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Foreword

As shown in this book, we have today a large variety of therapeutic options for patients with colorectal liver metastases. This would have been difficult to imagine some decades ago, when the only option was liver resection with narrow selection criteria.

In the 1980s, the consensus well established by the respected Mayo Clinic surgeons Drs. Stephen Wilson and Martin Adson [1] was that the only indication for liver resection was a solitary metastasis; there was no chance of long-term survival after resection of multiple lesions.

In the 1990s, a pessimistic view continued to prevail: in a debate article entitled "Resection of Liver Metastases from a Colorectal Carcinoma Does Not Benefit the Patient," Hunt et al. [2] stated, *"Survival after resection of small metastases is not markedly different from the natural history of similar tumours; patients with metastases apparently localised to one area of the liver are uncommon, and thorough investigation further reduces the proportion of such patients; the operative mortality of liver resection has a significant adverse effect on survival after resection, and may cancel out the benefits of surgery, and finally the alternative non-operative methods of treating these patients may offer similar benefits to resection."*

Despite these negative recommendations, some groups continued to perform hepatectomies in patients with colorectal liver metastases, gradually expanding the indications. Why not go beyond the Mayo Clinic recommendations and resect two or even more tumours located in the same lobe? At Paul Brousse Hospital, beginning in the early 1990s we decided to resect resectable liver metastases using major hepatectomies in association with segmentectomies. The paradigm changed from "resect only one" to "resect if resectable." But when we reported our approach at congresses in the United States, I had clearly the feeling that our message was received with skepticism.

Some years later, a new evolution occurred. While following patients with unresectable metastases receiving chemotherapy, we observed in some cases such a dramatic decrease in tumour size that resection became possible. Seeing that the outcome of resection in these cases was almost the same as the outcome of up-front resections in patients with initially resectable disease, we decided to consider liver resection for all patients with initially nonresectable disease if it was possible to resect all tumours after chemotherapy-induced downsizing.

The publication in 1996 of our paper "Resection of Nonresectable Liver Metastases from Colorectal Cancer After Neoadjuvant Chemotherapy" [3] showed the possibility of shrinking the tumour in order to permit resection, offering patients a chance of cure. In addition, this paper emphasized the shift in the role of chemotherapy from pure palliation to an essential element of multimodality treatment with curative intent. Neoadjuvant chemotherapy entered in force in the field of treatment of secondary tumours of the liver, and in the following years, the use of neoadjuvant chemotherapy was expanded to other digestive cancers: pancreas, colorectal, and esophagogastric cancers. Chemotherapy was the first neoadjuvant treatment, and others were later developed aiming to downstage tumours prior to surgical resection.

Surgery was no more the only therapeutic option, and the oncologist and the radiologist became important actors, creating the concept of multidisciplinary care.

This book perfectly shows the complete armamentarium in the management of colorectal liver metastases. Surgical techniques include a wide variety of resections: large and very large

resections (up to resection of 6 of the 8 liver segments), limited resections in the form of segmentectomies and sub-segmentectomies, associated hepatectomies in several parts of the liver, and use of two-stage hepatectomy and associating liver partition and portal vein embolization for staged hepatectomy (ALPPS procedure). Surgical possibilities can be enhanced by inducing pre-resection regeneration using portal vein and hepatic vein embolizations. There has been tremendous progress in anticancer drugs, with the development of new drugs, new regimens (doublet and triplet combinations, intra-arterial infusion), targeted or biologic therapies guided by tumour mutational status, and more recently immunotherapy. Interventional radiology, including percutaneous thermal ablation and radioembolization, is also playing a growing role. All these advances have led to the reappraisal of liver transplant for colorectal liver metastases, which may gain a place in the coming years.

Today, the patient is cared for not by the surgeon only but rather by a team of specialists proposing the best strategy for each patient.

For many years I wondered if a patient with colorectal liver metastases could be definitively cured without surgical resection. For many years, I did not think it was possible. But looking at all the progress made, I think that an increasing number of patients with this potentially lethal disease are being cured.

This book gives to all specialists an opportunity to learn the most recent advances in the management of this disease, which remains the most common indication for liver surgery.

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Foreword

Not quite a half century ago surgeons who dared to resect hepatic metastases from colorectal cancer reported the hoped for but unexpected cure in selected patients. Perhaps guided more from compassion than an understanding of oncology in an era of limited therapeutic alternatives, they provided the proof of concept of oligometastatic disease. In fact, to show that a distinct state of limited metastatic disease occurred as an intermediate step of cancer progression and extirpation of that disease had impact on survival, had tremendous clinical implications medically and surgically. While the impact of surgery on locoregional disease had long been established, resection of metastatic disease was a paradigm shift in clinical management. Early skepticism of clinical value gradually ebbed. Repercussions of these dated clinical observations have reverberated since and the management of patients with colorectal liver metastases has ever evolved. Subsequent progress in surgical techniques, systemic therapy, imaging, and cancer biology has redefined the clinical management of patients with colorectal liver metastases. The oncologic community now fully endorses the multidisciplinary treatment of these patients.

Worldwide the management of patients with metastatic colorectal cancer to the liver is a major focus of clinical oncology. Intermittent assessment of the state of the art is necessary for digestion, reflection, and future direction for clinician and scientist. *Colorectal Liver Metastasis* offers a timely state of the practice edited by three seasoned clinician-scientists. This ambitious undertaking highlights the essential importance of multidisciplinary management to improve survival in patients with stage IV metastatic colorectal cancer. Nearly half of the volume focuses on surgical management by reputable experts. Patient selection, perioperative therapy, preoperative hepatic intervention, surgical approaches from nonanatomic resection to liver transplantation and one- or two-stage resections and postoperative adjuvant therapy are addressed and integrated into coherent management schemes. The clinical and biological heterogeneity of patients is accounted and consequential impact on outcomes reviewed. Adjunctive and alternative liver-directed therapies, including ablation, radioembolization, and hepatic arterial infusional chemotherapy, are evaluated. The expanding role of systemic therapy in management pre- and postoperatively as well as its impact on surgical management is also detailed and incorporated into overall treatment plans. The importance of tumour biology in terms of treatment selection and measures of outcomes aptly are emphasized. Patient selection for management clearly has moved from the crude surrogates of metastases of size, number, and diagnostic interval from the primary tumour into genetic profiles and liquid biopsy. Biologic markers and genetic profiles are redefining oligometastatic disease. The theme of multidisciplinary management is reiterated throughout. Value in cooperative not competitive management is key. Future directions are proposed.

The editors and authors would likely be the first to admit their debt to their predecessors in the field and the profitable advantages of the expertise of their colleagues and peers in the preparation of this critical treatise—*Colorectal Liver Metastasis.* The emphasis on multidisciplinary management is clear and resounding but respectful of each specialist's contribution in management. They have provided physicians with timely state of the practice profile that is

well documented and practical approach for patients with colorectal liver metastases. They remain factual in the limitations of our ability and science today. *Colorectal Liver Metastasis* provides the solid steppingstone for future progress in the management of the complex patients with advanced colorectal cancer.

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David M. Nagorney

Foreword

Colorectal liver metastasis (CRLM) is a unique disease entity in three ways. First, it is the only hematogenous distant metastasis that can be cured by local treatment, i.e., liver resection. Distant metastasis is generally defined as stage IVb, which is systemic disease that can only be treated with systemic palliative chemotherapy. Colorectal cancer with liver metastasis should be regarded as stage IVb, but once R0 resection is achieved patients may be able to expect comparable or even better long-term outcomes compared to those for patients with only lymph node metastasis (stage IIIb). The oncological nature of CRLM has been explained by so-called classical "cascade theory," where metastasis develops in discrete steps: first in the liver, next in the lungs, and finally at other sites. This is why pioneering liver surgeons took on the challenge of CRLM more than 5 decades ago.

A tremendous potential for regeneration or volume restoration of the liver is another very unique feature of CRLM. Since most patients with CRLM have a normal liver, extensive liver resection is well tolerated with a minimum liver remnant volume of around 30%. To further expand the indications for major liver resection, an innovative technique to increase liver volume by embolizing the portal vein supplying the hemiliver to be resected (portal vein embolization: PVE) was developed by Professor Makuuchi, a pioneering surgeon, in the 1980s. Very recently, a combination of PVE and in situ liver splitting (the ALPPS procedure) or concomitant hepatic venous embolization has been shown to facilitate faster liver regeneration, and these approaches have been tried in many centers as extreme liver resections for very advanced CRLM.

Lastly, the impact of repeated liver resection is a third unique feature of CRLM. Tumour recurrence in the liver remnant is not uncommon even after curative resection with sufficient surgical margins. Repeated liver resection has been aggressively attempted in many centers specializing in the liver around the world, and there is a consensus among surgeons that repeated resection has much better outcomes than those of palliative chemotherapy. This is why overall survival is not parallel to disease-free survival and clinical trials involving adjuvant chemotherapy in this setting have failed to indicate a survival benefit despite positive outcomes in terms of disease-free survival.

Without doubt, Professors Jean-Nicolas Vauthey and Rene Adam are world-leading liver surgeons who have taken on the challenge of CRLM. I have known them for almost 20 years and have always been impressed by their pioneering efforts. I would like to congratulate Nic and Rene for compiling this wonderful book on cutting-edge management of CRLM, which is an extremely unique disease entity.

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Norihiro Kokudo

Preface

The concept for *Colorectal Liver Metastasis* arose from recognition of the need for an authoritative treatise on this important subject. In contrast with the usual paradigm, in which the treatment of liver metastasis is addressed in just a chapter in a broad surgical oncology or medical oncology textbook, our entire work is dedicated to the contemporary multidisciplinary management of liver metastasis. Throughout the text, experts discuss traditional and new approaches to optimize the treatment of liver metastasis. The goal is to present the information in a logical and informative way, from the history of treatment to diagnosis, staging, prognosis, and contemporary treatment of liver metastasis, with emphasis on a collaborative, multidisciplinary approach.

The treatment of colorectal liver metastasis is one of the most exciting areas in medicine in the twenty-first century thanks to the innovative works of expert investigators. Over the past two decades, imaging of metastasis has been refined, surgical indications and techniques have been perfected, and many effective systemic treatments have been developed. Specific advances include better identification of early disease with refined imaging, use of fiduciaries to mark the location of small deep metastases at risk for disappearing, after preoperative systemic therapy, two-stage resection for advanced bilateral disease, and the emerging role of liver transplant for selected patients. Molecular biology studies, including evaluation of somatic mutations and circulating tumour DNA, have become an integral part of the patient evaluation guiding therapy and surveillance after treatment. Patients whose disease would have been deemed incurable 20 years ago can now be offered the hope of a normal or near-normal life. A prime example of the positive impact of treatment advances is that institutions are now reporting 5-year survival rates approaching 60% in patients with resectable disease.

We have gathered contributions from some of the most important investigators in the field and believe that we have achieved our goal, which is to produce a textbook that is easy to read and that can be used as the ultimate reference by all healthcare providers involved in the treatment of patients with colorectal liver metastasis. We dedicate this effort to all patients with metastatic colorectal cancer and to our spouses and children, who have allowed us to dedicate precious spare time to write this treatise.

Houston, TX — Jean-Nicolas Vauthey
Tokyo, Japan — Yoshikuni Kawaguchi
Paris, France — René Adam

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Part I

Introduction

History of Treatment of Colorectal Liver Metastases

1

Andrew D. Newton and Yun Shin Chun

Learning Objectives

- Historical attempts at liver resection were impeded by uncontrollable hemorrhage.
- Knowledge of segmental anatomy, vascular inflow control, and innovative transection techniques has led to reduced blood loss with hepatic resection.
- Pre- and intraoperative identification of liver metastases has evolved from gross inspection and palpation to sophisticated cross-sectional imaging techniques and intraoperative ultrasound.
- Contemporary series report perioperative mortality of less than 3% and 5-year overall survival rates approaching 60% after resection of colorectal liver metastases.

1.1 Introduction

"Technical success has only italicized the limitations of our art because biological rather than anatomical factors predominate." Martin Adson, MD, Mayo Clinic, 1987.

The history of the treatment of colorectal liver metastases (CLM) reflects parallel breakthroughs in the fields of surgery, radiology, and medical oncology. Untreated CLM portends a dismal median survival of 6–9 months [1]. The combined efforts of international pioneers in multiple disciplines have led to an increase in overall survival (OS) after CLM resection from 25% in the 1980s to as high as 47–58% today, despite higher tumour burden among patients undergoing surgery in contemporary series [2]. Further advances in the understanding of molecular biology and patient selection will pave the path forward to continued improvements in multidisciplinary treatment and patient survival.

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1.2 Early Liver Surgery for Colorectal Liver Metastases

1.2.1 Anatomy

Modern hepatobiliary surgery is predicated upon an understanding of segmental liver anatomy. Although liver anatomy was intensely studied for centuries, our current understanding of liver anatomy was not attained until the mid-twentieth century. In 1640, Johannes Walaeus, a Dutch physician, described the vasculobiliary sheaths of the liver (Fig. 1.1) [3]. In 1654, Francis Glisson of England performed cast and

Fig. 1.1 Johannes Walaeus

J.-N. Vauthey et al. (eds.), *Colorectal Liver Metastasis*, https://doi.org/10.1007/978-3-031-09323-4_1

Fig. 1.2 Claude Couinaud

injection studies and detailed the fibrous framework of the liver and intrahepatic vascular anatomy in his book *Anatomia Hepatis*. [4] Hugo Rex in Germany (1888) and James Cantlie in England (1898) described a plane from the gallbladder bed to the right of the inferior vena cava that separates the right and left liver [5, 6]. In 1954, Claude Couinaud's seminal work transformed the understanding of liver anatomy by dividing the liver into eight segments based on the intrahepatic distribution of the portal vein (Fig. 1.2) [7].

1.2.2 Intraoperative Hemorrhage Control

The main deterrent to early hepatectomies was massive, uncontrollable hemorrhage. In 1908, J. Hogarth Pringle of Scotland described digital occlusion of the portal vein and hepatic artery at the hilum to temporarily arrest hemorrhage from the liver after trauma [8]. This strategy of temporary vascular inflow occlusion was subsequently named the Pringle maneuver. In addition to vascular inflow occlusion, various methods of parenchymal transection have been employed to reduce bleeding from the liver. In 1954, Tien-Yu Lin of Taiwan proposed finger fracture dissection with intrahepatic ligation of vascular and ductal structures [9]. In 1979, Hodgson developed an ultrasonic dissector that fragments tissue with high water content such as the liver parenchyma, while sparing collagen-rich blood vessels and bile ducts [10]. Vascular staplers to divide hepatic and portal veins were introduced by Voyles (1989) and McEntee (1991) [11, 12].

1.2.3 Tumour Identification

Early reports of CLM resection describe diagnosis either incidentally at laparotomy or by physical examination. As late as the 1970s, preoperative diagnostic and localization studies were limited to angiography and nuclear liver scans [13]. Subsequent cross-sectional imaging techniques, computed tomography (CT) and magnetic resonance imaging (MRI), revolutionized liver surgery planning. The first CT scan in North America was performed at the Mayo Clinic in 1973 [14]. The scanner was manufactured in England under the supervision of Godfrey Hounsfield, who, with Allan Cormack of South Africa, was awarded the Nobel Prize in 1979 for the development of CT. In the past 50 years, refinements in CT technology, protocols, and interpretation have led to the ability to detect subcentimeter metastases, measure liver volumes, and predict response to systemic therapy [15–17]. MRI was first introduced in 1977, and two of the major contributors to its development, Paul Lauterbur in New York and Peter Mansfield in England, also won Nobel Prizes. MRI has proven useful for evaluation of benign liver lesions, hepatic steatosis, bile duct tumour involvement, and identification of small liver metastases [18–22].

In early resections of CLM, tools for intraoperative tumour identification were limited to a surgeon's eyes and hands for inspection and palpation. In addition to high-quality, multiphasic CT or MRI, intraoperative ultrasound (IOUS) is essential for CLM resection in the modern era. In 1977, Masatoshi Makuuchi in Japan applied a linear array of transducers to perform real-time B-mode ultrasound of the liver [23]. The resulting two-dimensional image allowed identification of non-palpable lesions and tumour thrombi. In 1983, Licinio Angelini in Italy reported the first experience with IOUS to detect CLM in patients undergoing resection of colorectal cancer [24].

1.3 Surgical Outcomes

Advances in the understanding of liver anatomy, surgical techniques, anesthesia, and radiology have led to significant improvements in surgical outcomes, despite higher tumour burden and resection complexity in modern series (Table 1.1). The first reported CLM resection was performed by Richard Cattell at the Lahey Clinic in 1939 [25]. During a staged abdominoperineal resection for rectal adenocarcinoma, he

Table 1.1 Operative mortality and overall survival after resection of colorectal liver metastases

Author	Year	No. of patients	Operative mortality (%)	5-Year overall survival (%)
Wilson and Adson [40]	1976	60	1.7	28
Foster [26]	1978	162	4.9	30, solitary, vs. 13, multiple
Wagner et al. [27]	1984	141	2.1	32, Duke's B primary tumour, vs. 18, Duke's C
Schlag et al.	1990	122	4	30
Cady et al.	1992	129	5.4	50, negative margin, vs. 18, close margin
Scheele et al.	1995	434	4.4	39[a]
Nordlinger et al.	1996	1568	2.3	28
Jamison et al.	1997	280	4	27
Fong et al.	1999	1001	2.8	36
Minagawa et al.	2000	235	0	38
Kato et al.	2003	585	0	33
Pawlik et al.	2005	557	0.9	58
de Jong et al.	2009	1669	N/A	47

N/A not available
[a]Excluding postoperative deaths

discovered an isolated liver metastasis. He resected the metastasis as a partial hepatectomy and completed the first stage of the abdominoperineal resection—sigmoid colon division and colostomy. He completed the proctectomy 1 month later and wrote that the patient remained in "excellent condition" 12 months after liver resection.

In 1978, James Foster collected data on CLM resection from published reports and a survey of personal visits to 98 hospitals [26]. He recorded an operative mortality of 4.9% and 5-year OS of 30% and 13% after resection of solitary and multiple CLM, respectively. In the Mayo Clinic experience with CLM resection between 1948 and 1982, 74 patients underwent minor hepatectomy with 0% mortality [27]. Among 67 patients undergoing major hepatectomy, operative mortality was 4%. In 1987, Leslie Blumgart in London reported on 24 patients undergoing major hepatectomy for CLM, including 6 extended right hepatectomies (Fig. 1.3) [28]. Operative mortality and median survival rates were 8.3% and 30 months, respectively. Contemporary series report perioperative mortality rates of <3% and 5-year OS rates approaching 60% [29]. Today, more patients are eligible for CLM resection with low rates of morbidity and mortality owing to innovative strategies, such as portal vein embolization and two-stage hepatectomy, described in other chapters of this book.

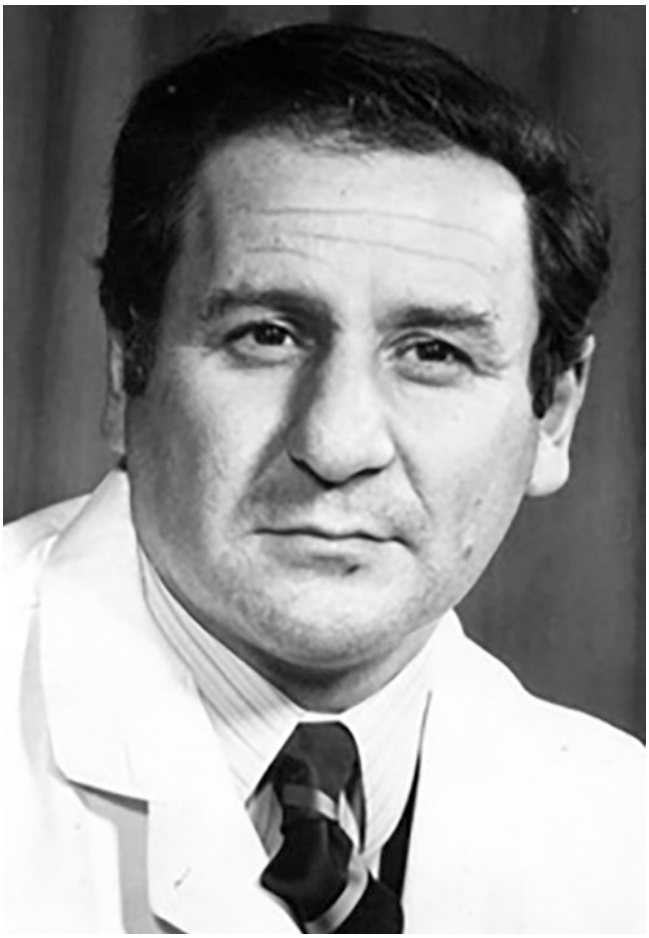

Fig. 1.3 Leslie Blumgart

1.4 Cytotoxic and Biologic Agents

In 1957, Charles Heidelberger at the University of Wisconsin observed that tumours preferentially use uracil for nucleic acid biosynthesis and showed tumour regression after treatment with 5-fluorouracil (5-FU), a fluorinated analogue of uracil [30]. Since the 1950s, 5-FU has been the mainstay of systemic therapy for metastatic colorectal cancer. However, single-agent 5-FU resulted in objective response rates of only 10–20% without improvement in survival. In 1978, Buddy Ullman in San Francisco reported that folinic acid (leucovorin) increases 5-FU cytotoxicity by enhancing binding of 5-FU to its target, thymidylate synthase [31]. Subsequent clinical trials showed improved response rates with the addition of leucovorin (LV) to 5-FU [32].

In the early 2000s, irinotecan, a topoisomerase I inhibitor, and oxaliplatin, a platinum derivative, were introduced into

the armamentarium to treat metastatic colorectal cancer. Both oxaliplatin and irinotecan were discovered by researchers in Japan in 1976 and 1983, respectively [33]. Regimens with a backbone of infusional 5-FU/LV, combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), have demonstrated objective response rates of >50% in the first-line treatment of metastatic colorectal cancer and led to substantial improvements in survival [34].

In 1971, Judah Folkman in Boston described a soluble tumour angiogenesis factor and suggested blocking angiogenesis as anticancer therapy [35]. Decades later, the addition of bevacizumab, a vascular endothelial growth factor inhibitor, was found to increase survival in patients with metastatic colorectal cancer compared with chemotherapy alone. In 1984, John Mendelsohn and Gordon Sato in San Diego demonstrated that monoclonal antibodies directed against epidermal growth factor receptor (EGFR) inhibited growth of cancer cells in vitro and in vivo [36]. Today, cetuximab and panitumumab, monoclonal antibodies targeting EGFR, are used to treat *RAS* wild-type metastatic colorectal cancer and have resulted in increased response rates and progression-free survival over cytotoxic chemotherapy alone.

Hepatic arterial infusion (HAI) of chemotherapy for CLM was introduced in 1964 by Sullivan at the Lahey Clinic [37]. The rationale for infusion of chemotherapy directly into the hepatic artery is the liver's dual blood supply, with metastases perfused predominantly by the hepatic artery and normal liver by the portal vein. In 1999, the group at Memorial Sloan-Kettering Cancer Center led by Nancy Kemeny published results of a randomized trial of adjuvant 5-FU plus HAI-floxuridine (FUDR) via an implantable pump, compared with systemic 5-FU alone after CLM resection (Fig. 1.4) [38]. Two-year OS was significantly higher with the addition of HAI-FUDR to systemic 5-FU (86% vs. 72%, $p = 0.03$). Two-year hepatic recurrence-free survival was also significantly higher with HAI-FUDR (90% vs. 60%, $p < 0.001$).

Fig. 1.4 Nancy Kemeny

1.5 Improved Patient Selection Based on Tumour Biology

In 1987, Martin Adson of the Mayo Clinic observed that despite improved surgical technique and decreased operative mortality, survival after CLM resection had not improved in the preceding 20 years (Fig. 1.5) [39]. He astutely asked the question of *when* CLM resection should be performed, rather than how, and recognized that the answer rested upon "the unseen presence of biological factors that prevail." Today, owing to landmark studies on multidisciplinary treatment and molecular biology, biological factors that remained invisible in the 1980s are being unveiled.

In the 1970s, resection of CLM was generally only considered for solitary metastases [40, 41]. By the late 1980s, resection of multiple hepatic metastases was becoming more accepted, but bilateral disease was still considered a contraindication to resection [42–45]. In 1990, Johannes Scheele identified the ability to achieve an R0 resection (resection margin of at least 1 mm) rather than number or location of metastases as the most important predictor of survival after CLM resection (Fig. 1.6) [46]. The following year, Scheele described the presence of satellite metastases as an important negative prognostic factor for survival [47]. In the late 1990s to early 2000s, Fong, Kokudo, and Scheele independently

Fig. 1.5 Martin Adson. (Reprinted with permission from Kelly et al.)

Fig. 1.6 Johannes Scheele

Fig. 1.7 Henri Bismuth

demonstrated that outcomes were not improved with wider margins (1 cm), compared with simply negative margins of 1 mm [48–50].

Response to preoperative systemic therapy is an important surrogate marker of tumour biology and guides selection of patients for hepatectomy [51]. In 1992, Eisenberg and Hoffman in Philadelphia described 11 patients who underwent CLM resection after chemotherapy, including 5 patients with initially unresectable disease [52]. This concept of neoadjuvant therapy for CLM was expanded by Henri Bismuth in France in 1996, who reported 53 patients with initially unresectable disease who underwent surgery after downstaging with chemotherapy (Fig. 1.7) [53]. He emphasized the importance of reconsidering liver resection in patients who respond well to chemotherapy. In 2008, pathologic response to preoperative chemotherapy was found to be an independent predictor of survival after CLM resection [54].

Historically, an unresected primary colorectal tumour represented a contraindication to CLM resection [55]. However, the advent of systemic therapy that effectively treats both the primary and metastatic disease encouraged Gilles Mentha in Geneva to investigate a reverse strategy of preoperative chemotherapy and liver resection before colorectal surgery (Fig. 1.8). In 2006, results of the liver-first approach were published among 20 patients with non-obstructing primary tumours and extensive synchronous CLM, including 70% bilateral and median of 5 metastases [56]. Complete resection of colorectal and liver tumours was achieved in 80% of patients, whose 4-year OS was 61%. Initially considered "unorthodox," the liver-first approach is routinely performed today for advanced CLM that responds to systemic therapy, recognizing that in most patients, the metastatic disease is the primary determinant of survival [57].

In addition to response to systemic therapy, tumour genetics represent a critical determinant of tumour biology and patient prognosis after CLM resection. In 1964, Jennifer Harvey in London described a virus causing rapid production of tumours in mice [58]. Many years and experiments later, the viral oncogenes discovered by Harvey were characterized as orthologs of the human *RAS* gene [59]. Today, *RAS* mutational status is used to guide anti-EGFR therapy for patients with *RAS* wild-type tumours. After CLM resection, *RAS* mutations predict survival and recurrence patterns [60]. Other somatic gene mutations, including *TP53* and *SMAD4*, and

Fig. 1.8 Gilles Mentha

their interactions are emerging as important determinants of tumour biology and survival after CLM resection [61].

1.6 Conclusion

The history of the treatment of CLM spans decades of international work in multiple disciplines. Technical success coupled with a deeper understanding of biology has led to improved postoperative outcomes and patient survival. Future generations will undoubtedly dispel myths that are falsely held today, while principles established by our forbearers in anatomy, oncology, and surgery will endure.

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Part II

Surgery

Liver Anatomy

2

Yujiro Nishioka and Junichi Shindoh

Learning Objectives

- Liver segmentation is based on the portal territory that is bordered by intersegmental planes including landmark hepatic veins.
- While Couinaud's theory for liver segmentation is practical and useful, actual portal ramification patterns, shapes of liver segment, and intersegmental planes are rather complex.
- Understanding of major variations of vascular structures at the hepatic hilum and inside of the liver is essential to avoid unnecessary intraoperative vascular injury or misunderstanding of anatomical structures encountered during hepatectomy.

2.1 Introduction

Surgical resection is the standard of care for patients with resectable colorectal liver metastases (CLM) and recent advances in perioperative therapy and surgical technique have offered a chance of cure even for patients with potentially resectable or initially unresectable disease. While anatomic resection is considered not to be beneficial for patients with CLM [1] and parenchymal-sparing hepatectomy is reportedly correlated with improved salvageability and survival [2], knowledge on liver anatomy remains mandatory for physicians to adequately determine resectability and select optimal treatment options.

Technical resectability of liver tumour is based on the estimated future liver remnant (FLR) volume, which is a major predictor for postoperative hepatic insufficiency and postoperative mortality [3]. Given that we need to balance the curability and safety of surgery, adequate surgical planning and appropriate surgical procedures based on the knowledge on liver anatomy are inevitable for successful resection of CLM. In this chapter, we review the basic knowledge of liver anatomy required for surgical resection of CLM.

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2.2 Functional "Unit" of the Liver

2.2.1 Liver Segment and Terminology

Claude Couinaud, a French surgeon, was the first to describe hepatic vascular structure systematically and define functional liver segmentation [4]. He defined four sectors (i.e., right lateral/paramedian, and left lateral/paramedian sectors) divided by three major hepatic veins (left hepatic vein [LHV], middle hepatic vein [MHV], and right hepatic vein [RHV]); then he divided each right-sided sector into superior and inferior segments (segments V/VIII and VI/VII) and left paramedian sector into two segments separated by the falciform ligament (segment III/IV). He additionally named the left lateral sector as segment II and the dorsal liver as segment I. The liver was eventually divided into eight segments in Couinaud's theory (Fig. 2.1). From the standpoint of hepatobiliary surgeon, Bismuth renamed each right-sided sector as anterior/posterior sectors. In addition, he bundled segments II, III, and IV into one sector because he thought portal branch should be located inside a segment and dividing segments II + III + IV into two sectors is not consistent with this rule, considering the presence of umbilical portion of the left portal vein [5]. Similarly, Takasaki also divided the liver into three segments (left, middle, and right) according to the ramification of extrahepatic portal branch and individual volumes of segments [6]. An international consensus regarding the terminology of liver anatomy, the Brisbane 2000 terminology, is nowadays widely accepted as a common rule for anatomical terms in the field of liver surgery [7].

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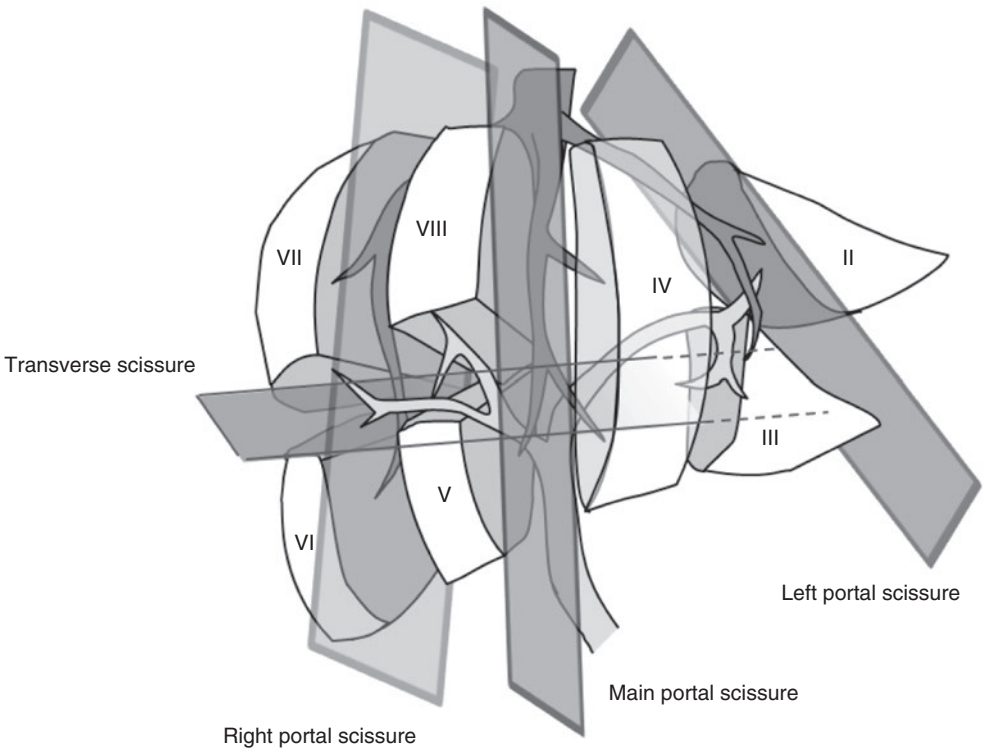

Fig. 2.1 Schema of liver segments and four portal fissures proposed by Couinaud

2.2.2 Liver Segmentation and Portal Territory

Couinaud's liver segment is systematically defined as a territory of portal vein that is bordered by so-called "landmark" hepatic veins. Makuuchi et al. were the first to achieve complete systematic removal of Couinaud's liver segment with intraoperative staining and visualization of the portal territory [8]. Kawasaki et al. reported anatomical resection of segments III + IV (i.e., Couinaud's left paramedian sector) using this method and clarified the LHV and MHV are fully exposed on the cur surface of the liver after complete removal of segments III and IV as predicted in Couinaud's theory [9]. Their works had not only established the techniques for systematic segmentectomy but also confirmed that landmark veins usually run through the intersegmental plane of the liver.

Recent advances in computed three-dimensional (3D) simulation techniques using contrast-enhanced computed tomography (CT) have enabled surgeons to have much deeper insight into the liver anatomy. For example, based on the meticulous volumetric analysis, Shindoh et al. reported the heterogeneity in each segmental volume of the liver: segment VIII is the largest, accounting for a median of 24.2% of total liver volume, whereas segments II and III each represented <10% (Table 2.1) [10]. They also reported that simple bifurcation of anterior portal branch into segments V and VIII was observed in only 7% of patients and clear definition of segments VI and VII based on portal ramification pattern was also difficult in 54% of patients in right lateral sector [11].

Table 2.1 Volume proportions of each liver segment in the whole liver

Liver segment	Volume (mL)	Percentage (vs. TLV)
Segment I	84 (55–123)	7.6% (5.4–9.9%)
Segment II	99 (15–181)	8.2% (1.6–15.8%)
Segment III	107 (35–232)	9.4% (2.6–19.8%)
Segment IV	131 (55–231)	11.7% (5.1–18.5%)
Segment V	135 (28–247)	12.0% (3.0–24.8%)
Segment VI	134 (46–371)	11.7% (3.4–29.8%)
Segment VII	151 (60–341)	13.8% (5.1–29.1%)
Segment VIII	270 (113–515)	24.2% (11.1–44.8%)
Total liver volume	1103 (781–2034)	100%

Figures represent median (range)
TLV total liver volume
Source: Adapted from Shindoh et al. *Ann Surg* 2010 [10], with permission

2.2.3 Intersegmental Plane

Three-dimensional simulation technique has also enabled us to visualize the actual shape of the boundary between sections/segments, which was assumed to be flat in Couinaud's theory. Shindoh et al. has evaluated the concordance between the theoretical planes (i.e., Couinaud's intersegmental plane) and their actual shape by 3D simulation. They reported that the main portal scissure is almost flat and usually fitted with the midplane of the liver defined by the MHV, while the right portal scissure and left portal scissure remarkably tilted dorsally from the imaginary flat venous planes defined by the RHV and LHV (Fig. 2.2) [10]. Hepatobiliary surgeons need to be familiar with these findings especially in performing

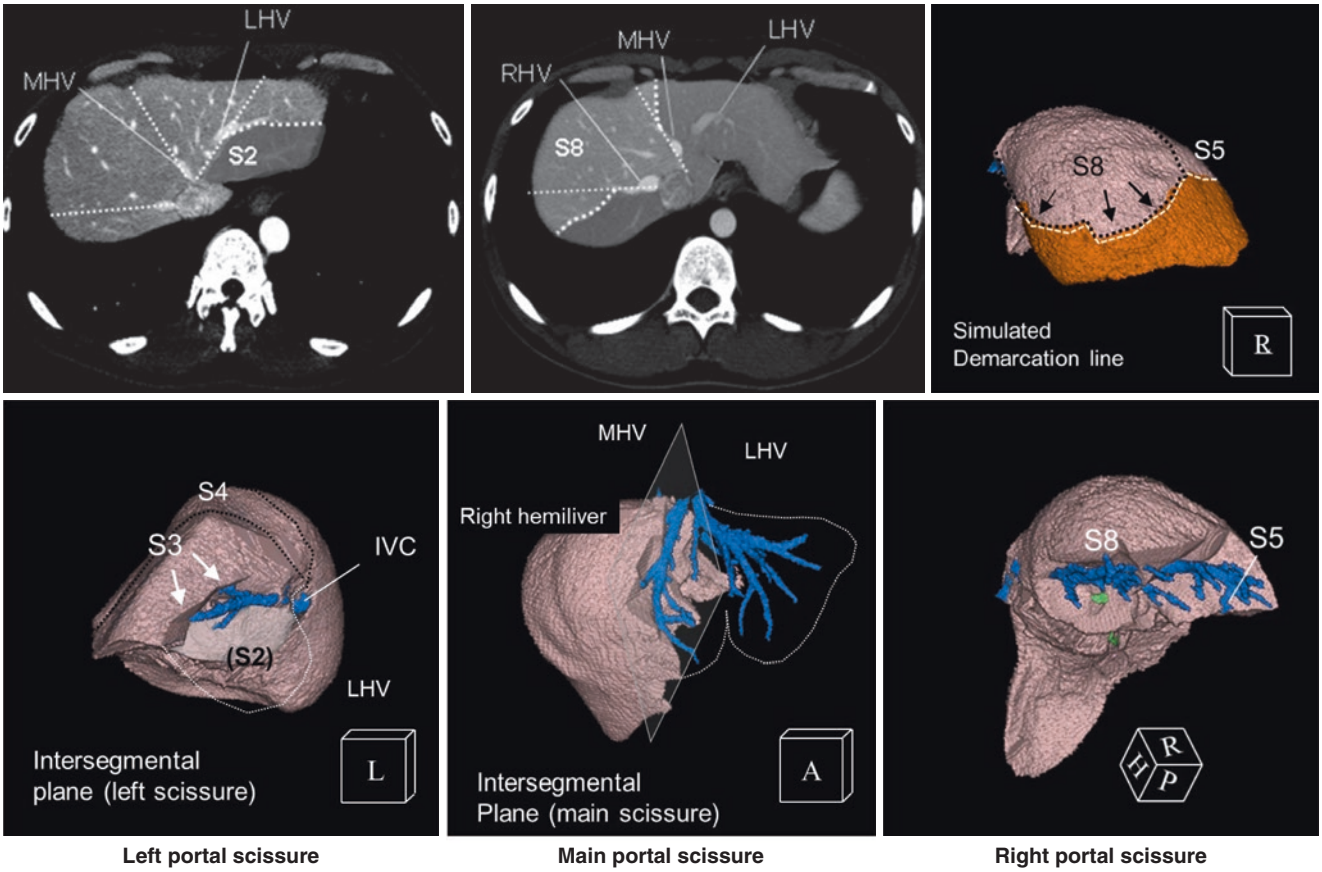

Fig. 2.2 Concordance between the imaginary venous planes (i.e., Couinaud's intersegmental plane) and their actual shape visualized by three-dimensional simulation of the liver. LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein

anatomic resection of the liver where the left or right portal scissure need to be transected because straightforward parenchymal transection from demarcation line to the inferior vena cava (IVC) without confirming the position of landmark veins may cause misunderstanding of anatomic structures during sectorectomy.

2.3 Portal Vein and Hepatic Vein

2.3.1 Symmetrical Configuration of Portal and Venous Ramification Patterns

Apart from Couinaud's segmentation, Hjortsjo proposed another anatomical concept of the liver in 1940s, in which the right paramedian sector was further divided into ventral and dorsal parts, and accordingly, the liver was divided into six segments with five fissures morphologically (Fig. 2.3) [12]. This concept has been reappraised in 2000s through the finding in 3D simulation that the branches of segment VIII portal vein (P8) are always divided into two directions: P8-ventral and P8-dorsal [13, 14]. Shindoh et al. and Cho et al. reported that portal territory can be divided almost symmetrically [11, 14]. They also reported that landmark veins always exist between the third-order portal territories (e.g., the umbilical fissure vein between segments III and IV; V8i between ventral and dorsal parts of segments V + VIII) [15], and the symmetrical configurations of both portal vein and hepatic vein on either side of the Rex-Cantlie line are preserved even in patients with right-sided ligamentum teres [16]. These findings are also supported by the embryological findings that four sectors and basic structures of portal veins and hepatic veins have established during symmetrical development stages of the liver [17].

2.3.2 Variation of Portal Vein and Hepatic Vein

Branching pattern of portal vein at hilum is classified into the following three types: Type I, bifurcation of left and right branches; Type II, trifurcation of left, right paramedian, and right lateral branches; and Type III, independent branching of the right lateral branch [18]. Type I anatomy is normal and observed in 80–90% of patients, while Type II anatomy is observed in about 5% and Type III in 5–10% [19, 20]. The

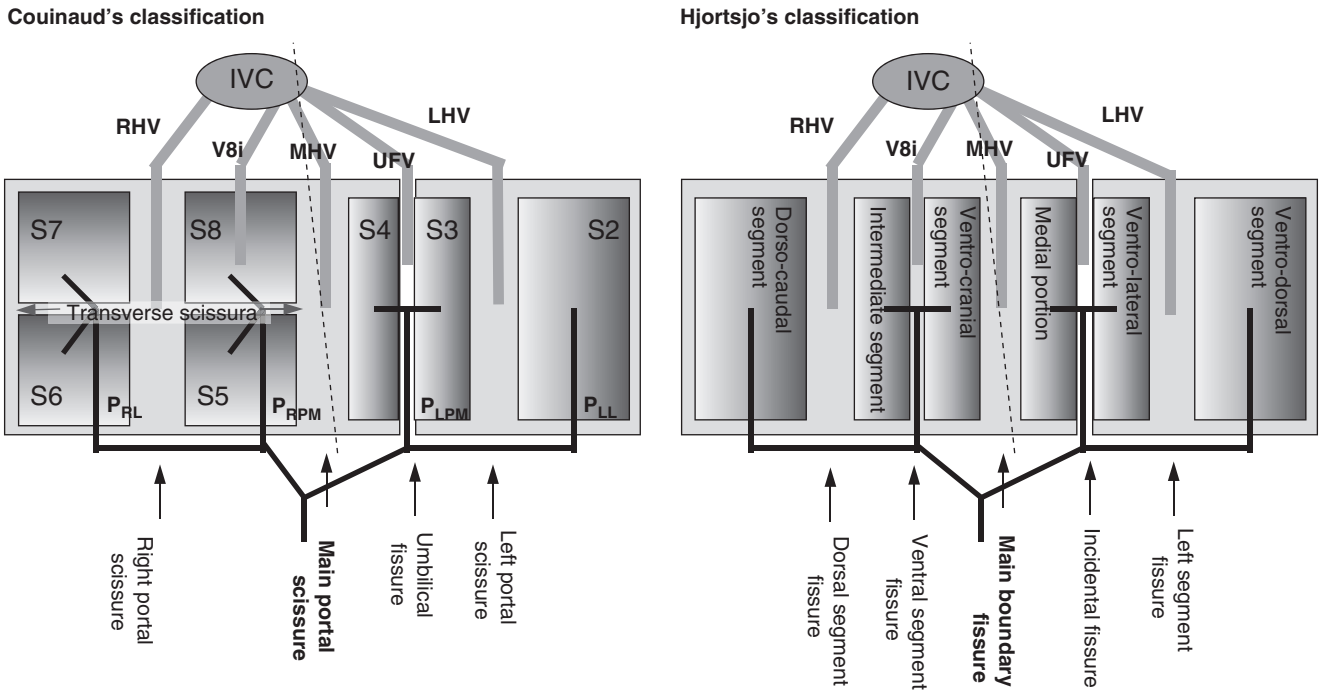

Fig. 2.3 Schematic representation of Couinaud's classification and Hjortsjo's classification. Couinaud divided the liver into eight segments with three longitudinal fissures and one transverse fissure, while Hjortsjo divided the liver into six longitudinal segments with five longitudinal fissures

variation of hepatic veins is also important. In terms of drainage area of RHV, two major accessory veins, the inferior right hepatic vein (IRHV) and middle right hepatic vein (MRHV), are well described. The IRHV, detected in 34% of patients, drains segment VI and the MRHV, detected in 20% of patients, drains segment VII [15]. These veins can be easily injured or needed to be ligated during the mobilization of right liver, and surgeons need to recognize the presence of these veins in preoperative images (Fig. 2.4).

2.3.3 Venous Drainage Map

Recognizing the distribution of venous drainage of the liver is important because congestion caused by deprivation of venous trunk may cause decreased function in the corresponding area of the liver [21]. Future congested area can be visualized by test clamping of feeding hepatic artery and hepatic veins and venous reconstruction should be considered in cases with larger congested area as appropriate [22]. Tani et al. analyzed the livers of 100 healthy donors using 3D simulation and described the typical venous drainage patterns of the liver [15]. In their analysis, LHV drains 20.7% of the whole liver, MHV drains 32.7%, and RHV drains 44.9% (Fig. 2.5). In cases with accessory veins of RHV, MRHV

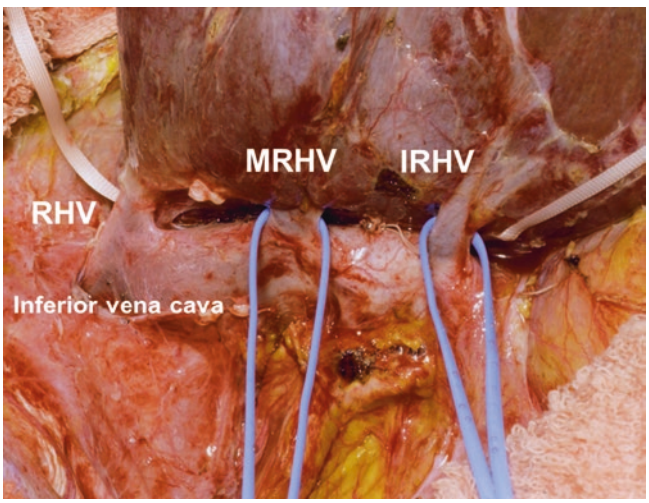

Fig. 2.4 Intraoperative picture of hepatic veins draining right liver. RHV, right hepatic vein; MRHV, middle right hepatic vein; IRHV, inferior right hepatic vein

drainages 6.0–9.4% of the whole liver and LRHV drainages 10.2–11.2%. It is important that the area drained by MHV in the right paramedian section accounts for about 20% of the whole liver, which could be congested after extended left hepatectomy with resection of MHV.

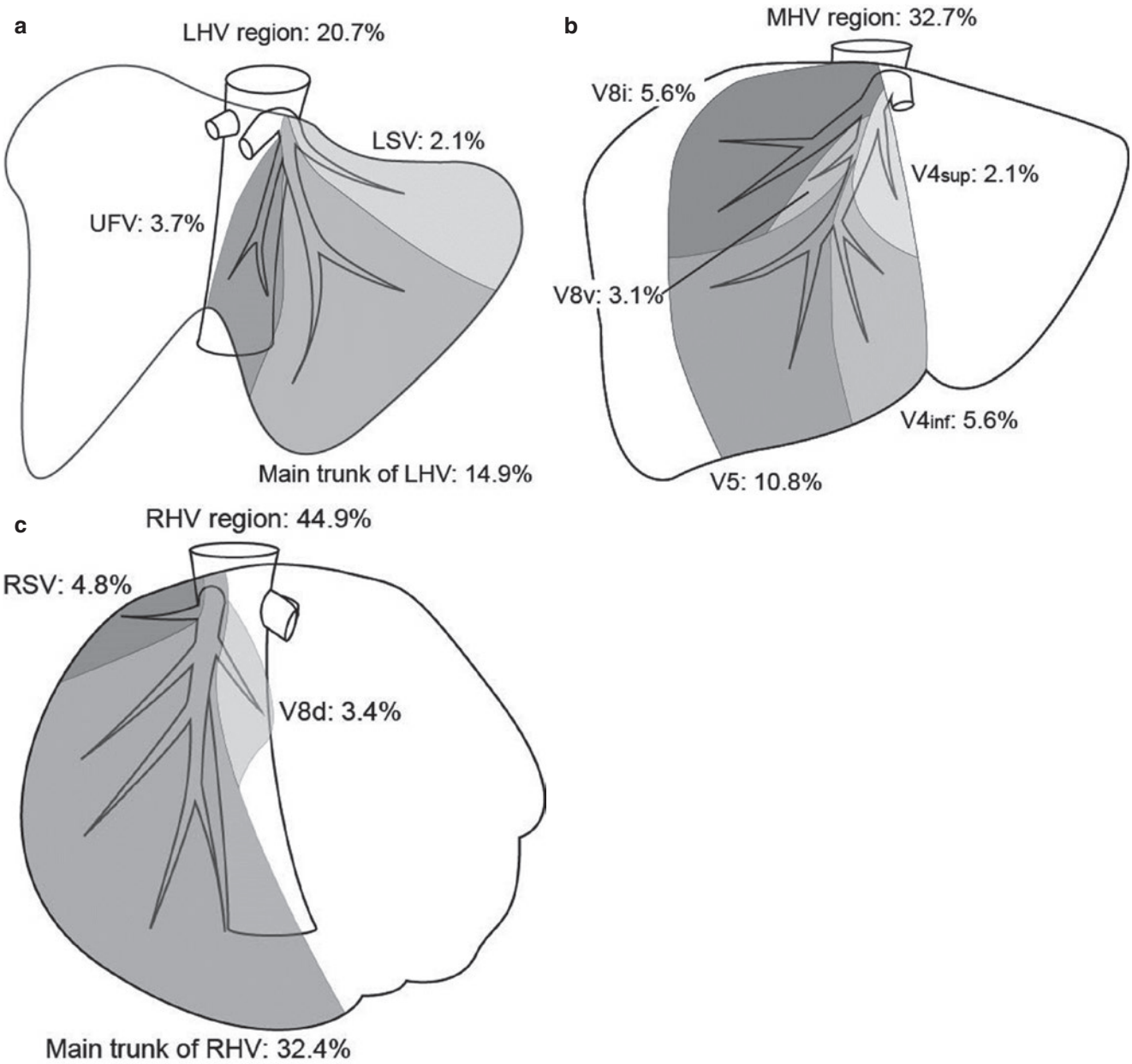

Fig. 2.5 The proportion of drainage area of (**a**) left hepatic vein, (**b**) middle hepatic vein, and (**c**) right hepatic vein tributaries. LHV, left hepatic vein; LSV, left superficial vein; UFV, umbilical fissure vein; MHV, middle hepatic vein; V4sup, superior vein for segment IV; V4inf, inferior vein for segment IV; V5, veins for segment V; V8v, ventral vein for segment VIII; V8i, intermediate vein for segment VIII; V8d, dorsal vein for segment VIII; RHV, right hepatic vein; RSV, right superficial vein. (Adapted from Tani et al. *HPB* (Oxford) 2016 [15], with permission)

2.4 Biliary Tract, Hepatic Artery, and Glissonian Pedicle

Both bile duct and hepatic artery run along portal vein in the peripheral part of the liver forming Glissonian pedicles; however, there exist several variations of their anatomy at the level of hepatic hilum.

2.4.1 Biliary Tract

The common hepatic duct (CHD) runs along and anterior to the root of the right portal vein (RPV) and the left hepatic duct (LHD) joins with the CHD at superior and medial side of the RPV [23]. Therefore, LHD is longer than right hepatic duct (RHD) and surgeons have to take care of the

risk for ligating the left hepatic duct during the right hepatectomy.

The anatomical variation of the right lateral sectional bile duct (RLS-BD) is also important. Ohkubo et al. analyzed the specimen of 110 patients who underwent major hepatectomy and classified them into three types according to the anatomic relation between RLS-BD and the RPV. They reported that 83% of patients had supraportal type in which RLS-BD runs dorsally and cranially to the RPV and joins with the RHD at its cranial side, while 12% of patients had infraportal type in which RLS-BD runs ventrally and caudally to the RPV and joins with the RHD at its caudal side and 5% of patients had combined type in which RLS-BD has two independent branches that drain segments VI and VII (B6, B7) and B7 joins with the RHD as supraportal type and B6 joins with the RHD as infraportal type [24] (Fig. 2.6a). They also described that RHD was absent in 26% of patients. In such cases, RLS-BD entered the LHD or the confluence of the right paramedian sectional bile duct and the LHD in supraportal type and entered the CHD in infraportal type (Fig. 2.6b). Recognition of these variants preoperatively is mandatory for surgeons in planning resection for tumours around the hilum.

2.4.2 Hepatic Artery

During embryological development of the liver, the liver initially receives arterial blood supply from the following three arteries: the embryological left hepatic artery (eLHA) from the left gastric artery (LGA) for the left lateral sector; the embryological middle hepatic artery (eMHA) from the common hepatic artery (CHA) for the bilateral paramedian sectors; and the embryological right hepatic artery (eRHA) from the superior mesenteric artery (SMA) for the right lateral sector. In standard development, the arteries for the left lateral sector and the left paramedian sector are anastomosed at the hilum forming the typical left hepatic artery (LHA). Similarly, the arteries for the right lateral sector and the right paramedian sector form the right hepatic artery (RHA) and

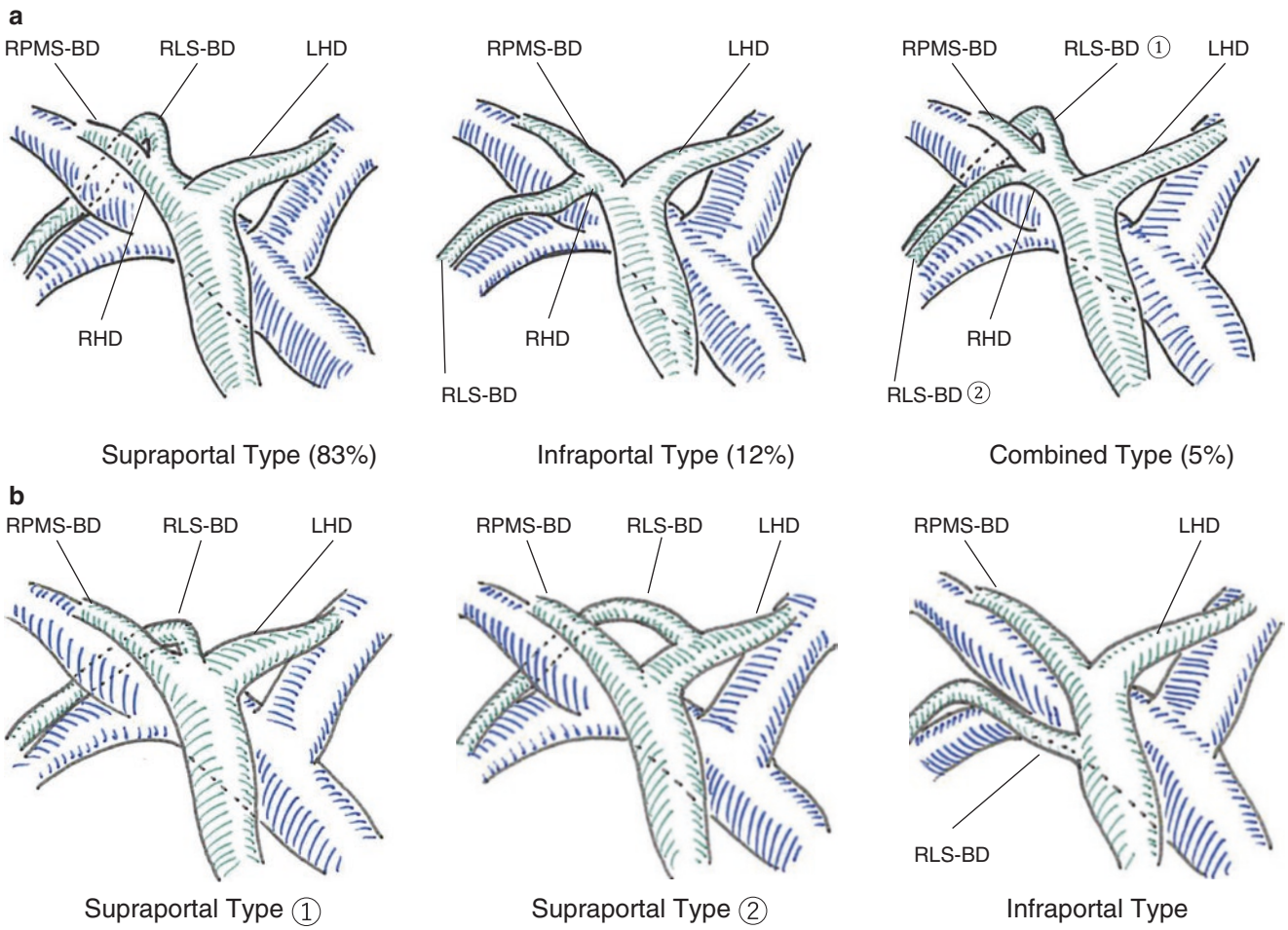

Fig. 2.6 Schema of the three confluence patterns of the right lateral sectional bile duct (RLS-BD) when right hepatic duct is (**a**) present and (**b**) absent. LHD, left hepatic duct; RHD, right hepatic duct; RPMS-BD, right paramedian sectional bile duct

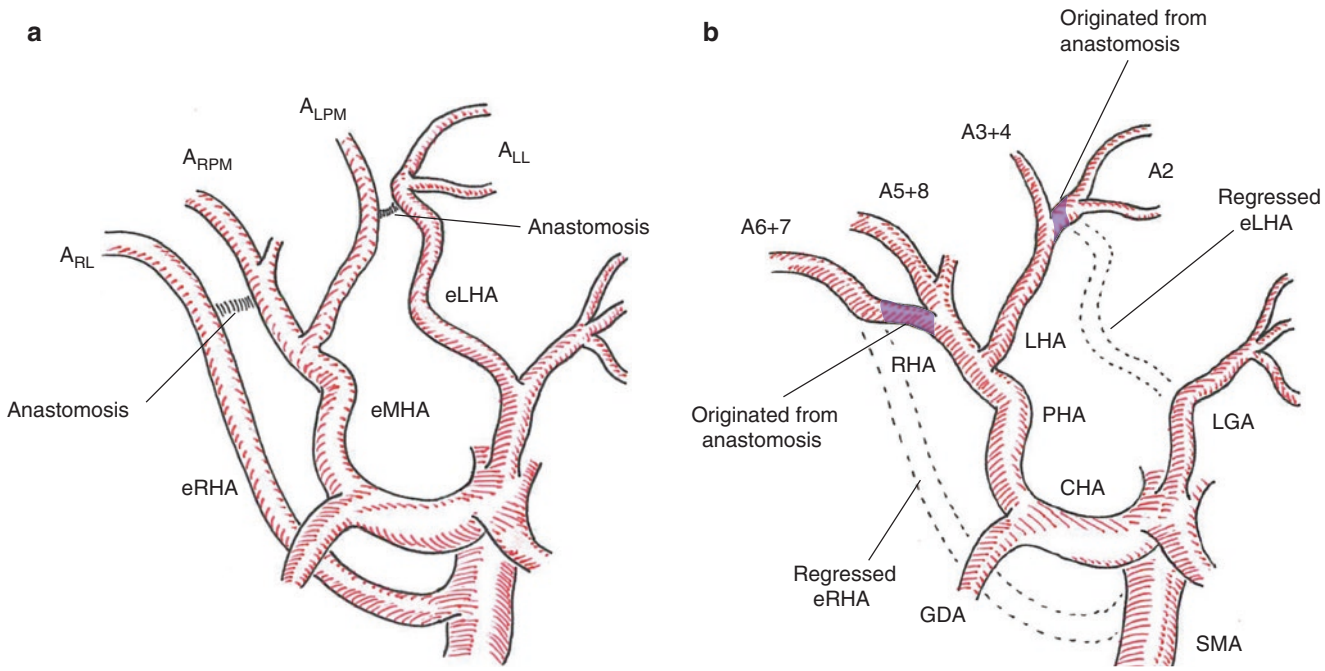

Fig. 2.7 (**a**) Embryological development of hepatic arteries and (**b**) typical anatomy of hepatic arteries. eLHA, embryological left hepatic artery; eMHA embryological middle hepatic artery; eRHA, embryological right hepatic artery; A_{LL}, artery of left lateral sector; A_{LPM}, artery of left paramedian sector; A_{RPM}, artery of right paramedian sector; A_{RL}, artery of right lateral sector; LGA, left gastric artery; PHA, proper hepatic artery; CHA, common hepatic artery; GDA, gastroduodenal artery; SMA, superior mesenteric artery

the initial route of eLHA and eRHA disappears. As a result, eMHA develops into the main arterial supply route for the liver and is called proper hepatic artery (PHA; Fig. 2.7). The PHA typically runs along the left side of the portal vein and RHA runs across between the CHD and portal vein.

When eLHA and/or eRHA do not regress during the development of the liver, these routes serve as accessory/replaced LHA or accessory/replaced RHA in combination with the presence of anastomosis from the PHA, and, accordingly, there exists wide variety of ramification pattern as Michaels reported [25]. Recent systematic review showed that the normal anatomy of the hepatic artery is observed in 80% of patients and the following three variants are observed most frequently (each type in about 3% of patients): a replaced LHA from the LGA, a replaced RHA from the SMA, and an accessory LHA from the LGA [26].

2.4.3 Glissonian Pedicle, Plate Systems, and Laennec's Capsule

Walaeus, a Dutch anatomist, and Glisson, a British anatomist, found a thick fibrous tissue forming a sheath surrounding portal pedicles in around 1650, which is the so-called Walean sheath. On the other hand, Laennec, a French physician, found a thin membrane originating from the peritoneum and wrapping the entire liver referred to as Laennec's capsule [27]. Couinaud described that the sheath extends to the hilum and forms a thick plate referred to as the hilar plate, which connects to the cystic plate, the umbilical plate, and the Arantius plate [28]. He also described that Glissonian pedicle and Laennec's capsule can be separated microscopically at the hepatic hilum.

The structure of portal triad (i.e., portal vein, hepatic artery, and bile duct) wrapped by Walean sheath is continuously observed even in peripheral part of the liver. Based on these findings, Takasaki et al. proposed a surgical approach in which the sheath pedicle for the left liver (or right paramedian/lateral sector) was encircled without dissecting the sheath by separating it from the liver parenchyma [29]. Recently, Sugioka et al. reported systematic method for extrahepatic Glissonian pedicle isolation [30]. This method is helpful in shortening the anatomic resection of the liver; however, adequate ligation margin should be left in order to avoid the postoperative stricture of vascular structures for the remnant liver. In right hemihepatectomy, ligation and transection at the level of right hilar plate should be avoided because of the risk of injury to left hepatic duct considering the relatively right-sided location of the confluence of bilateral hepatic ducts.

2.5 Caudate Lobe (Segment 1)

The caudate lobe is unique and embryologically develops as the dorsal liver that is separate from the remaining liver by around 40 days of development [31, 32]. The hepatic vein of the caudate lobe originating from the suprahepatic caval vein transforms into the retrohepatic portion of IVC in 44–45 days of development; therefore the caudate lobe completely encircles IVC in some cases.

Kumon et al. classified the caudate lobe into three parts: the Spiegel lobe, the paracaval portion, and the caudate process portion [33]. The Spiegel lobe is situated on the left side of the inferior vena cava, dorsal to the lesser omentum and divided from the paracaval portion by Arantius duct. Kogure et al. reported about half of patients had a notch that is a vestige of the portal segmentation of the caudate lobe in the Spiegel lobe, so-called "Kogure's notch," which is a boundary between the Spiegel lobe and the caudate process [34]. The Paracaval portion is covered by the right and middle hepatic veins and bordered on the dorsal side by the right portal pedicle, and the caudate process locates in the right side of IVC and posterior to the right portal pedicle (Fig. 2.8a, b). Although the right-sided boundary of the caudate process is still debatable, Kogure et al. analyzed 54 cadaveric livers and reported that the caudate process hepatic vein draining into IVC, IRHV, or RHV was identified between the caudate process and the right liver in all the cases and could be considered a true boundary [35, 36].

The caudate lobe reportedly has about three to five branches of portal vein and three to four branches of bile duct [33]. It is also reported that 88% of patients had one thick (≥ 3 mm) hepatic vein and 11% had two thick hepatic veins, which mostly drains into the left anterior side of IVC [34]. In cases with a large tumour located in paracaval portion, mobilization of the caudate lobe and the resection of the caudate lobe with the anterior liver parenchyma are required for sparing liver parenchyma [37]. Recognition of the anatomy of the caudate lobe is required for surgeons to achieve safe resection while preserving vascularized liver parenchyma.

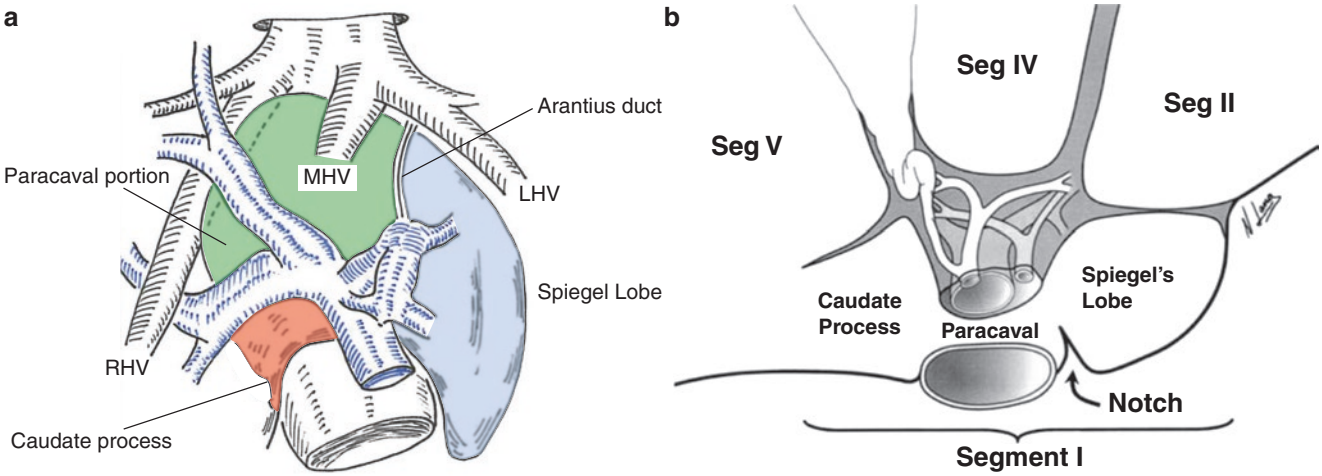

Fig. 2.8 (**a**) Three portions of the caudate lobe and landmark structures of boundaries between the portions. LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein. (**b**) En-face view of the caudate lobe. (Adapted from Abdalla et al. *Surg Oncol Clin N Am* 2002 [31], with permission)

2.6 Conclusion

The precise knowledge regarding liver segmentation is mandatory for all the physicians involved in the therapy of liver tumours, which contributes to appropriate description of tumour location and selection of therapeutic approach. Surgeons should review the anatomy during preoperative workup to avoid unnecessary injury caused by misunderstanding of anatomical variations.

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Exposure for Hepatectomy

3

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Learning Objectives

- Safe and oncologically successful hepatectomy for colorectal liver metastases requires optimal exposure through thoughtful choice of incision and effective retraction.
- The Inverted-L incision is the preferred incision for hepatectomy for colorectal liver metastases as it allows for unparalleled exposure of the right retroperitoneal structures, en face visualization of the inferior vena cava, hepatocaval junction, diaphragmatic crus, and esophageal hiatus.
- Compared to other incisions, the Inverted-L incision affords superior exposure of the right upper quadrant as well as the left hemiabdomen *without any need for left-sided extension of the incision.*
- Efficient retraction is required to realize the potential of all incisions for hepatectomy and thoughtful placement and setup of retraction systems are imperative for safe surgery.

3.1 Introduction

Safe and oncologically successful hepatectomy for CLM can be complex and requires thoughtful preparation and operative exposure. The open approach is the gold standard for resection of CLM, and a mastery of incisions and exposure techniques is paramount in a modern world that expects transfusion-free and mortality-free liver surgery. Despite an increasing proportion of hepatectomies for CLM being performed via a minimally invasive approach, facilitating optimal exposure for efficient open operations is a critical skill for locally advanced tumours and for patients needing complicated multifocal parenchymal-sparing resections [1]. There are many options for abdominal incisions that may be selected by the liver surgeon, and careful consideration of the critical steps in the operation may make certain incisions more advantageous.

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3.2 Incisions

Incisions selected by surgeons to perform safe liver surgery focus on exposure of the liver and right-sided retroperitoneal organs, including the hepatoduodenal ligament, duodenum, hepatic veins, adrenal gland, and inferior vena cava (IVC). Selection depends upon operation and anatomic location of lesions within the liver. Further, prior incisions and locations of anatomic features, such as stomas, may influence decision-making for incision type. Traditional incisions used for hepatectomy include the midline, "J" (Makuuchi), chevron, "Mercedes," "hockey stick," and Inverted-L (modified Makuuchi) incisions (Fig. 3.1).

3.2.1 Midline Laparotomy

The midline laparotomy incision is the most commonly performed incision for hepatobiliary (HB) and foregut surgery, owing to its ease and reproducibility. The decussation of fascial components at the linea alba allows for consistent landmarks, as well as the sparing of all muscular abdominal components. The midline laparotomy incision is often optimal for left-sided anatomic hepatectomy, and partial hepatectomy of left lateral, left medial, and right anterior sectoral lesions, provided it is extended to at least the level of the umbilicus. The midline laparotomy incision can be augmented by resection of the xiphoid process to provide an unobstructed view of the hepatic venous confluence and esophageal hiatus.

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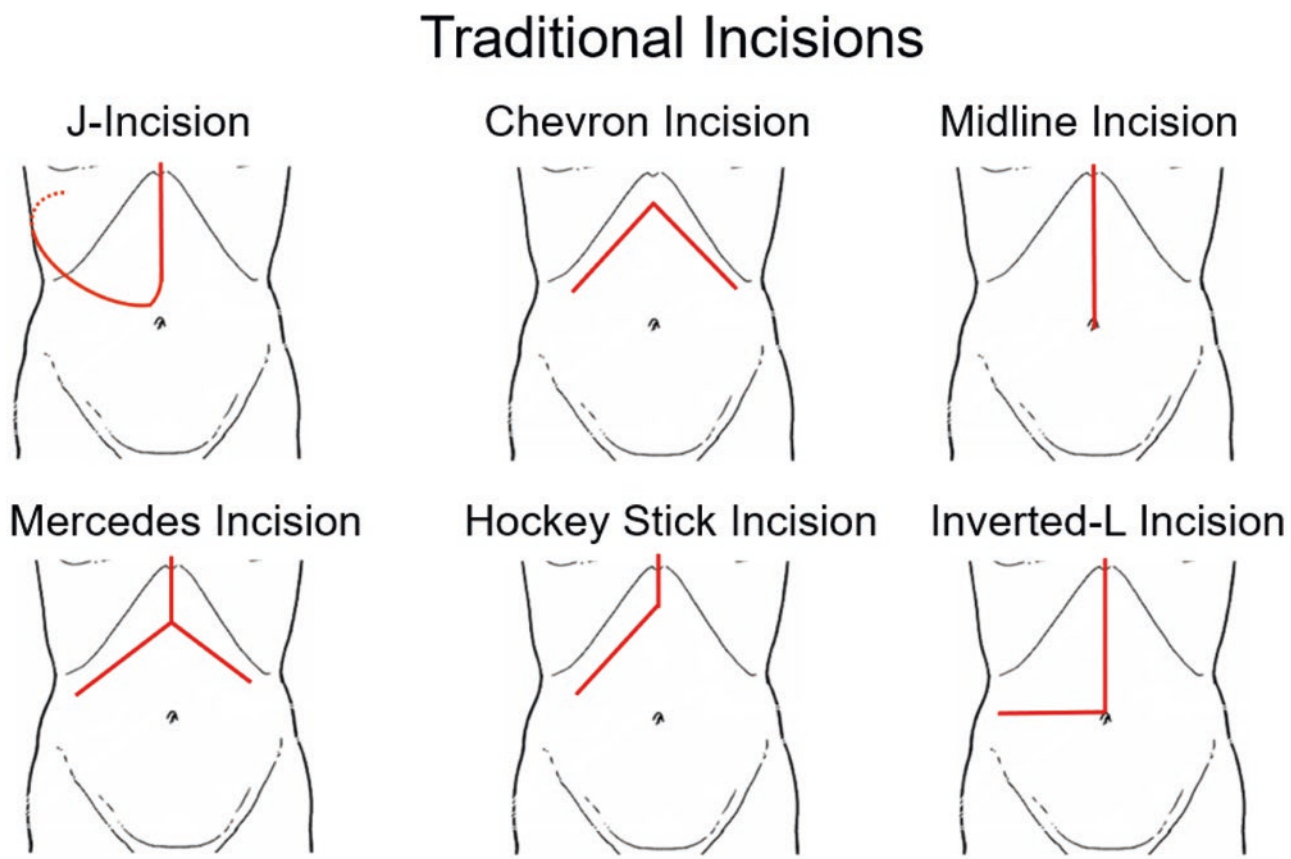

Fig. 3.1 Traditional incisions used for hepatectomy for colorectal liver metastases

An upper midline incision has been shown to be useful for left-sided operations, such as donor hepatectomy, as well as for resection of lesions ≤5 cm [2]. However, Kim and colleagues describe the safe application of upper midline laparotomies for even right-sided operations in well-selected patients [2]. In their description, the midline incision allows for visualization of the confluence of the hepatic veins and parallel to planes of major transection, and also allows for placement of a hanging maneuver [2]. This emphasizes the importance of physical examination, patient body habitus, and optimal retraction systems when selecting incisions, rather than a "one-size-fits-all" approach.

Despite its widespread use, the midline laparotomy incision is frequently inadequate for right retroperitoneal exposure as well as major right-sided hepatectomies, without being continued well below the umbilicus. The inability to view the IVC en face may preclude safe dissection of right posterior tumours, particularly if they involve the retroperitoneum and adrenal gland, right inferior accessory hepatic veins, short hepatic veins, or the IVC itself [3]. Thus, HB surgeons frequently opt for other incisions that allow for increased right-sided exposure.

3.2.2 J Incision (Makuuchi Incision)

The J incision, or Makuuchi incision, involves an upper midline laparotomy from the level of the inframammary fold to 5 cm above the umbilicus, followed by a gentle J curve along the ninth intercostal space to the posterior axillary line (Fig. 3.2) [4, 5]. This incision can be extended into a thoracoabdominal approach including entry into the thoracic cavity, allowing the surgeon luxurious visualization and control of the entirety of the right liver, hepatocaval confluence, diaphragmatic attachments, or tumour involvement, as well as efficient application of total vascular exclusion [6]. Further, the incision can be extended superiorly to include a median sternotomy in extreme circumstances.

Some surgeons advocate for extension of the incision into the thoracic cavity for the majority of right hepatectomies for safety; however, the transection of chest wall structures and diaphragm may lead to increased postoperative morbidity [7]. In fact, in a landmark report of 1056 hepatectomies by Imamura and colleagues, patients who underwent thoracoabdominal J incisions had significantly increased risk of pulmonary and overall complications [6]. Therefore, this approach should be only selectively used.

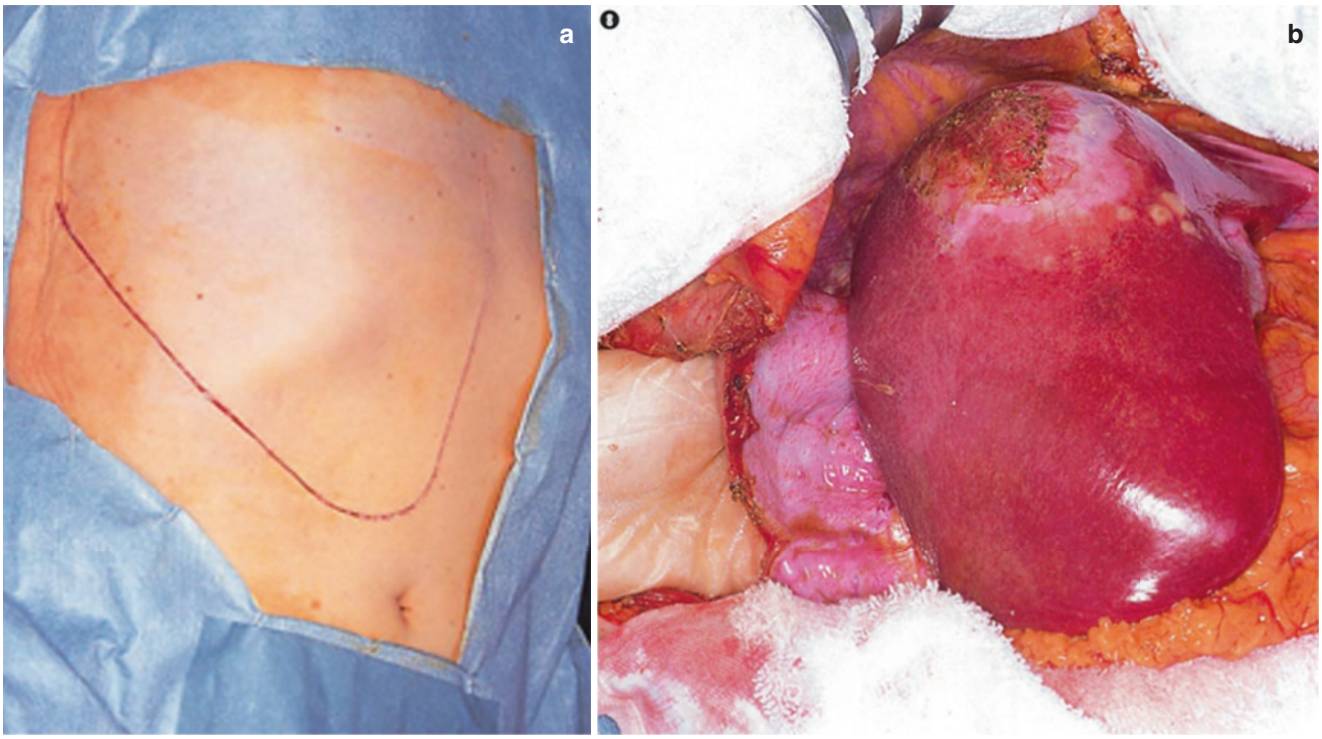

Fig. 3.2 Makuuchi incision. (**a**) Surface marking for planned Makuuchi incision with extension into right thoracic cavity. (**b**) Exposure from Makuuchi incision with a surgeon's hand in the right chest above the diaphragm. (Adapted with permission from: Makuuchi et al. [5])

3.3 "Inverted-L" or Modified Makuuchi Incision

George Clemens Perthes of Tübingen, Germany, is credited with the first description of the "Inverted-L" incision for the management of choledocholithiasis in 1910 [8, 9]. In his text "About Laparotomy Incisions for Operations of the Biliary Tree," Perthes illustrates an upper midline laparotomy to two finger-breadths above the umbilicus, followed by a 90-degree lateral extension until the fibers of the external oblique were exposed [8–10]. The anterior rectus sheath is then opened one finger-width off of midline in the paramedian location and the index finger of the left hand of the surgeon was inserted just below the posterior surface of the right rectus muscle and the right posterior rectus sheath (Fig. 3.3). After placement of two rows of mattress sutures to fix the rectus muscle to its anterior sheath, the muscle was then transected transversely and reflected cephalad over the costal margin (Fig. 3.3). Next, an oblique incision was made in the posterior sheath below and parallel to the costal margin to enter the peritoneal cavity (Fig. 3.3). This approach is further described in transactions of a meeting of the New York Surgical Society in 1912: Dr. H.M. Lyle of St. Luke's Hospital in New York described the use of a "Perthes's incision" for a bile duct exploration of a 57-year-old woman with obstructive jaundice from choledocholithiasis. Further, the approach was advocated for by H.M.W. Gray of Aberdeen, Scotland, as "an improved route of approach to the gall-bladder and biliary passages," with several advantages, such as the ease of approach, no risk of paralysis of the rectus muscle due to division of nerve innervating the upper rectus, more effective retraction of the stomach and intestines, and much reduced risk of hernia due to different locations of incisions in the posterior and anterior rectus sheath [10].

Almost a century later, a modern description of the "Inverted-L" or "Modified Makuuchi" incision by Chang and colleagues revisited the application of this approach to hepatectomy (Fig. 3.4) [3]. It is similar to the traditional J incision in that it allows for superb liver and right retroperitoneal structures, including a superior en face view of the IVC, hepatocaval junction, and esophageal hiatus. However, the Inverted-L incision *does not divide intercostal muscles*, and therefore reduces the risk for postoperative intercostal nerve pain and abdominal wall muscle atrophy [3]. Moreover, the placement of the incision lies at an area with rich blood supply and without dividing major perforating blood vessels. Therefore, this allows for optimal blood supply for wound healing and prevention of ischemic flaps (Fig. 3.5). The Inverted-L is different from Perthes's incision as originally described as the posterior sheath is entered at the same level as the anterior sheath and muscle, and does not include suture fixation of the rectus muscle. Specifically, the upper midline portion of the incision curves laterally as an *inverse L* at the level of the umbilicus and proceeds laterally ideally within the natural abdominal skin fold and ends at the midpoint

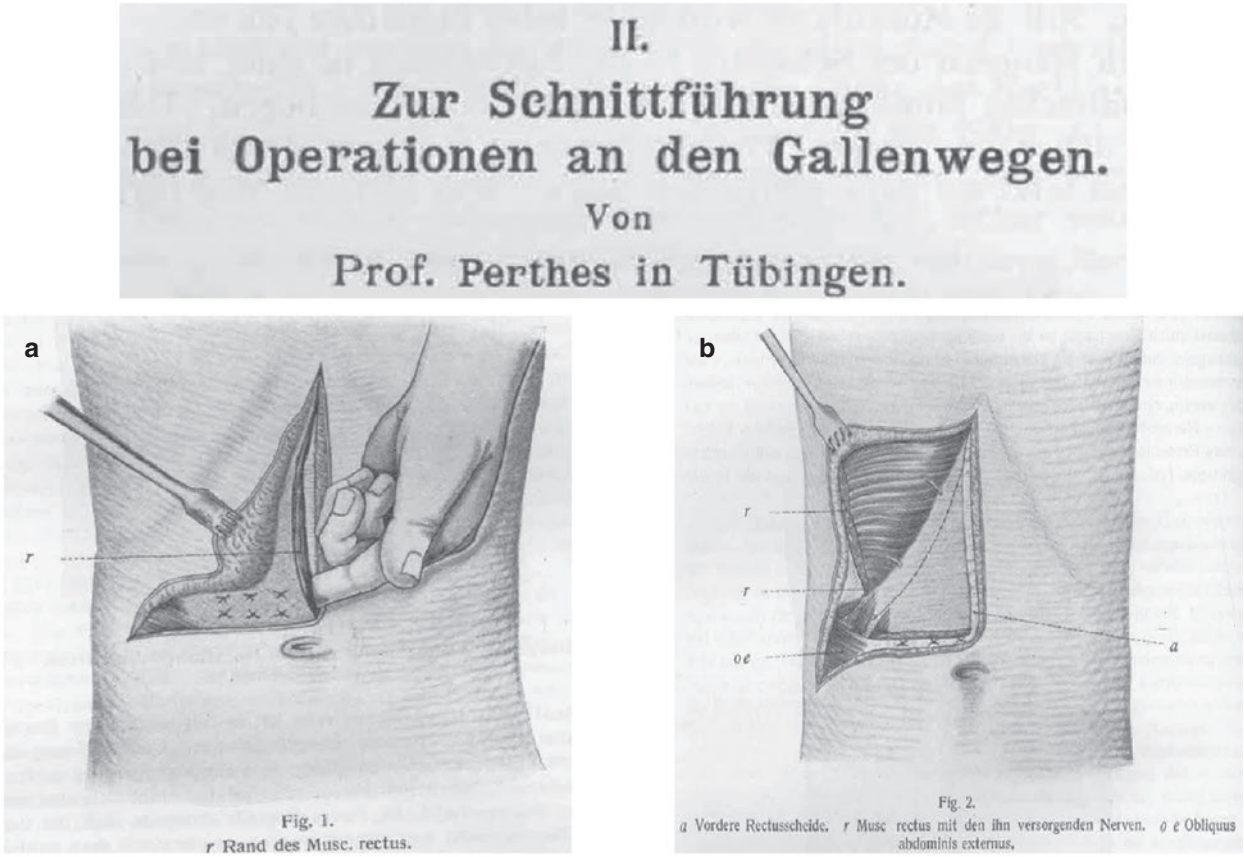

Fig. 3.3 Perthes's incision. (**a**) Suture fixation of the anterior rectus sheath and musculature. (**b**) Reflection of the right abdominal wall musculature and incision of the posterior sheath in the subcostal position

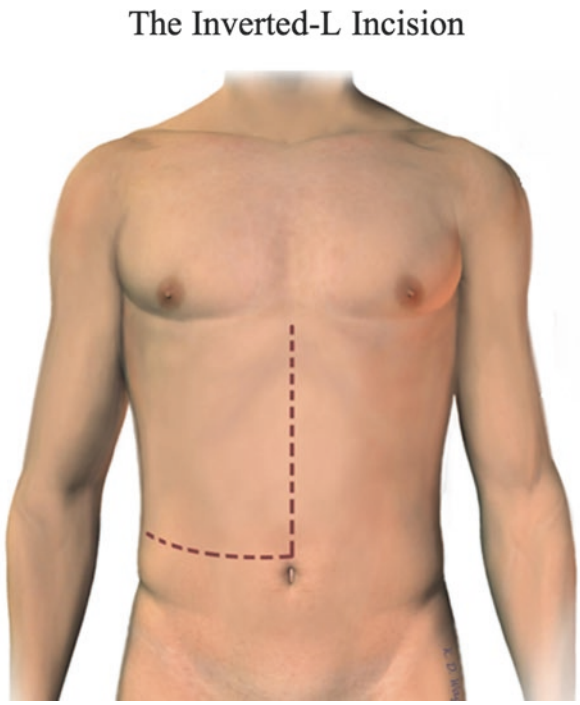

Fig. 3.4 The Inverted-L incision. (Adapted with permission from: Chang et al. [3])

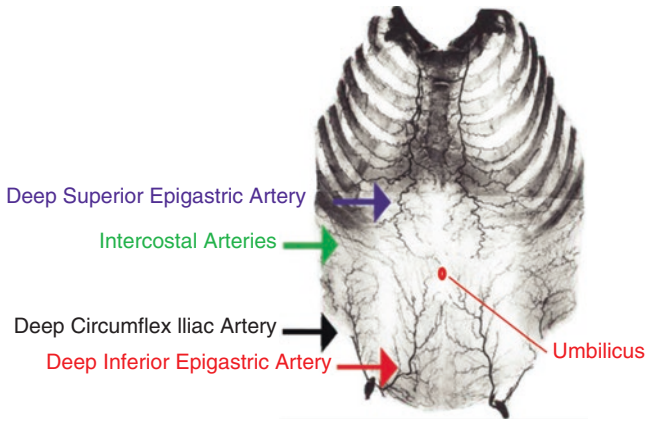

Fig. 3.5 Blood supply to the abdominal wall. (Adapted with permission from: Rozen et al. [13])

between the anterior iliac spine and the lowest rib. As there is no upward J toward the chest wall as in the Makuuchi incision, this modification allows for the incision to remain between dermatomal distributions of the nerves innervating the skin and musculature of the abdominal wall, thus reducing skin numbness and paresthesia, pain, and muscle atrophy [3]. The excision of the xiphoid process is commonly performed, however, may be at the discretion of the surgeon.

Lastly, the left hemiabdomen is easily visualized for synchronous operations via the Inverted-L incision *without any need for left-sided extension of the incision.*

The optimal exposure provided by the Inverted-L incision is realized with optimal retraction, and the oncology Thompson retractor is an excellent system for this purpose (Thompson Surgical Instruments, Inc., Traverse City, Michigan). The versatility of the Thompson retractor allows for optimal exposure of the left and right upper quadrants dynamically, as well as moving to the lower abdomen should that be required (Fig. 3.6). The right sidebar is positioned toward the floor and angled laterally to facilitate downward and right-sided retraction and, thus, excellent view of right retroperitoneal structures and an en face view

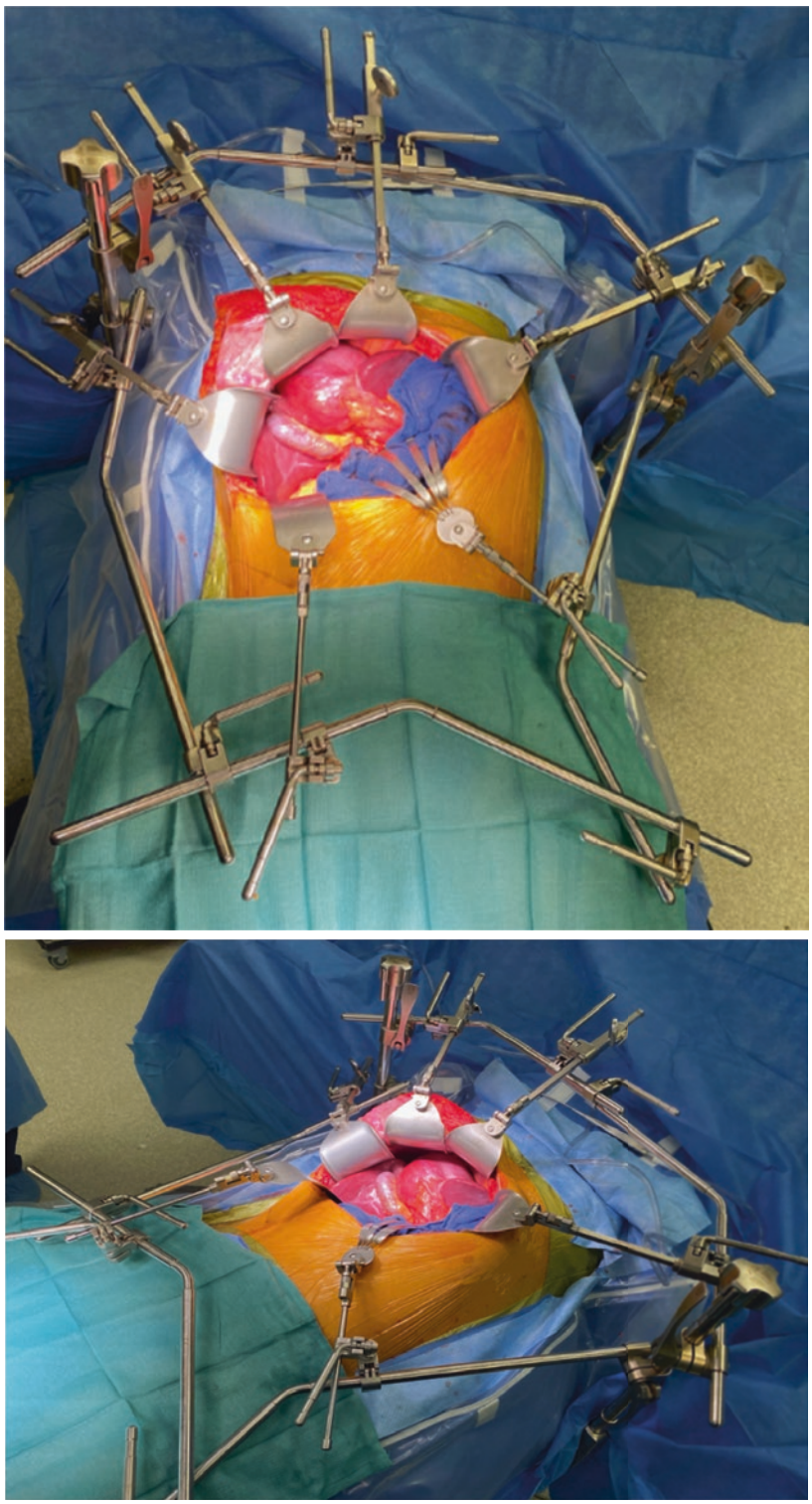

Fig. 3.6 Optimal retraction of the Inverted-L incision and subsequent exposure

of the IVC. The placement of the right and left upper quadrant bladder blades facilitates retraction of the bilateral costal margins cephalad (Fig. 3.6). Additionally, a malleable retractor may be placed over the right kidney for downward retraction, facilitating the view of the right adrenal and IVC (not shown).

Meticulous attention is given to closure of the Inverted-L incision, reconstructing the abdominal wall in an anatomic fashion to mitigate risk for incisional hernia. Closure is initiated with three interrupted braided 0 polyglactin 910 sutures at the cephalad portion of the upper midline incision to cover the xiphoid process and reconstruct the upper abdominal wall fascia. Next, the rectus sheath is reconstructed with three of the same interrupted stay sutures at the corner (the corner of the "L") of the incision and one at the edge of the right rectus muscle, therefore aligning the incision and serving as internal retention sutures. These sutures are secured with hemostats to facilitate atraumatic retraction to the abdominal wall during further closure. The remainder of the wound is closed using running looped 1-0 polydioxanone suture. The lateral extension of the Inverted-L is closed in two layers with the first layer closing the transversus abdominis muscles, the posterior rectus sheath, and the junction with the midline aspect of the incision. The second layer closes the oblique muscles and the anterior rectus sheath, stopping at the junction with the midline. The 0 polyglactin 910 retention sutures are then tied. The subcutaneous tissue is then closed in layers.

3.4 Other Incisions

Other incisions that may be used for hepatectomy include the extended subcostal incision, bilateral subcostal (chevron), the right or left subcostal (Kocher/Kehr), "Mercedes" incision, and reversed T incision (Fig. 3.1) [11, 12]. Shortcomings of the aforementioned incisions include suboptimal exposure of the superior liver segments and/or the midgut structures (extended subcostal, or "hockey stick" incision), frequent need for left-sided extension (subcostal incisions), or need for cephalad extension over the xiphoid process (bilateral subcostal). The Inverted-L incision does not cross the midline in the upper aspect as many of the aforementioned incisions do, and with extension from above the xiphoid process to the umbilicus luxurious exposure of both left- and right-sided structures is afforded. Further, the umbilical region of the abdominal wall has an abundant blood supply, which is optimal for wound healing [13]. The Inverted-L incision preserves the neurovascular supply on either side of the incision, thus preventing an area of relative ischemia and denervation at the umbilicus, or opposite sides of the other described incisions. This may lead to a decrease in wound complications, pain, and pulmonary complications as compared to other approaches.

3.5 Conclusion

Adequate exposure requires consideration between many possible incisions; however, visualization of critical structures is imperative. Depending on the proposed operation, many incisions may be considered for exposure. However, for major hepatectomy and superior view of both left- and right-sided structures, the Inverted-L incision is preferred. Moreover, the en face view of the inferior vena cava and right-sided retroperitoneal structures, as well as the muscle and nerve-sparing aspects of the Inverted-L incision make this approach particularly advantageous for both intraoperative exposure and patient recovery. Careful consideration of technical aspects required for the proposed hepatectomy as well as patient characteristics, such as prior incisions, is required by liver surgeons to select the optimal incision to perform a safe hepatectomy for patients with CLM.

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Parenchymal Preservation in the Operative Management of Colorectal Liver Metastases

4

Daniel W. Nelson and Timothy J. Vreeland

Learning Objectives

- Current available evidence has demonstrated parenchymal-sparing hepatectomy to have an improved safety profile compared to more extensive resection.
- Meanwhile, parenchymal-sparing hepatectomy does not compromise oncologic outcomes.
- Parenchymal-sparing hepatectomy increases the potential for salvageability with repeat hepatectomy following intrahepatic recurrence.
- Widespread use of parenchymal-sparing hepatectomy has led to other advancements, such as the two-stage hepatectomy, which have extended resectability criteria to many additional patients once considered unresectable.
- Parenchymal-sparing hepatectomy should be considered the standard of care for resection of colorectal liver metastases when feasible.

4.1 Introduction

For nearly three decades, complete resection has been the foundation of the multidisciplinary management of patients with colorectal liver metastases (CLM), achieving 5- and 10-year overall survival (OS) rates of 38% and 26%, respectively [1]. During this time, across the field of surgical oncology, the treatment paradigm has shifted away from the belief that quality oncologic outcomes can only be obtained through radical resections, and toward more precise resection that balances surgical aggressiveness and morbidity. Resection of CLM is no exception. The initial focus for resection of CLM was based on what was technically feasible and safe, which consisted of anatomic resection (AR) along well-understood transection planes. Over time, as experience has grown, surgeons have developed new techniques for more precise dissection of the liver parenchyma. This, in combination with the expansion of intraoperative ultrasound (IOUS), has allowed surgeons to precisely resect tumours while leaving behind normal hepatic parenchyma and led to the concept of parenchymal-sparing hepatectomy (PSH). Further improvements in perioperative care, identification of effective chemotherapeutic regimens, and development of novel surgical strategies such as portal vein embolization and two-stage hepatectomy have allowed for an ever-increasing proportion of patients with CLM to be considered candidates for curative-intent resection [2, 3].

The basic tenets of hepatic metastasectomy are (1) removal of all disease with clear pathologic surgical margins, and (2) preservation of sufficient remnant hepatic parenchyma [2]. Two well-described operative strategies include AR and non-anatomic PSH. While AR consists of formal hepatic resection based on portal tributaries to tumour bearing parenchyma with a negative margin [4], PSH aims to achieve an R0 resection without unnecessarily sacrificing uninvolved functional liver parenchyma [3]. It is important to realize there is some confusion around these terms, as anatomic resection of a single segment of the liver is relatively parenchymal-sparing as compared to anatomic lobectomy. In the majority of the literature on this topic, and for the purposes of this paper, however, PSH refers to non-atomic resections intended to achieve the goals as outlined above.

