out to be erroneous, particularly when the ambiguity is in the diagnostic information. On the other hand, providing information harshly should be avoided, as should be not adapting to the time a patient needs to process the situation in the least traumatic way.

In these cases, it is important to take into account that:

1. The patient is a subject with different degrees of vulnerability and needs a gradual approach to the truth of his clinical condition, and his real possibilities.
2. Honest dialogue, even if painful on occasion, is one of the building blocks of trust and cooperation in the doctor–patient relationship.
3. Vulnerability is not synonymous with incompetence.

Thus, communication is one of the main tools in health care. A powerful barrier is scarce, incomplete, or evasive information which the patient or family often face. Our task, then, is to explore what the patient knows and how much he wishes to know. Then we will assess how to gradually offer options and professional support, so that the patient and family can adapt to all the new and difficult situations they are going through. Focusing on communication with the patient with this outlook means that the healthcare team will strive to achieve what is best for him, with regard to the subjective parts.

For the communication of diagnosis, it is necessary to establish a possible action plan. For this, it is key that professionals talk to the patient and his affective environment with an accessible vocabulary, and permanently confirming understanding. Special attention should be paid to convictions and relationship conflicts which could affect decision-making.

The goal of communication should be for the patient to feel listened to and helped to explore

his innermost motivations to receive or reject treatment, as well as his preferences and fears at each stage of the illness.

It is also necessary to take into account that families can be dysfunctional or complex, and this affects the course of the illness and the way decisions are made.

The communication of goals in surgery, cure, attempts to control the disease's progression, or providing PC, is paramount, and has emotional implications for patients, relatives, and doctors. Other interventionist practices for specific treatment of pathologies that will be addressed in other chapters of the book are: systemic chemotherapy, regional techniques, thermoablative methods, radiofrequency ablation, vascular embolization, transarterial chemoembolization, and placement of stents or perihepatic catheters, among others [1].

Communicating in a sincere and cautious way, promoting ideas of hope of relief and togetherness, will be beneficial to all.

Competences in the areas of communication and decision-making regarding PC can be achieved through *specialized training*, even when these areas have not been discussed during in the undergraduate studies. This is the reason, and given the high frequency of palliative surgeries (with the technical and emotional complexities they entail), that the American College of Surgeons has created a Task Force of Palliative Care, and the American Board of Surgery has demanded that all residents receive training in the psychological support of patients, and in symptom control [15–17].

Contents in the process of communication and discussion of a surgery of resection of hepatic metastases:

- Goals of the surgery, possibilities of cure or palliative effects
- Details of the surgery or of interventionist procedures
- Estimated time of recovery
- Care in the short and mid- term after surgery
- Possible complications
- Possible evolution (cure, lengthening of life, palliative effects on complications, etc.)
- Availability of therapeutic support in the case of surgical non-resectability

These issues are quite emotionally moving, and they might affect the full understanding of all the information provided. This is why it is important to conduct the interview respecting privacy, with enough time, using open questions that will allow for the assessment of needs and preferences in the communication to patients and their affective environment.

If there isn't enough time to devote to every necessary issue, it is advisable to plan for shorter successive meetings, and prioritize subjects according to needs.

In addition to all this, we also have to take into account the nature of the surgical team–patient–family relationship, which in some cases is almost non-existent, or is too recent, which complicates consultation and the decision-making process which could lead to having or not having surgery. All of these are new challenges in the team–patient–family relationship. Some teams have the possibility of including a psychologist, who will help with the diagnosis of the psychosocial needs of the patient and his affective environment.

Role of the psychologist: The aim is to work with issues of the patient–family care unit at the same time as he supports the intervening team. The term "family" is made extensive to everybody who is affectively significant, such as friends, religious community, etc.

Psychological Response: **Stress and Adaptation**. An oncological disease is a stressful and painful situation that an individual will have to adapt with any resources available to him: cognitive, emotional, social, related to their family, economic, spiritual, and from their healthcare context. It creates a discontinuity in their personal history; sometimes it is a break, and sometimes it brings about personal growth. Nothing is ever the same after a diagnosis of serious illness: life plans, from the short to the long term, will be affected and transformed. Uncertainty starts taking on a central role; and with it, several fears arise, and the need to make important decisions. Each patient's *psychological response* will depend both on what they have to go through and the particular way they find to confront it, and the

meaning they give it in order to assimilate the disease to their lives, with the support they receive from their care team.

This *psychological stress* is a particular relationship between an individual and his environment, which is perceived as a threat to his resources and his well-being .The cause of suffering is not only facts, but the subjective meaning that is attributed to them. The experience of impotence when faced with adversity will always have the personal hallmark of each individual.