Historically, AR was favored largely based on improved outcomes associated with this operative strategy in the treatment of hepatocellular carcinoma (HCC) [5], and single-institution series reporting improved rates of tumour clearance in CLM [6]. With improved understanding of the biologic differences between HCC and CLM, evidence has increasingly supported the concept of PSH in the treatment of CLM. Unlike HCC, where microvascular invasion represents a key factor associated with early recurrence [7], micrometastatic disease is rarely identified around CLM and,

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Table 4.1 Summary of systematic reviews and meta-analyses of studies comparing perioperative outcomes and survival among patients undergoing parenchymal-sparing hepatectomy versus anatomic resection for colorectal liver metastases

Author	Year	Study type	No. of patients	Postoperative morbidity	Postoperative mortality	Margin positivity	Overall survival
Sui et al. [4]	2012	Meta-analysis: 7 non-RCTs	AR 989 vs. PSH 673	OR = 1.27; CI = 0.79–2.05; $p = 0.32$	OR = 1.26; CI = 0.43–3.67; $p = 0.68$	OR = 0.64; CI = 0.31–1.32; $p = 0.23$	[a]OR = 1.13; CI = 0.92–1.39; $p = 0.24$
Moris et al. [3]	2017	Systematic review: 12 non-RCTs	AR 1414 vs. PSH 1087	AR = 6.3–29.3%; PSH = 3.2–27.8%; $p = 0.22$	AR = 0–3.2%; PSH = 0–3.7%; p = NR	AR = 71.6–98.6%; PSH = 66.7–100%; $p = 0.58$	[a]AR = 44.6%; PSH = 44.7%; $p = 0.97$
Tang et al. [9]	2016	Meta-analysis: 21 non-RCTs	AR 3034 vs. PSH 2172	OR = 1.68; CI = 1.13–2.50; $p = 0.01$	OR = 3.74; CI = 1.60–8.75; $p = 0.002$	OR = 0.79; CI = 0.49–1.29; $p = 0.35$	OR = 1.06; CI = 0.95–1.18; $p = 0.18$
Deng et al. [10]	2019	Systematic review and meta-analysis: 18 non-RCTs	AR 3107 vs. PSH 3974	RR = 1.39; CI = 1.16–1.66; $p < 0.001$	[b]RR = 3.36; CI = 1.71–6.60; $p < 0.001$	RR = 0.86; CI = 0.71–1.03; $p = 0.09$	HR = 1.01; CI = 0.94–1.08; $p = 0.82$

AR anatomic resection, *CI* confidence interval, *NR* not reported, *OR* odds ratio, *PSH* parenchymal-sparing hepatectomy, *RCT* randomized controlled trial, *RR* relative risk

[a] Five-year overall survival

[b] Ninety-day mortality

if present, is typically found within 5 mm of the main tumour, rather than tracking along inflow pedicles [8].

Although randomized controlled trial data are lacking, a significant body of literature has accumulated comparing perioperative and oncologic outcomes between AR and PSH including several systematic reviews and meta-analyses (Table 4.1) [3, 4, 9, 10]. Despite growing evidence in support of non-anatomic resection of CLM, controversy persists as illustrated by a recent survey of 43 expert liver surgeons, which demonstrated no inter-rater agreement with regard to optimal therapeutic resection strategy in 10 cases involving patients with CLM [11].

In this chapter, we review the available literature comparing anatomic resection and parenchymal-sparing hepatectomy in the treatment of CLM.

4.2 Perioperative Outcomes

4.2.1 Perioperative Morbidity

In the absence of randomized controlled trials, the best level of evidence available for comparing perioperative outcomes between AR and PSH for CLM is derived from aggregate data from single- and multi-institutional retrospective series in systematic reviews and meta-analyses [3, 4, 9, 10, 12].

In the earliest published meta-analysis, Sui et al. examined seven non-randomized comparative studies and found that PSH was associated with shorter operative duration, decreased transfusion requirements, and a non-significant trend toward less intraoperative blood loss, although significant heterogeneity was found between studies [4]. In this series of 1662 patients (989 AR vs. 673 PSH), overall morbidity was not different between resection approaches [4].

In a subsequent systematic review, Moris and colleagues examined 12 comparative studies and found that median estimated blood loss was equivalent between resection approaches, although the rate of blood transfusion was higher among patients undergoing AR [3]. In the only series to compare duration of hospitalization, the authors found no difference in median length of stay between AR (7–15 days) and PSH (6–17 days; $p = 0.75$) [3]. Similar to Sui et al., overall major morbidity was not different between resection methods with major postoperative complications reported in 3.2–27.8% of patients undergoing PSH and 6.3–29.3% of patients undergoing AR [3].

Two additional meta-analyses have since been performed examining 18–21 comparative studies, each comprising more than 5000 patients undergoing AR or PSH for treatment of CLM [9, 10]. Both series consistently demonstrated shorter operative times associated with PSH. While Tang et al. found no difference in volume of intraoperative blood loss between cohorts, blood transfusion was more likely among patients undergoing AR [9]. Conversely, Deng et al. found that AR was associated with significantly increased blood loss and a more than two-fold increased risk for transfusion [10]. In regard to postoperative complications, both series demonstrated increased rates of postoperative morbidity associated with AR compared to PSH with Tang et al. finding AR to be associated with a 68% increased odds of major morbidity (odds ratio [OR] = 1.68; confidence interval [CI] = 1.13–2.50) and Deng et al. confirming a 39% increased relative risk (RR) of postoperative complications with AR (RR = 1.39; CI = 1.16–1.66) [9, 10].

4.2.2 Perioperative Mortality

With 90-day mortality rates of major hepatectomy ranging from 2.2% for right hepatectomy and up to 7.3% with more complex anatomic resections [13], perioperative mortality has generally favored PSH in the treatment of CLM. In the meta-analysis by Sui et al., perioperative mortality was low at 0.9% and 0.7% for AR and PSH groups, respectively [4]. Similarly, Moris et al. demonstrated low rates of early postoperative death following both PSH (0–3.7%) and AR (0–3.2%) [3]. Conversely, Tang et al. found a nearly fourfold increased odds of 30-day mortality following AR (OR = 3.74; CI = 1.60–8.75) [9] and Deng et al. demonstrated a 3.36 times increased relative risk of 90-day mortality following AR compared to PSH (CI = 1.71–6.60) [10].

Ultimately, while both AR and PSH can be accomplished safely, the major difference comes in the risk of posthepatectomy liver failure. With PSH, it is exceedingly rare to leave so little functional liver remnant that the patient develops liver failure. On the other hand, the incidence of posthepatectomy liver failure for a right hepatectomy may exceed 10% [13]. Furthermore, as referenced above, mortality from PSH is uncommon, while mortality after AR is three to four times as likely. Thus, if other measures of success can be achieved with equal frequency, and PSH is an option, it should be favored in hopes of avoiding perioperative mortality.

4.3 Oncologic Outcomes

Despite favorable perioperative outcomes, detractors of PSH have raised concerns about compromising oncologic outcomes in exchange for lower morbidity and mortality. AR was historically the treatment of choice, resecting the entire lobe of the liver that contained a metastasis to ensure a wide margin in hopes of decreasing recurrence and improving long-term oncologic outcomes. With growing evidence that PSH can provide equivalent oncologic outcomes, however, such radical resections have since been proven unnecessary for the majority of patients with colorectal liver metastases.

4.3.1 Margins

While a thorough discussion on appropriate margins for resection of CLM is beyond the scope of this chapter and will be discussed in a later chapter within this textbook, a brief discussion is necessary to understand the interaction between margins and PSH.

Over the last three decades, there has been a steady decrease in what is considered the desired resection margin, from 2 cm down to 1 mm, and this has simultaneously translated into a steady move away from AR and toward PSH [14]. The recommendations for wider margins arose in the 1980s, when Ekberg et al. recommended that a 2-cm margin was ideal, but a 1-cm margin was the minimum necessary [15]. Starting in the 2000s, however, several retrospective analyses showed that margins less than 1 cm were acceptable and did not affect oncologic outcomes [16–18]. With the understanding that subcentimeter margins were acceptable, an anticipated margin of less than 1 cm no longer precluded patients from curative-intent resection, extending resectability criteria to more patients.

Currently, the minimum necessary margin for an R0 resection is generally considered to be 1 mm, but some have questioned the utility of even a 1-mm margin. While this 1-mm margin is associated with improved overall survival in some retrospective analyses [19, 20], other analyses have shown that R1 resection is associated with more intrahepatic recurrence, but does not affect overall survival [21, 22]. In fact, there may be situations where a planned R1 resection may be acceptable as some have championed the idea of "R1-vascular" resections [23], which will be addressed in a later chapter within this book. This understanding that smaller margins are acceptable has opened the door to more precise dissection of tumours of key intrahepatic vascular and biliary structures, rather than the previous practice of resecting any structure within 1 cm of a tumour. This, in turn, has led to an increase in the utilization of PSH, and greatly expanded the cohort of patients who are considered to have resectable disease.

4.3.2 Recurrence and Survival

Regardless of data surrounding surgical margins, proponents of AR have raised concerns that the widespread use of PSH could lead to increased risk of local or distant recurrence after curative-intent liver resection. The accrued data on this topic, however, show that oncologic outcomes are equivalent between the two resection strategies. Again, with the lack of prospective clinical trials on this topic, we are left with only meta-analyses and retrospective reviews. Data supporting oncologic equivalence of PSH started in the 2000s. Zorzi et al. compared PSH, termed "wedge resection" in their analysis, to anatomic resection in 2006, showing no difference in positive surgical margins, recurrence rates, or patterns of recurrence [2]. A similar retrospective review from Memorial Sloan Kettering in 2008 showed that an increase in PSH over time led to decreased perioperative mortality without change in disease-specific survival or intrahepatic recurrence [24]. Since this time, there have been numerous studies looking at this topic with similar conclusions: oncologic outcomes are equivalent between PSH and AR [25].

Some critics of PSH have raised concerns that, even in the face of equivalent survival, certain outcomes, such as local or

intrahepatic recurrence, could be worse with PSH. When these specific outcomes are examined, however, there is again no difference between PSH and AR [26].

A final criticism of PSH is that it is not applicable to deeper metastases. While such location of disease can be technically more difficult to resect with a parenchymal-sparing approach, a study by Matsuki et al. is demonstrative of the efficacy of PSH in such scenarios. In their retrospective review of patients with lesions located at least 30 mm from the liver surface, they showed PSH led to half the liver volume being resected, but no detriment in margin positive rate and overall, recurrence-free, or liver recurrence-free survival. Additionally, they note that major hepatectomy without portal vein embolization would not have been possible in 40% of patients who underwent PSH due to small predicted functional liver remnant after proposed AR [27].

4.3.3 Salvageability

Perhaps the most compelling reason to perform a PSH is that intrahepatic recurrence is common regardless of the chosen strategy for resecting a liver metastasis [28]. In order to be able to continue with curative-intent therapy, whether in the form of repeat resection or additional chemotherapy, having more functional liver remaining after initial hepatectomy is an advantage. Specifically, PSH preserves salvageability, which is the ability to complete repeat curative-intent hepatectomy at time of intrahepatic recurrence. This was first reported by Mise et al., who showed in a retrospective review of patients with resectable, solitary metastases <3 cm in size, that PSH led to higher rates of re-resection at time of recurrence over AR [29]. In patients who did have intrahepatic recurrence, this increase in salvageability translated into improved 5-year survival in patients who underwent initial PSH as compared to those who had initial AR. Other studies have demonstrated similarly high rates of salvageability in the case of intrahepatic recurrence after PSH [26].

Similar to the concept of salvageability, the ability to perform curative-intent resection of bilobar metastases depends entirely on the PSH strategy. The presence of bilobar metastases was once considered a contraindication to curative-intent resection, as it would often be impossible if the only approach available was AR, but is now regularly accomplished through PSH. Finally, the ability to resect metastases throughout the liver while preserving the unaffected nearby parenchyma was a necessary prerequisite for the development of techniques such as the two-stage hepatectomy, and the ultrasound-guided one-stage bilobar hepatectomy, that have extended resectability to situations where patients were once considered unresectable [30–32].

Given that PSH offers improved perioperative outcomes, similar oncologic outcomes, improved salvageability, and improved ability to resect bilobar metastases, it should be considered the treatment of choice for resection of CRLM whenever feasible.

4.4 Special Considerations

4.4.1 Genomic Profiling

The recent understanding of tumour genetics has brought a number of changes to the treatment of metastatic colorectal cancer. These developments have led to the identification of subsets of colorectal cancer that have increased risk of recurrence, such as those with high-risk mutations [33–36]. In addition to the generally higher-risk nature of these patients' disease and high risk of distant recurrence, there is also some evidence of increased risk of local recurrence. Two separate single-institution reviews concluded there is a higher likelihood of satellite lesions, narrower resection margins, and higher rates of positive margins in patients with *RAS* mutated CLM [37, 38].

As a result of these findings, there was a suggestion that PSH might not be appropriate for those patients with high-risk tumours. Margonis et al. performed a single-institution retrospective review of AR versus PSH, focusing on the differential effects of this choice based on *RAS* mutation status. In their study, this group found that recurrence risk was higher for patients with *RAS* mutations after PSH, and recommended AR for all patients with *RAS* mutations [39]. Joechle et al., however, performed a similar review from MD Anderson Cancer Center, where PSH has been pioneered and practiced for two decades. Their study revealed no differences between AR and non-AR, regardless of *RAS* status [40]. Ultimately, there is no strong evidence that patients with any specific mutations require AR, but it is reasonable to adjust margins for patients with genomic profiles that put them at increased risk for satellite lesions and narrow margins.

4.4.2 Minimally Invasive Surgery

A final topic that is becoming important in the treatment of patients with CLM is the role of minimally invasive surgery (MIS). The vast majority of data accrued around the decision between AR and PSH are based on open resections. For a deep metastasis, it is often technically more challenging to perform PSH, preventing the application of PSH in the hands of many surgeons. The feasibility of fully laparoscopic PSH has been shown by early reports [41] and the one randomized trial comparing laparoscopic to open PSH showed decreased complications and shorter hospital stay with laparoscopic resection [42]. Given the promise of these early data, it is

increasingly important that the field develops the skills necessary for MIS PSH so that patients and surgeons are not forced to decide between a PSH and MIS.

4.5 Conclusion

Current available evidence has demonstrated PSH to have an improved safety profile compared to AR without compromising oncologic outcomes. In addition, there has been increasing recognition of the benefits of parenchymal preservation and the potential for salvageability with repeat hepatectomy following intrahepatic recurrence. Finally, the widespread use of PSH has led to other advancements, such as the two-stage hepatectomy, which will be covered in a later chapter in this textbook. There are situations when PSH is not possible or not feasible due to anatomic considerations such as a metastasis with significant contact to a major inflow vessel or multiple hepatic veins, but advanced techniques, such as ultrasound-guided dissection and planned R1 vascular resections, will continue to extend the reach of PSH.

In conclusion, PSH should be considered the standard of care for resection of colorectal liver metastases when feasible.

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Simulation and Navigation

5

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Learning Objectives

- Simulation and navigation are both useful modalities for performing parenchymal-preserving hepatectomy and repeat hepatectomy for the treatment of colorectal liver metastasis (CRLM).
- Simulation and navigation are essential for the intraoperative recognition of shrunken lesions of CRLM after chemotherapy.
- In order to remove downsized or disappearing tumours after chemotherapy, it is necessary to remove areas where the tumours were located on the basis of anatomical information (e.g., the vasculature) as a guide under intraoperative navigation.
- As a modality of intraoperative navigation, intraoperative ultrasound has been a standard method for a long time, followed by indocyanine green fluorescent imaging, real-time virtual sonography, and three-dimensional navigation software.

5.1 Introduction

Hepatectomy is the only potential treatment for colorectal liver metastasis (CRLM), while chemotherapy for colorectal cancer has developed remarkably in recent years. Multiple CRLMs often extend bilaterally in the liver and sometime recur in the remnant liver after resection. Repeat hepatectomy prolongs survival of patient with intrahepatic recurrence [1]. In the initial hepatectomy, the goal is to preserve as much liver parenchyma as possible and/or to preserve major blood vessels for blood perfusion in the remnant liver parenchyma to allow for future repeat hepatectomy. Parenchymal-preserving hepatectomy is now considered the standard surgical strategy for treatment of CRLM. However, it requires meticulous surgical planning to preserve the functioning liver parenchyma [2]. Therefore, surgical planning, including preoperative simulation and intraoperative navigation, is essential for the above-mentioned surgical strategy for treatment of CRLM.

Preoperative chemotherapy is often performed to control tumour progression, especially in patients with multiple CRLMs; however, the detection of downsized or disappearing tumours may be difficult during surgery. Despite the radiographic positive effect of chemotherapy, a complete response of chemotherapy for CRLM is rare [3]. Hepatectomy should be additionally performed even for chemotherapy-responsive lesions. To remove downsized or disappearing tumours after chemotherapy, it is necessary to remove the area where the tumours were located on the basis of anatomical information (e.g., the vasculature) as a guide under intraoperative navigation. Preoperative simulation and navigation, especially fusion images of tumours before chemotherapy displayed on the latest image play an important role. As a modality of intraoperative navigation, intraoperative ultrasound (IOUS) has been the standard conventional navigation method during hepatectomy for a long time, followed by contrast-enhanced IOUS, and indocyanine green (ICG) fluorescent imaging. Real-time virtual sonography (RVS) and three-dimensional (3D) navigation software have been recently developed. An update of these simulation and navigation modalities is presented in this chapter.

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5.2 Simulation

5.2.1 Three-Dimensional Simulation Software and Virtual Hepatectomy

Hepatectomy is technically challenging because the intrahepatic vasculature is complex and invisible and because safety volume limit of liver resection depends on the individual hepatic functional reserve. Application of the 3D simulation software helps surgeon understand the relationship between the location of tumour and intrahepatic vasculature preoperatively. This can be the key for a less technically challenging hepatectomy procedure. Additionally, accurate measurement of liver segment using 3D simulation softwares and estimation of hepatic function help surgeons for ensuring safety of aggressive and complicated hepatectomies. Since Hasimoto et al. [4] and Marescaux et al. [5] first reported hepatic surgery simulation using 3D reconstruction of the computed tomography (CT) images in the 1990s, many studies reported the effectiveness of the hepatic 3D simulation software [6, 7]. Mise et al. reported the efficacy of 3D simulation virtual hepatectomy in a large patient cohort [6].

Because CRLMs often develop bilaterally in the liver, preoperative visualization of the relationship between the location of the tumour and intrahepatic vasculature is essential, especially for patients who have tumours located in the deep part of the liver and/or tumours requiring concomitant resection of major vasculature. Moreover, to ensure that the liver parenchyma is preserved as much as possible in cases of high tumour burden or repeat hepatectomy, 3D simulation software was applied before hepatectomy to precisely estimate the future remnant liver volume. Figure 5.1 shows the 3D reconstruction images of the tumour and vasculature in patients with multiple CRLMs using the simulation software (SYNAPSE VINCENT: Fujifilm Medical Co., Tokyo, Japan) before hepatectomy at the authors' institution.

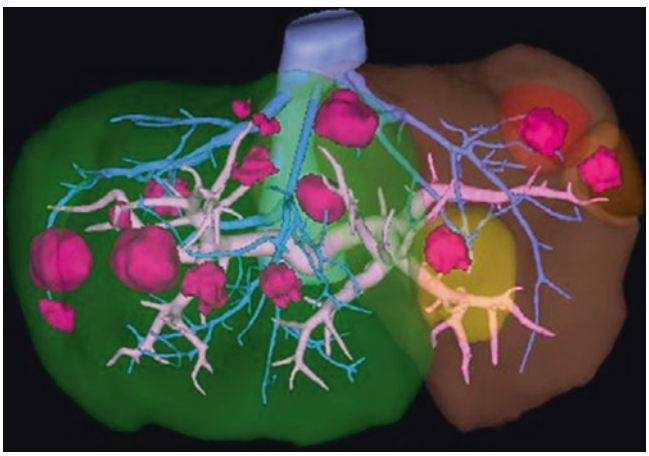

Fig. 5.1 Preoperative three-dimensional reconstruction image for navigation surgery. Three-dimensional reconstruction images in patients with multiple CRLMs are created by SYNAPSE VINCENT (Fujifilm Medical Co., Tokyo, Japan) before hepatectomy. A total of 15 tumours are detected preoperatively. If right hepatectomy and three partial resections of the tumours in left hemiliver are scheduled, volume of the remnant liver would be insufficient. Fortunately, multiple partial resections that are performed for all the tumours located relatively in the peripheral part of the liver, succeeded in their eradication

5.3 Navigation

5.3.1 Intraoperative Ultrasound

Makuuchi et al. developed the application of IOUS in the 1980s. The use of IOUS dramatically improved the accuracy and safety of hepatectomy [8]. Since then, IOUS has been a standard navigation method in both open and laparoscopic hepatectomies. In other words, IOUS has been the most useful navigation tool in hepatectomy for a long time. IOUS also visualizes parenchymal resection lines on the liver that can prevent tumour exposure on the cut surface of the liver. However, the use of IOUS requires surgeons for efficiently manipulating the ultrasound (US) probe and transforming 2D images into 3D images in surgeons' brains. However, the transformed US images are not shared with other healthcare providers. The use of a contrast material for IOUS is helpful for clearly visualizing tumours with unclear boundaries, and improved tumour detection rate during hepatectomy [9]. Figures 5.2 and 5.3 show the images of IOUS without (Fig. 5.2) and with (Fig. 5.3) perfluorobutane microbubbles as a contrast material.

5.3.2 Indocyanine Green Fluorescent Imaging

The soluble dye ICG has been used to estimate liver function because it is rapidly combined with plasma proteins and selectively taken up to the hepatocytes after intravenous injection and subsequently excreted into the bile. ICG fluo-

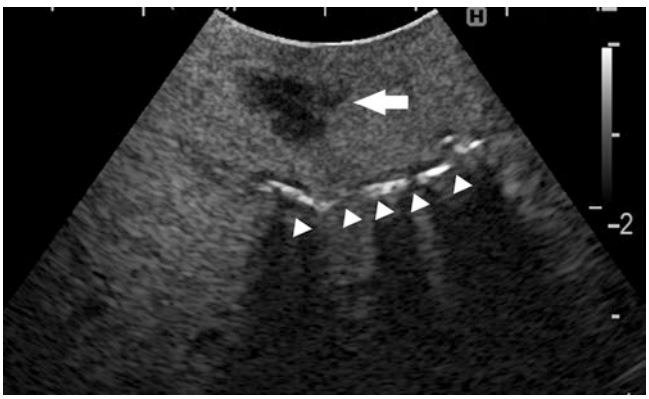

Fig. 5.2 Intraoperative ultrasound image of the tumour and hepatic parenchymal resection line. Tumour (arrow) and hepatic resection line (arrowheads) are visualized by intraoperative ultrasound

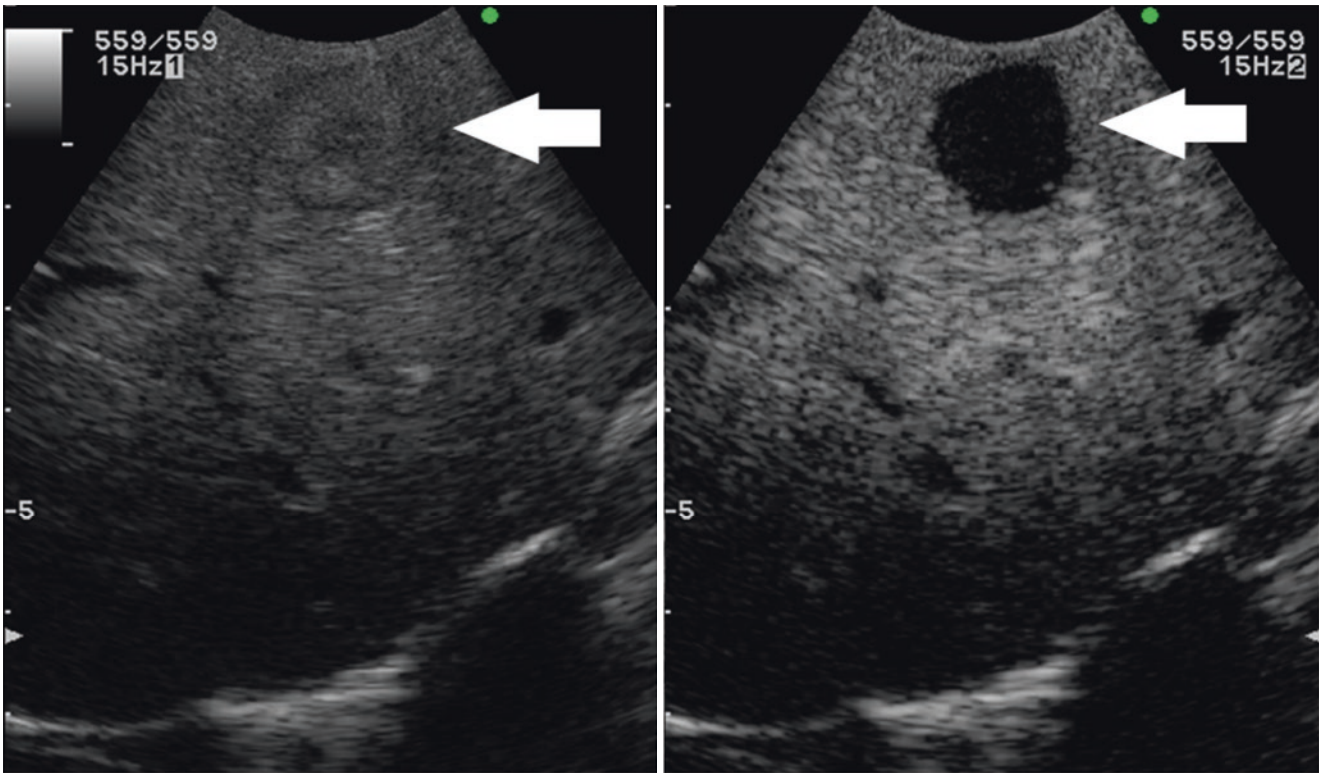

Fig. 5.3 Intraoperative ultrasound with perfluorobutane microbubbles as a contrast material. The tumour (arrow) can be clearly visualized with perfluorobutane microbubbles as a contrast material (right image)

rescence imaging is another method for the effective utilization of ICG. When ICG combined with plasma proteins is illuminated by near-infrared light, it emits fluorescence with a peak wavelength of approximately 840 nm, which lies within the range of absorbance spectra of hemoglobin (<600 nm) and water (>900 nm). Recently, ICG fluorescent imaging has been applied as an intraoperative navigation technique to examine lymph nodes and lymphatic flow, detect tumours close to the liver surface [10], and assist anatomical hepatectomy [11].

In the surgery for the treatment of CRLM, the tumour is detected as having rim fluorescence. This is due to the disorder of biliary excretion in the normal parenchyma that is compressed by the tumour and has trapped ICG-containing bile in it [12]. ICG fluorescent imaging can also identify tiny CRLMs after neoadjuvant chemotherapy (Fig. 5.4). Although a high detection rate of metastases close to and on the cut surface of the liver has been reported, ICG fluorescent imaging can only detect tumours located within approximately 8 mm of the liver surface or of the cut surface of the liver parenchyma. Another limitation of ICG fluorescent imaging is its high false-positive rate that is reported to be as high as 40% [12]. Another application of ICG fluorescent imaging in the surgery for the treatment of CRLM is its navigational use for anatomical resection. Although anatomical resection is not necessary for CRLM, deep disap-

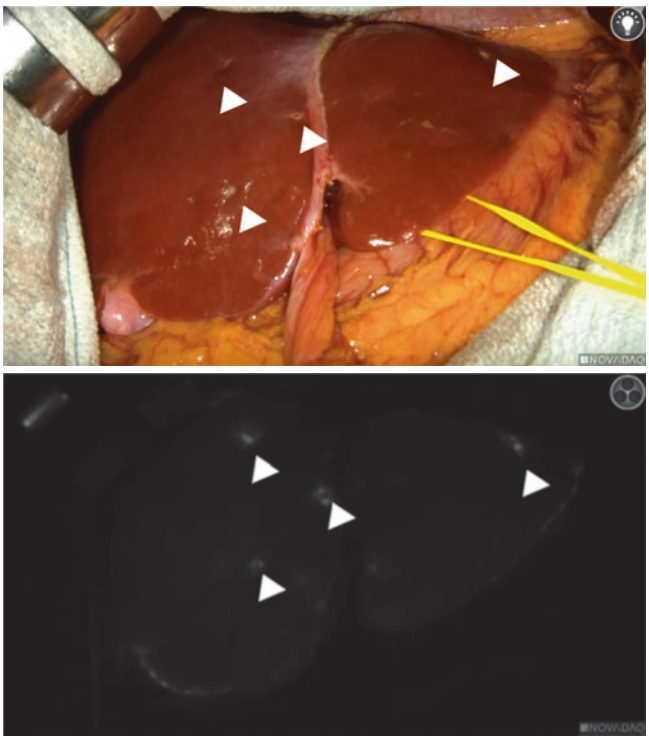

Fig. 5.4 Shrunken minute tumours after chemotherapy visualized by indocyanine green fluorescent imaging. Indocyanine green fluorescent imaging is used to visualize shrunken minute tumours (arrow heads) after chemotherapy

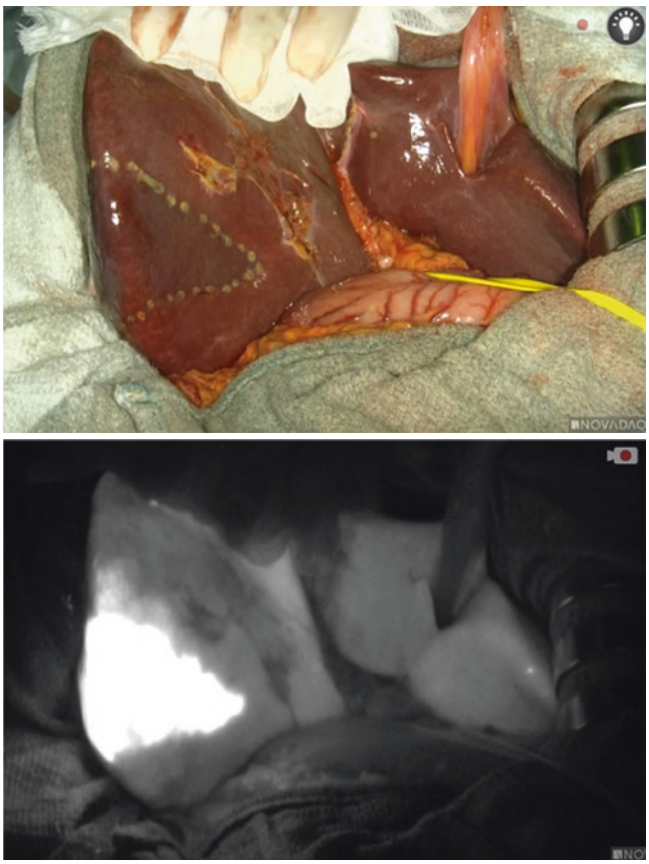

Fig. 5.5 Indocyanine green fluorescent image of anatomical boundary in anatomical hepatectomy. Fluorescent imaging on the liver surface is obtained using the fluorescence imaging system after injecting indocyanine green into a targeted portal vein

pearing metastases after chemotherapy may only be effectively removed with anatomical resection. After a diluted solution of ICG (0.25 mg) mixed with 5 mL of indigo carmine was injected into a targeted portal vein under IOUS guidance, fluorescent imaging of the liver surface was obtained using a fluorescence imaging system (Fig. 5.5). This technique helps for visualizing the boundaries of the liver segment not only on the surface of the liver but also deep part of the liver parenchyma during parenchymal resection. The advantages of ICG fluorescent segmental staining are its high reproducibility and sensitivity. In addition, it stays in the injected segment for a few hours because ICG is taken up by hepatocytes. Standard ICG imaging requires surgeons to confirm the ICG image on the monitor;

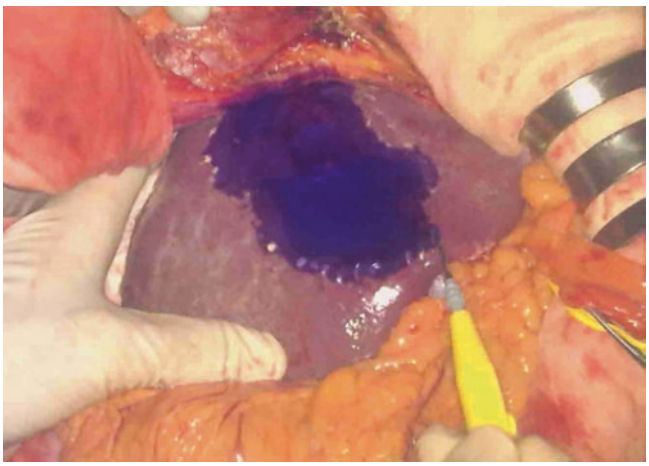

Fig. 5.6 Medical Imaging Projection System image of the liver surface for anatomical resection. Medical Imaging Projection System is used to describe anatomical hepatic segmental boundaries on the liver surface. A surgeon can confirm hepatic boundaries with the naked eye due to the application of projection mapping

however, the Medical Imaging Projection System (MIPS: Mitaka Kohki Co., Ltd., Tokyo, Japan) can directly overlay fluorescence imaging on the liver surface during hepatectomy [13]. Surgeons can confirm segmental boundaries of the liver with projection mapping. This reconstruction system reflects ICG images on the liver and helps surgeons determine segmental boundaries without watching the monitor. The MIPS image is shown in Fig. 5.6.

5.3.3 Real-Time Virtual Sonography

A real-time virtual sonography (RVS) navigation system (Hitachi Ltd., Tokyo, Japan) is a fusion imaging technology that simultaneously provides ultrasonographic images and synchronized two-dimensional CT images side-by-side on a monitor in real time [7, 14]. When the location of the tumour and/or scheduled liver transection line is marked using 3D simulation software preoperatively, the RVS system can act as a navigator by referring to the CT images synchronized with the IOUS image (Fig. 5.7). The advantage of this system in the treatment of CRLM is the ability to recognize the location of disappearing tumours after neoadjuvant chemotherapy or identify tumours that are difficult to detect using IOUS alone.

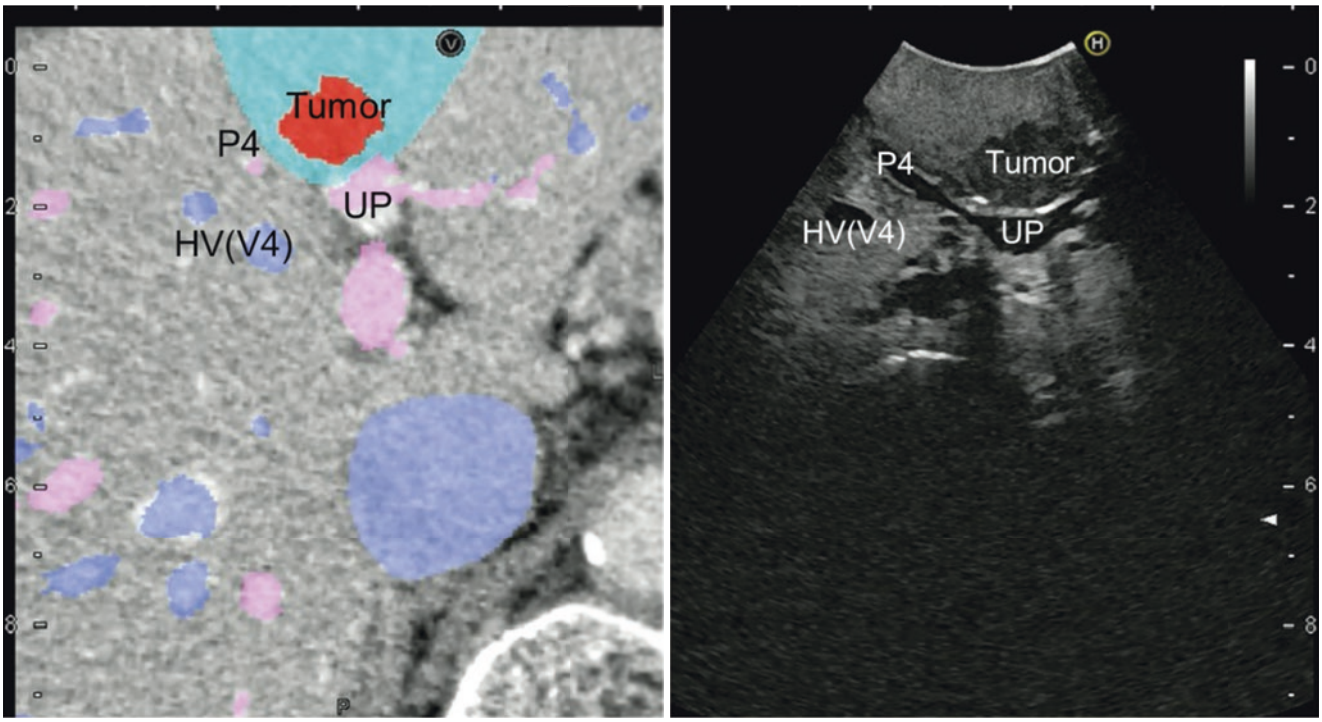

Fig. 5.7 Intraoperative image of the real-time virtual sonography. The real-time virtual sonography system is used as a navigator by referring to computed tomography images synchronized with the intraoperative ultrasound image. Abbreviations: UP, umbilical portion; P4, segment 4 portal vein; HV(V4), hepatic vein draining segment 4

5.3.4 Navigation Software and Augmented Reality

One feasible method of navigation in the surgery of CRLM is the manipulation of 3D reconstruction images on a tablet or monitor during operation. For example, a navigation software named ATRENA system (AMIN Co., Ltd. Tokyo, Japan) was first introduced in Japan (Fig. 5.8). Similar to other navigation softwares, 3D reconstruction images of structures, such as tumours and vasculatures, were created from the CT images preoperatively using the above-mentioned software. The most remarkable feature of this software is its ability to superimpose the image of the tumour shown in magnetic resonance imaging (MRI) before chemotherapy on the 3D reconstruction images of the tumour created by the latest CT image, which is sometimes difficult to detect because of tumour shrinkage due to chemotherapy. Using this software, surgeons can manipulate the image intraoperatively on the tablet and evaluate the location of the disappearing tumour. Furthermore, images of the surgically removed tumours can be erased from the reconstruction images on the tablet one by one, which is a useful function especially in patients with multiple CRLMs.

For laparoscopic surgery, augmented reality (AR) images created by CT or MRI are overlayed on the laparoscopic monitor simultaneously with the correction of the liver deformity semi-automatically during the operation. Bertrand et al. recently reported the feasibility of a new software named Hepataug for laparoscopic partial hepatectomy [15]. This software uses a biomechanical deformable preoperative 3D liver model and visual cues to capture the 3D shape of the liver from the laparoscopic image (Fig. 5.9), successfully detecting subsurface tumours in 17 patients with AR guidance. All patients underwent R0 resection. Although further validations to assess the efficacy of this system are warranted, adjustment of the liver deformity by this system seems to be the key to resolve the difficulty in applying navigation systems in hepatectomy.

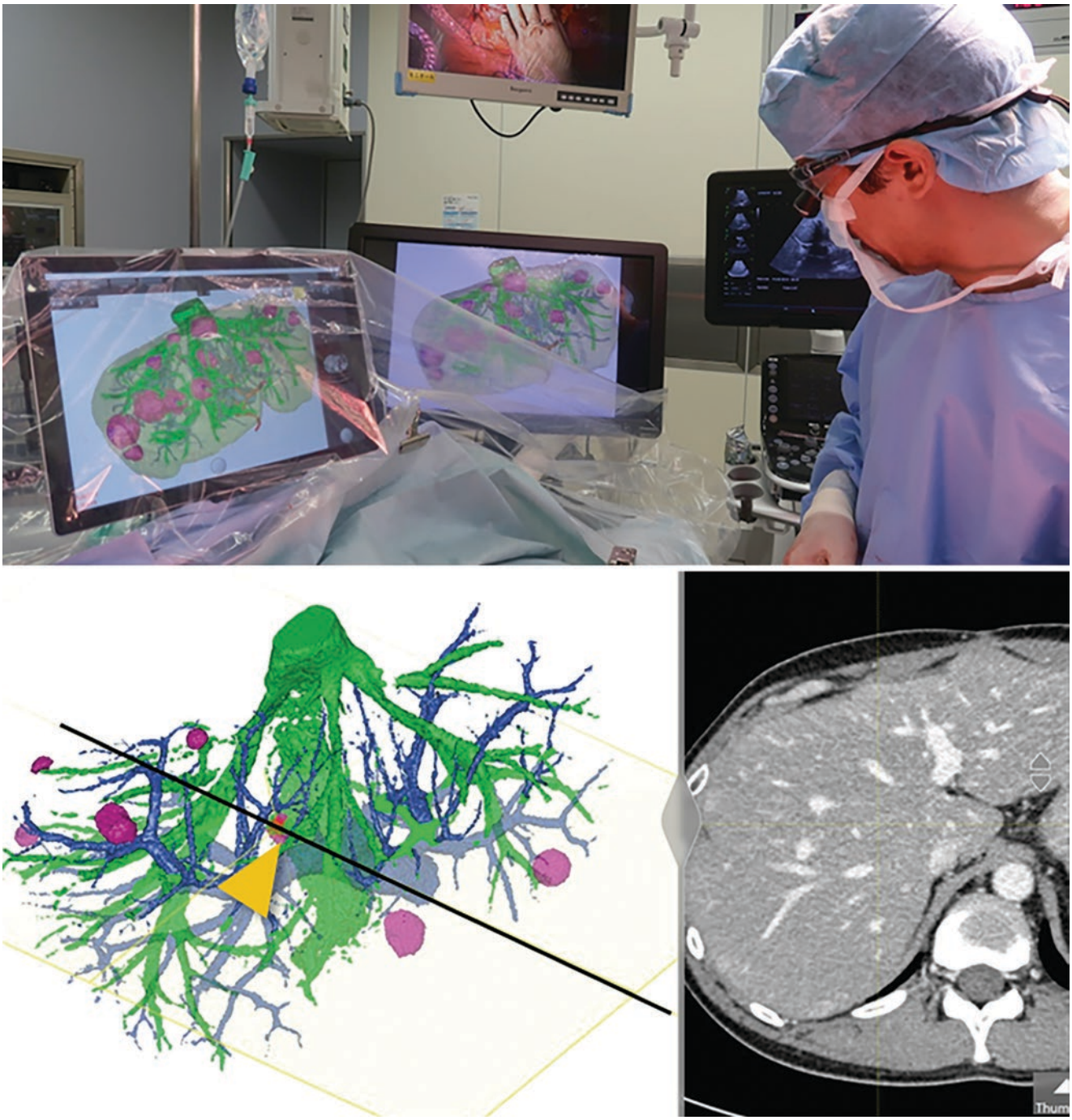

Fig. 5.8 Application of a navigation software in open hepatectomy. Using the navigation software, a surgeon manipulates the image intraoperatively on the tablet by checking the location of the tumour. Operatively removed tumours are erased in the reconstruction images on the tablet one by one in this software ARTENA system (AMIN Co., Ltd. Tokyo, Japan). The black line of the 3D reconstructed image (the lower left panel) indicates the CT image (lower right panel). One tumour (arrow head, the lower left panel) was not visualized in the corresponding CT image (i.e., a disappearing tumour)

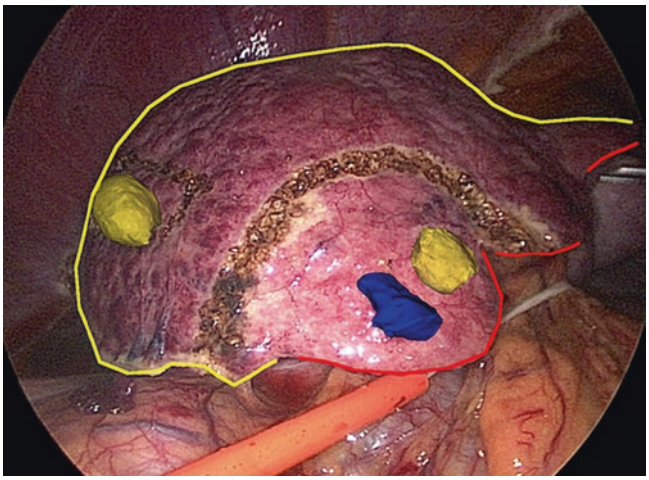

Fig. 5.9 Application of a navigation software in laparoscopic hepatectomy. Bertrand et al. recently reported the feasibility of a new software called Hepataug in laparoscopic partial hepatectomy [15]. This software uses a biomechanical deformable preoperative three-dimensional liver model and visual cues to capture three-dimensional shape of the liver from the laparoscopic image. Tumours that were not visible from the surface were overlaid on the liver surface of the laparoscopic monitor ([15], with permission)

5.4 Conclusion

Since the introduction of IOUS in liver surgery by Makuuchi et al. in the 1980s, various types of surgical navigation techniques have been developed and their usefulness has been reported; however, IOUS remains the gold standard for surgical navigation. Although the simulation and navigation techniques introduced in this section are useful, they require the combined use of IOUS to perform hepatectomy accurately. Future standardization and generalization of navigation technology are required for both open and laparoscopic hepatectomies.

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6 Advanced Techniques in Multiple Metastases: Fiduciary Markers and Completion Ablation

Masayuki Okuno, Yoshikuni Kawaguchi, and Bruno C. Odisio

Learning Objectives

- Although prehepatectomy chemotherapy can convert initially unresectable colorectal liver metastases to resectable disease, it has a risk for disappearing of metastatic lesions.
- To facilitate resection of disappearing liver metastases, preoperative percutaneous placement of a fiducial marker is an option to facilitate intraoperative lesion identification after chemotherapy.
- For patients with insufficient future liver remnant, a new sequential treatment strategy—planned incomplete resection and postoperative completion ablation for intentionally untreated tumours—can be utilized as an alternative to intraoperative concomitant ablation.
- For patients with multiple colorectal liver metastases, postoperative completion ablation for intentionally untreated lesions was associated with better local control and lower incidence of complications compared to intraoperative concomitant ablation.

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6.1 Introduction

R0-intent resection of colorectal liver metastases (CLM) is a potential local curative treatment. However, R0 resection is not always achieved in patients who present with extensive distribution of CLM while ensuring sufficient functional future liver remnant (FLR) and avoiding postoperative liver failure. Conversion therapy is one of the options for such initially unresectable CLM patients with 40–80% of conversion rate after systemic chemotherapy [1].

The drawback of preoperative chemotherapy for patients with small-size (<2 cm) CLM is disappearing liver metastases (DLM) [2]. Even if CLMs are not visualized using cross-sectional imaging following systemic chemotherapy, complete pathological response is achieved only in 17% of DLMs [3]. Therefore, surgical planning should consider eradication of all sites of macroscopic disease pre-chemotherapy; however, intraoperative ultrasound (US) identification of DLMs is extremely challenging given diminutive size of such CLMs and heterogeneous appearance of the adjacent liver parenchyma due to systemic chemotherapy-associated steatohepatitis and venous congestion. To facilitate resection of DLMs, MD Anderson Cancer Center group reported that preoperative percutaneous placement of a fiducial marker is an option to avoid misidentification of DLMs during surgery [2].

Another limitation to achieve R0 resection is insufficient future liver remnant. Even if downsizing of tumour is achieved after chemotherapy in patients who present with extensive distribution of CLMs, insufficient FLR may hinder complete removal of all CLMs while avoiding postoperative liver failure. For patients who have deeply located small CLM and who are at risk of developing liver failure after resection of the lesion, our group has proposed a new sequential treatment strategy: planned incomplete resection and postoperative completion ablation (termed as completion ablation) [4].

In this chapter, we detail the techniques and the treatment results with respect to fiduciary marker placement and completion ablation.

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6.2 Fiducial Marker Placement

6.2.1 Indication

CLMs that are less than 20 mm in the largest diameter and locate more than 10 mm deep from the liver surface are associated with high risks of disappearing after prehepatectomy chemotherapy [2]. If the lesion at risk of disappearing was located out of the field of planned liver resection, then fiducial marker placement is necessary. No upper limit of the number of lesions was set for fiducial marker placement. Figure 6.1a shows a tumour with a high risk for disappearing after chemotherapy.

6.2.2 Procedure

Percutaneous fiducial placement can be performed with either computed tomography (CT) or US-guided with or without the use of intravenous contrast at preference of the interventional radiologist. A guide needle (18–22 gauge) is advanced targeting the deep margin behind the lesion rather the tumour itself so as to obtain a precise intraoperative identification of the resection depth and to achieve a clear posterior margin, especially if the tumour cannot be visualized using intraoperative US. The stylet of the guide needle is removed, and bleeding through the needle was inspected to exclude inadvertent percutaneous vessel access. Confirming that no bleeding through

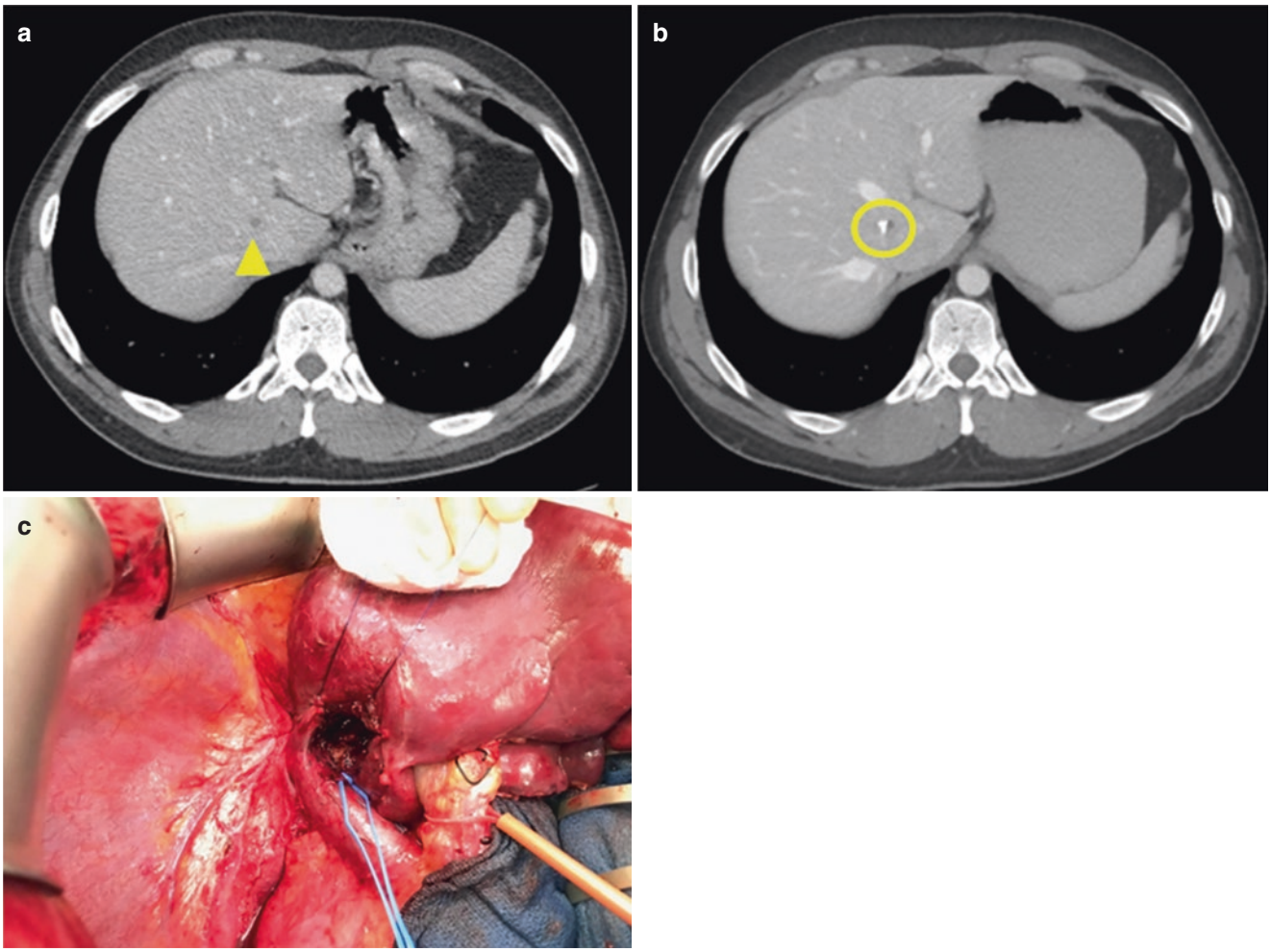


Fig. 6.1 Fiducial marker placement. (**a**) Preoperative contrast-enhanced CT of a patient presenting with a 9-mm colorectal liver metastasis (CLM) at the transition of segments I and VIII (arrowhead). Given its small size, the lesions were deemed at risk of disappearing following chemotherapy. (**b**) Given that surgical approach via a superior approach was planned, a fiducial marker was placed posteriorly and inferiorly to the deep margin of the lesion (circled). (**c**) The patient underwent targeted, parenchymal-sparing hepatectomy after preoperative chemotherapy

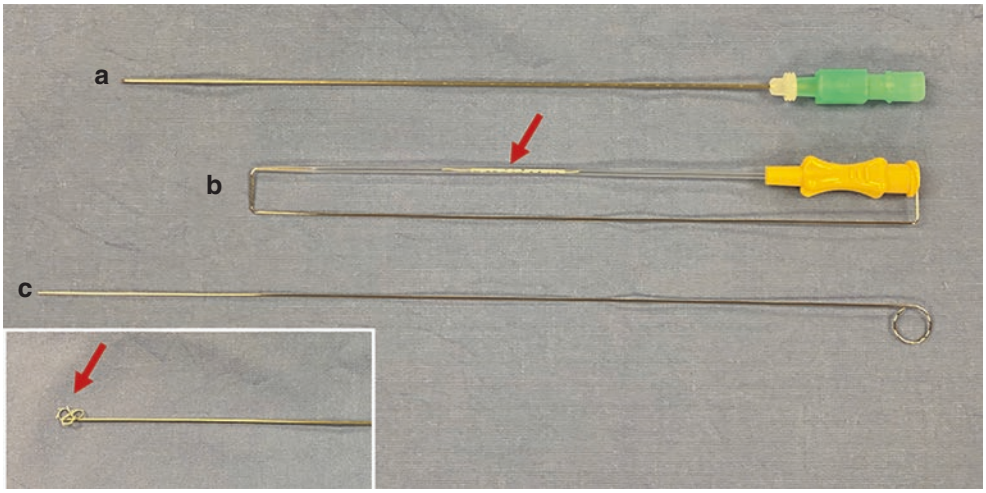


Fig. 6.2 Guide needle and coil utilized for percutaneous fiducial placement. (**a**) A 21-gauge 15-cm long Chiba biopsy needle. (**b**) A 6 × 6 mm pushable coil (arrow). (**c**) Coil plunger. Inset: Coil (arrow) partially deployed within the tip of the 21-gauge needle

the needle occurs, one or two embolization coils are carefully pushed through the needle and deployed. In our Institution, we give preference to 0.018-in. fibered platinum coils of 4–6 mm (Complex Helical—18 pushable coil, Boston Scientific) as they have a relatively short length (2–3 cm) and a complex shape, which make those less prone to migration during deployment (Fig. 6.2). Also, such coils cause limited streaking artifact on CT, which facilitates CLM identification on post-fiducial placement CT, while still being easily identified on intraoperative US imaging. Intermittent imaging evaluation with US or CT during coil deployment is strongly advised in order to reduce risks of inadvertent coil migration. Once complete deployment of the coils outside the guide needle is confirmed by imaging, the guide needle is removed and a CT is performed to confirm that the markers were placed as planned (Fig. 6.1b). The patient is then observed for 2 h to exclude immediate complications. Liver resection is then performed based on intraoperative coil localization (Fig. 6.1c).

6.2.3 Results

Between 2005 and 2015, 32 patients underwent fiducial marker placement at MD Anderson Cancer Center. No complication occurred after fiducial marker placement. A total of 41 CLMs marked with coils were treated with resection (n = 31) or ablation (n = 10). Neither local recurrences nor needle-tract seeding were observed during the median follow-up periods of 14 months (range, 0–64 months) [2].

6.3 Completion Ablation (Planned Incomplete Resection and Postoperative Completion Ablation)

6.3.1 Definition of Completion Ablation

Completion ablation is defined as postoperative percutaneous ablation for intentionally untreated CLMs within 180 days from liver resection. Target lesions for completion ablation are preoperatively visualized by cross-sectional imaging or intraoperatively identified by US.

6.3.2 Indication

Resection of CLMs should be the first choice of local therapy when an adequate FLR (i.e., to spare two continuous hepatic segments, and maintain vascular inflow/outflow and biliary drainage) can be ensured after resection. For patients with insufficient FLR, preoperative portal vein embolization and/or the strategy of two-stage hepatectomy may facilitate liver resection while avoiding hepatic insufficiency after surgery [5]. Nonetheless, ablation therapy together with liver resection may be indicated when liver resection alone is not able to ensure sufficient FLR. Concomitant use of intraoperative ablation during liver resection is the traditional approach to perform both ablation and liver resection for multiple CLMs. Completion ablation is a new sequential

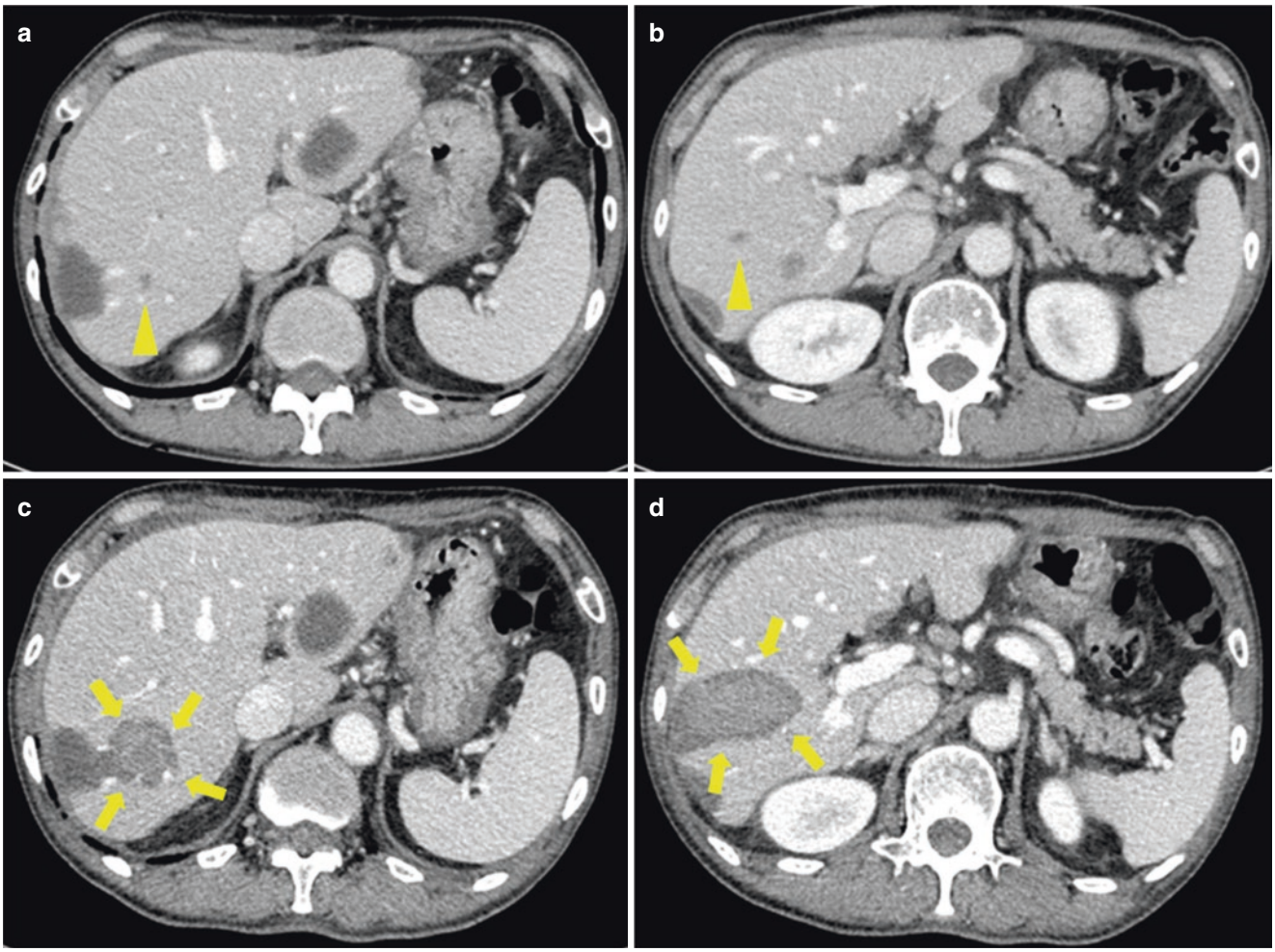


Fig. 6.3 Completion ablation. (**a, b**) The patient with multiple bilateral colorectal liver metastases who underwent parenchymal-sparing hepatectomy. Two small lesions were intentionally unresected for the purpose of completion ablation (arrowhead). (**c, d**) The lesions were treated with cross-sectional imaging-guided percutaneous ablation postoperatively (arrows)

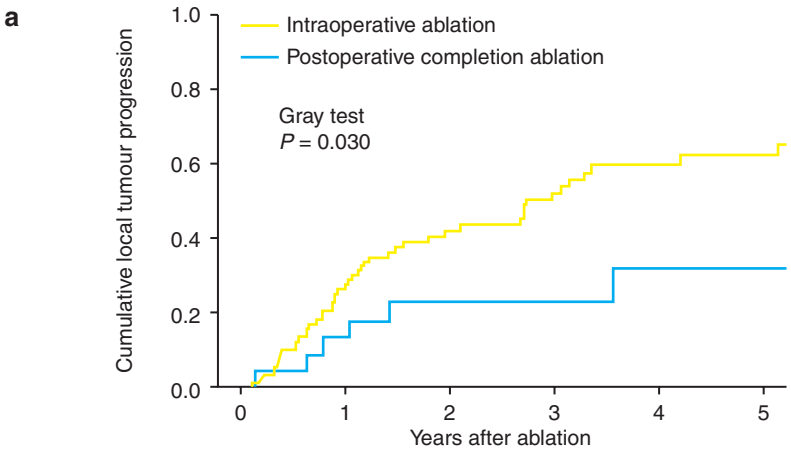
treatment strategy. Planned incomplete resection is performed to multiple CLMs that are amenable to resection, and postoperative percutaneous completion ablation (typically, deeply located small tumours) is performed under the guidance of cross-sectional imaging (Fig. 6.3) [4]. As per the protocol of our group, patients with ≤5 CLMs and the largest diameter < 3 cm are eligible for ablation.

6.3.3 Procedure

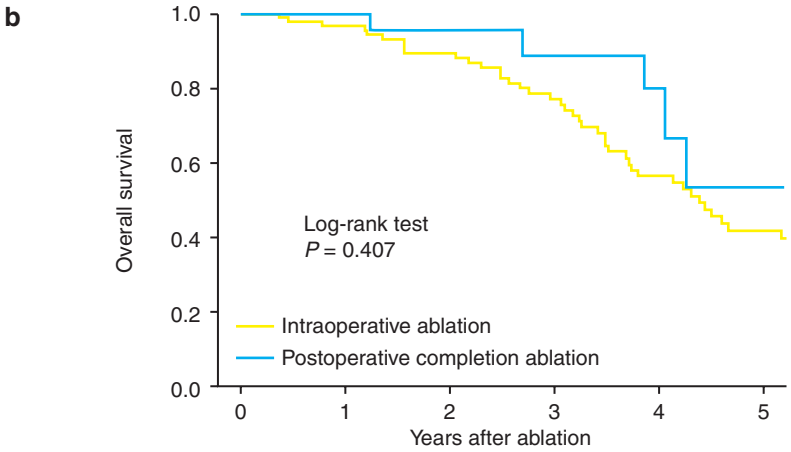
In our institution, completion ablation is performed with radiofrequency (Cool-tip ablation system, Covidien, Medtronic, Boulder, CO, USA) or microwave (Certus probe, Certus 140 2.4-GHz ablation system, Neuwave, Johnson & Johnson, Madison, WI, USA) according to operator's choice. The procedure is performed under CT or magnetic resonance imaging (MRI) guidance and general anesthesia with continuous hemodynamic monitoring by an anesthesiologist. Pre- and post-ablation contrast-enhanced CT or MRI are acquired for adequate tumour identification and assessment of sufficient ablation margins surrounding the ablated CLM, respectively. Patients are either discharged 3 h following procedure or recovered overnight in the hospital, depending on the ablation extent and post-ablation symptoms severity.

6.3.4 Results

Our recent study showed that patients undergoing CLM resection followed by completion ablation were associated with lower rates of complications (21% vs. 48%; $p = 0.033$) and lower local tumour progression at the ablation site (31.7% vs. 62.4%; $p = 0.030$, Fig. 6.4a) than patients undergoing resection and concomitant intraoperative ablation for CLM. Overall survival (OS) rates did not differ significantly



Patients at risk							5-year cumulative local recurrence rate
Intraoperative ablation	92	60	36	26	16	13	62.4%
Postoperative completion ablation	23	19	12	10	5	1	31.7%



Patients at risk							5-year OS rate
Intraoperative ablation	92	87	69	53	33	20	41.8%
Postoperative completion ablation	23	22	18	13	6	3	53.2%

Fig. 6.4 Treatment results of completion ablation [4]. Cumulative incidence of local tumour progression at ablation site (**a**) and overall survival (**b**) in 92 patients who underwent resection and concomitant intraoperative ablation and 23 patients who underwent resection and postoperative completion ablation [4]

between the groups (Fig. 6.4b) [4]. Splitting metabolic response to surgical resection and ablation to two distinct time-points is a potential explanation for lower rates of complications on the completion ablation group. Use of contrast-enhanced cross-sectional imaging (CT or MRI) with adequate 3D tumour identification and ablation margins assessment is a potential explanation for lower rates of recurrence toward the completion ablation group.

6.4 Conclusions

Recent advances in chemotherapy and molecular target therapy have provided better tumour response and improved the chance for conversion of initially unresectable diseases to resectable diseases [6]. However, the risk of DLM may be increasing in clinical practice. Fiducial marker placement

before chemotherapy may be an effective option to complete resection of DLMs, majority of which show regrowth. Even after use of preoperative portal vein embolization and/or two-stage hepatectomy strategy, patients are not always able to undergo R0 resection because of insufficient FLR. The strategy of completion ablation may be an effective option with better local tumour control and lower rates of major postoperative complications compared to the intraoperative ablation concomitant with CLM resection. The completion ablation, rather than the traditional approach of intraoperative ablation concomitant with liver resection, is the new standard at MD Anderson Cancer Center if our indication criteria are met. These advanced techniques may improve survival in patients with multiple bilateral CLMs.

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Two-Stage Hepatectomy for Bilateral Colorectal Liver Metastases: Experience of MD Anderson Cancer Center

7

Heather A. Lillemoe, Yujiro Nishioka, Harufumi Maki, and Jean-Nicolas Vauthey

Learning Objectives

- Two-stage hepatectomy is a safe and effective technique for the treatment of bilateral colorectal liver metastases.
- Portal and hepatic venous embolization can be combined with two-stage hepatectomy to increase future liver remnant hypertrophy.
- At MD Anderson Cancer Center, a "fast-track" approach combining first-stage hepatectomy and portal vein embolization into one procedure has been developed to minimize the time between first- and second-stage resections.
- Outcomes after two-stage hepatectomy are promising and ongoing investigation into the impact of tumour genetics may impact future management of this complex patient population.

7.1 Introduction

Liver resection, combined with systemic chemotherapy, is the standard of care for colorectal liver metastases (CLM). Unfortunately, many patients have unresectable disease at the time of presentation [1, 2]. For patients with bilateral CLM, two-stage hepatectomy (TSH) has been proven as a safe and effective treatment strategy [3, 4]. With this technique, combined with systemic chemotherapy, patients previously deemed unresectable can reach 5-year overall survival rates nearing 50% [4–6]. Originally described by Adam et al., the TSH technique entails a non-curative first-stage liver resection to clear as much of the future liver remnant (FLR) as possible, followed by a second-stage operation with a goal of curative resection [3]. This strategy, which may or may not involve portal vein embolization (PVE), allows for growth of the future liver remnant (FLR) and reduces the risk of postoperative liver failure. In general, the minimal FLR requirement in patients with normal liver is 20–30% [7]. The recommended FLR increases for patients with liver disease. Portal vein embolization is a commonly performed, safe, image-guided procedure during which the portal venous system of the hemi-liver planned for resection is embolized to assist with further hypertrophy of the non-embolized liver [8, 9]. In a streamlined sequence, TSH can be very successful.

7.2 The MD Anderson Cancer Center Approach

At MD Anderson Cancer Center, patients with bilateral CLM are considered for TSH after documented response to systemic chemotherapy and the FLR is determined to be appropriate using preoperative liver volumetry evaluation on computed tomography (CT) imaging with adequate inflow and outflow. As shown in Fig. 7.1a, the typical TSH treatment sequence begins with a first-stage liver resection to clear the FLR of disease. In most cases, this is followed by PVE after 2–5 weeks in order to augment FLR hypertrophy. In cases with very small FLR, liver venous deprivation (combined middle or right hepatic vein embolization and PVE) can be indicated, which has been recently reported to safely facilitate FLR hypertrophy (Fig. 7.2) [10, 11]. A subsequent second-stage major hepatectomy (most typically right or extended right hepatectomy) is performed. Interval chemotherapy between the first- and second-stage resections is not routinely used; however, it can be prescribed during this interval based on radiologic response, pathologic response, and somatic gene mutation results of first-stage hepatectomy. Patients with disease progression after the first-stage surgery are re-evaluated after 2 months of systemic chemotherapy

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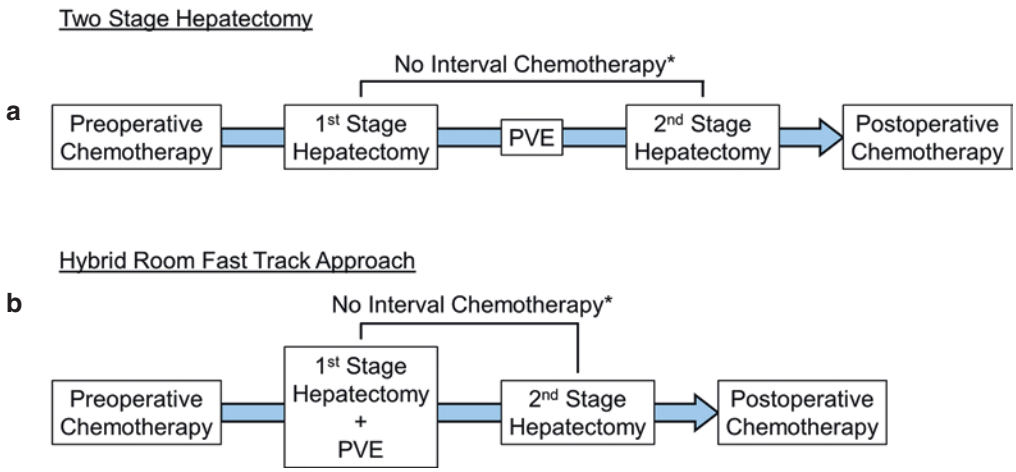

Fig. 7.1 Typical treatment sequence of (**a**) two-stage hepatectomy and (**b**) hybrid room fast-track two-stage hepatectomy approach. PVE: portal vein embolization. *In most patients, chemotherapy is not used between the first and second stage. It is used selectively after first stage hepatectomy based on radiologic response, pathologic response, and somatic gene mutation profile

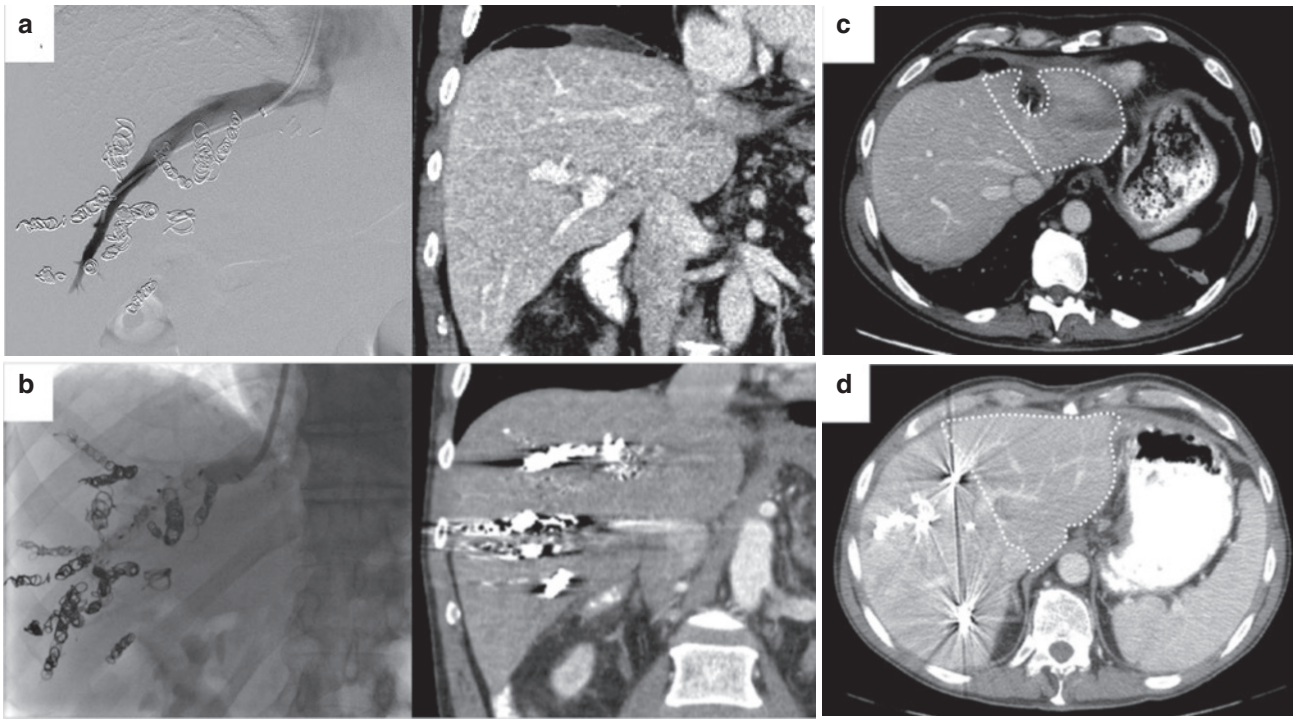

Fig. 7.2 A patient who underwent two-stage hepatectomy using portal vein and middle hepatic vein embolization. Venography and coronal computed tomography (CT) image following portal vein embolization (**a**) before and (**b**) after middle hepatic vein embolization. Axial CT image (**c**) after first stage hepatectomy and (**d**) 5 weeks after liver venous deprivation, which showed 10% of hypertrophy in future liver remnant (segment 1–3) and 2.0% / week of kinetic growth rate

and taken for the second-stage procedure if their disease is stable or chemo-responsive [4]. After TSH, postoperative chemotherapy is resumed to total 12 perioperative treatment cycles [12].

Regarding the management of the primary tumour for patients who present with synchronous disease, the reverse (or, "liver first") strategy is preferred over the traditional or combined approach at our institution. This treatment sequence avoids any delay in addressing the systemic disease that drives overall survival. Data suggest that the rates of complications related to the primary tumour, such as obstruction, perforation, or bleeding, are quite low [13–15]. Therefore, definitive management of the primary tumour can be safely delayed until after liver resection and systemic therapy have been administered if it is asymptomatic. In a study by Brouquet et al., the authors compared the three primary strategies for managing synchronous bilateral colorectal liver metastases and dis-

covered that over time, there has been a shift in the preferred strategy toward the reverse, liver-first approach [16]. In addition, this group has demonstrated that resection of the primary tumour combined with first-stage hepatectomy for patients with bilateral disease was associated with an increased risk of morbidity [5]. Thus, caution should be shown when considering a combined approach as part of TSH.

7.3 The MD Anderson Cancer Center "Fast-Track" Approach

More recently, a fast-track approach to TSH has been described by Odisio et al. [17] In order to minimize the time interval between first and second stages and reduce potential patient dropout between stages, we have pioneered a combined first-stage hepatectomy and PVE procedure in the same setting (Fig. 7.1b). The combined procedure takes place in a hybrid interventional radiology (IR)/operative room (OR) suite (Fig. 7.3). After first-stage liver resection has been completed by the hepato-pancreato-biliary surgeon, an interventional radiologist immediately performs PVE using ultrasound-guided percutaneous access. Failure to progress to second-stage hepatectomy can occur due to lack of FLR hypertrophy, but in most patients is the result of progression of disease, which is often the consequence of lack of response to chemotherapy and unfavorable biology. Our group recently reported on 19 patients who were scheduled for this approach. Only one patient had a major morbidity and no patient had postoperative mortality. The median interval between stages was 5.6 weeks (4.0–20.1) and no patient had an aborted second-stage hepatectomy due to insufficient liver hypertrophy [18]. Although the completion rate (53%) was not ideal, due to high tumour burden and unfavorable tumour biology, the hybrid IR/OR approach minimizes the time interval between stages and expedites the TSH treatment process (Table 7.1). For details related to the PVE procedure, please see Chap. 53.

A representative case of a 38-year-old female who underwent the hybrid IR/OR fast-track approach is shown in Fig. 7.4. The patient presented with sigmoid colon cancer and multiple liver metastases. Surgical resection of the primary tumour at the pre-referral center demonstrated a T3N1b moderately differentiated adenocarcinoma. Initial evaluation at our institution showed 14 bilateral CLM (4 tumours in the left hemi-liver, 10 tumours in the right hemi-liver) with the largest tumour 1.8 cm in size (Fig. 7.4a). Somatic gene mutation analysis indicated *KRAS* and *APC* mutations, but no *TP53* or *SMAD4* mutation. Fiduciary markers were placed in four lesions at risk for disappearing in the left liver prior to chemotherapy (Fig. 7.4b). She subsequently received 4 cycles of 5-fluorouracil and oxaliplatin (FOLFOX) with bevacizumab prior to first-stage resection. Subsequent CT images showed stable size of the metastases and optimal

Table 7.1 Interval between stages in series for bilateral colorectal liver metastases

Author	Year	TSH planned	TSH completed (%)	Interval between stages Median (range)
Adam	2000	16	13 (81%)	4 months (2–14)
Jaeck	2004	33	25 (76%)	NA
Wicherts	2008	59	41 (69%)	3.3 months (1.0–15.7)
Tsai	2010	45	35 (78%)	4.5 months (2–22)
Chun (MDACC)	2007	30	21 (70%)	8 weeks (5–64)
Brouquet (MDACC)	2011	65	47 (72%)	8 ± 4 weeks
Passot (MDACC)	2016	109	89 (82%)	NA
Mizuno (MDACC)	2017	126	92 (73%)	10 weeks (4–109)
Nishioka (MDACC)[a]	2021	19	10 (53%)	5.6 weeks (4.0–20.1)

MDACC MD Anderson Cancer Center, *NA* not available, *TSH* two-stage hepatectomy

[a]Hybrid room fast-track approach (combined first-stage hepatectomy and portal vein embolization)

Fig. 7.3 Hybrid interventional radiology/operating room suite at MD Anderson Cancer Center

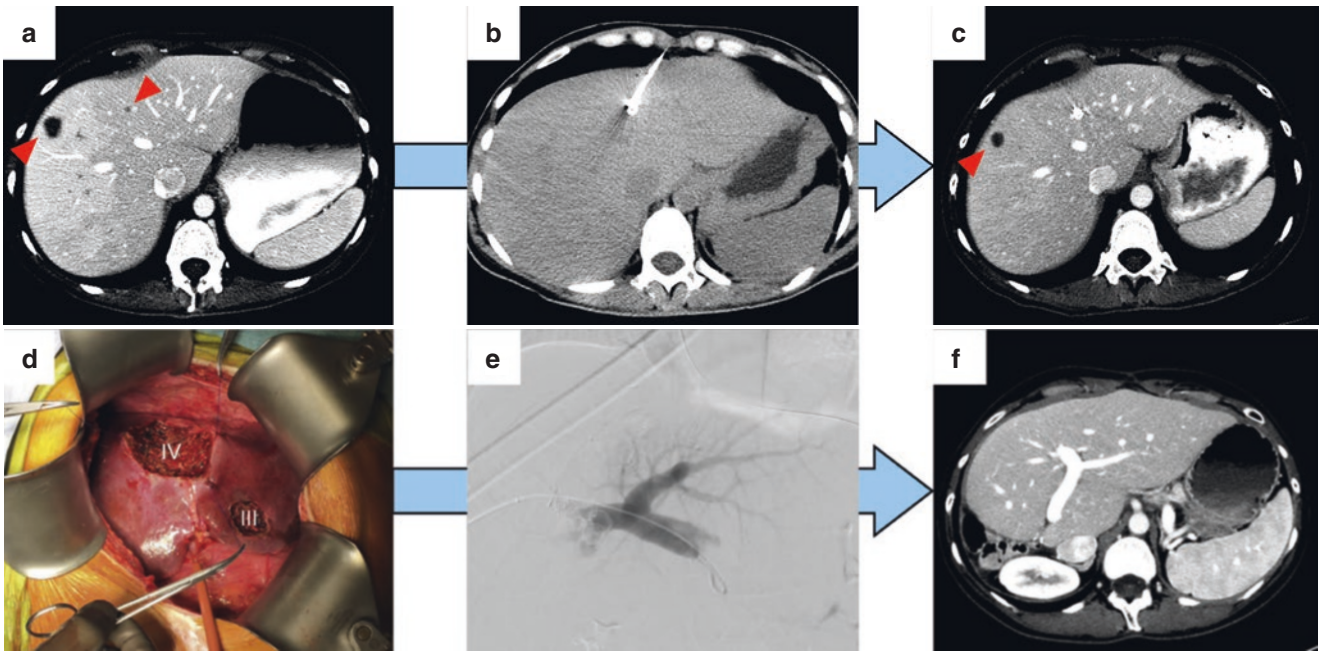

Fig. 7.4 Treatment sequence of a representative case who underwent fast-track two-stage hepatectomy approach. (**a**) CT images at presentation to our institution showing bilateral colorectal liver metastases. (**b**) Fiduciary marker placement in the left liver lesion. (**c**) CT images after preoperative chemotherapy showing good radiologic/morphologic response. (**d**) First stage hepatectomy (partial resections of the left liver). (**e**) Percutaneous embolization of the right portal vein immediately after hepatectomy. (**f**) CT images after second stage hepatectomy (right hepatectomy)

morphologic response (Fig. 7.4c); however, the FLR volume of segments 1–4 was less than 30%. Therefore, first-stage hepatectomy (partial hepatectomy of the left liver) (Fig. 7.4d) combined with concurrent percutaneous embolization of the right portal vein were performed in the hybrid IR/OR suite (Fig. 7.4e). Pathology showed complete response in all metastases in the left liver. CT images after 4 weeks showed 12.6% degrees of hypertrophy in segments 1–4 (kinetic growth rate 3.2%/week) and she underwent uneventful second-stage right hepatectomy (Fig. 7.4f). Final pathology of the right hemi-liver showed only two viable lesions with 20% of viable tumour cells and negative surgical margins. No complications were observed after the first- or second-stage hepatectomies. She resumed postoperative chemotherapy 6 weeks after second-stage hepatectomy and successfully completed eight cycles. She had a solitary lung recurrence 1.5 years after hepatectomy and underwent wedge resection of that metastasis. She is currently doing well 4 years after hepatectomy without evidence of disease.

7.4 Outcomes After Two-Stage Hepatectomy

A number of authors have described the outcomes of TSH (Table 7.2) [19]. The studies included anywhere from 16 patients in the early literature [3], to 126 patients in the most recent publication from MD Anderson Cancer Center [4]. Preoperative chemotherapy was used in the majority of cases and the use of PVE was variable. Morbidity rates ranged from 20% to 59% with low mortality rates. The rate of completion of both first and second stages ranged from 63% to 100% across. Among 91 patients across nine studies who did not complete TSH, [5, 6, 20–26] reasons included disease

Table 7.2 Outcomes after two-stage hepatectomy for bilateral colorectal liver metastases

	Region	Patient no.	Preoperative chemotherapy (%)	PVE (%)	PVL (%)	Completion rate (%)	Postoperative morbidity (%)	Postoperative mortality (%)	3-Year OS (%)	5-Year OS (%)
Adam et al. [3][a]	Europe	16	75	44	0	81	38	15	35	NA
Jaeck et al. [30][b]	Europe	33	91	100	0	76	56	0	54	NA
Tanaka et al. [20]	Asia	24	64	73	0	100	23	0	33	NA
Wicherts et al. [6][a]	Europe	59	97	78	0	69	59	7	60	42
Homayounfar et al. [21]	Europe	24	75	0	100	63	58	5	NA	NA
Tsai et al. [22]	USA/ Europe	45	71	7	71	78	26	6	58	NA
Brouquet et al. [5][c]	USA	65	100	70	0	72	49	6	84	64
Tsim et al. [23]	Europe	38	91	95	0	87	33	0	50	NA
Narita et al. [24][b]	Europe	80	84	86	4	76	54	0	59	32
Muratore et al. [25]	Europe	47	79	58	23	77	44	0	65	NA
Turini et al. [26]	Europe	48	100	100	0	71	20	6	59	35
Passot et al. [4][c,d]	USA	109	100	73	0	82	27	6	68[d]	49[d]
Mizuno et al. [31][c]	USA	126	100	62	0	73	35	4	54	35

NA not available, *OS* overall survival, *PVE* portal vein embolization, *PVL* portal vein ligation
Source: Adapted from Kawaguchi et al. [19]
[a]Reports from Paul Brousse Hospital
[b]Reports from Strasbourg University Hospital
[c]Reports from MD Anderson Cancer Center
[d]In 89 patients who underwent second-stage resection

progression after first stage, insufficient FLR, patient physical status, portal vein thrombosis, and death [19].

Overall survival rates have improved over time with refinements in operative technique and perioperative patient care. Three- and five-year overall survival rates ranged from 35% to 85% and 32% to 64%, respectively. Based on previous work published from our institution by Brouquet et al., patients who underwent TSH had significantly improved survival compared to those who underwent chemotherapy only (Fig. 7.5). Passot et al. analyzed factors associated with worse overall survival after TSH and identified rectal primary tumour, >5 CLMs, and need for interval chemotherapy between stages as independent risk factors [4]. This study also demonstrated the importance of genetic mutations in this patient population, as *RAS* mutation was the only factor independently associated with both overall and progression-free survivals for patients undergoing

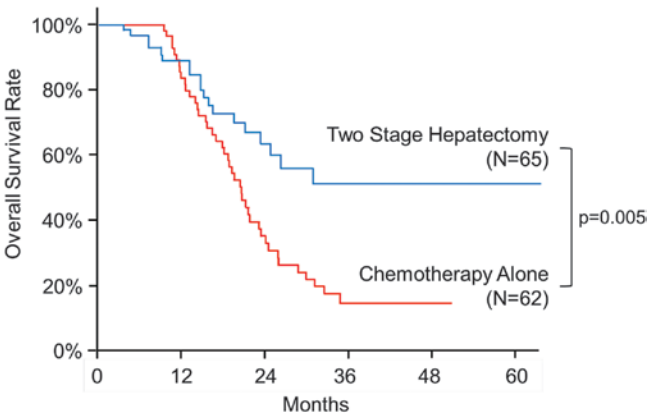

Fig. 7.5 Overall survival in patients with advanced bilateral colorectal liver metastases responding to chemotherapy enrolled in two-stage hepatectomy approach or receiving chemotherapy alone (adapted from Brouquet et al. [5] with permission)

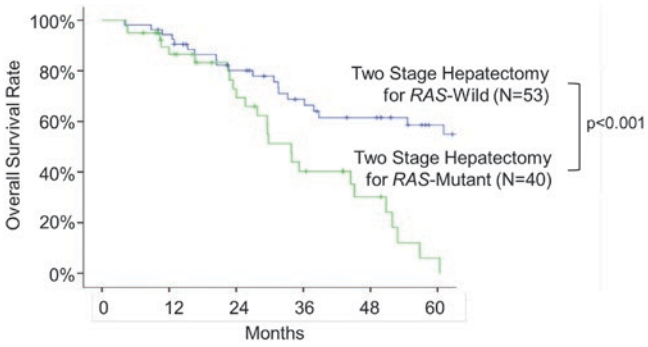

Fig. 7.6 Overall survival in patients with bilateral colorectal liver metastases who completed two-stage hepatectomy, by *RAS* mutation status (adapted from Passot et al. [4] with permission)

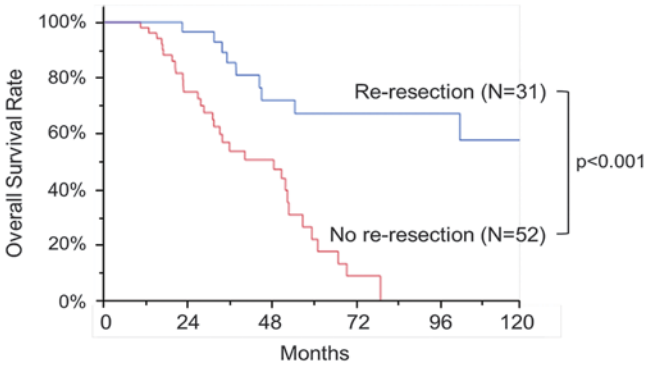

Fig. 7.7 Overall survival in patients with recurrence after two-stage hepatectomy, by re-resection or not (adapted from Lillemoe et al. [27] with permission)

TSH (Fig. 7.6). Finally, as survival improves, there are increasing data related to repeat resection for recurrence after TSH [27, 28]. Our institutional work suggests that re-resection for recurrence after a patient has previously undergone TSH is feasible, safe, and associated with improved overall survival compared to best medical therapy (Fig. 7.7) [27]. Similar to previous work, *RAS* mutation status was independently associated with worse overall survival in this patient group (Fig. 7.8). Recent data from our institution suggest that *RAS* mutations correlated with worse prognosis only in patients with co-occurring *TP53* mutations. In addition to double mutations in *RAS* and *TP53*, other genes such as *SMAD4* may have also a detrimental impact on outcome. Therefore, *RAS* mutation status alone may not be sufficient for prognostication after CLM resection [29].

7.5 Conclusion and Future Aims

For patients with bilateral colorectal liver metastases, two-stage hepatectomy has been established as a safe and effective treatment strategy. At our institution, the majority of patients benefit from combined portal vein embolization to maximize FLR, which in certain cases can be performed in a fast-track setting to minimize the time interval between first- and second-stage hepatectomies and thus reduce the total time away from systemic therapy. Continued investigation into the role of genetic mutations may help refine our treatment algorithms even further.

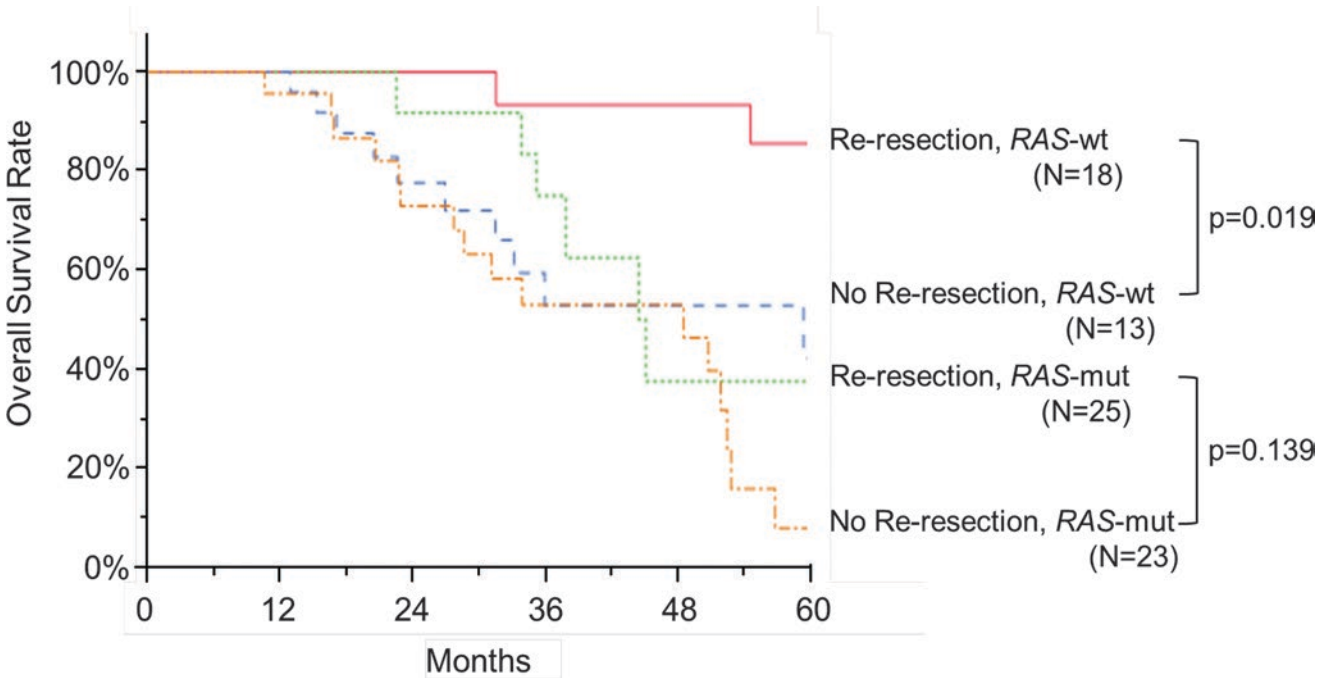

Fig. 7.8 Overall survival in patients with recurrence after two-stage hepatectomy, by re-resection status and *RAS* mutation status (adapted from Lillemoe et al. [27] with permission)

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8 Two-Stage Hepatectomy for Bilobar Colorectal Liver Metastases: Experience of Hôpital Paul-Brousse

Katsunori Imai and René Adam

Learning Objectives

- The concept of two-stage hepatectomy was introduced by our team in 2000, and since then it has been adopted, developed, and modified all over the world.
- Two-stage hepatectomy is indicated only for multiple bilobar diseases that are not amenable to complete resection by single hepatectomy.
- The predictive model for dropout, which is still the main drawback of two-stage hepatectomy, can contribute to a better selection of patients who are submitted to two-stage hepatectomy.
- Two-stage hepatectomy is now an established procedure with acceptable short-term outcomes and promising long-term outcomes.
- Repeat surgery for recurrence can improve long-term outcomes after two-stage hepatectomy.

8.1 Introduction

The liver is the most common organ for distant metastases from colorectal cancer. Although surgical resection of colorectal liver metastases (CLMs) remains the only treatment that can ensure prolonged survival, approximately 80% of patients with CLM are thought not to be resectable at the time of diagnosis [1–3]. Considerable effort has been made to overcome this initial unresectable condition. The advent of effective chemotherapy, including biologic agents, and developments in specific techniques such as portal vein embolization (PVE), local ablation therapy, vascular reconstruction, and two-stage hepatectomy (TSH) have dramatically expanded the pool of resectable patients with CLM, based on a multidisciplinary approach [4].

The concept of TSH was first introduced in 1992, and published in 2000 by our team, to treat extensive bilobar CLMs that were diagnosed as initially unresectable [5]. Subsequently, many specialized centers have adopted, developed, and modified this strategy. The TSH strategy is now adopted as an effective treatment modality for extensive CLM, with acceptable short- and long-term outcomes. In this chapter, we describe the "Paul Brousse experience" of TSH for extensive bilobar CLM.

8.2 Two-Stage Hepatectomy

8.2.1 Indication

At Paul Brousse Hospital, TSH is only indicated for multiple bilobar diseases that are not amenable to complete resection by a single hepatectomy, even in combination with PVE or local ablation therapy [6]. When multiple tumours are unilobar and thought to be unresectable because of a small future liver remnant (FLR; usually less than 30% or 40% when patients have received prolonged chemotherapy), we perform PVE followed by one-stage hepatectomy. Even when the multiple tumours are bilobar, TSH is not indicated for cases in which all the tumours can be treated by a single hepatectomy, such as parenchyma-preserving hepatectomy, or resection combined with local ablation therapy (Fig. 8.1). The presence of extrahepatic metastases is usually not considered a contraindication for TSH if these metastases are limited and resectable (or sometimes stable while on chemotherapy).

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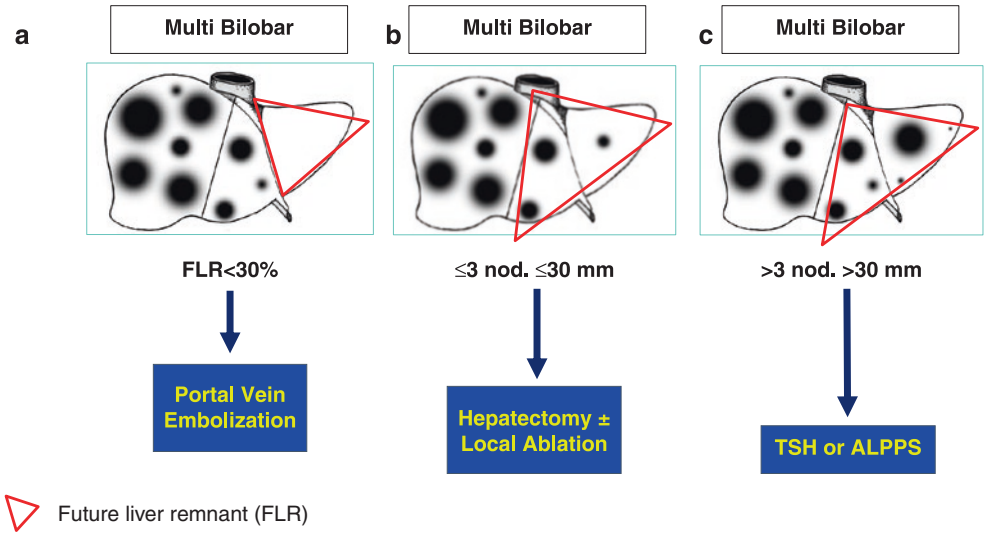


Fig. 8.1 Indication of two-stage hepatectomy (TSH) for colorectal liver metastases at Paul Brousse Hospital. (**a**) When the multiple tumours are distributed unilobar and thought to be unresectable because of small future liver remnant (FLR), portal vein embolization (PVE) followed by one-stage hepatectomy is performed. (**b**) When the multiple tumours are distributed bilobar but the largest tumour size is ≤30 mm and the tumour number in the FLR ≤ 3, standard one-stage hepatectomy with simultaneous local ablation therapy is performed. (**c**) When the multiple tumours are distributed bilobar, the largest tumour size is >30 mm, and the tumour number in the FLR > 3, TSH or ALPPS is performed. FLR, future liver remnant; TSH, two-stage hepatectomy; ALPPS, Associating Liver Partition and Portal vein embolization for Staged hepatectomy

8.2.2 Surgical Procedures of TSH

TSH is usually classified into four types (Fig. 8.2) [4]. In the early period of development of TSH, we performed the so-called "right-first approach" (Fig. 8.2a) [5]. The more invaded hemiliver (usually the right lobe) is resected at the first stage, leading to hypertrophy of the contralateral liver lobe. PVE or portal vein ligation (PVL) is not required. At the second stage, tumour cleaning of the FLR is performed. Subsequently, we adopted the "left-first approach" (Fig. 8.2b). The less-invaded liver lobe (usually the left lobe) is cleaned of its metastases in combination with intraoperative PVE/PVL at the first stage. At the second stage, the tumour-bearing liver lobe (deportalized liver lobe) is anatomically resected. At Paul Brousse Hospital, the left-first approach has been the main TSH procedure up to the present time [7, 8]. The third type of TSH with percutaneous PVE after first-stage hepatectomy is exceptionally used at our institution since we consider that PVE could be performed easily and safely during the first stage. If a primary tumour is in place, its resection is usually performed during the first stage or after the second stage (liver-first approach). Radiofrequency ablation is sometimes added, usually for deeply located small tumours, during the first stage, with the aim of preservation of the liver parenchyma [7–9]. The fourth type of TSH is ALPPS (Associating Liver Partition and Portal vein embolization for Staged hepatectomy; Fig. 8.2d) that we also perform in cases needing an extended right hepatectomy (+segment 4 ± segment 1) with a too small remnant liver but this is not on the scope of this paper. Thus, TSH in this chapter indicates the so-called classical TSH, including types 1, 2, and 3 TSH (Fig. 8.2a–c). After introduction of TSH, its ratio compared to the total number of hepatectomies has gradually increased at our institution. From 2013, however, the ratio of classical TSH has decreased with the emergence of ALPPS. Either procedure is selected depending on patients (Figs. 8.2d and 8.3).

8.2.3 Chemotherapy

Preoperative chemotherapy is administered to almost all patients who are scheduled for TSH. In fact, 98% of the patients who underwent at least first-stage hepatectomy received preoperative chemotherapy after 2000 [7]. We previously reported that disease progression after first-line chemotherapy and chemotherapy cycles more than 12 were independent predictive factors of dropout from TSH strategy [7]. Therefore, we consider that optimal chemotherapy combined with biologic agents for a short duration is crucial for the TSH strategy.

We generally recommend interval chemotherapy between first- and second-stage hepatectomies. Interval chemotherapy is usually delivered 3 weeks after the first stage using the same regimen as that used before the first stage. Although we consider that interval chemotherapy is the best way to prevent dropout from the TSH strategy, there is not yet any study providing evidence of the efficacy of interval chemotherapy for the feasibility of, or for, survival after TSH.

Postoperative adjuvant chemotherapy is routinely recommended at Paul Brousse Hospital. Our previous studies

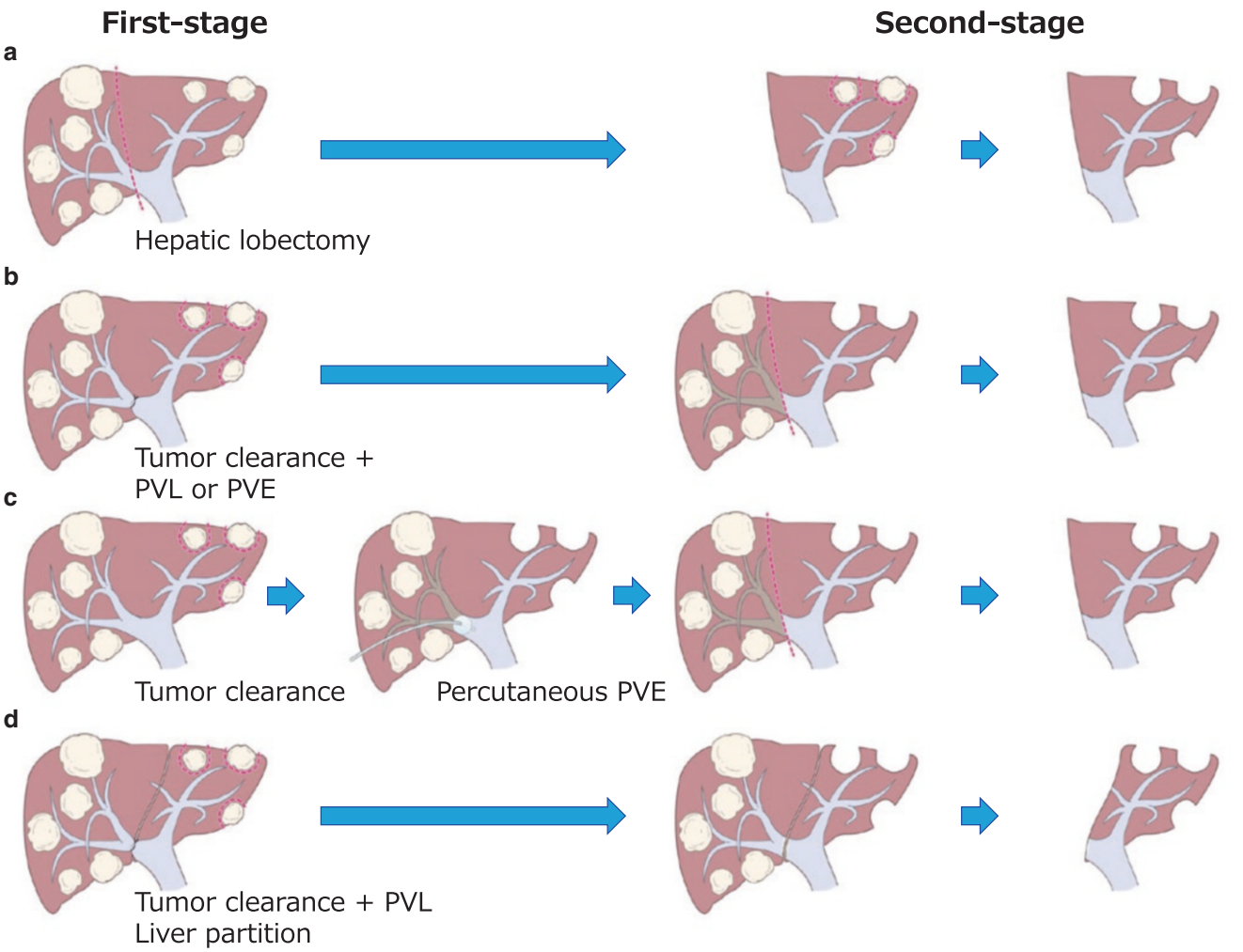


Fig. 8.2 Scheme of staged hepatectomy for colorectal liver metastases. (**a**) Right-first approach: most of the invaded hemiliver (usually the right lobe) is resected at the first stage, leading to hypertrophy of the contralateral liver lobe. At the second stage, tumour cleaning of the future liver remnant (FLR) is performed, usually by non-anatomical partial resection. (**b**) Left-first approach with portal vein ligation/embolization (PVL/PVE): the less-invaded liver lobe (FLR, usually the left lobe) is cleaned of its metastases in combination with intraoperative PVL/PVE at the first stage. At the second stage, the tumour-bearing liver lobe (deportalized liver lobe) is anatomically removed. (**c**) Left-first approach followed by PVE: percutaneous PVE is performed between the first and second stages. (**d**) ALPPS: the less-invaded liver lobe is cleaned of its metastases in combination with intraoperative PVL/PVE and in situ splitting of the hemiliver at the first stage. At the second stage, usually 7–14 days later, the tumour-bearing liver lobe is removed. ([4], with permission)

showed that postoperative chemotherapy was associated with prolonged survival after TSH. However, the efficacy of postoperative chemotherapy is still uncertain and needs to be validated [8, 10].

8.2.4 Dropout from the TSH Strategy

Dropout from the TSH strategy, that is, failure to complete both of the two sequential procedures, is the main drawback of TSH. We previously reported that among 125 patients with multiple bilobar CLMs who were scheduled for TSH between 2000 and 2012, 44 patients (35.2%) did not proceed to the second stage [7]. The reasons for dropout were as follows: disease progression (39 patients; 88.6%), insufficient FLR (3; 6.8%), poor general condition (1; 2.3%), and mortality after the first stage (1; 2.3%). Overall survival (OS) after first-stage hepatectomy for patients who dropped out from TSH strategy was significantly worse than those who completed (1-, 3-, and 5-year OS rates, 66.3%, 12.7%, and 0% vs. 95.0%, 69.0%, and 44.2%; $p < 0.0001$; Fig. 8.4) [6, 7]. We identified four independent predictive factors for dropout, namely carcinoembryonic antigen (CEA) at hepatectomy >30 ng/mL, maximum tumour size at hepatectomy >40 mm, chemotherapy cycles >12, and tumour progression during first-line chemotherapy. Subsequently, we developed a predictive model for dropout from the TSH strategy, using these four factors [7]. For patients without any factors, the

Fig. 8.3 Evolution of two-stage hepatectomy at Paul Brousse Hospital

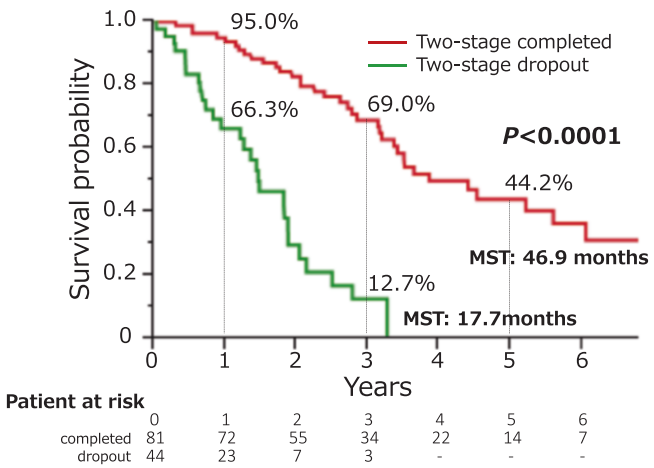


Fig. 8.4 Overall survival for patients who completed two-stage hepatectomy (n = 91) or dropped out (n = 44), between 2000 and 2012. MST, median survival time. ([6], with permission)

probability of dropout was 10.5%. The addition of subsequent risk factors increased the probability of dropout to 43.5% for one factor, 72.7% for two factors, 88.5% for three factors, and 95.5% for four factors (Fig. 8.5). This predictive model for dropout could contribute to a better patient selection for TSH strategy. In the literature, dropout rate has been reported to be 0–36% (median, 23%) [11]. The higher dropout rate observed in our institution compared to these reports was obviously due to more "aggressive" indication of TSH as assessed by a mean number of metastases >10 at diagnosis with a largest tumour size at 51.2 mm, a mean CEA levels of 1187 ng/mL, and 27% of patients having extrahepatic disease [7].

8.2.5 Short-Term Outcome

Although TSH was initially a challenging procedure, it is now accepted as an established strategy for patients with multiple bilobar CLMs. In our previous study [8], operating time, blood loss, and the rate of red blood cell transfusion were 337 min (150–773), 200 mL (50–7600), and 16.8% at the first stage and 391 min (190–894), 391 mL (170–6900), and 50.6% at the second stage, respectively ($p < 0.01$). At the first stage, a major complication (Clavien–Dindo ≥III) [12] was observed in 18 of 125 patients (14.4%) and the 90-day mortality rate was 0.8%. At the second stage, major compli-

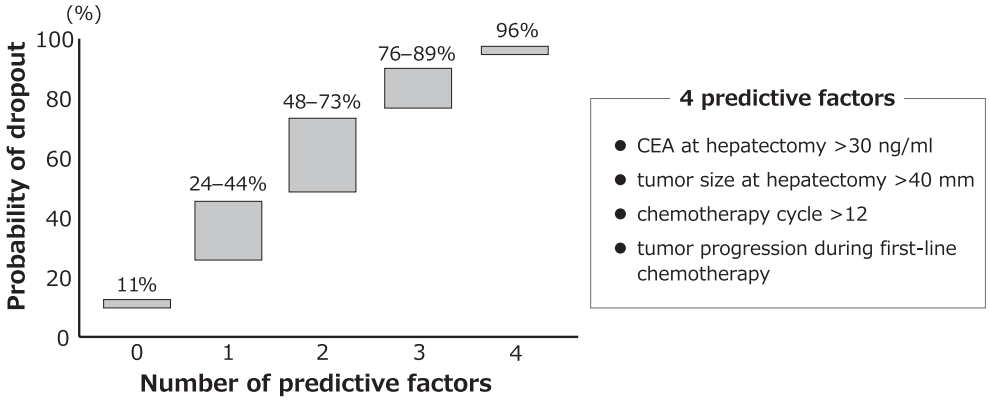


Fig. 8.5 Predictive model for dropout from the strategy of two-stage hepatectomy based on four factors. CEA, carcinoembryonic antigen

cations were observed in 27 of 81 patients (33.3%) and the 90-day mortality rate was 2.5%. Although the complications are more frequently observed after the second stage than after first stage, these morbidity and mortality rates are almost equivalent compared to those observed with one-stage hepatectomy. This short-term outcome at our institution was comparable to those reported from specialized centers in the world (Table 8.1).

8.2.6 Long-Term Outcome

We previously reported on a series of CLM patients who underwent hepatectomy, including TSH, between 1992 and 2012 [6]. A total of 1116 consecutive patients underwent initial hepatectomy for CLM at Paul Brousse Hospital. Among them, 139 patients (12.4%) were scheduled for TSH (6 patients who underwent ALPPS during this study period were excluded). Of these, 46 patients (33.1%) dropped out from the TSH strategy. On an intention-to-treat basis, the OS for patients who were scheduled for TSH was significantly worse than that for patients who underwent one-stage hepatectomy (5-year OS: 31.8% vs. 47.1%; $p = 0.0004$; Fig. 8.6a). However, the patients who completed TSH (at least liver-curative R0/R1 surgery) had comparable OS to those who underwent one-stage hepatectomy (5-year OS: 41.3% vs. 48.0%; $p = 0.40$; Fig. 8.6b). Thus, if both of two sequential procedures of TSH are completed, comparable survival with one-stage hepatectomy can be expected. The 5-year OS rate after completion of TSH at Paul Brousse Hospital was comparable to previously reported 5-year OS rates (32–64%) [13].

8.2.7 Surgery for Recurrence

We have consistently argued the importance of repeat surgery for recurrence in patients with CLM. The TSH strategy should not be an exception. We previously reported that surgical intervention for recurrence after TSH significantly improved survival in patients with multiple bilobar CLMs [4]. Among 93 patients who completed the TSH strategy, 81 patients achieved complete tumour removal for primary tumour, liver metastases, and concomitant extrahepatic disease. Of these, 62 had recurrence. Repeat surgery (not only repeat hepatectomy but also resection of extrahepatic recurrence) was performed in 38 patients (35 for recurrence after curative surgery and 3 for liver recurrence with unresected concomitant extrahepatic disease or primary tumour in place). Of these 38 patients, 31 were "salvaged" (all the detectable diseases were resected). Patients who underwent repeat surgery had a significantly better OS than those who did not (45.8% vs. 26.3%; $p = 0.004$). Similarly, patients who were salvaged by repeat surgery had a significantly better OS than those who were not (54.1% vs. 22.7%; $p = 0.001$). The performance of repeat surgery for recurrence was an independent prognostic factor for OS in patients who completed the TSH strategy. Accordingly, we always perform intensive oncosurgical surveillance after TSH, to avoid missing the opportunity for repeat surgery.

8.2.8 Case Presentation

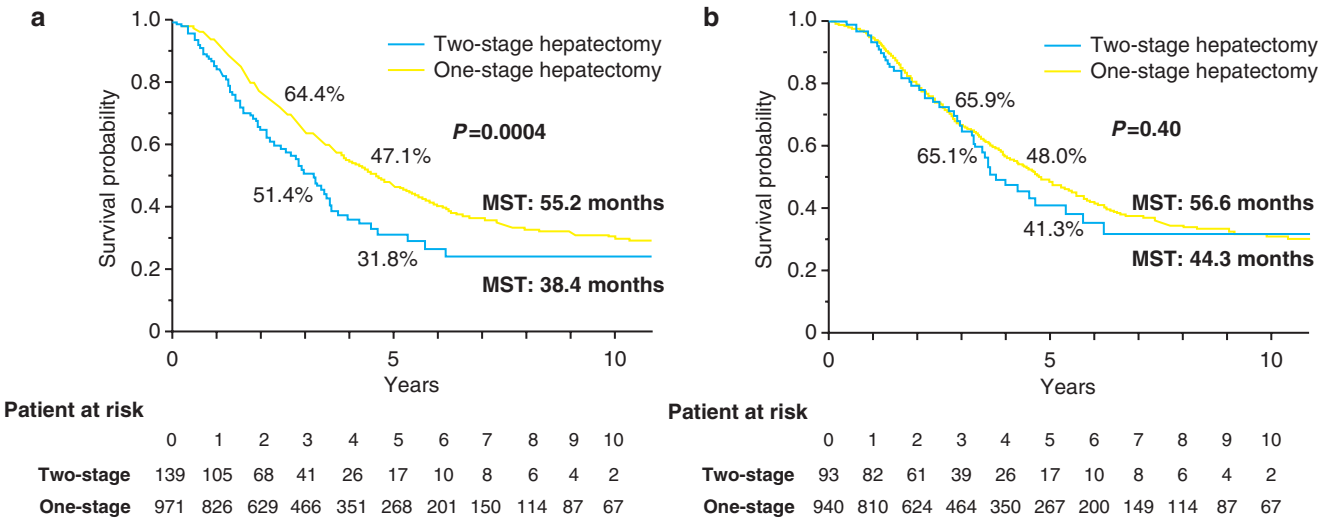
A 55-year-old female was admitted to Paul Brousse Hospital because of rectal cancer with multiple liver and lung metastases with a *KRAS* mutation. Enhanced computed tomography (CT) revealed more 20 liver metastases in both liver lobes and 5 lung metastases in both lung lobes (Fig. 8.7a). A multidisciplinary team meeting decided that both the sites were unresectable and we started chemotherapy using FOLFOX and bevacizumab. After 12 courses, a very good response was obtained (Fig. 8.7b), with significant decrease in tumour markers (carcinoembryonic antigen [CEA]: from 499 to 28 ng/mL, carbohydrate antigen 19-9 [CA19-9]: from 52,753 to 287 U/mL). We shifted the chemotherapy to FOLFIRI and bevacizumab because of neurotoxicity, and after 15 courses, an additional response was obtained (Fig. 8.7c). Serum CEA and CA19-9 levels were normalized

Table 8.1 Short-term outcomes of the TSH (literature review)

	Year	No. of patients planned for TSH	Preoperative chemotherapy (%)	Intraoperative PVE/PVL (%)	Morbidity after first stage (%)	Mortality after first stage (%)	Interval duration (days)	Interval chemotherapy (%)	Morbidity after second stage (%)	Mortality after second stage (%)	5-Year DFS after TSH (%)	5-Year OS after TSH (%)
Lygidakis et al.	2004	62	NR	100	11	0	40	100	11	3	14	35
Garcea et al.	2004	11	100	NR	NR	0	150	0	33	0	NR	NR
Pamecha et al.	2008	14	100	0	0	0	210	100	27	0	NR	50
Homayounfar et al.	2009	24	75	100	13	0	42	0	58	5	NR	NR
Tsai et al.	2010	45	71	73	26	4	135	62	26	6	NR	NR
Karoui et al.	2010	33	61	52	21	0	111	76	32	4	22	48
Tsim et al.	2011	38	97	0	11	0	NR	13	33	0	NR	NR
Brouquet et al.	2011	65	100	0	25	0	32	19	49	0	20	64
Narita et al.	2011	80	84	4	14	0	92	31	54	0	8	32
Stella et al.	2012	56	96	61	37	0	NR	84	49	0	NR	NR
Bowers et al.	2012	33	85	3	23	0	84	15	56	4	NR	NR
Tanaka et al.	2012	24	100	86	29	0	NR	52	38	0	NR	NR
Turrini et al.	2012	48	100	0	10	0	72	29	20	6	NR	35
Muratore et al.	2012	47	79	23	19	0	114	53	44	0	NR	NR
Cardona et al.	2014	40	100	9	14	0	150	86	60	0	NR	49
Giuliante et al.	2014	130	87	52	17	0	39	30	35	4	NR	32
Faitot et al.	2015	50	90	88	18[a]	2	NR	32	NR	NR	NR	23
Quénet et al.	2019	56	100	NR	14[a]	0	201	90	17[a]	6	NR	NR
Taillieu et al.	2021	23	83	NR	0	0	59	35	7[a]	0	NR	NR
Chavez et al.	2021	196	92	NR	5.1	0	120	61	23[a]	5	18	44
Paul Brousse	2015	125	98	76	14[a]	1	96	74	33[a]	3	11	44

DFS disease-free survival, *PVE* portal vein embolization, *PVL* portal vein ligation, *NR* not reported, *OS* overall survival, *TSH* two-stage hepatectomy

[a] Major complication (Clavien ≥ IIIa)



Patient at risk

	0	1	2	3	4	5	6	7	8	9	10
Two-stage	139	105	68	41	26	17	10	8	6	4	2
One-stage	971	826	629	466	351	268	201	150	114	87	67

Patient at risk

	0	1	2	3	4	5	6	7	8	9	10
Two-stage	93	82	61	39	26	17	10	8	6	4	2
One-stage	940	810	624	464	350	267	200	149	114	87	67

Fig. 8.6 (**a**) Overall survival for patients who were 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, median survival time. ([6], with permission)

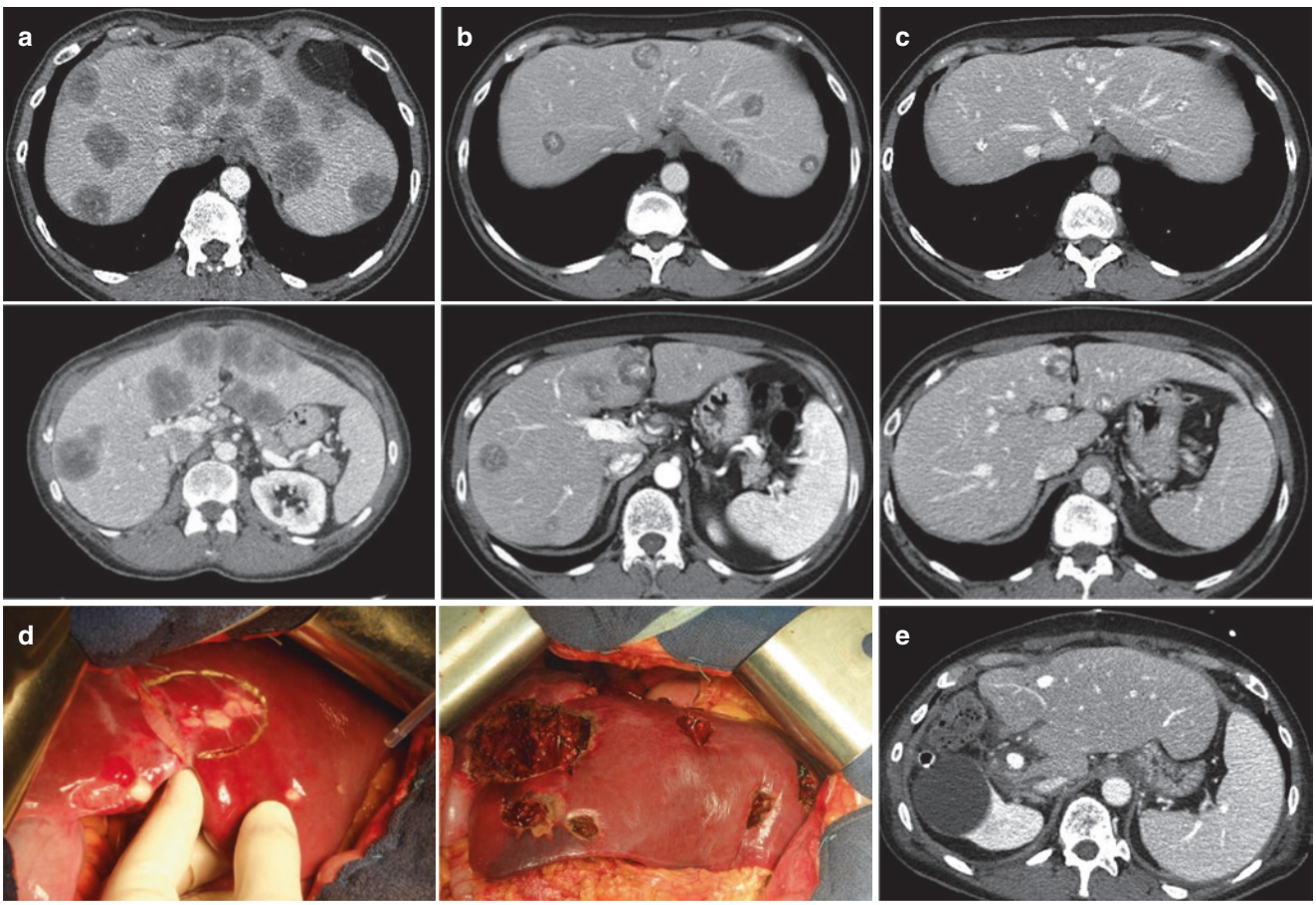


Fig. 8.7 (**a**) CT at the diagnosis. (**b**) CT after 12 courses of FOLFOX and bevacizumab as a first-line chemotherapy. (**c**) CT after 15 courses of FOLFILI and bevacizumab as a second-line chemotherapy. (**d**) Multiple partial resections of the left liver lobe during first stage. (**e**) CT after second-stage hepatectomy. There is no evidence of the residual disease in the liver

(CEA: 2.7 ng/mL; CA19-9: 23 U/mL) and lung metastases were also well controlled. We planned TSH, and first-stage hepatectomy was performed 16 months after initial diagnosis. At the first stage, multiple partial resections of the left lobe of the liver combined with right portal vein ligation were performed, with absolute alcohol injection of the distal stump of the right portal vein to avoid any cavernoma reperfusion from above the ligature (Fig. 8.7d). Interval chemotherapy was administered with four courses of FOLFIRI and bevacizumab, and second-stage hepatectomy (extended right hepatectomy) was performed 24 months after initial diagnosis. Macroscopically, all liver lesions were resected by these two sequential hepatectomies (Fig. 8.7e). Subsequently, resection of the primary rectal tumour was performed 32 months after initial diagnosis (pT3 N1 M1). For the lung metastases, a right superior lobectomy with hilar mediastinal lymphadenectomy was performed. However, before planned lung metastatectomy for left lung metastases, a liver recurrence with a single nodule in the segment 4 was observed. Therefore, repeat hepatectomy of segment 4 was performed. Lung metastases in the left lobe showed regrowth, and chemotherapy with FOLFIRI and bevacizumab was restarted. Lung metastases showed significant decrease in size, and resection of left lung metastases was performed 51 months after initial diagnosis. At this point, this patient was alive without evidence of disease. Unfortunately, after that, she developed new recurrences in the liver and lungs. She remained alive with liver and lung recurrence under late-line chemotherapy for >6 years after initial diagnosis, and finally died from progression of the disease at almost 7 years from diagnosis.

8.3 Conclusion

We have summarized the Paul Brousse experience of the TSH strategy for multiple bilobar CLMs. The TSH strategy introduced by our team two decades ago has now been accepted as an established procedure with acceptable short-term outcomes and promising long-term outcomes. However, some issues such as the dropout risk and the high rate of early recurrence should still be resolved. Further investigations are warranted including molecular biology to identify the patients more likely to benefit from the procedure. Under such a situation, we believe that there is still room for improvement in the TSH strategy within the spectrum of multidisciplinary teams including surgeons, medical oncologists, radiologists, pathologist, and hepatologists who treat CLM.

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9 One-Stage Hepatectomy for Bilateral Colorectal Liver Metastases: Experience of the University of Tokyo

Yujiro Nishioka, Yoshikuni Kawaguchi, and Kiyoshi Hasegawa

Learning Objectives

- One-stage hepatectomy is feasible and effective surgical procedure for patients with bilateral colorectal liver metastases.
- Precise preoperative evaluation of intrahepatic vascular structure by contrast-enhanced dynamic computed tomography and magnetic resonance imaging is essential.
- Contrast-enhanced intraoperative ultrasonography is useful in intraoperative inspection of CLM and the technique for staining portal vein territory is important for necessary and sufficient resection of tumour infiltrating Glissonean pedicle.

9.1 Introduction

Colorectal cancer (CRC) accounts for approximately 15% of cancer deaths and ranks second place next to lung cancer in Japan [1]. The liver is the most frequent site of CRC metastases [2] and colorectal liver metastases (CLM) is a major cause of death in patients with CRC.

Surgical resection has been established as a standard of care for CLM; however, only 25–30% of patients are considered eligible for surgical resection at diagnosis [3]. Recent advances in systemic medical therapy for CRC have enabled the down-staging of CLM and increased the chance of surgical resection for patients with bilateral CLMs. Surgical procedure for such cases is usually complex and associated with a high risk of postoperative complication. Especially, postoperative liver failure (POLF) is the most critical complication, resulting in higher postoperative mortality and longer hospital stay. Surgical resection for bilateral CLMs has a high risk of POLF because removal of large amount of liver parenchyma is needed. Therefore, evaluation of future liver remnant (FLR) volume is essential for deciding the indication of surgical resection. Portal vein embolization (PVE) [4] induces approximately 10% of liver hypertrophy in FLR [5]. As such, PVE is recommended prior to hemi-hepatectomy or extended hemi-hepatectomy in case that insufficient FLR volume is expected.

If PVE is expected not to ensure sufficient FLR, two-stage hepatectomy (TSH) combined with PVE is considered. However, approximately 20% of patients who underwent the first-stage hepatectomy cannot proceed to the second-stage surgery due to disease progression during the waiting period between the first- and second-stage hepatectomies and/or insufficient liver hypertrophy of FLR [6]. In order to facilitate liver hypertrophy and shorten the waiting period, Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) has been proposed [7]. A recent study reported that ALPPS decreased the dropout rate compared to TSH [8]; however, safety of ALPPS remains controversial considering the high morbidity and mortality rates. Additionally, even ALPPS cannot completely overcome the risk of dropout due to tumour progression between first- and second-stage hepatectomies. These strategies using sequential hepatectomy might take a role of patient selection that stratifies patients with poor tumour biology; however, complete resection has been reported to offer favorable outcome even in such cases [9].

After CLM resection, approximately 70% of patients experience recurrence, and re-do hepatectomy also offers the prolonged survival in patients with recurrent disease [10]. Parenchymal-sparing hepatectomy (PSH) was reported to increase the resectability for possible recurrent disease and improve postoperative survival [11]. Even in cases of tumour proximity to Glissonean pedicle, few cases actually have tumour invasion into main portal pedicle. Therefore, complete removal of CLMs can be achieved using multiple partial resection with or without anatomical resection of small

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portal territory (i.e., subsegmentectomy or sectorectomy) in most patients with multiple CLMs, and cases with truly insufficient FLR are thought to be rare.

Given these findings, our group at the University of Tokyo has routinely used the concept of "one-stage hepatectomy," which is multiple partial liver resection with or without PVE for over two decades and reported the favorable short−/long-term outcome after one-stage hepatectomy for patients with CLM [12]. We have applied this policy even to patients with bilateral CLM, and we rarely perform hemi-hepatectomy for bilateral CLM and try to preserve as many Glissonean pedicles as possible except in cases of tumour invasion. This concept theoretically maintains FLR compared to hemi-hepatectomy and partial liver resection for tumours located in the FLR.

In this chapter, we detail the requirement to plan one-stage hepatectomy in patients with bilateral CLMs (i.e., preoperative evaluation, intraoperative inspection of CLMs) and outcomes after one-stage hepatectomy.

9.2 Preoperative Evaluation

9.2.1 Diagnostic Approach

For patients with CLMs, precise evaluation of the distribution of CLMs is essential. Thin-sliced contrast-enhanced dynamic computed tomography (CE-CT) is widely used as a standard of diagnostic modality for CLM, which visualizes CLM as hypovascular low-density lesion. However, patients with CLM often have sub-centimeter nodules that are difficult to recognize and distinguish from benign diseases in CE-CT. Diagnostic power of CE-CT can be decreased in patients with fatty liver disease due to the low contrast between tumours and normal liver parenchyma. In addition, preoperative chemotherapy for CLM entails the risk of disappearing CLM, which makes surgeons difficult to recognize tumour intraoperatively. Therefore, our group performs contrast-enhanced magnetic resonance imaging (MRI) using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (EOB-MRI; Primovist®), which can visualize even small tumours as clear defect [13] and intra−/extra-hepatic biliary tract 15–20 min after injection. On the basis of these modalities, drawing schema of tumour distribution before surgery (Fig. 9.1a, b) in addition to three-dimensional liver imaging (Fig. 9.1c, d) improves the understanding of the relationship between tumours and intrahepatic vascular structure and facilitates liver resection under the concept of one-stage hepatectomy (Fig. 9.1e, f).

9.2.2 Evaluation of Liver Function and Future Liver Remnant Volume

Minimal requirement of FLR for safe resection varies according to the status of background liver. Our group established a decision-making algorithm for safe hepatectomy based on the

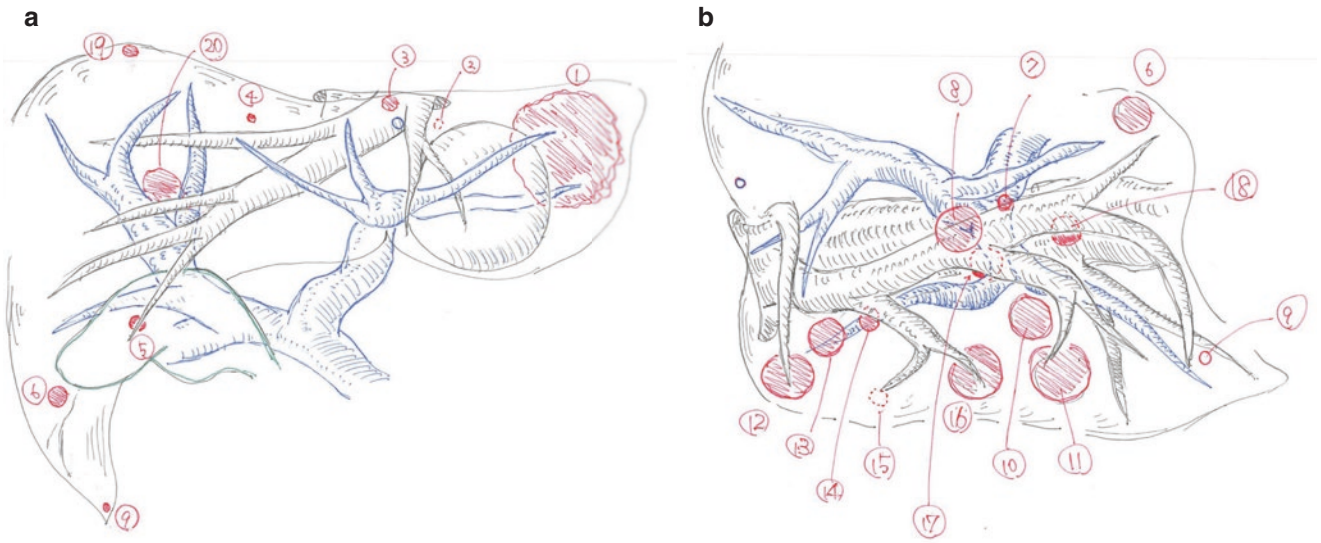


Fig. 9.1 Preoperative evaluation (**a–d**) and gross appearance of cut surface after resection (**e** and **f**). (**a, b**) Preoperative hand-drawn schema of 20 bilateral colorectal liver metastases from (**a**) the front and (**b**) the right side focusing on right hepatic vein and anterior/posterior portal pedicles, which showed that tumour #17 was located just behind the root of right posterior portal pedicle. (**c, d**) Preoperative three-dimensional imaging of (**c**) tumour location from the front of right hepatic vein and simulation of (**d**) right posterior sectorectomy (segment VI colored in green and segment VII colored in yellow). (**e, f**) Gross appearance of cut surface after one-stage hepatectomy (extended right posterior sectorectomy and six partial resections)

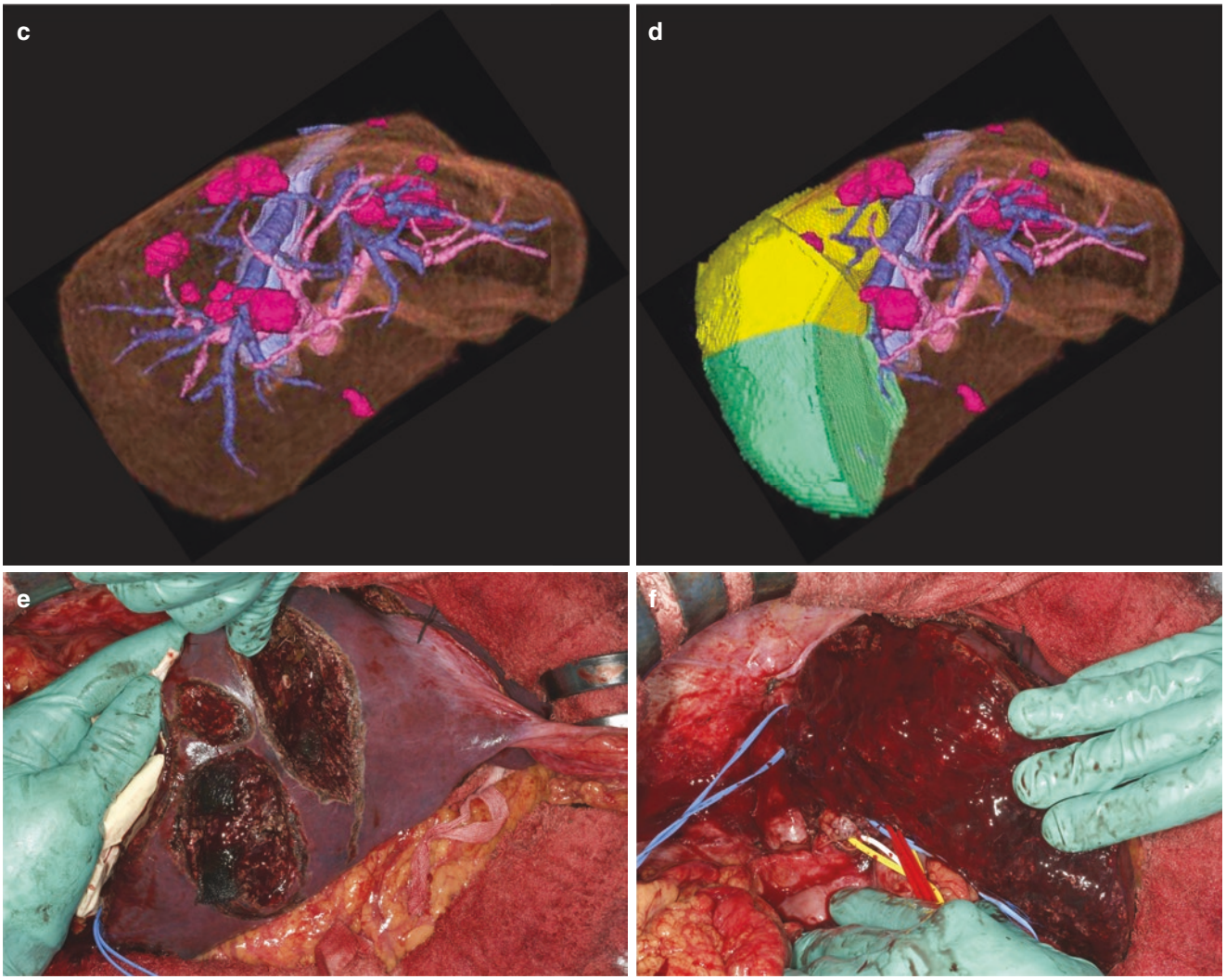


Fig. 9.1 (continued)

presence of ascites, serum bilirubin, the calculated indocyanine green (ICG) retention test after 15 min (ICG-R15), and FLR [14]. We have recently proposed a new algorithm for safe hepatectomy based on serum albumin value, ICG-R15, and the presence of portal hypertension [15].

Calculation of FLR is performed using a three-dimensional simulation software (SYNAPSE VINCENT®; Fujifilm, Tokyo, Japan) [16]. For tumour with possible invasion of peripheral Glissonean pedicle or for patients with tumours clustering in specific portal vein territory, volumetric assessment of the minimal portal vein territory of interest is performed (Fig. 9.2). For patients suspicious of invasion of major hepatic vein, volumetric assessment of the hepatic vein drainage area is performed [17]. We have previously reported approximately 60% of the functional decrease in veno-occlusive regions [18] and our group reconstructs hepatic veins using cryo-preserved homologous graft if necessary [19].

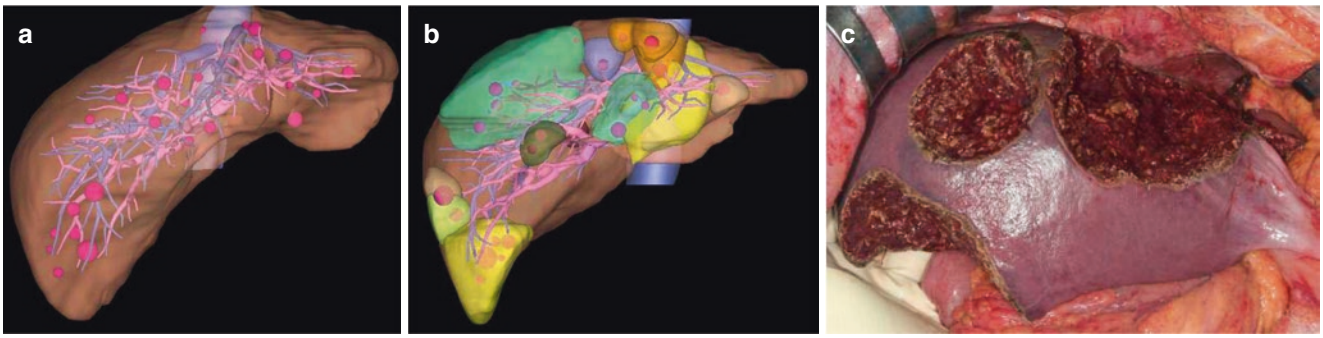


Fig. 9.2 Preoperative simulation of (**a**) whole liver, intraoperative vessels, and all the tumours and (**b**) planned multiple partial resections. (**c**) Intraoperative gross appearance of cut surfaces after one-stage hepatectomy (multiple partial resections)

9.3 Intraoperative Inspection of CLMs

The concept of one-stage hepatectomy approach is to perform multiple partial liver resection while preserving liver parenchyma. As such, precise intraoperative inspection of small and/or deep tumours is mandatory for this approach in patients with bilateral CLMs.

The usefulness of intraoperative ultrasonography (IOUS) was established in the 1980s [20, 21]. Our group reported the efficacy of the contrast-enhanced IOUS (CE-IOUS) using the second-generation contrast agent (Sonazoid®, GE Healthcare, Oslo, Norway). The agent has the peculiarity of accumulating in hepatic Kupffer cells and visualizing tumours as clear defect in IOUS [22]. The accuracy of CE-IOUS in detecting CLM reached to 97% and it also identified new nodules that could not be visualized by CE-CT and EOB-MRI [23].

No oncological benefit of anatomical resection for CLM has been demonstrated; however, resection of portal vein territory ensures surgical margin after resection of CLM infiltrating Glissonean pedicle. In these cases, the visualization of portal vein territory using intraoperative staining technique (e.g., dye injection, indocyanine fluorescence imaging) is useful in identifying the extent of resection. Our group reported the technique of anatomic resection of Couinaud mono-segment [24] and our technique is also used to visualize peripheral portal vein territories (i.e., smaller than Couinaud mono-segment). However, this technique entails problems such as a lack of information regarding intrahepatic segmental border. In order to overcome these problems, other staining techniques using contrast agents [25] (Fig. 9.3) and ICG fluorescence imaging [26] were reported. Studies reported that these techniques are effective in patients undergoing re-hepatectomy.

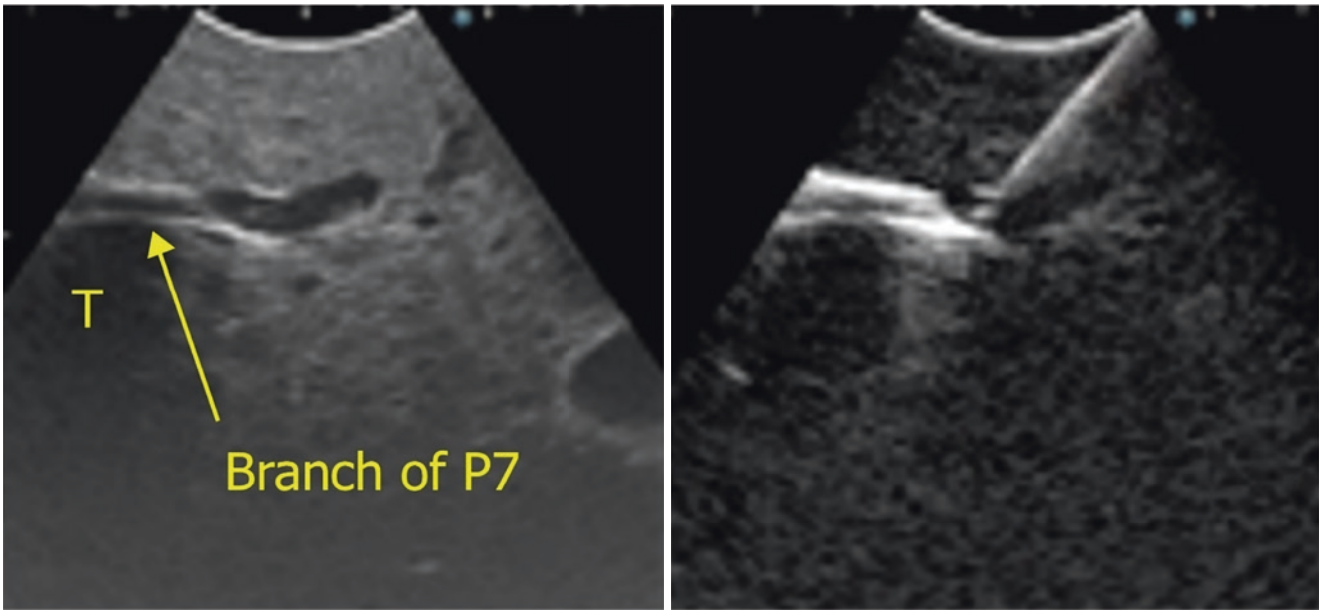
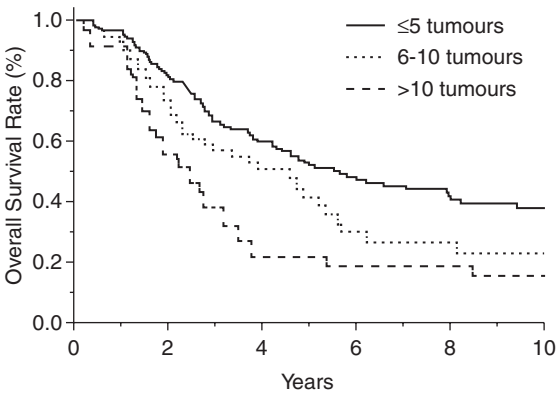


Fig. 9.3 Screenshot of intraoperative ultrasonography (IOUS) in staining of portal vein territory using contrast agents (Sonazoid®): (left) normal-mode IOUS showing a tumour (T) infiltrating into a branch of portal vein feeding liver segment 7 (P7); (right) contrast-enhanced IOUS showing a needle inserted into the branch of P7 and injected dye with Sonazoid® in real time

9.4 Outcomes after One-Stage Hepatectomy

At our institution, 322 patients underwent initial hepatectomy for bilateral CLMs between 1994 and 2017, and 308 patients (96%) underwent one-stage hepatectomy. Of these patients, 26 patients (8%) underwent preoperative PVE and 230 patients (75%) underwent partial hepatectomy. Median number of resected specimens was 3 (1–24) and median number of resected tumours was 5 (2–77). R0 resection was achieved in 76% of the patients, R1 resection in 24%, and R2 resection in only one patient. Postoperative morbidity was found in 44% of patients including 16% of patients who developed severe complication (defined as complication ≥ Clavien-Dindo Grade ≥ 3). There was no postoperative mortality. The 5-year recurrence-free survival (RFS) and 5-year overall survival (OS) were 14% and 44.7% in the entire cohort, 18% and 52% in patients with ≤5 tumours, 14% and 42% in patients with 6–10 tumours, and 0% and 22% in patients with >10 tumours, respectively (Fig. 9.4).

Previous studies reporting the outcome of one-stage hepatectomy for bilateral CLMs are summarized in Table 9.1. R0 resection was achieved in approximately 70–80% and severe postoperative morbidity was observed in 10–15%, and postoperative mortality rate was 1–2%. Although reported long-term outcome was various among studies, patients who underwent one-stage hepatectomy had approximately 40–50% of 5-year overall survival, which is consistent with the outcome of two-stage hepatectomy for bilateral CLMs [6, 27, 28]. Given the low morbidity and mortality rates, one-stage hepatectomy for patients with bilateral CLMs is feasible.



No. at Risk						
≤5 tumours	180	128	79	49	37	23
6-10 tumours	70	47	23	11	9	5
>10 tumours	58	26	10	7	7	6

Fig. 9.4 Overall survival by number of CLMs for patients who underwent one-stage hepatectomy at The University of Tokyo

Table 9.1 Outcomes after one-stage hepatectomy and two-stage hepatectomy for bilateral colorectal liver metastases

	Year	Patient no.	Preoperative chemotherapy, %	PVE, %	Major hepatectomy, %	Additional ablation therapy, %	TSH completion, %	R0 resection, %	Postoperative morbidity (all), %	Postoperative morbidity (C-D ≥ 3), %	Postoperative mortality, %	5-Year OS, %
One-stage hepatectomy												
Bolton et al. [35]	2000	44	68	0	52	0	–	NA	NA	NA	6	36
Sakamoto et al. [36]	2010	77	0	14	16	0	–	24	13	NA	1	37
Memeo et al. [37]	2016	691	34	NA	52	25	–	70	30	17	0.2	67 (PSH), 59 (non-PSH)
Philips et al. [38]	2016	101	80	0	46	100	–	86	32	14	1	40
Mizuno et al. [39]	2018	101	93	9	NA	71	–	NA	44	26	8	24
Spelt et al. [40]	2018	119	73	10	50	17	–	84	71	13	0	30 (PSH), 40 (non-PSH)
Torzilli et al. [41]	2019	52	77	0	0	0	–	21	46	8	2	(3-year OS) 43
D'Hondt et al. [42][a]	2021	36	56	0	0	0	–	89	6	3	0	76
Current report	–	308	38	8	25	0	–	76	44	16	0	45
Two-stage hepatectomy												
Passot et al. [6]	2016	109	100	73	100	0	80	61	NA	26	6	49 (TSH completed) 0 (TSH not completed)
Baumgart et al. [27]	2019	50	91	68	100	0	72	70	NA	34	4	22
Chavez et al. [28]	2021	196	92	65	78	28	100	78	47	23	5	44

C-D Clavien-Dindo classification, *NA* not available, *OS* overall survival, *PSH* parenchymal-sparing hepatectomy, *PVE* portal vein embolization, *TSH* two-stage hepatectomy

[a]All the patients underwent laparoscopic surgery

9.5 Future Perspective of One-Stage Hepatectomy

In order to improve tumour detection using IOUS, we performed a clinical study using real-time virtual sonography, IOUS combined with preoperative CT images [29, 30]. The shortcomings of this new modality include misalignment and intraoperative change in liver morphology; however, this may help surgeons for identifying tiny nodules.

Optimal surgical margin is an important issue to perform multiple partial resections under the one-stage hepatectomy approach. R0 resection remains essential for local control of CLM [31]. Studies reported that surgical margin more than 1 mm is sufficient [32, 33]. A recent retrospective study reported that R1 resection with detachment of CLMs from major intrahepatic vessels could achieve outcomes similar to R0 resection [34]. These data may reappraise surgical indication of multiple partial resection (one-stage hepatectomy) in patients with bilateral CLMs.

Finally, genetic profile of CLM has increasingly gained the popularity for clinical decision-making of CLM treatment. Somatic mutation in *RAS* of CLM is a well-known prognostic factor in addition to clinicopathologic factors. It should be elucidated how *RAS* mutation status influences the decision-making process of surgical approach; however, the clinical benefit of aggressive surgical treatments needs to be further investigated in patients with both extended tumour burden and poor tumour biology.

9.6 Conclusion

One-stage hepatectomy for bilateral CLM can be safely performed and provides favorable outcome, while preserving liver parenchyma. For successful one-stage hepatectomy, surgeons need better understanding of the liver anatomy, the intrahepatic vascular structures and location of tumours, and use of IOUS.

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Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis

10

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Learning Objectives

- "Associating Liver Partition and Portal vein ligation for Staged hepatectomy" (ALPPS) is a two-stage hepatectomy variant that induces rapid hypertrophy of the future liver remnant (FLR) in a short period of time and increases resectability rates of otherwise unresectable liver tumours.
- The International ALPPS Registry was founded in 2012 to collect data from ALPPS cases from all over the world and enable scientific analysis.
- ALPPS is a very complex surgical approach requiring a high hepato-biliary (HPB) expertise. Initially high perioperative morbidity and mortality rates could be reduced by several technical modifications of the original ALPPS technique and by a better patient selection.
- Because of early tumour recurrences seen in many patients, it is controversial whether the massive growth stimulation of the FLR also affects residual undetected tumour in the FLR, which may be oncologically detrimental.
- The role of ALPPS in the multimodal treatment of CLM is not yet defined. There is only one randomized controlled trial so far comparing ALPPS versus conventional TSH in patients with advanced CLM.

10.1 Introduction

"Associating Liver Partition and Portal vein ligation for Staged hepatectomy" (ALPPS) was a true surgical innovation in 2007 and has become a last-resort surgical approach for patients with otherwise unresectable primary and secondary liver tumours. The fascination about this technically demanding and ultra-radical surgery is ongoing. Initial safety concerns about high perioperative morbidity and mortality could be addressed by modification and refinements of the procedure, but oncological concerns about a high and early recurrence rate still persist.

The aim of this chapter is to give an overview of the evolution of ALPPS as a surgical procedure and to describe its current role in the multimodal treatment of patients with colorectal liver metastases (CLM).

10.2 Evolution of ALPSS as a New Surgical Strategy

ALPPS was found by serendipity in Regensburg, Germany, by Hans Juergen Schlitt and colleagues in September 2007. A 48-year-old woman suffering from a Bismuth type IV Klatskin tumour was planned for a right trisectionectomy [1]. When upon laparotomy the left-lateral section was found to be too small to proceed with a trisectionectomy, the "spontaneous decision" was made to "try and quickly induce hypertrophy of the left-lateral section by de-portalizing the right liver while already performing the parenchymal dissection along the right side of the falciform ligament, thereby completely devascularizing segment 4 after parenchymal transection." This description of the first ALPPS procedure (in this report still by the name of "In-situ Split Liver Resection") further mentioned that the bile duct was divided at the base of the round ligament and a Roux-en-Y hepaticojejunostomy was performed to the left duct. To facilitate completion surgery, the right artery was dissected free and encircled with a loop, the right lobe and segment 1 were fully mobilized from the retroperitoneum and the cava, and, finally, the middle hepatic vein was divided and the right vein extrahepatically encircled. Computed tomography (CT)-volumetry after 8 days showed a marked hypertrophy of 90% of the left-lateral section so that the completion surgery was performed the following day. The patient recovered quickly and was discharged on day 10 [1].

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With this successful first "in-situ split liver resection," a new surgical concept was born that gained first nationwide and soon global attention. Five (three in the abstract) first cases were presented at the european-african hepato-pancreato-biliary association (E-AHPBA) Meeting in Cape Town, South Africa, in 2011 [2]. And the first multicenter series of 25 patients from five German centers by Schnitzbauer et al. demonstrated the marked and rapid hypertrophy of the future liver remnant (FLR) of almost 75% after a median of 9 days leading to a 100% staged resectability in tumours considered unresectable under conventional auspices [3]. To avoid confusion with the term "in-situ split" technique in liver transplantation, Eduardo de Santibañes and Pierre-Alain Clavien suggested in 2012 the self-explanatory acronym "ALPPS" [4]. In the same year, the "International ALPPS Registry" was founded to collect data from ALPPS cases from all over the world and enabled scientific analysis.

The original ALPPS technique soon underwent multiple major and minor technical modifications. This was motivated first and foremost to cope with the high perioperative morbidity and mortality, which was reported in the early publications. A major reduction in invasiveness of both stages was achieved by performing ALPPS in a totally laparoscopic approach, which was published by Machado in 2012 [5]. A different take on reducing the invasiveness of stage 1 was to completely avoid manipulation of the hepatic hilum. The hilar surgical dissection and portal vein ligation (PVL) were omitted and an either intraoperative or postoperative interventional portal vein embolization (PVE) was performed combining surgical and interventional steps in a hybrid approach ("hybrid ALPPS") [6]. Trying to avoid the hepatic parenchymal dissection during stage 1, Robles and colleagues proposed a variant approach in 2014 occluding the intrahepatic vasculature in the future resection plane by tying down a tourniquet around the liver ("Tourniquet ALPPS" or "Associating Liver Tourniquet and Portal ligation for Staged hepatectomy" [ALTPS]) [7]. The ensuing years with a growing experience brought evidence that severe (Dindo-Clavien grade $\geq$ 3b) post-stage 1 complications were associated with a worse post-stage 2 outcome [8–10], in particular biliary fistulas or infected ascites being present at stage 2. So, at stage 1, special attention was paid to the vascularization and biliary drainage of segment 4 in order to avoid ischemia/necrosis or bile leakage. Petrowsky and colleagues suggested in 2015 to only partially transect the hepatic parenchyma preserving the middle hepatic vein ("Partial ALPPS") [11]. Interestingly, the transection of only 50–80% of liver parenchyma is associated with a significant reduction in perioperative morbidity but does apparently not compromise the extent of the hypertrophy induced [11, 12]. Combining this "partial ALPPS" approach with the above-mentioned "hybrid ALPPS" technique, de Santibanes and colleagues were able to even further reduce the trauma of stage 1 and "invert the ALPPS paradigm of an aggressive first surgical procedure followed by a shorter and less aggressive second step" by this "Mini ALPPS" approach [13].

The timeline of technical modifications of the ALPPS procedure is shown in Fig. 10.1. The efforts to modify and

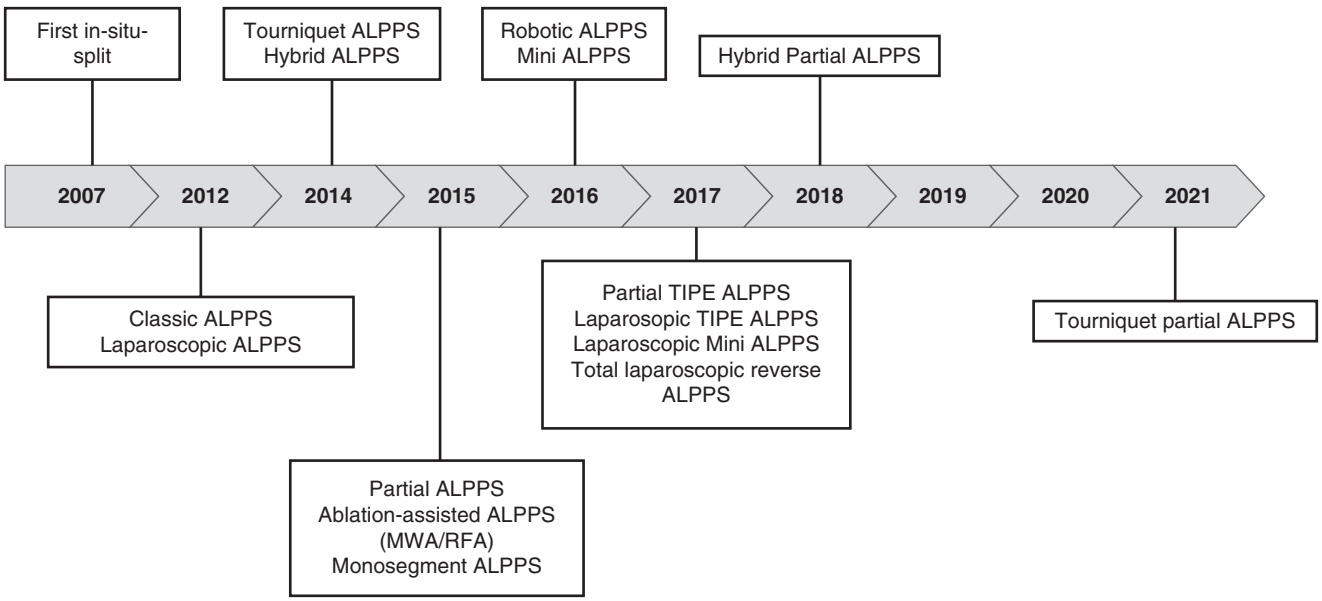

Fig. 10.1 Timeline of technical evolution and modification of the original ALPPS procedure

fine-tune this highly complex surgery are ongoing as can be seen by the latest proposition in 2021 by Robles-Campos and colleagues to modify their "Tourniquet-ALPPS" technique in that they were able to pass the tourniquet tape across an avascular plane transhepatically underneath the hepatic veins in order to preserve the middle hepatic vein flow [14].

10.3 ALPPS for Colorectal Liver Metastases

Colorectal liver metastases are the most frequent indication for ALPPS [15]. The original publications reporting the outcome of ALPPS for CLM are listed in Table 10.1. About two-thirds of all ALPPS cases comprised in the International ALPPS Registry are patients with colorectal liver metastases. ALPPS has empowered liver surgeons to achieve complete hepatic tumour removal in patients with CLM that were considered unresectable by conventional ways of liver surgery. Carefully spoken, ALPPS offers a curative perspective to patients who would otherwise go to palliative care. Because other methods were limited in this patient group, the use of ALPPS was justified. However, a couple of questions arise. When is ALPPS functionally indicated? How substantial is the curative perspective compared to alternative techniques of resection? How do results after ALPPS compare to palliative treatments? How can ALPPS be reasonably embedded into modern multimodal cancer therapy?

10.4 When Is ALPPS for CLM Functionally Indicated?

10.4.1 Where Do We Come From? Functional Resectability in the Pre-ALPPS Era

In the era before ALPPS, several milestone inventions have increased the chance of hepatic resectability for advanced liver tumours. In 1990, Masatoshi Makuuchi and colleagues found that preoperative portal vein embolization induced contralateral hypertrophy that can expand resectability by increasing the size of the future liver remnant [31]. This invention, originally published for patients with hilar cholangiocarcinoma, was in analogy applicable for any other liver tumour entity. Pursuing a different approach was the concept of downsizing unresectable liver lesions by preoperative chemotherapy to achieve secondary resectability. Henri Bismuth and colleagues introduced this liver-neoadjuvant approach in 1996 and demonstrated secondary resectability in 53 patients with primarily unresectable CLM (because of ill-location [8], size [8], multinodularity [24], or extrahepatic spread [13]). The overall 3- and 5-year survival rates in the Bismuth study were 54% and 40%, respectively, and, according to the type of lesions, 75% and 48% for ill-located, 62% and 62% for large, 54% and 40% for multinodular, and 43% and 14% for extrahepatic lesions. In 2000, a third novelty was introduced by René Adam and colleagues who proposed the concept of two-stage hepatectomy (TSH) to achieve complete resection of bilateral multinodular hepatic metastases not amenable to

Table 10.1 Primary studies on ALPPS in the literature

References	Year	No. of patients	1 Year (%)	2 Year (%)	3 Year (%)	5 Year (%)	Median survival (months)
Schadde et al. [16]	2014	141	76	63	–	–	–
Oldhafer et al. [17]	2014	7	57	–	–	–	–
Hernandez-Alejandro et al. [18]	2015	14	100	–	–	–	–
Lang et al. [19]	2015	7	–	–	64	–	–
Ratti et al. [20]	2015	12	92	–	–	–	–
Adam et al. [21]	2016	17	–	42	–	–	–
Björnsson et al. [22]	2016	23	83	59	–	–	–
Kambakamba et al. [23]	2016	41	–	–	–	–	24.7 ± 2.3
Olthof et al. [24]	2017	70	–	62	–	–	–
Wanis et al. [25]	2018	58	93	66	50	–	–
Robles-Campos et al. [26]	2019	21	76	–	57	23	36
Baumgart et al. [27]	2019	8	75	–	40	–	36.2
Bednarsch et al. [28]	2020	21	100	71	37	–	28
Petrowsky et al. [29]	2020	510	–	–	52	27	37
Hasselgren et al. [30]	2021	48	82	74	60	–	46

resection in a single procedure, not even after effective downsizing chemotherapy [32]. To address the problem of an estimated small future remnant, Daniel Jaeck and colleagues modified TSH by combining tumour clearance of one hemiliver with simultaneous contralateral portal vein ligation or subsequent portal vein embolization (PVE) to stimulate growth of the FLR [33]. The hypertrophy rates with TSH + PVE/PVL usually reach 20–40%, exceptionally about 60–70%, and take place after 4–12 weeks [34]. These two circumstances explain the inherent risk of dropout between stages 1 and 2 due to either an insufficient degree of hypertrophy of the future liver remnant or, more importantly, a tumour progression during the long interstage interval. Patients not proceeding to stage 2 have a poor survival similar or even worse than patients treated with chemotherapy alone. When both steps are completed, the outcome is as good as after surgery for primarily resectable CLM and 5-year overall survival can range at 64% at best [21, 35–39].

10.4.2 Functional Resectability With ALPPS

As opposed to the conventional two-stage strategies of liver resection of the pre-ALPPS era, ALPPS is a TSH variant that triggers a more pronounced and much faster hypertrophy of the future liver remnant allowing for a two-stage completion in a short period of time [3]. Not only gaining ground in resectability in otherwise unresectable cases, ALPPS was even shown to be effective after a failure of PVE and "rescue" or "salvage" ALPPS became possible after a failed intention of extended hepatectomy following PVE/PVL [40–42].

In fact, the growth rates seen with ALPPS are about fivefold higher (22–35 mL/day) than with TSH plus PVE (about 3–5 mL/day) [43, 44]. The underlying mechanisms of this unexpected and miraculous dimension of extent and speed of hypertrophy are still not fully understood. A more drastic deprivation of the right lobe of its portal flow by the combination of both portal inflow occlusion and division of compensatory collaterals to the right side may serve as part of the explanation as does the notion of a stronger systemic response to the add-on parenchymal transection compared to PVE/PVL alone. Of note, the extent of hypertrophy observed after ALPPS stage 1 seems to be not or only little mitigated by preoperative chemotherapy but data are controversial [18, 45, 46]. Similarly, data regarding proliferation indices (Ki67 index) are contradictory in the literature. While Fukami et al. found an increase in Ki67 expression from 60% to 80% between ALPPS stages 1 and 2, Joechle et al. did not reveal any differences in Ki67 between ALPPS and conventional hepatectomy [44, 47, 48].

Regardless, the extent of hypertrophy is achieved and the subsequent gain in technical resectability with ALPPS is second to none. Median hypertrophy rates of 160% (range 90–250%) in selected cases even allowed for removal of all but one liver segments—a variation called "monosegment-ALPPS." A series of 12 "monosegment-ALPPS" were reported by Schadde and colleagues in 2015, of note, with no postoperative mortality.

On the other hand, with more than 50% of the International ALPPS Registry cases performed as ALPPS in conjunction with a mere right hepatectomy (instead of an extended right hepatectomy), concerns were raised if ALPPS was really necessary in all these cases. A study in 2018 by Schnitzbauer et al. analyzed 183 right hepatectomy-ALPPS and 220 right trisectionectomy-ALPPS for CLM from the International ALPPS Registry and found that more than 15% of ALPPS procedures were performed in patients who may have had no indication for a two-stage hepatectomy, especially in the group of patients with right hepatectomy [49]. Criteria to assess the justification for ALPPS were the presence of metastases in segments 2/3, presence of liver damage, number of chemotherapy cycles, and a liver-to-body-weight-index of 0.5 or less. The great potential of ALPPS to induce rapid volume growth, the authors concluded, would bear a risk of overuse and, therefore, should be carefully weighed against the still high perioperative risk [49].

High morbidity and mortality rates that were reported in early ALPPS papers (in patients with CLM of up to 12%) could be addressed by technical modifications mentioned above and with growing experience and expertise, ALPPS has become continuously safer over the years. A randomized controlled trial (RCT) from Scandinavia in 2018 comparing ALPPS to conventional TSH for advanced CLM (LIGRO-Tial) found no significant difference in the 90-day mortality (8.3% vs. 6.1%) between the two surgical approaches [50]. And in one of the most recent and largest studies on ALPPS for CLM analyzing 510 patients from in- and outside the International ALPPS Registry, the 90-day mortality was 4.9% [29].

10.5 ALPPS for CLM in a Curative Intention

From an oncological point of view, hepatic resection is currently still the treatment of choice if a curative approach is intended offering 5-year survival rates of up to 50–60% depending on patient selection. However, at the time of diagnosis, only a minority of about 15–30% of patients are candidates for upfront hepatic surgery.

If the treatment stratification is strict in the sense that ALPPS is indicated as a last-resort strategy for patients who are considered unresectable by all other conventional ways of hepatic resection (either because their FLR is too small or their hepatic disease is too advanced), these ALPPS patients are an oncological cohort of their own and their surgical and oncological outcomes are difficult to compare to patients

after other sorts of hepatic resection. The outcome of these "exclusive" ALPPS-patients who do not have a surgical alternative can only be compared to patients going to palliative care.

However, in reality, there is an overlap of surgical indications between ALPPS, conventional TSH strategies with or without PVE/PVL, and one-stage hepatectomy (OSH), which is worthwhile to be looked at.

While the extent and speed of hypertrophy seen with ALPPS are often desirable from a functional point of view, it remains a matter of debate whether the enhanced liver recovery is curse or blessing from an oncological perspective. Some authors have argued that a slower hypertrophy rate with TSH plus PVE/PVL may be beneficial because of the longer waiting time in between steps allowing for a better assessment of tumour growth and thereby a better patient selection. On the one hand, TSH with PVE/PVL offers a better chance to detect and remove small tumour deposits and metastases during stage 1. On the other, up to 24–40% of patients do not undergo stage 2 hepatectomy mostly due to disease progression during the long interval of several weeks [21, 36, 39]. Patients not proceeding to TSH stage 2 have a dismal outcome [38, 51]. With ALPPS, the interstage interval of usually 7–14 days has become so short that the detection of tumour progression has shifted from the interstage period to the post-stage 2 period. With almost no patients dropping out during this short interstage, a high rate of formally complete resections is achieved. This significantly higher resectability rate after ALPPS compared to TSH with PVE/PVL is almost unanimous in all studies [16, 18, 52, 53]. The Scandinavian LIGRO-Trial that compared ALPPS and TSH for FLR <30% reported a 92% versus a 57% resection rate after ALPPS and TSH, respectively, with similar surgical margins and a similar perioperative morbidity and mortality [50]. This is confirmed by another most recent study from Scandinavia, which analyzed the extent of hypertrophy and the resection rate in 172 patients with CLM who underwent either upfront ALPPS or PVE with the possibility of rescue ALPPS on demand [54]. The resection rate was 84.5% in the upfront ALPPS cohort and 73.3% in the PVE and rescue ALPPS on demand cohort, respectively. The 20% of PVE patients required rescue ALPPS. Interestingly, the hypertrophy of the FLR was highest in the group of patients who had undergone both PVE and rescue ALPPS (96% [range 2–113%] compared to 71% [range 48–97%]) after upfront ALPPS.

While it seems beyond doubt that ALPPS offers significantly better resection rates compared to TSH, the question arises if this translates into an oncological benefit for the patient. It is argued that a share of patients with undetected micrometastases in the FLR is subjected to the risks of ALPPS stage 2 with no oncological benefit or even potential harm presuming that the massive stimulation of hepatocellular hypertrophy could simultaneously simulate residual tumour cell proliferation in the FLR. The data in the literature are controversial. Adam and colleagues for example reported a significantly better median survival after TSH (37 months) compared to after ALPPS (20 months) [21], and Baumgart and colleagues found higher recurrence rates (87.5% vs. 60%) but similar median overall survival after ALPPS compared to TSH (36.2 months [range 11.3–61.2] vs. 26.7 months [range 21.8–35.1]) [27]. In the middle of these controversial data are studies by Morris et al., Ratti et al., and Kambakamba et al. that showed similar disease-free survival rates after TSH and ALPPS [20, 23, 55]. At the opposite end of the spectrum, a study by Bednarsch and colleagues for example demonstrated (almost significantly) better disease-free survival data for ALPPS (19 months) than for TSH (10 months), respectively. It must be noted that both the discrepancies in the relative comparison of ALPPS and TSH and the reported differences in absolute survival times reflect a large variety of center-, patient-, and disease-based factors that are difficult to compare to one another. The so-far only randomized controlled trial on this topic is the aforementioned LIGRO-Trial from Sweden. This RCT included 100 patients with CLM and a standardized FLR of <30% who were randomly assigned to either ALPPS or TSH (with the option of rescue ALPPS in the TSH group). On an intention-to-treat basis, resectability rates were 92% in the ALPPS cohort and 80% in the TSH cohort (including 24% of TSH patients requiring a rescue ALPPS), respectively. While the median disease-free survival did not differ significantly between groups (11 months after ALPPS vs. 8 months after TSH), the median overall survival after ALPPS was significantly longer (46 months [range 34–59]) compared to TSH (26 months [range 16–36]). This was largely attributed to the higher resection rate achieved with ALPPS. The authors also concluded that the differing observations with regard to overall and disease-free survivals may indicate that recurrent disease is not the only factor determining the outcome. Of note, the survival rate of patients not successfully resected was low in either group. Having in mind the poor survival if TSH stage 2 is not completed, it is not surprising that the question arises whether a dropout during the TSH interstage can be considered an advantage of better selection rather than a loss of chance for the patient [56].

The largest study (and the first to report long-term oncological results) so far including 510 patients treated with ALPPS for CLM from in- and outside the International ALPPS Registry was published by Petrowsky and colleagues in 2020 [29]. The 90-day mortality in all 510 patients was 4.9%, which is, on the one hand, still above that of an average liver resection for CLM (<2%) [57] but, on the other, well below the mortality of >10% reported in the initial series [3]. All patients had multifocal hepatic tumour burden with a median number of metastases of 6 [4–10], 9% had

concomitant lung disease, and 92% of patients had been treated with chemotherapy (67% with antibodies) prior to ALPPS. Median overall survival, cancer-specific survival, and recurrence-free survival were 39, 42, and 15 months, respectively. Also, 3- and 5-year overall survival, cancer-specific survival, and recurrence-free survival were 52%, 59%, and 19% and 27%, 33%, and 12%, respectively. Multivariate analysis identified tumour characteristics (primary T4, right colon), biological features (*K/N-RAS* status), and response to chemotherapy by response evaluation criteria in solid tumours (RECIST)-criteria as independent predictors of cancer-specific survival. When hepatic tumour recurrence was amenable to surgery or ablation, the median cancer-specific survival was significantly superior compared to chemotherapy alone (56 vs. 30 months, $p < 0.001$).

Analyzing ALPPS and other approaches of liver resection for advanced CLM, we also have to consider one-stage hepatectomy (OSH). By its nature, OSH does not carry a risk of dropout. A study by Vigano and colleagues compared the outcome after TSH versus ultrasound-guided OSH [56] in patients with advanced CLM. Aside a dropout rate of 38.1% in the TSH group (and evidently none in the OSH group), the survivals after OSH and completed TSH were similar. Despite a pronounced multifocality in this study with a median number of seven metastases in both arms and one-third of patients exceeding ten lesions, it may be argued that stimulation of hypertrophy such as in the TSH arm in the presence of tumour does not necessarily lead to a worse outcome when full tumour clearance is subsequently achieved. On the other hand, these findings cannot exclude an effect of hypertrophy induction on promotion of tumour growth. The R0-resection rates were noteworthy low in both arms (19% in OSH and 15.9% in TSH), which is likely explained by the high number of lesions approaching a situation of diffuse intrahepatic spread. Ensuing studies with a larger number of patients by Torzilli and colleagues have demonstrated that parenchyma-sparing OSH was associated with better safety and a tendency toward a better survival compared to major resections [58–60]. Challenging a basic surgical rule, nevertheless, the potential benefit of circumferential and particularly vascular R1 resections has been shown in recent years especially in those patients responding well to chemotherapy [61, 62]. With OSH, sparing parenchyma and sparing a second surgery are the advantages that come at the expense of a high risk of an incomplete tumour removal, which altogether as a surgical strategy is at the opposite end of ALPPS.

On the contrary, the goal of ALPPS (and also of TSH) is to achieve R0-resection. In an analysis by Margonis and colleagues, achieving an R0-resection was a prognostic factor in liver resection for CLM and a resection margin of >1 mm was associated with an improved overall survival, and a margin >10 mm with an improved disease-free survival [63]. In order to achieve tumour-free resection margins (R0-resection) in TSH and ALPPS, complete tumour clearance of the future liver remnant during step 1 is paramount. The number and size of metastases in the FLR seem to be of greater importance for the success of these procedures than the total tumour burden. In this same light, Narita could show in a series of 80 intended TSH (61 performed, dropout rate 24%) that the presence of more than two metastases detected in the FLR during step 1 was a predictor of not achieving step 2 [39].

Regardless of the surgical strategy applied, an exact and comprehensive characterization and documentation as possible not only of the lesion number, size, and distribution in the liver and the FLR, but also of other factors such as kind and intensity of oncological pretreatment, presence of extrahepatic disease, molecular characteristics, etc. will help to better define the contribution each surgical approach can make, and to enhance the comparability of our data. For example, several studies have analyzed molecular markers such as KRAS, NRAS, BRAF, PIC3CA, and TP53 genes of the metastases and found a likely role in tumour recurrence after hepatic resection and also ALPPS for CLM [29, 64–66].

10.6 ALPPS in a Multimodal Treatment of CLM

Over the last 20 years, we have witnessed a tremendous change in the therapeutical options by themselves as well as their multimodal orchestration we have to offer to patients with CLM. Besides improvements in surgical techniques, the development of effective chemotherapy in particular targeted therapy led to much better response rates and tumour shrinkage. Nowadays, downsizing therapy is one of the cornerstones in the treatment of CLM. Effective converting chemotherapy enables so-called "secondary" hepatic resectability and facilitates more parenchymal-sparing resections instead of major hepatectomies. With these advances in chemotherapy and biologicals, major hepatectomies for CLM are less and less required and more and more reserved for very advanced hepatic disease. Furthermore, due to the increasing number of options and the increasing intensity of their multimodal use, it has become a frequent scenario that patients are treated over the years with numerous operations/interventions/ablations in combination with multiple and varying chemo- or targeted therapies. This not at least, as each modality can be performed or administered with a decreasing morbidity and mortality. Nowadays, the overall perioperative mortality after hepatic resection for CLM is below 2% in most specialized hepatobiliary centers [57].

For patients with CLM that are so advanced and exclusively resectable by ALPPS alone (i.e., unresectable by all other surgical options), the literature is still scarce. A ran-

domized comparison of ALPPS as a curative option with palliative chemotherapy alone is still not available and will be, needless to say, difficult to achieve. The only study in this regard is by Olthof and colleagues who compared in a case-matched fashion ALPPS patients (otherwise truly unresectable) from the International ALPPS Registry to historic controls receiving palliative chemotherapy and concluded a non-superiority in early oncological outcome in the ALPPS group [24]. With a median of seven liver segments affected and a median of four lesions in the FLR, the disease in the surgical group was admittedly super-advanced, maybe too advanced for any surgical approach whatsoever. Instead of considering this a conceptual failure of ALPPS, these results should be rather seen in the light of a failed patient selection since a reasonable indication for ALPPS—as for any other cancer surgery—is limited and bound by both extent and biology of the cancer treated.

For patients with advanced CLM who can be treated by either ALPPS or conventional TSH with or without PVE/PVL, the so-far only RCT on this topic from Sweden seems to indicate a tendency toward a longer overall survival after ALPPS than after TSH with however equally short disease-free survival times in both arms. Promising glimpse of cure or just improved palliation? ALPPS is too young and the data too scarce to draw definitive conclusions.

ALPPS is one of the most complex hepatobiliary procedures currently performed. Despite the growing experience and expertise along with the above-mentioned technical modifications and refinements during the more than 10-year learning curve, the largest study on ALPPS so far by Petrowsky and colleagues documented an improved but still substantial perioperative morbidity and a 90-day mortality, which was about 5%. Not underestimating the complexity and complication of a TSH with PVE/PVL and of other advanced surgical approaches, it is still controversial to consider ALPPS when an already "established" conventional surgical approach is feasible [67, 68]. As for now, ALPPS remains a last-resort option at the end of the spectrum in the treatment of CLM [10]. And here, where patients have no surgical alternative to ALPPS, its oncological outcome needs to be compared to that of palliative chemotherapy. On the other hand, the oncological long-term survival data in the mentioned largest ALPPS cohort were at least promising particularly in those subgroups with favorable predictors of a cancer-specific survival.

At our own institution, since the beginning of our ALPPS program in 2009, out of more than 1000 liver resections for CLM (nearly half of them for bilateral metastases, overall perioperative 90-day mortality rate below 1%), we performed 9 ALPPS, thus accounting for about 1% of all resections for CLM, only. ALPPS was done after a median of 7 months of chemotherapy (range 4–11 months) and all resections performed were exclusively right trisectionectomy, with additional excision of segment I ($n = 4$) and excision of 1–3 metastases out of the FLR ($n = 4$).

10.7 Conclusion

ALPPS is an ultra-radical two-stage hepatectomy variant that induces rapid hypertrophy of the future liver remnant in a short period of time and increases resectability rates in patients with advanced CLM beforehand considered unresectable. While the functional advantage is evident and undoubtedly expands the surgical armamentarium, the oncological benefit of such an aggressive approach is still unclear. Initially reported substantial morbidity and two-digit perioperative mortality rates provoked serious safety concerns. These could be addressed by surgical modifications mainly aiming to reduce post-stage 1 complications as well as by a better patient selection. Oncological concerns are mostly about an early tumour recurrence in many cases with persistently short disease-free survival times in almost all studies. ALPPS is indicated in patients with no surgical alternative. In patients with CLM amenable to either ALPPS or conventional TSH with portal vein embolization, long-term results from the only RCT comparing both approaches showed an improved overall survival after ALPPS with no significant differences in disease-free survival. Of note, rescue ALPPS was a valid option for patients after failed portal vein embolization.

As always in cancer therapy, biology is key and cannot be overcome, in particular not by surgery alone. Therefore always embedded into a multimodal treatment setting, ALPPS, for now, remains a last-resort surgical option that may offer a chance for complete tumour removal, for prolonged survival, and, maybe, for cure.

"Biology is King, selection of cases is Queen, and the technical details of surgical procedures are the Princes and Princesses…." [69]. With this in mind, further research will help us to better assess the value of ALPPS and define its role in the treatment of CLM.

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Open Resection Technique

11

Myrddin Rees and Senthil Sundaravadanan

Learning Objectives

- How to individualise the approach to patients undergoing open liver resection for colorectal metastases.
- The setup and method for liver resection creates a more controlled environment that results in improved outcomes.
- How to perform 'Bloodless' liver surgery by adhering to certain principles.
- Intra-operative attention to detail enables enhanced recovery.

11.1 Introduction

Over the last few decades, hepatic resection for colorectal liver metastases (CRLM) has become a refined procedure that combines multi-modality therapeutic options and various approaches to minimise morbidity and prolong disease free and overall survival. Although improved knowledge of liver anatomy has allowed for safer and precise parenchymal sparing procedures, the interpretation of this anatomy through advanced imaging techniques has played a major role in pre-operative planning. The combined effort of the anaesthetist and the surgeon is the key to peri-operative bloodless liver surgery and the use of technology, although not mandatory, has made liver transection easier in experienced hands. The boundaries of resection have increased corresponding to advances in oncology, with an increasing number of patients eligible for potentially curative liver resection after conversion chemotherapy [1]. We prefer a time period of 6–8 weeks between the completion of chemotherapy and liver resection to minimise the risk of infection and surgical complications [2]. In addition, we are undertaking many more repeat liver resections, which produce further benefits in long-term outlook [3, 4].

Table 11.1 Liver Resections done for colorectal metastases across three decades

	C: Pre 2000	B: 2000–2010	A: 2010–2020	Total
Resections				2822
Major	319 (73%)	641 (54%)	462 (38%)	1422 (50%)
Minor	111 (25%)	418 (36%)	400 (33%)	929 (33%)
Wedge only	9 (2%)	117 (10%)	345 (29%)	471 (17%)
Median blood loss (mL)	365	330	193	270
Median length of stay (days)	10	7	5	7
Combined liver and bowel	8	10	37	55

This chapter is based on 33 years of our experience in liver resections during which time we have performed more than 3400 resections, of which 2822 were done for colorectal metastases with a total mortality of 1.4% (39/2822) (Table 11.1). This includes 24 patients who died within 30 days, 13 between 30 and 90 days and 2 patients after 90 days.

Open resection for liver metastases requires thorough pre-operative planning, specialised (low central venous pressure) anaesthesia and meticulous technique. Standardisation of a technique and teamwork have helped to significantly reduce the morbidity and mortality that has long been associated with liver resections [5–7].

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11.2 Anaesthesia

Patients are admitted on the morning of the operation after a prior pre-anaesthetic assessment. They are allowed clear liquids up to 2 h before the operation and no intravenous fluids are administered. After the induction of general anaesthesia, a central venous catheter (CVC) and an arterial line are inserted in all patients for optimum peri-operative management. We are aware that others have challenged the need for such invasive and intensive monitoring, and have carefully carried out liver resections without it [8]. The patient is placed in supine position with the right arm elevated and elbow flexed at 90 degrees and strapped in parallel with the chest. The table height is adjusted to allow the operating surgeon to sit and operate.

All efforts are made to maintain a low central venous pressure (CVP). The CVP is reduced to 0–4 cm of H_2O by restricting fluids and with a glyceryl trinitrate infusion. This ensures a bloodless field during transection and precise identification of all intrahepatic structures. In our own experience, we found that the mean blood loss and mean blood transfusion were significantly reduced by maintaining a low CVP [7]. In the last decade, our median blood loss has been 193 mL in over 1200 resections. The objection to a low CVP has been the risk of air embolus, which in our experience has been as rare as three cases in more than 3400 resections. Two patients recovered well without any complications, but unfortunately one of the patients who had a previously undiagnosed patent foramen ovale succumbed in the immediate post-operative period after a near-irreversible cardiac arrest toward the end of a straightforward posterior sectionectomy for colorectal metastases.

11.3 General Principles

The planning for resection and the approach to resection are minimalistic in volume—so-called parenchymal sparing approach. That is to emphasise that only enough liver tissue to obtain an R0 result is resected along with the tumour. While it is imperative to leave behind adequate functional liver volume, it is also important not to disturb surgical planes unnecessarily during mobilization. This is in anticipation of recurrent disease with potential for a second curative resection [3, 4]. In most cases, it is routine to perform a parenchymal sparing resection depending on the number and location of the lesions. The gall bladder is removed only if necessary as it serves as a useful marker to guide the dissection of the porta hepatis and gastro-duodenal ligament during repeat surgery.

11.4 Access—Incision, Retraction, and Mobilization

Although traditionally the liver was approached via a thoraco-abdominal incision, subsequently surgeons adopted a bilateral subcostal 'Mercedez Benz' incision. In our unit, a right subcostal incision is the favoured approach and occasionally a short upper midline extension to the xiphoid process is needed. Fixed costal retractors (Fig. 11.1) are used to provide adequate exposure (Teasdale Surgical limited™, Sheffield, United Kingdom). We find that it is rarely necessary to extend beyond the midline to the left. Some centres prefer a midline incision up to the umbilicus, with or without a lateral extension to the right. It is important that the surgeon does not have a routine length of incision. Gradually, over many years, the extent of the incision in our unit has reduced in its lateral extension. We usually go to the tip of the eighth rib rather than beyond. The incision is tailored to the patient's girth size, as well as to the location of the tumour, and can easily be extended if required (Fig. 11.2). Resection of a lesion in segment II, III or IV usually requires less exposure than a lesion in the caudate or right hemiliver. Technical tip—the ideal choice and length of the incision is one that achieves an adequate resection and the extent of mobilisation of the liver should only be as much as required. This simplifies repeat resection in the future.

On exploration, the liver is assessed grossly for any surface lesions and any obvious signs of cirrhosis. Extra-hepatic disease is excluded by looking for any nodal disease at the porta, omental deposits, or any peritoneal nodules. Inspection and palpation of surface lesions continue to be important as small lesions in segment II or III can be missed even on MRI with liver-specific contrast.

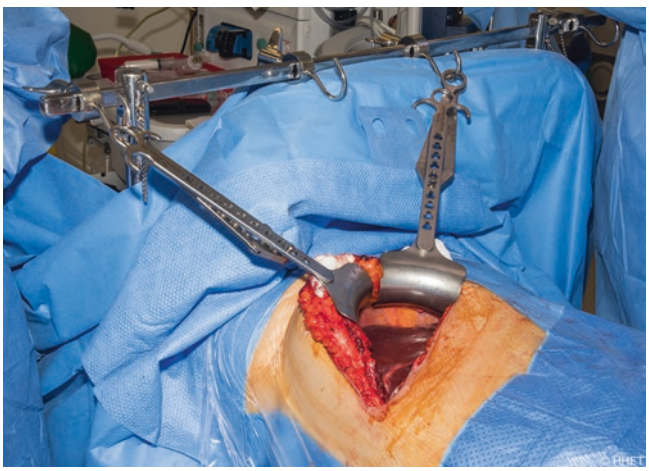

Fig. 11.1 The set up for liver resection—Fixed costal retractors

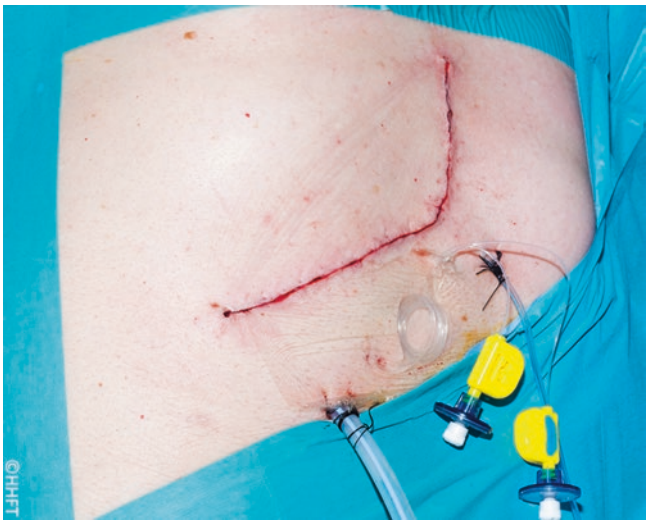

Fig. 11.2 Post-operative incision with intercostal catheters, silicon drain and wound suction drain

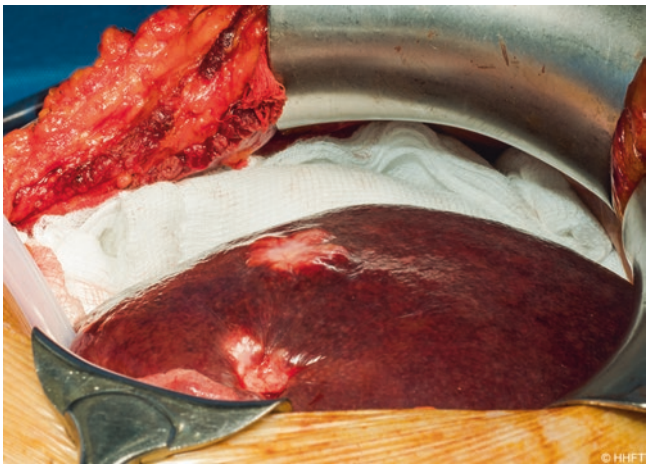

Fig. 11.3 Packs maintaining the rotation of the right lobe to aid access to transection

The aim of mobilization should be to deliver the liver to the incision. A standard mobilization involves division and ligation of the falciform ligament, followed by the coronary ligament up to the point of entry of the hepatic veins and division of the triangular ligaments on the side required. The phrenic veins on either side are good landmarks to the entry point of the hepatic veins, but could also be a potential source of troublesome bleeding if accidentally divided. The hepatic vein that requires ligation may be identified during mobilization by sharp dissection. We prefer to divide the vein during or at the end of transection. Mobilization of the left lobe is done by placing a pack below the left triangular ligament to separate it away from the stomach and spleen. The left half of the lesser omentum is divided and the lesser sac entered.

On the right side, the assistant retracts the liver outward and away from the diaphragm to facilitate peritoneal mobilization along the lateral aspect. This allows separation of the diaphragm and right adrenal up until the plane meets the complete division of the triangular ligament up to the right hepatic vein. In case of large right-sided tumours, the right lobe is completely mobilised off the IVC beginning at the inferior aspect and proceeding upward, with careful ligation of the short hepatic veins draining directly into the IVC. Prior to the identification of the right hepatic vein at the superior aspect of this dissection, the hepatocaval ligament that connects the segment VII and the caudate lobe requires division. Although this ligament is said to be bloodless, a small vein may be found near the lower border, a second one in the middle and rarely even a bile duct may run through it. Hence, most surgeons prefer to ligate it either with sutures or if feasible a stapler is used. After full mobilization, if necessary, the liver is attached only by the hepatic veins to the vena cava and by the structures in the porta hepatis.

Adequate mobilisation allows the liver to be rotated and converts the plane dividing the two halves of the liver into a vertical rather than oblique plane, allowing the surgeon an easier direction to follow during transection. The position of the liver can be supported using adequate packs placed between the liver and the diaphragm (Fig. 11.3). With the fixed retractors applied to elevate the anterior costal margin, the liver is now ready for resection. Technical tip—in cases of a larger tumour in the right lobe, it is necessary to divide adhesions in the left upper quadrant to enable rotation of the liver toward the left.

11.5 Intra-Operative Ultrasound

The reliance on ultrasound for diagnosis alone has diminished with improved pre-operative contrast imaging. However, it is still a standard part of liver resection as it aids technical feasibility by giving important information on the depth of the lesion and proximity to the vascular structures in real time. It is also a useful adjunct for cases with combined resection and ablation—usually with microwave in our hands.

11.6 Laparoscopy

Traditionally, laparoscopy was performed for patients with high risk factors from their primary tumour. However, the routine use of diagnostic laparoscopy has diminished secondary to improved and advanced liver-specific contrast imaging techniques and the evolution of our specialised peritoneal radiologists. At our centre, we have abandoned routine laparoscopy for CRLM. Rarely in select cases we perform an exploratory incision in patients with a large dis-

ease burden to assess and proceed. One to two per cent of patients may still be inoperable at the time of laparotomy. In certain select patients identified to have peritoneal disease on pre-operative scans, laparoscopy may still be useful to clarify the full extent of extra-hepatic spread and allow for combined liver and peritoneal resection.

11.7 Pringle Manoeuvre

At our centre, we routinely perform the Pringle's manoeuvre (first described in 1908) in all cases of liver resection [9]. Historically, a soft small bowel clamp was used across the hepatoduodenal ligament as opposed to a vascular clamp. For more than 10 years, we have preferred an umbilical tape slung across the porta through the Foramen of Winslow. Occlusion of the inflow is secured when the tape is pulled snuggly through a rubber tube and clamped tight (Fig. 11.4). It is important not to use a heavy crushing clamp too tightly across the porta which may induce thrombosis of the portal vein. This is done prior to transection along with confirmation that the CVP is adequately low. Technical tip—significant bleeding during transection despite this manoeuvre should raise suspicion of an aberrant left hepatic artery that arises from the left gastric artery. A separate arterial clamp applied usually corrects the lack of inflow control. The safe clamp time varies depending on the quality of the liver tissue and any underlying liver disease. The present author favours transection of the liver with removal of the clamp and reperfusion of the liver for about 5 min after each 20-min period of occlusion. This is reduced to 15 min in fatty livers, whilst in cirrhotic livers, the occlusion time is limited to 10 min. This has worked favourably as the results show minimal blood loss and mortality in more than 3400 cases spanning three decades. The total median Pringle clamp time was 34 min with no detected incidence of portal vein thrombosis.

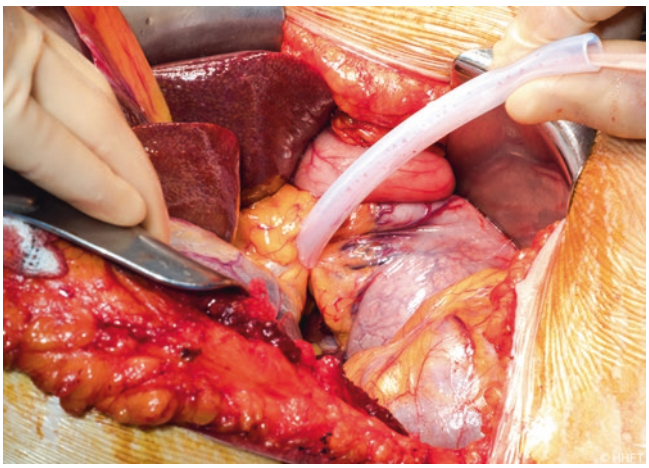

Fig. 11.4 Pringle clamp in place using a snugger

11.8 Liver Dissection/Transection

This step of the operation is technically challenging as any incision on the liver has the potential to cause profuse bleeding from multiple small vessels within the parenchyma [10]. This bleeding can be reduced by lowering the CVP, and by temporary occlusion of the inflow to the liver with a Pringle clamp, as outlined above. During anatomical resection, bleeding can be further reduced by following planes that separate the segments of the liver or the line of demarcation created by ligating the inflow to that area. There are various methods and technological advancements that allow more precise dissection. It is a matter of surgeon preference although we recommend standardization of one technique which may improve the safety of the operation with better outcomes. After careful palpation, the resection margin is outlined using diathermy, with additional input from ultrasonography if needed.