There are other stressful aspects associated to disease and treatment:

- Threats to: life, physical integrity, well-being, self-image, self-esteem, changes in body image, sexuality, loss of autonomy or of ordinary roles, future plans, long-term life plans.
- The need to adapt to a new environment (doctor's appointments, hospital stays) and having to make tough decisions.

Adaptation is, then, a process of psychological adjustment of resources in order to confront the illness in the long term. Its highest aspiration is to integrate the illness to life.

Maladaptive Response: There will be an emotional impact (EI) which will be normal and anticipated, and part of the "normal response", which will have different stages, each one with particular characteristics: *before the diagnosis, when it is confirmed*, *with treatment, and in connection to prognosis.*

If the illness has not responded to treatment, or if there isn't any treatment available, the adaptation to incurability and the possibility of dying emerge, in all their emotional expression and dimension. The psycho-spiritual task is vast, and setbacks and progress will be unique for each individual. A main goal of this process will be to preserve as high a quality of life as possible.

If personal resources, family support, and professional help have been effective, the adaptation and the adjustment to the experience of the illness, its integration to the patient's life and the possibility of giving it meaning and hope may provide the patient with the long-sought peace he needs in order to go through it.

It is very important *not to pathologize the process*, to be able to listen, and assist patients and relatives with all the humanity and compassion professionals can muster. Emotional responses may be quite intense, and nevertheless be normal. An example of this is fear, a feeling that will appear, oscillate, and maybe linger until the end of the process, as long as the threat to life also continues. This extremely valuable signal, indicating a disproportion between the object of fear and the resources available to deal with it, will take on another, much greater dimension, for the sense of loss of control, anticipation of pain, or idea of death might emerge with an intensity never felt before.

It is crucial, both for patient and doctor, to see if that emotional disarray still persists, is harmful to quality of life, prevents decisions from being taken, or seriously affects relationships. In case any of that happens, it is recommended to consult with a psychologist.

Each person gets ill with his own life history behind, but at the same time we have a unique potential for change, as well as for growth, that we don't know about beforehand.

The tasks of a psychologist are to analyze therapeutic priorities and goals with the patient and his family. That is, to assess, design strategies, carry out psychological interventions, and provide support in every step of the way [18].

The goals of interventions are to alleviate emotional symptoms of the patient and family, support the coping with tasks linked to the disease, enhance control and self-sufficiency, and facilitate matters related to the existential dimension, pending issues, taking stock of one's life, reconciliations or mending relationships, among others.

During the clinical interview, and through therapeutic dialogue (focusing on the connection between individuals), it is crucial to produce an accurate assessment, with a flexible framework, and adapted to the present time. This will allow us to:

(a) Assess cognitive state, type of coping, degree and type of information, need or lack thereof of receiving further information.

(b) Identify the patient's needs, priorities, and resources (related to their personality, emotions, intellect, economy, family, and spiritual background).
(c) To know the life story of the patient and his family structure, the principal people in his support network, and care providers.
(d) To know how the patient expresses EI, if they are able to request and receive help, and if there are indicators of vulnerability.
(e) To distinguish adaptative responses from the ones that are not.
(f) To know the context of care and its resources it has.

The main criteria for referral or psychological intervention are: patient or family with signs of intense or persistent emotional or spiritual distress, behaviors which could be pointing towards dysfunctional adaptation, insufficient support, or physical symptoms which are difficult to control, as well as an emotional response which severely interferes with the capacity to find enjoyment, meaning, and connect with the patient. If past or present emotional restrictions are expressed through psychiatric symptoms (generalized anxiety, depression, suicidal ideation, personality disorders) the pain and other symptoms may be amplified, which generates great worry in relatives and the healthcare team.

Even if these would constitute valid reasons for intervention, emotional, and spiritual care must be available during the whole process.

The goals of family assistance are to facilitate the individual and group coping to the reality of the disease, to provide training for the better care of the patient, and to optimize his own support, decreasing his vulnerability to the crisis. Also, to promote a fluent relationship between the family and the healthcare team, train them to make decisions together with the patient and his team, and prepare them for the loss, in order to prevent a complicated bereavement.

Psychological support in PC has to deal with people that do not always have mental health issues themselves, or previous demands for psychological treatment. It is a situation of life crisis, and as such tackling it requires flexibility, an optimal use of time (which might mean from a single interview to years of follow-up), creativity, handling of different techniques, and sensitivity on the part of professionals.

Pain: Over 80% of cancer patients will suffer from pain at some stage of the illness, both early and late. This can be controlled effectively with simple measures in 70–90% of the cases. The rest of the cases will require more complex procedures, with the participation of specialists and the use of other strategies, pharmacological and non-pharmacological.

Postoperative pain: As described in an earlier section on the communication process and how to discuss a surgery of resection of hepatic metastases, management of postoperative pain is of paramount importance in surgery preparation. As part of the psychoprophylaxis, the guarantee of pain treatment is key to alleviating the stress of those who will undergo surgery.

It is crucial that surgeons work together with pain-specialized teams that are part of the structure that each institution has (anesthesia, pain, and PC).

Persistent pain due to cancer: A high percentage of patients on whom it is not possible to perform curative or palliative surgery show persistent pain, which requires assessment and a multi-dimensional approach [19].

Multi-dimensional Assessment: The assessment includes, firstly, the pain's location, intensity, characteristics, irradiation, time pattern, response to previous treatment, associated symptoms, emotional impact, cultural factors, etc. Secondly, the determination of the pathophysiological mechanism, and thirdly, the probable etiology, related or unrelated to cancer and its treatment. In patients with CLM, a dull ache is common in the right hypochondrium, or referred to the shoulder because of stretching of the liver capsule, or epigastric because of growth of the left lobe with stomach compression.

Predictive factors of pain management complexity: The neuropathic mechanism, somatization, substance abuse, cognitive failure, and alcoholism may condition treatment and may require greater doses of opioid, and are recognized as predictive factors independent of the poor prognosis of pain management [20].

Pharmacological Management: WHO's analgesic ladder is the main guide for the treatment of cancer pain [21, 22]. It is composed of three levels or steps which illustrate the selection process of a specific drug according to the intensity of pain:

1. Mild: acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs)
2. Moderate: mild opioids or strong opioids in low doses
3. Severe: strong opioids

In each step, the analgesic can be combined with adjuvants, drugs with analgesic effects for certain types of pain (anticonvulsant co-analgesics, antidepressants, corticoids) or which may be useful for the control of opioid side-effects (antiemetics, laxatives, etc.).

The treatment of pain must start at the step related to the intensity of the pain suffered by the patient. If a patient suffers from severe pain, a strong opioid such as morphine, oxycodone, or methadone must be directly prescribed, not starting with one of the first-step drugs such as acetaminophen or ibuprofen. If the pain is mild or moderate and/or adequate control is not achieved with NSAIDs or acetaminophen, second-step opioids must be prescribed, such as codeine, propoxyphene, or tramadol. It has recently been established that morphine and oxycodone, too, in low doses (≤30 or ≤20 mg/day respectively) may be used at this stage.

NSAIDs have a "ceiling effect" and must be monitored because they can bring about severe toxicity such as gastrointestinal bleeding, platelet dysfunction, and kidney failure. Furthermore, selective inhibitors of cyclooxygenase-2 may bring about adverse cardiovascular and thromboembolic reactions, and do not protect from kidney damage.

Degree of Response to Opioids and Analgesia–Side-Effects Balance

Opioids are first-line drugs for the management of moderate or severe pain caused by cancer. Pure agonists such as morphine, oxycodone, methadone, and fentanyl do not have "ceiling effect", and that is why one must gradually titrate the opioid dose until we reach a proper analgesia with absence of intolerable adverse effects.

General Guidelines for the Use of Analgesic Opioids

- Perform multi-dimensional assessment
- Select opioid according to the WHO's analgesic ladder
- Choose the most convenient route of administration, oral or SC.
- Plan the fixed intervals of administration to prevent the reappearance of pain.
- Prescribe *breakthrough doses:* prn, from 10 to 15% of the daily dose, to treat or prevent the crisis of interdose pain. The interval depends on the type of opioid and the route used (1 h with oral route, half an hour for SC, and 15 min for IV)
- Titrate the dose according to the analgesia/adverse effects balance until the one which controls the pain is found. There is no optimal or maximum dose for powerful opioid analgesics. For most patients, pain control is achieved with 200–300 mg of oral route morphine in 24 h or less, but some with severe pain might require higher doses, which have to be administered by specialized teams.
- Increase the previous doses by 30–50%, or add the breakthrough doses used in 24 h if the pain lingers.to here
- If it is necessary to reduce the dose, decrease the daily dose by 30–50% and assess response.
- Report on possible adverse effects such as drowsiness, constipation, and nausea, and how to prevent and treat them.
- Prevent/treat adverse effects with laxatives and antiemetics. Nausea with metoclopramide 10 mg every 4 h or domperidone: 10 mg every 8 h during the first 3–4 days, and constipation with bisacodyl 5–20 mg per day, or magnesium citrate 30 mL per day, every day.
- Address some of the misconceptions: the need to constantly increase doses to maintain the effect, the connection of their exclusive use to the end of life, substance abuse, and the loss of mental faculties, among others.