11.9 Inflow Control

Traditionally, and certainly in cases in which the tumour encroaches on the porta, we would perform an extra-hepatic approach. The first step for right hepatectomy is to dissect the Calot's triangle as part of the cholecystectomy and ligate the cystic artery and the cystic duct individually. Next, we divide the peritoneum on the porta to divide the right hepatic artery with suture ligation as close to the hilum as possible. Palpation of the left hepatic artery can confirm adequate flow prior to the division of the right. The portal vein is exposed and a 3/0 ligature tie (Polyglactin) is applied to find the junction between the right and left portal veins. A second tie is placed as close to the liver as possible, two small clips are applied and each end suture ligated with a 3/0 Prolene suture. In major hemi-hepatectomies, with no tumour near the porta, it is possible to safely staple the portal inflow intra-hepatically using a stapler after identification and careful retraction of the opposite portal triad away from the bifurcation [11] (Fig. 11.5). Technical note—as outlined by Professor Blumgart, before stapling, a tape should be used to pull the portal vein junction medially to avoid damage to any structures on the left side [12]. In case of a trifurcation, it is necessary to separately staple the right anterior and posterior portal triads. It is often not possible to isolate the segmental

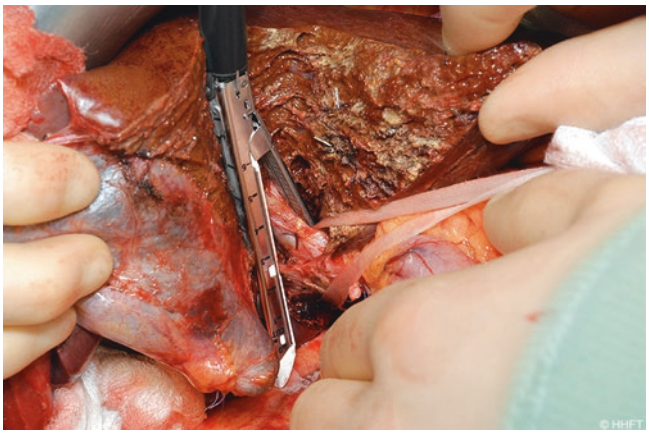

Fig. 11.5 Stapling the right portal inflow for right hepatectomy

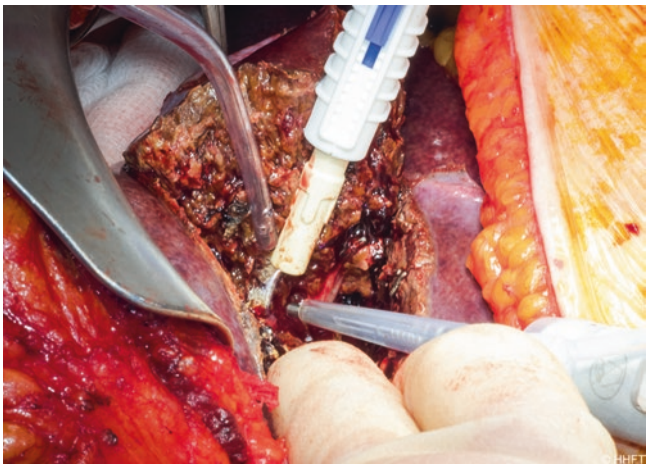

Fig. 11.6 CUSA hand piece and Argon beam coagulation in action during the transection

inflow vessels for occlusion until more extensive parenchymal dissection has been undertaken. Even with extra-hepatic division of the vessels, the duct is normally divided during transection of the parenchyma as it will become a lot easier to define. Occasionally a tumour encroaches the porta closely and the duct may need to be divided extra-hepatically.

Increasingly in straight forward cases, we would do an intra-hepatic approach to the portal inflow especially on the right side. In the last 10 years, an intrahepatic approach for right hepatectomy was performed in 97 cases. Over the years, our staplers have evolved in line with technological advances. Our current favoured instrument is the electronic battery-charged stapler gun (Signia™ Power Shell with COVIDIEN™ Endo GIA™ Articulating reload with Tri-staple™ Technology, Covidien Ireland limited, IDA Business & Technology Park, Tullamore, Ireland).

11.10 CUSA

At our centre, we prefer to use the Cavitron Ultrasonic Surgical Aspirator (CUSA Excel™ 2014 Integra LifeSciences Corporation, Tullamore, Ireland). During transection, 70% power is applied unless the liver is fibrotic, in which case power may need to be increased to 90%. Technical tip—the operating hand should be kept supple with gentle forward movements though never losing sight of the CUSA tip. Side-to-side waving of the handpiece is unproductive. The liver cells are vaporised by the sound waves and aspirated, while all fine tubular structures, including small vessels and bile duct radicles, are skeletonised and can be seen straddling the operative field. The capsular extension that surrounds portal divisions makes them particularly resistant to ultrasonic damage. The CUSA is delicate and precise and ensures a clean operative field (Fig. 11.6) (CUSA settings Aspiration 80%, Irrigation 8 cc, Amplitude 100%, Tissue select +). Other centres may prefer Kelly clysis or energy devices, which work on similar principles with comparable outcomes [13].

11.11 Intrahepatic Ligation

The smallest structures <1 mm may be secured using diathermy. Some small vessels are ligated between haemostatic clips (COVIDIEN™ Premium Surgiclip™ Auto Suture™ Clip Applier). Any larger structures should be ligated with fine absorbable material (e.g. 3/0 Vicryl) supplemented by a haemostatic clip applied close to the suture. Any vessel that can be recognised as a named branch must be secured by either suture ligation or a stapler on the side that remains in-situ. An Argon laser is used for coagulation and haemostasis as we carefully proceed along the line of transection (Fig. 11.6). This spray diathermy produces a very superficial coagulation and has proved extremely valuable in arresting the surface ooze from a large raw area.

11.12 Outflow Control

The hepatic veins draining the resection zone are identified and ligated extra-hepatically (though this can easily be done intra-hepatically during transection), usually using a stapler (Fig. 11.7). Staplers to divide the right or middle hepatic vein have replaced suturing. However, one must exercise caution while stapling to ensure that the angle is correct and the stapler lies completely across the vein without tension and no metal clips or thick tissue intervening. Simple ligation is insecure as the veins are short and wide, and transfixion ligation should be avoided as it may inadvertently distort the

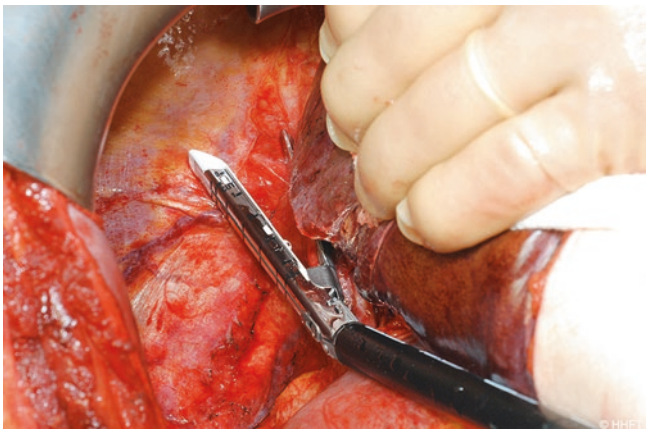

Fig. 11.7 Stapling the right hepatic vein

wall of the vena cava. If a stapler is not available, a sutured closure is satisfactory. The vein is divided between vascular clamps, and is oversewn with a fine polypropylene vascular suture. A monofilament suture that slides through tissue without tearing is essential, as all the continuous suture must be in place before the clamp is removed and the suture tightened. If the clamp slips during this manoeuvre, haemorrhage from the vena cava can be torrential. Technical tip—stay sutures placed superiorly and inferiorly on the vena cava before suturing can help control bleeding in case of slippage of vascular clamps.

It is possible during resection to inadvertently create an opening in a major vein and not have much bleeding due to the low CVP. It is therefore important to identify this early, during or immediately after resection and secure the vein, to prevent bleeding and the rare complication of air embolism.

11.13 Sealing the Parenchyma

After the specimen is removed, the priority is to achieve haemostasis and secure any bile leaks bearing in mind any difficult areas during the resection. This can be physiologically augmented by bathing the liver in hot water as clotting is optimal at body temperature. At this stage the liver is restored to its normal anatomical position and gentle steady pressure is applied to the cut surface using swabs. Technical note—too many packs behind the liver may impede venous return and make it difficult to achieve haemostasis. This is easily remedied by removing some of the packs. Resections of lesions in segments IVA, VII and VIII have an increased potential for bile leaks. It is also common to encounter larger biliary radicles closer to the porta that must be secured using sutures. At our centre, we prefer to closely inspect the surface for bile leaks and apply gentle pressure across the entire surface with a dry swab and look for staining. In our unit, the recorded rate of bile leakage using this simple technique is minimal (1%). Haemostasis is augmented using fibrin glue and collagen. The glue is sprayed onto the entire cut surface and then collagen is applied across the cut surface and pressure is applied with a dry swab for 4 min. In our experience, the combination of fibrin sealants (thrombin) and collagen achieves optimal haemostasis (Fig. 11.8). Technical tip—if there are multiple sites of resection, ensure haemostasis at each site before proceeding to the next. The liver is then fixed to the anterior abdominal wall/diaphragm in its anatomical position, with sutures usually to the falciform ligament to prevent a volvulus of the liver that may precipitate a Budd-Chiari-like situation.

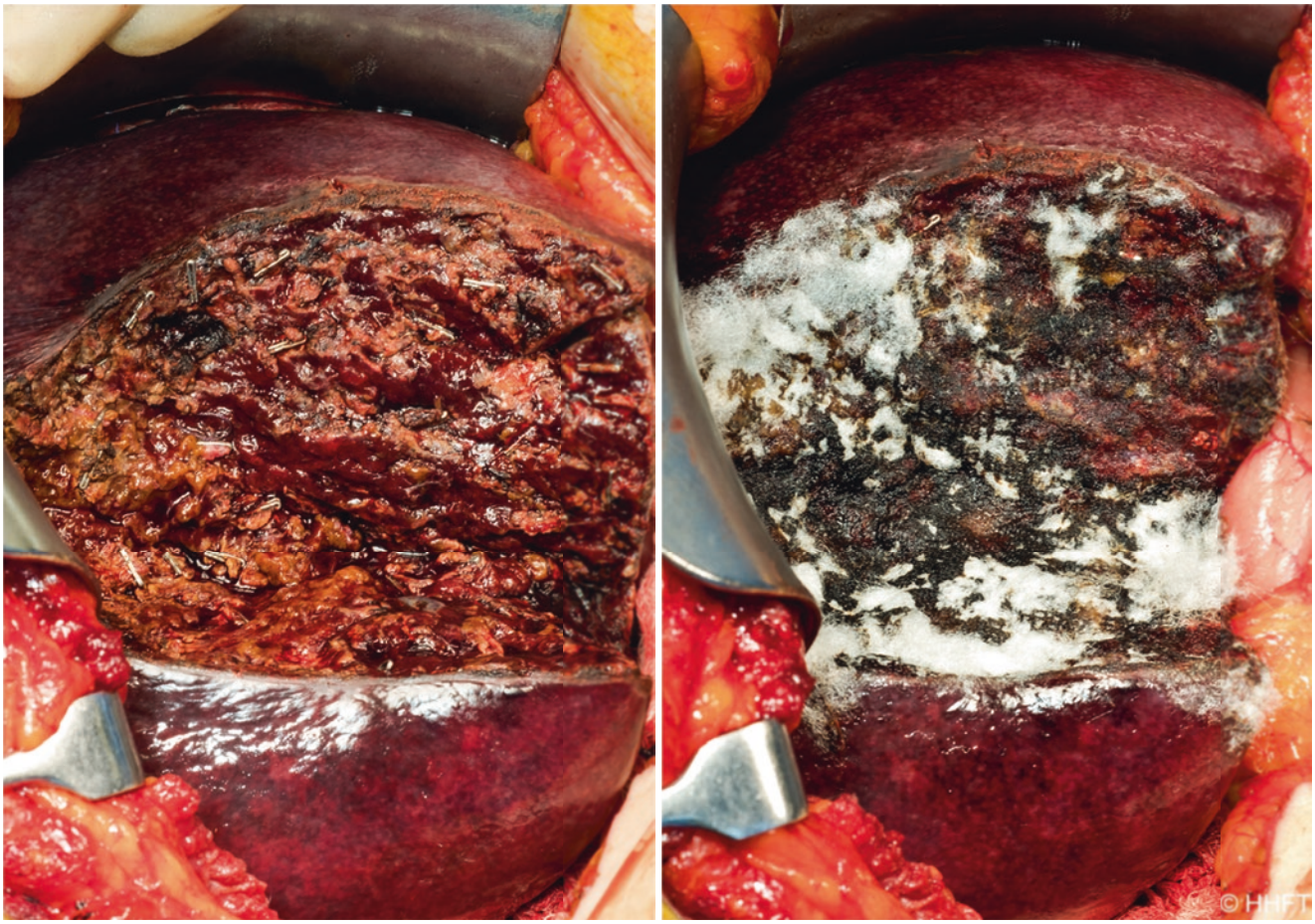

Fig. 11.8 Transected surface sealed with both fibrin glue and collagen

11.14 Wound Closure

A 24 Fr Silicone drain is placed in the right flank with the tip near the cut surface in almost all cases. It is removed between 24 and 72 h post-op if there is no bile leak. Several studies have shown that drain placement may not be necessary as it does not affect the morbidity of the operation or prevent complications [14]. However, there may be a higher chance of radiological re-intervention. Wound closure is achieved by sympathetic continuous suturing, with an appropriate length of the non-absorbable suture. A 1 in 6 ratio of wound length to suture length can help achieve an adequate closure with minimal post-operative discomfort. During closure, we routinely place two intercostal catheters (Fig. 11.9) and this has replaced the use of an epidural for post-operative pain relief [15, 16]. The length of stay has significantly reduced using this technique and there have been no complications in comparison to an epidural. Occasionally, one of the catheters may be accidentally displaced, but the other one works just as well. The requirement for analgesics has also reduced, which aids with early mobilisation. Patients are started on oral analgesics as early as day 2. A subcutaneous suction drain is placed along the wound for 48 h and subcuticular sutures are used for approximating the skin.

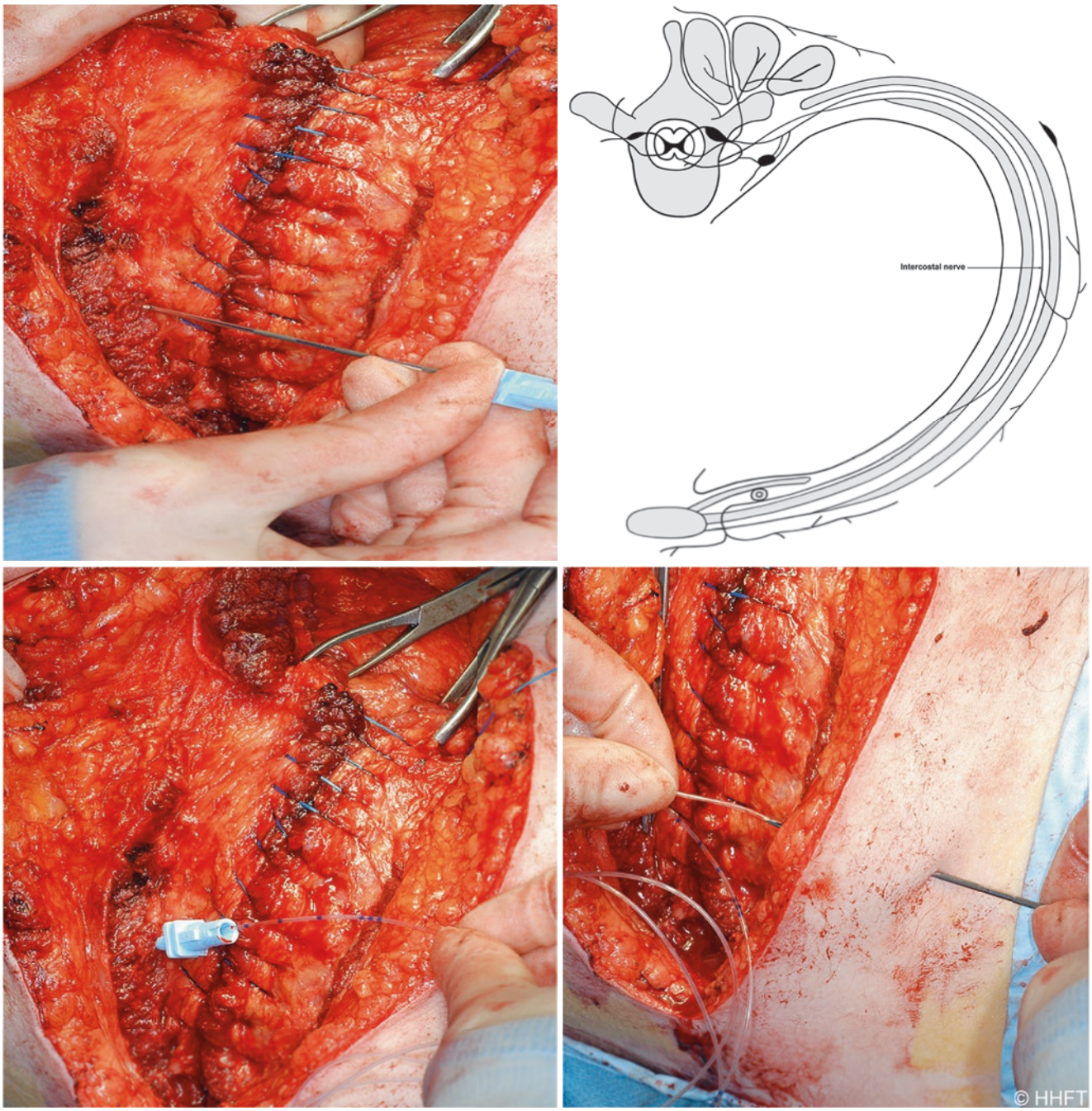

Fig. 11.9 Intercostal catheter placement

The patients spend the first night after the operation in the theatre recovery area (one to one nursing) and are shifted to the ward the next morning. It is very rare for any of our patients to require admission in a critical care environment. The nasogastric tube is usually removed at the time of extubation or once they arrive in recovery. They are started on liquids and soft solids as soon as tolerated and are mobilised out of their bed on to a chair. They are encouraged to use the patient-controlled analgesia (PCA) sufficiently to be pain free, take deep breaths and perform incentive spirometry. All

patients are kept in A-V intermittent pressure boots, until they are fully mobile, and started on subcutaneous enoxaparin on the first evening. After 48 h, the CVC, the abdominal drain, the wound drain, and Foley's catheter are removed. The PCA may be maintained for one more day depending on patient comfort and mobility. Oral analgesics are started on day 2 and most patients go home before day 5.

11.15 Special Situations

Bilobar metastases are not a contraindication for curative resection. It is now accepted that a successful resection for secondaries is one that involves the removal of all the disease while preserving sufficient liver. Options for treating bilobar disease are extended hemi-hepatectomies, staged resections, combined resection and ablations and combined segmentectomy and local excisions (Fig. 11.10). For example, a left lateral resection or posterior sectionectomy can be combined with wide local excision or ablations on the opposite side. A 1 mm margin is sufficient to achieve oncologic clearance [17]. Local excisions are useful for an additional small secondary not included in the major resection. In certain cases, which are beyond the scope of this chapter, portal vein resection and bile duct resection may be necessary to facilitate oncological clearance (Fig. 11.11).

Synchronous colorectal metastases may be dealt with at the same time as a bowel resection, except in cases where both the primary and secondary require a major resection. As a routine, we avoid major bowel resections and major liver resections, because as a larger portion of the liver is removed, the resistance of the liver to infection, determined by Kupffer cell activity, reduces significantly [18]. A right hemicolectomy can be combined with a segmentectomy VI and an anterior resection with a left lateral resection. However, if a right hepatectomy is required for synchronous metastases from a rectal cancer, the liver resection should be deferred in our opinion for a second operation. A temporary diversion stoma in the right hypochondrium, and the timing of its closure can be an additional surgical challenge.

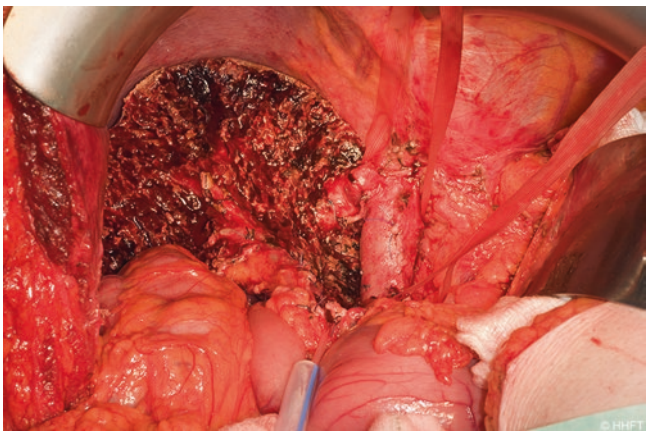

Fig. 11.10 Extensive resection with skeletonisation of the porta and veins

Some patients are unsuitable for resection during initial evaluation due to extensive disease or proximity of lesions to major vascular structures that cannot be compromised. These patients may still have a potentially curative resection if they respond well to chemotherapy, which can shrink the periphery of a tumour. The drawback is that chemotherapy may be detrimental to liver quality and may temporarily impair its function and regeneration [19]. Patients who have a prolonged course of chemotherapy and a short period of cessation prior to an operation are at higher risk of post-operative liver failure and septic complications [2].

If a second resection is planned, either as a staged resection or as part of an ALPPS procedure, it is imperative that the mobilisation is limited in extent. Seprafilm^{R} (seprafilm adhesion barrier, Genzyme Biosurgery, Framingham, U.S.A) may be inserted to cover the transected surface to aid mobilisation the second time. Some patients may recur with isolated liver metastases over time. The selection criteria for repeat liver resections are same as the first time [20]. A repeat resection is made more difficult by adhesions, fibrosis and the distortion of anatomy following regeneration of the remnant. The prognosis is similar to the first time, especially if there is a prolonged disease-free interval after the first operation. The necessity to mobilise the porta in a repeat resection depends on the complexity of the liver resection. We have unpublished data comparing 1206 first-time liver resections versus 318 repeat resections that shows no significant change in morbidity or mortality. The repeat resection group had a shorter Pringle clamp time (28 vs. 36 min), more blood loss (380 vs. 270 mL), longer operative time (270 vs. 240 min) and shorter stay (6 vs. 7 days).

Elective liver surgery can be performed safely during the SARS-COV-2 pandemic and may even be associated with a shorter hospital stay as shown by the following study at our centre. A study group of 24 patients who underwent liver resection during a 3-month study period in 2020 was compared with 34 patients over the same period in 2019. The median total LOS during the COVID-19 pandemic was four (4–6) days, 2 days shorter (p = 0.006) than in 2019, and no patients contracted COVID-19 during their hospital stay [21].

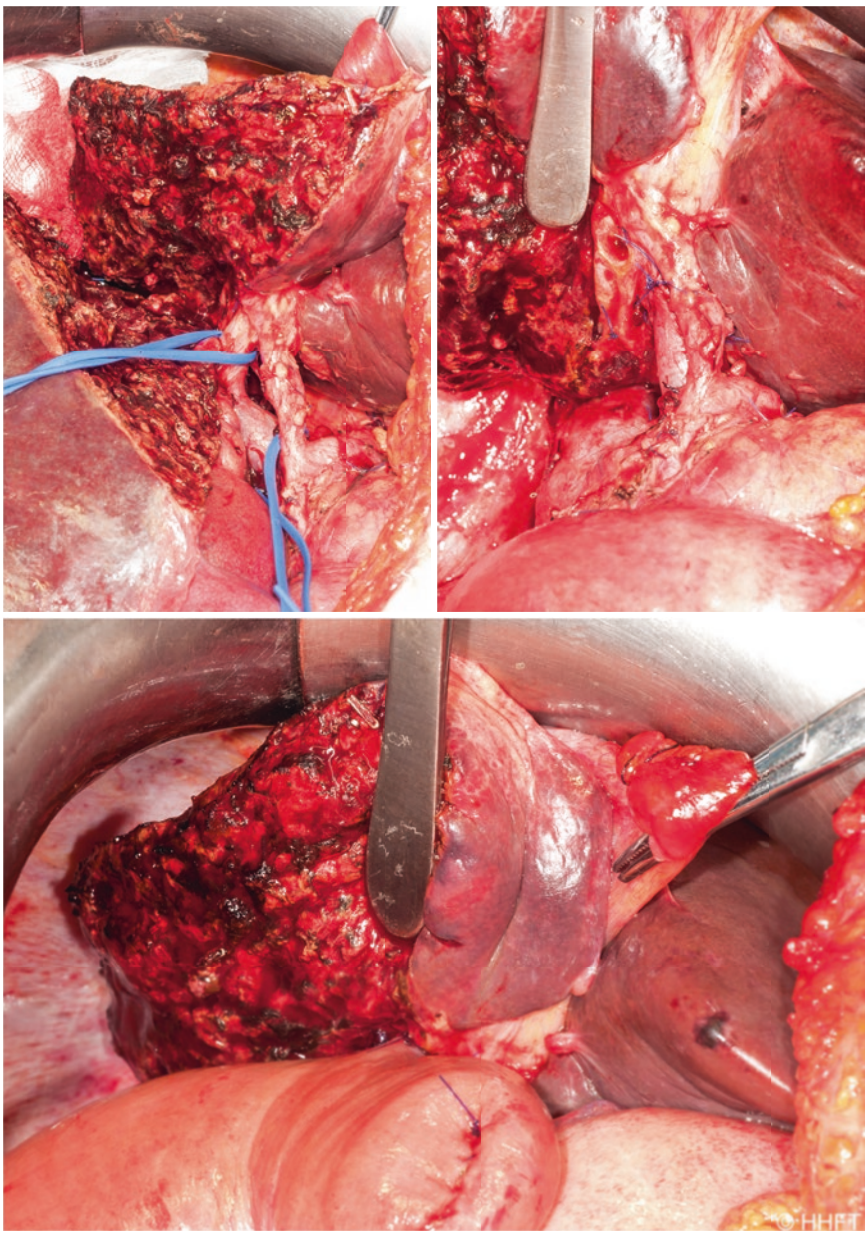

Fig. 11.11 Portal vein resection with bile duct reconstruction

11.16 Conclusion

Open liver resection offers the best outcomes compared to various non-surgical treatment options and in specialised centres. It can be done with minimum morbidity and mortality, short hospital stay and superior outcome. Successful open liver resection requires careful pre-operative planning based on imaging, meticulous attention to detail intra-operatively, precise CUSA technique and team work. It is possible to perform safe, bloodless and oncologically successful liver resections while individualising the approach and setup for each patient to achieve an enhanced recovery.

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Laparoscopic Liver Resection Technique: The Norwegian Experience

12

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Learning Objectives

- Being an experimental surgical technique, laparoscopic surgery has become a standard approach for various liver tumours.
- Laparoscopic liver resection is a first-line approach in the surgical treatment of patients with colorectal liver metastases in our center.
- The Norwegian technique of laparoscopic liver resection is described here. The formal hepatectomies described here are similar to those described by our colleagues from other European specialized centers. The main specificity of non-anatomic resection, which we also call atypical resection, used in parenchyma-sparing strategy is characterized by performing a dissection from the surface to the pedicle/"feeding portal veins of the tumour." These are identified on preoperative imaging (CT/MRI) and on intraoperative ultrasound. The modified clamp-crushing technique alone or in combination with an ultrasonic aspirator is an important method in dissecting the intrahepatic vessels when performing parenchyma transection.

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12.1 Introduction

Since the introduction of laparoscopic liver surgery in Norway in 1998, it has evolved and become the first-line surgical approach for most liver neoplasms in our center [1]. Up-to-date over 1800 procedures have been performed in our center.

Having begun as an experimental surgical technique, laparoscopic surgery has advanced to become a standard approach for most liver tumours, particularly for colorectal liver metastases. Since its introduction, with advancements in laparoscopic surgical instruments, laparoscopic liver resection has undergone several modifications and nowadays, in our unit, as well as in other specialized centers, laparoscopic liver resection is safely implemented as a standard practice.

Colorectal liver metastases remain the most common indication for liver resection in Norway. About 70% of laparoscopic liver resections are performed for colorectal liver metastases in our center, and parenchyma-sparing resection is the method of choice for these tumours [2].

Laparoscopic liver resection for patients with colorectal metastases is now documented to have several advantages over open surgery such as shorter hospital stay, better quality of life after surgery, and less postoperative morbidity, while long-term oncologic outcomes are similar [3–6].

In this chapter, we describe our technique of laparoscopic liver resection of colorectal liver metastases.

12.2 Laparoscopic Liver Resection for Colorectal Liver Metastases

12.2.1 Selection and Limitations

In our practice, patients generally need to have the following characteristics to become candidates for resection of colorectal liver metastases:

1. Radical resection of metastases (including R1 vascular) possible with an adequate future liver remnant.

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2. Biological disease control, either in the form of stable disease or as a response to neoadjuvant chemotherapy or in the form of (easily resectable) metachronous disease or in settings where chemotherapy is not advised.
3. Limited extrahepatic disease. The more extrahepatic the disease is, the stronger is need for biological disease control. We are reluctant to operate on patients with lymph node metastases outside the hepatic hilum. Non-resectable extrahepatic extrapulmonary metastases is considered a contraindication for liver surgery.

A mutational analysis and the sidedness of the primary tumour are taken into account when tumour biology is assessed, but there are no absolute contraindications here—even a BRAF mutated patient will be operated if biologic disease control is achieved on neoadjuvant chemotherapy. It is essential to discuss the risk for surgical complications and the potential benefits of the surgery with the patient.

Regarding the selection for laparoscopic surgery, we have a few absolute contraindications. Non-anatomical resection is our main technique but anatomical mono- and bi-segmentectomy and hemihepatectomy are on the routine repertoire. Extended hepatectomy and resections that need reconstruction of vessels or bile ducts are usually performed using an open approach. In the case of simultaneous ablation and laparoscopic resection, we usually first do percutaneous ablation and then the resection, to avoid problems related to ultrasound and intraabdominal carbon dioxide (CO_2). Multiple resections can be time consuming, and access will be decided on an individual basis.

We have no medical or anesthesiologic contraindications to laparoscopic surgery. Cardiac failure, especially in combination with pulmonary disorders and obesity, is the main concern for our anesthesiologists, but these caveats are the same for open and laparoscopic surgery. Risks and benefits are closely discussed with the patient before a decision to operate is made.

12.2.2 Surgical Techniques

Pneumoperitoneum is established by open technique, and intraabdominal carbon dioxide (CO_2) gas pressure is set at 12 mmHg (can be increased up to 15 mmHg if needed). A 30° laparoscope (Olympus Medical Systems Corp, Tokyo, Japan) and 5- and 12-mm trocars are used. The number of trocars depends on the lesion location and the patient's body build, and usually varies from a standard 4 up to 6 (Fig. 12.1).

Pringle maneuver and bleeding control. Hepatoduodenal ligament clamping or Pringle maneuver is used on demand to temporarily reduce or stop the blood inflow into the liver, decreasing blood loss during liver resection (Fig. 12.2).

Pringle maneuver is always useful in controlling the situation and deciding what the best option for repair is. Increasing the intraabdominal pressure is also an effective method in the event of bleeding from the hepatic veins. Small bleedings during liver resection will be effectively controlled by compression and patience. If compression is not sufficient, bipolar diathermia can be directly applied on the bleeding vessel and it is important to remove the bipolar diathermia when it is still activated. In case of bleeding from the liver surface, monopolar diathermia applied in a circular pattern around the bleeding can be helpful. Larger bleedings from the portal veins must often be sutured; in that case, we prefer a barbed suture with a pledget attached to the end of the suture that prevents it from tearing through the soft liver parenchyma (Fig. 12.3). The hepatic veins can be more difficult to suture and hepatic bleedings can often be stopped with a hemostatic patch, as it is a low-pressure system (Fig. 12.4).

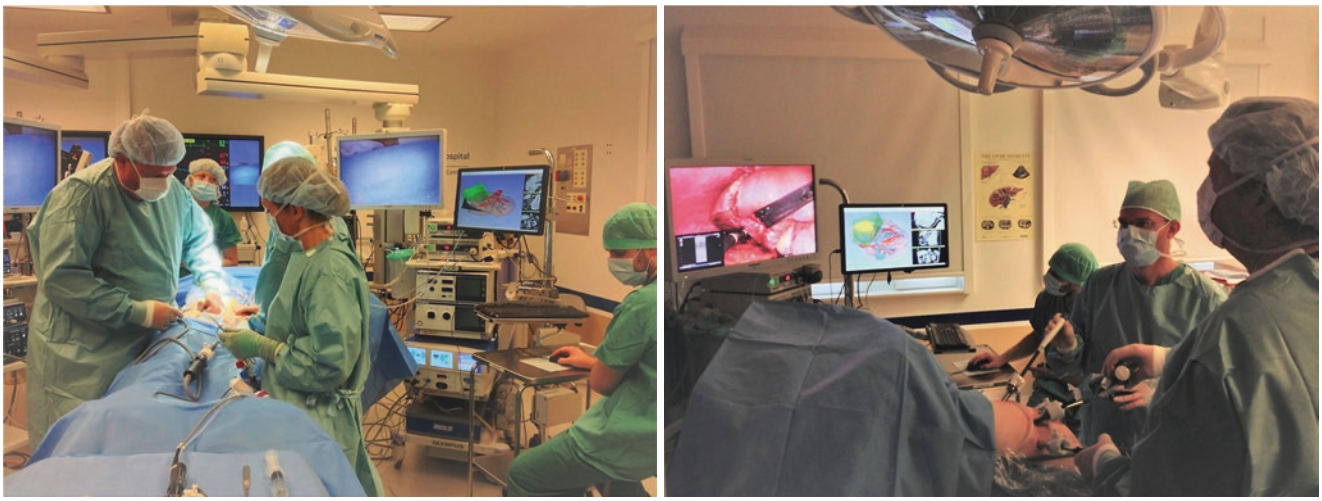

Fig. 12.1 Laparoscopic liver resection. (Reproduced with permissions from Egidijus Pelanis)

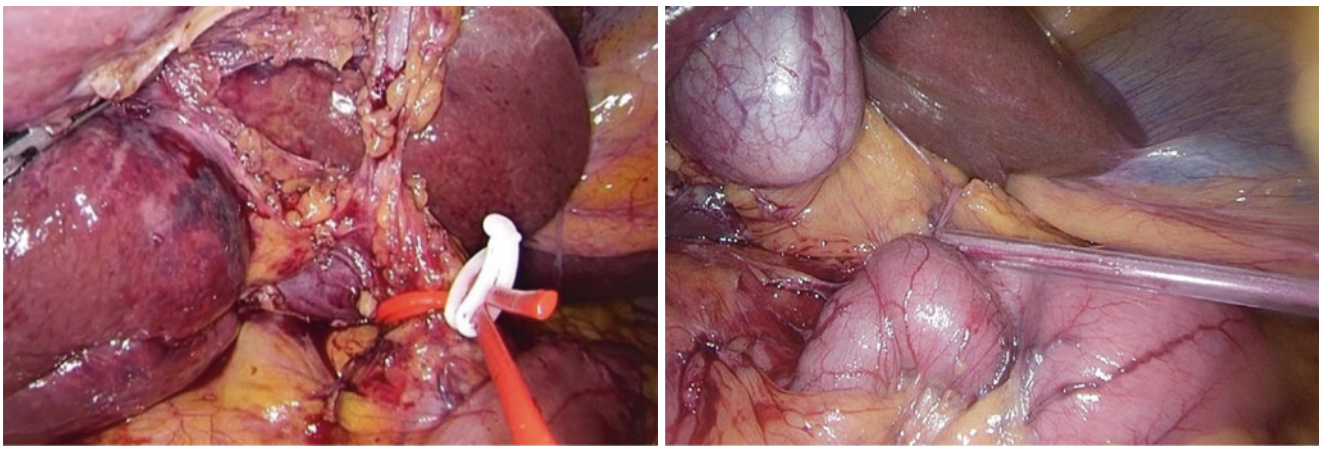

Fig. 12.2 Internal and external Pringle maneuver (Reproduced with permissions from Egidijus Pelanis)

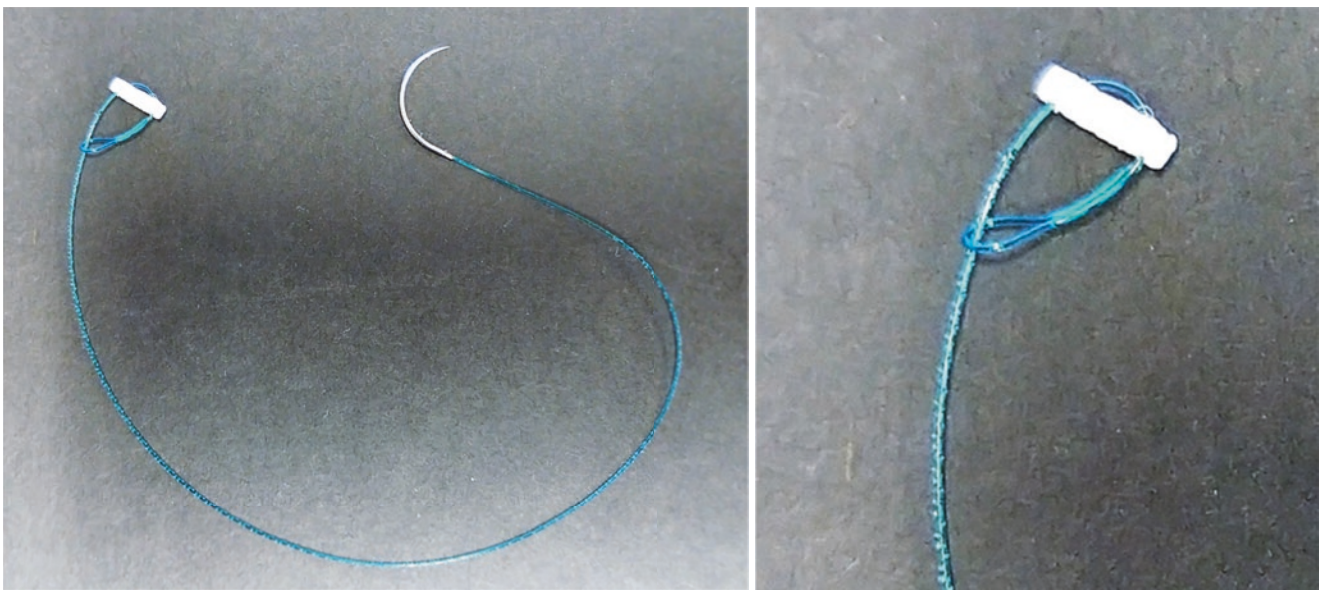

Fig. 12.3 A pledgeted barbed suture

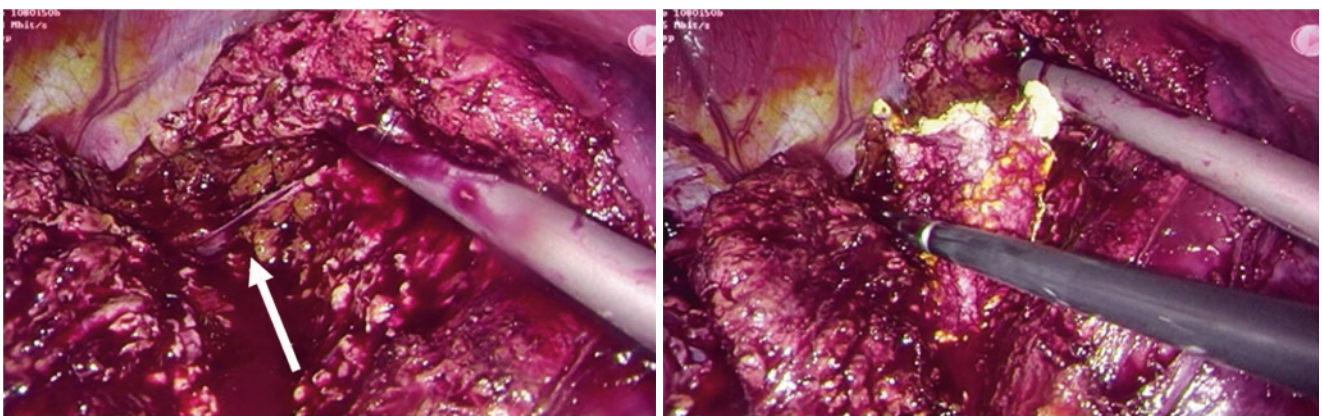

Fig. 12.4 A hemostatic patch on the bleeding hepatic vein

12.2.2.1 Laparoscopic Nonanatomic Resection (Cauliflower Technique)

Cauliflower technique was established by our group and is used widely for non-anatomic liver resections, especially in patients with colorectal liver metastases. The main aspect of this technique is to resect the tumour with a necessary margin by approaching the supplying vessel/vessels from the surface rather than from the hilum of the liver (Japanese technique), especially when removing tumours that affect several liver segments (Fig. 12.5). We prefer this "from surface to central" resection approach, because it is easier and not potentially dangerous , not time consuming, and is very straight-forward as it uses the Pringle maneuver and intraoperative ultrasound.

Patient's position. The patient's position may vary depending on location of the tumour. The patient is placed in the supine position (antero-lateral segments) or in the 30–45-degree side with the right side up (postero-superior segments) (Fig. 12.6). Usually, the surgeon stands to the patient's right side.

After the establishment of pneumoperitoneum and trocar placement, the liver is thoroughly examined to define exact tumour location and its relation to major vessels using laparoscopic ultrasonography with Doppler function. For resections in the posterior-superior segments, it is essential to perform proper mobilization of the right lobe to achieve appropriate access and visualization to the resection area.

The resection line is marked at the liver surface by electrocautery following an ultrasonographic examination to clarify the resection margin (Fig. 12.7). We aim for a rectangular resection line in line with the surgeon's instruments, and a curved lower margin. It may be of value to prepare for a Pringle maneuver before parenchyma transection, especially for resections in the postero-superior liver segments. Parenchymal transection is performed by using a bipolar electrosurgical device and an ultrasonic aspirator. The jaws of the bipolar device are used to crush the parenchyma with or without activating it (modified clamp-crushing technique). This way one can identify the vascular structures without damaging them and then divide them selectively. The laparoscopic ultrasonic aspirator is a good alternative used to skeletonize the vascular structures. A combination of these two methods is preferred in our team.

The longitudinal resection lines are opened first, and then the transversal. Then, the specimen can be lifted out of the liver, and the afferent pedicle structures can be identified and divided. The dissection beneath the tumour is easier when the specimen can be retracted. We find that this is the easiest and most gentle when done using a grasper with open jaws, rather than grasping the specimen or using a stay suture (Fig. 12.8).

The resection is guided by repeated ultrasonography to ensure free resection margins and to define the portal and hepatic branches in the resection area. Vessels in the resection area are divided with clips or laparoscopic linear staplers, depending on the size of the vessels (Fig. 12.8).

12.2.2.2 Left Lateral Sectionectomy

Patient's position. The patient is placed in the supine position. The surgeon stands to the patient's right side (Fig. 12.9).

After the establishment of pneumoperitoneum and trocar placement, the left lobe is mobilized by dividing the triangular and coronary ligaments up to the ligamentum venosum Arantii and the left hepatic vein, using bipolar

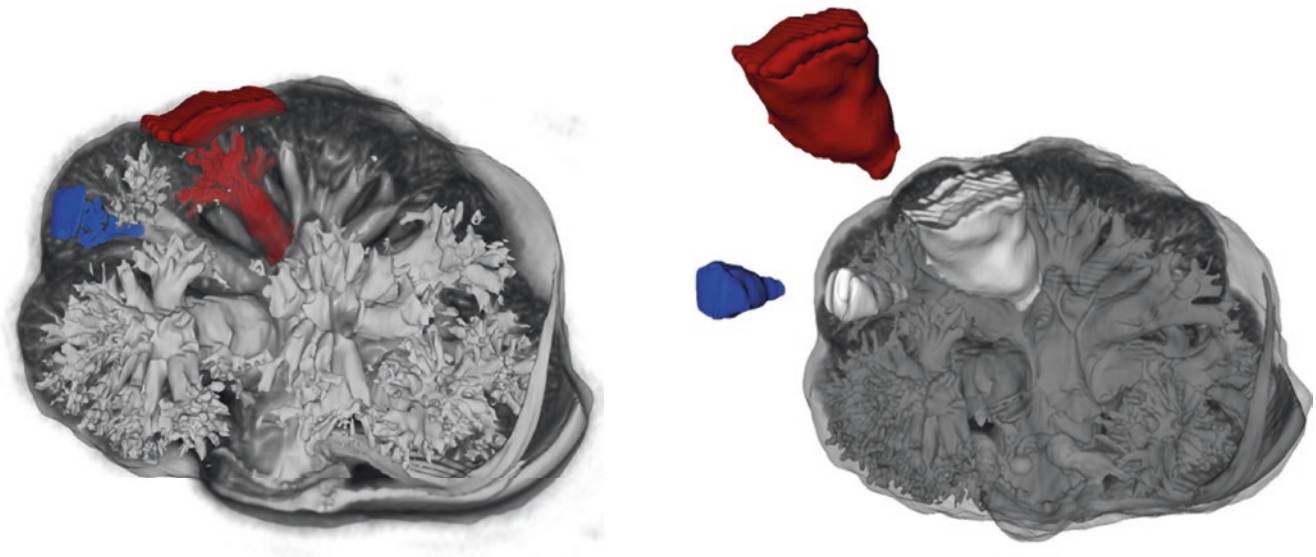

Fig. 12.5 Cauliflower technique (Reproduced with permissions from Egidijus Pelanis)

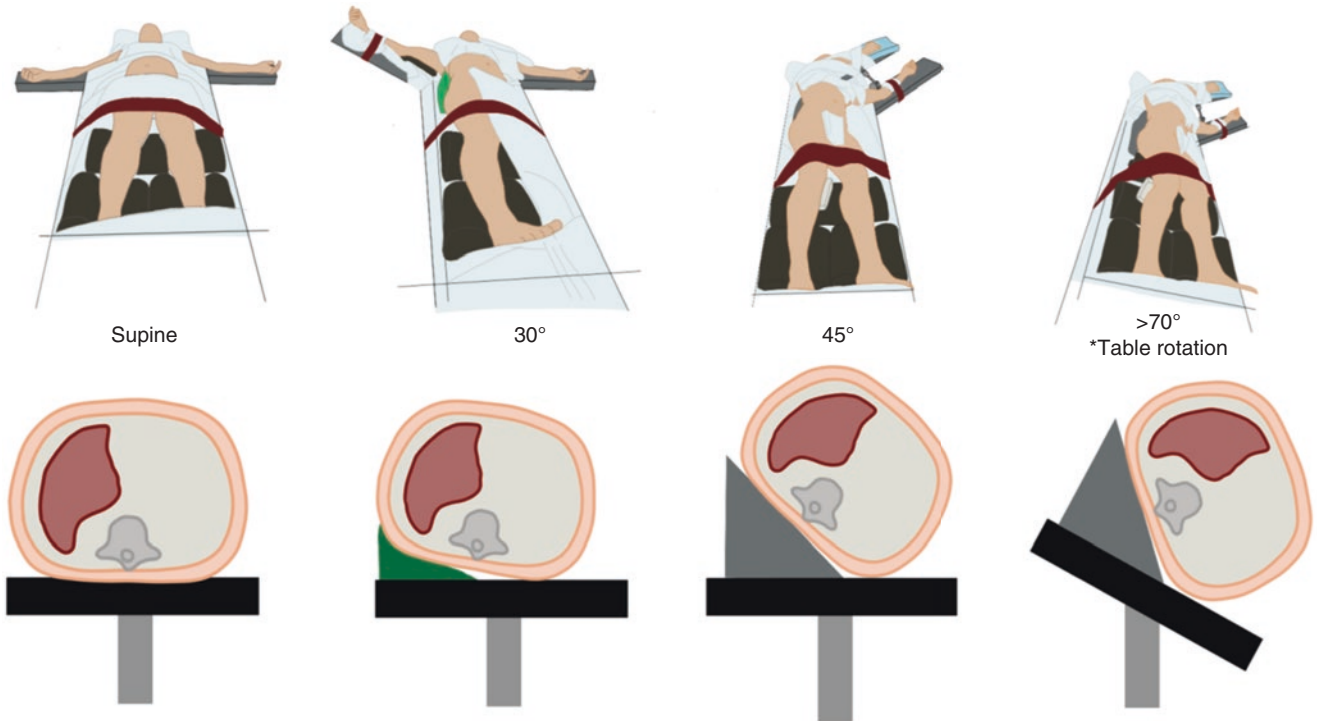

Fig. 12.6 Patient positioning. (**1**) Supine position (segments 1–4). (**2**) 30-degree right side (segments 5–8). (**3**) 45-degree and arm across the body (segment 7 and posterior part of the segment 6). (**4**) >70-degree (extreme access to the postero-superior segments) (Reproduced with permissions from Egidijus Pelanis)

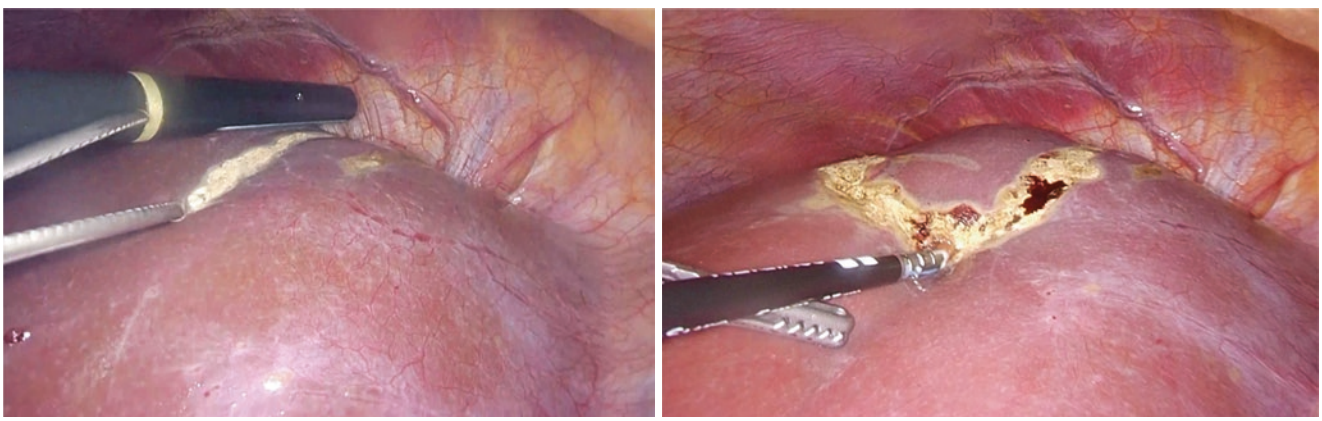

Fig. 12.7 Resection line marking by monopolar electrocautery

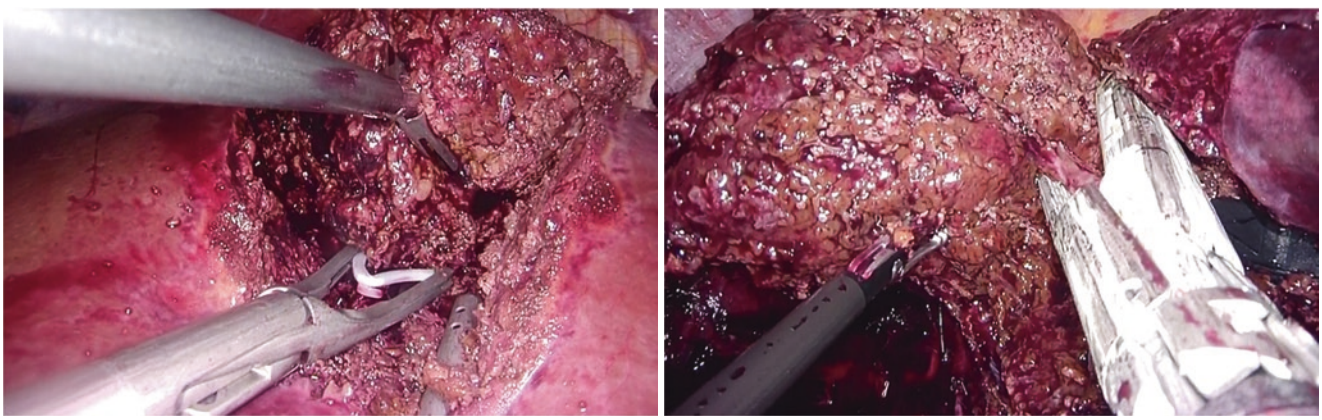

Fig. 12.8 Division of intrahepatic veins

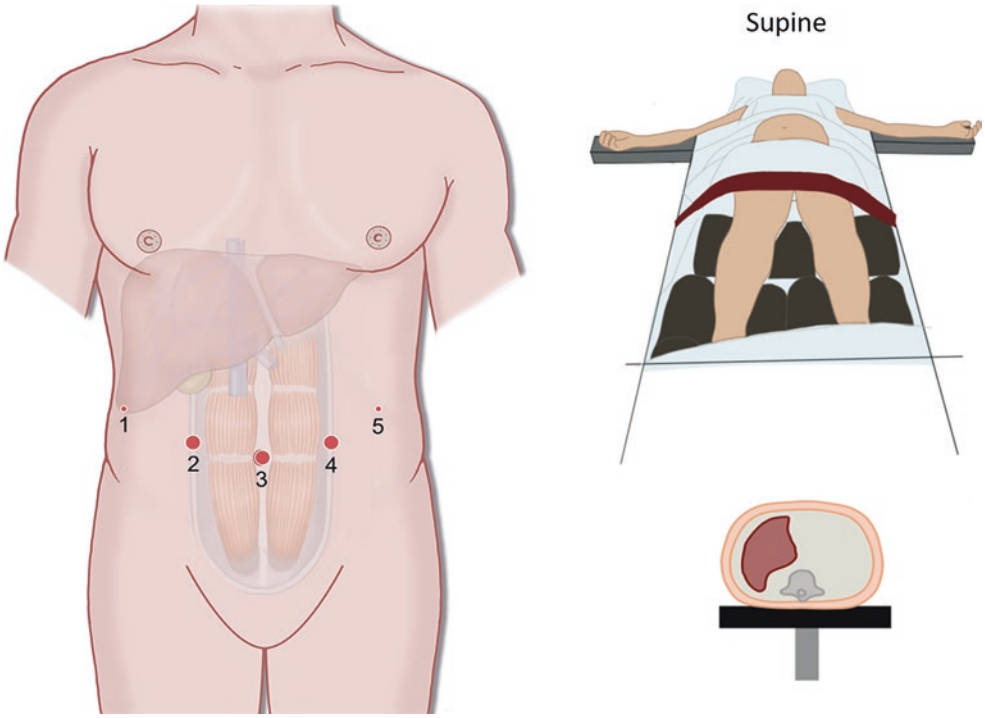

Fig. 12.9 Patients position and trocar placement (left lateral sectionectomy and left hemihepatectomy). (Reproduced with permissions from Kari C Toverud and Egidijus Pelanis)

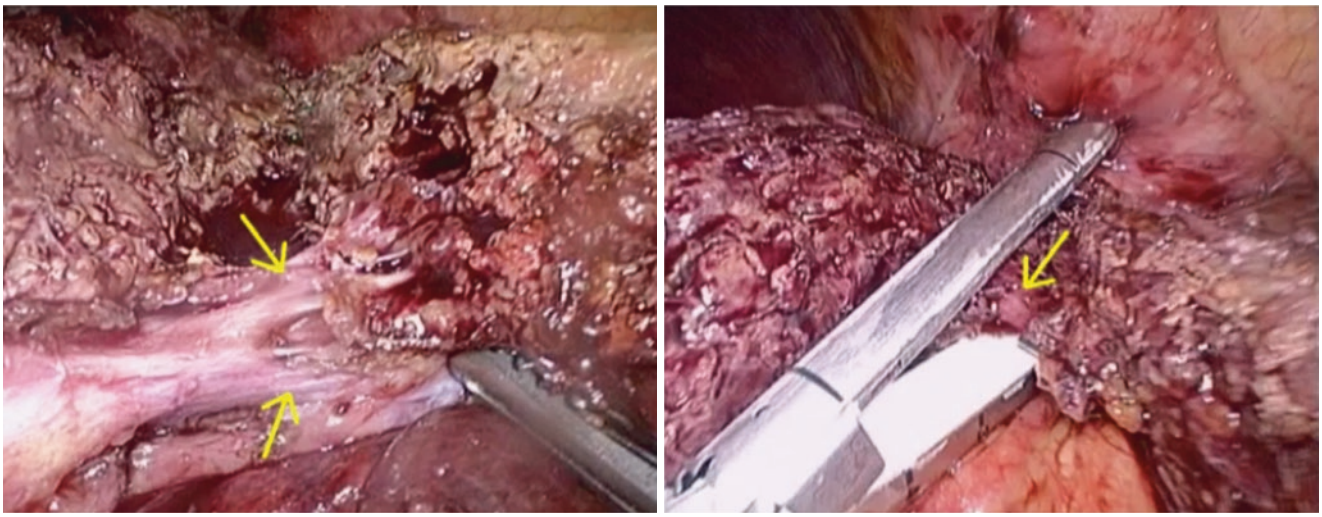

Fig. 12.10 Dissection of the s2 and s3 portal branches, and the left hepatic vein

electronic scalpels. The round ligament is divided and then the falciform ligaments are dissected up to the inferior vena cava and the left hepatic vein. The round ligament can be used as a handle to facilitate the parenchymal transection. The liver parenchyma is then transected parallel to the falciform ligament (approx. 1 cm medial) with the bipolar electronic or ultrasonic scalpel avoiding damaging the portal branch to segment 4 ("opening the book"). After exposing the portal branch to segment 3, it is dissected between clips, or with a linear endo-stapler without skeletonizing it (Fig. 12.10). Thereafter, the parenchymal transection is continued to the portal branch of the segment 2, which is dissected by the same technique. The resection is continued up to the left hepatic vein, which is sectioned by an endo-stapler (Fig. 12.10). To avoid unintentional damage to neighboring structures, we angle the endo-stapler so that the lower branch can be visualized behind the liver.

12.2.2.3 Laparoscopic Left Hemihepatectomy

Patient's position. The patient is placed in the supine position. The surgeon stands to the patient's right side (Fig. 12.9).

Pringle maneuver. The Pringle maneuver is usually not performed unless a risk of severe bleeding appears.

The main steps. As it is described for the right hepatectomy, the procedure may be divided into four main steps: *liver (left lobe) mobilization, vascular inflow control, parenchymal transection, and hepatic venous outflow control*.

Liver Mobilization

The procedure is started with the mobilization of the left liver by dividing the left triangle, the round, the falciform, and the coronary ligaments. The coronary ligament is divided until the supra-hepatic vena cava and the left hepatic vein are exposed (Fig. 12.11).

Control of Vascular Inflow

It is essential to properly analyze the liver images (CT, MRI) and if possible, 3D images of the liver with its vascular system to identify the anatomical variations. The liver is lifted upward by forceps or a liver retractor. The peritoneum of the hepatic pedicle is incised in its left aspect, and the left arterial and portal branches are dissected and isolated on vessel loops. The left hepatic artery is then secured between clips and divided or by using an endo-stapler. The left portal branch is separated from the surrounding tissue and managed by applying clips (e.g., Hem-o-lok®) or an endo-stapler (Fig. 12.12).

Parenchymal Transection

After visualization of the clear demarcation line between the left and right liver lobes, the liver parenchyma is transected using different electronic surgical devices, an ultrasound aspirator, and endo-staplers. The division of the left hepatic bile duct is done during parenchymal transection, with an endo-stapler, to minimize the risk of damage to the right bile duct (similar way as for right hemihepatectomy—see below). The left hepatic bile duct can also be managed by applying a clip (Fig. 12.13).

Outflow Control

Transection of the liver parenchyma is continued until the left hepatic vein, which is then dissected and divided by an endo-stapler as the last step of the procedure (Fig. 12.14).

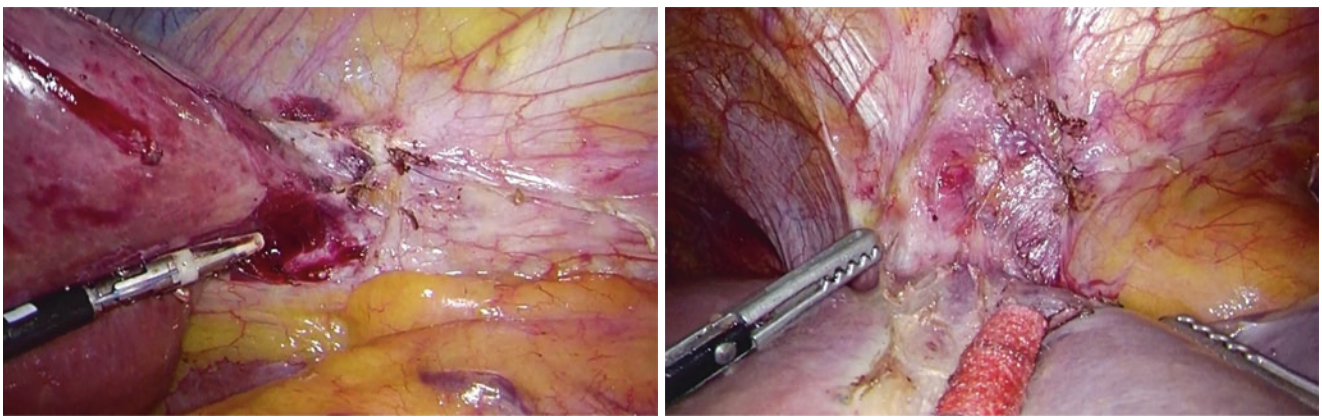

Fig. 12.11 Mobilized left liver lobe

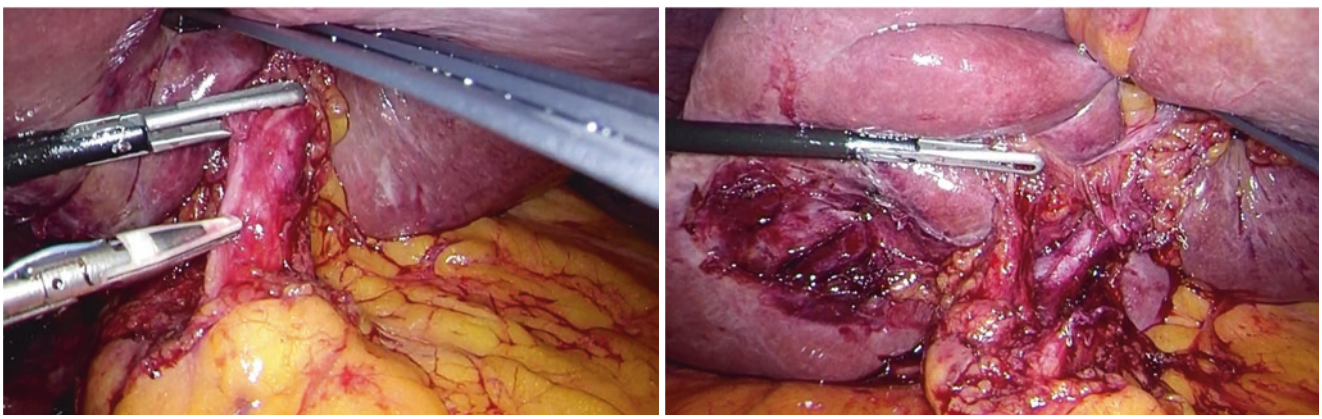

Fig. 12.12 Exposed the left hepatic artery and the left portal vein

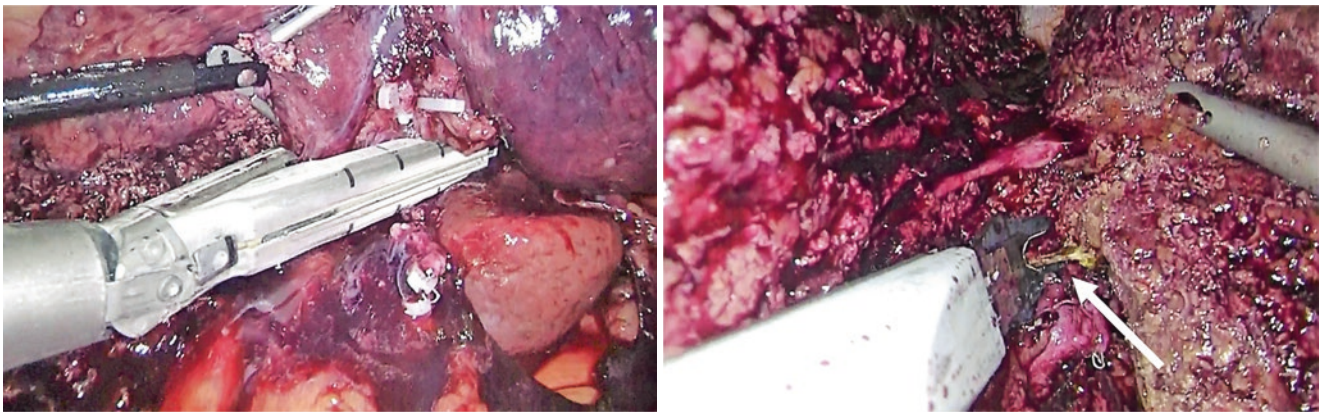

Fig. 12.13 The left hepatic bile duct dissection using (**1**) an end-stapler and (**2**) a metal clip

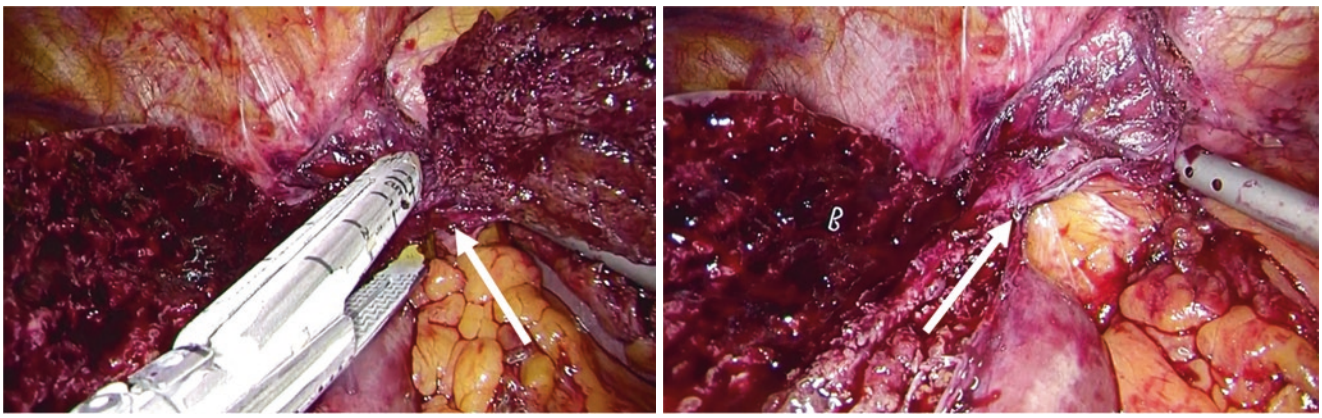

Fig. 12.14 Division of the left hepatic vein

12.2.2.4 Laparoscopic Right Hemihepatectomy

Patient's position. The patient is placed in the 45-degree side with the right side up. Depending on the step of the procedure, the patient's position can be changed by rotating and/or tilting the table. The surgeon stands to the patient's right side (Fig. 12.15).

The right hepatectomy may be divided into four main steps: *liver (right lobe) mobilization, vascular inflow control, parenchymal transection, and hepatic venous outflow control*. The Pringle maneuver can be applied if the dissection of hilum and the parenchyma is expected to be difficult.

Liver Mobilization

After the falciform ligament division, the liver is gently pushed downward using a retractor. The coronary ligament is divided until the supra-hepatic vena cava and the right hepatic vein are exposed. The right liver is then totally mobilized from ligamentous (coronary and triangular) attachments (Fig. 12.16). The Makuuchi ligament is not necessary to dissect free and divide, because it will be divided in the last step with an endo-stapler. Short hepatic veins opening to the inferior vena cava are sealed with a bipolar sealer or are ligated individually, before the transection of the parenchyma starts. It can be dangerous to use clips alone on these small vessels because the clips may fall off. The round ligament is usually saved to avoid postoperative torsion of the left lobe, and to preserve the umbilical vein in cirrhotic patients.

Vascular Inflow Control

Vascular inflow control starts with cholecystectomy. The gallbladder is dissected, but not divided from the main bile duct and used as a handle to better visualize the portal trunk. The different structures in the ligament (the right hepatic artery and the right portal vein) are dissected free and divided. First, the right hepatic artery is identified, clipped, and sectioned. The right portal vein is identified, mobilized, and dissected after identifying portal bifurcation and the left portal vein. Both dissection and division can be done with different instruments; each surgeon has their own preference. A small endo-swab can be useful when dissecting the vessels. During the portal vein dissection, it is important to dissect in the layer close to the wall of the vein. It is important to place a vessel-loop around the right portal vein for the

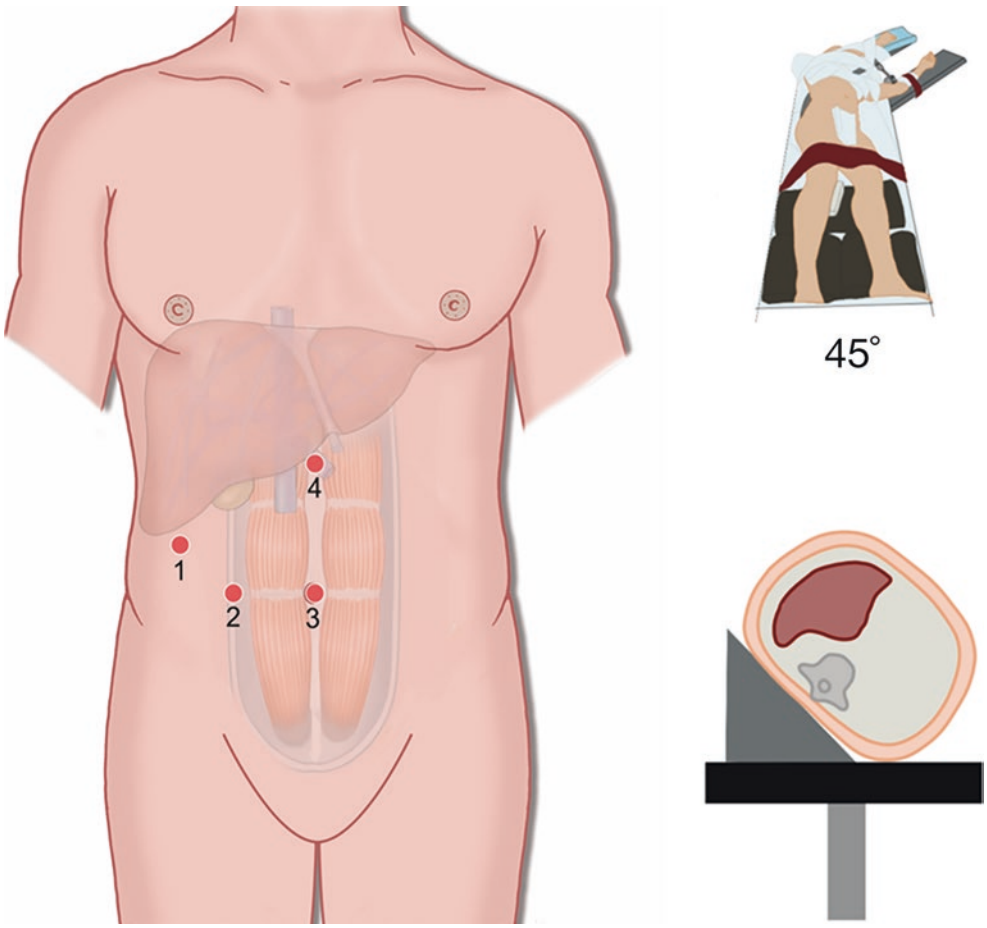

Fig. 12.15 Patients position and trocar placement (right hemihepatectomy). (Reproduced with permissions from Kari C Toverud and Egidijus Pelanis)

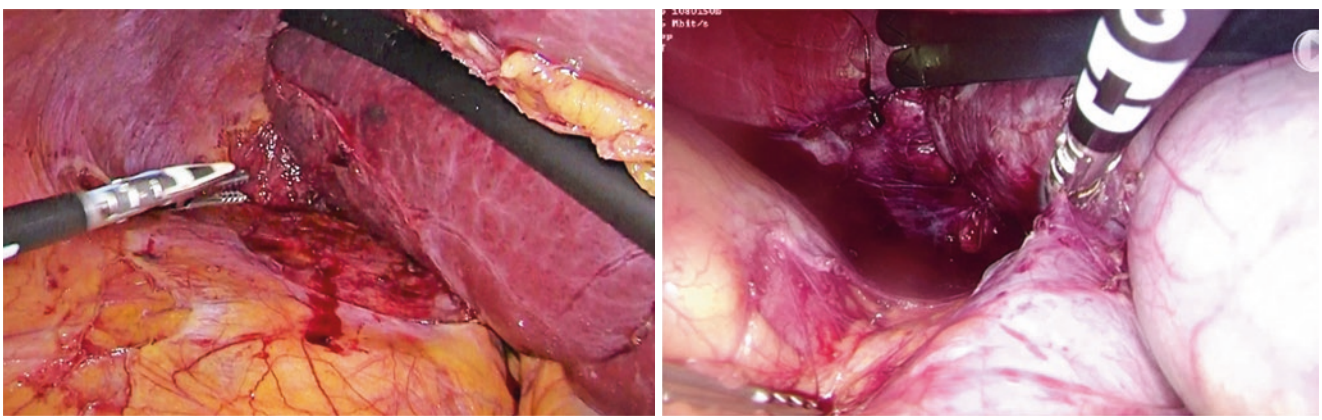

Fig. 12.16 The right liver lobe mobilization

retraction and better access. Most used for division are clips (e.g., Hem-o-lok®) or endo-staplers (Fig. 12.17). At this step, the surgeon should be aware of the small branches to the segment 1.

Parenchymal Transection

Different techniques have been described for dividing the parenchyma. Parenchyma transection can be performed using different electronic surgical devices, an ultrasound aspirator and endo-staplers (Fig. 12.18). On the surface and deeper down, approximately 2–3 cm, ultrasound scissors work well for transection but deeper into the parenchyma, we would recommend to use a bipolar sealer in combination with an ultrasound aspirator. One should be aware of the hepatic veins along the middle hepatic vein draining segments 5 and 8 that need to be sealed/ligated. The division of

the right hepatic bile duct is done inside the parenchyma during parenchymal transection, with an endo-stapler, to minimize the risk of damage to the left bile duct (Fig. 12.19).

It is essential to visualize the vena cava inferior, which serves as a landmark for the whole transection line up to the right hepatic vein.

Hepatic Venous Outflow Control

After parenchyma transection completed, the right hepatic vein is divided with the remaining ligament by an endo-stapler (Fig. 12.20). We prefer to divide the right hepatic vein at the end of the operation as the last step. The dissection of the right hepatic vein before the right lobe is fully mobilized

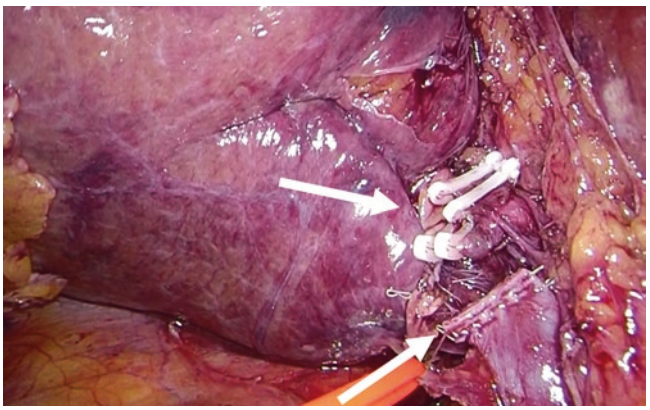

Fig. 12.17 Inflow control to the right liver lobe (stapled the right portal vein and clipped-divided the posterior and anterior right hepatic arteries)

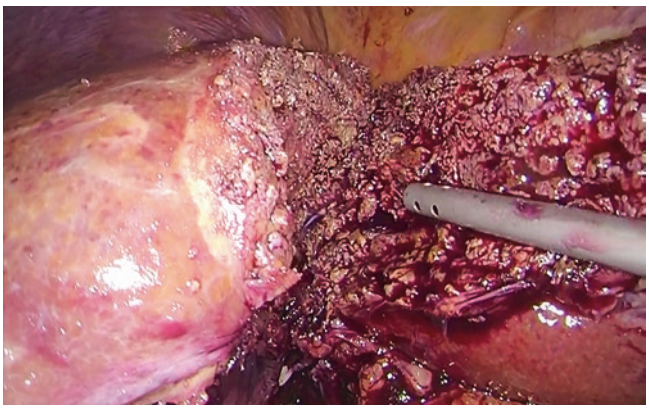

Fig. 12.18 Parenchyma transection along the middle hepatic vein and parallel to the vena cava inferior (opening the book)

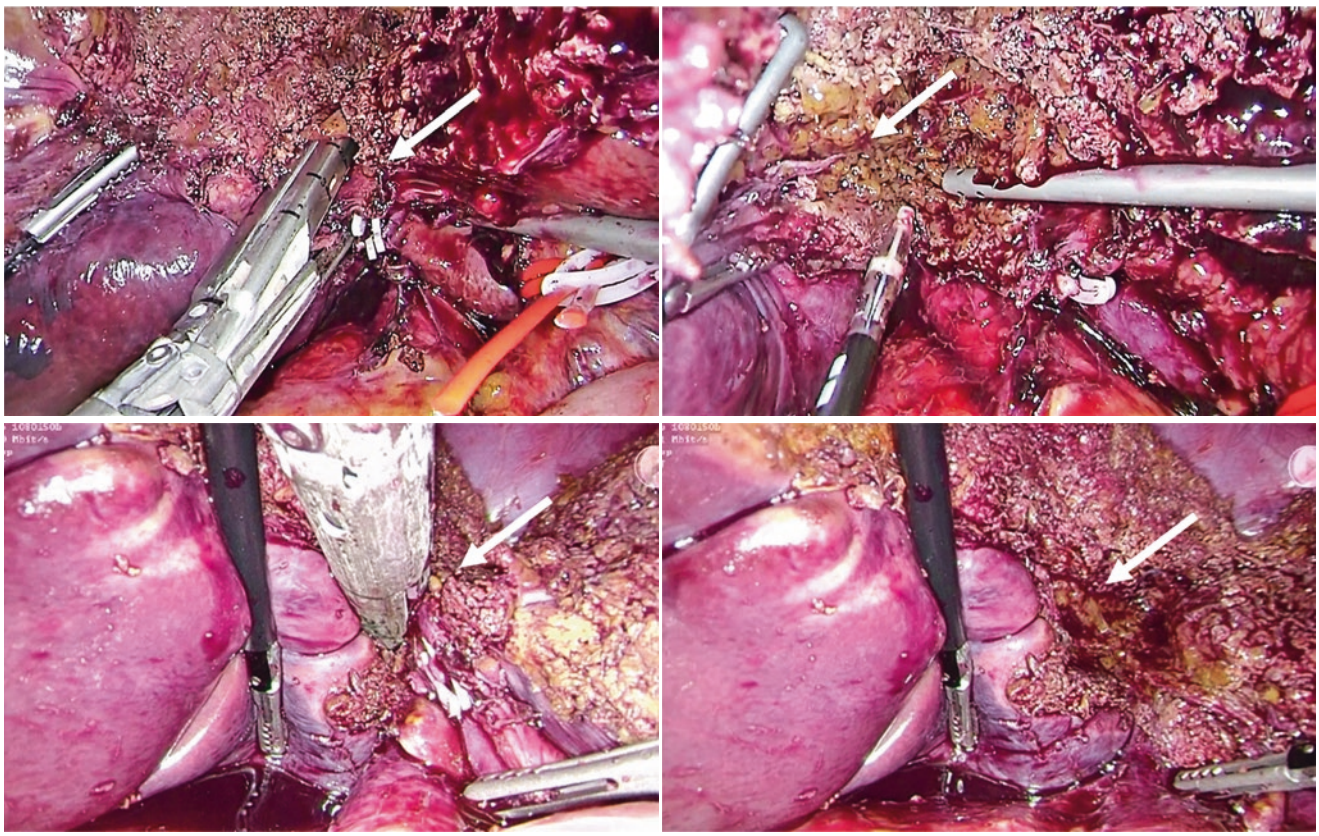

Fig. 12.19 Division of the right hepatic duct within the parenchyma (two examples)

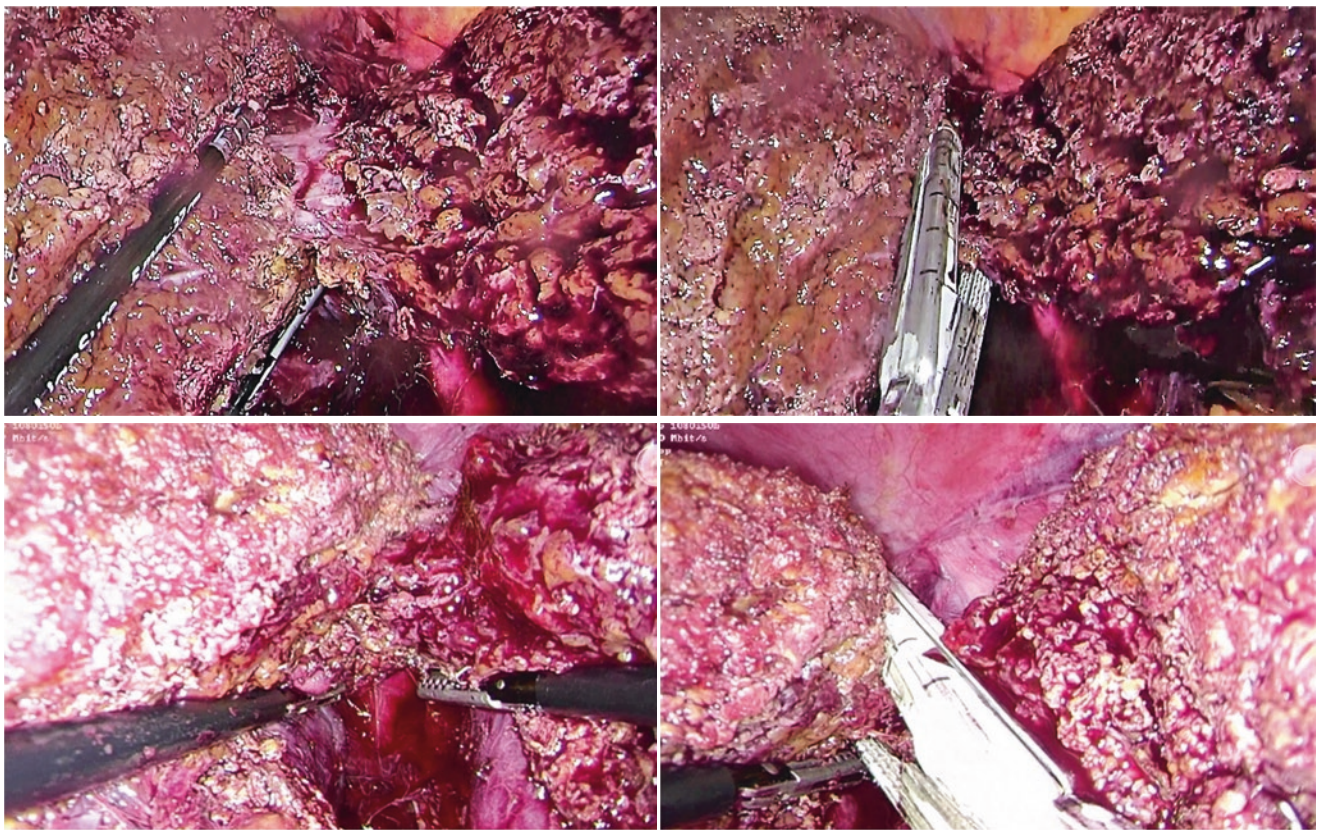

Fig. 12.20 Division of the right hepatic vein (two examples)

and the parenchyma is transected; it may be difficult, and bleeding from this region can be disastrous.

12.3 Conclusion/Personal Opinion

In recent decades, a paradigm shift has occurred in the management of colorectal cancer liver metastases. Surgical treatment has changed from major hepatectomies to parenchyma-sparing solutions and from open surgery to minimally invasive surgery. More and more high-level evidence is now available supporting and strengthening the position of minimally invasive surgery in the treatment of liver malignancies, especially colorectal cancer metastases.

Medicine and technology are merging and new technological solutions are accessible. The parenchyma sparing approach can be improved with the help of new liver imaging modalities, such as patient-specific 3D models, and navigation systems in new operation theatres (hybrid rooms).

The measurement of medical outcomes that matter to the patients or create value for the patients is crucial and therefore minimally invasive "patient friendly" surgery is a central contribution in the multimodal treatment. The use of big data and multi-omics data (genomics, proteomics, radiomics, etc.) will give a possibility to further personalize cancer treatment.

Based on our over 20 years of experience in laparoscopic liver surgery, we believe that more hospitals should establish minimally invasive liver surgery programs. Interdisciplinary collaboration and teamwork will be the best path to achieve this.

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Laparoscopic Liver Resection Technique: French Experience

13

Chady Salloum and Daniel Cherqui

Learning Objectives

- Laparoscopic liver resection provides perioperative benefits including better short-term outcomes compared to open liver resection.
- Complex laparoscopic procedures (repeat liver resection, two-stage hepatectomy, associating liver partition, and portal vein embolization for staged hepatectomy) are feasible in expert hands.

13.1 Introduction

Despite the significant advancements achieved in recent decades in terms of screening programs, chemotherapy regimens, and surgical treatments, colorectal cancer (CRC) remains an important health issue that affects nearly 1.8 million people worldwide with around 880,000 deaths each year. The incidence and mortality rates are third and second, respectively, among all cancers worldwide [1]. The liver is the most common site for metastases from CRC. Approximately 15–20% of patients have synchronous colorectal liver metastasis (CLM) at the time of diagnosis, and up to 40% of patients develop metastatic lesions during follow-up [2]. The standard of care for patients with resectable CLM is surgical resection which, combined with chemotherapy, offers the best chance of cure. Studies report 5- and 10-year survival rates of 33–58% and 23–39%, respectively. In Western countries, CLM resection is the primary indication [3]. Surgical treatment relies on two principles: [1] complete resection of CLM and [2] negative surgical margin.

Advances in minimally invasive procedures have completely revolutionized the landscape of abdominal surgery in the last few decades. The first laparoscopic liver resection (LLR) was reported in 1991 by Reich et al**.** [4]. LLR had difficulty in gaining popularity due to its complexity, the risk of bleeding, reservations regarding potentially inferior oncological results, and the long learning curve required. LLR was first performed for minor hepatic resections such as left lateral sectionectomies and wedge resections for lesions located in the antero-lateral liver segments with good outcomes. The evolution of technology and experience broadened the indications, enabling resections of lesions in the posterior and superior liver segments previously considered unfeasible. The French multicentric study published in 2015 [5] showed that from a total of 2620 patients operated for CLM, the laparoscopic approach was used only on 176 patients (6.7%). An analysis of the French Healthcare database showed that LLRs accounted for only 15.2% of all hepatectomies [6]. In a recent large systematic review of 9527 LLRs worldwide, 65% were performed for malignant lesions [7], which was a significant increase from 50% just a decade ago [8] with a low mortality of 0.39%. This study demonstrated the growing safety of this complex procedure in select patients when performed by expert surgeons in high-volume centers.

CLM is one of the most common indications for LLR. Meta-analyses [2, 9–16] and two randomized controlled trials (RCTs) have been published to date on this topic [17, 18], with additional ongoing prospective trials. The first European Guidelines Meeting on laparoscopic liver surgery in Southampton in 2017 [19] suggested that LLR

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was recommended as a valid alternative to open liver resection in experienced hands due to superior short-term outcomes and noninferior oncologic and survival outcomes.

13.2 Perioperative and Short-Term Outcomes

Fretland et al. reported the first single-center RCT (OSLO-COMET trial) in patients with CLM who underwent minor parenchyma-sparing liver resection, and successfully demonstrated the safety of LLR and its superiority compared to open liver resection (OLR) in terms of postoperative morbidity. In this trial, LLR for CLM was associated with lower postoperative complication rates (19% vs. 31%, $p = 0.021$) and shorter postoperative hospital stay (53 vs. 96 h, $p < 0.001$) compared to OLR, with no differences in blood loss, operation time, and 90-day mortality rates [17]. In a subgroup analysis of this trial considering only patients with tumours in the posterosuperior segments, the LLR group similarly showed shorter postoperative length of stay (LOS) and significantly better health-related quality of life [20]. The recently published LapOpHuva study was the second RCT comparing outcomes following LLR versus OLR for CLM [18]. In line with the results of the OSLO-COMET trial, patients undergoing LLR had lower overall morbidity (11.5% vs. 23.7%, $p = 0.025$) and shorter hospital stay (4 vs. 6 days, $p < 0.001$) than patients undergoing OLR, and similar surgical times, blood loss, blood transfusion, and mortality rates as patients undergoing OLR**.** In the incomplete Orange II trial, no difference was found between patients randomly assigned to open or laparoscopic left lateral sectionectomy. This trial was, however, stopped prematurely due to slow patient accrual, and results should be interpreted with caution [21]. Another randomized controlled trial, the ORANGE II PLUS trial (NCT01441856) comparing the early outcomes of right and left hepatectomy either by laparoscopy or open approach is still accruing and its results are not yet known [22]. Meta-analyses have been published on this topic [2, 9–16], with two of the largest studies involving more than 4000 patients each [2, 15]. The common results of the two studies were that LLR was associated with lower blood loss and blood transfusion rates and shorter LOS, and reduced postoperative complications than OLR, with similar mortality rates to OLR. Lower blood loss in patients undergoing LLR for HCC [23, 24] and improved short-term outcomes in patients undergoing major hepatectomy for HCC were reported [25, 26]. This could be attributable to the hemostatic effect of the pneumoperitoneum reducing oozing and venous bleeding during the transection and the increased clarity of surgical view due to enhanced magnification during laparoscopic surgery. Zhang et al. performed a meta-analysis of 10 propensity-matched studies involving 2259 patients (980 LLR and 1279 OLR) [16]. They concluded that LLR resulted in lower blood loss, blood transfusion rates, and overall morbidity, and shorter LOS, but slightly longer operative time, while there was significant heterogeneity in these studies. The same benefits of LLR were reported in the meta-analysis by Schiffman et al., including eight case-matched studies, where both groups were well balanced in terms of demographics, tumour characteristics, and extent of operation [12]. Ciria et al. showed that for minor resections, the LLR group had lower bloodloss and shorter LOS, with similar complication rates and operative time. For major resections, LLR resulted in reduced LOS only, with no differences in blood loss, operative duration, or postoperative morbidity rates [27]. Martinez-Cecilia et al. assessed the impact of LLR, compared with OLR, in an elderly population undergoing liver resection specifically for CLM. A large, multicenter cohort was used for a propensity score-based analysis. The cohort was divided into three subgroups (70–74 years subgroup, 75–79 years subgroup, and over 80-year-old subgroup) to assess whether the comparative results between laparoscopic and open resection varied with age. When the whole cohort was compared before matching, a number of significant perioperative advantages of the laparoscopic approach were observed. However, when the subgroup analysis was performed, a gradual loss of these advantages was noted with increasing age. In patients between 70 and 74 years old, all the advantages observed in the entire cohort analysis were replicated. In patients between 75 and 79 years old, a lower incidence of overall morbidity, minor morbidities, including lower respiratory tract infections, and a shorter high dependency unit stay were found after LLR, whereas the difference in major morbidity and total hospital stay were not statistically significant between the two groups. Finally, when only octogenarian patients were considered, there was a trend toward better short-term results in the laparoscopic group but none of those advantages were statistically significant except for the shorter high dependency unit stay [28]. One of the main advantages of laparoscopic surgery is the absence of large incisions, which leads to less postoperative pain, analgesia use [29], and early return to bowel function and tolerance of diet [30]. These advantages resulted in early ambulation and quicker recovery after surgery and allow patients to be discharged sooner. This fact was associated with an up to 30% reduction in respiratory functional residual capacity and a 60% reduction in vital capacity [31]. A predefined substudy of the OSLO-COMET trial proved definitively that patients undergoing LLR for CLM enjoyed better postoperative health-related quality of life (HRQoL) at 1 and 4 months compared to their counterparts in patients undergoing OLR [32].

Several reasons have been proposed to account for the encouraging peri-operative and short-term outcomes following laparoscopic resection of CLM. The magnified view pre-

sented by the camera facilitates meticulous dissection of vasculobiliary structures; the pneumoperitoneum tamponades venous oozing from the liver, while the smaller incisions result in less bleeding from the abdominal wall [9]. This is particularly useful in minimizing blood loss during hepatectomy for CLM, where chemotherapy-associated sinusoidal obstruction, regenerative nodular hyperplasia, or steatohepatitis of the liver may render patients more susceptible to bleeding [33, 34]. In LLR, all blood is aspirated and collected for charting, hence the estimated bloodloss is likely to be more accurate compared to open surgery where sponges are used to absorb and tamponade bleeding [12]. This may facilitate a more restrictive blood transfusion policy in laparoscopic resections.

13.3 Oncologic and Long-Term Outcomes

Special concerns with regard to oncological relevance of laparoscopy include recurrences at port entry sites, the trophic effect of the pneumoperitoneum on cancer cells, the inability to properly inspect the peritoneal cavity, and the lack of tactile feedback during liver inspection which no longer permitted the palpation of solid lesions within liver parenchyma. When indications for LLR expanded to include malignant tumours, the adequacy of resection margin status was one of the main concerns. To overcome this and other limitations involving laparoscopic liver mobilization particularly of posterosuperior segments, hand-assisted laparoscopic surgery (HALS) was initially employed [35]. However, the presence of a gloved hand in a limited field often impaired the surgical view. Hence, surgeons learned to perform careful intra-operative ultrasonography (IOUS) to identify deep-seated malignant lesions, thus ensuring that acceptable resection margins were achieved in laparoscopic resections [36]. The possibility to perform an IOUS has been mentioned by the consensus of international experts in hepatic surgery as being an indispensable preliminary examination before any liver resection, regardless of the technique used [37, 38]. Cipriani et al., using a propensity score matching, showed that LLR for CLM provides R0 resection rates and OS comparable to OLR for CLM [39]. Most meta-analyses to date have concluded that resection margin status and recurrence rates following LLR were similar to those following OLR, with several studies reporting even higher rates of R0 resection in the laparoscopic groups [2, 9, 11, 12, 15]. Only Tian's study concluded than the LLR patients had lower recurrence rates than the OLR patients [14]. In the OSLO-COMET prospective trial, there were no differences in the rates of R0 resection and positive resection margins between the LLR and OLR groups [17]. Recently, real-time indocyanine green (ICG) fluorescence imaging has also been reported to be useful in laparoscopy for the detection and localization of hepatic tumours including CLM [40–42]. The long-awaited survival outcomes of the OSLO-COMET trial were reported recently. The primary outcome was postoperative morbidity within 30 days. Five-year rates of OS and RFS were predefined secondary end points. At a median follow-up of 70 months, rates of 5-year OS were 54% in the laparoscopic group and 55% in the open group ($p = 0.67$). Rates of 5-year RFS were 30% in the laparoscopic group and 36% in the open group ($p = 0.57$). In this randomized trial of laparoscopic and open liver surgery for CLM, no difference in survival outcomes was found between the treatment groups. However, differences in 5-year OS up to about 10 percentage points in either direction cannot be excluded. In fact, the trial was not powered to detect differences in secondary end points and was not designed to address a noninferiority hypothesis for survival outcomes [43]. In the LapOpHuva randomized trial, a secondary endpoint was to compare long-term outcomes, which were found to be similar between the laparoscopic and open surgery groups [18]. The cumulative 1, 3, 5, 7-year OS for LLR and OLR were 92.5%, 71.5%, 49.3%, 35.6% vs. 93.6%, 69.7%, 47.4%, 35.5%, respectively ($p = 0.82$). Disease-free survival (DFS) for LLR and OLR was 72.7%, 33.5%, 22.7%, and 20.8% vs. 61.6%, 27.2%, 23.9%, and 17.9%, respectively ($p = 0.23$). In keeping with the findings from these trials, almost all the meta-analyses of retrospective studies found no significant differences in OS, DFS, or RFS between the laparoscopic and open groups [2, 9–15]. Interestingly, in a meta-analysis of propensity-matched studies comprising 2259 patients, LLR was associated with a better 3-year OS ($p = 0.003$) [16]. Similarly, a recently published meta-analysis of individual patient data from two randomized trials and 13 propensity-matched studies found a survival advantage of laparoscopic resection of CLM at 10 years after surgery, and in elderly patients [44]. Selection bias may explain these results to a certain extent. In early studies, patients chosen to undergo laparoscopic resection were a highly selected population with small tumours in easily accessible peripheral segments, while large complex tumours invading vessels or adjacent organs were reserved for the open approach [9, 12]. We insisted that patient selection for laparoscopic hepatectomies should be very strict and based on the size of lesions and their favorable topography [45]. It was mandatory that the laparoscopic approach did not modify the operative procedures used for open surgery, and hepatectomy indications needed to be respected, as did the carcinological rules for malignant tumours. Furthermore, LLR was mainly performed by experienced surgeons in high-volume centers. For example, the LapOpHuva trial was only started after the authors had completed at least 50 LLRs and had standardized their surgical technique, while OSLO-COMET was commenced after more than 400 laparoscopic resections were performed

in the center [17, 18]. Surgical expertise and experience are independent predictors of overall survival, and hence this may have influenced outcomes [46–48]. There are several other plausible mechanisms to explain the encouraging survival outcomes following LLR. Blood transfusion and postoperative morbidity are well-known to be independently associated with survival [49–51], and the reduced rates of these in LLR may have contributed to the long-term outcomes. A sizable fraction of patients experience intrahepatic recurrence of CLM after the index hepatectomy. For these individuals, an initial laparoscopic approach has been shown to increase the feasibility of future salvage hepatectomies through reduction in the burden of dense adhesions [52]. Adjuvant chemotherapy is a pivotal component in the treatment of CRC with metastatic liver disease, and patients undergoing LLR can resume chemotherapy regimens sooner than their counterparts who undergo open surgery [53–56]. Immune-mediated mechanisms must also be considered. In an exploratory biomarker analysis of the OSLO-COMET trial, open resection was found to induce heightened levels of pro-inflammatory molecules such as the HMGB-1 chemokine [57]. Indeed, recent translational studies have demonstrated that inflammatory molecules that aid wound healing after surgery also promote oncogenesis and trigger the outgrowth of dormant metastases, and this biological phenomenon has been proposed to account for the sharp rise in distant recurrence rates after surgery for certain cancer types such as breast cancer [58]. Anti-cancer immunosurveillance has been found to be diminished by surgical stress; therefore, higher levels of surgical stress after laparotomy may render patients more susceptible to cancer recurrence than their counterparts who undergo laparoscopy [59–62]. Experimental studies, in vitro and in vivo, suggested that laparoscopy was associated with decreased perturbation of proinflammatory cytokines, acute phase proteins, delayed type hypersensitivity response, and growth factors [63].

In patients over 70 years old, LLR for CLM offered comparable oncological outcomes to OLR for CLM. However, the benefits of the laparoscopic approach faded with increasing age, with no statistically significant benefits in octogenarians except for a lower high dependency unit stay [28].

13.4 Repeat Liver Resection

Because recurrence after CLM resection is frequent and difficult to predict or prevent, efficient treatments for recurrent CLM are needed. Repeat liver resection (RLR) has been reported as a safe and effective approach to the curative-intent treatment of recurrent CLM, which occurs in up to 70–80% of patients. Although repeat liver resection, together with chemotherapy, offers patients the best chance of survival [34, 64], it has inherent surgical challenges (e.g., adhesions and altered anatomy as a result of the previous resection), which could delay its diffusion and implementation in clinical practice. After laparotomy, peritoneal adhesions are inevitable and the incidence of adhesions was reported as 70–95% [65, 66]. The degree and range of peritoneal adhesions after laparotomy are difficult to predict. The presence of hypervascularized adhesions makes repeat laparotomy technically demanding. When performing repeat laparotomy for patients undergoing previous liver resection, surgeons must perform additional adhesiolysis to obtain an optimized surgical field. The factor of tumour location is important because laparoscopic repeat liver resection (LRLR) for tumour of segment 7 or 8 needs the mobilization of the right liver lobe. LRLR might be more challenging especially in patients who had previous mobilization of the right lobe and require repeat right lobe mobilization. In their multi-institutional study from the French Surgical Association Database, Hallet et al. showed that RLR was performed with good short-term outcomes similar to those obtained with initial liver resection. While recurrence free survival following RLR was inferior than after initial liver resection (HR 1.27, 95% CI 1.00–1.68), 5-year OS did not differ significantly (HR 0.92, 95% CI 0.51–1.67) [67]. LRLR was discussed at the first European Guidelines Meeting on Laparoscopic Liver Surgery at Southampton in 2017. In the consensus guideline of the meeting, it was described that redo liver surgery could be an appropriate option but should be avoided in the initial learning curve and experts suggested that an initial laparoscopic resection may facilitate repeated resections by limiting the amount of adhesions, thereby providing an important advantage [19]. Ban et al. proposed the Iwate difficulty scoring system to assess the difficulty of LLR in 2014 [68], and subsequent studies have validated this scoring system and confirmed its usefulness [69–72]. When the Iwate difficulty scoring system is used to classify patients into low- (difficulty index $\leq$3), intermediate- (difficulty index of 4–6,), and high-risk groups (difficulty index of $\geq$7), the intraoperative blood loss volume and operation time reportedly significantly differ between the low- and high-risk groups and between the intermediate- and high-risk groups, but not between the low- and intermediate-risk groups. However, the Iwate difficulty scoring system did not include factors related to repeat hepatectomy. In the study by Okamura et al. concerning novel patients' risk factors and validation of the Iwate difficulty scoring system in laparoscopic repeat hepatectomy, the volume of intraoperative blood loss significantly differed between the low- and intermediate-risk groups, which was not seen in the original study by Ban et al. Their results showed that the presence of tumours located adjacent and cranial or dorsal to the previous surgical site was an independent risk factor for massive intraoperative blood loss in LRLR [73].

A number of studies from high-volume centers have demonstrated the safety and feasibility of LRLR in expert hands. Morise reviewed 16 reports of LRLR compared to open repeat liver resection and concluded that LRLR has better short-term outcomes (similar or longer operation time, reduced bleeding, less blood transfusion, less or similar morbidity, and shortened hospital stay) with comparable long-term outcomes [74]. Shafaee et al. mentioned that the optimal candidates for LRLR are those with previous laparoscopic resections, rather than open resections. They had overall conversion rates of 11% and 16% when LRLR was done following a previous laparoscopic and open liver resection, respectively. Patients with previous open surgery were associated with higher amount of blood loss and needed intraoperative transfusion, but the complication rates were not significantly different between the two groups [75]. Shelat et al. showed that, even in expert hands, LRLR is associated with significant intraoperative difficulties when compared to primary LLR. This is reflected by a higher operative time, blood loss, and conversion rate. Interestingly, it appears that LRLR has no impact on postoperative outcomes, including mortality, morbidity, and hospital stay [76]. Isetani et al. reported that the surgical outcome of LRLR was safe and the morbidity rate was 5% [77]. Noda et al. demonstrated that LRLR reduces blood loss and postoperative complications compared with open repeat liver resection (ORLR) [78]. Ome et al. showed that LRLR had better short-term outcomes with respect to blood loss, intraoperative transfusion, and postoperative hospital stay than ORLR. LRLR is also considered useful for patients with poorer liver function, because it requires less hepatic mobilization, less destruction of the body wall, and less bleeding [79]. Inoue et al. showed that LRLR can be safely performed with more favorable results than with ORLR, in terms of surgical outcomes including intraoperative bleeding, intraoperative transfusions, postoperative complication rates, and postoperative length of hospital stays [80]. Mahamid et al. showed that hand-assisted LRLR is safe, feasible, and effective in a subset of carefully selected cases. This procedure does not appear to compromise perioperative outcomes nor the status of resection margins [81]. A recent meta-analysis of eight studies shows that LRLR after OLR is associated with longer operative time and higher blood loss compared to LRLR after LLR. However, no difference between LRLR after OLR and LLR was shown with no increase in morbidity rates or hospital stay [82]. A propensity score-matched study of repeat liver resection for CLM conducted across nine high-volume European centers showed that LRLR was associated with a shorter operative time, less intraoperative blood loss, and a shorter postoperative hospital stay than ORLR. Postoperative morbidity and mortality rates were also similar after LRLR and ORLR [83]. Nomi et al. analyzed patients who underwent second and third LLRs for recurrent CLM, and found no significant differences in postoperative overall and major morbidity rates, as well as mortality rates [84].

Peng et al. showed in their meta-analysis that LRLR could be safe and feasible in select patients when performed by experienced surgeons and had superior short-term outcomes and similar oncological features compared with ORLR. Additionally, it did not increase postoperative morbidity and mortality compared to primary LLR [85]. In their systematic review and meta-analysis including 10 studies of 767 patients, comparing LRLR with ORLR for posthepatectomy recurrent liver cancer, Liang et al. showed that LRLR is a safe and effective technique in clinical practice and is associated with lower intra-operative blood loss, less complications rate, shorter hospital stays, as well as higher R0 resection than ORLR [86]. While these results seem to contradict guideline recommendations, a number of explanations exist. Regarding the technical aspects of LRLR, several authors suggestively summarized the theoretical advantages of laparoscopy compared to open procedures. An initial LLR may result in minimal adhesions, thereby facilitating subsequent repeat procedures [87, 88]. LRLR facilitates more meticulous dissection of adhesions strained by the pneumoperitoneum using a magnified laparoscopic view. There is a decreased need for extensive adhesiolysis as certain adhesions may be circumvented by laparoscopic equipment without any separation and without compromising the operative view. Laparoscopy requires a smaller working space between adhesions and this allows minimal adhesiolysis, reducing operative time and bleeding, while conventional laparotomy involves unnecessary exfoliation and surgical operations to secure a suitable space for the operative field [74].

From 2009 to 2018 (data not published yet), we operated 27 patients of LRLR, of whom 21 (group 1) were after an initial laparoscopic hepatectomy and six (group 2) after open hepatectomy. CLM was the indication in eight cases (29%). There were no conversions in group 1 and only 1 in group 2 (16.7%). No significant differences were observed in median operative time (180 vs. 257 min; $p = 0.397$) and blood loss (150 vs. 125 mL; $p = 0.575$). No transfusions were needed in both groups. One patient died in group 2 of postoperative pancreatitis; this patient had been converted to open during LRLR. Morbidity rates were 23.8% and 17%, respectively, without significant differences. All complications except for the patient who died were minor ones. R1 resection was observed in 9.5% and 16.7%, respectively ($p = 0.545$). In our opinion, the initial laparoscopic approach facilitates subsequent repeat hepatectomy for several reasons. The main reason is that it is associated with less inflammation and surgical stress, resulting in smaller anatomical changes such as adhesions.

13.5 Synchronous Resection of CLM

Simultaneous resection of CRC and synchronous LM is considered to be associated with several risks: intraoperative bacterial contamination of the surface of the resected liver with bacteria from the resected colorectum and postoperative impairment of the liver might influence the risk of postoperative anastomotic leakage. Liver pedicle clamping can lead to an increased risk of anastomotic leakage because of the onset of intestinal edema [89]. The simultaneous resection approach avoids two operative procedures, thereby reducing risk for the patient and costs for the community while keeping acceptable morbidity and good oncologic results [90]. Therefore, the paradigm for the surgical management of synchronous CLM appears to be moving toward simultaneous resection. The advantages of simultaneous laparoscopic resection of synchronous CRC and CLM are known to be decreased damage and reduced wound length in the abdomen. In conventional open surgery, it usually needs a long midline wound from the xiphoid process to the pubic symphysis for an adequate abdominal approach, especially the combination of sigmoid colon or rectal resection and simultaneous liver resection. The shorter length of incision may lead to less postoperative pain, faster gastrointestinal recovery, and reduced bowel adhesion. This will improve the early outcome and allow better tolerance of adjuvant chemotherapy. The resection sequence of CRC and liver metastases has not been uniformly established. It is recommended in laparotomy that the resection of liver metastases precede that of CRC. The underlying rationale is that the dissection of liver disease requires a low central venous pressure to minimize blood loss, and the preceding liver resection will not interfere with the subsequent fluid resuscitation in the process of CRC dissection. However, the reverse sequence has also been reported, mainly based on the likelihood that the liver resection may not be clinically meaningful in the case of unresectable primary tumour.

In 2006, two cases of simultaneous laparoscopic resection of synchronous CRC and CLM were reported [91, 92]. Patriti et al. demonstrates in a pilot study that both the primary and the metastatic tumours can be safely resected laparoscopically during the same operation. The postoperative course was excellent without morbidity, allowing all patients to resume their normal activities early. These data were not paralleled by the duration of the hospital stay, which did not differ significantly from historical series of open one-stage colorectal and liver resection [93]. In 2011, Huh et al. reported that simultaneous resection of synchronous CRC and CLM showed similar outcomes to the open approach and resulted in less intraoperative blood loss and earlier postoperative bowel movement [94]. The option to perform simultaneous laparoscopic colorectal and major liver surgery for synchronous CRC and CLM was first described by Tranchart et al., who reported two cases with operative times of 310 and 345 min, respectively [95]. Furthermore, in 2015, at experienced centers, simultaneous laparoscopic resection of synchronous CRC and CLM was reported to be technically feasible and safe, and resulted in good oncological outcomes [96]. In a propensity score-matched analysis reported in 2016, Tranchart et al. demonstrated that simultaneous laparoscopic resection of synchronous CRC and CLM provided similar short- and long-term outcomes as the open approach—except for the prolonged operative time in laparoscopic hepatectomy—under the condition that laparoscopic hepatectomy met the indications for wedge resection or left lateral sectionectomy [97]. Ivanecz et al. also showed that a pure laparoscopic approach to treat synchronous CLM reduced the length of postoperative hospital stay without worsening survival outcomes compared with an open approach [98]. By matching propensity scores, Shin et al. compared 109 patients who underwent laparoscopic simultaneous resection of synchronous CRC and CLM, and 109 patients who had an open approach. There was no difference in hospital stay ($p = 0.078$), transfusion rate ($p = 0.686$), or time of bowel function return ($p = 0.570$) between the two groups. The laparoscopic group and the open approach group also showed similar 3-year overall survival rates (74.4% vs. 79.1%; $p = 0.792$) and 3-year disease-free survival rates (58.5% vs. 55.2%; $p = 0.391$). However, the postoperative morbidity rate was significantly lower in the laparoscopic group (20.2% vs. 33.0%; $p = 0.032$) [99]. Kawakatsu et al. showed that laparoscopic simultaneous resection of synchronous CRC and CLM (no more than five lesions with a maximum diameter of 4 cm) was associated with significantly less intraoperative blood loss and a significantly shorter postoperative hospital stay than the open approach [100]. Lupinacci et al. analyzed 14 articles, which included 39 laparoscopic simultaneous resections, and concluded that LLR associated with CRC resection is safe and feasible, and should be routinely proposed [101]. More recently, Moris et al. reviewed the literature and selected 12 studies, eight of them retrospectively comparing laparoscopic versus open simultaneous resection. The short-term and oncologic results were analyzed, and similar outcomes for open and mini-invasive resections were observed, with a trend favoring the laparoscopic approach in terms of length of stay and estimated blood loss [102]. Ye et al. performed a meta-analysis of 10 retrospective studies involving 502 patients [216 minimally invasive surgery

(MIS), 286 open resections] who underwent simultaneous resection. Unsurprisingly, the MIS approach was associated with less intraoperative blood loss ($p = 0.002$) and blood transfusion ($p = 0.03$), faster recovery of intestinal function ($p = 0.01$) and diet ($p < 0.0001$), shorter length of postoperative hospital stay ($p < 0.0001$), and lower rates of surgical complications ($p = 0.04$) [1]. The extent of liver resection during synchronous resection is a matter of contention. While most surgeons recommend on the principle of caution that only minor hepatectomies should be performed in the same setting as a colectomy, some authors have recently demonstrated that simultaneous major liver resections can be performed with comparable outcomes to staged resection [103–105]. In the systematic review by Moris et al., although the majority (83.6%) of cases were minor liver resections only, four comparative studies were included where synchronous major liver resections were performed with low conversion rates and similar morbidity and mortality outcomes compared to the open resection groups [106–109]. Although there was significant heterogeneity among most of these studies, this provides early evidence of the safety and feasibility of simultaneous laparoscopic resection of synchronous CRC and CLM in select cases.

13.6 Two-Stage Hepatectomy (TSH)

In the presence of extensive bilobar CLM, an inadequate future remnant liver (FRL) is a contraindication to surgical resection. To circumvent this, our group introduced the concept of TSH in 2000 for patients with bilobar CLM which cannot be resected in a single procedure [110]. Although a variety of staged procedures have been described, the usual sequence of TSH relies on the clearance of the left lobe in the first stage associated with right portal vein ligation in the same surgery or postoperative radiological embolization, followed by a standard/extended right hepatectomy in the second stage after an adequate time interval to allow hypertrophy of the FLR. This strategy developed in association with chemotherapy is a remarkable breakthrough because it allows patients who were formerly considered to have an inoperable disease, providing 5-year overall survival rates of 30% to 70% [111, 112]. But the procedure may still be technically demanding, especially during the second stage. The formation of heavy adhesions due to the first-stage operation along with the inflammation and hypertrophic changes due to portal vein occlusion and chemotherapy-associated steatohepatitis or sinusoidal obstruction syndrome, may lead to increased intraoperative blood loss, transfusion, and postoperative morbidity. To overcome these difficulties, several technical refinements have been proposed including the use of bioresorbable membranes to avoid adhesions [113] or taping the major vascular structures and performing a hanging maneuver during the first stage to make the second-stage dissection easier [114]. The laparoscopic approach has multiple theoretic benefits in the technical aspects of TSH. Laparoscopy provides less adhesion formation after the first stage, less intraoperative bleeding because of the pneumoperitoneum, good visibility of the operative field due to the magnifying effect, which could be a fundamental solution to overcome the above-mentioned difficulties, and the possibility to use the same trocar incisions. Moreover, to facilitate laparoscopic vascular control during the second stage it is better to ask the interventional radiologist during portal vein embolization procedure to leave patent at least 1 cm of the proximal right portal vein. Furthermore, preserving the gallbladder intact during the first stage may facilitate dissection of the right pedicle during the second stage. Machado was the first to describe in 2010 totally LLR for both stages [115]. The first stage involved laparoscopic resection of segment 3 and ligature of the right portal vein. The second stage involved laparoscopic right hepatectomy using the intrahepatic Glissonian approach. A number of case series demonstrated the safety and feasibility of performing LLR for the first-stage procedure, with the advantages of minimal postoperative pain, short hospital stay, early commencement of chemotherapy, low morbidity and mortality rates, and frequent progression to second-stage surgery with no eventual compromise of oncologic results [116–119]. The second-stage surgery is technically more demanding than a standard right hepatectomy because it is a repeat hepatectomy, as the operation is often complicated by dense abdominal and perihepatic adhesions, anatomical alteration in the hypertrophied remnant liver, chemotherapy-induced liver injury, and an inflamed porta hepatis following portal vein embolization/ligation, which makes hilar dissection treacherous. Preservation of the middle hepatic vein is paramount in these patients. There can be a tendency to leave a devascularized portion of segment 8 at the root of the middle hepatic vein to preserve FRL volume and protect the vein. This should be avoided, if possible, to minimize the risk of prolonged bile leaks. Gayet's group reported in 2015 their early experience with laparoscopic TSH, where almost 80% of patients completed the second stage, with 3- and 5-year overall survival and disease-free survival rates of 78% and 41%, and 26% and 13%, respectively [120]. Okumura et al. compared outcomes following laparoscopic versus open TSH in a bi-institutional,

Table 13.1 Overview of previously published research articles discussing the role of the laparoscopic approach in two-stage hepatectomy for colorectal liver metastases

Study	Title	Inclusion period	Country	Laparoscopic FSH	Laparoscopic SSH
Gelli et al. [119]	Planned laparoscopic two-stage strategy for patients with multiple bilobar colorectal liver metastases (CLM)	2000–2011	France	13	12
Di Fabio et al. [116]	Exploring the role of laparoscopic surgery in two-stage hepatectomy for bilobar colorectal liver metastases	2003–2011	UK	8	3 (including 1 conversion)
Sandri et al. [118]	Two-stage hepatectomy, 10 years of experience	2004–2014	Italy	5	0
Fuks et al. [120]	Laparoscopic two-stage hepatectomy for bilobar colorectal liver metastases	2000–2013	France	34	26
Kilburn et al. [117]	Laparoscopic approach to a planned two-stage hepatectomy for bilobar colorectal liver metastases	2007–2013	Australia	7	1 (including 1 conversion)
Okumura et al. [121]	Laparoscopic versus open two-stage hepatectomy for bilobar colorectal liver metastases: a bi-institutional, propensity score-matched study	2007–2017	France	25	25
Görgec et al. [123]	Surgical technique and clinical results of one- or two-stage laparoscopic right hemihepatectomy after portal vein embolization in patients with initially unresectable colorectal liver metastases: a case series	2003–2019	UK	NA	12
Taillieu et al. [124]	The role of the laparoscopic approach in two-stage hepatectomy for colorectal liver metastases: a single center experience	2011–2020	Belgium	22	7

FSH first stage hepatectomy, *SSH* second stage hepatectomy
Not applicable because only second stage procedures were evaluated in this research paper

propensity score-matched study: laparoscopic TSH was performed in 38 patients and open two-stage hepatectomy in 48. After propensity score matching, 25 laparoscopic and 25 open patients showed similar preoperative characteristics. For the first stage, the laparoscopic approach was associated with shorter hospital stays (4 vs. 7.5 days; $p < 0.001$). For the second stage, the laparoscopic approach was associated with less blood loss (250 vs. 500 mL; $p = 0.040$), less postoperative complications (32% vs. 60%; $p = 0.047$), shorter hospital stays (9 vs. 16 days; $p = 0.013$), and earlier administration of chemotherapy (1.6 vs. 2 months; $p = 0.039$). Overall survival, recurrence-free survival, and liver-recurrence-free survival were comparable between the groups (3-year overall survival: 80% vs. 54%; $p = 0.154$; 2-year recurrence-free survival: 20% vs. 18%; $p = 0.200$; 2-year liver-recurrence-free survival: 39% vs. 33%; $p = 0.269$). Although the two groups had comparable recurrence patterns, repeat hepatectomies for recurrence were performed more frequently in the laparoscopic TSH group (56% vs. 0%; $p = 0.006$) [121]. Fewer adhesions following a laparoscopic first-stage procedure, reduced bleeding due to pneumoperitoneum, and magnified visualization of the surgical field were cited as some of the factors responsible for producing positive outcomes in the LLR group [122]. Gorgec et al. reported a low incidence of severe morbidity rates (10.5%) with an R0 rate of 94.7% in a series of 12 patients who underwent laparoscopic right hepatectomy after portal vein embolization in a context of TSH for initially unresectable CLM demonstrating the safety and feasibility of this procedure in experts centers [123]. In the study of Taillieu et al., 23 patients were planned to undergo a TSH. The first-stage hepatectomy (FSH) was performed laparoscopically in 22 patients (96%) without the need for conversion. R0 resections were obtained in 18 FSHs (78%), while all others were R1 vascular (22%). Fourteen patients (61%) underwent a second-stage hepatectomy (SSH). All SSHs were anatomically major hepatectomies. SSH was performed laparoscopically in seven patients (50%), with need for conversion in one case (14%) [124]. Table 13.1 provides an overview of previously published research articles in which the role of the laparoscopic approach in TSH for CLM was evaluated.

13.7 Associating Liver Partition with Portal Vein Ligation (ALPPS)

In the last few years, there have been a number of publications about a new surgical approach termed associating liver partition and portal vein ligation for staged hepa-

tectomy (ALPPS) following the original publication by Schnitzbauer et al. in 2012 [125]. By ligating the portal vein and splitting the liver parenchyma "in-situ," distinct and rapid hypertrophy of the liver tissue occurs to increase FLR volume by 74% in an average of approximately 9 days, in the presence of high tumour load, and hepatectomy for CLM is the most common indication for this [126]. In 2012, the first totally laparoscopic ALPPS was performed by Machado et al. on a 69-year-old woman with multiple bilobar CLM. Stage 1 of their procedure involved laparoscopic partial resection of segment 3 followed by right portal vein ligation and in situ split. Full mobilization of the right liver was performed in the first stage. Computed tomography at postoperative day 7 showed an 88.0% increase in FLR volume. Stage 2 was performed on postoperative day 9. Adhesion was not severe. Division of the remaining liver parenchyma, pedicle, and right hepatic vein was done using a stapling device. The postoperative course was uneventful [127]. In 2015, Jiao introduced the concept of virtual splitting of liver parenchyma by using an energy source, named as radiofrequency assisted liver partition with portal vein ligation (RALPP), whereby surgical portal vein ligation and radiofrequency ablation of the liver parenchyma is performed as stage I, without splitting liver parenchyma to avoid complications related to ALPPS, before completion hepatectomy as stage II [128]. The initial enthusiasm surrounding ALPPS was curbed by reports showing high morbidity and mortality rates [129, 130], which became subsequently low by careful patient selection and adopting a less aggressive approach in stage I ALPPS [131]. Using a minimally invasive approach for the first stage offered the benefits of reduced blood loss, surgical trauma and inter-stage adhesions [132–137]. A meta-analysis of nine retrospective studies in patients with unresectable CLM confirmed a faster kinetic growth rate of the FRL in ALPPS compared to TSH [138]. In 2015, a consensus meeting on ALPPS was held among international hepatic surgeons in Hamburg. The conclusion was that further studies were needed before ALPPS should be used for routine pre-operative induction of the FLR volume for staged hepatic resections [139]. Two randomized clinical trials were proposed at this meeting: the multicenter LIGRO Trial from the Scandinavian group led by Sandström, comparing ALPPS and PVE, which showed that ALPPS was associated with a higher resection rate, with no differences in morbidity, 90-day mortality, or R0 resection rates compared to TSH [140] and the regeneration of the liver. The portal vein embolization versus radiofrequency-assisted ligation for liver hypertrophy (REBIRTH) trial showed that RALPPS was significantly associated with an increase in liver volume and within a much shorter period compared to PVE, without increased morbidity and mortality [141].

A recent systematic review of 15 studies comparing minimally invasive approach for ALPPS with the open procedure found that the laparoscopic patients experienced low morbidity rates (15.4% complications of Clavien-Dindo Grade 3b) and no procedure failures between the first and second stages, with 0% perioperative mortality after either stage [142]. Another systematic review by Michal et al. included in the analysis 1088 open and 46 minimally invasive ALPPS cases. There were significant differences in the baseline characteristics: the open ALPPS patients had a more diverse profile of underlying pathologies ($p = 0.028$) and comparatively more right-extended hepatectomies ($p = 0.006$) as compared to right hepatectomy and left-extended hepatectomy performed. Operative time and blood loss did not differ significantly between the two groups. Minimally invasive ALPPS had a lower rate of severe Clavien–Dindo complications ($\geq$ IIIa) following stage I ($p = 0.063$) and significantly lower median mortality (0.00% vs. 8.45%) ($p = 0.007$) compared to open ALPPS [143]. However, these results should be considered with caution. Only a limited number of cases exist in the literature, and selection biases should be considered when comparing open versus minimally invasive ALPPS series.

"Partial" or "Mini" ALPPS is another technical modification to minimize complications after stage I. This entails strict avoidance of liver mobilization, ligation of the right portal vein followed by partial transection of the liver parenchyma only halfway up to the middle hepatic vein, which is preserved in order to maintain outflow and prevent congestion of the excluded liver segment avoiding the deleterious necrosis of the segment IV, and decreasing the incidence of biliary leak. Truant et al. reported a series of five patients who underwent laparoscopic partial ALPPS with impressive results of a median FLR volume increase of +60% (+18.6% to +108.1%) and a median FLR function increase of +47% (+37% to +64%). These changes occurred earlier, allowing the second-stage surgery to be done successfully within a week with no liver failure or deaths in their series [144]. Another innovation that has been described combines laparoscopic Mini-ALPPS with laparoscopy-assisted percutaneous cannulation of the inferior mesenteric vein for embolization of the portal vein (instead of ligation) [145]. Table 13.2 summarizes the reported laparoscopic ALPPS for CLM.

Table 13.2 Reported total laparoscopic ALPPS and variant for CLM

Reference	Number	Age (ranges)	Sex (M/F)	Method	FLR volume increase % mean	Time between stages (days, range)	Operative times (minutes)	Morbidity Clavien –dido > IIIA (%)	Mortality (%)	LOS(days, range)
Machado et al. [127]	1	69	F	Laparoscopic ALPPS	88.0	9	NA	0	0	NA
Gall et al. [128]	5	62 (48–71)	3/2	Laparoscopic RALPPS followed by open stage 2 resection	62	11	Stage1: 165 Stage 2: 215	20	0	NA
Cillo et al. [132]	1	53	M	Laparoscopic microwave ablation and portal Vein ligation for staged hepatectomy	90.4	15	Stage 1: 170 Stage 2: 630	0	0	10
Jiao et al. [133]	1	76	M	Laparoscopic RALPPS followed by laparoscopic stage 2 resection	57.9	21	Stage 1: 110 Stage 2: 270	0	0	NA
Surjan et al. [134]	1	65	M	Laparoscopic ALPPS	42.3	21	Stage 1: 250 Stage 2: 200	0	0	26
Machado et al. [135]	1	42	F	Laparoscopic reversal ALPPS	70	21	Stage 1: 300 Stage 2: 180	0	0	10
Machado et al. [136]	10	58(36–69)	6/4	Laparoscopic ALPPS	105.3	21 (9–30)	Stage 1: 300 Stage 2: 180	0	0	11 (8–20)
Ferko et al. [137]	1	54	F	Laparoscopic ALPPS	60	8	Stage 1: 300 Stage 2: 200	0	0	15
Jiao et al. [141]	20	62.4 (mean age)	11/9	Laparoscopic RALPPS followed by open or laparoscopic stage 2 resection	80.7	20 (14–36)	Stage 1: 115 Stage 2: 180	15	5	15.3 (mean)

13.8 Technical Tips and Tricks

13.8.1 Positioning

Patient positioning is important for LLR. For left-sided resections, we recommend to place the patient in a supine position with the lower limbs apart on a split-leg table, sometimes referred as the "French position" (Fig. 13.1). The surgeon stands between the patient's legs with one assistant on each side of the patient. The scrub nurse and instruments are positioned lateral to the patient's leg or behind the surgeon. Ideally, two monitors should be available at the patient's head so that the surgeon, assistants, and scrub nurse have good visual access (Fig. 13.2). For right-sided resections, except for isolated resections of segment VII, the patient is placed in a hybrid lateral decubitus (left lateral decubitus position with right arm elevated and split leg) (Fig. 13.3). For lesions located in segment VII, the surgeon and one assistant stand on the patient's right side, with the scrub nurse opposite at the patient's legs. For tumours in segment VII, we recommend a full left lateral decubitus, with the surgeon standing on the patient's right side to obtain a better view and direction to operate (Fig. 13.4). The monitor towers are positioned across from the surgeon. Advantages of the left lateral decubitus position are to facilitate mobilization of the right liver by gravity and having the scope facing the posterior segments. The table can also be tilted to the right or left to create necessary space according to various stages of the operation. In all cases, the reverse Trendelenburg position allows the bowel to

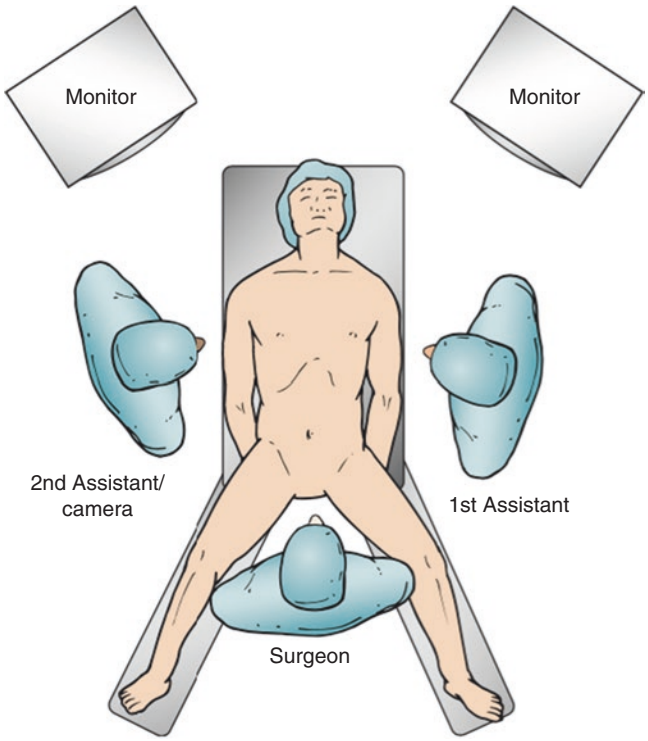

Fig. 13.1 Split-leg position

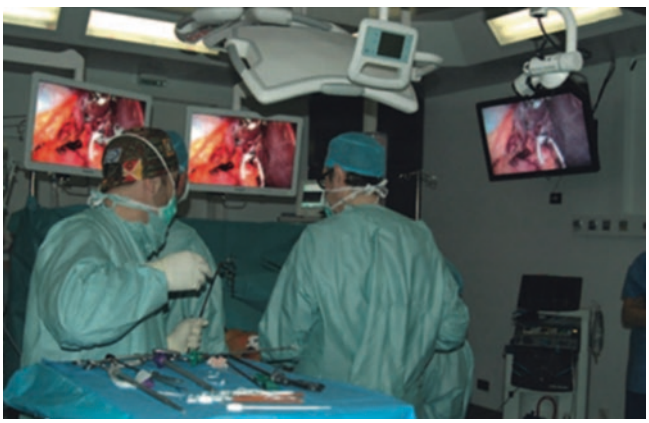

Fig. 13.2 Operating room setting of laparoscopic liver resection

drop into the lower abdomen and help vision and exposure. Sometimes the surgeon must change the laparoscope port and take a co-axial position with respect to the hepatic resection site and the laparoscopic monitor, and secure a triangular formation centered on the laparoscope. This avoids unusual positioning of the surgeon's body, which could potentially decrease the surgeon's ability to recognize cavities due to unforeseen adhesions. It also facilitates better control of the left and right instruments in the direction of the organs. Thus, operability is improved and blind maneuvering is avoided.

Fig. 13.3 Hybrid left lateral decubitus position for right-sided resections

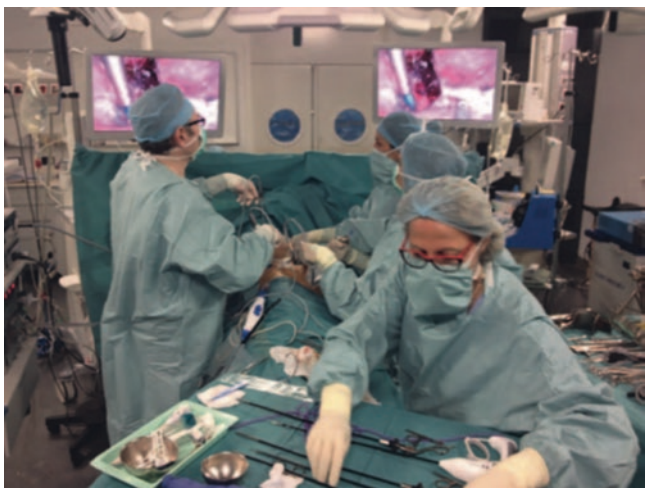

Fig. 13.4 For tumours in segment VII, surgeons stand on the patient's right side to obtain a better view and direction to operate

13.8.2 Incisions, Exploration, and Exposure

The open technique is preferred to the blind insertion of the Veres needle for the first trocar placement (12 mm for the 30°

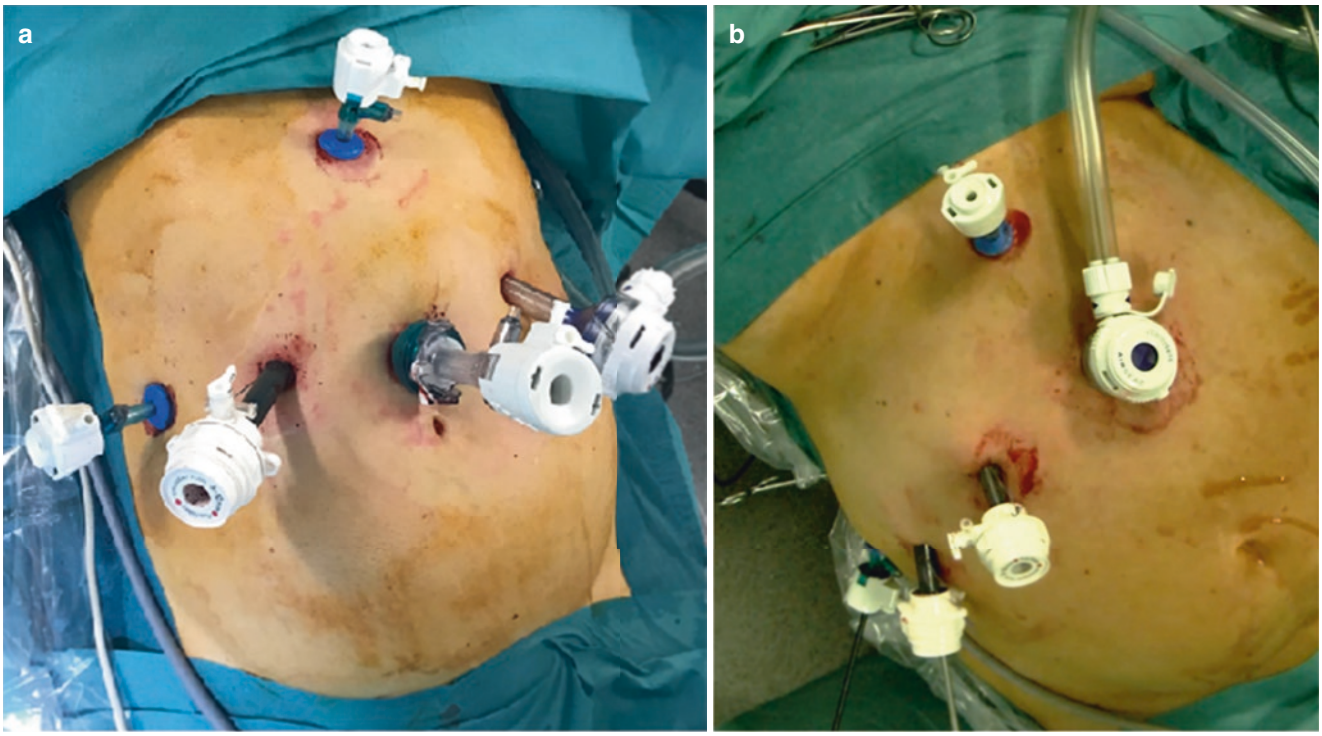

Fig. 13.5 Trocars in split-leg position. (**a**) Left-sided resections. (**b**) Right-sided resections

laparoscope) in gaining access to the peritoneal cavity. In the case of a previous open surgery, it was placed remotely from the previous operative incision. Continuous carbon dioxide (CO_2) pneumoperitoneum was induced at a pressure limit of 12 mmHg and flow of 6 L/min to decrease the risk of gas embolism. The following ports are placed under direct laparoscopic vision, with incisions sized to accommodate the necessary trocars (Fig. 13.5). The median trocar is the camera port, the paramedian ports are the working ports, and the most lateral right and left ports are for retracting assistance. Care should be taken not to place the ports too far from the costal margins as pneumoperitoneum will increase the distance, especially in males. This may cause a problem of instrument length not able to reach the liver dome. This particularly happens when using the CUSA. For segment VI and VII resections, four or five ports are usually used (Fig. 13.6). Transthoracic trocars at the right lateral intercostal space are sometimes necessary for manipulation of the liver dome area, especially the junction of the right hepatic vein and the inferior vena cava.

After a thorough inspection of the peritoneal cavity for ascites and carcinomatosis, attention is turned to the liver for signs of superficial lesions, steatosis, or other gross findings. Laparoscopic ultrasound is crucial, and a thorough knowledge of liver anatomy and both B-mode and Doppler ultrasonography is mandatory for accurate LLR. In addition to intraoperative ultrasonography, laparoscopic indocyanine green (ICG)-fluorescence imaging was also used to facilitate tumour identification. In repeat hepatic resections, thermocoagulation is easy to perform when adhesions have been detached and the liver has been mobilized. Tumours on the liver surface are not clearly detected by intraoperative ultrasonography.

The round ligament is divided close to the abdominal wall. This prevents a dangling remnant that might obstruct the view or soil the tip of the scope. Then, the falciform ligament is divided along its length to the insertion of the hepatic veins into the vena cava. The round ligament, along with the gallbladder remnant, can be used as "handles" for manipulation of the liver. In the case of repeat hepatectomy involving detachment of the left lobe, the stomach and the duodenum may have adhesions connecting them to the remaining liver. If the previous surgery involved detachment of the right lobe, then it would be common for the diaphragm, colon, retroperitoneum, and adrenal gland to have adhesions to the remaining liver. In mobilizing the liver, we then must take care to preserve the liver membrane as much as possible, so that anatomical landmarks which are lost due to adhesions are preserved and we avoid damage to other organs. To prepare hepatic hilum occlusion, an instrument is passed behind the hepatoduodenal ligament to encircle it with a tape. The tape is then extracorporeally inserted through a short rubber tube to serve as a tourniquet, and it is returned to the abdomen (intracorpo-

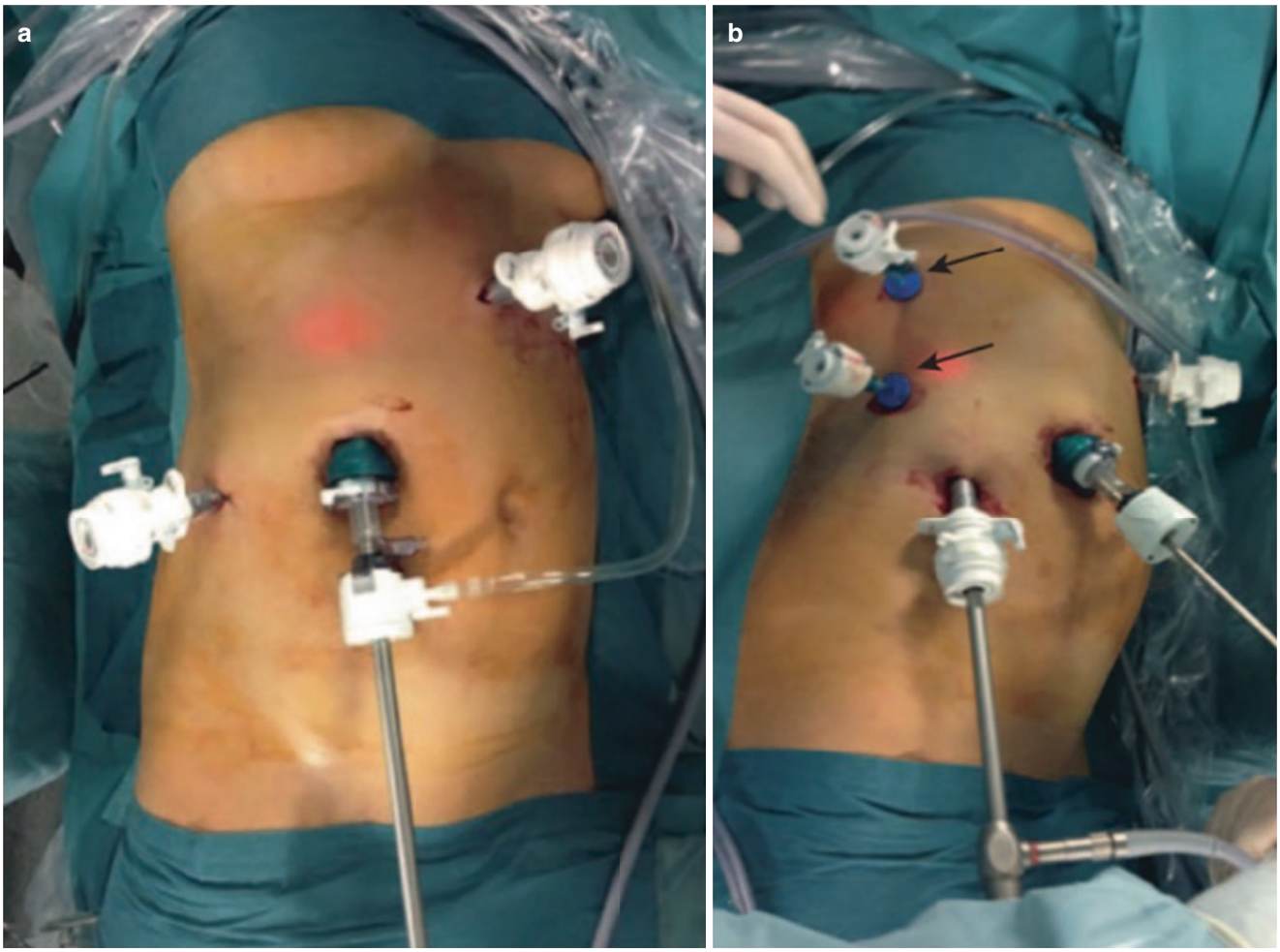

Fig. 13.6 Trocars in full left lateral decubitus position. (**a**) Initial trocars. (**b**) Additional trocars at intercostal space (arrows)

real Pringle maneuver) (Fig. 13.7) or externalized and passed through a catheter (extracorporeal Pringle maneuver) (Fig. 13.8). We currently prefer the extracorporeal Pringle maneuver. If pedicle clamping is used, we favor 15 min of clamping the pedicle flow interrupted by 5 min of release. Although we do not systematically clamp the pedicle, this should be regarded as another safety tool in the arsenal of surgeons, because even mild parenchymal bleeding may obscure visualization. In repeat hepatectomy, the passage of the grasper through the Wislow foramen for the Pringle maneuver can be difficult due to adhesions in the hepatic portal pedicle from the previous surgery. This problem may occur in the second stage of a two-stage hepatectomy or after PVE. In this case, we attempt to pass from the left to the right. The Goldfinger (Blunt Dissector and Suture Retrieval System, Ethicon Endo Surgery, Johnson & Johnson, New Brunswick, N.J., USA) may facilitate this procedure. The use of on-demand intermittent inflow occlusion, meticulous technique, pneumoperitoneum, low central venous pressure anesthesia, reduced ventilatory volume, and reduced positive end-expiratory pressure is effective for decreasing blood loss during LLR.

13.8.3 Transection Techniques

Transection is a critical time in laparoscopic resection. Continuous suction interferes with pneumoperitoneum pressure, and bleeding control by compression or suture is more difficult than in open surgery. Consequently, prevention rather than treatment of bleeding is paramount in laparoscopic surgery. The superficial part of the liver (approximately 2 cm from the surface) includes only small vessels that can be easily managed. Large vessels are located at the deep part of the liver, especially fragile hepatic veins, while inflow pedicles are more solid and surrounded by the Glissonean sheath. Therefore, deeper transection requires identification of large vessels and avoidance of blind maneuvers. In our experience, location of the tumour in proximity to important vascular structures and the potential size of the

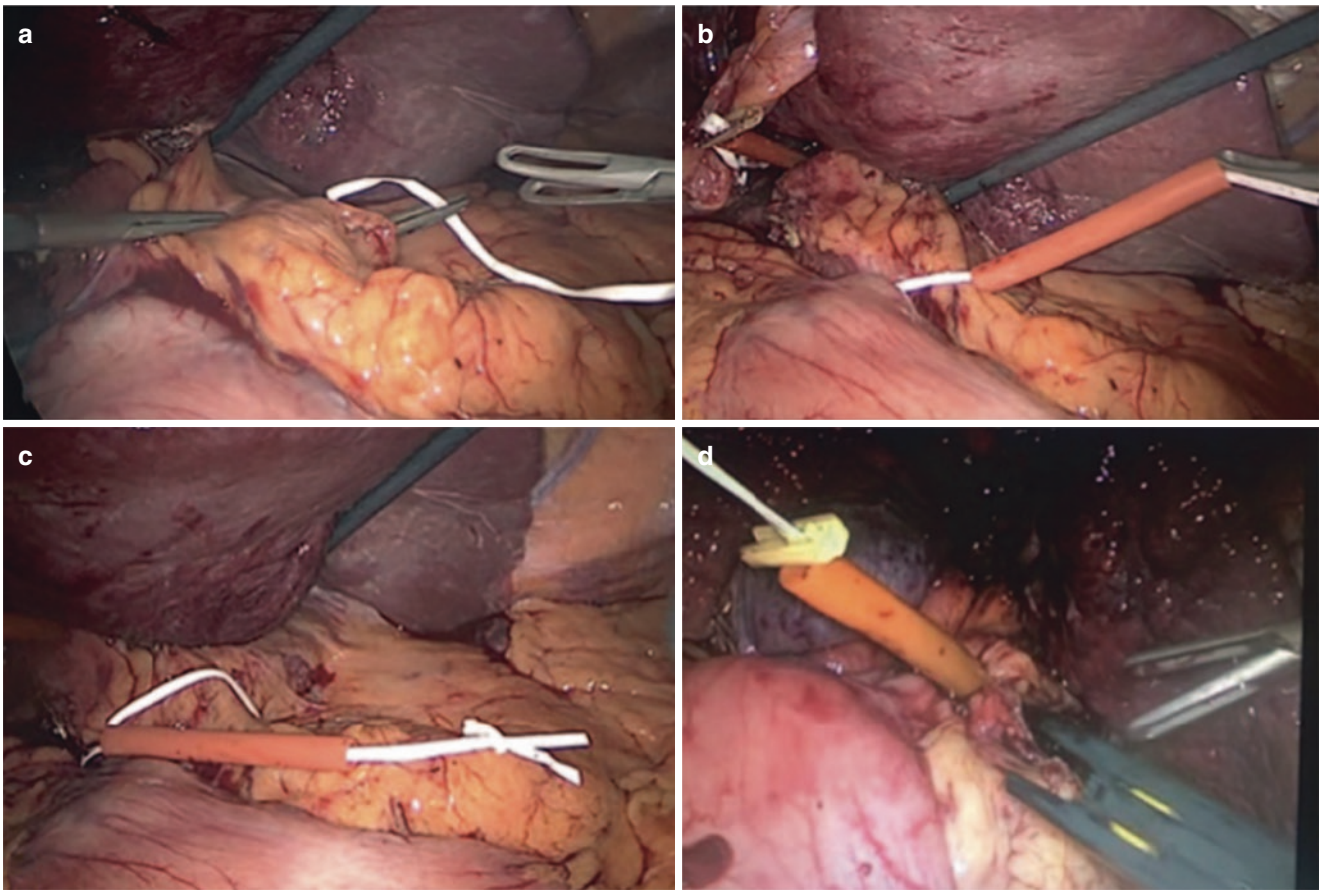

Fig. 13.7 Pringle maneuver in laparoscopic liver resection; preparation and locking of tourniquet. (**a**) Umbilical tape passed behind hepatic pedicle from right-side port. (**b**) Rubber tube used to prepare tourniquet. (**c**) Tourniquet ready. (**d**) Inflow occlusion is obtained by locking the tourniquet with a locked clip

liver remnant are critical factors in dictating the magnitude of resection margin. Although a surgical resection margin of 10 mm has been advocated, one must balance the importance of margin with the risk of hepatic insufficiency due to inadequate liver remnant.

The transection line is outlined along the liver capsule with monopolar diathermy based on preoperative imaging, knowledge of hepatic anatomy, laparoscopic ultrasonography, and demarcation lines when inflow pedicles are interrupted. Whereas in open surgery the clamp-and-crush method is a useful and inexpensive transection technique, newer technologies such as energy devices and staplers are required for laparoscopic operations. Several instruments are available, and individual surgeons have developed preferences and habits with specific instruments based on their history and access. There is no evidence that one device is better than another, and the choice of devices should be left to the surgeon. The energy devices are mainly divided into three classes: (1) ultrasonic shears (Harmonic ACE, Ethicon Endo-Surgery, Cincinnati, OH, USA; Sonicision, Covidien, Mansfield, MA, USA), (2) bipolar vessel sealant (LigaSure, Covidien; Enseal, Ethicon Endo-Surgery), and (3) combined ultrasonic and bipolar device (Thunderbeat; Olympus, Tokyo, Japan). The energy devices are effective for transecting the superficial part of the liver parenchyma (Fig. 13.9). For dissection of the deep part of the liver parenchyma, prior identification and selective hemostasis of larger vessels are recommended. We recommend the use of an ultrasonic aspirator (CUSA; Integra Neurosciences Ltd., Andover, UK) (Fig. 13.10).

Subsequently, vascular and biliary structures less than 5 mm are coagulated and transected using an energy device or bipolar diathermy, or closed by clips. Vessels and bile ducts 5 to 10 mm in diameter are ligated with plastic locking clips (Hem-o-lok, Teleflex Medical, Research Triangle Park, NC; Lapro-Clip, Covidien) and then divided. Laparoscopic linear staplers (Endo GIA, Covidien; Echelon Endopath, Ethicon Endo-Surgery) are used for larger vessels. The stapler can be applied to segmental portal pedicles or to isolated large portal or hepatic veins. It can also be used for division of the right or left bile duct surrounded with hilar plate during hemihepatectomy. The stapler should never be forced closed over a thick tissue mass, and excessive tissue length should not be squeezed into the jaws; such maneuvers risk

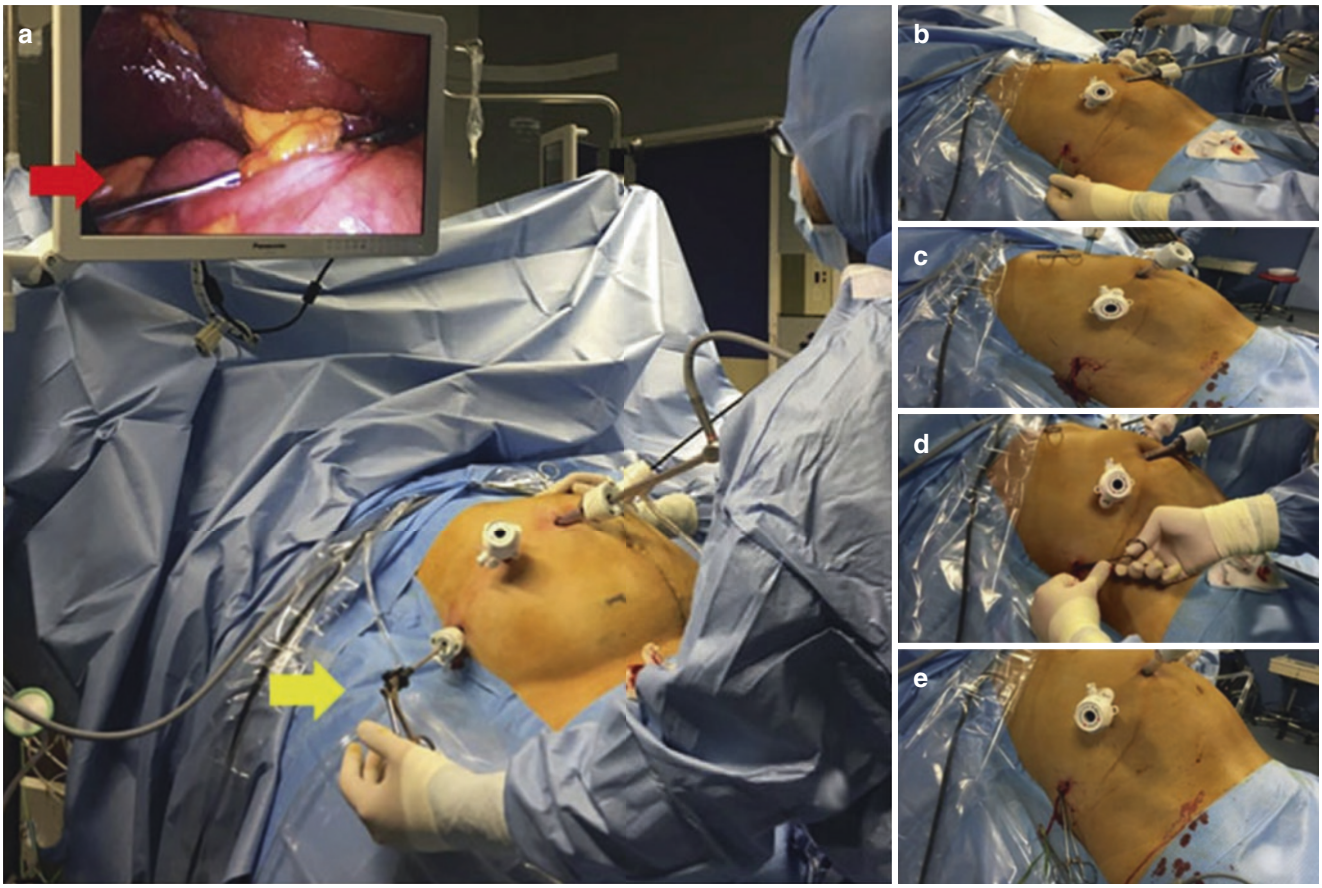

Fig. 13.8 Extracorporeal Pringle maneuver. (**a**) From the trocar inserted on the right flank (yellow arrow), a grasper (red arrow) is passed behind the hepatoduodenal ligament to place an 80 cm long cotton tape around it. (**b–e**) The tape is externalized through the trocar in the right flank and passed through a catheter

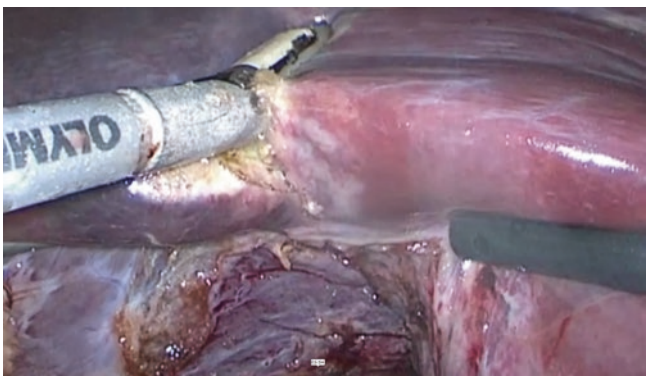

Fig. 13.9 Energy devices are effective for transecting the superficial 2 cm of liver parenchyma

misfiring, which can lead to difficult-to-control bleeding. Rather, further dissection should be performed until the tissue fits effortlessly within the stapler. Before stapling the right or left portal vein branch near the bifurcation, flow to the opposite pedicle should be confirmed for safety. Some surgeons perform parenchymal transection with repeated application of linear staplers [146], but we do not favor this technique, which, although quicker, lacks precision and may lead to severe bleeding. We prefer meticulous parenchymal dissection to completely visualize intrahepatic vessels and bile ducts, believing that blind application of the linear stapler is a risky technique.

13.8.4 Extraction, Drainage, and Closure

All lesions should be extracted without fragmentation using an endoscopy-protective plastic bag. Small lesions can be removed through extension of trocar incisions. Larger specimens are usually removed through a 5- to 8-cm suprapubic Pfannenstiel incision without muscle section. Specimens can also be removed through preexisting McBurney or midline incision. The extraction incision should fit the size of the specimen to retrieve. It should not be underestimated, so as to allow easy extraction and avoid rupture of the protective bag. The fascia layers are then reapproximated, the pneumoperitoneum is reintroduced, and the operative site is lavaged and examined for hemostasis and possible bile leak.

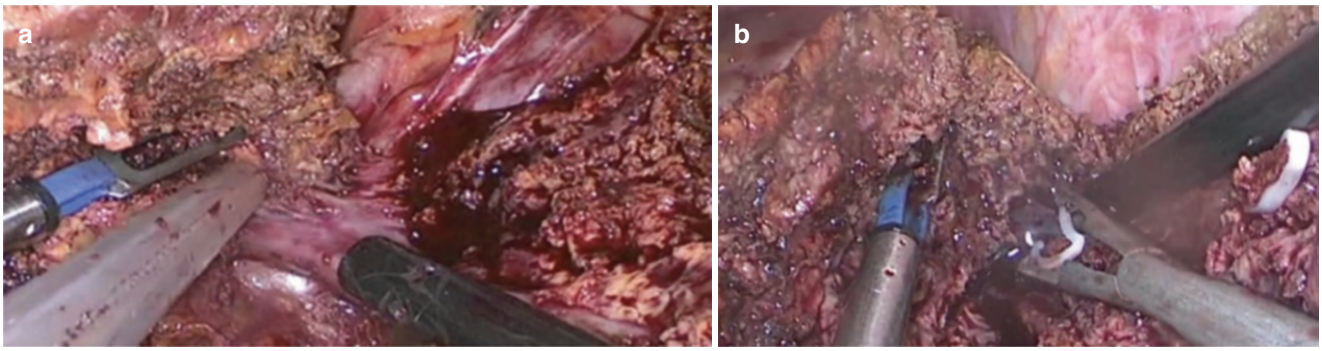

Fig. 13.10 (**a**) For dissection of deeper parenchyma, prior identification and selective hemostasis of larger vessels are advised. We recommend the use of an ultrasonic aspirator (CUSA). (**b**) Hemostasis is achieved through bipolar cautery or clips, according to the size of the vessels. Staplers are used for portal pedicles and main hepatic veins

The use of abdominal drainage depends on surgeon preference. It is often used in case of major resections. The fascia of port sites of 10 mm or more should be closed. The skin of the extraction and port-site incisions is closed with absorbable subcuticular sutures. Postoperatively, patients were transferred to the step-down unit for 24 h after which they were transferred to the surgical ward, unless their condition mandated continuous monitoring. On the surgical ward, the patients received prophylactic anticoagulation, proton pump inhibitors, intravenous fluids until satisfactory oral intake was achieved, respiratory physiotherapy, and early mobilization.

13.9 Conclusions

LLR for CLM is a safe and feasible procedure when performed by appropriately trained surgeons. In well-selected patients, it offers considerable perioperative benefits and superior short-term results compared with open hepatectomy with comparable oncologic and survival outcomes. As such, every liver surgeon should strive to include this requisite skill set in their technical armamentarium. Laparoscopic complex hepatectomies for CLM (repeat liver resection, TSH, ALPPS) are now increasingly reported, but require high levels of expertise. We await the results of RCT in order to further advance the management of this disease.

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14 Laparoscopic Anatomical Liver Resection Technique: The Japanese Experience

Kohei Mishima and Go Wakabayashi

Learning Objectives

- The indications of laparoscopic anatomical liver resection for liver malignancies are expanding, and many institutions have reported their efforts to standardize the surgery.
- Laennec's capsule is the anatomical landmark for the Glissonean approach and "Gate theory" allows for the performance of the procedure with reproducibility.
- Hepatic veins are important anatomical landmarks for parenchymal transection and the craniocaudal approach has the advantage of preventing venous bleeding.

14.1 Introduction

Since the first case was reported in 1991 [1], laparoscopic liver resection (LLR) has become widespread worldwide in the last 30 years [2]. During this period, two international consensus conferences [3, 4] were held to discuss a wide range of topics, including standardization of terminology [3], difficulty scoring system [5, 6], and recommendations from experts on surgical techniques [4]. In Japan, the proportion of LLR in total liver resections has increased from 9.9% in 2011 to 24.8% in 2017, according to a nationwide survey of the national clinical database (NCD) [7]. Because short-term outcomes of LLR were superior to those of open LR (OLR) [7], there is currently a tendency to apply LLR to more advanced cases in Japan. Hence, indications of laparoscopic anatomical liver resection (LALR) for liver malignancies are expanding, and many institutions have reported efforts to standardize the surgery. Here, we describe the current status of LLR for colorectal liver metastasis (CRLM) in Japan, focusing on surgical techniques of LALR.

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14.2 Techniques Based on the Anatomical Landmarks for LALR

14.2.1 Glissonean Approach

14.2.1.1 Anatomical Landmarks for Glissonean Approach

Takasaki reported the Gllisonean pedicle isolation technique for anatomical liver resection (ALR) as Glissonean approach (Fig. 14.1), and proposed a novel liver segmentation as the cone unit, in which the region of the liver is defined by the tertiary branch of Glissonean pedicles [8]. From the anatomical point of view, the Glissonean pedicle is surrounded by connective tissue referred to as the Walaeus sheath, and Laennec's capsule is the membrane that covers not only the entire surface of the liver but also the intrahepatic parenchyma surrounding the Glissonean pedicles (Fig. 14.2) [9]. Sugioka et al. proposed a systematic extrahepatic Glissonean pedicle isolation technique for ALR based on Laennec's capsule (Fig. 14.3) [9]. Appropriate starting points of the Glissonean approach are the gaps between Laennec's capsule and the Glissonean sheath, and can precisely be defined as "Gates" [9]. Several anatomical landmarks for identifying six gates were reported including the Arantius plate, the umbilical plate, the cystic plate, and the Glissonean pedicle of the Caudate process (G1c) [9].

14.2.1.2 Techniques of Glissonean Approach for LAR at Ageo Central General Hospital

Left Hepatectomy

The Arantius ligament is used as a landmark for extrahepatic isolation of the left Glissonean pedicle (Glt) and a guide for surgeons to achieve an optimal plane during surgery [10].

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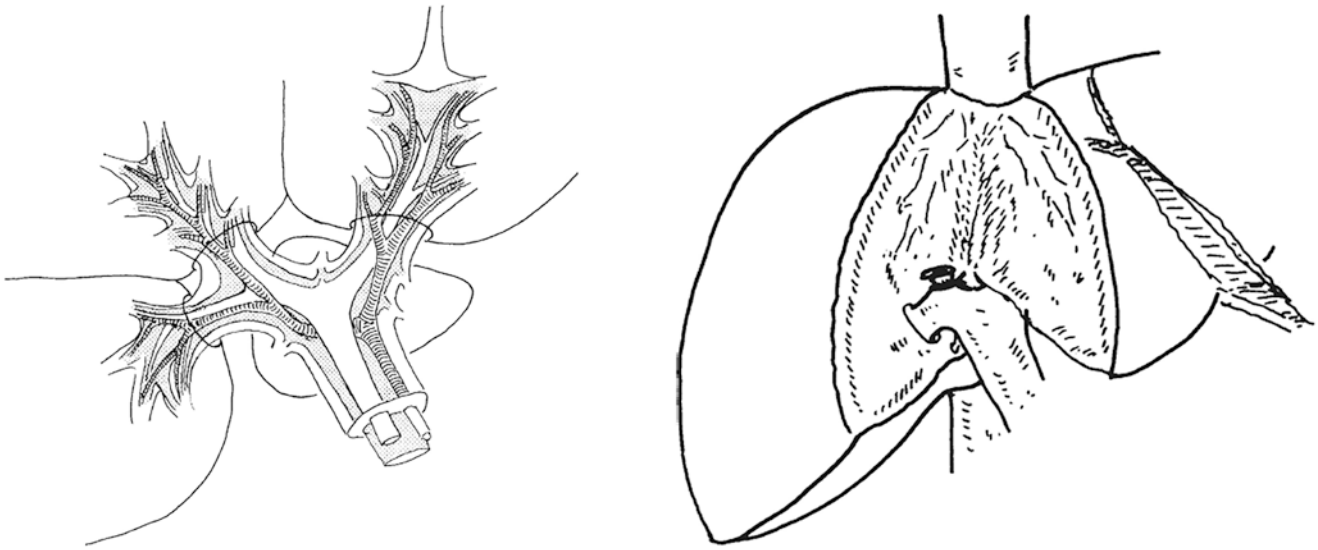


Fig. 14.1 Takasaki's Glissonean approach for ALR [8]

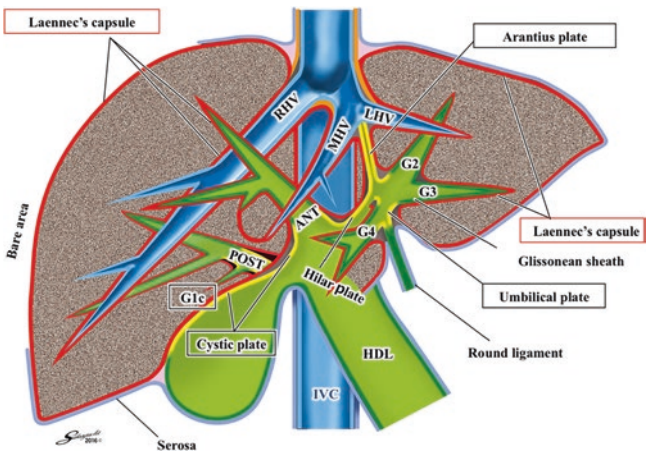


Fig. 14.2 The concept of Laennec's capsule [9]

The Glt isolation should start from detaching the Arantius ligament from Laennec's capsule to identify Gate I, followed by detaching the right edge of the Glt at Gate III. The Glt could be isolated by connecting these two gates (Fig. 14.4).

Right Anterior Sectionectomy

Glissonean pedicle isolation of the right anterior pedicle (Gant) should start from detaching the cystic plate from Laennec's capsule covering the cystic fossa [9]. Once Gate IV and V are identified, the right Gant could be isolated by connecting two of these three gates (Fig. 14.5).

Laparoscopic Parenchymal-Sparing Anatomical Liver Resection (Lap-PSAR)

In 2019, we reported a novel technique of Lap-PSAR with the Glissonean approach [11]. The liver segmenta-

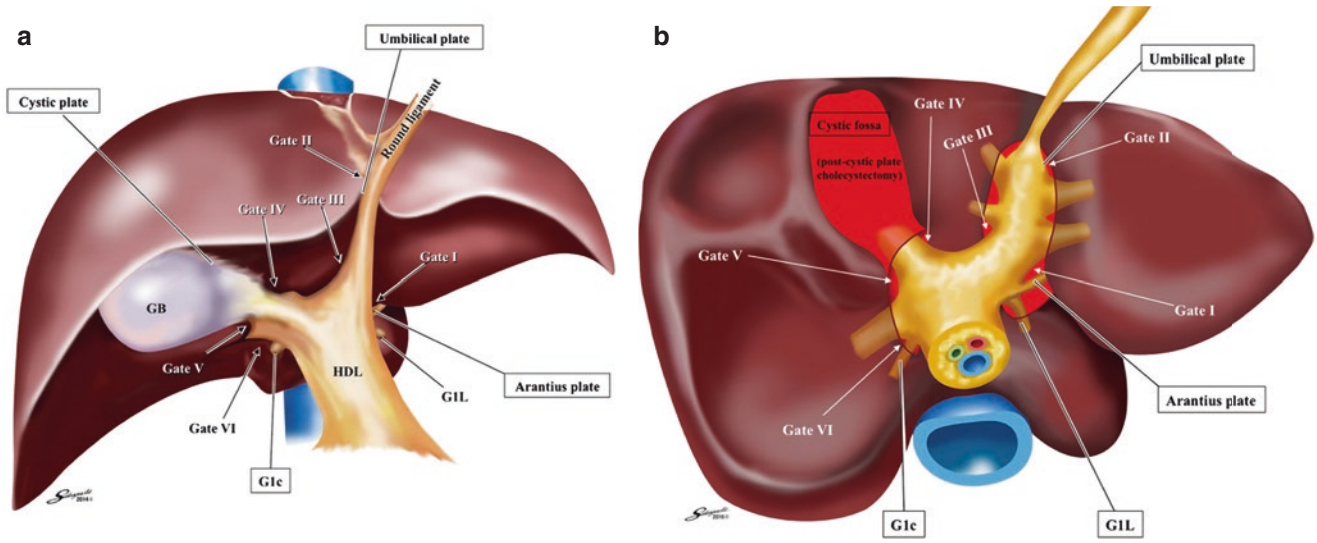


Fig. 14.3 ((**a**) The schema of the four anatomical landmarks and six gates in the frontal view, (**b**) The schema of the six gates and Laennec's capsule in the caudal view). Sugioka's "Gate" theory and extrahepatic Glissonean pedicle isolation technique [9]

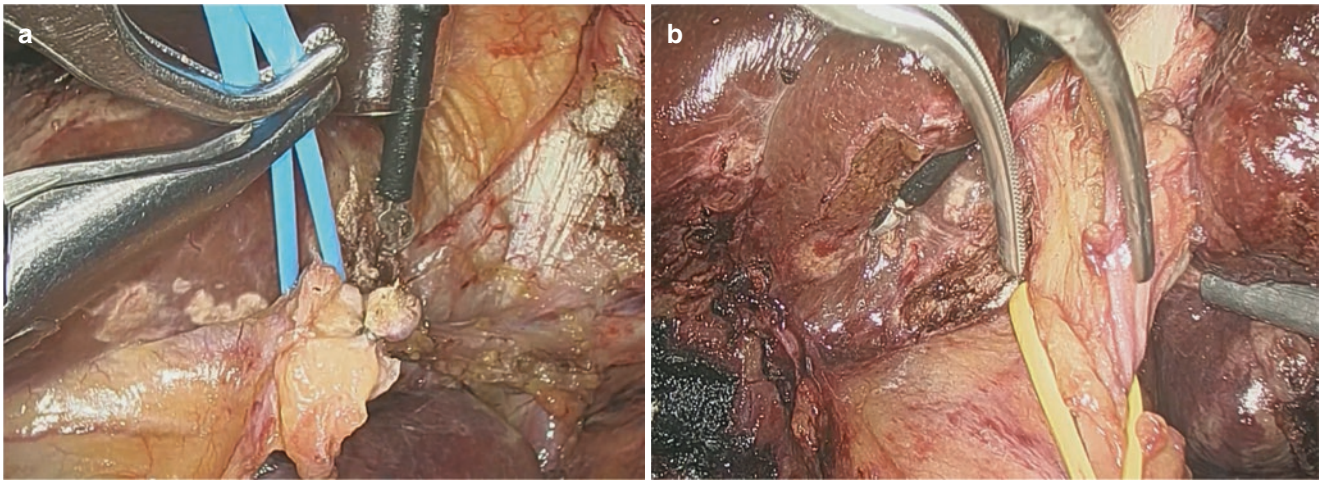


Fig. 14.4 Glissonean approach for laparoscopic left hepatectomy ([**a**] encircling the Arantius' ligament, [**b**] clamping the Glt)

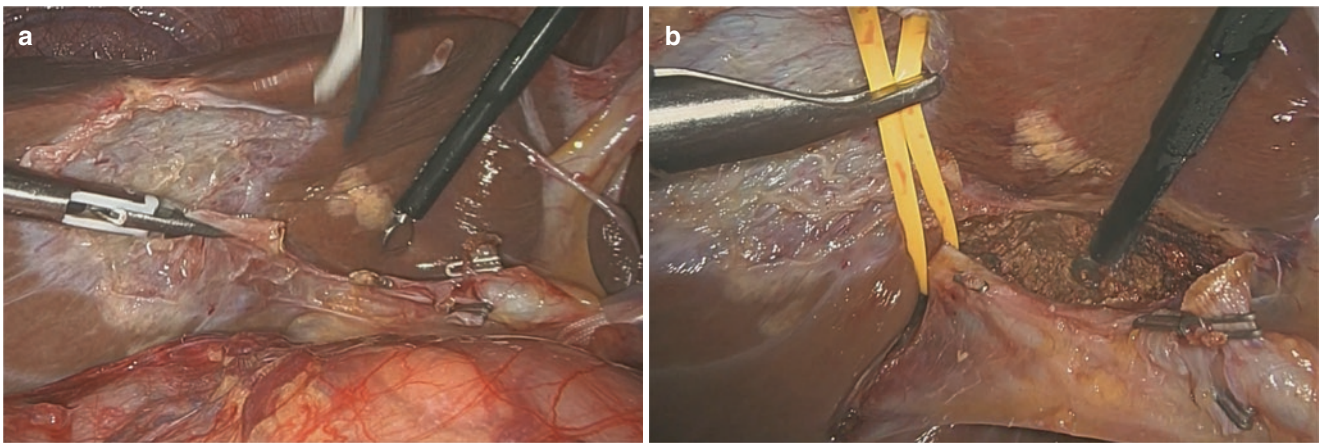
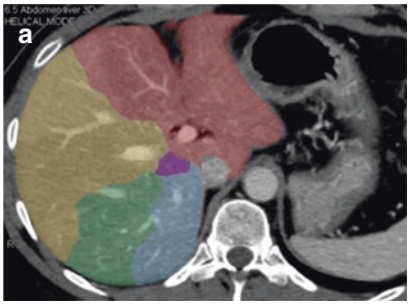


Fig. 14.5 Glissonean approach for laparoscopic right anterior sectionectomy ([**a**] cholecystectomy with cystic plate transection, [**b**] encircling the Gant)

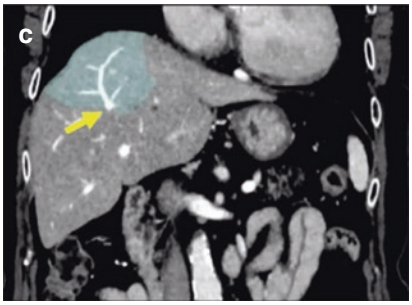
tion of Lap-PSAR is based on the tertiary branch of Glissonean pedicles (=Takasaki's cone unit concept [8]). Precise preoperative planning and a standardized surgical technique enable the performance of this procedure (Fig. 14.6).

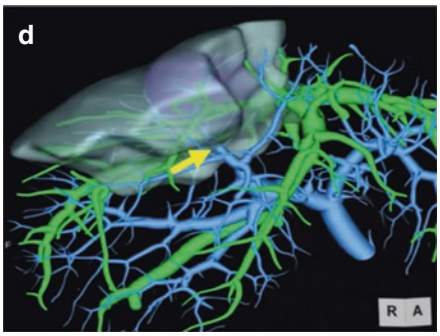
During segmentectomy for a left-sided lesion, we routinely dissect and transect small Glissonean pedicles one by one and encircle the targeted pedicles (Fig. 14.7).

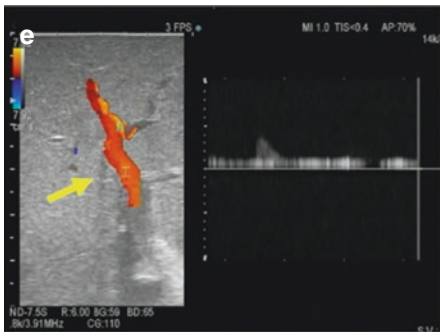
Segmentectomies for right-sided lesions are more technically demanding. Glissonean approach for superior-posterior lesions (Segment 7 or 8) usually requires a subtraction method for encircling targeted pedicles (Figs.14.8 and 14.9). Because the procedure is complicated and takes longer surgical time compared to segmentectomies for left-sided lesions, surgeons should try to gently encircle the Glissonean pedicles to prevent postoperative bile leakage.



LIVER AREA	VOLUME (cc)	%
Total Liver Volume	1274 cc	100%
Remnant Liver Volume	1077 cc	84.6%
Right Lobe	821 cc	64.4%
S8	196 cc	15.5%
S8 Dorsal	165 cc	13%
S8 Ventral	31 cc	2.5%
S7	189 cc	14.8%
S6	203 cc	15.9%
S5	233 cc	18.2%







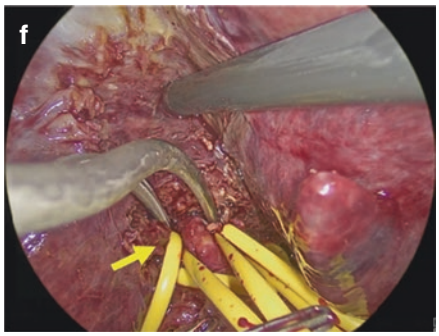
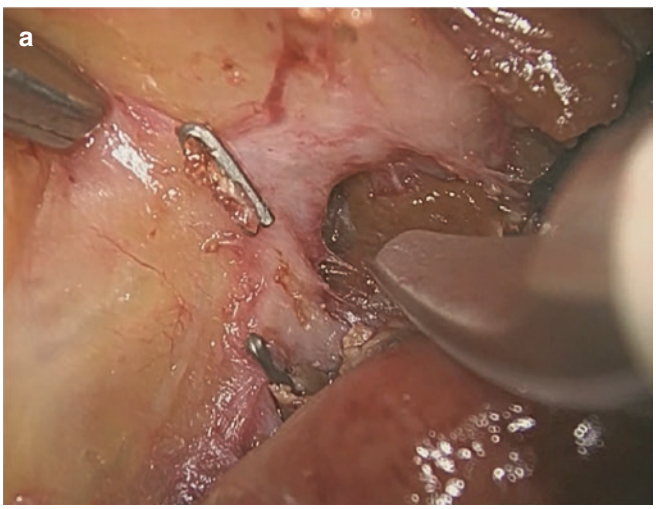


Fig. 14.6 ((**a**) Axial images of preoperative CT. (**b**) Preoperative assessment of the resection area and volume. (**c**) Preoperative CT showing S8 dorsal area (in blue) and S8 dorsal Glissonian pedicle (arrow). (**d**) 3D simulation of resection showing the tumour (purple), S8 dorsal area (blue), and S8 dorsal Glissonian pedicle (arrow). (**e**) Intraoperative ultrasonography: S8 dorsal Glissonian pedicle is identified (arrow). (**f**) S8 dorsal Glissonian pedicle is clamped). Precise preoperative simulation and Glissonean approach for Lap-PSAR [11]



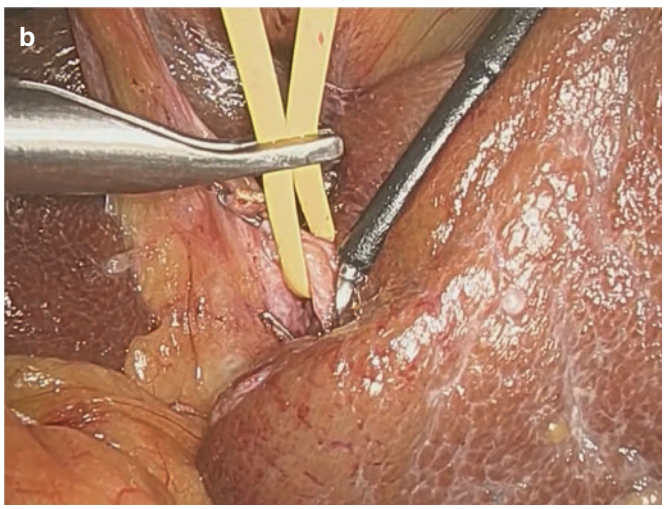


Fig. 14.7 Segmentectomy (Segment 3 resection) ([**a**] transection of small Glissonean pedicles, [**b**] encircling main G3 trunk)

14.2.2 Parenchymal Transection on the Intersegmental Planes

14.2.2.1 Anatomical Landmarks for the Hepatic Veins

A common disadvantage of LLR is that the surgeon may become disoriented due to the following reasons: (a) difficulties in generating an overview of the liver; (b) difficulties with tactile feedback; and (c) restriction of manipulation [12]. Transecting the liver parenchyma along with hepatic veins is useful for avoiding disorientation during LAR [13]. There are several anatomical landmarks for exposing the hepatic veins.

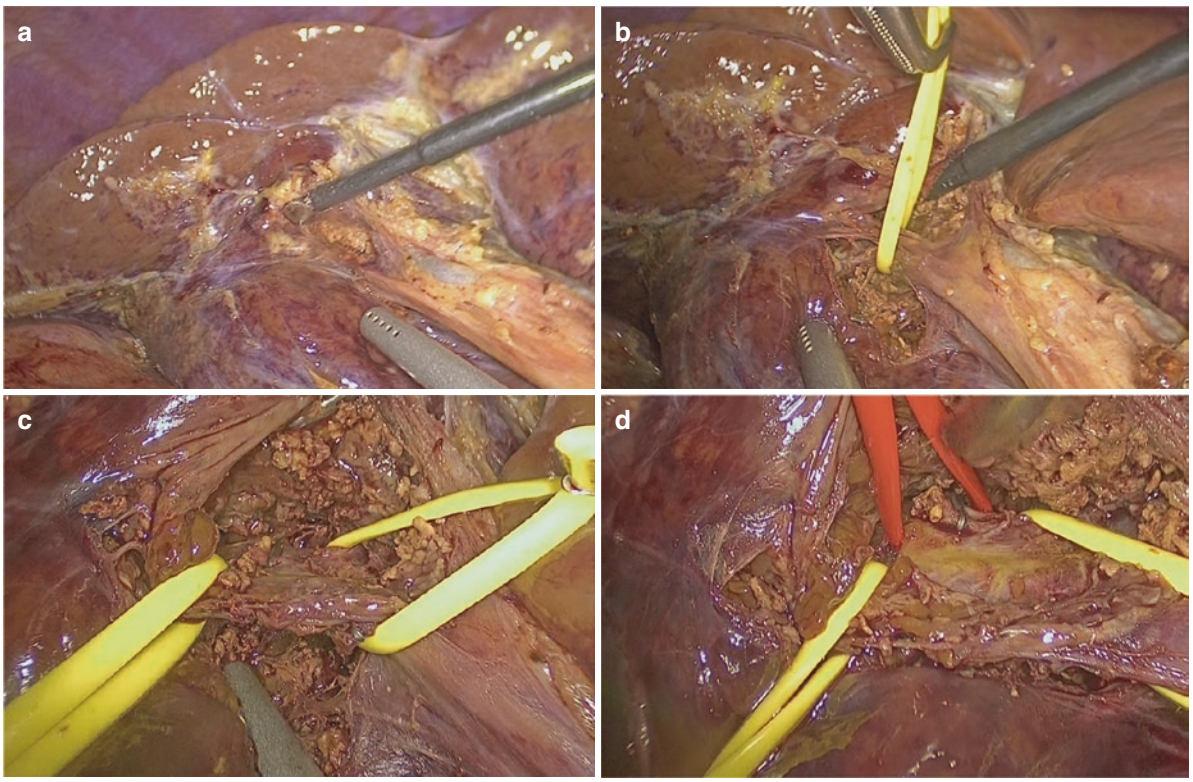


Fig. 14.8 Segmentectomy (Segment 7 resection) ([**a**] cholecystectomy, [**b**] encircling G6, [**c**] encircling Gpost, [**d**] subtraction method for encircling G7)

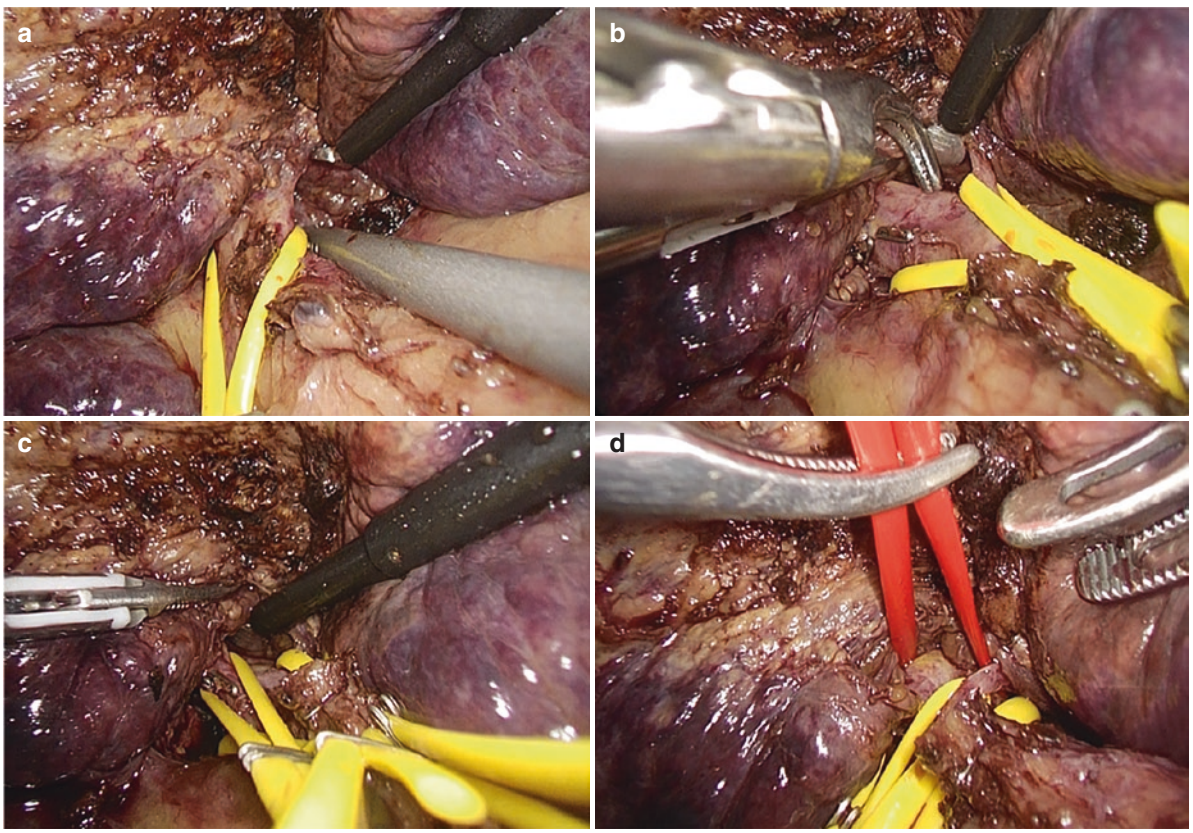


Fig. 14.9 Segmentectomy (Segment 8 resection) ([**a**] encircling G ant, [**b**, **c**] encircling G5s, [**d**] subtraction method for encircling G8)

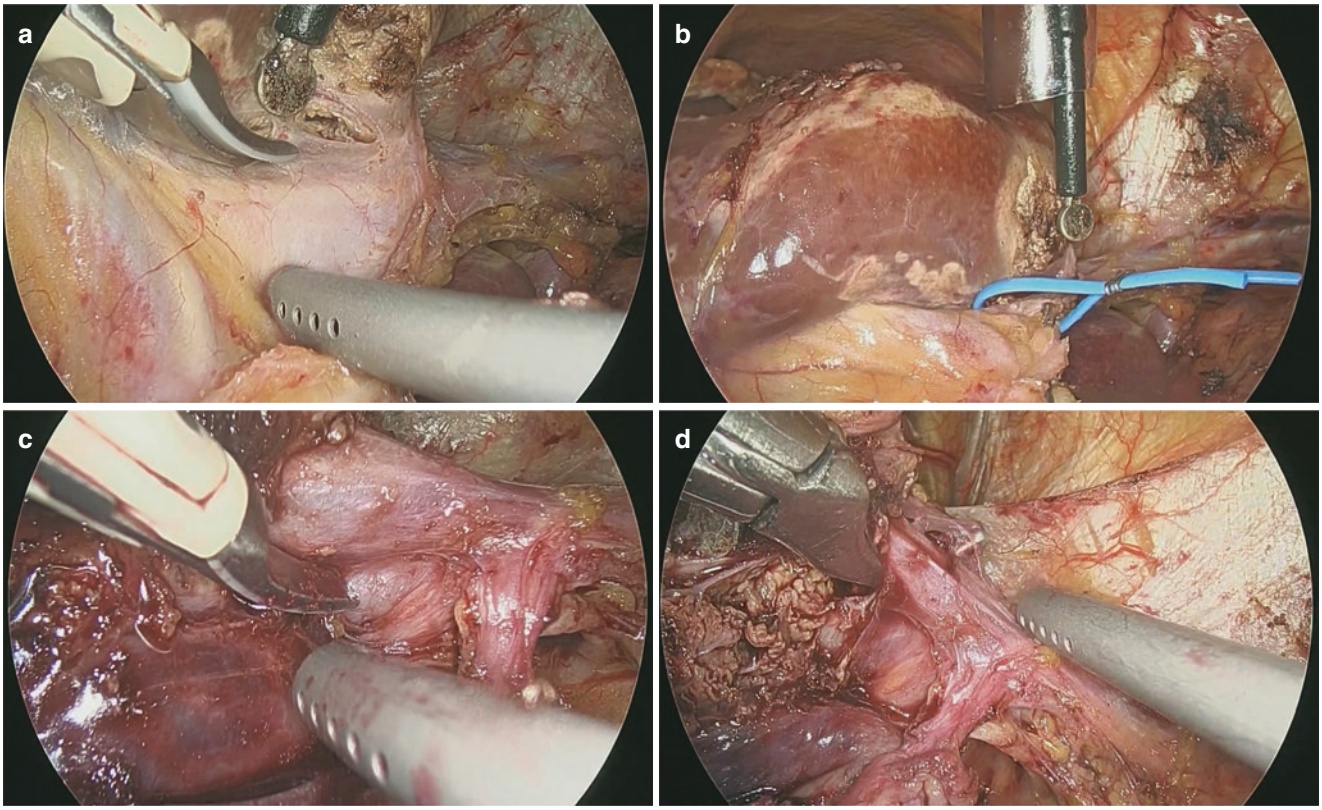


Fig. 14.10 Isolation of the LHV for laparoscopic left hepatectomy ([**a**] dissecting around Arantius' ligament, [**b**] encircling the Arantius' ligament, [**c**] separating the MHV and LHV, and [**d**] encircling the LHV)

Inferior Phrenic Vein (IPV)

The right IPV drains into the inferior vena cava (IVC)—inferior to the diaphragm— in 90% of cases, and into the right HV in 8% of cases [14]. The left IPV drains into the IVC—inferior to the diaphragm—in 37% of cases, and into the left HV in 14% of cases [14].

Arantius Ligament

The Arantius ligament is a thin fibrous cord that is a remnant of the ductus venous; it extends from the left branch of the portal vein to either the IVC or the root of the left HV [10]. Transection of the Arantius ligament usually facilitates the encircling of the left hepatic vein (LHV) (Fig. 14.10).

14.2.2.2 Approaches for Exposing the HVs

Overall, two main HV approaches were described: (a) from the root to the peripheral side of the HV, and (b) from the peripheral side to the root of the HV (Fig. 14.11) [13]. Many studies demonstrated the techniques and described the advantages of exposing the HVs from the root side to the peripheral side branches [15]. Awareness of both the devices' vectors of movement and the exposure of the HVs in a cranial direction was emphasized to avoid split injuries (Fig. 14.12) [13, 15].

14.2.2.3 Parenchymal Transection under Indocyanine Green (ICG) Fluorescence Image Guidance at Ageo Central General Hospital

1. Left hepatectomy using the dorsal approach (Fig. 14.13).
2. The MHV was exposed from the root side toward the periphery using a dorsal approach in laparoscopic left hepatectomies. Apart from avoiding split injuries, the dorsal approach prevents blood from pooling at the dissection site, as blood spontaneously flows from the upper portions of the liver to the lower portions.
3. Right hepatectomy with the caudate lobe-first approach (Fig. 14.14).

For right hepatectomy, we use the caudate lobe-first approach. This refers to the early exposure of the roots of the right and middle HV (RHV and MHV) by first dividing the caudate lobe [16]. The main trunk of the HVs can be continuously exposed from the root side to the periphery. This approach prevents split injuries, which can cause severe bleeding at the confluences of the HV branches.

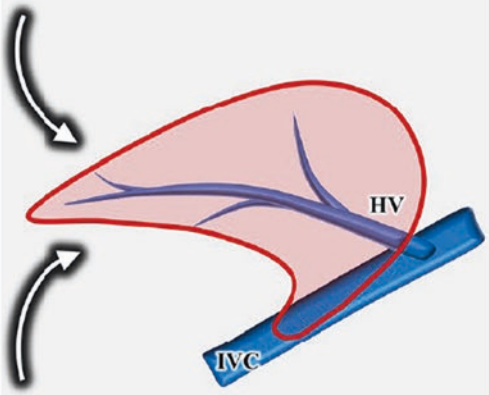
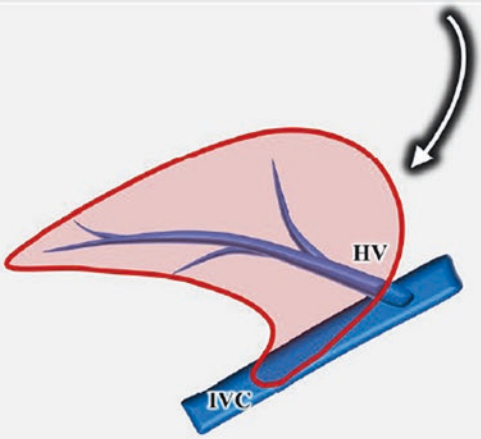
The names of approaches	Caudal approach [43, 64, 65] Caudo-dorsal approach [18]	Ventral approach [5, 44, 45, 49] Cranial approach [61, 62, 65] Cranial-to-caudal approach[67]
Direction of the hepatic venous exposure	Periphery to root	Root to periphery
		

Fig. 14.11 Approaches for exposing the HVs

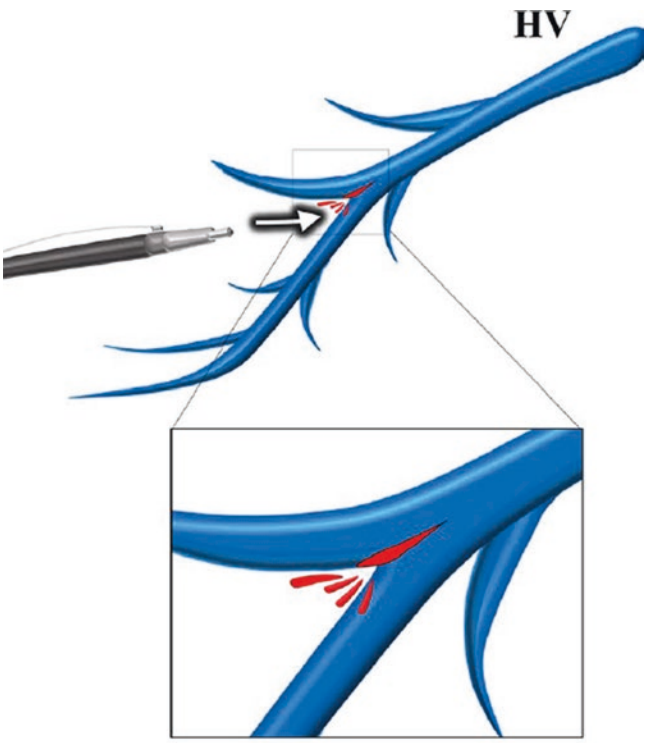


Fig. 14.12 Split injury of the HV due to CUSA being moved from the peripheral side to the root side [13]

14.3 Future Prospects (The Long-Term Advantages of LLR for CRLM)

The long-term advantages of LLR over OLR for CRLM have not yet clearly shown. In 2020, Syn et al. [17] reported that LLR was associated with longer survivals than OLR for patients with CRLM with a meta-analysis of 15 studies (two randomized-controlled and 13 propensity-matched studies). Although various biases need to be considered in the results of this article, an earlier induction of chemotherapy, a lower postoperative complication rate [7], and easier access for repeat hepatectomy [18] may contribute to the improvement of prognosis in combination. Many issues need to be investigated in the future, including the indications for LLR for multiple colorectal liver metastases and the impact of LAR on prognosis.

14.4 Conclusion

Currently, in the process of pursuing the efficiency and safety of LAR, more anatomical findings and ingenuity of surgical techniques have been reported. We believe that these efforts will contribute to the further spread of this surgery worldwide.