- Consider some of the warning guidelines that require anticipated contact with professionals: nausea, vomiting, drowsiness, confusion, hallucinations, myoclonus, and/or constipation longer than 3 days.
- Indicate, according to mechanism of pain, co-analgesic contributories. Corticoids are useful to treat pain caused by stretching of the liver capsule.
- Monitor response and adverse effects within 24/48 h at the start of treatment; and at least once a week when the situation is stable.

Examples of Treatment in Particular Situations [19]

(a) **Patient with moderate pain**, **without previous opioid treatment**:
- Codeine 60 mg every 4 h, or tramadol 50–100 mg every 6–8 h, or morphine: 2.5 mg every 4–6 h ± paracetamol 500 mg, oral route, every 4–6 h.

(b) **Patient with severe pain without opioids**, **or with persistent pain with weak opioids**:
- Morphine 10 mg every 4 h oral route, of immediate release (IR) or 5 mg every 4 h. IV/SC, or
- Oxycodone oral route, IR 2.5–5 mg every 4 h oral route, or
- Methadone oral route or sublingual, 2.5–5 mg every 8–12–24 h.

Methadone is an opioid of long half-life and great power, which requires expert handling and strict monitoring of the patient's condition.

(c) **Patient with persistent pain**, **in treatment with strong opioids without limiting adverse effects**:
Increase dose by 30–50%, or increase the number of breakthrough doses per day. For example: he receives one dose of 15 mg every 4 h (90 mg) with breakthrough doses of 10 mg. He needed six breakthrough doses to control the pain (a total of 90 mg + 60 mg = 150 mg per day). The new dose is now 25 mg every 4 h, and breakthrough doses of 15 mg.

(d) **Switch to sustained-release opioids (SR) in patients with controlled pain with IR opioids**:
1. Determine the daily dose in mg of the IR opioid in use (fixed dose + breakthrough doses).
2. Prescribe the equivalent dose of the SR opioid (**morphine** or **oxycodone**) split into two doses (every 12 h), or in three doses (every 8 h) if needed.
3. Prescribe breakthrough doses of IR opioid, preferably of the same opioid.
4. SR pills must be ingested whole; they mustn't be split or crushed.

(e) **Opioid switching in patients with persistent pain, and limiting adverse effects to opioids.**
A therapeutic strategy, that is to suspend the opioid being used and to replace it by another to restore the right balance of analgesia and adverse effects.
- Work out the daily dose of the opioid in use.
- Work out its analgesic equivalence to another strong opioid according to reference charts.
- Reduce the calculated dose by 25–50%.
- Replace opioids. Discontinue the rapid-action opioid being used, and simultaneously start with the new one. Totally or progressively discontinue the long-acting opioid being used, and progressively start with the new one. Set up a new scheme of breakthrough doses.

It is advisable that opioid rotation and the use of methadone are guided or performed by specialists, particularly if high doses are prescribed. For these procedures to be safe, round-the-clock professional care must be available for the patient.

Equianalgesic conversion chart: **10 mg of morphine oral route** are equivalent to approximately, 5 mg of morphine SC, 7 mg oxycodone oral route, 4 mcg/h fentanyl TD/SC/IV, 6 mcg/h of buprenorphine TD, 70 mg codeine oral route, and 6 mg tramadol oral route [19].

The conversion equivalences of morphine to methadone vary greatly, and depend on the dose

of the previous opioid: 1:4 if receiving <90 mg of morphine, 1:8 if receiving between 90 and 300 mg, and 1:12 if receiving <300 mg.

Opioids that are not recommended for the treatment of severe pain: Agonists such as **nalbuphine** or partial agonists such as **buprenorphine** have limited value because of their "ceiling effect", and because they can trigger withdrawal syndrome when given to patients already receiving agonist opioids. **Meperidine** is not recommended; it is only administered parenterally, it is short-acting (2–3 h) and it can bring about neurotoxicity because of the accumulation of its metabolite, normeperidine.

Conclusion

When surgery of CLM is possible, it allows to increase the likelihood of cure, survival time, and quality of life. All existing treatments must be complemented, through the integration of interdisciplinary strategies, surgical and non-surgical, as palliative care.

The delicate process of decision-making for this group of patients always has a great component of uncertainty, applied to the singularity of each individual. Thus, it merits a broad-scoped approach based on advances of technology, communication, symptom control, psycho-social and spiritual support.

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