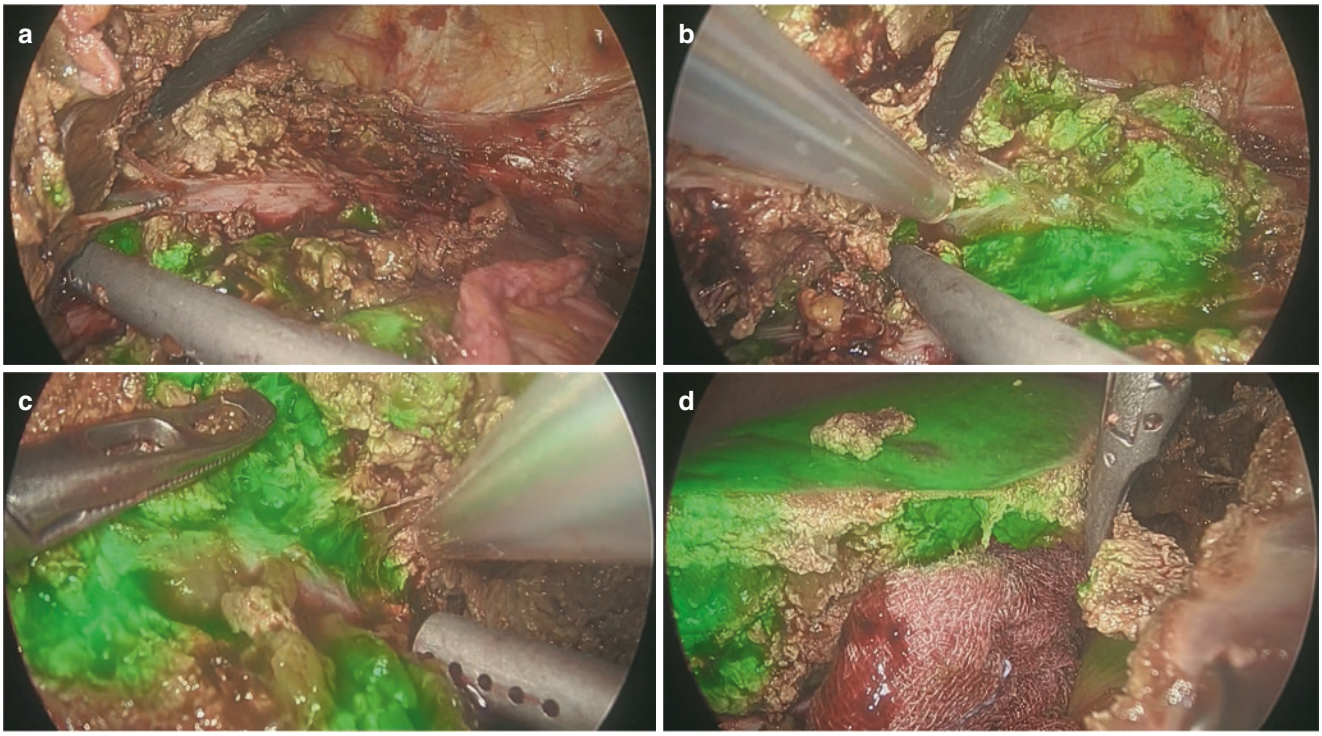


Fig. 14.13 Laparoscopic left hepatectomy with dorsal approach ([**a**] Parenchymal transection along with the MHV from the root side, [**b**] ICG fluorescence guidance matching the intersegmental planes formed by the MHV, [**c**] peripheral side of the MHV, and [**d**]. completion of the specimen removal)

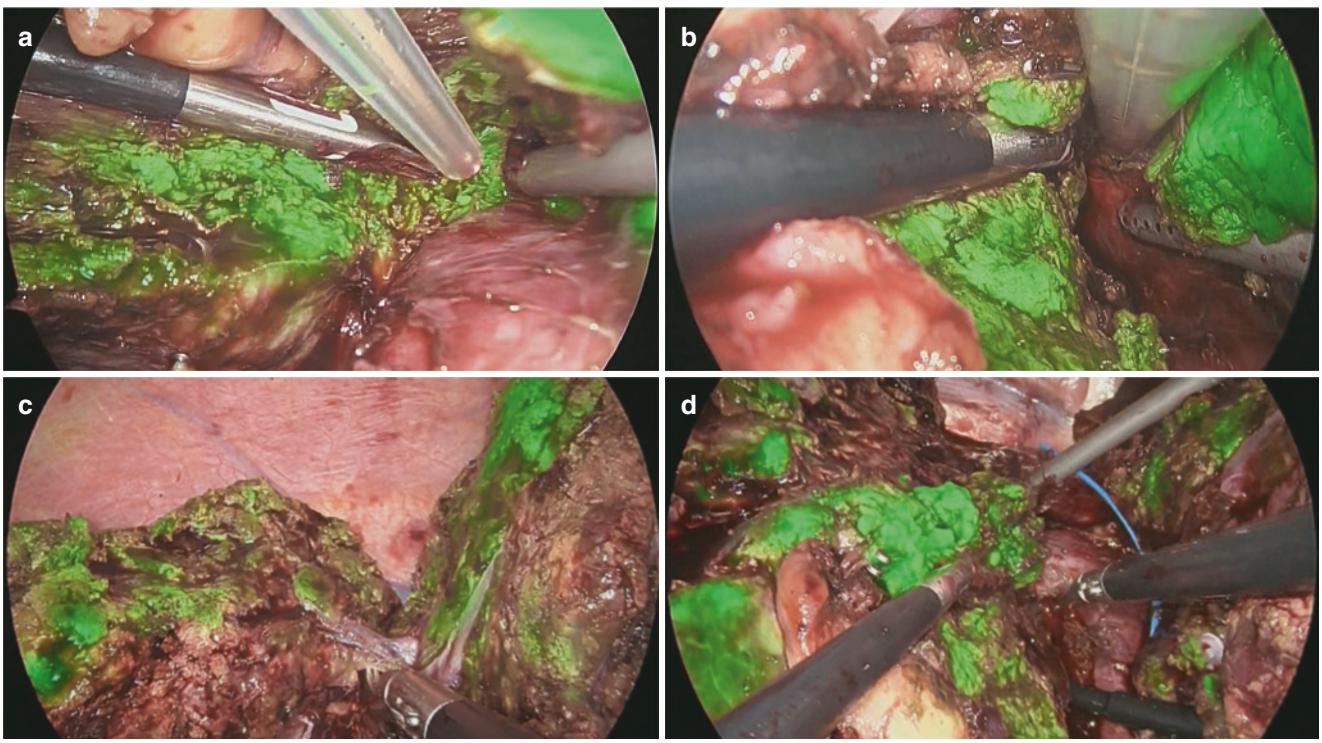


Fig. 14.14 Laparoscopic right hepatectomy with the caudate lobe-first approach ([**a**] Parenchymal transection of the caudate lobe just above the IVC, [**b**] exposing the root of the RHV and MHV, [**c**] parenchymal transection under ICG fluorescence guidance and the MHV, and [**d**] completion of the specimen removal)

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Is There a Place for Robotic Resection?

15

Andrew D. Newton and Hop S. Tran Cao

Learning Objectives

- To understand the current literature on minimally invasive surgery for colorectal liver metastases
- To describe the benefits of robotic surgery in the resection of colorectal liver metastases
- To recognize the limitations of robotic surgery in the resection of colorectal liver metastases
- To describe the technical approach to robotic liver surgery

15.1 Introduction

Hepatobiliary surgery is one of the final frontiers of minimally invasive surgery due to the complex three-dimensional anatomy and dense vascularity of the liver. The first laparoscopic liver resection was reported in 1991 [1], but it took 17 years until consensus guidelines for laparoscopic hepatectomy were reported in the Louisville statement. The consensus opinion among the experts was that "the best indications for laparoscopic liver resection are in patients with solitary lesions, 5 cm or less, located in the peripheral segments (segments 2–6)" [2]. While they conceded that most liver resections can be performed laparoscopically in experienced hands, there are inherent limitations of laparoscopic equipment that make some liver resections particularly challenging with this approach. Meanwhile, the first reports of robotic hepatectomy were published in 2003 [3, 4]. The robotic platform affords certain advances and advantages over laparoscopy that facilitate technically challenging liver resections.

Colorectal liver metastases (CLM) represent the most common indication for hepatectomy in the United States, and as more hepatobiliary surgeons gain experience with the robotic platform, the number of robotic resections of CLM will undoubtedly increase. In this chapter, we will summarize the advantages and limitations of robotic hepatectomy, the existing data on perioperative and oncologic outcomes for CLM, and share our approach to robotic hepatectomy, including patient selection, technical considerations, and perioperative management.

15.2 Rationale for Minimally Invasive Resection of Colorectal Liver Metastases

15.2.1 Laparoscopic Hepatectomy

Retrospective studies demonstrate improved perioperative outcomes with laparoscopic compared to open resection of CLM [5–7]. Reported advantages of laparoscopy over open surgery include fewer complications, fewer transfusions, less blood loss, and shorter stay [8–10]. It is thought that the pneumoperitoneum used during minimally invasive surgery tamponades bleeding during parenchymal transection to some extent, thus reducing blood loss. These perioperative benefits may translate into improved quality of life with laparoscopic compared to open hepatectomy [11]. Two randomized controlled trials and high-quality propensity-matched studies suggest long-term oncologic outcomes for patients with CLM are at least non-inferior with laparoscopic compared to open resection [12, 13]. However, laparoscopy presents several technical disadvantages to the surgeon including poor ergonomics and long rigid instruments with limited degrees of freedom. Laparoscopic resection of tumours in the posterosuperior segments is particularly challenging.

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15.2.2 Theoretical Advantages of a Robotic Approach

The robotic platform theoretically provides all the advantages of laparoscopy over open surgery with regard to postoperative recovery due to smaller incisions. In addition, there are several aspects of the robot that provide technical advantages over laparoscopy. These include wristed articulating instruments at the end of long shafts, which have more degrees of freedom and allow for a longer reach, a tremor filter, and elimination of hand dominance [14]. These features make it easier to work in difficult-to-reach or small spaces and to suture intracorporeally (Fig. 15.1). Another major advantage of the robot is improved visualization thanks to a high-definition camera providing stable three-dimensional images, controlled by the operating surgeon rather than the assistant. Likewise, the long camera shaft allows for further reach and looking over and around the curvature of the liver.

Robotic surgery is also less physically demanding than laparoscopic surgery as demonstrated by EMG recordings and postural observations of surgeons during robotic and laparoscopic surgery. During robotic compared to laparoscopic surgery, the surgeon experiences decreased neck muscle activity, static shoulder muscle activity, forearm muscle activity, need to change posture, and perceived exertion, with increased micropauses [15, 16]. As the importance of ergonomics in surgery becomes increasingly recognized, the impact of robotic surgery on surgeon comfort and performance may soon be better defined.

The robotic platform is particularly advantageous for CLM, which can be multiple and in disparate parts of the liver. With laparoscopy, resection of metastases that are far from one another, especially if in separate segments (e.g., segment 7 and segment 1), may require vastly different positioning and port placement. For example, a tumour in segment 7 is best approached with the patient in left lateral decubitus position, while a tumour in the left lateral section would necessitate supine positioning. With robotic surgery, nearly all tumours can be approached with the patient in supine position, with only slight variations in port placement for disparate portions of the liver. When necessary, an additional robotic trocar may be placed, and port-hopping, combined with paired or unpaired bed tilting, can allow safe resection of tumours.

Another advantage of the robotic system is ubiquitous availability of built-in near-infrared (NIR) fluorescence imaging capability. The fluorescent imaging system is designed for detection of indocyanine green (ICG), a water-soluble small molecule (775 Da) that rapidly binds albumin in circulation. One of the more common applications of fluorescence imaging with ICG is for the purpose of tissue perfusion evaluation. Examples include examination of the blood supply to bowel anastomoses or reconstructive soft tissue flaps [17, 18]. In liver surgery, this same principle is useful in identifying individual hepatic segments or perfusion to a lobe of the liver during anatomic resections [19–21]. After clamping of the Glissonean pedicle to a segment or the inflow to a hepatic lobe, a small dose of ICG (0.25–5 mg) is injected systemically and fluorescence imaging is used to map the line of demarcation for that segment or lobe (Fig. 15.2). Additionally, a unique benefit of ICG in hepatobiliary surgery rests in its metabolic clearance. Indeed, ICG is processed in the liver and excreted in bile, passing through the biliary tree as a result. This has led some surgeons to advocate for its routine use in the performance of cholecys-

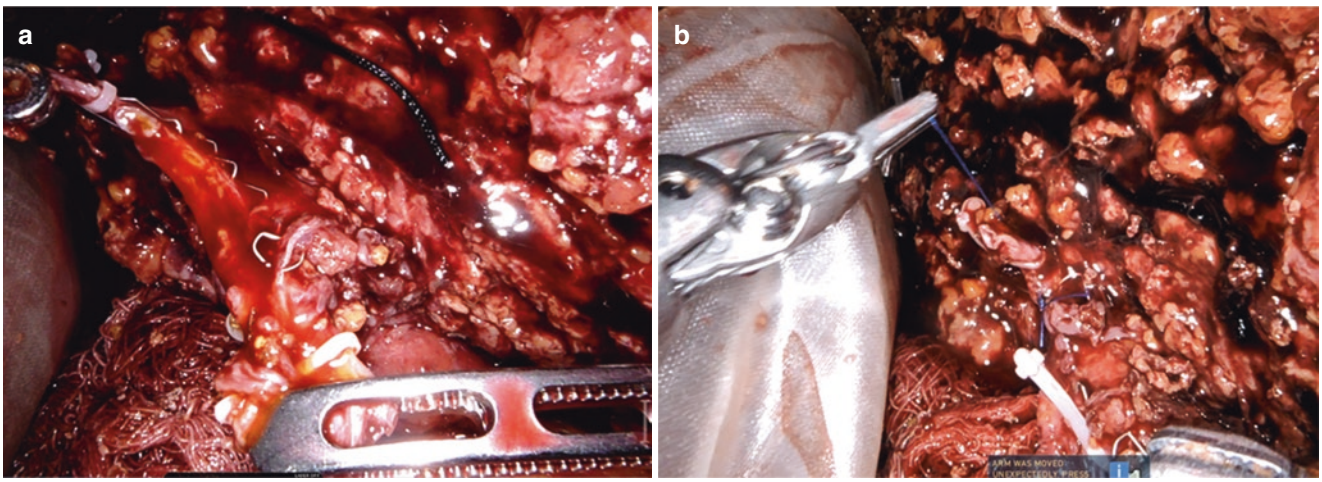

Fig. 15.1 A staple line disruption (**a**) is easily sutured and repaired (**b**) with the wristed instruments available on the robotic platform

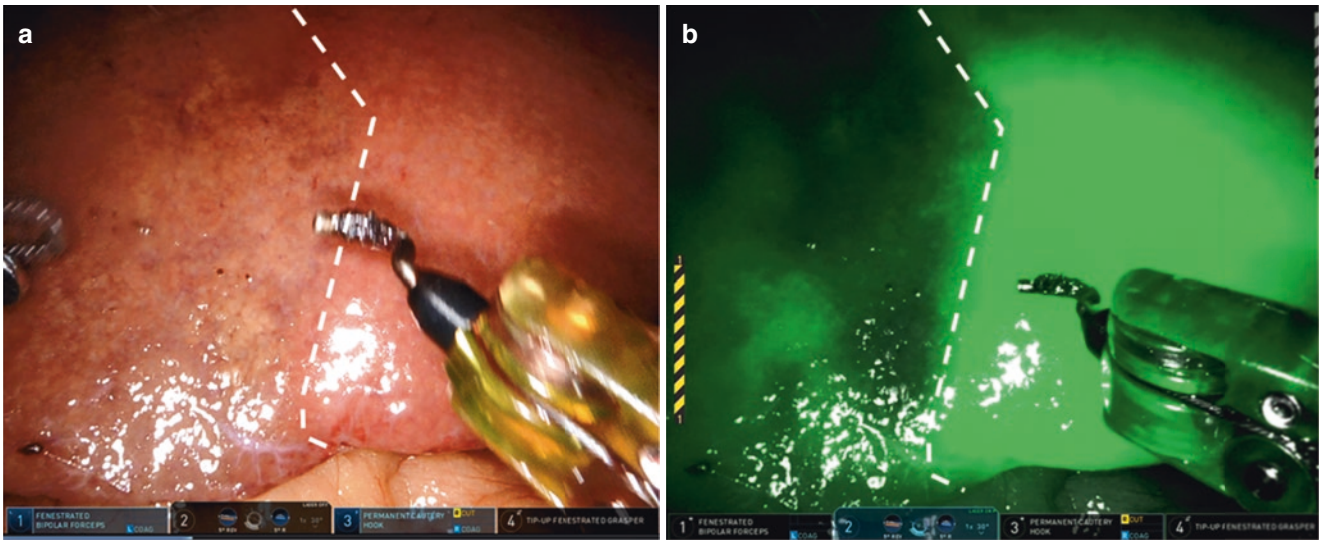

Fig. 15.2 (**a**) White light and (**b**) near-infrared images from right hepatectomy after the clamping of the right hepatic inflow. The white dashed line indicates the line of demarcation, which is more obvious with the aid of fluorescence imaging

tectomy to decrease the risk of bile duct injury. When surgery for CLM is performed, bile ducts can be identified by obtaining fluorescence imaging approximately 15 min or more after ICG injection, which may aid in distinguishing biliary from vascular structures. By the same concept, ICG may be helpful in identifying bile leaks following liver transection. While some have described performing bile leak tests via ICG cholangiography through a transcystic ICG injection and distal bile duct occlusion [22, 23], we have not felt this to be necessary. Instead, thanks to the magnified view afforded by the robot, close inspection of the parenchymal transection surface may detect bile leaks when fluorescent fluid is seen pooling or excreting from the liver surface after the pre-transection systemic injection of ICG. Finally, ICG has also been reported to be helpful in identifying occult tumours, including CLM [24–26]. When given intravenously a day or more before surgery, ICG will accumulate around metastases due to impaired biliary excretion of the dye from hepatocytes surrounding the tumour.

Laparoscopic NIR imaging systems do exist, but they often require additional equipment that is not built in to standard laparoscopic equipment, and those with integrated NIR imaging are not commonly available in most operating rooms. Therefore, these systems require additional training of the operating room staff on their use. On the other hand, the Da Vinci® system is the only commercially available robotic platform currently used for all robotic surgeries in the United States, and its built-in Firefly™ feature requires no additional training, as the surgeon can easily alternate between white light and NIR images on the surgeon's console.

15.3 Learning Curve

The learning curve for laparoscopic hepatectomy is steep, at approximately 45–75 cases [27–29]. It may be even steeper for the most difficult resections. In one recent study, 65 anatomical resections of the posterosuperior segments were required to reach the peak of the learning curve [30]. On the other hand, the learning curve may be shorter as pioneers of laparoscopic liver surgery train the next generation [31]. By comparison, even in these relatively early stages of robotic hepatectomy, the learning curve appears to be favorable and may require as few as 16–30 cases [32–34]. Efanov et al. found that only 16 cases were necessary to increase the rate of posterosuperior segment resection and the overall difficulty index of operations with the robotic approach. With laparoscopy, on the other hand, 29 cases were necessary to increase the rate of posterosuperior segment resection, and no increase in the overall difficulty index was seen even after 91 cases [34].

15.4 Robotic Hepatectomy Outcomes

The first large series of robotic hepatectomy published by Guilanotti et al. in 2011 demonstrated that both major and minor hepatectomy could be performed safely with acceptable conversion rates, blood loss, and postoperative complication rates [35]. In their study of 27 major (≥3 liver segments) and 43 minor hepatectomies, the conversion rate was 5.7%, the median blood losses were 300 and 150 mL, and the major morbidity rates were 14.8% and 9.3% for

major and minor hepatectomy, respectively. Since that report, numerous retrospective studies have compared perioperative and oncologic outcomes between robotic and open or laparoscopic hepatectomy. Here we summarize select comparisons with substantial sample size.

15.4.1 Robotic Versus Open Perioperative Outcomes

The benefits in postoperative recovery with a minimally invasive approach to liver resection are well established through comparisons of the laparoscopic and open approaches; consequently, few studies have sought to compare robotic and open approaches. However, a comparison of robotic and open approaches for tumours in the posterosuperior segments is relevant as even skilled laparoscopists may choose an open approach for these tumours, which are difficult to reach with laparoscopy. In the largest comparison of robotic and open hepatectomy, 64 patients in each group were propensity matched by diagnosis and segments resected [36]. Robotic hepatectomies had less blood loss and shorter stay. Interestingly, robotic hepatectomies also took less time on average. In a retrospective matched comparison of 31 robotic and 31 open resections of only the posterosuperior segments, the median length of stay was 4 versus 8 days, $p < 0.001$, with no other differences in perioperative outcomes between the groups [37]. This study suggests the incision is the predominant factor contributing to the length of stay following hepatectomy. A study by the same group demonstrated that fast-track discharge is possible after robotic hepatectomy; in 97 consecutive hepatectomies approached robotically, over two-thirds of patients had a length of stay ≤3 days, and 14 patients were discharged on the day of surgery [38].

15.4.2 Robotic Versus Laparoscopic Perioperative Outcomes

Comparisons of robotic versus laparoscopic hepatectomy for mixed tumour types have shown no differences in perioperative outcomes including blood loss, transfusion rate, length of stay, and postoperative complications [39–46]. While the operative time was longer with robotic compared to laparoscopic hepatectomy in most early series, operative times are more comparable in contemporary series as experience with robotic hepatectomy has grown. In the largest early comparison, Tsung et al. compared robotic ($n = 57$) and laparoscopic ($n = 114$) hepatectomy in patients matched 1:2 based on demographics, comorbidities, performance status, and extent of liver resection. There were no differences in blood loss, transfusion rate, postoperative peak bilirubin, postoperative intensive care unit (ICU) admission rate, length of stay, or 90-day morbidity [45]. Robotic resections had longer operative times, but major hepatectomies were more likely to be completed in a totally minimally invasive fashion. In a more contemporary comparison of all robotic ($n = 57$) and laparoscopic ($n = 116$) major hepatectomies at a single center from 2011 to 2016, there were no differences in complications, blood loss, operative times, or length of stay. Patients who underwent robotic major hepatectomy were admitted to the ICU less frequently and readmitted less frequently [46]. In a study designed primarily to examine long-term outcomes between robotic ($n = 115$) and laparoscopic ($n = 115$) hepatectomy for CLM, there were no differences in the rates of complications, serious complications, reoperations, ICU admission, or length of stay among propensity-matched patients [47].

15.4.3 Oncologic Outcomes

There are no major series comparing overall or disease-free survival with robotic versus open resection of CLM. In the largest comparison of oncologic outcomes with robotic versus open resection for any malignancy, there was no difference in outcomes between 81 robotic and 81 open propensity-matched resections of hepatocellular carcinoma including no differences in disease-free (72.2% vs. 58.0%, $p = 0.062$) or overall (92.6% vs. 93.7%, $p = 0.431$) survival [48].

Studies of the R1 resection rate and margin width with robotic versus laparoscopic hepatectomy show no differences in the R1 resection rate or margin width [42–44, 47, 49–54]. In the only study of long-term oncologic outcomes following robotic versus laparoscopic hepatectomy exclusively for CLM, outcomes were compared between 115 propensity-matched patients per group from six high-volume centers in the US and Europe. There was no difference with robotic versus laparoscopic resection in 5-year overall (61% vs. 60%, $p = 0.78$) or disease-free (38% vs. 44%, $p = 0.62$) survival [47]. Oncologic outcomes with respect to margins and survival in studies including patients with CLM are summarized in Table 15.1.

15.4.4 Cost

One of the major criticisms of the robotic approach to any surgical procedure is the cost. In a meta-analysis of studies with cost data available, robotic hepatectomy was more expensive than laparoscopic or open hepatectomy [55]. The mean cost was $20,205.92 with robotic hepatectomy,

Table 15.1 Summary of studies comparing oncologic outcomes with laparoscopic versus robotic resection of colorectal liver metastases

	Laparoscopic	Robotic				
Study	*N* (CLM)	*N* (CLM)	Margin width in mm	R1 resection	OS CLM	DFS CLM
Berber [49]	23 (14)	9 (4)	11 vs. 14 (NS)			NS
Troisi [50]	223 (108)	40 (24)		7.5 vs. 5.4 ($p = 0.71$)		3 year: 62 vs. 44 (NS)
Montalti [43]	72 (44)[a]	36 (21)[a]		11.1 vs. 12.5 ($p = 1$)	40.4 vs. 62.9 ($p = 0.24$)	46 vs. 33 ($p = 0.56$)
Croner [53]	19 (5)	10 (5)	5.7 vs. 7.6 ($p = 0.882$)	0 vs. 0		
Lee [42]	66 (8)	70 (13)	15 vs. 16 ($p = 0.815$)	1.8 vs. 1.6 ($p > 0.999$)		
Lim [44]	55 (11)[a]	55 (13)[a]	10 vs. 6 ($p = 0.054$)	6 vs. 9 ($p = 0.40$)		
Beard [47]	115 (115)[a]	115 (115)[a]		17 vs. 20 (NS)	61 vs. 60 ($p = 0.78$)	38 vs. 44 ($p = 0.62$)

CLM colorectal liver metastases, *OS* overall survival, *DFS* disease-free survival
[a]Number after propensity score matching

$15,789.75 with laparoscopic hepatectomy, and $14,027.18 with open hepatectomy. In the one study that demonstrated lower costs with robotic hepatectomy, perioperative costs were higher with the robot ($6026 vs. 5474, $p = 0.047$), but patients were discharged over 2 days earlier on average compared to open surgery, resulting in net lower total hospital direct costs ($14,754 vs. 18,988, $p = 0.001$) [56]. As surgeons become more comfortable with fast-track discharge following robotic hepatectomy, patients may be discharged even earlier, further reducing total hospital costs.

15.5 Limitations of Robotic Hepatectomy

Beyond cost, the robotic platform presents some limitations during liver surgery. First, the lack of haptic feedback translates into an inability to palpate the liver, which could result in missed small lesions or inadequate margins [2]. However, as mentioned above, studies of robotic versus open or laparoscopic hepatectomy for CLM have found no differences in the R1 resection rate or in overall or recurrence-free survival [12, 57, 58]. A second theoretical limitation of robotic surgery relates to the docking and undocking of the robot. This may be time-consuming and add to the overall time for the case; it also theoretically presents a danger when rapid control of bleeding is necessary. However, as surgeons become more facile at controlling even catastrophic hemorrhage with the robot, emergency conversion is rarely indicated. In fact, it may be better to safely control hemorrhage first—including with compression alone—before conversion rather than to emergently convert to open surgery. Finally, for open hepatectomy and laparoscopic hepatectomy, our group prefers to use an ultrasonic dissector with paired aspiration, such as the Clarity Ultrasonic Surgical Aspirator (CUSA®), for parenchymal transection; this instrument allows for delicate and safe dissection along the hepatic and portal veins and biliary structures. There is no equivalent tool on the robotic platform to date.

15.6 Robotic Surgery in Practice: Our Approach

15.6.1 Patient Selection for Robotic Hepatectomy

The role of minimally invasive hepatectomy is especially important in the management of CLM. Given that intrahepatic recurrence occurs in up to 70% of patients who undergo resection of CLM, and re-resection is associated with improved survival over non-operative management, a minimally invasive approach has the potential to facilitate future repeat resections by minimizing adhesions. For this reason, we preferentially use a minimally invasive approach to hepatectomy for CLM whenever possible; we find it especially useful in obese and morbidly obese patients. In this patient population, right liver mobilization can be particularly challenging, and postoperative wound healing problems are common with an open approach. However, certain patient and tumour characteristics do cause us to favor an open approach for select patients. These include (1) significant cardiopulmonary disease that presents a significant risk for cardiopulmonary intolerance of pneumoperitoneum, (2) complex combined colorectal and liver resections such as a proctectomy and hemihepatectomy or complex partial hepatectomy, and (3) >3 partial hepatectomies in disparate parts of the liver.

When dealing with CLM via a minimally invasive approach, we will preferentially use the robotic platform, especially when dealing with multiple (up to three) tumours in different parts of the liver. We still choose a laparoscopic approach when resecting CLM that abut vascular structures and for which we require fine dissection directly on the hepatic vein or portal pedicles, thus permitting skeletonization of the vessels as needed. This will result in a vascular (and not parenchymal) R1 resection, which has been demonstrated to yield equivalent survival compared to R0 resection.

15.6.2 Technical Aspects of Robotic Hepatectomy

15.6.2.1 Positioning and Setup

The technical aspects described here pertain to the da Vinci® Xi system and may be different from other da Vinci® models. We position the patient supine and tuck the arm opposite the robot, which can be docked from either side thanks to the rotating boom. The patient is securely strapped with belts around the chest and legs. Ideally, we use a paired bed when it is available, particularly for cases with tumours in disparate parts of the liver. A bump may be placed under the patient's right side when dealing with tumours in the right posterior sector.

Our preferred method to establish pneumoperitoneum is with a Veress needle inserted at Palmer's point in the left upper quadrant. We insert the camera in a paramedian location to either side of the umbilicus (see below) through a robotic 8-mm trocar. We avoid placing any ports through the umbilicus itself, which is a natural point of weakness on the abdominal wall and prone to hernia formation. A diagnostic laparoscopy is performed next during which we ensure that the Veress needle did not cause an inadvertent injury, rule out peritoneal disease, and visually evaluate the quality of the liver. Prolonged chemotherapy can result in significant liver injury, which may manifest as a blue or a congested liver. If there is concern for advanced liver injury, especially in the context of a planned hemihepatectomy, a core needle biopsy of the future liver remnant can be obtained. Barring any contraindication to proceed, we then place three additional robotic ports in a straight line across the abdomen with at least a hand's breadth between each. Typically, all robotic ports used are 8-mm ports. If a stapler is required to divide a hepatic vein or a major portal structure, we prefer to use a laparoscopic stapler by the bedside assistant. For this and other reasons, including ease of passage of a drop-in ultrasound or surgical gauze, and to minimize unnecessary robotic instrument exchanges, we use a 12-mm trocar for the assistant port.

For right hepatectomies and partial hepatectomies for tumours in segments 5, 6, 7, and 8, trocars are shifted toward the right side of the abdomen, with the assistant port between arms 1 and 2 (Fig. 15.3a). For left hepatectomies and partial hepatectomies for tumours in segments 2, 3, or 4A, we shift the ports to the patient's left, and the assistant port is placed between arms 2 and 3, inferior to the umbilicus (Fig. 15.3b). We routinely perform a laparoscopic transversus abdominis plane (TAP) block with liposomal bupivacaine before docking the robot.

15.6.2.2 Intraoperative Ultrasound

After docking the robot, we divide the falciform ligament and perform an intraoperative ultrasound to identify the vascular anatomy, look for biliary dilatation, and confirm tumour resectability. This includes systematic examination of the liver anatomy beginning with the identification of the hepatic venous anatomy, followed by the portal venous anatomy. We inspect the liver for additional small tumours not seen on preoperative imaging, especially near the liver capsule, and we assess tumour anatomy with respect to major vascular

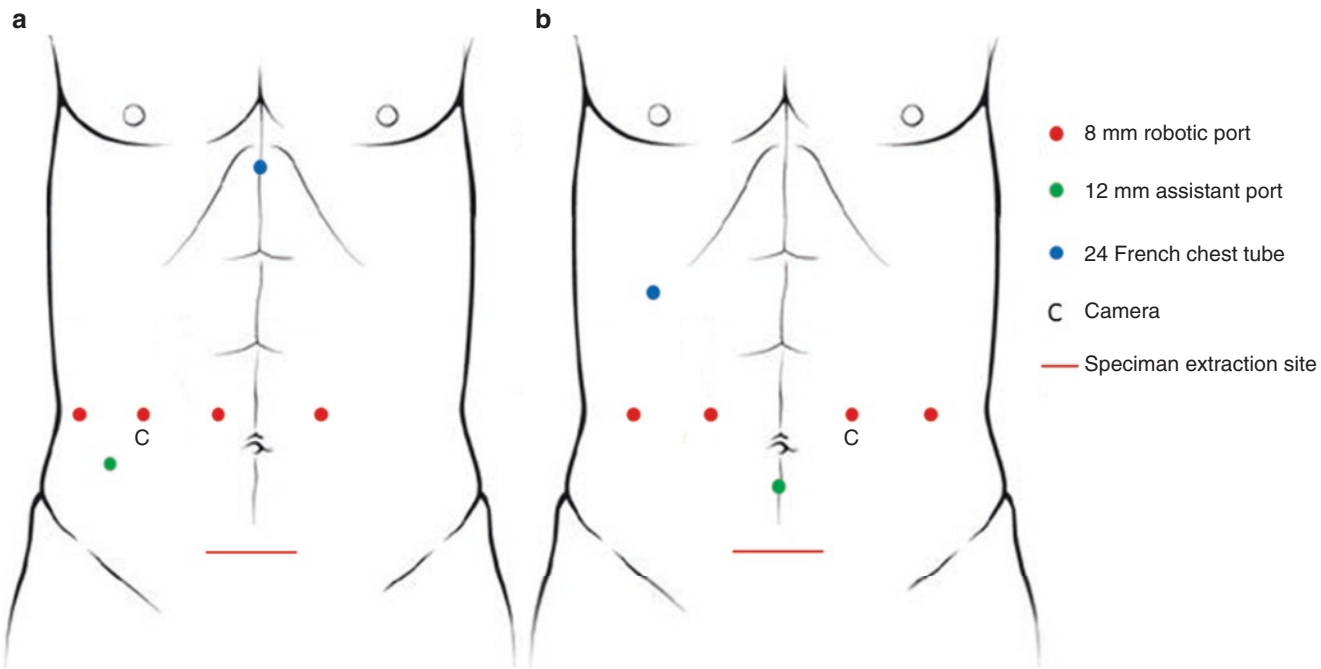

Fig. 15.3 Robotic port placement for (**a**) right hepatectomies and (**b**) left hepatectomies

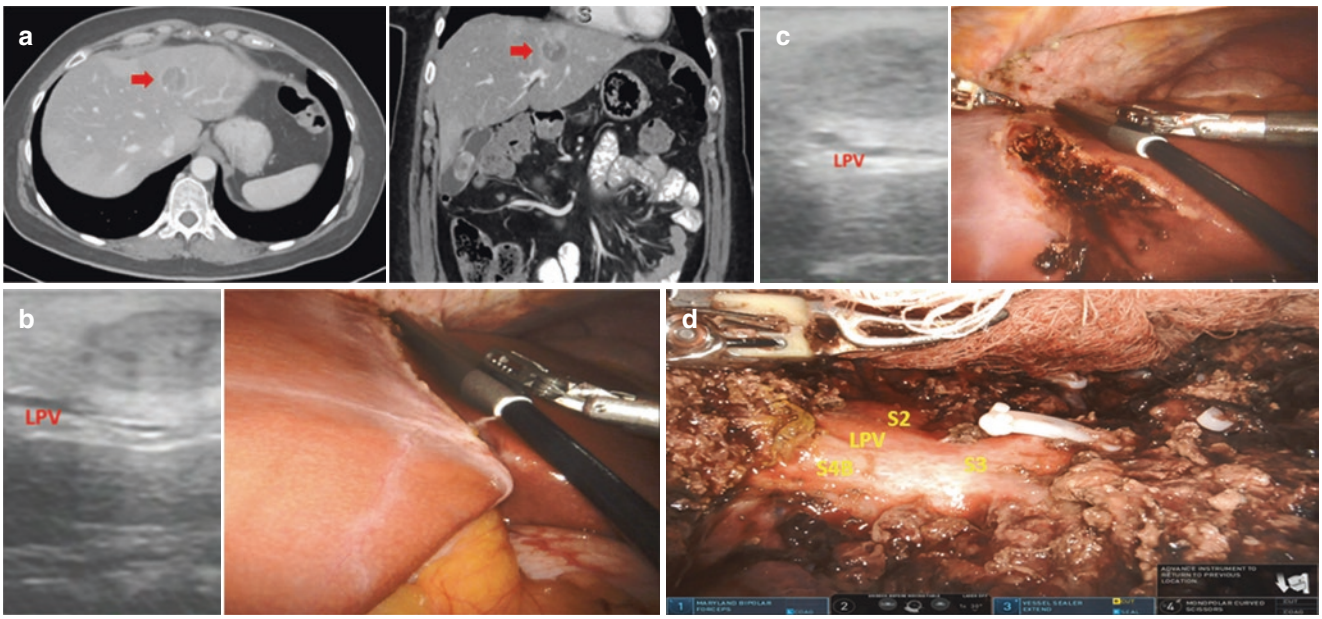

Fig. 15.4 (**a**) Preoperative CT images demonstrating colorectal liver metastasis anterior to the left Glissonean pedicle. (**b**) Intraoperative ultrasound prior to transection for resection planning. (**c**) Intraoperative ultrasound after partial transection to assess relationship of tumour to vasculature and transection margin. (**d**) Skeletonized left Glissonean pedicle after tumour resection. Arrows denote colorectal liver metastasis. LPV, left portal vein; S2, segment 2 portal pedicle; S3, segment 3 portal pedicle; S4b, segment 4b portal pedicle

and biliary structures. Once resectability is confirmed, we introduce the additional robotic instruments. Ultrasound is used liberally throughout the case to identify margins and the relationship of tumours to major vasculature or bile ducts, especially when off Pringle. Placement of a piece of Surgicel® in the transection margin can enhance its visibility on ultrasound and aid in margin detection and monitoring. The use of ultrasound for a partial left hepatectomy is demonstrated in Fig. 15.4.

15.6.2.3 Instrumentation and General Principles

The choice of instruments for robotic hepatectomy is user-dependent, and we encourage surgeons to explore the different available options and refine their skills with those with which they are most comfortable. Our group's preferred instruments include a fenestrated bipolar, most often used in arm 1 or 4 to assist with retraction and control of small bleeding vessels. Grasping forceps, or less often a robotic suction-irrigator, is used in the fourth arm for retraction and exposure. The main working arm will rotate several instruments based on the task at hand. The monopolar hook cautery is helpful in mobilizing the liver and marking the transection surface. A vessel sealer is used to divide structures like the falciform ligament, and for parenchymal transection. Peripherally, the activated vessel sealer is usually sufficient to seal small blood vessels and biliary structures. As the dissection proceeds more centrally, it is used in a crush clamp technique to expose and isolate vascular or biliary structures, which are then divided with clips, ties, and/or prolene sutures. When clips are used, we divide the structure with the vessel sealer to create a char on the stay side of the liver that can prevent slipping of the clip.

Although some surgeons argue that inflow control with a Pringle maneuver is unnecessary during minimally invasive hepatectomy thanks to the tamponade effect of pneumoperitoneum, in our experience, it can significantly reduce nuisance surface oozing and improve visualization during parenchymal transection. We routinely set up a Rummel tourniquet if possible. An umbilical tape marked in its middle is passed through the foramen of Winslow to encircle the hepatoduodenal ligament. A 24-French chest tube is then inserted through an epigastric incision (for right-sided hepatectomies) or the right lateral abdomen (for left-sided hepatectomies) and the two ends of the umbilical tape pulled through the chest tube to use as a Rummel tourniquet.

15.6.2.4 Right Hepatectomy

For a right hepatectomy, we begin by mobilizing the right liver by dividing the right triangular ligament and retroperitoneal attachments of the liver. We then perform a cholecystectomy, which helps expose the structures for inflow control. The right hepatic artery is dissected out and divided between clips, with the stay side reinforced with a silk tie. Next, we dissect out and loop the right portal vein, making sure to identify the portal vein bifurcation and the takeoff of the left portal vein before test-clamping the right portal vein. The retained flow in the left portal vein can be verified with

Doppler ultrasound. Once confirmed, the right portal vein is divided with a vascular stapler or with ties and clips. Once the inflow to the right liver is divided, we inject ICG to demonstrate perfusion of the left liver and mark the line of demarcation.

Although we generally follow the demarcation line, we still use ultrasound guidance to map out the middle hepatic vein and its tributaries (especially branches to segments 5 and 8). Using the middle hepatic vein as a guide ensures safe surgery and adequate resection. We suture a vessel loop onto each edge of the liver for retraction and to "open the book." The bedside assistant grasps the two ends with a suture passer and externalizes them. We then divide the hepatic parenchyma with a crush clamp technique with a combination of energy, clips, ties, and sutures as described above. Near the end of the transection, we identify the right hepatic duct in the liver, place vessel loops around it, and divide it with a stapler. We divide the right hepatic vein with a stapler last. The right liver is then placed in a specimen bag, which is removed through a Pfannenstiel incision. This is our extraction site of choice, as it is associated with the lowest risk for hernia formation. We then verify hemostasis and look for bile leakage, which may be aided by fluorescence imaging. We apply hemostatic material on the hepatectomy bed as needed. If the falciform ligament was divided to facilitate resection, we always resuspend the left liver to avoid any possibility of torsion resulting in inflow or outflow impairment.

15.6.2.5 Left Hepatectomy

Most of the principles of a left hepatectomy are the same as a right hepatectomy. After the cholecystectomy is complete, we divide the left triangular ligament to mobilize the left liver. We dissect the origin of the left hepatic vein and divide the ligamentum venosum. We divide the left hepatic artery as a single vessel or as separate branches to segments 2/3 and to segment 4 as they head toward the umbilical fissure. We follow the steps detailed above, this time walking along the left side of the middle hepatic vein, unless the vessel is to be sacrificed to achieve complete tumour resection. Figure 15.5 demonstrates retraction with vessel loops and the use of a chest tube as a Rummel tourniquet for a left hepatectomy.

15.6.2.6 Partial Hepatectomy

We make every effort to minimize the resection of normal liver parenchyma during robotic partial hepatectomy for CLM, just as we would with open surgery. In general, we approach positioning and liver mobilization for tumours in segments 6, 7, and 8, the same as we would a right hepatectomy, and for tumours in segments 2, 3, and 4a, the same as we would a left hepatectomy. For tumours in segments 4b and 5, often no liver mobilization is needed. As mentioned, it is more cumbersome to switch back and forth between intraoperative ultrasound and dissection for robotic compared to open hepatectomy. Therefore, it is critical to clearly identify margins and major surrounding vasculature with ultrasound prior to starting the resection and create a mental picture of the three-dimensional relationships and to strategically ultrasound during breaks between Pringle maneuvers.

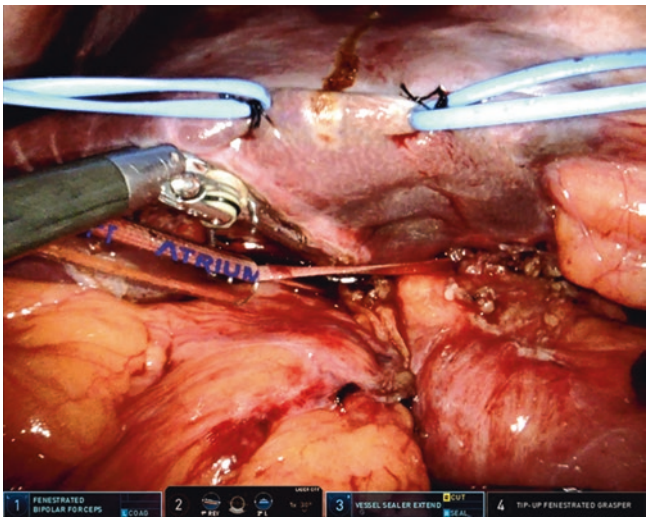

Fig. 15.5 Vessel loops for retraction are placed on either side of the transection line, and a 24 French chest tube is placed to be used as Rummel tourniquet for a left hepatectomy

After identifying margins and closing major vasculature, we mark the resection borders with a monopolar hook cautery. We aim for a 1 cm final margin around the tumour on the specimen. Therefore, we mark an initial transection line on the liver surface that is even wider than 1 cm whenever possible to account for a natural tendency to skive and cone in toward the deep surface of the specimen. The width of the ultrasound probe serves as a rough guide for a measurement of 1 cm. We then begin division of the hepatic parenchyma with the hook cautery followed by the bipolar vessel sealer for a depth of approximately 1 cm. At this depth, the vessel sealer is sufficient to control small vascular or biliary structures, and the bipolar forceps can control nuisance bleeding [59]. We then proceed with a crush clamp technique as detailed above. Once the transection is complete, it is critical to evaluate the resection bed for any residual tumour and check the specimen on the back table to confirm complete removal by performing a specimen ultrasound. We remove small partial hepatectomy specimens from the assistant port and larger specimens through a Pfannenstiel incision.

15.6.2.7 Perioperative Management for Robotic Hepatectomy

In preparation for surgery, we encourage all patients to engage in a daily exercise regimen. Postoperatively, patients are started on a clear liquid diet and encouraged to ambulate on postoperative day 0. The diet is quickly advanced as toler-

ated. We use a multimodal analgesic approach including an intraoperative TAP block and postoperative acetaminophen, muscle relaxants, and non-steroidal anti-inflammatories to minimize narcotic use. This has resulted in a median length of stay between 1 and 2 days after robotic hepatectomy, including for major hepatectomies.

15.7 Future Directions

As robotic liver surgery for CLM continues to evolve, surgeons will undoubtedly continue to push the envelope with more complex robotic procedures. One of these procedures is robotic associating liver partition and portal vein ligation (ALPPS), a strategy to produce rapid liver hypertrophy prior to hepatectomy in the case of an inadequate future liver remnant, which has already been described in case reports [60, 61]. Another procedure that is likely to increase in frequency is simultaneous robotic hepatectomy and colectomy or proctectomy for synchronous colorectal liver metastases, which has been reported in case series [62, 63]. This strategy presents technical challenges given the potential need for different port placement and repositioning with robotic hepatectomy compared to colectomy. In our experience, coordination between hepatobiliary and colorectal surgeons can strategize port placement and positioning to enable combination surgery. This may have significant benefits for appropriately selected patients as data suggest fewer complications with a totally minimally invasive approach to the entire treatment sequence in the management of stage IV colorectal liver metastases [64]. It will be important to critically evaluate outcomes with each of these new techniques as it is developed.

More studies on oncologic outcomes, cost, and long-term patient-reported outcomes following robotic hepatectomy for CLM are needed. If perioperative and oncologic outcomes with robotic and laparoscopic hepatectomy are equivalent, but cost is greater with robotic resection, it is possible that some resections should be preferentially performed robotically and others laparoscopically. For example, more straightforward resections such as left lateral bisegmentectomies may be better approached laparoscopically, while more complex resections such as posterosuperior segment resections may be better approached robotically. Of course, cost is but one aspect of surgical decision-making; ultimately, surgeons should use whatever technique they are most comfortable with that will allow them to perform safe operations following sound oncologic principles. While there is a growing body of literature showing excellent perioperative outcomes following robotic hepatectomy, there is a paucity of data on the long-term benefits of robotic hepatectomy on patient-reported outcomes and quality of life.

15.8 Conclusion

The robotic platform offers certain advantages over laparoscopy that improve visualization and the ability to work in small spaces to facilitate complex resection of CLM. The available data suggest that robotic hepatectomy is safe and may be associated with better perioperative outcomes compared to open hepatectomy and equivalent perioperative outcomes compared to laparoscopic hepatectomy. More data is needed on long-term oncologic outcomes following robotic resection of CLM. Limitations of robotic resection include increased intraoperative cost and limited instruments for challenging parenchymal dissection on major vasculature, although the extra cost may be mitigated by faster postoperative recovery and shorter length of stay. There is clearly a role for robotic resection of colorectal liver metastases that will continue to evolve with experience over time.

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Advanced Resection Technique with Vascular Reconstruction

16

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Learning Objectives

- To be able to plan the resection of colorectal liver metastases in contact with hepatic vessels.
- To identify the advantages of vascular resection with or without reconstruction in marginally resectable liver metastases.
- To discuss the techniques and materials available for vascular reconstruction in complex liver resection.

16.1 Introduction

Vascular contact with major vessels defines marginally resectable colorectal liver metastases (CLM). Resection of liver metastases, even in these cases, has shown to be the only chance for cure. In such challenging cases, preoperative chemotherapy is a prerequisite in order to achieve long-term acceptable results. Once selection chemotherapy has achieved the objective response without significant impairment in functional liver reserve, liver surgeons have two major options: "R1 resection by necessity" [1] or liver resection with vascular reconstruction.

Liver resection for tumours invading major vessels does not always require major hepatectomy but may require complex resections. The concept of minor-but-complex is increasingly being used in the literature to emphasize the impact of vascular or biliary reconstruction on outcome [2].

This chapter describes advanced techniques enabling safe resection of liver metastases with or without reconstruction for tumours encasing or invading the portal vein, bile ducts, and hepatic veins. Understanding the safe techniques for this type of resection and the long-term oncological results facilitates clinical decision-making. This chapter reviews the selection criteria for R1 resection versus vascular resection with reconstruction.

16.2 Rational for Resection and Reconstruction

The debate is ongoing regarding the optimal surgical margin to ensure improved survival in patients undergoing CLM resection. Apart from liver transplantation, which achieves the largest possible margin, tumours in contact with hepatic vessels are best approached with the resection of hepatic vessels in close contact with the tumour in order to achieve a negative surgical margin. This approach potentially provides the best oncological outcome if it does not increase postoperative morbidity.

Surgeons' experience including selection, planning, and resection technique may influence postoperative morbidity. Experience in both liver surgery and vascular reconstruction is mandatory when multiple vascular reconstructions or combined vascular and biliary reconstruction are needed. This is the case when resecting tumours centrally located at the portal bifurcation because both vascular reconstruction and biliary reconstruction are needed, increasing the complications specifically associated with reconstruction. Selection and planning play a major role in achieving the lowest possible mortality and morbidity. Postoperative management is the most significant factor that influences the time for returning to intended postoperative chemotherapy. "Return to the intended oncologic treatment" (RIOT) is a marker of quality of the oncosurgical strategy [3].

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For patients with marginally resectable CLM, achieving complete resection may be challenging while ensuring favorable postoperative outcomes. Indeed, most patients undergo chemotherapy for a long period before resection. Chemotherapy-induced liver toxicity increases the risk of postoperative morbidity. As such, the technical quality of CLM resections in contact with hepatic vessels is a major determinant of the outcome. Ensuring proper inflow and outflow control may make the difference between an uneventful resection and an adverse outcome. Partial liver resection with excision of the part of hepatic vessels and direct suture of the wall of vessels may increase the risk of venous outflow obstruction and may expose patients to the risk of liver failure especially when the remnant functional liver remnant is limited.

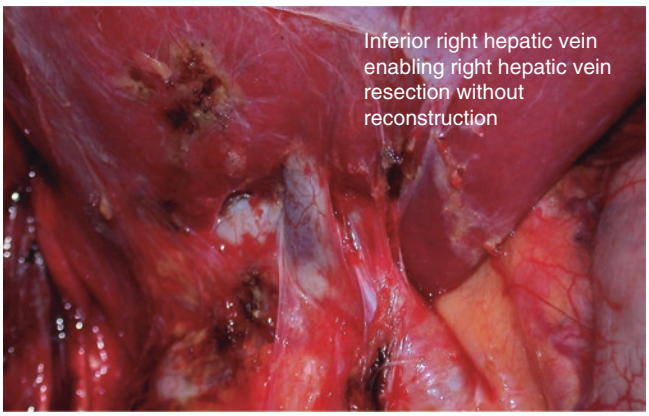

Fig. 16.1 Intraoperative view of the inferior right hepatic vein that enables resection of the right hepatic vein without the need for reconstruction

16.3 Advanced Technique for Resection of CLM

Situations are diverse but one parameter can help in planning the most appropriate resection of CLM with major vessel contact: the localization of the tumour distinguishing upper segment liver metastases needing unique venous reconstruction, central upper tumours in contact with the hepatic vein confluence, and central lower tumours in contact with portal bifurcation.

For each of the situations, we will describe the need for reconstruction, its means, and specific tips and tricks to avoid complications.

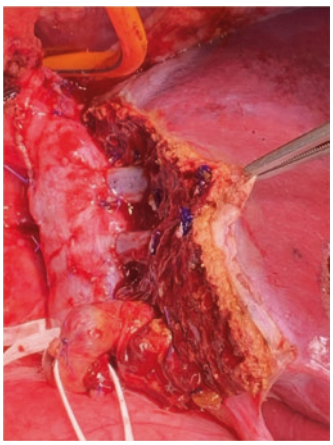

Fig. 16.2 Intraoperative view of direct anastomosis between the inferior vena cava and the left hepatic and scissural veins after right hepatectomy extended to segment 4 and the hepatic vein confluence

16.3.1 Tumours Located in the Posterosuperior Segments

For tumours located at the posterosuperior segments (segments 7 and 8), and encasing or invading the right hepatic vein, anatomical resection with venous reconstruction is often needed.

However, surgical planning takes an important place in this situation because the presence of an inferior right hepatic vein that drains directly from the inferior segments in the vena cava may avoid reconstruction as described by Makuuchi [4] (Fig. 16.1). In case of severe obstruction of the hepatic veins by tumours located in the upper segments, the identification of intrahepatic collateral veins connecting the right and middle hepatic veins, which draws a "half-moon," may enable safe resection of the upper segments with satisfactory postoperative liver function [5]. However, in this situation, the surgeon should be aware of a higher risk of intraoperative bleeding and the need for specific clamping techniques [6].

Direct reconstruction requires a tension-free anastomosis, which can be achieved in case of extended hepatectomy, for example, when the two stumps can be easily mobilized (Fig. 16.2). In case of upper-middle hepatic vein resection, reconstruction through the digging technique avoids interposition of a graft through intraparenchymal dissection of the vein [7] (Fig. 16.3). Often venous reconstruction with an interposed graft should be performed. In these cases, reconstruction is achieved using either autologous veins or synthetic material. End-to-end anastomosis at the transection surface and end-to-side at the vena cava ensures perfect venous outflow.

The most used autologous veins are the external saphenous veins (Fig. 16.4). Other veins such as the umbilical vein, the ovarian vein, external iliac veins, or even the portal vein harvested on the explant have all been described as feasible with low rates of thrombosis.

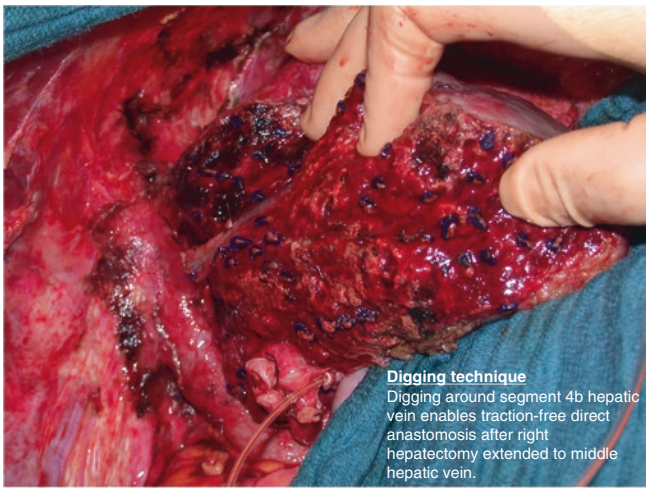

Fig. 16.3 The digging technique: "digging" around segment 4b hepatic vein enables traction-free direct anastomosis after right hepatectomy extended to the middle hepatic vein

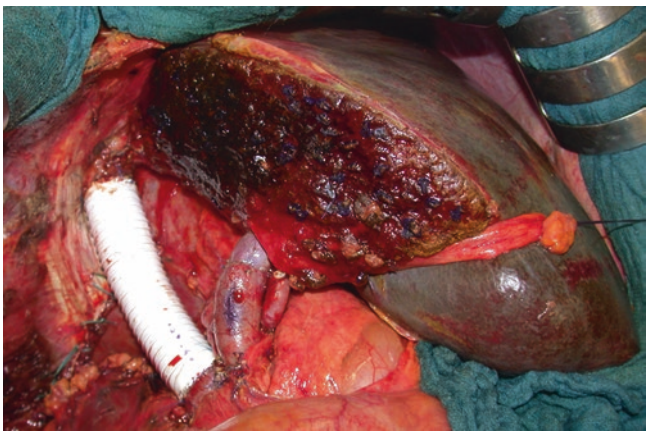

Fig. 16.5 Intraoperative view of an extended right hepatectomy to segment 4 with vena cava resection and reconstruction using a Goretex graft. Left hepatic vein confluence with vena cava was preserved. Tension-free direct end-to-end portal anastomosis is possible with duodenopancreatic block mobilization and extended lymphadenectomy

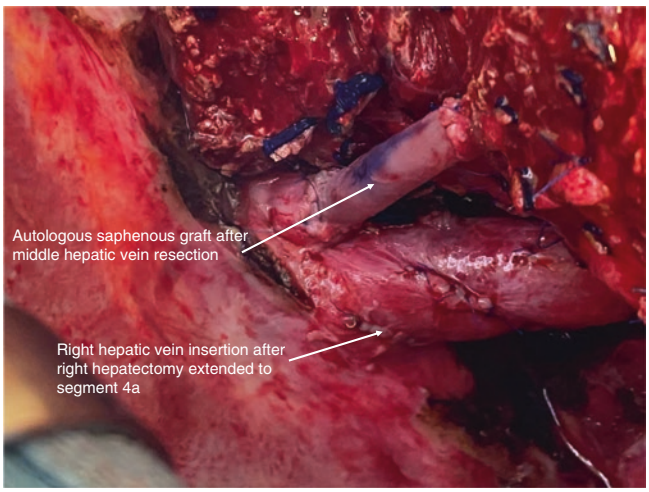

Fig. 16.4 Intraoperative view of a right hepatectomy extended to segment 4a with middle hepatic vein root resection and reconstruction using an autologous saphenous graft

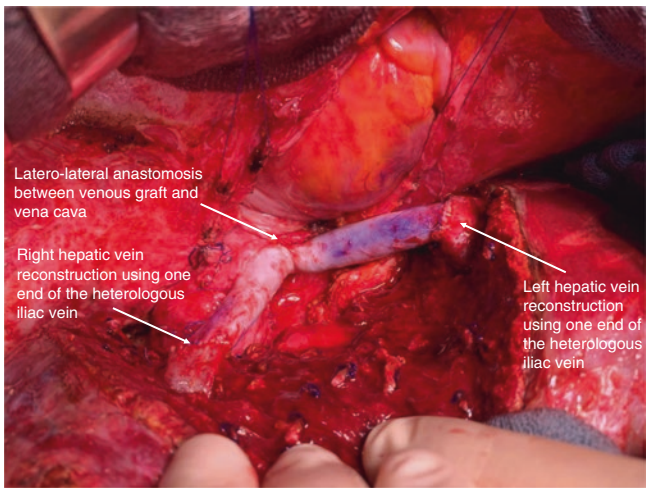

Fig. 16.6 Intraoperative view of upper segments resection with a two-vein (right and left hepatic veins) reconstruction using the heterologous iliac vein with latero-lateral anastomosis to the vena cava and two end-to-end anastomoses

16.3.2 Resection of Tumours Located at Central Upper Segments with Reconstruction of Hepatic Veins Confluence

Tumours involving all three hepatic veins at the hepatocaval junction require complex resection and reconstruction because at least one hepatic vein needs to be reconstructed.

Whereas some teams propose different types of reconstruction according to the degree of wall involvement, we advocate complete resection of the involved segment with subsequent reconstruction either directly or via an interposed graft. Hepatic veins may be reconstructed either directly (although it is rare for the resection of the upper part of the liver), or using interposed vessels using a peritoneal or synthetic graft.

The vena cava is usually reconstructed using prosthetic grafts (such as a ringed Goretex tube), with reimplantation of the vein(s) in the prosthesis after resection of a small patch (Fig. 16.5). The authors reported patch resection of the vena cava with reconstruction with autologous peritoneum or various venous grafts. Heterologous iliac venous grafts have the benefit of their length and larger diameter (Fig. 16.6). Autologous peritoneum has also been shown to be usable in complex situations for colorectal liver metastases, [8, 9] as well as in emergency [10].

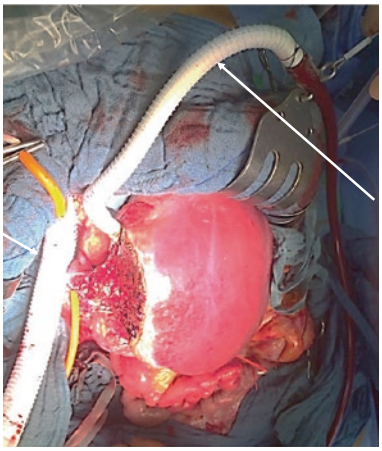

Fig. 16.7 Intra-operative view of an alternative to total vascular exclusion maintaining intrahepatic flow through a cannula inserted in the remaining hepatic vein

The techniques described above can be safely used after vessels are dissected while avoiding uncontrollable intraoperative bleeding.

Because the risk of bleeding is high and the time for reconstruction is long, vascular exclusion may be warranted to reduce blood loss and postoperative complications [11, 12]. Total vascular exclusion (TVE) may be needed to achieve safe resection and reconstruction. The "classical" TVE involves intrapericardial vena cava control either through a diaphragmatic incision or through the Healy way of dissecting the fibers of the vena cava hiatus at the anterior aspect of the vein, and enters the pericardial space without opening the diaphragm. Portal clamping is preceded by the insertion of a mesenteric cannula in the inferior mesenteric vein, which is branched in Y to the femoral cannula. Reinjection is usually performed via an axillary cannula. Cannulas may be inserted either through direct access or via ultrasound-guided puncture. One of the main rules is the need for cooling through an additional portal cannula placed downstream to the portal clamping. Optimal solutions for perfusion are the ones for organ procurement. It is accepted that an expected >30-min vascular exclusion needs cooling, eventually with hepatic temperature monitoring. Two technical adaptations to the classical vascular exclusion may be particularly interesting for their ease of use and safety while avoiding cava clamping. When the roots of the three hepatic veins are controlled, vascular exclusion with in situ hypothermic portal perfusion with caval flow preservation avoids the need for veno-venous bypass. A cold preservation solution is instilled via the clamped portal vein with its outflow through a hole in the hepatic vein of the resected segments [13]. Adaptation of TVE with selective exclusion have also been described. In these situations, veno-venous bypass uses only the outflow of the remaining liver during caval resection and reconstruction before reimplantation of the remnant liver outflow (Fig. 16.7).

16.3.3 Central Lower Tumours with Portal and Biliary Reconstruction

This situation is close to that of hilar cholangiocarcinoma requiring extended liver resection. In these cases, a major hepatectomy is associated with the resection of the portal bifurcation and resection of the bile duct with hepaticojejunostomy as a reconstruction.

Portal resection and reconstruction are preferentially realized via direct anastomoses, limiting the risk of thrombosis [11].

These reconstructions are facilitated by complete hilar pedicle lymphadenectomy, which enables mobilization of the proximal portal vein above the pancreatic head up to the hepatic hilum and the portal branches. Extended lymphadenectomy further ensures mobilization of the pancreas head to enable direct reconstruction with no graft interposition. This helps reduce the risk of thrombosis and infection, which is increased due to (1) the high risk of bile leak in central resections (segment 4, 8, and 1), and (2) the risk of bile leak associated with complex biliary reconstruction, especially in left-sided hepatectomy where there are the two right bile ducts to be reconstructed, either together or separately.

With extended length hepatic artery resection, an autologous saphenous graft may be used to ensure tension-free anastomosis [14] (Fig. 16.8).

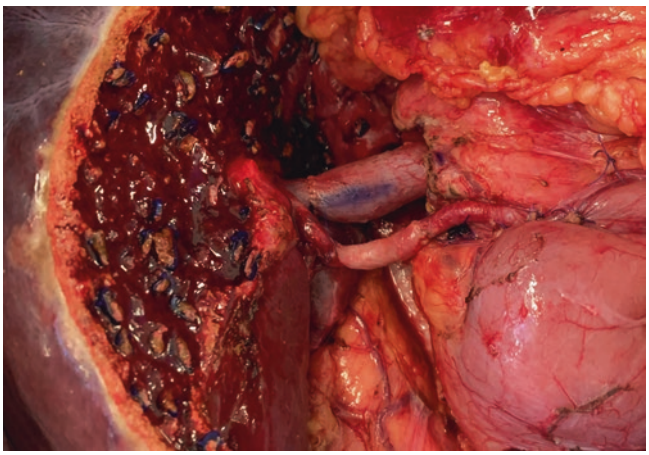

Fig. 16.8 Intraoperative view of extended hepatectomy with hilar reconstruction for centrally located CLM. Arterial reconstruction uses autologous saphenous graft. Portal reconstruction is realized through a direct end-to-end anastomosis

16.4 R1 Resection by Necessity Versus Complex Resection with Vascular Reconstruction

It is accepted for liver surgeons that vascular contact is not a contraindication for resection. Nonetheless, the postoperative management is complex and associated with a higher rate of complications. As an alternative to complex resection with vascular reconstruction, R1 resection is the most conservative way of resecting tumours in contact with major vessels. Many different techniques have been described with acceptable oncological results. R1 resection due to vascular contact may be feasible and may achieve results comparable to R0 resection, which is not the case for parenchymal R1 resection [15]. This may be dependent on tumour biology, particularly KRAS mutation [16]. Parenchymal preservation tends to transform a life-threatening incurable disease in a chronic disease with the possibility of repeat hepatectomy. When this strategy is chosen, resection with vascular reconstruction may be needed after multiple hepatectomies.

Surgeons taking care of patients with tumour(s) in close contact with major liver vessels should evaluate the situation before the intervention and be prepared to use the best strategy.

Some preoperative parameters may lead the surgeons to prefer radical resection over parenchymal sparing techniques. One of the main parameters is the "true" efficacy of preoperative chemotherapy.

Imaging techniques have made significant progress and MRI is now a standard in the evaluation of resectability of CLM. However, even in recent papers, it has been shown that MRI may not be as performant as it appears. Detachment from major hepatic vessels after chemotherapy is associated with residual tumour in only 53% of the cases [17]. The risk of residual tumour with persistent vascular contact depends on the type of chemotherapy. As such, cetuximab is associated with a higher level of "true" contact reduction, whereas a tumour retraction on the vessel was more frequently observed in chemotherapy with targeted therapy using bevacizumab [17]. A contact >25% of the vessel circumference was associated with a higher risk of invasion [18].

The balance between the efficacy of chemotherapy and its toxicity is important to be taken into consideration. Complex resection is associated with a higher risk of liver failure and postoperative morbidity. Long chemotherapy (more than eight cycles) is often associated with chemotherapy-induced toxicity. The liver functional reserve is also a parameter to be taken into consideration. Ensuring optimal outflow in these situations may be sometimes easier through a vascular reconstruction rather than with multiple resections associating partial wall resection with direct suture that may lead to venous stenosis, thrombosis, and impaired outflow.

16.5 Oncological Results of Complex Resection with Vascular Reconstruction in CLM

The oncological results are mainly dependent on the postoperative outcomes. For instance, the occurrence of liver failure has shown to significantly impact the long-term outcome [19].

Oncologically, vascular invasion is a determinant of long-term survival with a three time lower chance of 5-year survival [20]. A recent review reported a 5-year survival of 40% in 240 patients undergoing resection with vena cava resection of whom 43% were CLM [21]. In the largest series reporting complex resection with total vascular exclusion, 5-year survival is between 20% and 30%, which is equivalent to the results of initially non-resectable CLM [12].

16.6 Conclusion

In the hands of experienced surgeons, complex resection with vascular reconstruction achieves good oncological results in patients with marginally resectable CLM provided that the intervention has been planned and performed well. Except in situations where the anatomy is favorable, vascular resection needs vascular reconstruction with or without grafts. Technical adaptations with specific clamping techniques or even hepatic vascular exclusion ensure safety.

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Resection Margins

17

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Learning Objectives

- Resection margins and oncologic outcome.
- Resection margins and preoperative chemotherapy.
- Resection margins and surgical techniques.
- Resection margins and somatic gene mutations.
- Resection margins and recurrence at the hepatic resection margin.

17.1 Introduction

Removal of all viable tumour tissue has been considered essential to achieve long-term survival in surgical oncology. In patients with colorectal liver metastases (CLM), the status of the resection margin has been discussed with particular interest [1–4], particularly due to the use of effective modern chemotherapy [5, 6], and the implementation of more aggressive surgical approaches [7, 8]. Parenchymal-sparing hepatectomy (PSH) is now considered as gold standard [9], where the aim is at least 1 mm of normal liver tissue from the resection margin to the border of the tumour (i.e., R0 resection). To achieve this, surgeons should macroscopically aim for a 10 mm margin from tumour. If the anatomical distribution of the disease allows, formal sectorectomies, segmentectomies, or a wider (beyond 10 mm) margin are no longer considered required, as the frequency of local recurrence with PSH is low. Modern chemotherapy has influenced our attitude toward patients with tumours affecting intrahepatic vessels. R0 resection remains the objective, but R1, meaning tumour cells less than 1 mm from the resection margin has been accepted, especially in patients with good response to preoperative chemotherapy [5, 6] and where the tumour is located at intrahepatic vessels (e.g., R1 *vascular*) [10]. Furthermore, the prognostic impact of R1 has also been questioned with the use of modern high-energy tissue transection devices [3]. Ultimately, the tumour biology determines the outcome and more recently, molecular markers such as somatic gene mutations have been suggested to aid surgical approach with respect to the surgical margin [2, 11–13].

17.2 Resection Margins in Colorectal Liver Metastases

17.2.1 Resection Margins Status as a Predictor of Tumour Recurrence and Overall Survival

The current criteria of resectability for CLM include the ability to resect the entire radiologically evident tumour burden with tumour-free surgical margins (R0 resection) [6], while preserving sufficient future liver remnant (FLR) [14]. R1 resection has been previously associated with increased recurrence rates [15] and worse overall survival rates [15, 16]. The impact of microscopically positive resection margins on oncologic outcome has been controversially discussed in the past and some previous studies have even advocated that R1 resection is not essential to achieve optimal long-term outcomes [4]. Nevertheless, the main objective of current surgical strategies for CLM remains R0 resection of all liver lesions [1]. In order to achieve this without risking postoperative liver insufficiency, modern techniques have been developed including portal vein embolization with two-stage hepatectomy [17] and ALPPS procedure (Associating Liver Partition and Portal Vein Ligation) [18], some of them associated with an increased

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risk for postoperative morbidity and mortality during implementation [19].

Pawlik et al. demonstrated that the presence of tumour cells <1 mm from the resection margin was significantly associated with higher recurrence rates at the surgical margin and worse oncologic outcome, whereas the margin width between 1 mm and 1 cm did not have an impact on recurrence rates and overall survival [3] (Fig. 17.1). However, this study predated the era of modern perioperative chemotherapy associated with major response rates. A more recent study evaluating the resection margin width, including submillimeter measurements (0.1–0.9 mm) confirmed that negative resection margins were associated with prolonged overall survival and indicated that the submillimeter margin clearance may even have a positive impact on overall survival [1]. Furthermore, a meta-analysis from 2018 indicated that a wider resection margin of >1 cm may result in even better oncologic outcomes and should be taken into consideration when performing hepatectomy for CLM depending on the size and location of the liver lesions [20].

When evaluating resection margins as a prognostic factor of long-term survival, studies have raised the question if R1 resection is a marker of surgical technique or rather a surrogate marker for advanced disease [21]. This hypothesis have been supported by recent findings showing that positive resection margins are associated with RAS mutations [2], more major resections, less minimal-invasive hepatectomies, increased postoperative morbidity, and mortality [21]. Another finding underlining the association between resection margins and tumour biology was delivered by *Oshi* et al. who showed that extended tumour burden defined as a tumour burden score (TBS) ≥ 6 [TBS^2 = (maximum tumour diameter in cm)^2 + (number of lesions)^2)] neutralized the effect of negative resection margins on overall survival [22]. Thus, although R0 resection may prolong survival of patients undergoing hepatectomy for limited CLM, in case of advanced disease, surgery alone cannot achieve cure without adjuvant modern systemic therapy.

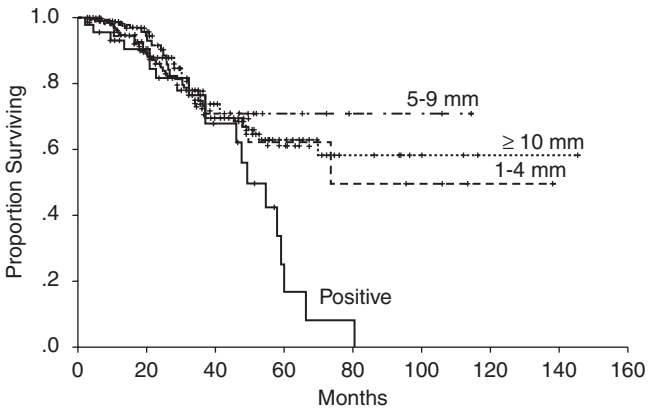

Fig. 17.1 Overall survival stratified by surgical margin width. Survival in patients with positive margins was significantly lower than that in patients with negative margins ($p = 0.005$), while no significant difference in survival was seen in patients with a negative surgical margin, regardless of the width of the margin. (Adapted from Pawlik, et al. Ann Surg 2005 [3] with permission)

17.2.2 Resection Margins and Perioperative Chemotherapy

In the current era of modern cytotoxic and biologic agents [23], patients with CLM regularly undergo perioperative systemic therapy. Radiologic morphologic [24] and pathologic response [25] can be assessed using advanced criteria guiding the individualized multimodal treatment strategy. Major pathologic response and optimal radiologic response to chemotherapy have been associated with improved disease-free and overall survival and have been proven to be more reliable predictors of oncologic outcome compared to traditional parameters such as tumour size and number [26, 27].

Standardized administration of perioperative chemotherapy and biologic agents may downsize CLM, increase resectability, and reduce R1 rates [28–30]. Within the framework of these treatment strategies, the impact of R1 resection on survival among patients treated with systemic therapy remains controversial. Whereas some studies identified a significant benefit of R0 over R1 resection regarding overall survival in patients treated with preoperative chemotherapy and hepatectomy for CLM [15], others have identified interesting differences regarding the value of margin status according to the type of chemotherapy and extent of response. *Andreou* et al. showed, in a homogeneous cohort of patients treated with modern chemotherapy (oxaliplatin- or irinotecan-based), that R1 resection and minor pathologic response to chemotherapy were the only factors independently associated with worse overall survival in multivariate analysis. Interestingly, subset analysis of patents with major pathologic or optimal morphologic response showed that R0 resection did not significantly prolong survival compared to R1 resection. However, in patients with minor pathologic or suboptimal morphologic response, R1 remained a determinant of worse outcome [6] (Fig. 17.2). A more recent study including patients who received neoadjuvant chemotherapy with or without bevacizumab before liver resection for CLM also investigated the impact of R1 resection on survival according to the response to chemotherapy and the inclusion of bevacizumab into the treatment regimen [31]. In this study, Sasaki et al. confirmed that R1 resection was relevant with regard to the outcome among patients with progressive or stable disease following preoperative systemic therapy. However, when partial or complete response was achieved, R1 resection did not have a negative influence on overall survival. Moreover, R0 resection resulted in a survival benefit in

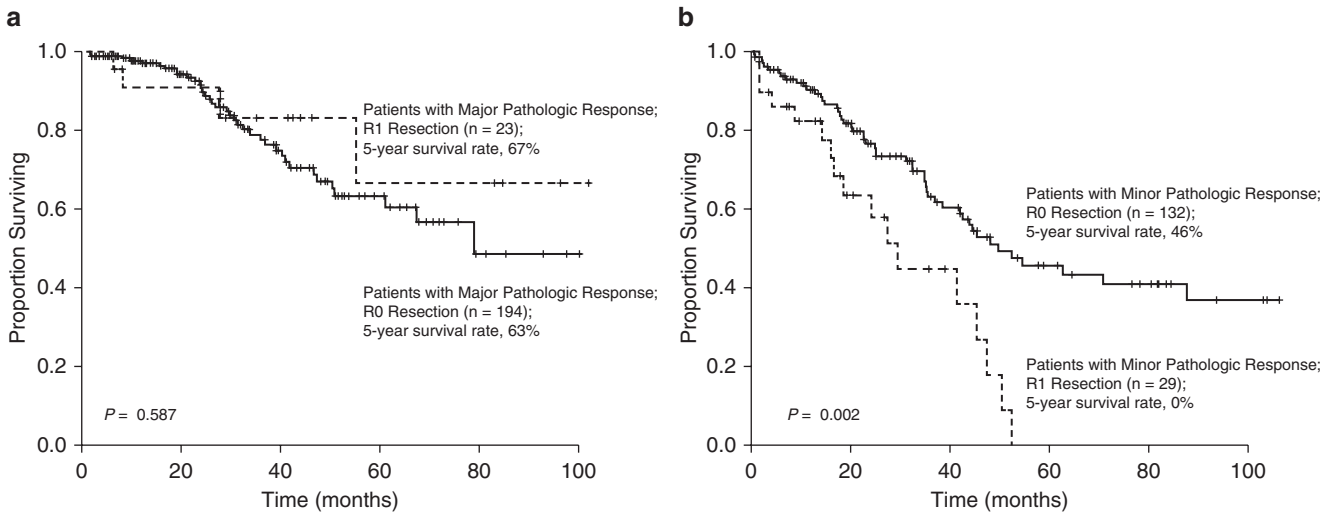

Fig. 17.2 Overall survival by surgical margin status in patients who underwent hepatectomy for colorectal liver metastases with (**a**) a major pathologic response to preoperative chemotherapy and (**b**) a minor pathologic response to preoperative chemotherapy. (Adapted from Andreou, et al. Ann Surg 2013 [6] with permission)

patients receiving preoperative chemotherapy without bevacizumab. On the contrary, the addition of bevacizumab in the neoadjuvant setting neutralized the negative effect of R1 resection status [31]. Both studies delivered further hints that resection margin status represents a surrogate factor of tumour biology. Thus, in patients with favorable tumour biology as indicated by major response to chemotherapy, R0 resection may not be essential for optimal long-term outcome within a multimodal treatment concept [6].

17.2.3 Resection Margins and Parenchymal-Sparing Hepatectomy

Recently, the concept of PSH has been introduced for the treatment of CLM, both in patients with limited disease and those with multiple and/or bilateral lesions [32, 33]. Several advantages have been associated with this technique including lowering the risk for small FLR volume with subsequent liver failure [34]. This advantage is most pronounced among patients treated with preoperative systemic therapy associated with chemotherapy-induced hepatic injury such as the sinusoidal obstruction syndrome (SOS) [35]. SOS has been correlated with an increased risk for postoperative complications including liver failure and bleeding following hepatectomy [36].

Recent studies described further advantages of PSH such as lower postoperative morbidity [37, 38], less intraoperative blood loss [39], and shorter length of hospital stay [37, 38]. The most important advantage of this technique may, however, be the ability to improve salvageability, by enabling repeat hepatectomy in case of recurrent disease and thus potentially improve overall survival [34, 39]. However, several concerns have been expressed regarding the oncological radicality of this technique and whether PSH may be responsible for increased positive surgical margins and thus higher recurrence rates [21, 40]. Older studies predating the use of modern chemotherapy showed higher R1 resection rates and worse overall survival following PSH compared to anatomical resections [40]. However, recent studies indicated that PSH is not inferior to non-PSH regarding margin status and oncologic outcomes [38], not only for patients with solitary lesions [39] but also for patients with advanced [32], multiple [34], bilobar [41], and deep-placed CLM [33]. Therefore, PSH is currently considered as the preferred procedure for the treatment of CLM, if allowed by the extent and location of tumour burden [42].

17.2.4 Resection Margins and Minimally Invasive Hepatectomy

Minimal-invasive hepatectomy has been increasingly performed for benign and malignant liver lesions [43, 44], including CLM [45]. Laparoscopic resection for CLM has been previously reported to be associated with less intraoperative blood loss, lower need for transfusions, lower postoperative complication rates, and shorter duration of hospital stay in comparison to open hepatectomy [46, 47]. The benefits of laparoscopic hepatectomy have been even confirmed in more vulnerable patient cohorts of elderly patients requiring oncologic resection for CLM [48]. However, the most important question is whether minimally invasive techniques result in adequate negative resection margin rates and equivalent recurrence-free and overall survival rates. Several retrospective studies including those using propensity-score

matching analysis showed comparable R1 resection rates between laparoscopic and open hepatectomy for CLM [46, 49, 50]. The non-inferiority of minimally invasive hepatectomy compared to open procedures regarding operative time, intraoperative bleeding, incidence of blood transfusion, surgical margin positivity, and postoperative morbidity has been also identified in patients with CLM located in the posterosuperior liver segments 4a, 7, and 8, which are considered to be technically more challenging to resect [51]. A most recent bicentric study, which compared minimally invasive resections with propensity-score matched open resections for CLM showed that R1 rates could be even significantly reduced using the laparoscopic technique [52]. The authors speculated that surgeons might have determined the resection margins more conservatively when performing minimally invasive hepatectomy due to the different tactile feedback and during the learning curve to explain this difference. The first randomized-controlled trial comparing laparoscopic with open parenchymal-sparing resection for CLM confirmed the postoperative advantages of minimally invasive hepatectomy together with the adequate ability to achieve R0 resection [53]. The long-term evaluation of the same randomized cohort resulted in equivalent recurrence-free and overall survival rates between the two techniques [54]. Current evidence and guidelines have thus recommended laparoscopic PSH as the standard of care for patients with CLM, when possible [42, 55].

17.2.5 Resection Margins and Somatic Gene Mutations

Size, number, and synchronicity of CLM have been previously used as surrogate markers of tumour biology in patients with CLM [56, 57]. Recently, medical and surgical oncologists have been exploring the role of molecular markers, especially somatic gene mutations, to achieve a better understanding of selection and prognostication in the same patients [58–61]. The most common somatic gene mutations in patients with CLM are TP53, KRAS, APC, PIK3CA, SMAD4, FBXW7, NRAS, and BRAF [62]. Among these, RAS mutations have been of particular interest in patients with resectable CLM [60]. One of the hypotheses has been that CLM with different growth patterns, determined by biology, will require different margin widths to clear all disease. RAS mutated metastases may represent a more migratory and infiltrative type over its RAS wild-type counterpart [63], as RAS mutated metastases have been associated with higher frequency of R1 resections [2]. Whether this can be explained by inherent phenotypical characteristics of the mutated metastases or the worse response to preoperative chemotherapy is not fully elucidated [64]. The consequence is, however, that a wider resection margin or ablation zone has been suggested in patients with mutated RAS [37, 65].

Margonis et al. found that PSH for RAS mutated tumours was associated with reduced disease-free survival and concluded that anatomical resections may be warranted in patients with RAS mutation [65]. The same recommendation could not be drawn by *Joechle* et al. reporting similar outcomes with anatomical and non-anatomical resections, regardless of RAS mutation status [37]. While the latter adjusted for the reasons for either resection technique in propensity-score matching, adjusting for determining factors may be challenging in retrospective studies.

There has been great interest in the true prognostic impact of R1 versus R0 resection. While most early investigators reported significant differences in recurrence-free or overall survival, some more recent reports have not observed the same differences. It is likely that the discussion needs to be more nuanced. With more effective chemotherapy, R1 may be sufficient but that presupposes a biology that responds to the treatment, which unfortunately is not the case in all patients. It is likely that R0 remains especially important in patents with poor response to perioperative chemotherapy [6]. Furthermore, *Torzilli* and colleagues have presented data that there is a difference, whether the R1 margin is toward the liver parenchyma or vascular structures (R1 *parenchyma* vs. R1 *vascular*). R1 *vascular* had similar results as R0 resection, while R1 toward the parenchyma was associated with higher rates of liver recurrence and was a negative prognostic factor of overall survival [10]. It is clear that the understanding of tumour biology in patients with CLM is likely to impact the surgical approach on several levels. A recent report suggested increased mobilization of neutrophils in the vicinity of RAS mutated metastases compared to RAS wild-type metastases [66]. As such, somatic gene mutations may also play a role in tumour immunology and the important peritumoural microenvironment.

17.2.6 R1 Resection as a Predictor of Recurrence at the Hepatic Resection Margin

Positive resection margins following hepatectomy for CLM have been associated with higher recurrence rates, and worse overall survival rates [6, 67, 68], although the appropriate margin width is still a matter of controversy ranging from <1 mm to <1 cm [1, 20]. It remains unclear whether positive resection margins are associated with a higher risk for recurrence at the surgical margin. In an older era lacking systemic therapy regimens including modern cytotoxic and biologic agents, R1 resection was correlated with an increased incidence of marginal recurrence [3]. This finding has contrib-

uted to the establishment of the current definition of resectability for CLM as the technical ability to remove all radiological evident disease with histologically negative surgical margin [69].

Most of the studies, that investigated the impact of resection margins on intrahepatic tumour recurrence, have not differentiated between recurrence at the resection margin and recurrence elsewhere in the liver [70]. A study from 2008 has merely indicated that positive surgical margins were not associated with increased marginal recurrence despite more frequent intrahepatic recurrence [4]. More recent studies have hypothesized that R1 resection may rather represent a surrogate marker of tumour biology and does not necessarily influence the location of tumour recurrence [21]. Lee et al. showed that positive resection margins were not associated with more frequent in situ recurrence at the resection margin compared to de novo recurrence elsewhere in the liver. R1 resection was nevertheless correlated with combined in situ and de novo intrahepatic recurrence as a sign of poor tumour biology with multiple sites of disease failure [71]. Andreou et al. confirmed that detection of tumour cells <1 mm from the transection line following resection of CLM was not responsible for more frequent recurrence at the surgical margin compared to any other intrahepatic recurrence location. In fact, in this study there was no correlation between resection margin status and any pattern of intrahepatic or extrahepatic recurrence. Additionally, patients with recurrent disease at the resection margin did not have worse overall survival than those with other intrahepatic or extrahepatic recurrences [21]. These findings may guide decision making regarding treatment strategy, when evaluating patients with borderline resectable CLM.

Recently, Nishioka et al. evaluated the incidence of local recurrence in 552 patients who underwent R0-intent resection for CLM and genetic analysis of tumour tissue using next-generation sequencing [72]. *RAS*/*TP53* co-mutation increased the incidence of intrahepatic recurrence; however, the incidence of local recurrence did not differ by *RAS*/*TP53*, *BRAF*, *SMAD4*, *FBXW7* mutations (Table 17.1) as well as surgical margin width (Table 17.2). The group also reported that there was no statistical difference on overall survival between patients who had local recurrence and other intrahepatic recurrence (Fig. 17.3). The findings suggested that prognosis is likely driven by individual tumour biology rather than surgical margins. However, it should be emphasized that these data were derived from patients in whom resections were performed with R0-intent. R1- or R2-intent resection should be avoided to minimize the risk of local recurrence.

Table 17.1 Relationships between somatic gene mutations and surgical margin width

Mutation and status	Total no. of patients	No. (%) of patients with Margin				*P* value
		<1.0	1.0–4.9	5.0–9.9	≥10	
RAS/TP53						
Co-mutant	184	39 (21)	54 (29)	38 (21)	53 (29)	0.378
Others	368	98 (27)	99 (27)	83 (23)	88 (24)	
BRAF						
Mutant	17	3 (18)	4 (24)	5 (29)	5 (29)	0.795
Wild-type	535	134 (25)	149 (28)	116 (22)	136 (25)	
SMAD4						
Mutant	70	13 (19)	22 (31)	16 (23)	19 (27)	0.602
Wild-type	482	124 (26)	131 (27)	105 (22)	122 (25)	
FBXW7						
Mutant	40	9 (23)	10 (25)	12 (30)	9 (23)	0.674
Wild-type	512	128 (25)	143 (28)	109 (21)	132 (26)	
Any mutation						
Positive	524	132 (25)	144 (27)	113 (22)	135 (26)	0.663
Negative	28	5 (18)	9 (32)	8 (29)	6 (21)	

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Table 17.2 Patterns of recurrence by surgical margin width

	Margin				*P* value
	<1.0 mm[a] (*n* = 137)	1.0–4.9 mm (*n* = 153)	5.0–9.9 mm (*n* = 121)	≥10 mm (*n* = 141)	
Any recurrence, no. (%)	112 (82)	119 (78)	95 (79)	109 (77)	
Local recurrence, no. (%)	11 (8)	12 (8)	7 (6)	8 (6)	0.840
Other intrahepatic recurrence, no. (%)	73 (53)	73 (48)	57 (47)	62 (44)	
Extrahepatic recurrence alone, no. (%)	28 (20)	34 (22)	31 (26)	39 (28)	
No recurrence, no. (%)	25 (18)	34 (22)	26 (21)	32 (23)	

[a]R0 resection

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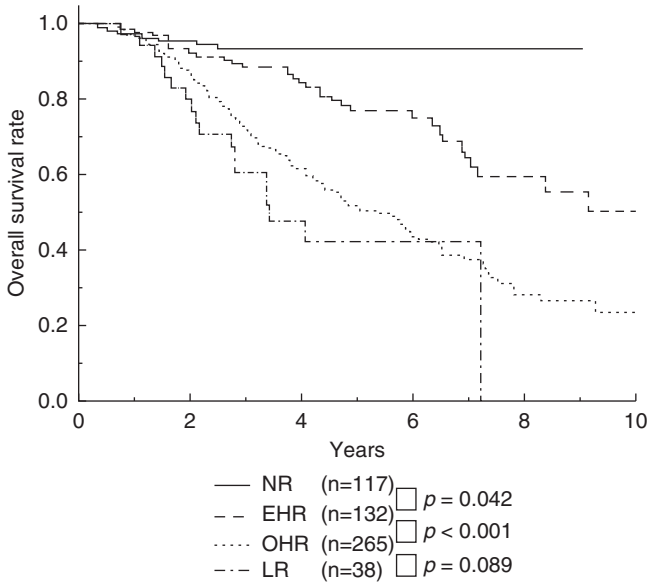

Fig. 17.3 Overall survival by pattern of recurrence. NR, no recurrence; EHR, extrahepatic recurrence alone; OHR, other intrahepatic recurrence; LR, local recurrence. (Adapted from Nishioka, et al. J Gastrointest Surg 2021 [72] with permission)

17.3 Conclusion

Positive resection margins following hepatectomy for CLM are associated with worse overall and disease-free survival and therefore R0 resection remains primary goal of the surgical treatment of patients with CLM. However, increasing evidence has indicated that R1 resection is not only a matter of technical feasibility but rather a surrogate marker for unfavorable tumour biology. This hypothesis has been supported by recent studies correlating positive resection margins with the presence of somatic gene mutations such as RAS mutations. In the current era of modern cytotoxic and biologic agents, R0 resection may be put into another perspective, as it has been shown that in patients with optimal response to systemic therapy, negative resection margins do not necessarily improve oncologic outcomes. Thus, surgical indication for borderline resectable CLM may be expanded in patients with favorable tumour biology within the framework of multimodal treatment strategies. New advances in liver surgery such as PSH and laparoscopic hepatectomy have been increasingly established for the treatment of CLM and were proven to be equivalent to the traditional open and anatomic procedures in regard to surgical margins and long-term survivals. Finally, R1 resection was not associated with the location of tumour recurrence in recent studies. Neither recurrence at the resection margin nor intrahepatic recurrence in general was more frequent in patients with positive surgical margins. In case of marginal recurrence, survival was also not inferior to that of patients with other intrahepatic or extrahepatic recurrence patterns. Therefore, the question whether hepatectomy for patients pretreated with modern chemotherapy is justified, if the risk for R1 resection is high, remains a matter of discussion.

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R1 Vascular Surgery

18

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Learning Objectives

- Background of surgical alternatives to R1 vascular surgery.
- Rationale for R1 vascular surgery, technical background, and results.
- Additional elements to afford R1 vascular surgery.
- Technical results achieved utilizing R1 vascular surgery.
- Future perspective of this approach.

18.1 Introduction

Liver surgery is required to deal with advanced disease either for primary or metastatic tumours. Adequate oncologic margins, and enough future liver remnant (FLR) with proper inflows and outflows are the pillars for any successful liver surgery strategy. Given that tumour-free margin remains the mainstream of any oncologic surgery to the liver, inducing liver regeneration has been considered the most suitable path to address both surgical radicality and safety for advanced oncologic liver involvement. Venous embolization to hypertrophy the FLR has been the most practiced approach since the 1990s [1, 2], to now [3]. However, the failure of portal vein embolization (PVE) to obtain an adequate FLR is not rare, and has limited this approach for colorectal liver metastases (CLM) [4]. Then, a temporary debulking surgery splitting into two operations, the organ clearance with or without PVE, has been proposed for multiple bilobar CLM: the two stage hepatectomy (TSH) [5, 6]. The not negligible drop out due to tumour progression in between the two procedures induced some authors to shorten the interval between them by combining in the first operation the right portal vein ligation, the clearance of the left liver, and the division of the two hemilivers: the so-called associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) [7, 8]. The ALPPS resulted in a better and faster increase in FLR size. However, mortality and morbidity remain relatively high [9]. Refinements in technique, and variants will probably contribute to better position this approach among those available [10]. Liver venous deprivation (LVD) followed by major hepatectomy is a new technique to improve liver regeneration. Simultaneous occlusion of portal vein inflow and hepatic vein outflow for diseased part of the liver seems safe, and efficient in terms of FLR increase and consequent limitation of patients' drop-out but results need further validation particularly in patients with cirrhosis [11]. Anyhow, all these solutions aiming at boosting the FLR reduce the chance of redo surgery in case of relapse. Indeed, it seems somehow obvious that less remnant vascular structures offer lower chances of finding technical solutions in case of hepatic recurrence. Because the liver regenerates after surgery, there is room for more systematic technical solutions between major liver vessel occlusion and peripheral parenchymal sparing resection. In early 2000, the so-called radical but conservative policy was introduced [12, 13] on the basis of the guidance of intraoperative ultrasound (IOUS). This approach aimed to challenge conservatively the deeply located lesions and leverage on the organ anatomy it relies on IOUS in order to achieve vessel-guided parenchyma sparing hepatectomies [14, 15].

18.2 Tumours and the Intrahepatic Vessels

Major intrahepatic vessels, namely Glissonean pedicles (GP) and hepatic veins (HV), are totally separate entities. GP and HV are further separated by hepatic parenchyma not just by Glissonean sheath, and the vein wall respectively, but also by the *Laennec* capsule like the inferior vena cava [16]. With these

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premises, detaching a tumour from the intrahepatic vessel (R1 vascular), but not from the liver parenchyma (R1 parenchyma) could be at least acceptable. The encouraging preliminary findings featuring similar recurrence risk of R1 vascular and R0 surgery, also for CLM [17], strengthened the impression, confirmed more recently on larger series [18, 19]. Indeed, in 226 patients receiving 627 resection areas with a median follow-up of 33 months, local recurrence rates according to the R0, R1 vascular, and R1par status resulted 6%, 4%, and 20% per patient, while 1.5%, 4%, and 14% per resection area, respectively [18].

18.2.1 Tumour in Contact with Glissonean Pedicle

Glissonean pedicles may be spared even when in contact with CLM. The integrity of the vessel wall can be appreciated with IOUS, and lack of involvement can be further confirmed by the absence of bile duct dilation. Bile duct dilation, presence of tumour thrombus, invasion of the vessel wall, usually require pedicle resection (Fig. 18.1). In these conditions, an R1 vascular resection could not be carried out and extension of the hepatectomy should be pursued for complete tumour clearance.

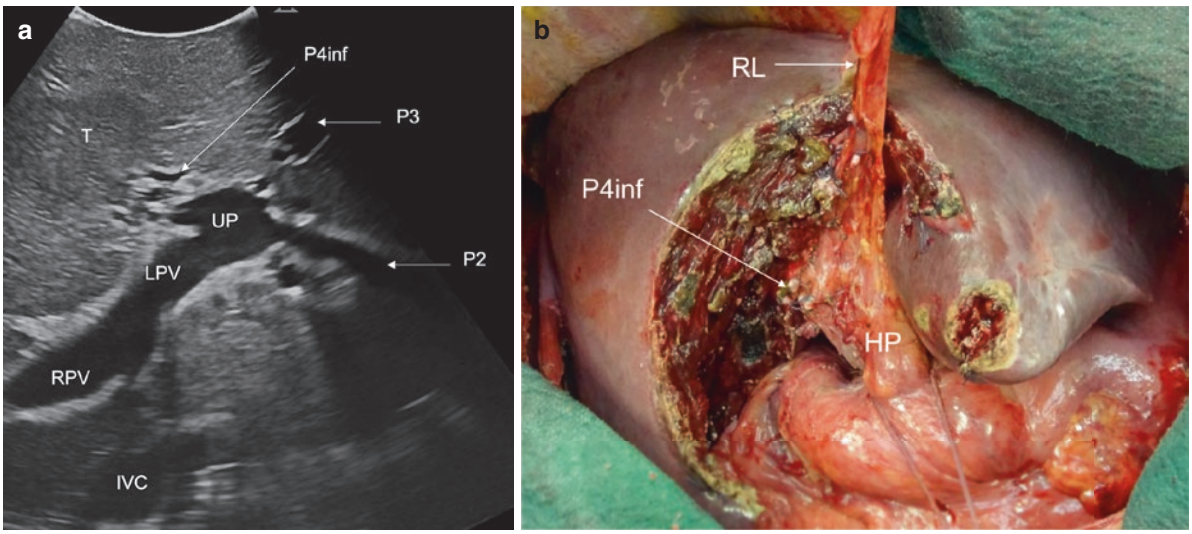

Fig. 18.1 (**a**) IOUS scan shows a CLM (T) invading the Glissonean sheath of segment 4 inferior (P4inf). (**b**) the cut surface at the end of S4inf subsegmentectomy. HP, hepatic pedicle; IVC, inferior vena cava; LPV, left portal vein; P2, portal branch to segment 2; P3, portal branch to segment 3; RPV, right portal vein, UP, umbilical portion

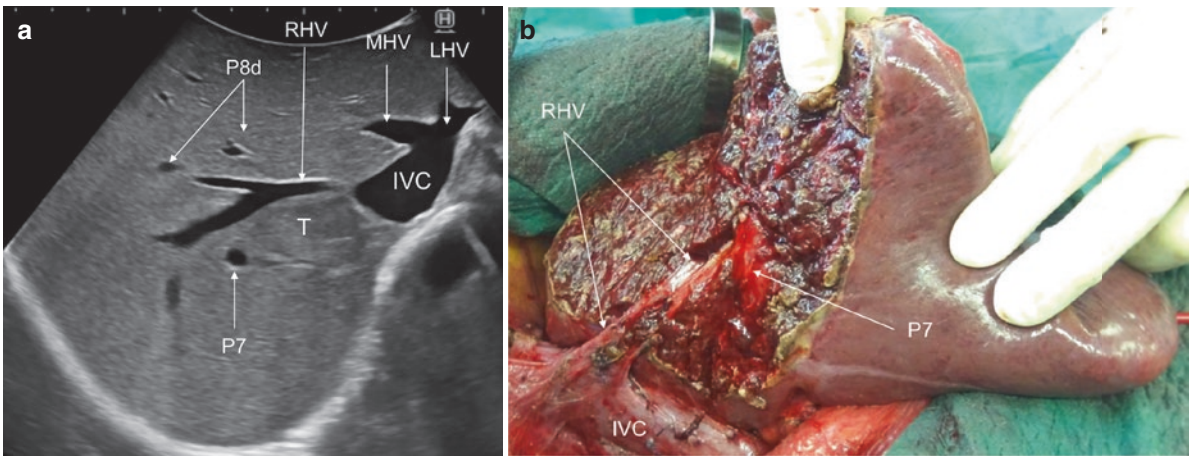

Fig. 18.2 (**a**) IOUS scan shows a CLM (T) in contact with the right hepatic vein (RHV) at caval confluence. (**b**) The cut surface at the end of segment 7 extended to segment 8 resection with CLM detachment from the RHV clearly exposed on the cut surface. IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; P7, portal branch to segment 7; P8d, portal branch to subsegment 8 dorsal

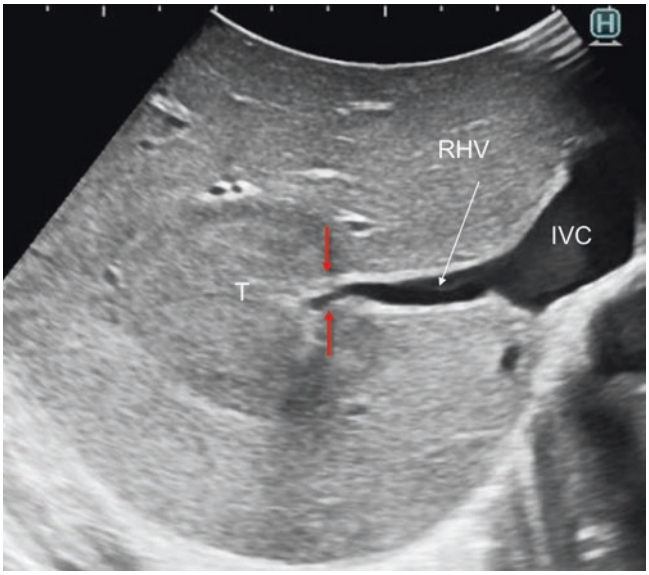

Fig. 18.3 IOUS scan shows a CLM (T) invading (red arrows) the right hepatic vein (RHV) at caval confluence and demanding its sacrifice. IVC, inferior vena cava

18.2.2 Tumour in Contact with Hepatic Vein

Similar to the GP, the HV may be spared when in contact with a CLM. The integrity of the vessel wall can be appreciated on IOUS (Fig. 18.2). Given the integrity of the vessel wall, a contact extension less than two-thirds of the vein circumference at IOUS would allow the HV sparing, inversely it should have not (Fig. 18.3). Anyway, in the case of partial infiltration of the HV wall, should not compulsorily demand HV sacrifice, indeed a partial resection with reconstruction by direct suture or patching, still allow to preserve the original venous outflow. In a series of 135 patients with CLM in contacts with HV at caval confluence, 50% of contacts could be managed with detachment, 32% with partial resection and just 2% by means of patching; the remaining contacts required HV resection, but less than 1% of patients had major hepatectomies [19]. The reason for that will be disclosed in the next paragraph.

18.3 The Outflow

Sometimes R1 vascular surgery could not be performed. In the event that the invaded major vessel would be a first/second order GP, there could be no alternative than removing the fed liver parenchyma together with the invaded vessel. In contrast, for the HV, major parenchymal resection should not be considered as inevitable. Several authors have shown the feasibility of grafting an invaded hepatic vein to spare parenchyma and expand the FLR. Technically sophisticated HV grafting has resulted in high morbidity and mortality [20]. Recently, Urbani et al. combined this approach with R1 vascular surgery successfully [21]. Makuuchi et al. in the 1980s suggested the possibility of parenchymal sparing surgery despite invasion of HV at the caval confluence just profiting of the accessory HV as a thick inferior right hepatic vein (IRHV) [22], which is present in 15–20% of patients [23]. In 2010, we showed that in presence of tumour-HV contact not amenable to detachment at the caval confluence, a compensatory circulation between the adjacent HVs could be almost always detected [24]. These communicating veins (CV) can be preoperatively detected by direct visualization or just confirming a uniform enhancement of the liver parenchyma during the venous phase of the CT or hepato-specific delayed phase for MRI. The CV patency is definitively detected by IOUS color-flow analysis: once recognized and preserved keep the chance of sparing liver parenchyma (Fig. 18.4). Indeed, in our reported experience in 30 contacts (16% of the whole) in 28 patients HV could not be spared, but despite that just one patient among 135 had major hepatectomy [19]. Given that, an extension of the resection to the liver parenchyma theoretically drained by the hepatic vein to be resected is considered only if all of the following IOUS signs are missing:

- Presence of accessory hepatic veins at IOUS, such as an inferior right hepatic vein (IRHV) [22], in the presence of an invasion at the caval confluence of the right hepatic vein.

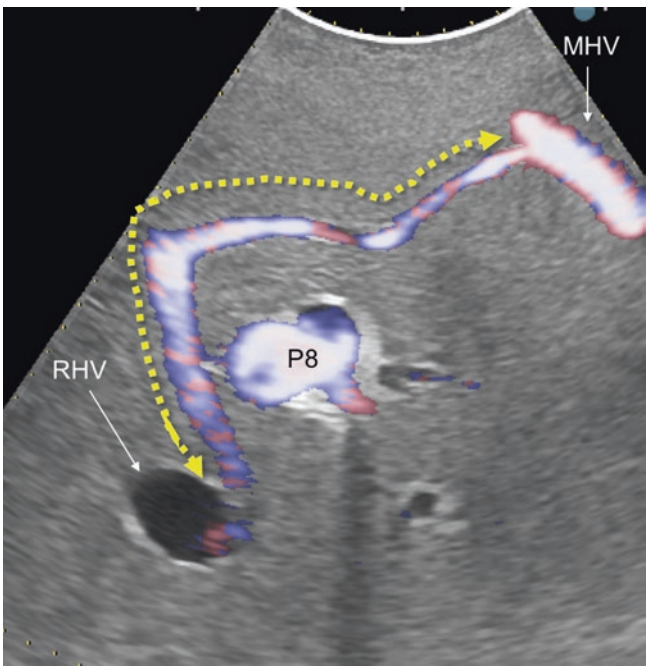

Fig. 18.4 Color-flow IOUS scan shows a communicating vein (the yellow dotted line is disclosing the path) connecting the middle hepatic vein (MHV) and the right hepatic vein (RHV). P8, portal branch to segment 8

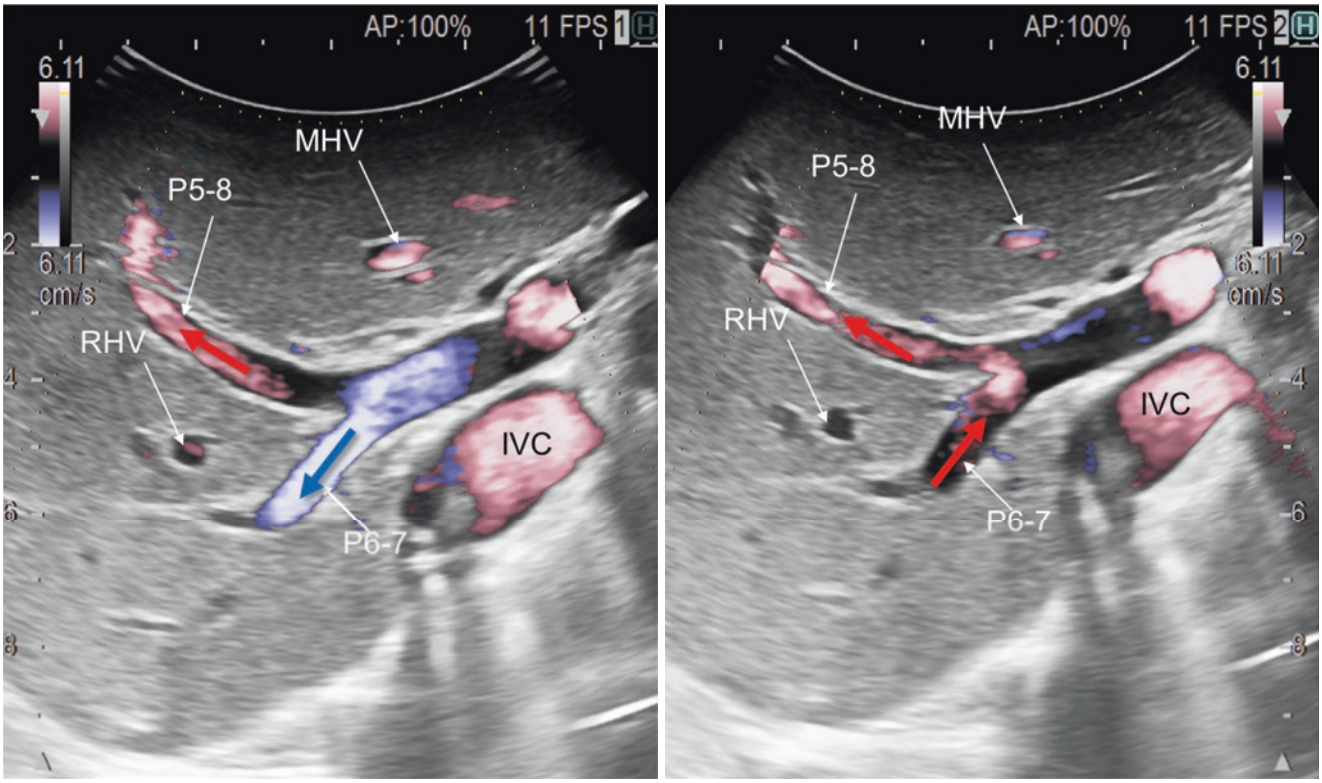

Fig. 18.5 Color-flow IOUS scan shows on the left the hepatopetal blood flow (colored arrows) in portal branches to segments 5 and 8 (P5–8), and segments 6 and 7 (P6–7); the right hepatic vein (RHV) was patent and color flow can be seen in its lumen. On the right, once RHV was occluded the blood flow in P6–7 became hepatofugal regurgitating towards the hepatic hilum as shown by the arrow. IVC, inferior vena cava; MHV, middle hepatic vein

- Color-flow (CF) IOUS showing hepatopetal blood flow in the feeding portal branch (Fig. 18.5), once the hepatic vein to be resected is clamped [13] by encirclement or finger compression of the vein extrahepatically [25].
- Communicating veins connecting adjacent hepatic veins, which are more easily detectable by using CF-IOUS (Fig. 18.4) [24].

18.3.1 Vessel Guided Hepatectomies

Results of R1 vascular surgery, and the existence and reliability of CV in the event of compromised outflow, and the use of IOUS constitute the pillars for a new approach: the vessel guided hepatectomies. According to this strategy, surgeons intentionally spare major vessels, and use them to guide the liver resection. Sparing the main GP and HV allows to keep cleared by the tumours the core of the organ, in a parenchyma sparing approach. Furthermore, following vessel from the surface to the depth of the liver warrantees anyhow an anatomical approach, inserting more freedom degrees compared to those offered by resection areas disclosed by vessel compression or dye injection. Recognizing and tracking, peculiarities as accessory veins, and CV further expand technical solution in case of unsuitability of R1 vascular surgery.

Vessel guided hepatectomies open a scenario of interaction with the liver anatomy, the tumours, their relations, and the consequent rearrangements, resulting in an implementation of the surgical options [26], and in the increase of the salvageability in case of relapse [19, 27]. Sculpturing rather than simply dividing the liver has induced a revision of the concept of minor and major hepatectomy [28], leading to the description of new hepatectomy approaches.

18.3.1.1 Systematic Extended Right Posterior Sectionectomy

Systematic extended right posterior sectionectomy (SERPS) is a surgical technique that allows the sparing of part of the right anterior section in the presence of tumours shown in Fig. 18.6 [29]. Patients suitable for SERPS are those with tumours showing one of three conditions: (a) invasion of the right hepatic vein (RHV) within 4 cm of the hepatocaval confluence with other lesions involving segment 6 and even-

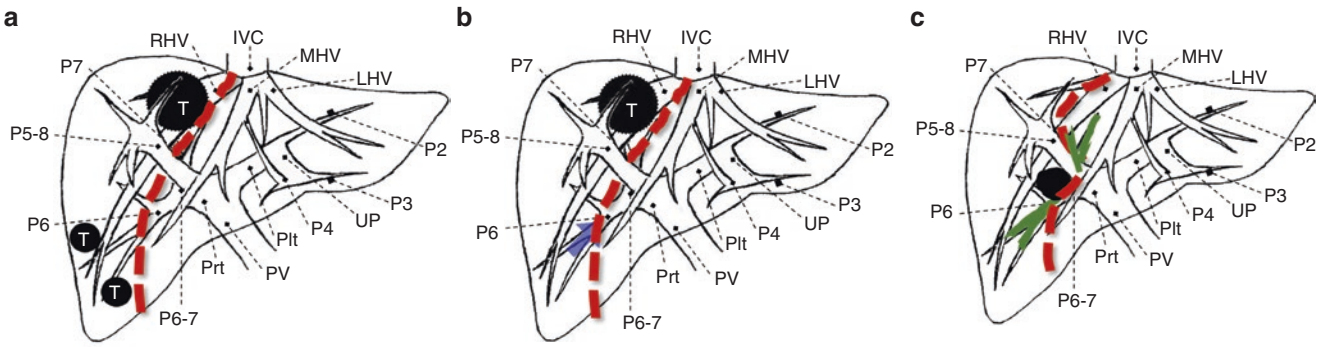

Fig. 18.6 Eligibility criteria for systematic extended right posterior sectionectomy (*SERPS*). In all circumstances, at color-flow IOUS hepatopetal portal blood flow (*arrows*) has to be evident in the main portal branch to the right anterior section (*P5–8*), once the right hepatic vein (*RHV*) is clamped, if not already occluded; (**a**) Presence of vascular invasion of the RHV at the hepatocaval confluence (within 4 cm) with other tumours (*T*) in segment 6; (**b**) Presence of vascular invasion of the RHV at the hepatocaval confluence (within 4 cm) without tumour in segment 6 but with hepatofugal portal blood flow (*blue arrow*) in the portal branch to the right posterior section (*P6–7*), once the RHV is clamped, if not already occluded; (**c**) Presence of vascular invasion of the right posterior portal branch (*P6–7*) or biliary dilation of sectional branches (*green lines*), with tumour (*T*) in contact with the P5–8 without signs of vascular invasion or biliary dilation. IVC, inferior vena cava; MHV, middle hepatic vein; LHV, left hepatic vein; P2, portal branch to segment 2; P3, portal branch to segment 3; P4, portal branch to segment 4; P6, portal branch to segment 6; P7, portal branch to segment 7; Plt, left portal branch; Prt, right portal branch; UP, umbilical portion

tually segment 7; (b) invasion of the RHV within 4 cm of the hepatocaval confluence in patients who do not have proper outflow for segment 6 (IRHV or CV) once the RHV is divided; (c) when a CLM is in contact without infiltration with the right anterior Glissonean sheath but shows infiltrative pattern with the right posterior one.

18.3.1.2 Mini-Mesohepatectomy

Mini-mesohepatectomy (MMH) represents an alternative to the conventional mesohepatectomy in patients with tumours invading the middle hepatic vein (MHV) at its caval confluence. MMH consists of a limited resection, including the tract of the invaded vein without reconstruction while sparing segments 4 inferior, and 5 [30]. The operation is possible in presence of CV between the MHV and RHV and/or LHV and/or IVC. If no CV are evident at color-flow IOUS, reversal flow in the peripheral portion of the clamped MHV should be confirmed: this finding suggests the existence of communicating veins with the adjacent hepatic veins. As additional confirmatory finding, hepatopetal flow in the residual portion of the central segments (4, 5, 8) indirectly confirms the existence, although undetected, of communicating veins with the adjacent hepatic veins.

18.3.1.3 Transversal Hepatectomies

For tumours involving 1, 2 or even all the hepatic veins at the hepatocaval confluence, the traditional approach is between a major hepatectomy with possible vascular reconstruction and unresectability. In 1987, Makuuchi reported that once the presence of a thick IRHV is evident on preoperative imaging and/or IOUS, resection of the tumour together with the RHV is feasible without carrying out a formal right hepatectomy, limiting the liver parenchyma removed to only segments 7 and 8. This was the first paper showing how a particular anatomic feature can allow a surgical procedure that previously was not considered feasible [22]. R1 vascular surgery and CV detection have further established transversal hepatectomies as reliable approaches. According to the resection or detachment of the hepatic veins and in the event of resection by the number of hepatic veins sacrificed they can be classified as follows:

Rollercoaster Hepatectomy

Transversal hepatectomies for one to multiple tumours in detachable contact (fully detachable or by means of partial HV wall resection) [31] (Fig. 18.7).

Transverse Hepatectomy with HV Resection

Transversal hepatectomies for tumours in no-detachable relation with one or more HVs at hepatocaval confluence in presence of an IRHV, and CVs or just CVs. The tumour could lie over the hilar plate with contact but no invasion of the right and left portal branches, and eventually over the segmental portal branches to the antero-inferior segments. According with the number of HV sacrificed we recognize: *Mini-Upper Transversal Hepatectomy:* resection of S7–8 with section of the RHV (right Mini-Upper) (Fig. 18.8) or S2–4s with section of LHV (Left Mini-Upper) in presence of IRHV or just CV [32, 33]; *Upper Transversal Hepatectomy*: resection of S7–8-4s and partial or total of S1 with section of the RHV and the MHV [34] or resection of S2–4s-8 and the cranial portion of S1 paracaval with section of the LHV and

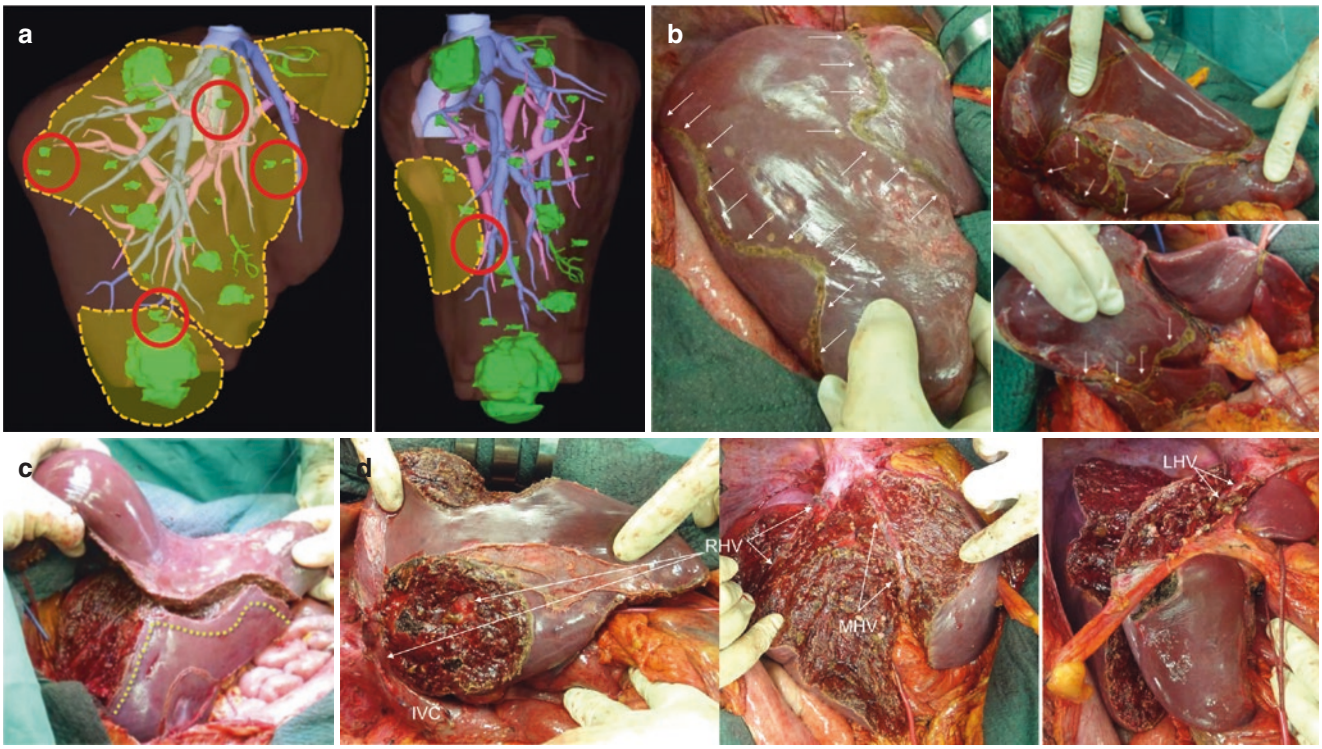

Fig. 18.7 Surgical treatment of a patient with multiple bilobar CLM. (**a**) In this liver cast based on preoperative imaging the orange-dotted lines and red circles highlight single resection area grouping a cluster of lesions, and those compound CLM featured by being deeper and/or in relation with vascular structures and or more peripheral, respectively: clusters and compounds are the landmarks for performing these geometrically complex resections; (**b**) the resection areas (*arrows*) drawn on the liver surface according to that drawn on the preoperative cast; (**c**) A rollercoaster dissection plan (yellow dotted line); (**d**) the multiple cut surfaces with exposure of the 3 hepatic veins. IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein

the MHV [33], in presence of double arch CV; *Total Upper Transversal Hepatectomy:* resection of S2–4s-7-8 with section of the RHV, the MHV and the LHV in presence of an IRHV and CVs among the liver-sided stumps of the HVs, which guarantees the outflow of S3-4i-5-6 [33, 35].

18.3.1.4 Liver Tunnel

The liver tunnel [27, 36] procedure represents an extension of the MMH [30], with or without removal of the MHV, and including the total removal of segment 1 (Fig. 18.9)**.** Patients eligible for this approach are those with tumoural involvement at various degree of segments 8, 4 superior, and 1. There could be contacts between the tumour or the tumours with the MHV, the LHV, and the RHV at caval confluence, and similarly with the right, and the left first and second order portal branches. In the event the MHV is invaded by the tumour, to proceed CVs between the MHV, the RHV, and/or the LHV should be confirmed.

18.3.1.5 Parenchyma Sparing Major Hepatectomies

The aforementioned procedures, strictly linked to the concepts of R1 vascular and CV, have been often adopted in combination with other resection for successfully affording patients with multiple bilobar CLMs. Combining them and associating them with other minimal procedures as simple limited resections results as a sum of parenchyma sparing procedures which more or less could be assimilated to major hepatectomies [15]. The only but distinctive difference between the conventional major hepatectomies and these parenchyma sparing major hepatectomies consists in the fact that the first imply vessel transection while the others are based exactly on the opposite. Maintenance of the liver scaffold, and the main vessel harboring of the organ are the pillars while removing liver tissue in an amount which is comparable with that removed for any right or even extended right/left hepatectomy. Based on new oncologic principles and anatomical conditions as the R1 vascular and the CV respectively, the technical pillars for performing such procedures are essentially two:

1. recognition of suitable metastatic clusters. The possibility of grouping lesions in recognizable clusters enables the optimization of the ratio between normal and diseased tissue removed which is crucial for performing these kinds of procedures (Fig. 18.7a).

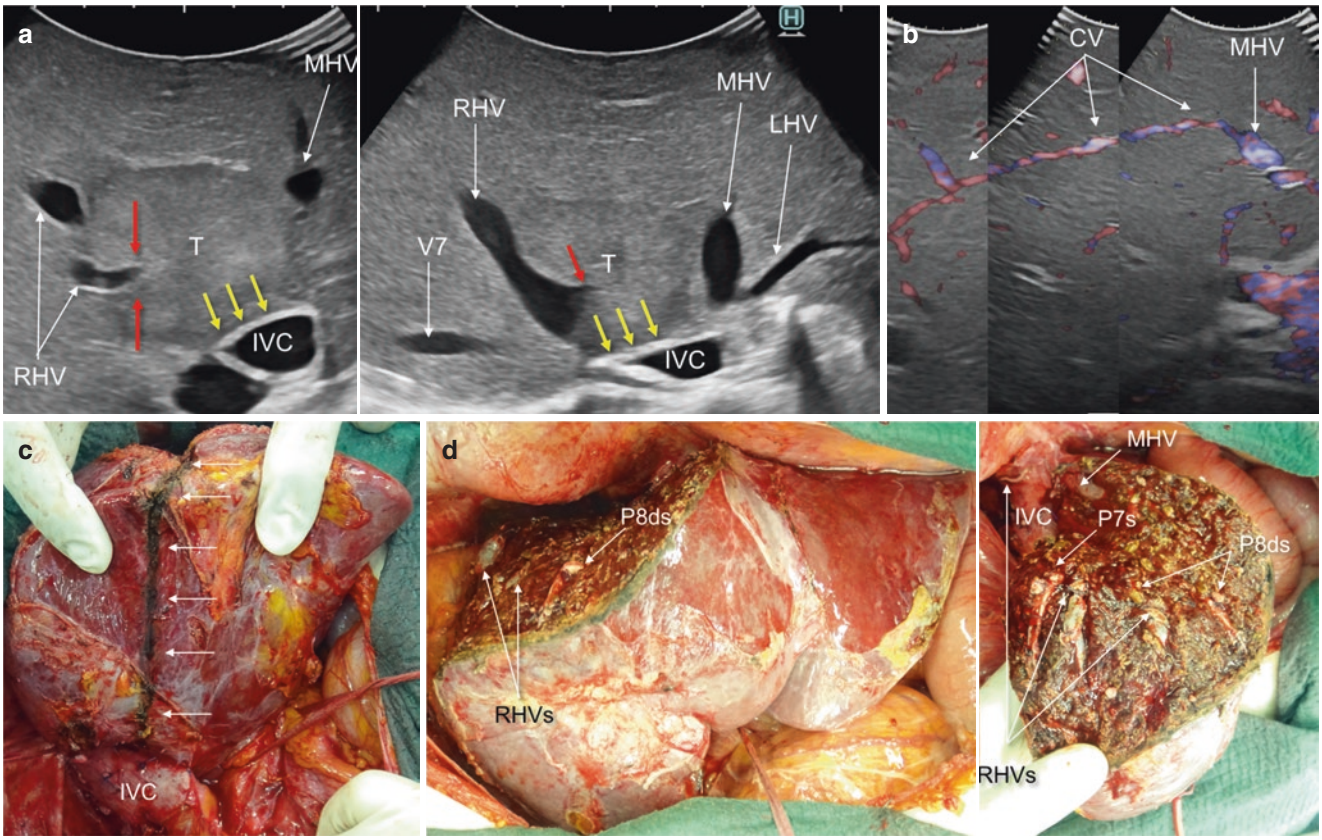

Fig. 18.8 (**a**) From left to right IOUS scan shows the tumour (T) invading (*red arrows*) the right hepatic vein (RHV) at caval confluence, in close adjacency with the middle hepatic vein (MHV), and in contact (*yellow arrows*) with the inferior vena cava (*IVC*); (**b**) At color-flow IOUS a communicating vein (*CV*) between the MHV, and the RHV was confirmed; (**c**) the resection area drawn on the cut surface (*arrows*); (**d**) the cut surface shown into two perspectives. RHVs, right hepatic vein stumps; P7, stump of portal branch to segment 7; P8ds, stump of portal branch to segment 8 dorsal

2. identification of the compass points of each group of lesions: these are represented by the deepest lesion, those in contact or close proximity with major intrahepatic vessels, and those most peripheric in the cluster (Fig. 18.7a).

For the safety, and the proper result of the parenchyma sparing major hepatectomies, some tools, tricks, and tips are needed. An accurate preoperative estimation of the FLR is a key factor for successful hepatectomy. The manual plotting of resection areas on each CT/MRI scans (so-called "hand-trace technique") remains the gold standard for assessing the liver volume. The planning of anatomical hepatectomy using this method can be relatively easy to perform, and a certain degree of accuracy in the volume estimation can be achieved [37, 38]. The introduction of 3D simulation modalities has standardized the FLR estimation in the anatomical resections by computing the modality, limiting the operator-dependence of the hand-trace technique, and speeding up the process [39–41].

Things become more complex when the resections have a multiplanar path, and furthermore once they are multiple: for such a condition, the hand-trace estimation of FLR is not feasible. Although, for complex parenchyma-sparing resection, intraoperative findings may impact the surgeon decision-making resulting in a modified strategy, a reliable preoperative estimation of the FLR according to the previous planning could act anyway as trustable baseline. Recently, the authors demonstrated the reliability of 3D virtual cast in predicting the FLR exclusively in patients with bilobar, and deep-located CLMs [42]. A minimal difference between the pursued and real FLR, with a slight preoperative underestimation (median error rate was 0.6%) was disclosed. The intraoperative "adjustment" of the planned surgical procedure, aiming to maximize the parenchyma-sparing in these patients, could partially explain a minimal and negligible difference. For sure 3D virtual cast applied in the peculiar setting of parenchyma sparing major hepatectomies for multiple bilobar CLM resulted in increased safety and as consequence could act as a further element favoring its standardization and at the end diffusion (Fig. 18.7).

Furthermore, the surgical treatment of multiple bilobar CLM, irrespective of the procedure, requires a precise definition of the liver involvement before starting preoperative

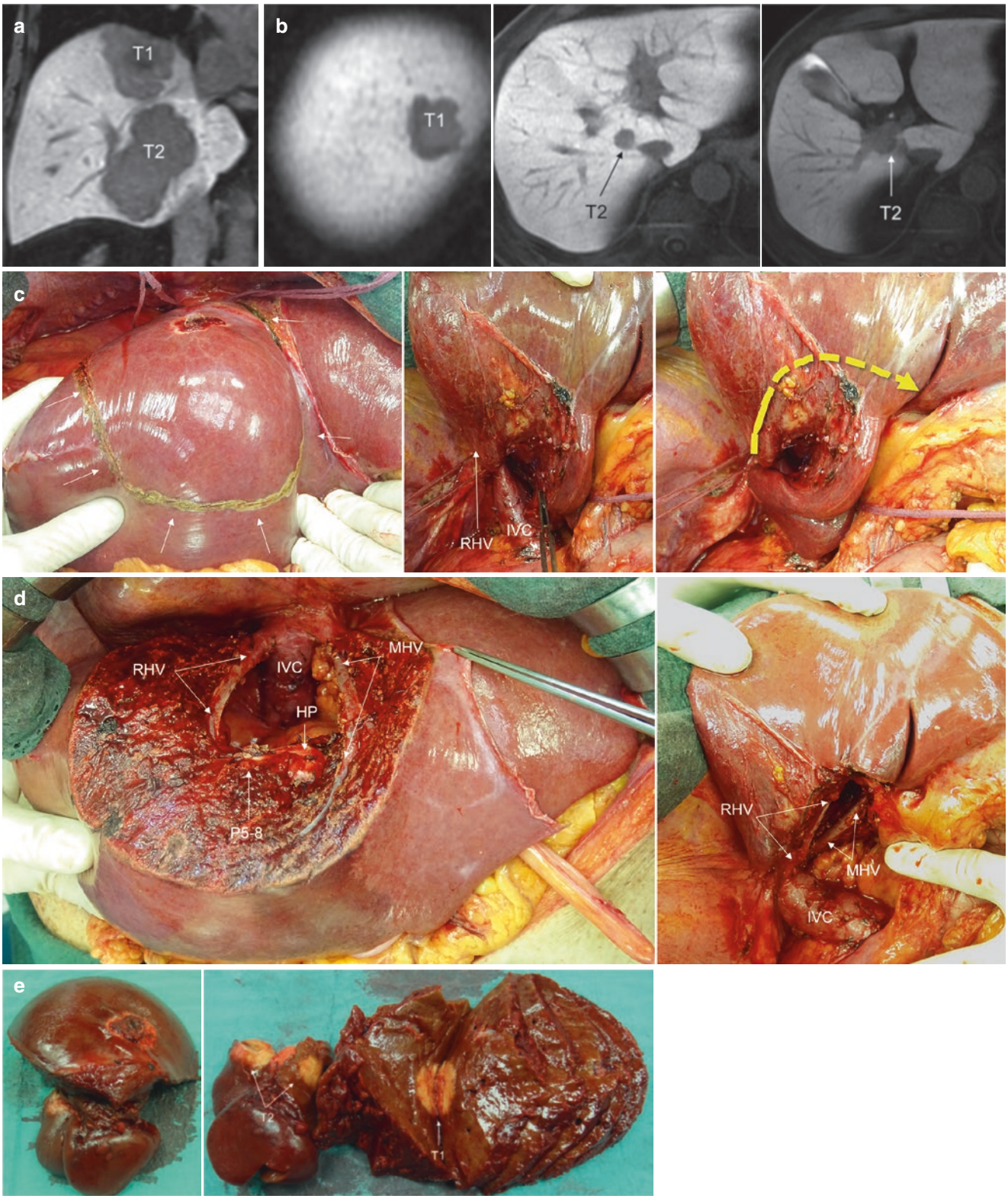

Fig. 18.9 (**a**) This picture shows the frontal MRI image of two CLM (*T*) occupying segments 8 (*T1*) and 1 (*T2*) as they appeared before neo-adjuvant chemotherapy; (**b**) this picture shows the transverse MRI images of the two tumours preoperatively: T2 remained in contact with the posterior surface of the portal bifurcation; (**c**) resection areas (*arrows or yellow-dotted arrow*) as drawn on the liver cut surface after complete detachment of the liver from the inferior vena cava (*IVC*); (**d**) panoramic view of the cut surface; notably the primary and secondary Glissonean sheath, and the IVC are exposed, as the middle hepatic vein (*MHV*), and the right hepatic vein (*RHV*) which resulted exposed both in their upper (*left-sided image*) and posterior (*right-sided image*) aspects; (**e**) this pictures show the specimen after removal. P5–8, portal branch to the right anterior section

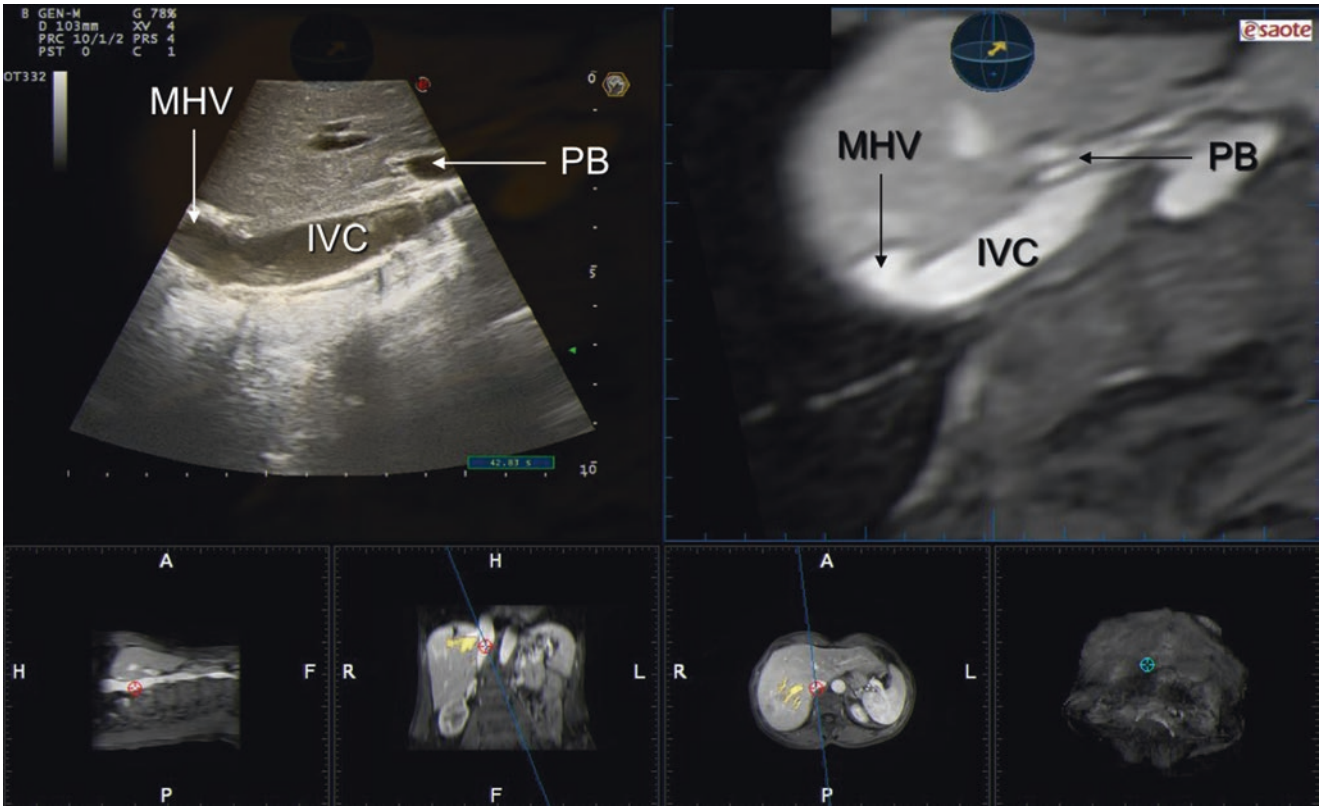

Fig. 18.10 From left to right the picture shows the IOUS and MRI images at the same scan in a fusion imaging modality released by the US machine once the MRI images are pre-uploaded. IVC, inferior vena cava; MHV, middle hepatic vein; PB, portal branch

therapy. Indeed, measurement of the treatment response and disclosure of any CLM disappearance are the most relevant issues to be defined after systemic treatment and prior to surgery. CLM disappearance of these lesions at the preoperative imaging does not mean complete pathological response and their removal should be pursued [43]. As mentioned, the event surgical strategy would consist in a single session parenchyma sparing major hepatectomy the identification of the clusters' compass points represents one of the pillars. That becomes essential in those conditions featured by multiple CLM disappeared after chemotherapy. For this reason, pre-chemotherapy imaging assumes a crucial role since it may act as standard of reference for visualizing CLMs and particularly those acting as compass lesions, and eventually disappeared. The fusion imaging featuring most of advanced US systems is able to match in real-time any preoperative imaging, with pre-chemotherapy CT or MRI, with the IOUS resulting in a simplified and low-cost solutions for intraoperative navigation in these particular circumstances (Fig. 18.10).

18.4 Conclusions

The authors hope that this chapter convinced the reader of the oncological suitability of R1 vascular surgery for CLM. This suitability further enhances its application for surgery of complex conditions including multiple bilobar CLM. Case-match comparative reports have shown how short- and long-term results of this policy are at least comparable if not superior to those of TSH [44] and ALPPS [45]. Furthermore, R1 vascular CLM surgery, keeping the liver scaffold has offered more chances than liver resections accomplished by vessel excision for salvageability in case of relapse.

In such context, R1 vascular should be subcategorized to characterize its different local recurrence risks. For now, factors related to mutational status of the CLM, type of growth, and reaction to different preoperative systemic treatments have been explored. In a preliminary experience, while KRAS mutation (mKRAS) support the lower risk of local recurrence after R1 vascular resection compared to R1par, this seems not the case for wtKRAS, which exposed to similar recurrence risk both for R1 par and R1 vascular procedures [46]. For sure, this result suggests that a status normally associated with a greater biological aggressiveness like mKRAS could protect from local recurrence after R1 vascular resection when compared to wtKRAS. This needs further confirmation. In addition, recent data showed how the growth pattern may correlate with the recurrence risk [47]. This aspect may deserve some consideration in the R1 vascular surgery perspective. Indeed, CLM featured by a tissue replacement growing pattern seems associated to a higher

risk of recurrence [48]. Furthermore, progresses in imaging modality and particularly radiomics may help in better selecting patients by more precisely foreseeing the tumour-vessels relations and the type of tumoural growing patterns.

In conclusion, given the possible existence of R1 vascular subcategories, when suitable, tumour-vessel detachment for CLM, provided a more tolerable large tissue deprivation, and opened the scenario to parenchymal sparing surgery for those settings up to now unresectable or at best suitable for staged approach.

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Prevention and Treatment of Perihepatic Fluid Collection Including Two-Step Air Leak Test

19

Ching-Wei D. Tzeng

Learning Objectives

- Recognition and timely treatment of perihepatic fluid collections and bile leaks are vital to mitigate sepsis risk and negative effects on liver regeneration.
- Almost any bile leak test is better than doing no bile leak test.
- A negative bile leak test can help the surgeon omit a surgical drain.
- Surgical drains should not be placed for uncomplicated cases.
- The air leak test is inexpensive, reproducible, and highly sensitive for detecting and fixing occult bile leaks to reduce fluid collections and clinical bile leaks.

19.1 Introduction

Despite significant technical advances over the past couple decades which allow surgeons to safely operate on more patients and to perform more complex hepatectomies, the morbidity of postoperative perihepatic fluid collections and bile leaks persists. Depending on the patient population, complexity of resection (with or without biliary reconstruction), and bile leak definition, the bile leak incidence can range from low single digits up to one-third of patients [1–5]. Symptomatic fluid collections and bile leaks are significant causes of extended hospitalizations, readmissions, and associated downstream complications, including invasive procedures and even death. Nomenclature issues (e.g., definitions of leaks) have limited the ability to compare these complications across institutions and across secular eras. As an example, in the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) database, percutaneous drainage associated with a database-recorded event of perihepatic fluid collection/abscess was twice as common as biloma [4]. But the reality is that without a bilirubin level to document the drain bilirubin/serum bilirubin ratio, a registrar is unable to classify a likely biloma as a biloma and must simply call it a fluid collection or abscess. Thus, it is reasonable to consider these symptomatic fluid collections and bilomas as a composite outcome, since both need similar workups and treatment, as further described below.

The International Study Group on Liver Surgery (ISGLS) [6] defines bile leak grades based on morbidity rather than simply drain bilirubin levels [7]. A bile leak is any drain fluid bilirubin concentration ≥ 3× the serum bilirubin on or after postoperative day 3, a bilious fluid collection requiring intervention, or a clinically evident (by drain fluid color/character) bile leak. A Grade A bile leak does not affect usual care. A Grade B leak requires a change in usual care (i.e., adding a percutaneous drain) but does not require an unplanned return to the operating room. A Grade C leak involves a takeback and is associated with extremely high mortality risk from the downstream sequelae. While it is easy to assume that Grade C leaks are potentially deadly, it is worth highlighting that even Grade A and B leaks had a 6% mortality in a multicenter validation study of 11 expert centers, implying that bile leak-associated death rates could be even higher in real-world data outside of expert centers [7].

19.2 Diagnosis and Management of Fluid Collections and Bile Leaks

The management of a symptomatic perihepatic fluid collection or bile leak requires timely workup and intervention. Delays can lead to worse inflammation, potential sepsis, and even issues with liver regeneration [8]. Depending on the presence or absence of a surgical drain, a bile leak can be

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diagnosed in several ways. With a surgical drain in situ, the fluid color/character or the drain fluid bilirubin, on postoperative day 3 (which would prompt early removal if negative), can diagnose at least a Grade A leak. If this prophylactic drain works well and there is not a separate undrained fluid collection, then the surgical drain can remain until resolution with no significant change in usual care or longer hospitalization. In the absence of sepsis, surgical site infection, other undrained collection, or biliary-enteric anastomosis as the source of leak, antibiotics are not needed for simple leaks from hepatectomies without biliary reconstructions.

If the drain volume does not steadily decrease, then percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) may be needed to find the nidus of the leak and to place a stent to increase preferential biliary drainage toward its outflow. PTC and ERCP should not be reflexively ordered before the drain output has been followed for several days because both procedures have their associated risks, especially with nondilated ducts. ERCP can lead to pancreatitis, and PTC can lead to hemobilia.

If there is no surgical drain or if the leak is diagnosed after surgical drain removal, then a computed tomography (CT) scan can identify a fluid collection. These patients will often be symptomatic with worsening abdominal pain, a reincrease in postoperative pain medication use, fever, tachycardia, nausea or ileus, and diaphragm irritation manifested as scapular pain or hiccups. Antibiotics should be started early if there are signs of sepsis. Antibiotics are quickly tailored to culture data if available. CT is important because it can help differentiate drainable collections such as bilomas, abscesses, and contaminated fluid collections, versus benign collections such as seromas and chylomas. When diagnosed after discharge, these patients require a readmission for imaging, percutaneous drainage, and antibiotics. After the sepsis is controlled, patients can be discharged and managed similarly to patients who had a perihepatic fluid collection or bile leak found during the original surgical admission.

19.3 Bile Leak Prevention Tests

Risk factors for bile leak include complexity of resection, caudate resection, hepatic duct resection, higher blood loss requiring intraoperative transfusion, repeat hepatectomy, and, in numerous contemporary studies, surgical drain placement [5, 7, 9–11]. After resection, the transection surface and any Glissonian pedicle staple/suture line should be inspected for bile staining. Figure 19.1 shows a right hepatic duct staple line (after robotic-assisted right hepatectomy) with incomplete closure of the "B's" of the staples of the endovascular stapler. This overt leak requires direct suture repair. The liver capsule should be inspected for inadvertent fractures or lacerations, even from simple injuries such as instrument retractors or "stay" sutures used for retraction.

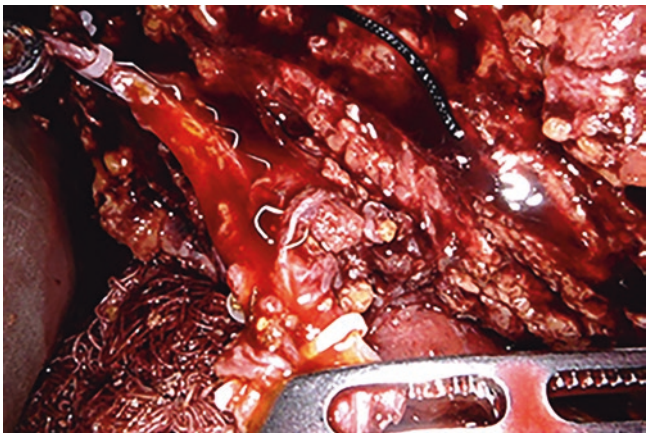

Fig. 19.1 Staple line after robotic assisted right hepatectomy with endovascular stapler used for right hepatic duct with Glissonian sheath. Because the "B's" of the staple line did not properly form, this overt leak required a suture repair

There is no consensus on post-resection bile leak testing among surgeons. This mirrors the lack of consensus on parenchymal transection technique as well. However, there are enough data which exist to suggest that performing a bile leak test is worth the time invested.

Bile leak test options include biliary injection of radiographic contrast, saline [12], methylene blue [13], fat emulsion ("white test") [14, 15], indocyanine green (ICG) [16, 17], or air [5, 18], for intraoperative detection and repair of occult bile leaks. Systematic reviews of surgical studies have shown that methylene blue, fat emulsion (with saline flushes), ICG, and air, are all reasonable options to consider, in that they all show a high detection rate of occult leaks (more than 50% of cases) which leads to a decrease in clinical leaks manifesting postoperatively [19, 20]. All these prospective and retrospective studies compared one type of bile leak test versus no test. There are no studies comparing one fluid injection method to another fluid (e.g., fat emulsion vs. methylene blue). Also, limiting reproducibility is the inexact volume of fluid and pressure that should be delivered to induce an occult leak [20].

In most large US retrospective cohort studies, the rate of surgical drain placement is almost exactly half of all hepatectomies but may be slightly increasing toward 60% from just under 50% in the past decade [4, 10, 21]. This reflects a true debate on the topic of prophylactic surgical drain placement. In a recent Japanese randomized controlled trial of 400 patients across seven hospitals of drain versus no drain after uncomplicated hepatectomy, the no-drain group had zero bile leaks versus 8.0% in the drain group. The authors concluded that drains should not be placed routinely after uncomplicated hepatectomy. The fine print that pro-drain

surgeons will point out is that 37 patients were excluded from the study due to an intraoperative assessment by the surgeon of a high risk for bile leakage or hemorrhage.

To supplement the level 1 data above, there are numerous national and multicenter cohort studies which show the consistent association between surgical drain placement and bile leaks [4, 10, 11, 21]. In total, these retrospective studies show the *effectiveness* and the randomized trial shows the *efficacy* of omitting a surgical drain after hepatectomy.

Despite these data, some surgeons will continue to routinely place drains with the putative reason that it can prevent a secondary drain placement, if a leak happens. However, accumulated data show that most percutaneous drains are placed in patients who already had a surgical drain. If a surgeon chooses to place a drain due to a perceived high-risk situation, it should be removed in a timely fashion by postoperative day 3, when it is no longer needed as a transabdominal window for detecting bleeding or bile leak [10, 22]. One can see that a practical benefit of a bile leak test is the ability to directly repair occult leaks before abdominal closure and to thus feel less anxious about omitting a surgical drain.

19.4 Air Leak Test

Developed at MD Anderson Cancer Center by Dr. Vauthey and colleagues, the "air leak test," or "air cholangiogram" is a novel bile leak test which reduces both perihepatic fluid collections and bile leaks [5, 18]. During the operation, the cystic duct stump is left longer than usual when the cholecystectomy is performed, so that it is easy to intubate after all hepatic resections are completed. Then at the end of the resections, a 6.5 Fr cholangiogram catheter is intubated into the cystic duct after removal of the temporary tie. It is not necessary to push the catheter into the common bile duct. The tip of the catheter is secured with a medium caliber (e.g., 2-0/3-0 silk) tie to prevent air leaking out of the cystic duct. A surgeon's left hand is used to clamp the distal bile duct as air is injected until there are shadows in the Glissonian pedicles and eventually what looks like "bright lights in a night sky" (Fig. 19.2). This view confirms biliary tree patency and no injury to the remnant duct post-transection. Air is injected until the catheter has a "bounce," or recoil, of 1 mL on the Luer-Lock syringe (Fig. 19.3). This allows an objective barometric test with that 1 mL "bounce" without excess barotrauma, since the goal is simply to expose occult leaks, and not to blow off ties and clips. Once the liver is filled of air, the remnant is dunked under sterile water to look for bubbles. Any bubbles thus represent overt bile leak areas which should be repaired with 6-0 polypropylene sutures if staples or small anchor ducts are leaking on the major Glissonian stump, or with 4-0 sutures if just a tiny duct that needs to be sewn shut. In our experience, the most common areas for an occult leak are the edges of the hepatic duct transection line due to nonoverlapping staples or nonformed "B's" of the staple line. Hemostatic agents can be placed after completion. If any agents are placed on the transection line before the air leak test, the material should be washed off to ensure a clean look at the entire transection surface.

Our positive experience with the air leak test, or air cholangiogram, has led to its adoption as standard of care in our

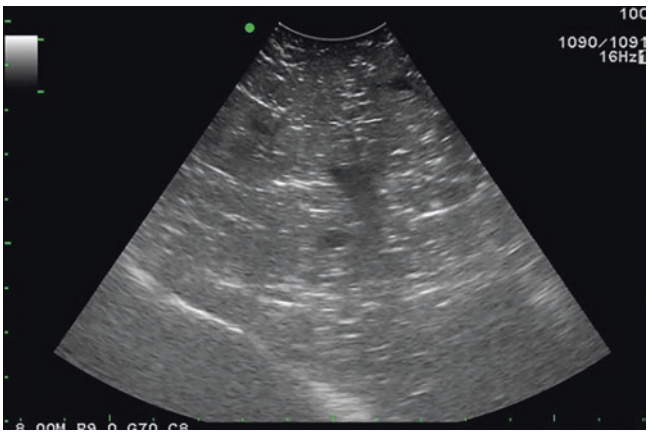

Fig. 19.2 Intraoperative ultrasound confirms air filling the biliary tree with echogenic signals that look like bright lights in a night sky. The shadows coming off the Glissonian pedicles confirm a patent biliary system without accidental injury to the remnant side

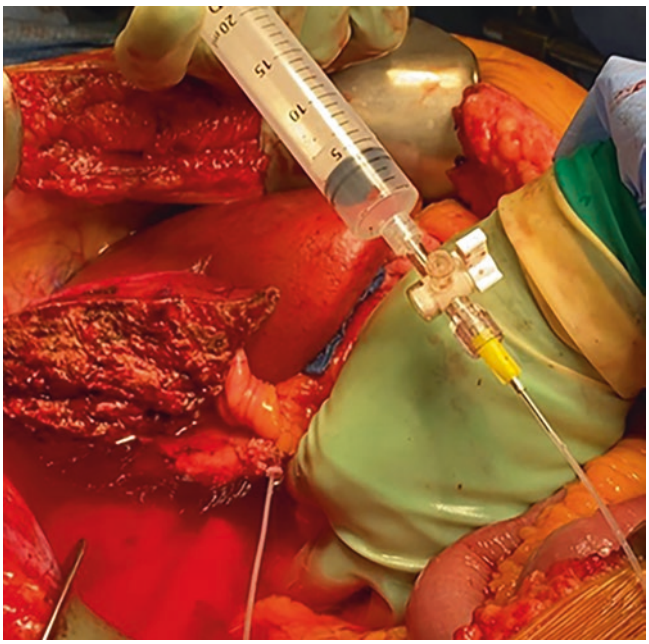

Fig. 19.3 A standard Luer-Lock syringe is connected to a 3-way stopcock and then the cholangiogram catheter. Air is injected until the biliary tree is full enough to see a 1 mL "bounce," or recoil of the syringe stopper due to complete pressurization of liver remnant. The left hand is occluding the distal bile duct during this time

department over the past decade with our open hepatectomies. Based on our retrospective matched cohort study of 103 air leak tested patients versus 120 matched nontested patients, the clinical bile leak rate was reduced from 10.8% to 1.9% ($p = 0.008$) after major hepatectomy [5]. While this was not a prospective study, the mechanistic reasoning for this reduction is clear. Sub-clinical, or occult, leaks were more often found (62.1% in the intervention cohort vs. 8.3% in the control cohort). The air leak test is so sensitive (due to the positive pressure of injection) that surgeons find leaks that would never manifest clinically. However, by fixing each area of bubbling, the leak rate is reduced to as close to zero as realistically possible in high-risk operations. As clinical and sub-clinical leaks are likely the biggest driver of organ space infections and further complications, the air leak test also reduced the organ space infection rate from 13.0% in a control group to 5.2% in an intervention group and 90-day morbidity from 40.7% to 24.8%, in a follow-up study of 210 air leak tested patients versus 108 nontested patients. This in turn reduced 45-day readmissions for these major hepatectomy patients from 12.3% to 7.2% [18].

Perhaps its greatest advantage over other bile leak tests is that there is no white, blue, or green mess to clean up or to obscure repeat injections. This can continue until all occult leaks have been repaired. Then the catheter is removed, excess air can be milked out, an orogastric tube can decompress the stomach and duodenum, and the cystic duct is tied off lower that the original cut line. Using the intraoperative ultrasound, we also recommend checking the vascular flow of the remnant portal vein and hepatic artery, especially if a Pringle maneuver was used in the operation. This documents no thrombosis. This should be done before air injection so that the air shadows and echoes don't obscure the flow images. The air leak test, or air cholangiogram, can offer the surgeon reassurance in terms of perihepatic fluid collection and leak risk, and help obviate the need for a surgical drain [23].

19.5 Conclusions

In summary, postoperative symptomatic perihepatic fluid collection and bile leak remain major sources of potentially preventable morbidity and mortality, with associated patient sequelae. Based on available data, it is strongly recommended to use a bile leak test when possible to identify occult leaks to prevent clinical leaks from manifesting. Based on level 1 data, routine surgical drains should not be placed for uncomplicated hepatectomies. The air leak test is an easily reproducible bile leak test which is highly sensitive for occult leaks and can facilitate a reduction in routine surgical drain placement.

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Synchronous Presentation of Primary and Colorectal Liver Metastasis: Classic, Reverse, and Combined

20

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Learning Objectives

- Management of synchronous liver metastases is complex and remains controversial.
- The classic, the reverse, and the combined approaches should not be mutually exclusive but rather proposed to different types of patients.
- Surgical strategy should be based on liver and colorectal tumour burden, and on evaluation of surgical risk of planned surgery.
- Liver-first approach is more often chosen in patients with bilobar hepatic disease, rectal tumour, and receiving more neoadjuvant chemotherapy.

20.1 Introduction

The liver is the most common site of metastatic disease, with an estimated 15–25% of CRC patients at the time of diagnosis presenting with synchronous colorectal liver metastases (SCRLM) [1]. Although different and various definitions of synchronous metastases exist (i.e., at or before diagnosis of the primary tumour, metastases detected up to 3, 4, 6 months or patients with a disease-free interval from the primary to discovery of the liver metastases (LM) of less than 12 months), for the purpose of this chapter, we will refer to patients presenting with imaging indicating a presence of both colorectal tumour and liver metastases at or before the time of diagnosis of colorectal tumour, as proposed in the international multidisciplinary consensus published in 2015 [2].

Patients with synchronous liver metastases presenting at clinical evaluation for resection have increased in number, and dealing with these patients has become extremely frequent in the daily practice of a hepatobiliary center. In the experience of our own center, out of 1025 patients resected for colorectal liver metastases during the last 20 years, rate of resection for synchronous metastases increased from 53% between 2000 and 2009 to 75% between 2010 and 2019 (unpublished data).

Management of synchronous liver metastases is complex and remains controversial for the wide variety of factors influencing the strategy related to primary tumour as presence of symptoms, site, local infiltration, or to LM as initial resectability and liver tumour burden. Further conditioning factors include need to consider radiotherapy for rectal cancer and the role of laparoscopic surgery. Significant variations exist regarding the choices of a therapeutic strategy for CRLM not only between surgeons and oncologists, or between general and hepatobiliary surgeons, but also even among experts [3].

Traditional approach to patients with synchronous liver metastases considers simultaneous colorectal and hepatic resection (combined approach), or colorectal resection followed by liver resection (primary tumour-first approach), with chemotherapy performed in the perioperative period. In 2006, Mentha et al. proposed a reverse strategy (liver-first approach) scheduling first liver resection and then primary tumour resection to prioritize removal of the most prognostically relevant disease (liver metastases) and to ease inclusion of radiotherapy for locally advanced rectal tumours [4]. Other factors to be considered in the decision-making process are related to tumour biology, which has a growing role in risk stratification of these patients. To date, the choice of the treatment strategy of synchronous CRLM relies on a case-by-case evaluation by multidisciplinary expert teams rather than on robust evidence-based data.

In routine clinical practice, however, many patients with synchronous colorectal liver metastases never meet a hepatobiliary surgeon before primary tumour resection. The early involvement of a hepatobiliary surgeon in the management of these patients is crucial to best determine the timing and sequence of chemotherapy with primary tumour and liver surgery, and hence improve patient outcomes and survival

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[5]. In fact, it has been clearly shown and repeatedly advocated that multidisciplinary specialistic evaluation of these patients improve survival [1, 2, 6].

In this chapter, the three surgical treatment strategies for patients with SCRLM are presented and discussed.

20.2 Primary Tumour-First Approach

The primary tumour-first approach is the traditional approach to patients with synchronous colorectal cancer (CRC) and liver metastases. According to this approach the colorectal resection is the first procedure, followed by systemic chemotherapy, and then followed by the resection of liver metastases for patients without progression of disease. Theoretical advantages of this approach include: avoidance of potential complications from the primary tumour (obstruction, bleeding, perforation) and progression of the primary tumour; selection of patients with optimal tumour biology with chemotherapy before hepatectomy; abolishment of the primary source of metastatic disease. The disadvantages include: possible occurrence of complications after colorectal resection precluding further treatment of LM; progression of LM, eventually beyond resectability [7].

In agreement with the international multidisciplinary consensus published in 2015 [2], for symptomatic patients, the treatment is related to the type of symptoms and resectability of liver metastases. In patients with resectable LM, who have bleeding CRC controlled with blood transfusions, preoperative chemotherapy should be advocated. In case of perforation, resection of the primary to remove the tumour (mainly for right colon), or creating a stoma (mainly for left sided colon cancer) is recommended. In patients with evidence of colonic obstruction, resection of the primary should be performed first. The use of stents as bridge to surgery is also an option, but conflicting results are available in literature and currently is not considered as a standard treatment. This option could be evaluated and considered according to several factors: availability of technical expertise, risk of stent-related perforation according to location and length of obstruction, age and general conditions of the patient [8].

Regarding surgical resection of the primary tumour, colorectal surgery should be performed by a colorectal surgeon whenever possible with respect to oncological criteria also in patients with unresectable LM. In fact, the possibility to obtain resectability in these cases accounts for 15–30% of patients [1].

The major criticism of *primary-first tumour approach* is that in general, according to tumour burden, liver metastases have a greater impact on patient's prognosis than that of an asymptomatic primary tumour [9], and the initial treatment of colorectal tumour could cause delay in starting chemotherapy and then progression of liver metastases beyond resectability, particularly in patients who develop postoperative complications. Laparoscopic resection and enhanced recovery after surgery (ERAS) pathways can lead to shorter length of hospital stays, decreased morbidity, and earlier starting of chemotherapy [10]. Despite these advantages, primary-first tumour approach should be reserved to patients with symptomatic tumours and to patients with advanced primary tumour and limited liver disease, preferably after neoadjuvant chemotherapy, and to those excluded for simultaneous approach.

The recent advances in systemic chemotherapy have revolutionized the treatment landscape of these patients, thanks to the increased response rates of both primary tumour and liver metastases. Therefore, the initial approach to all asymptomatic, or minimally symptomatic patients with synchronous metastases should be chemotherapy at the onset of the disease [2].

Proponents of primary-first approach in the metastatic setting without previous chemotherapy highlight the prevention of possible complications related to the primary tumour (such as bleeding, obstruction, or perforation) during chemotherapy. However, the risk of developing such symptoms is negligible and appears lower than the risk of developing complications of primary tumour resection that ranges from 15% to 25% [1, 11].

A major concern with the primary-first approach is that it ignores that the majority of colorectal cancer-related mortality is due to metastatic disease [12] and that there is a real risk that the patient becomes or remains unresectable after resection of the primary tumour especially in two categories of patients: those with borderline resectable liver metastases, and those with initially unresectable liver metastases, who could become resectable if systemic treatment started early.

Most of the comparison studies on the three possible surgical strategies ("Primary-first," "Liver-first," and "Simultaneous" approaches) are retrospective studies with significant baseline imbalances between groups, the majority of the studies do not have intention-to-treat analysis and therefore do not report the proportion of patients in which scheduled approach could not be completed. The risk of "drop-out" is commonly perceived as higher in patients with synchronous liver metastases scheduled for *Primary-first approach*, given presence of liver metastases is associated with worse prognosis compared to that of metastases in other sites [9]. Available results on this topic are controversial. A recent review and network meta-analysis shows that the proportion of patients who did not complete the strategy was 34% after the "Liver-first approach" versus 6% after the "Primary-first approach," but weakness of these results is underlined by the same authors [7]. On the other side, Sturesson et al. [13] in a study with intention-to-treat analysis showed that drop-out rate was non-significantly different between the two approaches: 35% in liver-first group and 29% in primary-first group ($p = 0.664$).

Chemotherapy before surgery is undoubtedly indicated in patients with unresectable liver metastases to render patient suitable for resection. In case of synchronous resectable

metastases, use of chemotherapy is widely accepted, but remains debatable in absence of strong evidence. However, presence of synchronous metastases is considered itself a poor prognostic factor and many centers prefer to start with chemotherapy in near all patients [2, 14]. Conversely, there is wider consensus on neoadjuvant chemotherapy in high-risk patients, who can be identified according to different factors including site of primary tumour, lymph-node primary tumour status, mutation features, metastatic liver burden diseases [5]. Regarding duration of preoperative chemotherapy, it is widely accepted that chemotherapy used until resectability is reached for unresectable patients, with early imaging revaluation after 2–3 months [14], and after 2 months for resectable patients in order to limit the chemotherapy-induced liver injury [2, 5]. Some oncologists, based on experimental and clinical data, would suggest some benefit on overall survival of initial resection of the primary tumour for a better response to chemotherapy, but there is no evidence that this attitude offers real advantages [15]. Indeed, some limited evidences also support the hypothesis that upfront primary-first resection surgery might stimulate the progression of liver metastases [16].

20.3 Liver-First Approach

In 2006 Mentha et al. proposed a reverse strategy (*liver-first approach*) based on chemotherapy upfront, resection of liver metastases and at a second stage resection of the primary tumour. This strategy is mainly based on the concept that the initially removal of liver metastases, the most determinant for prognosis could improve survival of these patients [4]. This reverse approach seems particularly adequate in patients with advanced liver metastases and rectal cancer with indication to chemo-radiotherapy, which could delay resection of the liver metastases and favor the risk of liver disease progression up to unresectability [4]. Improvements of more effective chemotherapy and safer liver surgery permitted overtime to include patients with more advanced liver disease, often with synchronous multiple and bilateral metastases. In this setting, the liver-first approach has been progressively increasingly used overtime [17] (Fig. 20.1). Ghiasloo et al. in a recent review and network meta-analysis show that *liver-first approach* is more often chosen in patients with bilobar hepatic disease, rectal tumour, receiving neoadjuvant chemotherapy, and some recent population-based analyses reported its application in up to 20–40% of patients with synchronous liver metastases [7, 17, 18]. The authors also show a higher rate of recurrence after liver-first approach suggesting a higher risk of R1 resection, despite similar overall survival emphasizing the effectiveness of this strategy on prognosis in patients with more advanced disease [7].

The main concern with the liver-first approach is the risk of not completing the planned strategy. The risk of drop-out ranges between 3% and 34% [19, 20], and is mainly related to disease progression or less frequently to morbidity of liver resection. The relatively high reported rate of non-completion of the strategy may be explained by the significantly higher liver tumour burden of the patients scheduled for liver-first approach, who are usually borderline resectable or initially unresectable patients [18]. The risk of not completing the strategy does exist also in the classical primary first strategy, although this data is difficult to obtain from studies that rarely have intention-to-treat analysis, mainly for patients treated with primary first approach. However, in one of the papers in which this analysis is reported, Sturesson et al. reported a similar rate of failure of the two strategies, 35% and 29% for liver-first and primary-first, respectively (p = 0.664) [13]. Therefore, this issue cannot be used for choosing the appropriate strategy.

The risk of progression of primary tumour or occurrence of colorectal complications during the liver first approach is quite low. In the intention-to-treat analysis reported by Sturesson, 5 out of 75 patients chosen for liver-first approach had semi-emergent surgery of the bowel because of obstruction symptoms, representing 7% of the entire liver-first cohort of patients which is similar to that reported by Brouquet et al. [13, 20]. Also, in the subgroup of patients with rectal tumour, the rate of complications related to the primary seems low, less than 10% as reported by Nierop et al. [21]. These results show the relative safety of upfront new chemotherapeutic regimens in the liver-first strategy, probably related to the high response rates, both on liver metastases and on primary cancer even in the case of rectal tumours (Fig. 20.2).

As previously reported liver-first approach is mainly planned in case of primary rectal tumour [18], and especially in patients with locally advanced rectal cancer and indication to radiotherapy (RT). On this topic, a recent Sweden population-based study showed a significantly increased survival of patients with rectal cancer and synchronous liver metastases compared to patients with primary colon cancer, with 5-year overall survival of 62% versus 47% respectively (p = 0.033) [22]. The authors show that 70% of patients with rectal cancer were treated with the "liver first" strategy and about 90% of patients underwent radiotherapy. There is no consensus on the RT protocol, long or short course, to prefer in these patients. The use of short course radiotherapy seems particularly suitable in patients with planned liver-first approach, to avoid delaying of systemic treatment, and improving distant as well as local control. In fact, after completion of neoadjuvant chemotherapy, hepatectomy can be performed, followed by short-course radiotherapy and then by rectal surgery (Fig. 20.3) [23]. When long-course radiotherapy is preferred, this can be performed after chemotherapy, followed by hepatectomy during the waiting interval for rectal surgery (Fig. 20.4) [24]. The use of laparoscopic technique for both or one of the two surgeries could be evaluated in expert centers in order to keep both short-terms out-

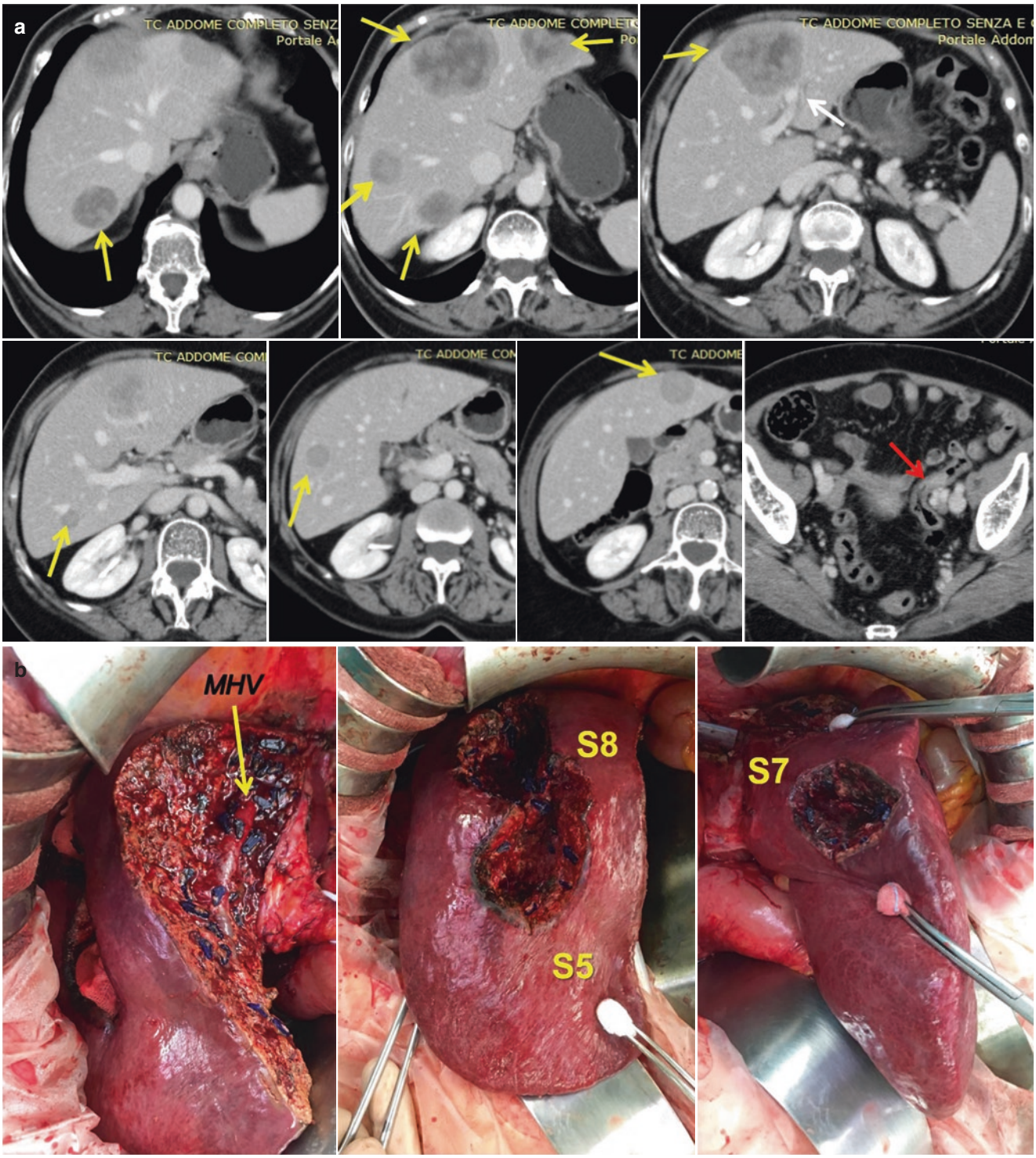

Fig. 20.1 Asymptomatic colon cancer with multiple bilateral synchronous metastases in a 68-year-old female patient. (**a**) CT scan at diagnosis showing a sigmoid cancer (red arrow) and multiple bilateral liver metastases (yellow arrows), the major one in the left hemiliver infiltrating the left Glissonean pedicle (white arrow). (**b**) Operative field after left hepatectomy with exposure of median hepatic vein (MHV) and multiple US-guided liver resection in S8, S5, and S7

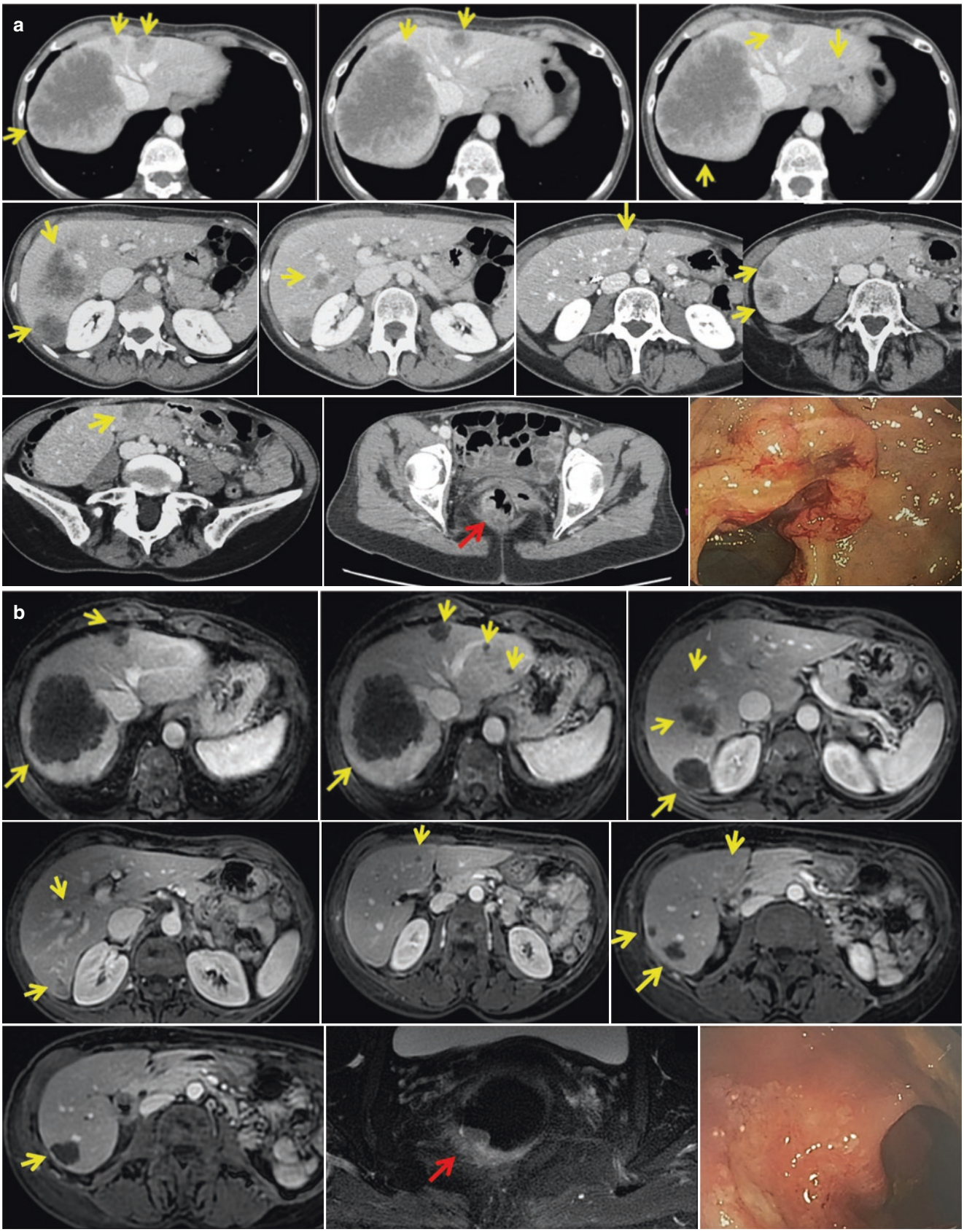

Fig. 20.2 Asymptomatic middle rectal cancer with multiple bilateral synchronous metastases in a 58-year-old female patient. (**a**) CT scan at diagnosis showing a middle rectal cancer (red arrow) with multiple bilobar synchronous CRLM (yellow arrows). Endoscopic view of rectal cancer. (**b**) MRI after six courses of chemotherapy (FOLFOXIRI + Bevacizumab) showing good response of liver metastases and rectal cancer, also at endoscopic view

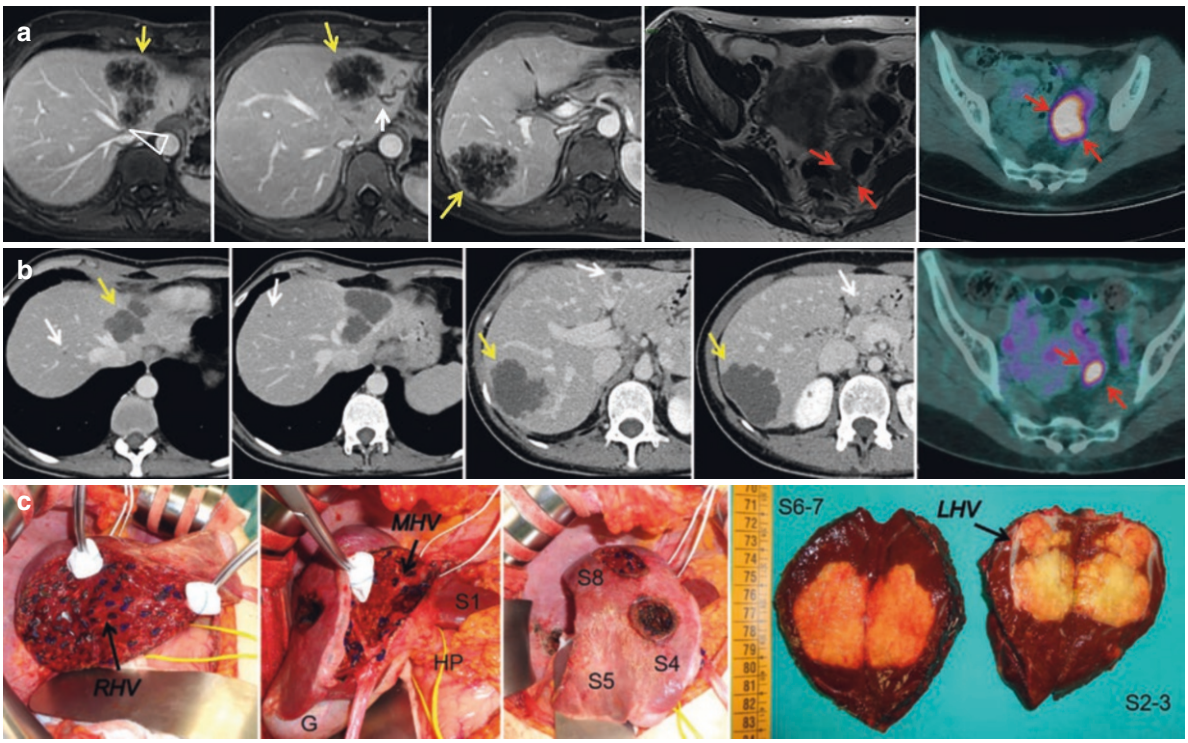

Fig. 20.3 Asymptomatic high rectal cancer with multiple bilateral synchronous metastases in a 78-year-old female patient. (**a**) MRI at diagnosis showing a high rectal cancer (red arrow) and two CRLM (yellow arrows), one in the left lobe (S2–3) infiltrating the left hepatic vein (LHV) and near to middle hepatic vein (MHV) at confluence in vena cava (head arrow) with biliary dilatation (white arrow) and one in the right posterior sector (S6–7). Rectal cancer at FDG PET/CT performed at baseline. (**b**) CT scan after 12 courses of chemotherapy (FOLFOX + Bevacizumab) showing good response of liver metastases with visibility of other small four CRLM, two in the left lobe and two in the right hemiliver (white arrows) and response of rectal cancer at FDG PET/CT. The patient was scheduled for liver first-approach, bilateral liver resections, and 4 weeks later anterior rectal resection. (**c**) Operative field after right posterior sectionectomy (S6–7) with exposure of right hepatic vein (RHV), left lateral sectionectomy (S2–3) with exposure of middle hepatic vein, and two limited resections of S4 and S8. HP, hepatic pedicle; G, gallbladder

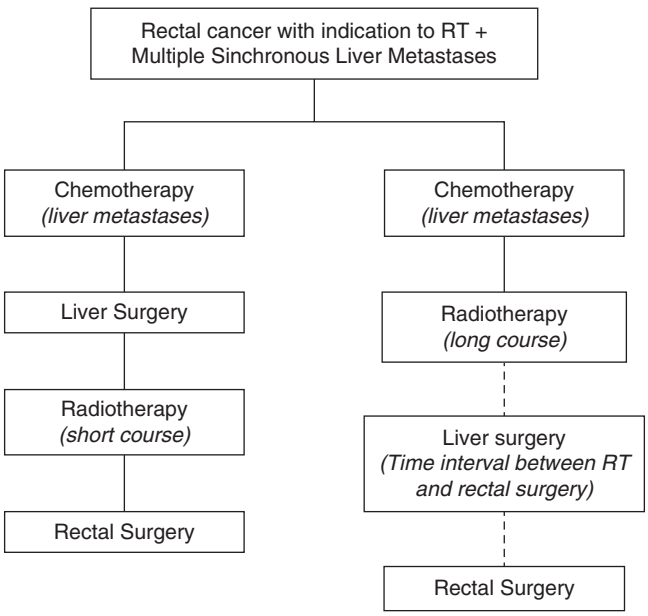

Fig. 20.4 Treatment options algorithm for patients with locally advanced rectal cancer and synchronous liver metastases candidate for liver-first approach

come benefits and oncological advantages related to this approach [25, 26].

20.4 Simultaneous Combined Approach

In recent years, improvements in patients' selection, increased efficacy of perioperative chemotherapy and safety of liver resections have expanded surgical indications and interest in simultaneous colorectal and liver resection for synchronous colorectal liver metastases (CRLM) [11, 27]. The reported advantages related with a simultaneous approach include the performance of only a single procedure, reducing the costs of hospital treatment [28] and facilitating earlier and less interrupted systemic chemotherapy [29, 30]. Many retrospective studies have compared the classical strategy (the delayed approach) with the simultaneous approach [31–39]. Most found similar postoperative morbidity and mortality rates (Table 20.1), similar overall survival (Table 20.2) and shorter lengths of stay for patients undergoing simultaneous resections [20, 31–39].

Table 20.1 Short-term results following simultaneous colorectal and liver resections compared with delayed liver resections in patients with synchronous CRLM

Author	No. of pts	Mortality simultaneous	delayed	*P*	Morbidity simultaneous	delayed	*P*
Reddy, 2007 [31]	610	1%	0.5%	n.s.	36%	38%	n.s.
Martin, 2009 [32]	230	2%	2%	n.s.	56%	55%	n.s.
Kaibori, 2010 [33]	74	0	0		38%	14%	0.021
de Haas, 2010 [34]	228	0	0.6%	n.s.	11%	25.4%	0.015
Luo, 2010 [35]	405	1.5%	2.0%	n.s.	47.3%	54.3%	n.s.
Abbott, 2012 [36]	144	3.3%	1.2%	n.s.	38.3%	40.5%	n.s.
Mayo, 2013 [37]	976	2.7%	3.2%	n.s.	19.1%	19.8%	n.s.
Valdimarsson, 2020 [38]	537	0.6%	0	n.s.	52%	36%	<0.001
Boudjema, 2021 [39]	105	7.4%	3.2%	n.s.	49%	46%	n.s.

Table 20.2 Long-term results following simultaneous colorectal and liver resections compared with delayed liver resections in patients with synchronous CRLM

Author	No. of pts	5-year overall survival simultaneous	delayed	*P*
Brouquet, 2010 [20]	115	55%	48%	n.s.
de Haas, 2010 [34]	228	74%[a]	70%[a]	n.s.
Mayo, 2013 [37]	976	42%	44%	n.s.
Valdimarsson, 2020 [38]	537	46%	54%	n.s.

[a]3-year overall survival

In a recent meta-analysis, Gavriilidis et al. compared the outcomes between simultaneous and delayed approach, including 30 retrospective studies with 5300 patients, there was no evidence of significant difference in postoperative complications and overall survival [40]. However, it was evident how the proportion of patients with advanced CRLM (bilobar distribution) was significantly lower in the simultaneous group. Furthermore, in the simultaneous group the rate of major hepatectomies was significantly lower.

In a recent paper by Idrees et al. [41] that used the data from the Nationwide Inpatient Sample (NIS) Healthcare Cost Utilization Project (HCUP) database, the results of 83,410 patients, who underwent surgical resection with a primary diagnosis of synchronous CRLM between 2004 and 2014, were analyzed. The authors showed that the number of simultaneous resections in the United States increased from 423 procedures in 2004 to 580 procedures in 2014, representing an increase of 37%. Patients undergoing simultaneous operations were compared with patients undergoing delayed operations. Simultaneous resections demonstrated lower postoperative morbidity and mortality rates and shorter length of hospital stay. Furthermore, median hospital costs were $13,093 lower for patients undergoing simultaneous resections if compared with delayed resections. However, after stratifying patients into low-, medium-, and high-risk groups according to patient demographics, preoperative comorbidity and hospital characteristics, it was clear that patients undergoing simultaneous resections were proportionally more likely to be low-risk patients. Moreover, the proportion of low-risk patients undergoing simultaneous resections significantly increased over the study period, suggesting that this type of procedure can be safely performed among selected patients.

In all these retrospective published studies, the different selection of patients represents a strong and unavoidable bias. Indeed, low-risk patients (e.g., patients with colon cancer and requiring minor liver resections) are more frequently found in the simultaneous approach group. The optimal surgical approach remains widely debated and no statistical model such as multivariate analyses after propensity score matching can replace the randomization.

The only prospective randomized control study comparing the two strategies was recently published by Boudjema et al. [39]: the METASYNC trial. A total of 105 patients were randomized between 2006 and 2015 and 85 were finally evaluable. The study showed that postoperative morbidity was similar between simultaneous and delayed resections. Indeed, the rate of major postoperative complications were 49% in the simultaneous group and 46% in the delayed group ($p = 0.70$). However, also in this study, despite the randomization, the rate of complex surgical procedures was not statistically balanced between the two groups: the distribution of rectal cancer and major resections was not similar. Indeed, in the simultaneous group the proportion of right colon and of minor resection was higher than that in the delayed group.

It has been clearly showed in the literature that the extent of hepatectomy represents one of the strongest predictors of postoperative complications and mortality in liver surgery. This issue is particularly evident in patients with synchronous CRLM in whom chemotherapy-induced liver injury may increase the risk of major postoperative morbidity.

In the paper by Shubert et al. [11] which analyzed the data of the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) database between 2005 and 2013, 922 patients undergoing simultaneous resection were stratified into four possible synchronous resection categories: (1) high-risk colorectal resection and major hepatectomy, (2) low-risk colorectal resection and major hepatectomy, (3) high-risk colorectal resection and minor hepatectomy, (4) low-risk colorectal resection and minor hepatectomy. As such, the postoperative risk was stratified according to the individual risks of both the hepatic and colorectal resection components. This study showed that the overall 30-day mortality rate was 1.7%. However, this rate was significantly different according to the risk associated with both procedures, increasing from 1.4% in group 4 (low-

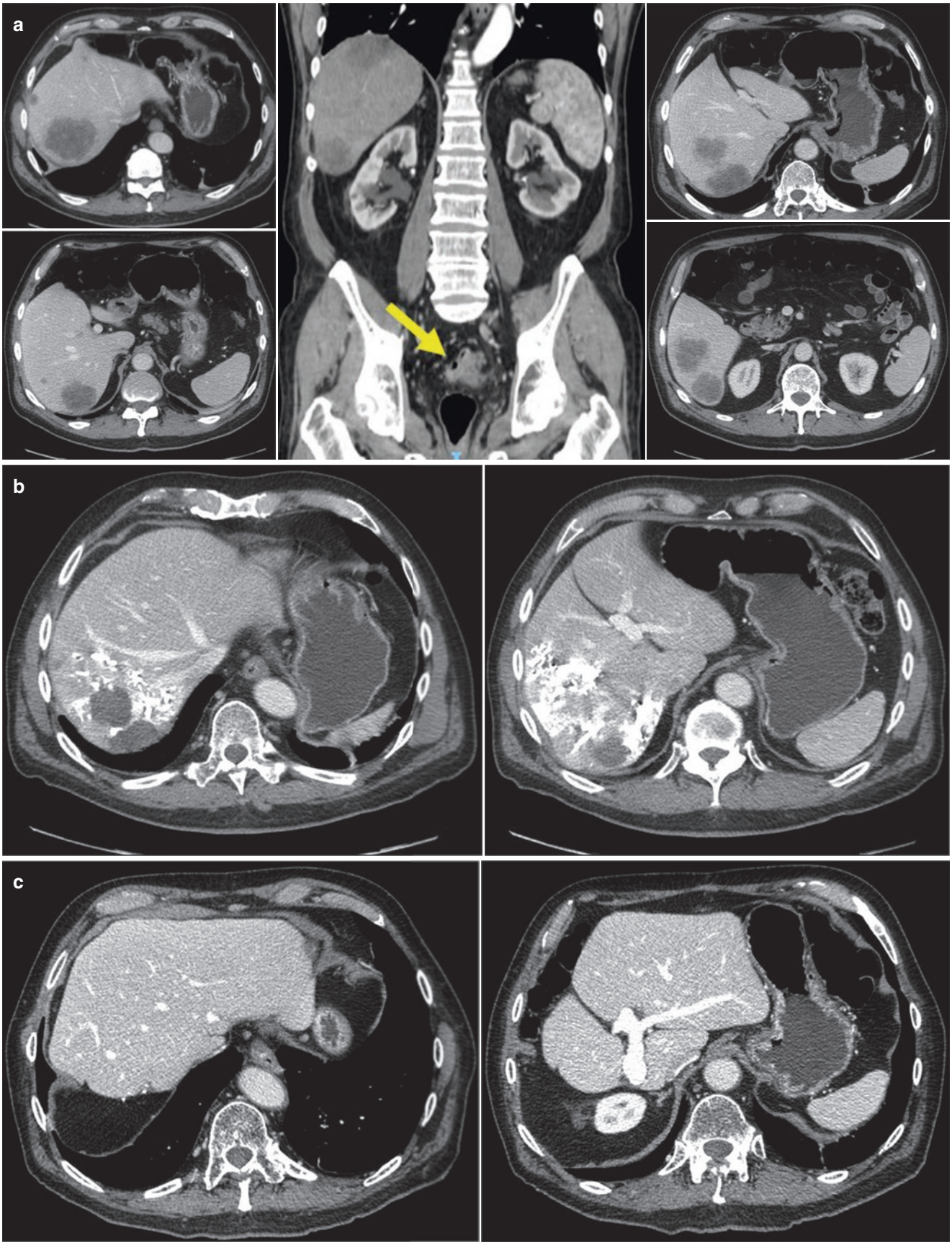

Fig. 20.5 High-risk colorectal resection and major hepatectomy: a 73-year-old male patient. Preoperative CT scan showing a high rectal cancer (yellow arrow) with four synchronous CRLM of the right hemiliver (**a**). CT scan 1 month after right portal embolization (**b**). CT scan 94 months after simultaneous right hepatectomy and anterior rectal resection (**c**)

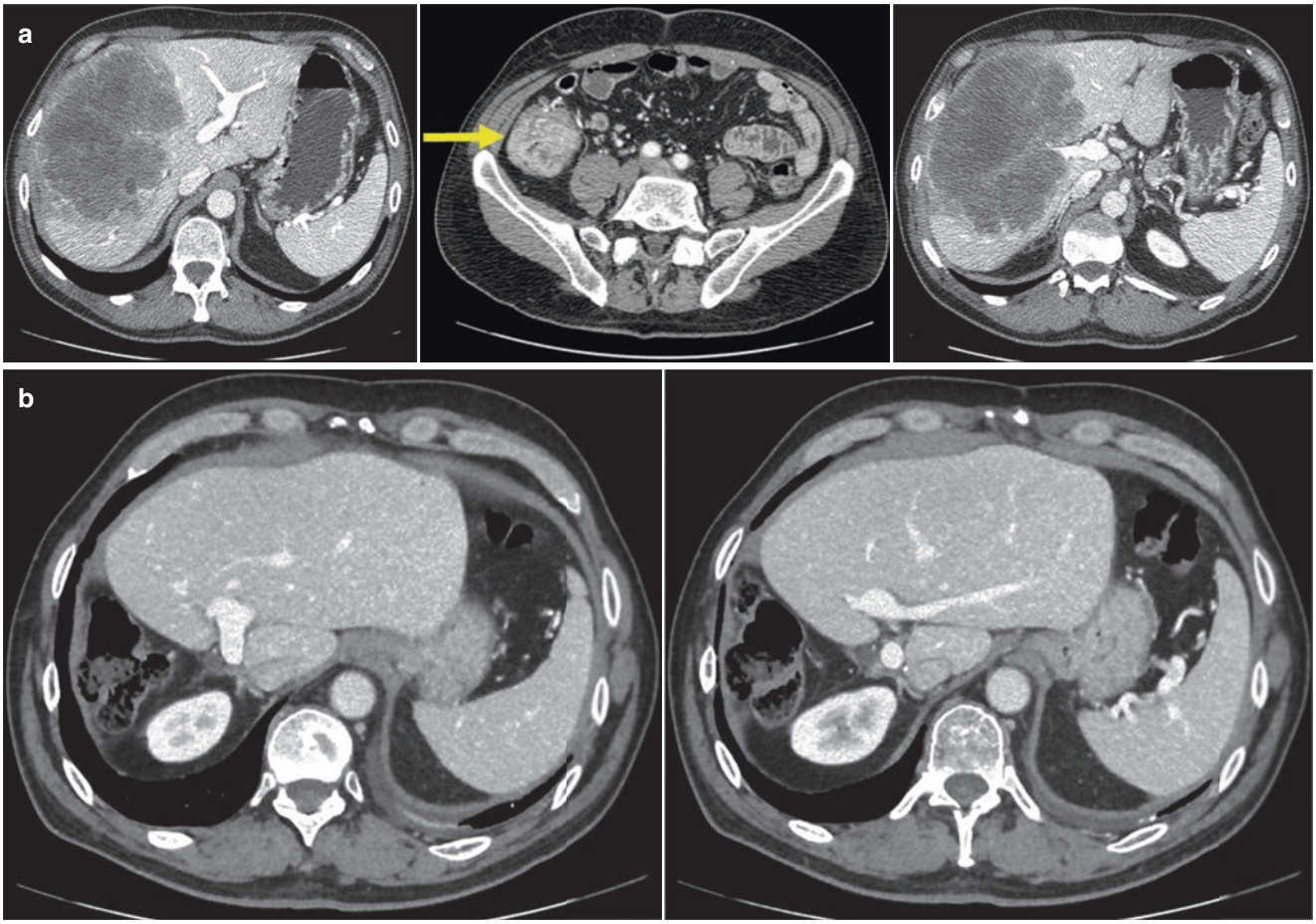

Fig. 20.6 Low-risk colorectal resection and major hepatectomy: a 64-year-old male patient. Preoperative CT scan showing a right colon cancer (yellow arrow) with synchronous large CRLM of the right hemiliver (**a**). CT scan 18 months after simultaneous right hepatectomy and right hemicolectomy (**b**)

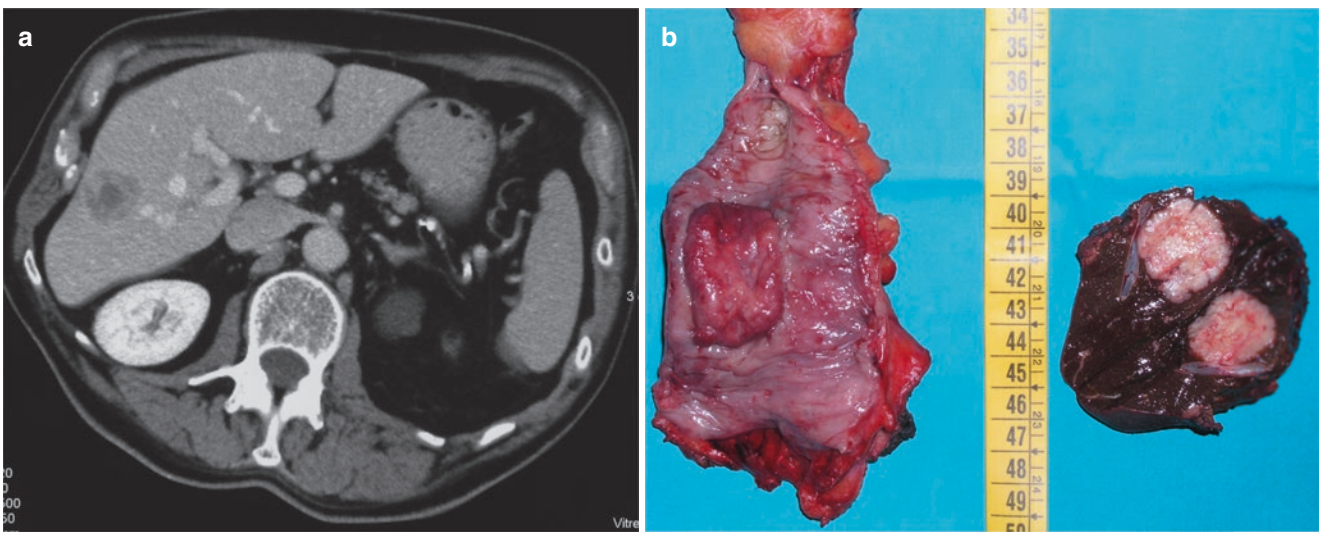

Fig. 20.7 High-risk colorectal resection with minor hepatectomy: a 75-year-old male patient. Preoperative CT scan showing a single CRLM in segment 5 in a patient with synchronous low rectal cancer (**a**). Simultaneous rectal resection and segmentectomy 5 (**b**)

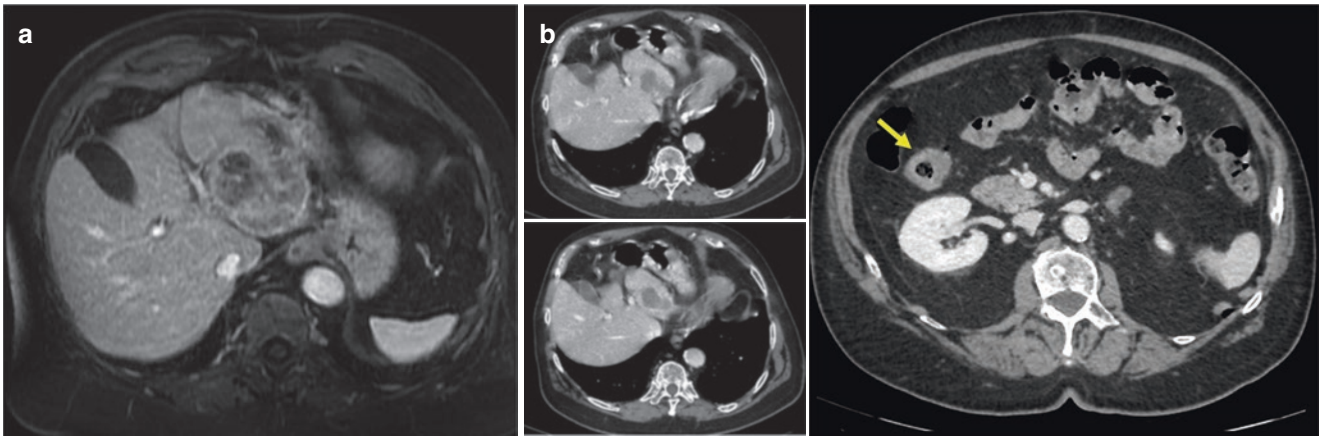

Fig. 20.8 Low-risk colorectal resection and minor hepatectomy: a 77-year-old male patient. MR showing a single CRLM in the left hepatic lobe (segments 2–3) synchronous with a right colon cancer (**a**). CT scan after preoperative chemotherapy: the CRLM showed a partial response to chemotherapy and now is quite far from the left Glissonian pedicle; the thickening of the wall of the right colon showed a reduction in size (yellow arrow) (**b**). The patient underwent simultaneous right hemicolectomy with left lateral sectionectomy

risk colorectal resection with minor hepatectomy) to 5% in group 1 (high-risk colorectal resection with major hepatectomy). The four possible simultaneous resection categories are showed in Figs. 20.5, 20.6, 20.7, and 20.8.

With regard to the indications for the type of surgical approach, most published data suggest that patients selected for a simultaneous resection present with a surgical plan requiring less extensive liver and colorectal resection [42]. In such patients results of the literature have demonstrated the safety of simultaneous resections. On the other hand, there are insufficient data and sample size to clearly define the safety of a simultaneous approach involving a high-risk colorectal resection associated with a major hepatectomy. The accurate selection of best candidates for simultaneous high-risk procedures remains fundamental. However, it should be highlighted that the degree of safety and not simply the technical ability of performing a simultaneous resection must be always compared with the safety associated with a delayed procedure.

20.4.1 Type of Approach for Simultaneous Resection

Simultaneous resection can be performed in open fashion or by minimally invasive approach. Several types of incisions have been described for open simultaneous resections. Of course, the choice of incision should be related according to the localization of the primary tumour and of CRLM. The reversed L-shaped incision may be useful to guarantee an adequate surgical field in patients with right colon cancer regardless the CRLM localization [43]. The midline incision is generally used for left colon cancer or rectal cancer and it may be used safely and effectively in combined conventional open surgery in various liver resections [44]. However, the midline incision, in some complex cases, may be not useful to have a good access to the posterior segments of the liver. In such cases an additional extension may be required by a right transverse incision [45] (see Chap. 3).

With recent advances of modern laparoscopic technology, the minimally invasive approach for colorectal surgery and for liver surgery are both accepted worldwide. With regard to the simultaneous approach, several single-center retrospective studies have been published reporting the results of totally laparoscopic simultaneous colorectal and liver resection. Data from the literature show that in experienced centers, simultaneous laparoscopic approach is technically feasible, safe, and associated with good oncological outcomes. Moreover, the advantages of the minimally invasive approach include the reduction of the abdominal wall damage with a decreased postoperative pain, shorter hospital stay, and an earlier return to previous activity. A recent retrospective multicenter international study by Ferretti et al. [46] confirmed these results by analyzing the data of 142 simultaneous resections performed by laparoscopic approach. Conversion rate in this series was 4.9%, the overall postoperative morbidity was 31.0% and mortality was 2.1%. However, by analyzing these results, it continues to be evident how the accurate selection of patients is fundamental to achieve the best results. Also, in these series it is clear how the degree of complexity of liver surgery and the hepatectomy's extent are the most important driver for the procedure selection. Indeed, in the study by Ferretti et al., among the 142 simultaneous laparoscopic resections, only 12% were major hepatectomies. Moreover, the median number of resected metastases was 1 and the median larger diameter was 28 mm [46].

Finally, some surgical teams have showed that in selected patients a combined laparoscopic-open approach may be beneficial [47]. They described that the laparo-

scopic approach for left colon or rectal cancer may be associated with open hepatic resection. This approach may reduce the risk of complications related to extensive laparotomy and may be associated with decreased complication rate if compared with patients undergoing simultaneous open colorectal and liver resection. A single-center retrospective study by Ratti et al. [48], analyzed the results of 106 simultaneous resections performed between 2004 and 2014. In this study, 69 patients underwent laparoscopic resection of colorectal cancer associated with simultaneous open liver resection and 37 underwent simultaneous open colorectal and liver resection. The authors showed that laparoscopic resection of colorectal cancer associated with simultaneous open liver resection was associated with a reduction of blood loss, morbidity, and postoperative hospital stay.

20.5 Conclusion

Management of patients with synchronous liver colorectal metastases remains not defined by results of dedicated clinical trials and indeed is based on individualized approach established during multidisciplinary specialistic discussion. The primary-first, the liver-first, and the simultaneous combined approaches should not be mutually exclusive but rather proposed to different types of patients. Surgical strategy should be based on liver and colorectal tumour burden, and on evaluation of surgical risk of planned surgery. The real possibility to obtain prolonged survivals and cure of these patients is based on the best combination of modern systemic chemotherapy with safe surgery. Preoperative chemotherapy should always be considered. In patients with initially unresectable liver metastases, the high response rate to modern systemic treatments could frequently lead to complete surgery, whereas in patients with resectable liver disease evaluation of response to chemotherapy, it is useful to better select those who could benefit from liver surgery, avoiding surgery in patients with rapidly progressing tumours. The early discussion involving dedicated medical oncologist, liver surgeon, colorectal surgeon, radiotherapist in the management of a patient with colorectal cancer and synchronous liver metastases is crucial to best determine the timing and sequence of chemotherapy and surgery, the radiotherapy when indicated, and hence to improve patient outcomes and survival.

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21 Approach to Synchronous Lung and Liver Metastases and Single-Incision Combined Resection

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Learning Objectives

- Removal of lung metastases via a transdiaphragmatic route is a novel method for patients with synchronous liver and lung metastases.
- Transdiaphragmatic resection reduces the burden of multiple surgical procedures on patients' quality of life and on the medical system.
- The advantages of transdiaphragmatic resection are a single anesthesia and procedure and avoidance of the additional pain associated with a second resection.
- Transdiaphragmatic resection of lung metastases is safe and cost effective without compromising surgical and oncological outcomes.

21.1 Introduction

Colorectal cancer is the third most commonly diagnosed malignancy in the United States. Despite advances in screening techniques, 25% of patients have metastatic disease at the time of diagnosis [1]. The most common sites of metastases are the liver (in 20–70% of patients with metastases) and lung (in 10–20%) [2]. For patients who develop synchronous or metachronous liver and lung lesions, resection of disease at both sites has been shown to confer a survival benefit over non-resection [3, 4]. Therefore, for the past 20 years, resection of synchronous and metachronous colorectal liver and lung metastases has been advocated [5–7].

For synchronous colorectal liver and lung metastases, either simultaneous resection or staged resection (i.e., of liver metastases and then lung metastases or vice versa) can be performed. Previously, the simultaneous resection was completed using abdominal and thoracic incisions which was technically challenging for the surgical team and physiologically taxing for the patient. For this reason, some surgeons prefer a staged approach which requires patients to recover from the first procedure prior to undergoing the second [8–10].

To reduce the invasiveness of synchronous abdominal and thoracic surgery, our group developed a technique that creates an opening in the diaphragm on the side of the pulmonary metastasis(es) through which the lung metastasectomy can be performed, thus avoiding the need for a thoracic incision. We have shown that when compared to staged procedures, simultaneous resections via this transdiaphragmatic approach are safe and associated with lower blood loss and shorter length of hospital stay [11].

Long-term outcomes for staged resection of synchronous and metachronous liver and lung metastases have previously been described [8, 12]. We have recently shown that the safety and short- and long-term outcomes for the simultaneous transdiaphragmatic approach are similar to those of staged and transthoracic resections [13].

21.2 Transdiaphragmatic Resection of Lung Metastases

21.2.1 Patient Selection

Whether to perform simultaneous or staged resection in patients with synchronous liver and lung metastases needs to be discussed in a multidisciplinary forum where the liver and lung surgeons review the images and identify the best resection strategy. For patients in whom simultaneous resection is recommended, we select the transdiaphragmatic approach when the following criteria are met:

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1. The lung lesion must be palpable at the time of the pulmonary digital exploration. In general, this means that the lesion is at least 5 mm in diameter and within 2 cm of the surface of an inflated lung.
2. Hilar or mediastinal adenopathy must be absent.
3. Resection of all pulmonary lesions must be possible. Large number, large size, and bilateral distribution of lung metastases are not considered contraindications for the transdiaphragmatic approach if all lesions can be removed safely.
4. No prior resection have been performed, and no prior pulmonary or pleural pathology, which would complicate a safe pleural access exist.
5. Performance status must be suitable to tolerate both lung and liver surgery complications.

21.2.2 Technique of Transdiaphragmatic Resection

Prior to induction, an epidural catheter is placed by the anesthesiologist. General anesthesia is induced with placement of a double-lumen endotracheal tube to allow selective pulmonary ventilation. The patient is placed in the supine position, and an inverse L or midline abdominal incision is generally performed for liver resections. Following resection of the liver metastasis(es), we stop ventilating the targeted lung. The hemi-diaphragm is divided peripherally in a curvilinear fashion leaving a cuff of muscle for the closure, with the surgeon making sure not to damage the phrenic nerve. The patient bed is positioned in a Trendelenburg position. Meticulous finger palpation is conducted to find lung lesions in each lobe. Lung resections are performed using an endoscopic 45- or 60-mm stapler on a thick load to ensure a surgical margin of at least half of the diameter of the lesion is removed along with the lesion [14]. A thoracoscope may also be used to provide better surgical visualization if necessary. After confirming hemostasis and the absence of air leak, a 24-Fr thoracic tube is placed through the intercostal space. Recently we have replaced the transthoracic chest tube with a transdiaphragmatic 19-Fr Blake drain. The diaphragm is closed using a running #1 polypropylene suture. The stich is cut long to avoid piercing by the end of the stitch. In cases with bilateral pulmonary involvement, following closure of the diaphragm on the initial side, the lung is ventilated. The contralateral lung is rendered atelectatic and incision on the contralateral diaphragm is made.

21.2.3 Clinical Outcomes

Five-year survival rates following lung metastasectomy for colon cancer range from 27% to 68% [15]. In patients who are diagnosed with synchronous liver and lung metastases, survival is improved with resection of lesions at both sites. No significant difference in survival is seen between patients with resected lung and liver metastases and those with resected solitary liver metastases [12]. In terms of short-term outcomes, there are no meaningful differences in perioperative complications between cohorts undergoing staged versus simultaneous resection. Further, overall survival and recurrence-free survival do not significantly differ by resection technique [13]. Between October 2010 and December 2019, we have performed 17 transdiaphragmatic pulmonary resection procedures, two of which were bilateral. The average length of stay was 6 days. Two patients had surgical site infections, one necessitated placement of a wound vac. Three patients had pulmonary complications, two of which were effusions requiring drainage and one was a pneumothorax necessitating placement of a chest tube. Of the two cases performed for bilateral disease, one was performed without complication and one patient developed a unilateral pleural effusion that was subsequently drained. Eleven patients demonstrated recurrence of disease within 1 year of surgery. Despite this, 11 of 17 patients remain alive after a median follow-up time of 42 months.

21.2.4 Benefits of Simultaneous Resection

While perioperative complication rates and long-term outcomes do not meaningfully differ between patients undergoing staged and simultaneous resections, the adoption of transdiaphragmatic pulmonary resection has many benefits to both the patient and the health care system. The total duration of hospital stay has been found to be shorter for patients undergoing simultaneous resection than for patients undergoing two separate staged procedures. In turn, this has been shown to lead to meaningful cost reductions for simultaneous resections [13]. In addition, by eliminating the time interval between surgeries, simultaneous resection may enable patients to begin adjuvant chemotherapy sooner [16]. The use of adjuvant chemotherapy following metastasectomy has been shown to extend the disease-free interval [17]; while this does not translate to improved overall survival, it may lead to improved quality of life over a longer period of time, which is nonetheless meaningful.

21.2.5 Future Directions

When treating patients with metastatic disease at multiple sites, surgeons have historically performed staged procedures in order to allow patients to recover between procedures [18]. The staged approach has repeatedly been demonstrated to increase the total duration of hospital stay, which is a burden to both the patient and the hospital system [19]. Transdiaphragmatic simultaneous resection of pulmonary and liver metastases can be performed without compromising oncologic outcomes or patient safety and with obvious cost benefits to the hospital. Recently, it was demonstrated that a patient with stage IV colon adenocarcinoma safely underwent resection of the primary colon cancer along with lung and liver metastases by the same transabdominal approach [20]. Additionally, thoracic surgeons are exploring the use of laparoscopic approaches to pulmonary resections with the aim of reducing postoperative pain [21].

21.3 Conclusion

A transdiaphragmatic approach for simultaneous resection of liver and lung metastases can benefit both patients and the hospital system without compromising short- or long-term surgical and oncologic outcomes.

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Perioperative Chemotherapy: Review of Randomized Trials and Recommended Approach

22

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Learning Objectives

- To understand issues regarding the safety and deliverability of perioperative or postoperative chemotherapy.
- To appreciate the effect of chemotherapy on disease-free/progression-free survival and overall survival.
- To recognize the arguments concerning the utility of giving chemotherapy to patients with resectable colorectal liver metastases.

22.1 Introduction

Liver resection remains the treatment of choice for colorectal liver metastases and confers favourable long-term survivals [1]. Patients who achieve 10-year relapse-free survival can be considered to be cured [2]. Nevertheless a substantial proportion will experience recurrence of the disease [3]. Consequently the use of systemic chemotherapy in combination with liver resection has been evaluated as a strategy to reduce disease recurrence, and improve survival. Systemic therapy may be given before surgery (neoadjuvant), after surgery (adjuvant), or before and after (perioperative).

Neoadjuvant systemic therapy is frequently administered in the setting of initially unresectable liver metastases. Adjuvant therapy is given with the purpose of addressing micrometastatic disease, thereby reducing the likelihood of recurrence. In addition to the systemic administration of chemotherapy, hepatic artery infusion pump chemotherapy is used in both the adjuvant and neoadjuvant settings. This chapter will focus specifically on the evidence for systemic therapy for resectable and borderline resectable colorectal liver metastases and hepatic artery infusion is covered only minimally to give context.

There is a relative paucity of evidence for systemic therapy for resectable colorectal liver metastases. The key trial that has been conducted to evaluate the use of perioperative chemotherapy is the EORTC 40983 (EPOC) study of chemotherapy with FOLFOX4 (5-fluorouracil/leucovorin and oxaliplatin) before and after liver resection versus surgery alone [4, 5]. A further trial evaluated the benefit of the addition of cetuximab, an antibody to the epidermal growth factor receptor, to perioperative chemotherapy [6, 7]. More recently a clinical trial has been published that evaluated the benefit of chemotherapy after liver resection [8]. These are the only truly randomized clinical trial data available in the perioperative/adjuvant setting.

22.2 Early Trials

Before the publication of EORTC 40983 [4] all of the trials of systemic therapy for resectable colorectal liver metastases focused on the adjuvant setting and are summarized in systematic reviews and meta analyses [9–11]. The era in which these trials were conducted may not reflect the developments in imaging, chemotherapy, surgery and pathology that have taken place over the last few decades. It is therefore questionable whether these trials are of value. Furthermore all of these trials had difficulty in recruiting participants, a common feature of trials evaluating chemotherapy in patients undergoing liver resection. Putting those caveats to one side, the meta-analyses suggest a benefit of treatment, both systemic and intra-arterial chemotherapy, in respect of progression-free survival. A significant effect on overall survival was not

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observed, although in the systemic treatment group this was only narrowly missed. In summary, there is a suggestion of benefit even with effete systemic chemotherapy. This does support the pursuit of further trials in this area.

22.3 EORTC 40983 (EPOC) Trial

This was a phase III randomized controlled trial conducted across 11 countries. A total of 364 participants with resectable colorectal liver metastases were randomized to chemotherapy with FOLFOX4 [12, 13] before and after surgery (6 and 6 cycles) versus surgery alone. Notable inclusion criteria were the presence of one to four liver metastases, no detectable extrahepatic disease, WHO performance status 0-2, and no previous chemotherapy with oxaliplatin. In the perioperative chemotherapy group, liver resection was performed 2–5 weeks after the last chemotherapy treatment. Intriguingly the published methods state that patients in this group had to be performance status 0-1 prior to liver resection, despite the entry criteria to the trial including performance status 2 patients.

Randomization achieved a reasonable balance of patients between the two groups. The median age was 63 years and all but three patients' performance status was 0 or 1. Less than half of patients had more than one metastasis. Approximately two-thirds had non-synchronous disease. Over half of the patients had a node positive primary and 42% had received prior adjuvant chemotherapy for a primary cancer. None had received prior oxaliplatin, as per the trial entry criteria. This, together with the restriction to four or fewer metastases, is probably the key consideration when considering the applicability of this trial to current patients.

The primary endpoint of the trial was progression-free survival. This was defined as the time from randomization to the date of progressive or recurrent disease, the date of surgery if metastases were deemed not resectable, or death from any cause. Owing to the differential management of patients in both groups of the trial there was inherent lead time bias. Allowances for this were built into the definition of progression-free survival and can be described as thought provoking at best, and have contributed to the debate about the meaning of the trial result.

The interim analysis [4] of the intention to treat population reported progression-free survival to be longer in the group assigned to perioperative chemotherapy at 18.7 months compared to 11.7 months. This did not reach statistical significance: hazard ratio (HR) for progression-free survival 0.79 (95% confidence interval [CI] 0.62–1.02, p = 0.058). The authors performed a further analysis restricted to just those patients eligible to enter the trial (11 patients in each group were ineligible) and this did reach statistical significance (Fig. 22.1).

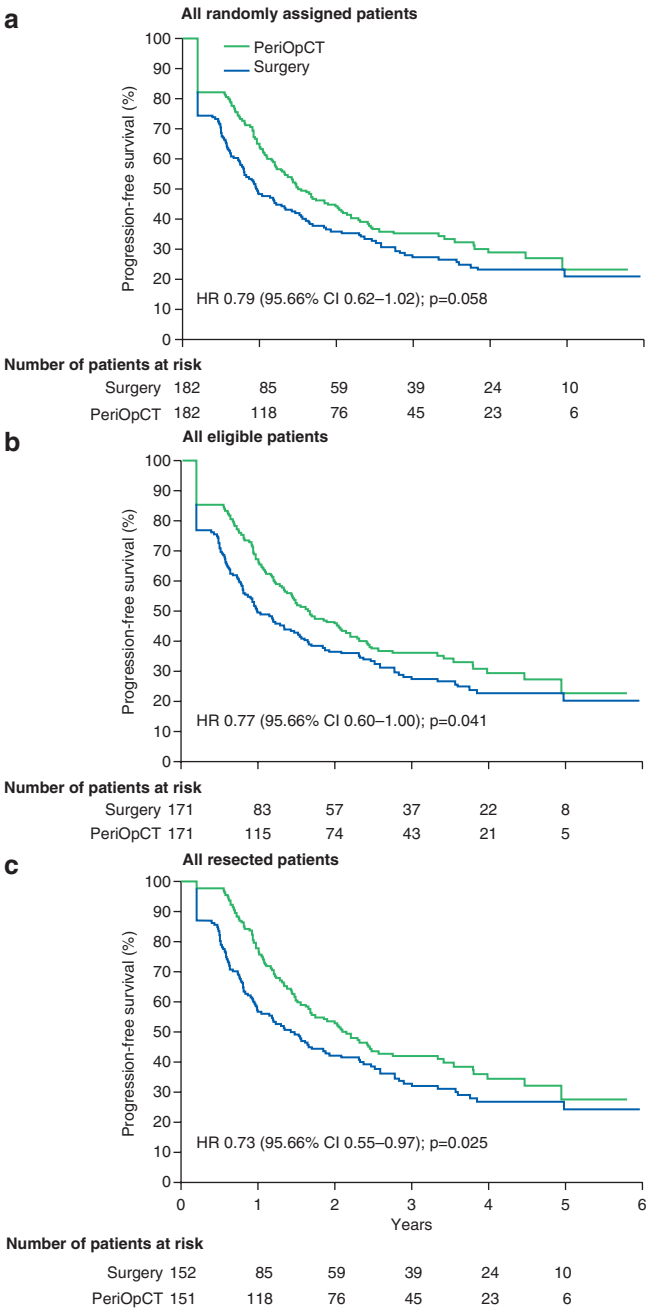


Fig. 22.1 Progression-free survival by treatment group in EORTC 40983 (EPOC) (**a**) All randomly assigned patients. (**b**) All eligible patients. (**c**) All resected patients. For all patients randomly assigned and those who were eligible, no surgery or no resection were regarded as events for the primary endpoint of progression-free survival. PeriOpCT, perioperative chemotherapy with fluorouracil plus leucovorin, and oxaliplatin. Reproduced by permission

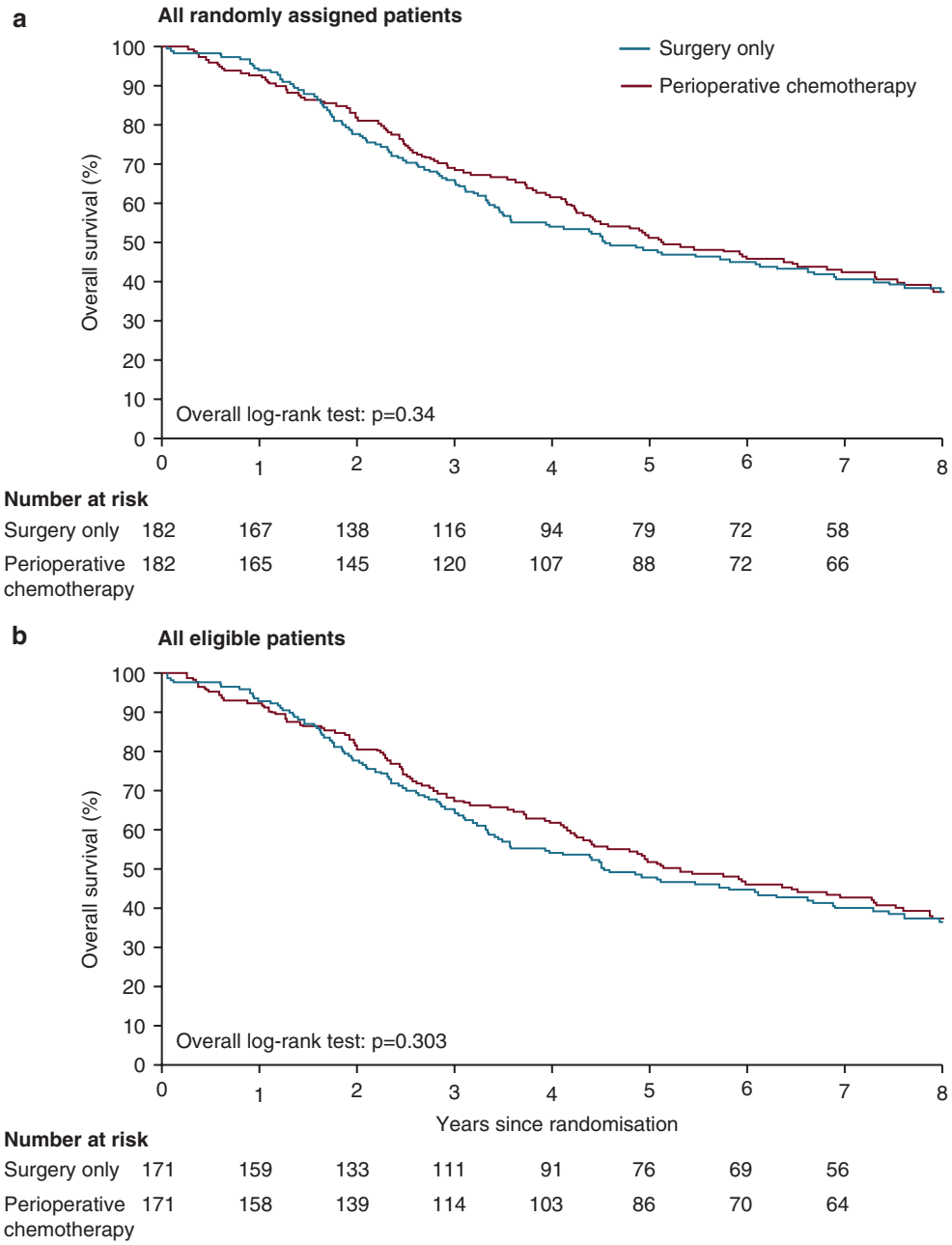


Fig. 22.2 Overall survival by treatment group in EORTC 40983 (EPOC). Kaplan–Meier curves of overall survival in all randomly assigned patients (**a**) and all eligible patients (**b**) per treatment group. Reproduced by permission

The three analysis populations (intention-to-treat, eligible and a further population of just those that underwent resection), coupled with the definition of progression-free survival, have introduced some complexity when trying to draw definitive conclusions from the results. The mature overall survival data was therefore awaited with interest. This analysis was performed at a median follow-up of 8.5 years and demonstrated a median overall survival of 61.3 months (95% CI 51.0–83.4) in the perioperative chemotherapy group and 54.3 months (41.9–79.4) in the surgery alone group [5]. This corresponded to 5-year overall survival rates of 51.2% (95% CI 43.6–58.3) in the perioperative chemotherapy group versus 47.8% (40.3–55.0) in the surgery alone group. These differences were not statistically significant (Fig. 22.2).

Overall survival is commonly held to be the ultimate endpoint of interest for cancer trials. The authors correctly highlight that the trial was never powered to detect a difference in overall survival. It is perhaps reasonable to conclude that if there is a benefit in overall survival then it will be small. Moreover it is likely that there is a differential effect of perioperative chemotherapy across different patient groups.

A post hoc subgroup analysis on progression-free survival performed by the authors serves to highlight this. These analyses suggest that the benefit of perioperative FOLFOX chemotherapy is in patients with an elevated carcinoembryonic antigen (CEA, >5 ng/mL) [14] rather than other factors commonly argued to be prognostic, such as number of metastatic lesions or larger lesion size [15, 16]. That said lesion size was numerically associated with benefit from chemotherapy but was not significant in the interaction test. The elevated CEA may be a reflection of biologically unfavourable disease, the presence of micrometastatic disease, or both.

The other prognostic factor identified was the patient's performance status. This may be explained by such patients being less likely to complete all protocol treatment. The manuscript combines high CEA and better performance status to identify a subgroup most likely to benefit from chemotherapy. Unfortunately, no similar analysis has been done for overall survival rather than in this case the progression-free survival.

22.4 New EPOC Trial

This trial did not have a surgery alone arm but rather compared 5-fluorouracil based doublet perioperative chemotherapy with chemotherapy plus cetuximab. Owing to the time taken to develop, fund and recruit to clinical trials, this study was devised prior to the 40983 trial fully reporting. The rationale was that cetuximab had shown efficacy in the phase II setting in advanced disease [17] and therefore this may have reduced the chance of relapse in the setting of resectable colorectal liver metastases.

In contrast to the 40983 trial, New EPOC randomized patients with both resectable and borderline resectable disease and there was no limit on the number of metastases. Shortly after recruitment had commenced, data supporting a benefit of cetuximab only in KRAS exon 2 wild-type patients were presented [18], leading to a protocol amendment to exclude patients with KRAS mutated cancers. The primary endpoint was progression-free survival defined as time from randomization to progression or death, whichever occurred first. Owing to the fact that both groups commenced systemic treatment there were no issues with lead-time bias to be accounted for. Secondary endpoints included overall survival and safety.

A total of 257 KRAS wild-type (codons 12, 13, 61) patients were randomized before the trial was halted due to earlier progression in the group allocated to cetuximab. Approximately two-thirds of patients received chemotherapy with modified FOLFOX6, with smaller numbers receiving CAPOX (oxaliplatin intravenously with oral capecitabine). Patients who had received adjuvant oxaliplatin could receive FOLFIRI (5-fluorouracil/leucovorin with irinotecan intravenously instead of oxaliplatin). The different chemotherapy regimens were balanced between the groups. There were some numerical imbalances in other baseline characteristics between the groups with more patients having synchronous disease and a metastasis larger than 3 cm in the chemotherapy plus cetuximab group.

An interim analysis was undertaken with an overall median follow-up of 20.7 months and 123 (58%) of 212 required events observed. This demonstrated progression-free survival to be 14.1 months (95% CI 11.8–15.9) in the chemotherapy plus cetuximab group and 20.5 months (95% CI 16.8–26.7) in the chemotherapy alone group (hazard ratio 1.48, 95% CI 1.04–2.12, $p = 0.030$) (Fig. 22.3) [6]. The liver was the most frequent site of progression in both groups of the trial (chemotherapy alone 67% (32/48); chemotherapy plus cetuximab 66% (40/61)) [19]. Interestingly a higher proportion of patients in the chemotherapy plus cetuximab group had multiple sites of progressive disease (chemotherapy alone 8%, 4 of 48 progression events; chemotherapy plus cetuximab 23%, 14/61; $p = 0.04$).

This result was unexpected and to this day remains an enigma, and to some, a controversy. Nevertheless, the mature overall survival data demonstrated a similar effect [7]. This analysis was carried out 5 years after the last patient was recruited. Median overall survival was 81.0 months (59.6 to not reached) in the chemotherapy alone group and 55.4 months (43.5–71.5) in the chemotherapy plus cetuximab group (HR 1.45, 1.02–2.05; $p = 0.036$). In keeping with the earlier analyses suggesting a less favourable progression profile in the group randomized to cetuximab, the updated analysis demonstrated post-progression survival to be shorter for the chemotherapy plus cetuximab group: median 33.5 months (95% CI 25.3–41.2) in the chemotherapy alone group compared with 23.5 months (16.0–31.3) in the chemotherapy plus cetuximab group (HR 1.55, 1.07–2.24; $p = 0.020$) (Fig. 22.4). The addition of cetuximab seemed to not only accelerate disease progression, but also may have led to the development of a more aggressive disease genotype and phenotype.

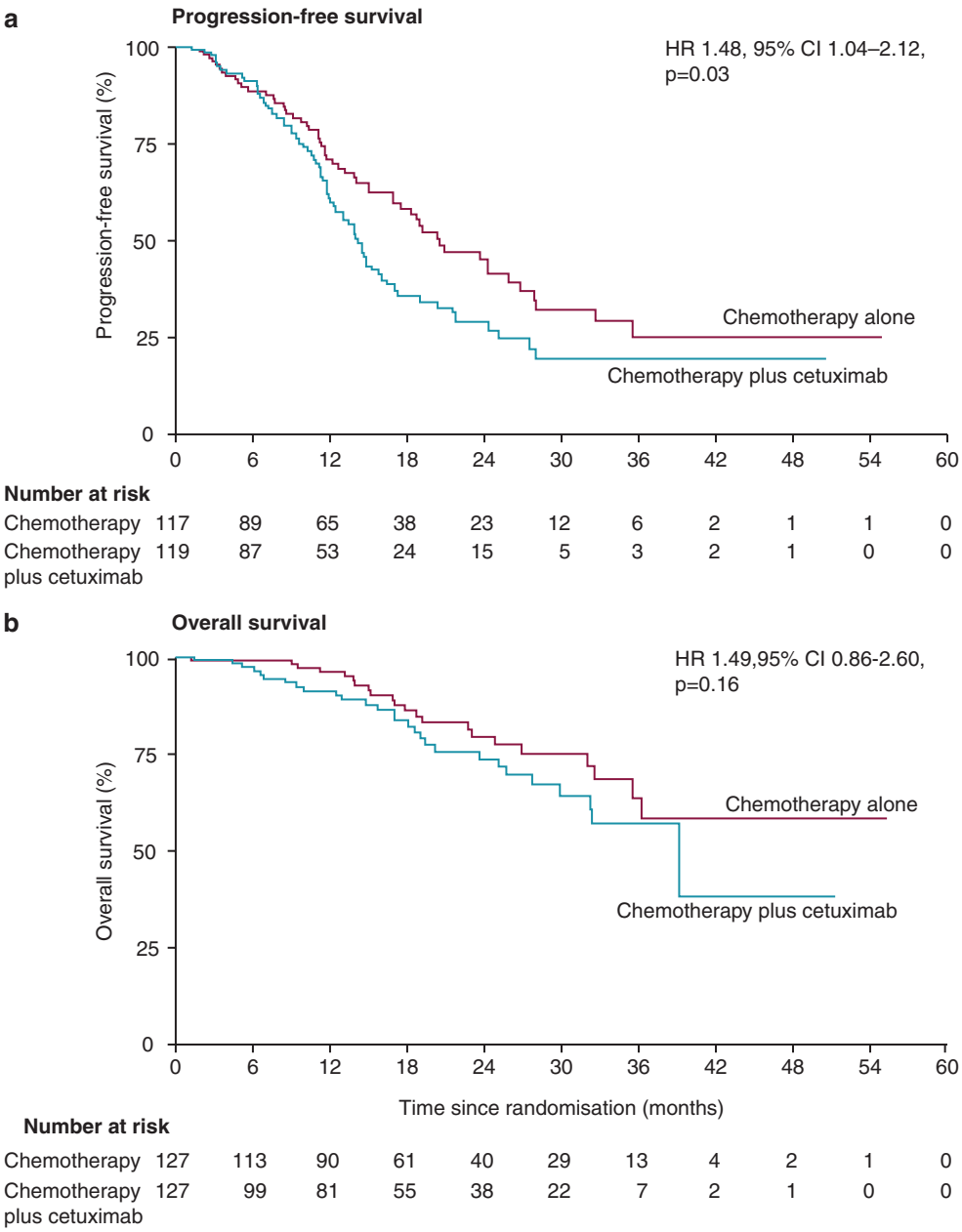
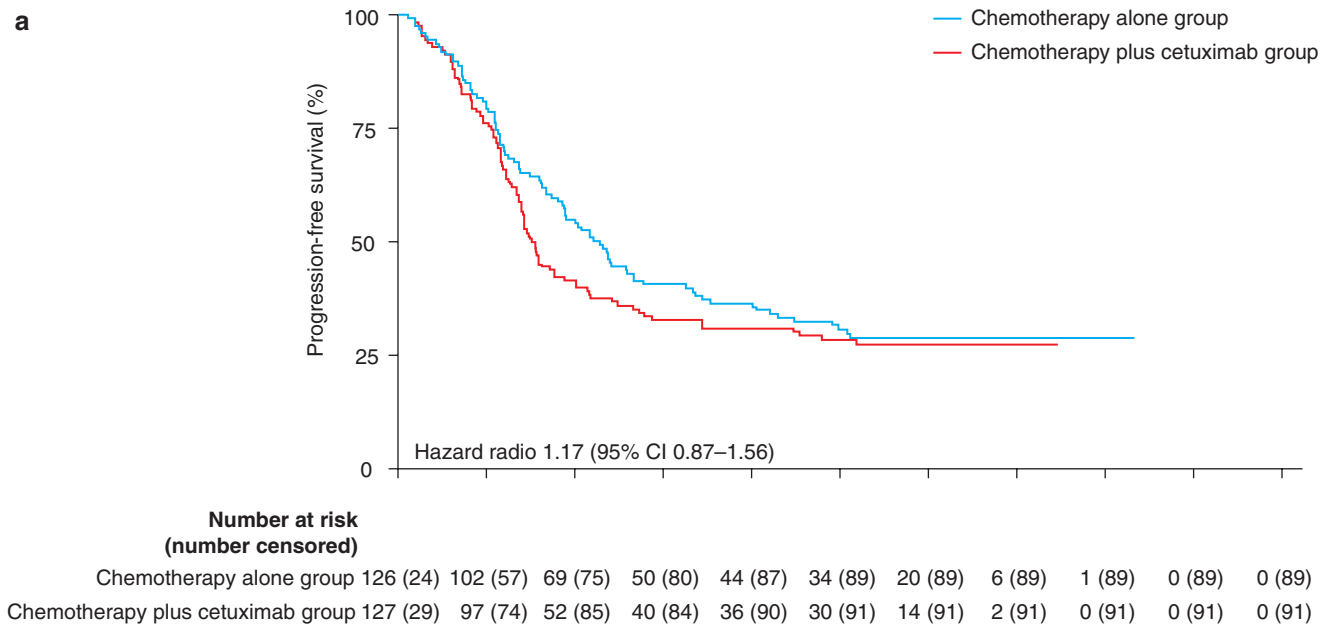


Fig. 22.3 Progression-free and overall survival in New EPOC interim analysis. Kaplan–Meier curves of progression-free survival (**a**) and overall survival (**b**) by treatment group in KRAS exon 2 wild-type patients only. Reproduced by permission

Lastly, the results of predefined subgroup analyses led to an interesting observation. As already stated, randomization did not achieve perfect balance between the groups, with the chemotherapy plus cetuximab group having numerically more patients with less favourable characteristics. However, the detriment with cetuximab in this present study occurred in patients with favourable characteristics (not poorly differentiated, not N2 disease, fewer than four metastases: HR 2.35 95% CI 1.37–4.03). The subset with less favourable prognostic features (poorly differentiated histology and/or N2 disease and/or or four or more metastases) did not benefit from the addition of cetuximab to chemotherapy, but equally were not disadvantaged (HR 0.95, 95% CI 0.60–1.51; p value for interaction 0.01).



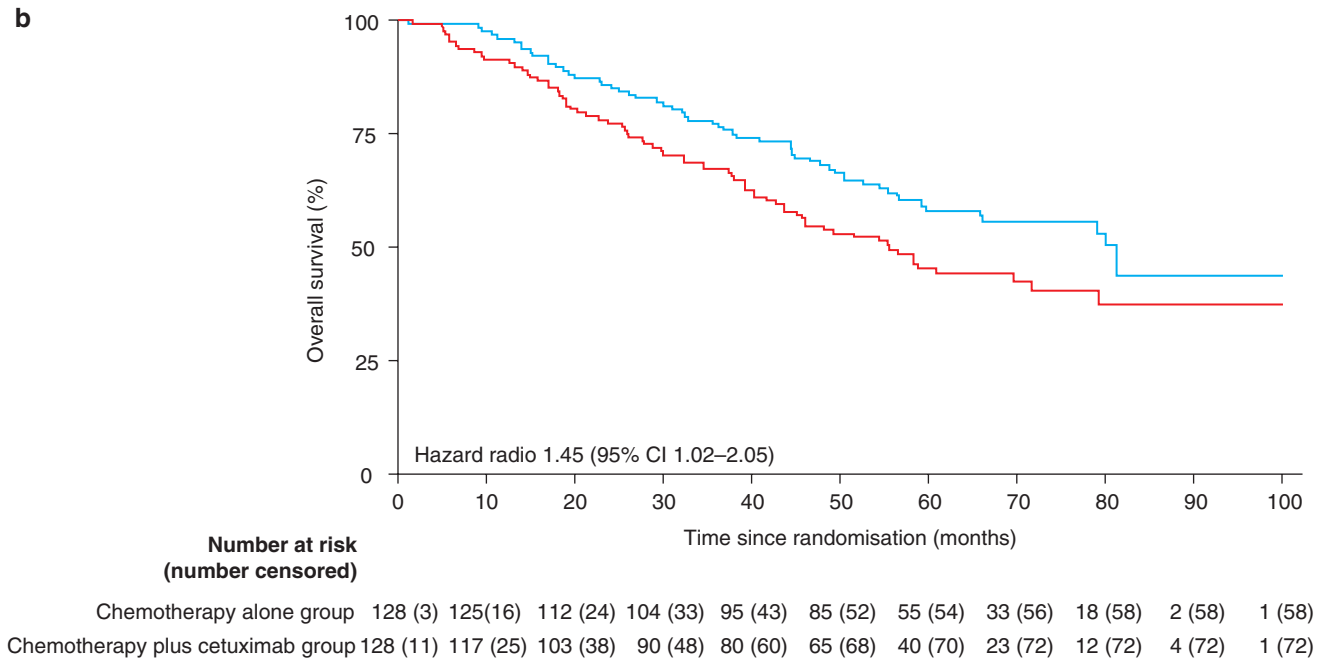


Fig. 22.4 Progression-free and overall survival in New EPOC final analysis. Kaplan–Meier curves of progression-free survival (**a**) and overall survival (**b**) by treatment group in the primary analysis population. Reproduced by permission

22.5 JCOG0603 Trial

This trial only recently fully reported despite recruitment commencing in 2007. Indeed it serves to highlight the complexities in completing such studies as the 300 patients were recruited over a 12 year period from 46 centres in Japan. The trial was a randomized phase II/III to investigate the safety and efficacy of adjuvant oxaliplatin and 5-fluorouracil chemotherapy versus surgery alone for patients post R0 resection of colorectal liver metastasis. Consistent with the EORTC 40983 trial, patients who had received prior chemotherapy with oxaliplatin were not eligible.

Between March 2007 and January 2019, 149 patients were randomly assigned to hepatectomy alone and 151 patients to adjuvant chemotherapy (12 cycles of mFOLFOX6). This included the patients recruited in the phase II stage during which changes were made to the protocol for high levels of toxicity from chemotherapy that was resulting in low rates of completion of all planned cycles of chemotherapy.

Randomization achieved good balance between the groups. The median age was comparable to EORTC 40983, although patients were possibly fitter as nearly all (97%) had a performance status of 0. Unlike EORTC 40983 the eligibility criteria were not restricted to four or fewer metastases, but just 9% of patients had four or more metastases. A smaller proportion had non-synchronous disease (44%) and likely consequently fewer had received adjuvant chemotherapy after primary tumour resection (22%).

The primary endpoint of the trial was disease-free survival defined as days from random assignment to the first evidence of recurrence, secondary cancer, or death from any cause. In the updated analysis (Fig. 22.5) with a median follow-up of 59.2 months (interquartile range, 26.5–95.3),

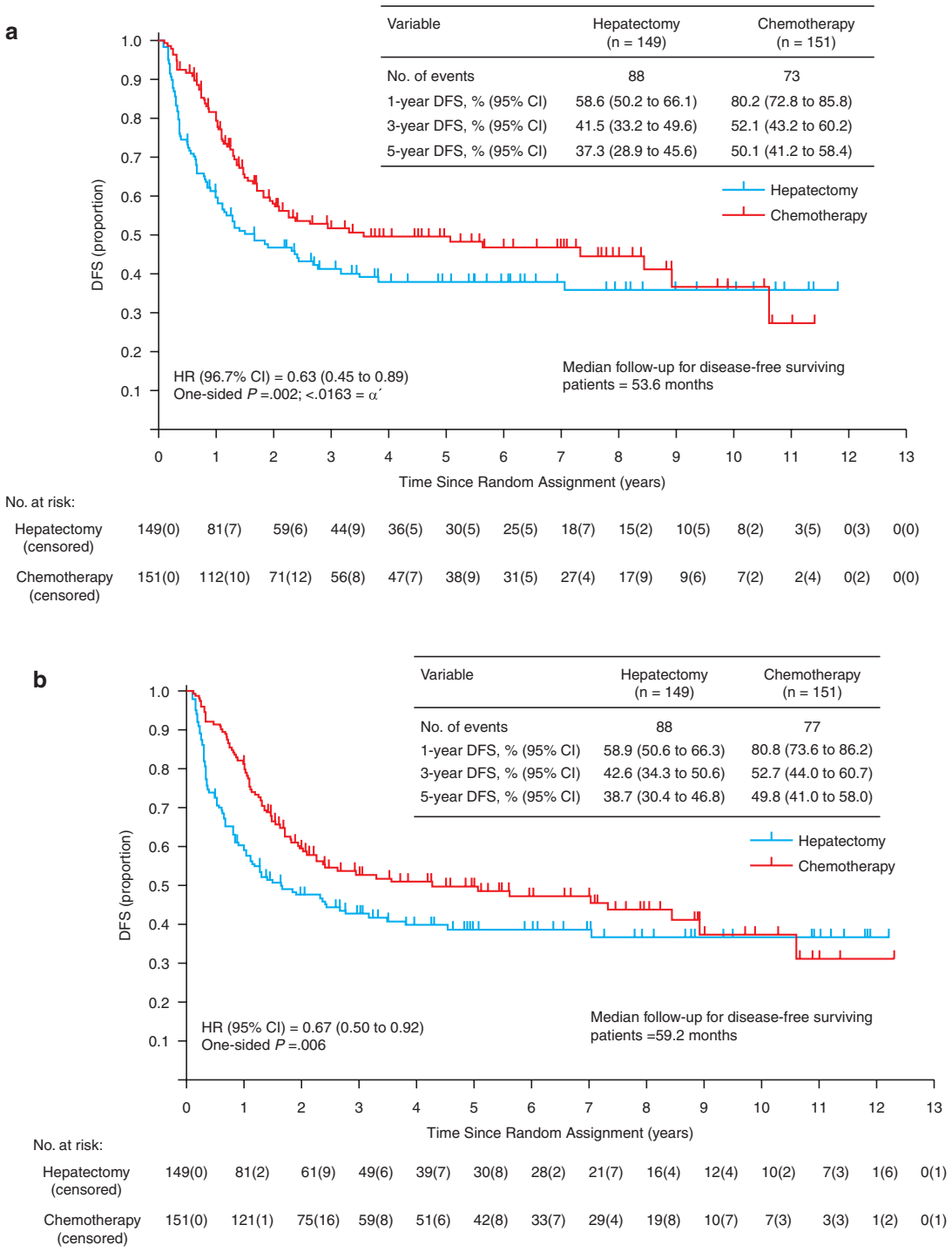


Fig. 22.5 Kaplan–Meier curves in the intention-to-treat population in the JCOG0603 trial: (**a**) disease-free survival in the third interim analysis (data cutoff date, June 5, 2019), (**b**) disease-free survival in the updated analysis (data cutoff date, November 26, 2019), and (**c**) overall survival in the updated analysis (data cutoff date, November 26, 2019). Reproduced by permission

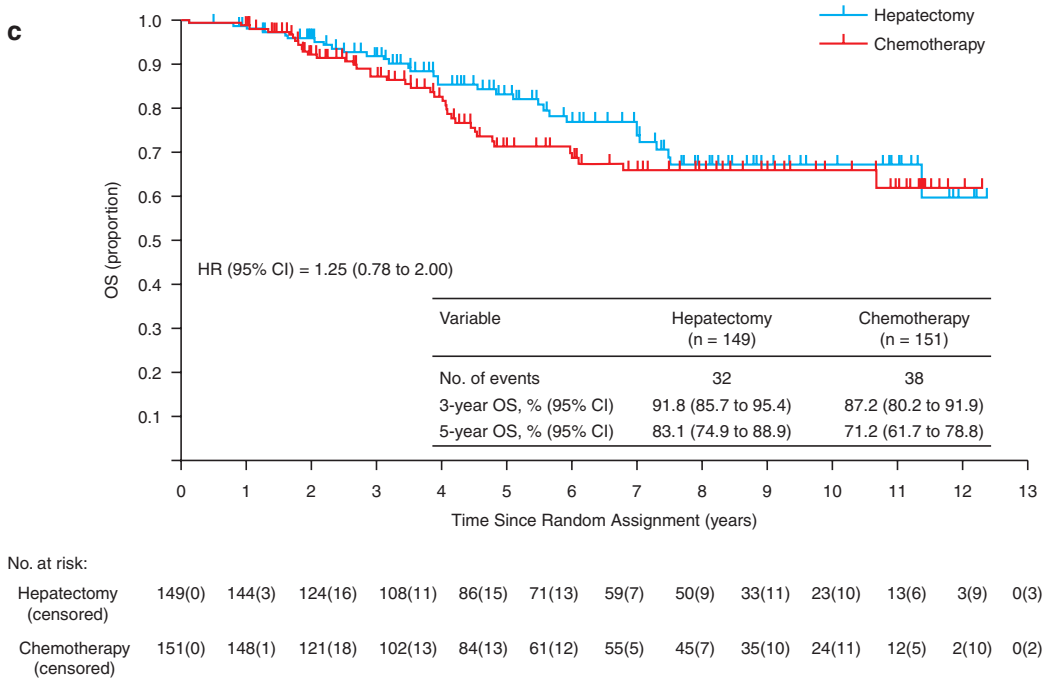


Fig. 22.5 (continued)

disease-free survival was shorter in the group allocated to surgery alone. The 5-year disease-free survival was 38.7% (95% CI, 30.4–46.8) for hepatectomy alone compared with 49.8% (41.0–58.0) for chemotherapy (HR, 0.67; 95% CI, 0.50–0.92; one-sided $p = 0.006$).

The interpretation of this trial has however been complicated by the overall survival analysis. As with EORTC 40983, and indeed New EPOC, the trial was not powered to detect a difference in overall survival but it was, as always, a crucial secondary endpoint. It is, therefore, perhaps unsurprising that there was no statistical difference in overall survival between the groups. There was however a numerical and 'visible' difference when regarding the Kaplan–Meier curve favouring surgery alone (Fig. 22.5c) and the majority of the discussion of this trial is focused on trying to understand the disparity between the disease-free survival and overall survival trends.

The authors presented interesting results regarding sites of disease recurrence. Distant recurrence rates were comparable between the groups (40/149 in the hepatectomy group and 43/151 in the adjuvant chemotherapy group) whereas recurrence in the remnant liver occurred in 43/149 in the hepatectomy group compared to just 25/151 in the chemotherapy group. The subgroup analyses of disease-free survival demonstrated an interaction according to primary tumour site with left-sided patients benefiting from chemotherapy (HR 0.60, 0.42–0.84) compared to right-sided patients (HR 1.32) (0.65–2.68; p value for interaction 0.04). With this in mind it would be interesting to view similar analyses based on RAS/RAF mutation status and microsatellite instability.

22.6 Other Trials

While a number of other trials have been conducted, these are predominantly in the phase II setting and often failed to recruit sufficient patients. As such although some give interesting insights, no specific conclusions can be made save that it is very difficult to perform trials in this population of patients.

A series of three trials were designed to address the question of whether all systemic therapy delivered as adjuvant was superior to perioperative systemic therapy in terms of progression-free survival. The three trials were the ATTACHE trial in Australasia, EPOC B in the United Kingdom, and NSABP C-11 in the United States. The systemic therapy regimens used reflected the local prescribing practice at the time, and were 5-fluorouracil and oxaliplatin based, with irinotecan permitted for those patients who had received prior oxaliplatin as adjuvant. Both the ATTACHE and NSABP C-11 trials allowed the addition of bevacizumab, an antibody to the vascular endothelial growth receptor, to chemotherapy. The individual studies were set up as randomized phase II trials with endpoints of perioperative morbidity. They were always designed with the intention of meta-analysis to address a progression-free survival endpoint. Unfortunately all of these trials failed to recruit and remain unpublished

save in outline form [20]. Although little useful information was obtained, the trials did demonstrate the feasibility of delivering 5-fluorouracil and oxaliplatin-based chemotherapy completely in the postoperative setting.

Bevacizumab in combination with chemotherapy administered in the neoadjuvant setting has been evaluated in two single arm phase II studies of patients with resectable disease. In the first instance it was combined with capecitabine and oxaliplatin (CAPOX) [21], and in the second 5-fluorouracil with irinotecan (FOLFIRI) [22]. The results appeared to be acceptable both in terms of response and progression-free survival, possibly warranting further investigation. However, a randomized phase II/III study of CAPOX with or without bevacizumab failed to recruit and has closed [23].

Lastly, there have been additional studies examining the role of cetuximab in the perioperative treatment of colorectal liver metastases. One phase II non-randomized study examined 5-fluorouracil and oxaliplatin (mFOLFOX6) plus cetuximab in KRAS wild-type patients with technically unresectable disease and/or five or more metastases. This trial demonstrated a 54% R0 resection rate, but again no specific conclusion can be drawn [24]. The same group attempted a phase III trial comparing surgery followed by adjuvant FOLFOX with perioperative FOLFOX plus cetuximab. The trial closed due to poor recruitment (77 patients) and has only been published in abstract form [25]. The small numbers of patients make it difficult to draw any meaningful conclusions but the Kaplan–Meier curves if anything appear less favourable for the perioperative cetuximab group.

22.7 Conclusions from the Available Evidence

A limited number of definitive conclusions can be drawn from the available trial data of perioperative chemotherapy for colorectal liver metastases. The first is that these trials demonstrate the feasibility of administering systemic chemotherapy perioperatively both in terms of safety and actual deliverability. For the purpose of examining this, data from the chemotherapy plus cetuximab group of New EPOC is not included, since this did not demonstrate oncological efficacy.

In both the EORTC 40983 and New EPOC trials, a substantial proportion of patients received the planned treatment. In the chemotherapy group of 40983, 143 (84%) of 171 eligible patients completed the planned six cycles of preoperative chemotherapy with dose modifications and delays in 34% and 44% respectively [4]. In the New EPOC trial analyses were based on the intention to treat population. A similar proportion, 99 (77%) of 128 patients in the chemotherapy alone group, completed 12 weeks of preoperative chemotherapy [7]. Dose modifications occurred in 45% (58/128) and delays in 51% (65/128) of patients.

The toxicities of the systemic treatments did not appear to impact on the ability of patients to undergo surgical resections. In the chemotherapy group of 40983, 151 (83%) of 182 patients (intention to treat population) underwent surgical resection compared to 108 (84%) of 128 patients in the chemotherapy group of the New EPOC trial. For those patients who did not proceed to resection the main reason was progression of disease preoperatively or the finding of more extensive disease at operation. In 40983 the surgical complications were higher in the perioperative chemotherapy group (40/159 [25%] vs. 27/170 [16%]; $p = 0.04$) but were reversible. Although there were higher complication rates with chemotherapy and surgery, the perioperative mortality was extremely low and comparable to the surgery group with one postoperative death in the chemotherapy group and two in the surgery group. There were no postoperative deaths in the chemotherapy alone group of New EPOC.

In the chemotherapy group of 40983, 115 (63%) of 182 patients started postoperative protocol chemotherapy, of whom 80 (44%) of 182 patients received the full six cycles. Dose modifications occurred in 60% (69/115) and delays in 64% (73/115) of patients. In the chemotherapy group of New EPOC 59 (46%) of 128 patients completed 12 weeks of postoperative therapy. Dose modifications occurred in 43% (49/113) and 34% (38/113) of patients experienced a dose delay.

There was one death in each of the chemotherapy groups of 40983 and New EPOC attributed to toxicity of chemotherapy. The adverse event data for both trials is reported for both the preoperative and postoperative chemotherapy periods, which if completed equate to a total of 6 months of treatment respectively. The toxicity profiles were as would be expected for a group of patients predominantly receiving FOLFOX chemotherapy with the most common being neutropenia, sensory neuropathy/neurological toxicity and diarrhoea.

The JCOG0603 trial delivered all chemotherapy as adjuvant and in the early phase of the trial, this was associated with high rates of toxicity in particular neutropenia. Modifications to the protocol were made including dose reduction levels and in the later phase of the trial 55% of patients completed 12 cycles of the mFOLFOX6 chemotherapy.

The second definitive conclusion is that cetuximab should not be used in the perioperative setting in patients with resectable or borderline resectable liver metastases. The caveat to that statement is that the trial did not ask investigators to report whether the multidisciplinary team/tumour board considered the patient to be borderline resectable or not. Certainly the baseline characteristics suggest that the

majority are likely to have been within the resectable category and therefore it is perhaps difficult for there to be certainty around the efficacy of cetuximab in those patients with truly borderline disease.

Lastly, the lack of definitive conclusions that can be drawn from these data serve to highlight the need for more randomized studies in this patient group.

22.8 Ongoing Uncertainties

There are a number of considerations such as timing, duration and choice of regimen which have only partly been addressed by the available studies.

22.8.1 Timing

The two phase III trials, EORTC 40983 and New EPOC, evaluated the use of the systemic therapy before and after surgery. Prior to the publication of the JCOG0603 trial, it could be argued that there was a stronger evidence base for delivering treatment perioperatively since there was no evidence for using modern chemotherapy regimens in the adjuvant setting. With knowledge of the results of the JCOG0603 trial, evidence now exists for both approaches albeit with ongoing uncertainty as to the overall survival gains from either.

One argument for the use of perioperative chemotherapy over adjuvant therapy is that it does provide an indication of which patients may not benefit from the treatment. Treatment with measurable disease in situ permits an evaluation of the response of the metastases to the neoadjuvant treatment. The radiological and pathological assessments of the metastases are used as a surrogate for the likelihood of the systemic therapy being effective against micrometastatic disease. In the 40983 and New EPOC trials, patients with evidence of progression on neoadjuvant treatment proceeded directly to surgery if possible and did not receive postoperative protocol treatment. If such patients had undergone surgery first then they would have potentially received a full 6 months of adjuvant systemic treatment, with the associated toxicity, and arguably may have derived little benefit.

Another closely related argument is that a period of preoperative chemotherapy permits assessment of the disease biology. Some contend that patients with disease progressing to inoperability on neoadjuvant systemic treatment would be unlikely to derive benefit from a major operation, i.e., recurrence would be fairly rapid post-surgery [26]. Of course this is impossible to know with certainty and others may argue that patients with metastases who do not respond to first line chemotherapy may still derive benefit from surgery albeit with a worse overall prognosis.

As such whether to deliver systemic therapy perioperatively or as adjuvant remains unclear. In clinical practice it is often decided on an individual case basis by the multidisciplinary teams/tumour boards).

22.8.2 Choice of Regimen

This has stemmed from knowledge of the systemic agents that are effective in treating colorectal cancer in both the metastatic and adjuvant setting. 5-fluorouracil, an inhibitor of thymidylate synthase, has formed the backbone of systemic treatment for colorectal cancer for decades. It is administered in conjunction with leucovorin, a reduced folate, which potentiates the efficacy of 5-fluorouracil [27, 28]. More recently 5-fluorouracil has been combined with the topoisomerase inhibitor irinotecan and the platinum containing agent oxaliplatin to treat colorectal cancer. Both have shown efficacy in advanced disease [12, 29, 30], and indeed the authors of the EORTC 40983 trial state that FOLFOX4 was chosen for this reason. It is also noteworthy that only oxaliplatin-based regimens have shown efficacy as an adjuvant treatment in early colon cancer [31–36]. Indeed, this was the rationale for the use of mFOLFOX6 regimen in the JCOG0603 trial where all chemotherapy was being delivered after surgery. It therefore could be argued that FOLFOX may be preferable to FOLFIRI in the setting of resectable colorectal liver metastases where the primary goal is to treat micrometastatic disease.

The New EPOC trial similarly focused on 5-fluorouracil and oxaliplatin containing regimens as the backbone of treatment. It did, however, permit patients who had received oxaliplatin as adjuvant to receive irinotecan instead of oxaliplatin. Relatively few patients received the FOLFIRI regimen and therefore it remains the case that there is a limited evidence base for its use in this setting.

22.8.3 Duration of Treatment

The duration of treatment has typically been a total of 6 months of systemic therapy which is in line with the standard duration of treatment used in the adjuvant setting for colon cancer [31, 33]. One of the main disadvantages to this duration of systemic therapy with oxaliplatin containing regimens is the neurotoxicity, specifically peripheral sensory neuropathy, that can result. This can be disabling and long lasting [37, 38].

When compared to modern trials of doublet chemotherapy with 5-fluorouracil and oxaliplatin used in the adjuvant setting for primary colon cancer, the incidence of peripheral neuropathy in 40983 and New EPOC is broadly comparable. It is difficult to make absolute comparisons between the trials due to differences in collection methodologies and the

focus on grade of toxicity reported. Furthermore, and as already highlighted, some patients in New EPOC received irinotecan in place of oxaliplatin, although this was in the setting of previous administration of oxaliplatin.

The peripheral neuropathy from oxaliplatin is related to the dose and duration of therapy. Consequently trials have been conducted in the setting of adjuvant treatment of colon cancer to evaluate whether 3 months of therapy is non-inferior to the standard duration of 6 months. While a pooled analysis of six randomized trials did not confirm non-inferiority in the overall population, it is widely accepted that in patients with low-risk disease treated with CAPOX, 3 months of therapy is non-inferior to 6 months [39]. In terms of peripheral neuropathy, this was significantly worse in the group receiving 6 months of treatment and persisted for at least 5 years [40].

Most trials do not collect toxicity data beyond the period during which the patients are receiving systemic treatment. For many toxicities this is sufficient but the severity of peripheral neuropathy from oxaliplatin often increases, and certainly persists, after the treatment is stopped. It is therefore highly likely that the reported incidence of peripheral neuropathy in both 40983 and New EPOC underestimates the actual disability experienced by patients. This, combined with the recent evidence in the adjuvant setting of colon cancer, raises the question as to whether a shorter duration of systemic treatment may achieve adequate efficacy in some patients with resectable colorectal liver metastases with reduced toxicity.

22.8.4 Impact on Overall Survival

The largest trials available are EORTC 40983 and JCOG0603 and neither were powered to assess an impact on overall survival. The primary endpoint of EORTC 40983 was progression-free survival and statistical significance was only achieved in the 'eligible' rather than the intention to treat population. The overall survival impact was not statistically significant and can be at most a few per cent if at all. The apparent discordance between disease-free and overall survival in JCOG0603 adds further confusion. A number of explanations have been put forward but perhaps the strongest is that this is simply down to statistical chance. Nevertheless, taking these two trials together, it is possible that chemotherapy defers rather than altogether prevents disease progression and an overall survival benefit is at most very small.

22.9 Summary and Recommendations

Chemotherapy in combination with liver resection has been evaluated as a strategy to reduce disease recurrence, and improve survival of patients with resectable colorectal liver metastases. While tumour shrinkage before surgery is desirable in some patients, the predominant role of the systemic treatment in the majority is to treat micrometastatic disease. As with adjuvant therapies for many cancers, it is inevitable that some, but not all, patients will derive benefit. This is a key consideration when the treatment confers morbidity and in some cases mortality. It is important to consider that both 40983 and the JCOG0603 trial recruited patients with easily resectable disease, the large majority with four or fewer metastases. They are not representative of the majority of patients presenting at a multidisciplinary team/tumour board who will often have a primary cancer with adverse features and liver disease that is either borderline or unresectable without chemotherapy to shrink the disease. Such patients would not be recruited to any trial that had a no chemotherapy arm.

The majority of multidisciplinary teams/tumour boards decide the treatment strategy according to the technical resectability of the disease and the apparent disease biology. This is of course, by necessity, an oversimplification and the suggestions below are for guidance rather than absolute recommendations. It is important to note, as highlighted in other chapters, that there is no one definition of what is surgically resectable. This has changed over time and varies according to the expertise and 'ambition' of the surgical team.

The disease biology is also sometimes termed the oncological criteria or prognosis. There is similarly no international consensus regarding this. Scoring systems have been developed that predict a longer disease-free interval and likelihood of cure [15, 16]. Factors thought to confer a less favourable prognosis include higher number of metastases, larger lesions and synchronous presentation. It is often considered that such patients should receive chemotherapy although the post hoc analysis of the EORTC 40983 trial only suggested the CEA level to be predictive of benefit from perioperative chemotherapy. Of course the trial was restricted to patients with relatively favourable disease.

There are other characteristics, such as development of liver metastases while on adjuvant therapy for the primary cancer, that are likely to confer a worse prognosis yet these patients may not benefit from further chemotherapy. Certainly factors such as the fitness of the patient and whether or not they have received chemotherapy previously for colorectal cancer need to be incorporated into the decision making.

Indeed it could be argued that both the EORTC 40983 and JCOG0603 trials comprised populations of patients with relatively easily resectable disease and with a tendency towards more favourable disease biology. Perhaps therefore one of the key limitations is that it is difficult to directly extrapolate these results to patients with operable disease that is higher volume or considered to be at high risk of progression. Even notwithstanding the eligibility criteria for these trials, such patients would have been unlikely to have been recruited to a trial with a 50% chance of randomization to no systemic therapy.

In summary, chemotherapy for resectable colorectal liver metastases, whether delivered perioperatively or all postoperatively, is likely to benefit some but not all patients. At present the tools to accurately identify those patients who will derive benefit and those that will only receive toxicity are lacking. Future trials are likely to focus on selection of patients for treatment and this may involve biomarkers such as circulating tumour DNA [41].

Using the current available evidence, a suggested approach is outlined below:

- Patients considered to have technically resectable (R0 achievable) liver metastases and favourable 'biological' criteria (e.g., low volume disease, non-synchronous presentation with more than 1 year since treatment of primary cancer) could be offered surgery alone. This might be especially appropriate for older and/or poorer performance status patients.
- For younger and/or better performance status patients, perioperative/postoperative chemotherapy could be considered. In this case 5-fluorouracil and oxaliplatin-based chemotherapy should be offered, although FOLFIRI (5-fluorouracil with irinotecan) is an option if the patient received oxaliplatin as an adjuvant treatment for primary disease.
- Perioperative chemotherapy may also be considered in patients with technically resectable (R0 achievable) liver metastases but with less favourable 'biological' criteria (such as elevated CEA).
- In patients with synchronous presentation, chemotherapy will usually form part of the treatment plan. The sequencing of therapies will be influenced by both the stage of the primary and the resectability of the liver disease.
- Patients for whom the surgical team suspect that the margins could be compromised should be offered preoperative systemic therapy. Whether to offer doublet chemotherapy, triplet chemotherapy or doublet chemotherapy with bevacizumab, is likely to be influenced by the degree of shrinkage desired, the performance status of the patient, and the available treatments in the respective healthcare system.
- Cetuximab should not be used in patients with easily resectable metastases.

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Disappearing Liver Metastasis

23

D. Brock Hewitt and Timothy M. Pawlik

Learning Objectives

- Patients with disappearing liver metastasis should undergo a magnetic resonance imaging (MRI), especially patients with steatosis.
- A complete radiologic response does not necessarily signify a complete pathologic response.
- When possible, surgical resection of colorectal liver metastasis should include all original sites of disease/disappearing liver metastasis.
- A durable clinical response for disappearing liver metastasis in situ can be expected in up to 50% of patients treated with systemic chemotherapy.
- Resection of residual macroscopic disease while leaving some disappearing liver metastasis in situ may be considered in select cases.

23.1 Introduction

Colorectal cancer is the second leading cause of cancer mortality in the world, with over half of patients developing hepatic metastatic disease [1, 2]. While surgical resection remains the best chance at long-term survival among patients with colorectal liver metastases (CRLM), less than 25% of patients present with resectable disease [3]. For patients with unresectable CRLM, as well as select patients with resectable CRLM, chemotherapy is first line treatment. The introduction of more effective cytotoxic and biologic agents has improved radiographic response rates, rates of conversion to resectable disease, and overall survival among patients with CRLM [4–8]. Modern combination regimens can achieve a complete radiographic response in almost 50% of patients [9]. Consensus guidelines on the management of disappearing liver metastases (DLM) are lacking. Significant variation exists in the imaging modality used to define DLM, the operative approach to DLM, and the utilization of adjuvant therapies for patients with DLM. This chapter focuses on the definition, management, and outcomes of DLM.

23.2 Defining Disappearing Colorectal Liver Metastasis

DLM are liver lesions initially identified on cross-sectional imaging that regress and become radiographically absent after chemotherapy. The sensitivity and specificity of the imaging modality determines the incidence of DLM. Computed tomography (CT), with or without contrast, FDG-PET, FDG-PET/CT, and MRI, with or without contrast, have all been utilized to identify CRLM with varying degrees of accuracy. Liver parenchymal changes seen in fatty liver disease, as a consequence of preoperative chemotherapy or underlying steatosis, mitigate the contrast between the fatty liver and the liver metastases, limiting the diagnostic accuracy of CRLM and DLM by CT or FDG-PET [10, 11]. The fat suppressing techniques available with MRI improve the diagnostic accuracy to detect DLM with a pathologic complete response compared with CT [12–14] (Fig. 23.1). MRI evaluation should be encouraged in all patients with CRLM, especially patients with steatosis.

The incidence of DLM varies from 7% to 48% with a median of three lesions per patient [12–25] (Table 23.1). Factors associated with DLM include sub-centimeter lesions, synchronous metastatic disease, the presence of three or more liver metastases, and patients receiving a greater duration of preoperative chemotherapy [13, 20, 24] (Table 23.2). More specifically, each additional cycle of chemotherapy has been associated with an 18% increase in the likelihood of DLM [20]. Serial imaging is required to monitor response to chemotherapy. The median time to CRLM disappearance is approximately 5 months from chemotherapy initiation and 90% of DLM occur by 9 months [17].

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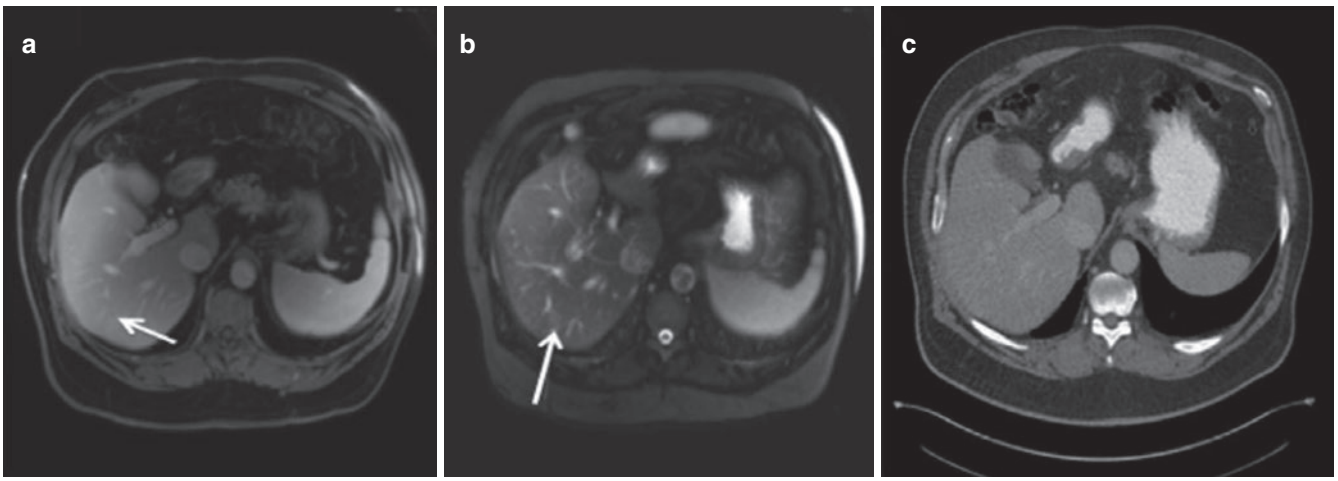

Fig. 23.1 (**a**) and (**b**) show a CRLM; however, the same lesion is not seen on CT imaging (**c**)

Table 23.1 Outcomes of patients with disappearing liver metastases

Study	Patients with DLM (%)	Initial CRLM	DLM	DLM/ patient	CPR/ resected DLM	CCR/DLM left in situ	Time to recurrence (months)	Median follow-up (months)	DLM with CR	DLM with CR + IOUS
Benoist 2006	38 (7)	183	66	1.7	3/15	8/31	–	12	17%	24%
Elias 2007	16 (7)	134	69	4.3	n/a	10/16	–	50	–	–
Auer 2010	39 (9)	166	118	3	44/68	31/50	Mean 21	41	64%	65%
Tanaka 2009	23 (37)	472	86	3.7	6/17	16/27	Median 14	44	69%	80%
Goéré 2011	27 (n/a)	523	96	3.6	n/a	18/27	Median 14	55	–	–
Van Vledder 2010	40 (24)	–	127	3.2	26/67	24/45	–	20	45%	54%
Ferrero 2012	33 (19)	624	67	2	22/57	4/10	Median < 12	–	39%	64%
Park 2017	87 (n/a)	393	CT 203	0.6 (MRI)	CT 47/168	CT 24/35	Median < 12	12	CT 35%	CT 69%
			MRI 55		MRI 28/39	MRI 15/16			MRI 78%	MRI 94%
Kim 2017	43 (31)	289	168	3.9	8/8	128/150	–	22	85%	–
Arita 2014	11 (15)	234	32	0.4	10/37	4/7	–	–	41%	IOUS 46%
										CE-IOUS 75%
Owen 2016	11 (48)	200	77	7	10/36	20/41	–	46	40%	–
Tani 2018	20 (24)	619	111	5.6	CT 54/78	CT 11/33	Median 8	27	CT 59%	86%
					MRI 24/29	MRI 16/18			MRI 85%	
Sturesson 2015	29 (16)	141	66	2.3	24/56	3/4	–	–	45%	96%
Oba 2018	59 (32)	764	275	4.7	103/233	36/42	–	27	CT 51%	92%
									MRI 65%	

DLM disappearing liver metastases, *CRLM* colorectal liver metastases, *CPR* complete pathologic response, *CCR* complete clinical response, *CR* complete response, *IOUS* intraoperative ultrasound, *CE-CT* contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *CE-IOUS* contrast-enhanced intraoperative ultrasound

Table 23.2 Factors predisposing to the development of disappearing liver metastases

Smaller size (<2 cm) of liver metastases
Greater number of liver metastases (≥3)
Synchronous disease
Greater number of chemotherapy cycles tolerated
Platin-based chemotherapy

23.3 Intraoperative Assessment of DLM

Despite improved imaging techniques and the increased utilization of MRI, 30–55% of preoperatively determined DLM will have evidence of macroscopic residual disease at the time of surgery [15, 20]. At the time of surgery, a complete liver evaluation needs to be done prior to surgical resection. In particular, the surgeon should perform full mobilization, palpation, and visual inspection of the liver, as well as intraoperative ultrasound (IOUS), preferably with contrast enhanced IOUS as this modality improves the detection rate of DLM [23, 26]. Factors impacting the discovery rate of macroscopic disease at the time of surgery include the underlying degree of liver steatosis, location of DLM such as capsular/peripheral versus central/deep, relative proximity to certain anatomic landmarks, surgeon skill with IOUS, and type of pre-operative imaging utilized [15]. In particular, if MRI was not used in the preoperative setting, the chance of identifying a lesion "missed" will be higher at the time of surgery. However, even after an exhaustive assessment of the liver, the location of DLM may still prove elusive. To this point, placement of a fiducial marker at the site of a CRLM prior to the initiation of chemotherapy can improve localization of DLM and ensure all lesions receive accurate therapeutic intervention [27, 28] (Fig. 23.2). As such, consideration of marker placement should be given for lesions <2 cm in size, located deeper than 1 cm from the capsule, or lesions outside the proposed resection field [27, 28].

23.4 Management and Outcomes of DLM

A radiographic complete response does not always coincide with a pathologic complete response (Fig. 23.3). Data from a systematic review noted that pathologic complete response rates varied considerably among patients with DLM, ranging from 17% to 85% (median 54.5%) [29]. The reason for the wide variation in "true" complete response is likely multifactorial and includes differences in MRI utilization as well as variable chemotherapy regimens and durations. Among patients with DLM, a pathologic complete response is more likely in younger (≤60 years) patients with a lower initial CEA; patients with no disease on preoperative MRI, or patients

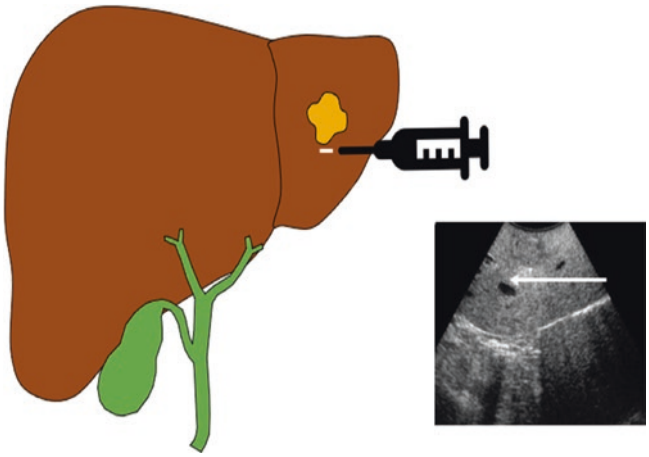

Fig. 23.2 Representative image of an ultrasonic fiducial marker placement to mark a CRLM

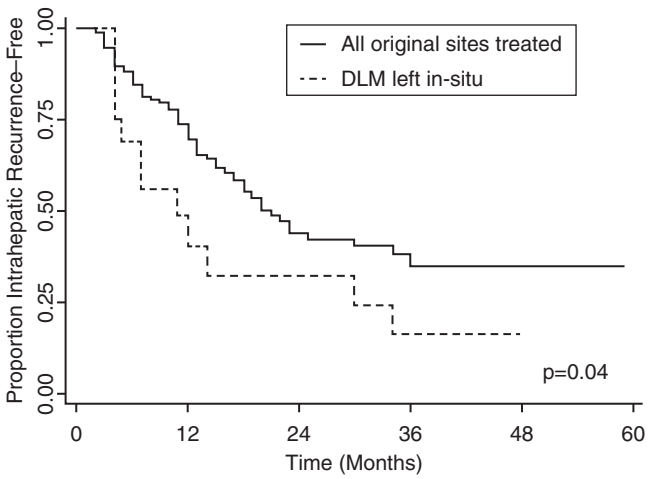

Fig. 23.3 Kaplan–Meier curve of intrahepatic recurrence-free survival in patients with untreated disappearing liver metastases when compared to patients in whom all original disease sites were restricted

treated with hepatic artery infusion (HAI) chemotherapy [17, 30].

Few studies have directly compared overall survival and recurrence-free survival by treatment approach in patients with DLM, and none are prospective, randomized controlled trials [16, 18–20, 24] (Table 23.3). Furthermore, most studies are underpowered and have significant heterogeneity regarding preoperative chemotherapy regimens, imaging modalities, and adjuvant therapies. Despite these limitations, current evidence suggests that patients with a complete resection of their DLM have a lower incidence of intrahepatic recurrence compared with DLM left in-situ; however, overall survival may not be different—largely due to the ability to salvage patients who experience intrahepatic recurrence. In addition, when DLM are left in-situ, a durable clinical response may be possible in up to 50% of patients [15, 17, 20].

Table 23.3 Patient survival: resection of disappearing liver metastases vs. no resection

Study	Lesions resected	Lesions left in-situ	Resection vs. no resection
Elias 2007	–	3-year OS: 94%	–
	–	3-year DFS: 64%	–
Van Vledder 2010	1-, 3-, and 5-year OS: 93%, 59%, and 38%	1-, 3-, and 5-year OS: 94%, 64%, and 64%	Not significant
	1- and 3-year DFS: 69% and 35%	1- and 3-year DFS: 40% and 16%	$p = 0.04$
Tanaka 2009	Median OS: 53 months	Median OS: 63 months	Not significant
	Median DFS: 22 months	Median DFS: 16 months	Not significant
Goéré 2011	–	3- and 5-year OS: 87% and 80%	–
	–	3- and 5-year DFS: 23% and 23%	–
Owen 2016	Median DFS: 483 days	Median DFS: 360 days	Not significant

OS overall survival, *DFS* disease free survival

Table 23.4 Basic principles of disappearing liver metastases diagnosis and management

- DLM definition: Complete response (disappearance) of CRLM after chemotherapy on cross-sectional imaging studies
- Predisposing factors: Small size (<2 cm), increased number of chemotherapy cycles, oxaliplatin-based therapy, increased number of CRLM (≥3), synchronous CRLM
- Imaging: Baseline and preoperative MRI with IV contract (preferred)
- Pretreatment fiducial placement may guide identification of DLM during surgery
- HAI chemotherapy administration, young patients (<60 years) with an initially low CEA, and patients without detectable lesions on preoperative imaging have the highest chance of a pathologic complete response
- Intraoperative exploration with palpation and IOUS after full liver mobilization, especially in the absence of preoperative MRI
- Resection of all DLM sites is preferred as resection has been associated with lower intrahepatic recurrence
- Leaving DLM in-situ has been associated with a higher incidence of intrahepatic recurrence but not necessarily worse overall survival
- Treatment of patients with DLM should be guided by a multidisciplinary approach as treatment is highly individualized and may include surgical resection, additional systemic or local therapy, or close surveillance

DLM disappearing liver metastases, *CRLM* colorectal liver metastases, *CEA* carcinoembryonic antigen, *MRI* magnetic resonance imaging

Since a significant number of patients do not obtain a pathologic complete response or a durable clinical response, surgical resection of DLM is recommended. Sometimes patients can have a mixed response where some lesions persist and other lesions disappear. In this setting, resection should include all sites of disease identified before initiation of chemotherapy—both lesions that are still present as well those sites where the lesion disappeared. In the setting of multiple initial lesions throughout the liver—some of which have disappeared—it may be prudent to wait a brief period either off chemotherapy or on maintenance chemotherapy to see if the disappeared lesions re-appear before committing to an operative plan. When considering the surgical approach, a parenchymal-sparing hepatectomy (PSH) has equivalent oncologic outcomes (R0 resection rate, liver recurrence-free survival, and overall survival) compared with an anatomic resection during the index operation and better 5-year survival in cases of recurrent liver disease [31, 32]. The inability to resect all DLM site should not necessarily preclude surgery. In selected situations where not all the original DLM disease sites can be safely resected or identified intraoperatively, close surveillance is needed as patients can still have acceptable outcomes with adjuvant therapies for DLMs that regrow including surgery. In fact, for patients who have completely disappeared lesions with no evidence of persistent disease on MRI, close surveillance may be warranted with resection only employed when/if the lesions reappear.

23.5 Conclusion

Modern chemotherapeutic regimens have improved overall survival for patients with CRLM and increased the incidence of DLM. While clear guidelines are lacking, several consensus recommendations can provide patients with the best chance at long-term survival (Table 23.4). MRI is the preferred imaging modality to evaluate DLM. For patients with CRLM at high risk to disappear, surgeons can consider marking the site with a fiducial before the initiation of chemotherapy. DLM is not equivalent with a pathologic complete response and surgical resection of all original disease sites should generally be performed at the time of surgery. However, patients with DLM left in-situ can expect a reasonable complete durable clinical response rate, especially when the disappearance of the lesion has been confirmed with MRI. Well-powered studies are needed to further elucidate the appropriate management of DLM.

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Downsizing Chemotherapy for Liver Metastases from Colorectal Cancer

24

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Learning Objectives

- The evolution of the concept and definition of resectability.
- The best strategy to achieve resectability in patients initially unresectable and the survival benefit.
- How and when to propose resection after efficient conversion chemotherapy?
- The optimal management of patients escaping first-line chemotherapy, in view of resection.
- Why the multidisciplinary team approach is mandatory for a successful oncosurge approach?

24.1 Introduction

Colorectal cancer (CRC) is cancer that represents 1,900,000 new cases and more than 900,000 deaths each year worldwide, and two-thirds of which are related to liver metastases [1]. It is a problem of public health as the third most frequent cancer in the world. In Asia, including Japan, China, South Korea, and Singapore, the incidence of CRC has increased two- to fourfold in the past two decades [2]. In patients with CRC, the liver is the most common site of metastases and about half of patients develop liver metastases during the course of their disease [3]. Hepatic resection is the only treatment associated with prolonged survival or even cure for patients with colorectal liver metastases (CLM). Results from the LiverMetSurvey, involving 28,081 patients from 366 centers in 63 countries, who underwent surgery for liver metastases, showed a 5-year and 10-year survival of 43% and 26% in patients who underwent the first resection of liver metastases versus 10% and 2% in those who do not (Fig. 24.1) [www.livermetsurvey-arcad.org, update June 2020)]. In a systematic review of 142 studies published in 1999–2010 [4], 5-year survival rates ranged from 16% to 71% after liver resection (median, 38%).

Unfortunately, approximately 80% of patients with CLM are unresectable at the time of diagnosis. Recent innovations in the treatment of CLM have enabled hepatic resection for such patients, and the 5-year survival rate reached 33% to 50% [5–7]. Consequently, the treatment strategy for CLM, either initially resectable or unresectable, should be directed toward their potential resectability.

In past decades, many efforts have been made to increase the resectability of patients with unresectable CLM, and various strategies have been established to improve their prognosis [4, 8]. First, the increasing efficacy of systemic chemotherapy with or without targeted therapies has enabled surgical treatment for initially unresectable CLM by downsizing the tumours, through the so-called "OncoSurge approach" [4, 9]. Currently, this strategy has shown clinical benefits in many studies and a recent systematic review reported that the objective response (OR) rate and R0 resection rate were 64% and 87%, respectively [7]. Second, a shift of surgical indications for CLM from old to new criteria has increased the population of resectable CLM [4, 10–12]. Widening the indications for surgery along with improvements in surgical techniques and perioperative managements have expanded resectability criteria, and many published studies have shown the efficacy and safety of these shifts [13–18]. Third, the development of surgical procedures such as radiofrequency ablation (RFA) or microwave ablation (MWA) combined with hepatectomy [19], two-stage hepatectomy (TSH) [20–22], and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [23, 24] have expanded the indications of surgery for unresectable CLM, with a clear survival benefit in selected patients [25].

The management of CLM is complex because of the absence of data from randomized controlled trials (RCT) to

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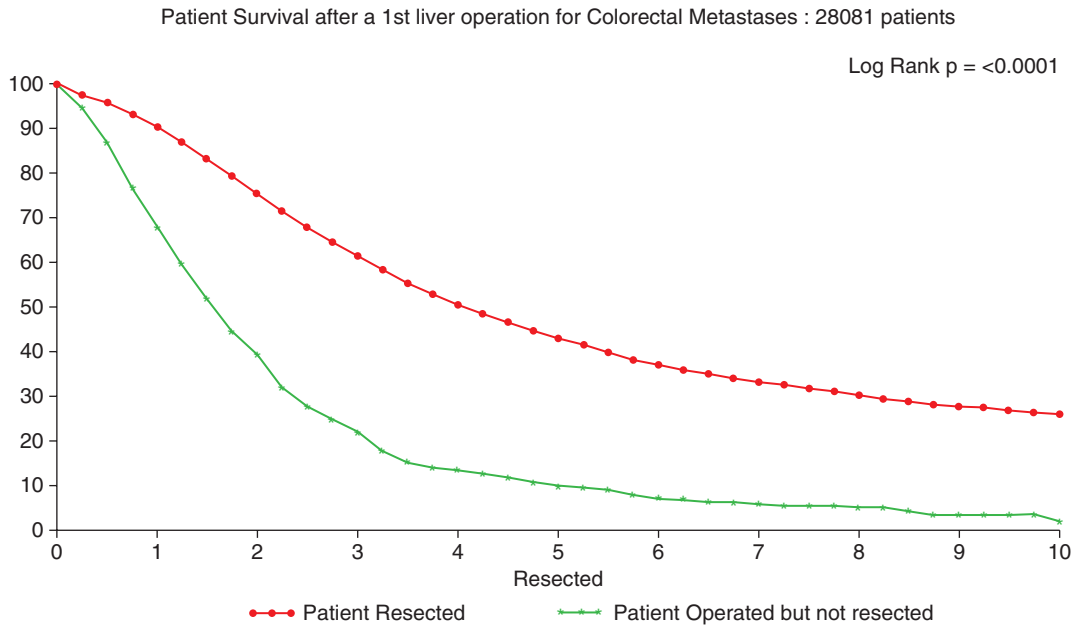


Survival %

Resected	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Not Resected	68%	39%	21%	13%	10%	7%	5%	5%	3%	2%
Resected	90%	76%	62%	50%	43%	37%	33%	30%	27%	26%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Not Resected	1410	688	330	154	75	48	28	15	9	4	1
Resected	26671	18170	12760	8730	5879	4059	2799	2045	1479	1055	767

Fig. 24.1 Overall survival probability after hepatic resection of all patients operated from CLM in relation to the performance of resection or of nonresection procedures

guide decisions and because of the wide variety of factors that may affect the outcome (e.g., the resectability for CLM, the type of chemotherapy regimen, the management of synchronous CLM, the timing of surgery, the role of laparoscopic surgery …) [8]. In the current era of precision medicine, each patient can benefit from an individualized approach, based on a growing number of features, including sidedness of the primary tumour, pharmacologic genotyping (i.e., UGT1A's and DPYD), and tumour mutations (i.e., RAS, BRAF, and MSI) including their dynamics along the course of the disease. This latter aspect can now be assessed through the determinations of circulating tumour DNA mutations in liquid biopsies [26, 27]. To achieve this objective, a multidisciplinary approach (MDA) has increasingly been implemented for cancer care services throughout Europe, the United States, and Australia [28, 29]. For the improvement of patients' prognosis, the treatment strategy for CLM should be directed toward resectability, and it is recommended that all patients with CLM should be treated by specialized multidisciplinary teams (MDTs) to decide the best strategy [4, 8, 30]. In view of the multiple parameters to consider for each individual patient, a real "personnalized medicine strategy" should be adopted for each case with the support of MDTs.

24.2 Defining the Resectability Perspective of the Patient

While it was usual to subdivide patients with CLM) into two groups: resectable vs. unresectable, it appeared through clinical practice that the following three groups of patients appeared more suitable for planning a treatment strategy (Fig. 24.2):

1. Patients with *initially resectable CLM*: In such patients, chemotherapy, if used on the preoperative setting, will be called as "neoadjuvant" chemotherapy.
2. Patients with *definitively unresectable CLM* because of a widespread tumoural liver involvement or to the presence of unresectable extrahepatic disease: In such patients,

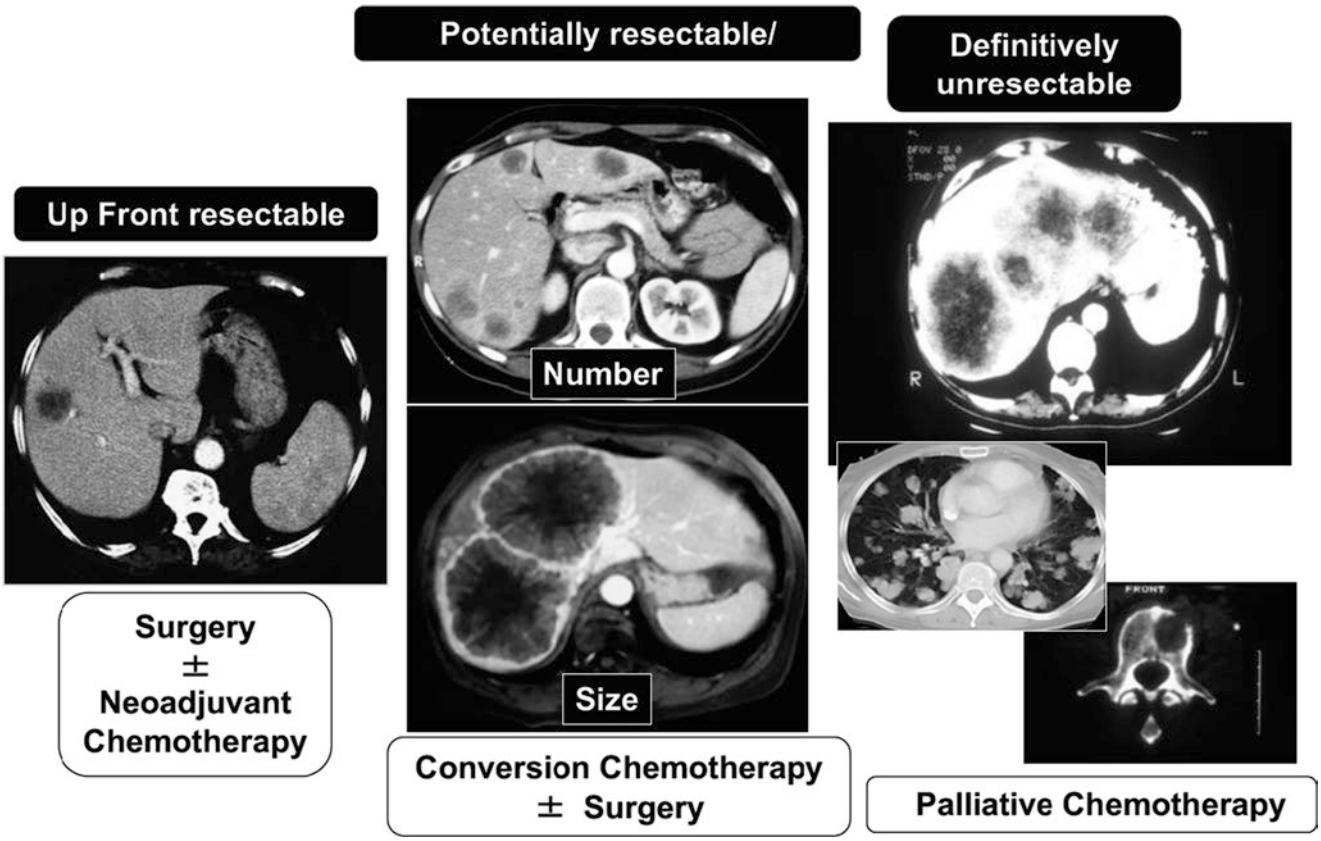


Fig. 24.2 Characterization of the patients in relation to the perspective of resectability

chemotherapy will be called "palliative" because of the near-impossibility of cure.

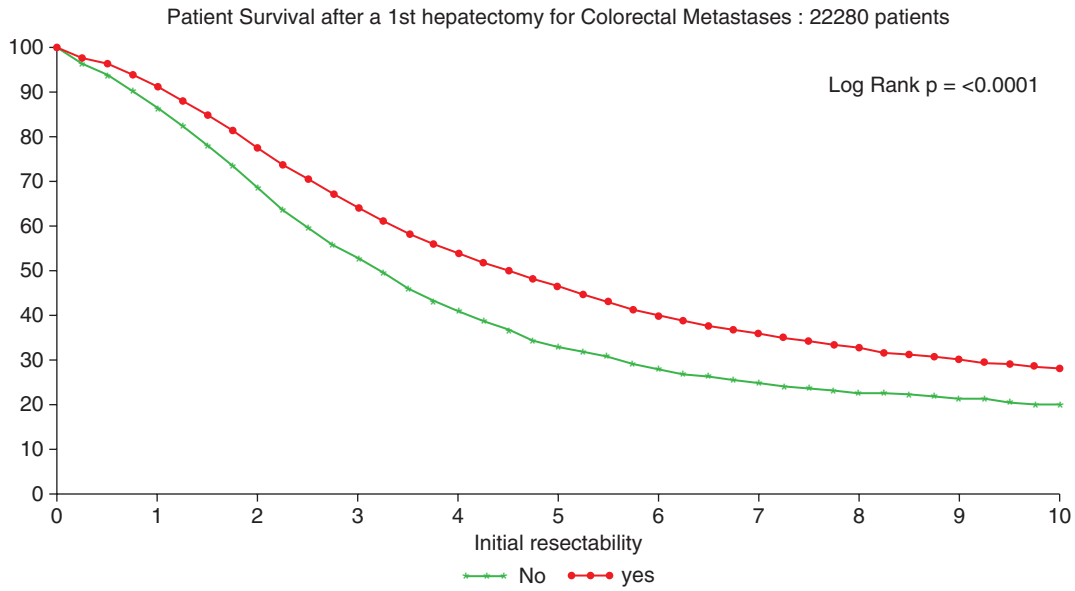
3. Patients with initially unresectable but with a possibility of resection in case of efficient downsizing with chemotherapy, that is, *potentially resectable patients*: Chemotherapy in such case should be called "conversion" chemotherapy.

24.3 Conversion Chemotherapy to Achieve the Resectability: The Onco-Surge Approach

The majority of patients with CLM are initially unresectable, and they must be treated with chemotherapy to achieve resectability because from previous reports, it is obvious that the prognosis of patients with CLM is much better if metastases can be removed surgically than if they cannot [5–7]. In the 1990s, our group first proposed resection of metastases in patients who had experienced a significant downsizing of their initially unresectable metastases when the diseases became resectable. At that time, the standard of care was to continue the chemotherapy as long as possible. However, there was no chance of long-term survival using that strategy. By reviewing our initial experience, we showed that the 5-year survival of patients who had initially unresectable disease and had the resectable disease after chemotherapy was 33%. This was lower than that of patients who underwent resection of resectable diseases (48%) but was significantly higher than that of patients treated by chemotherapy only [5, 6]. Data from the LiverMetSurvey International Registry confirmed that the 5-year survival rate was 32% in approximately 4000 patients who had initially unresectable disease and had resectable disease after chemotherapy (Fig. 24.3). Accordingly, two questions were raised to achieve liver resection: (1) The conditions in terms of first chemotherapy regimen, timing, and outcome of resection. (2) The possibility of rescue strategies in patients in whom the unresectability status had unchanged.

24.4 What Are Favorable Conditions for an OncoSurge Approach?

1. The first one is an ***optimal first-line chemotherapy*** because there is a strong correlation between the resection rate and the response rate to chemotherapy [31, 32].



Survival %

Initial resectability	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	86%	69%	53%	41%	33%	28%	25%	23%	21%	20%
Yes	91%	78%	64%	54%	46%	40%	36%	33%	30%	28%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	4077	2649	1744	1129	699	441	288	202	143	104	76
Yes	18203	12468	8788	6032	4125	2863	1969	1426	1022	723	520

Fig. 24.3 Overall survival probability after hepatic resection of patients initially resectable versus those initially nonresectable

Before 1990, 5-fluorouracil (5-FU) and its biochemical modulation with leucovorin (LV) were the only chemotherapeutic options for CRC with OR rates below 20%. In the 1990s, oxaliplatin and irinotecan became available [33, 34], and their chronomodulated delivery as combination chemotherapies with 5-FU-LV increased response rates and progression-free survival in patients with colorectal cancer metastases. Doublet cytotoxic regimens including FOLFOX (5-FU, leucovorin, and oxaliplatin) and FOLFIRI (5-FU, leucovorin, and irinotecan) became standard therapies in the 2000s [32]. The subsequent development of triplet cytotoxic combinations of 5-FU-LV, oxaliplatin, and irinotecan (FOLFOXIRI or FOLFIRINOX), including their chronomodulated delivery, has further improved response and resectability rates [35] both in the first-line and in second-line settings [36]. Subsequently, the addition of anti-epithelial growth factor receptors (EGFR) or anti-vascular endothelial growth factor (VEGF) antibodies to these combination chemotherapy regimens further increases response rates (>50%) and prolonged median survival (~30 months) (Tables 24.1 and 24.2) [8]. Anti-EGFR therapy should be limited to RAS and BRAF wild-type patients, while anti-VEGF therapy has no restriction for its use in terms of biologic molecular profile. However, regarding the better choice of targeted therapies in patients with RAS wild-type tumour, the FIRE-3 trial comparing FOLFIRI + cetuximab and FOLFIRI + bevacizumab showed that the response rate, the survival rate, the early tumour shrinkage, and the median depth of response were higher in the FOLFIRI + cetuximab group than in the FOLFIRI + bevacizumab group [37]. This was confirmed by the CALGB/SWOG 80405 trial which showed the overall survival benefit of cetuximab + doublet chemotherapy over bevacizumab + doublet chemotherapy in left-sided RAS wild-type metastatic CRC [38]. The effect of anti-EGFR for downsizing tumours is further supported by a controlled study comparing chemotherapy alone with chemotherapy plus cetuximab. The study showed that the overall response rate was improved (29–57%, $p = 0.001$) and that the resectability of metastases significantly increased from 7.4% to 25.7% ($p = 0.004$)

Table 24.1 Conversion chemotherapy for patients with unresectable disease

Study	Chemotherapy regimen	Controlled study	*n*	Response rate (%)	Liver resection rate (%)
Vie-LM-Bev [39]	Capecitabine + oxaliplatin + bevacizumab	No	56	73	93
CELIM [40]	FOLFOX6/FOLFIRI + cetuximab	No	106	70	33
GONO [41]	FOLFOXIRI + bevacizumab	No	30	80	40
POCHER [42]	Chronomodulated FOLFOXIRI + cetuximab	No	43	79	60
BOXER [43]	Capecitabine + oxaliplatin + bevacizumab	No	45	78	40
OLIVIA [44]	FOLFOXIRI + bevacizumab versus FOLFOX + bevacizumab	Yes	80	81 versus 62	49 versus 23 (R0)
Ye et al. [45]	FOLFIRI/FOLFOX ± cetuximab	Yes	116	57 versus 29	26 versus 7 (R0)

CAPOX (XELOX) capecitabine and oxaliplatin, *Chrono-IFLO* chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin, *CTx* chemotherapy, *FOLFIRI* infusional 5-fluorouracil, leucovorin and irinotecan, *FOLFOX* infusional 5-fluorouracil, leucovorin and oxaliplatin, *FOLFOXIRI* infusional 5-fluorouracil, leucovorin, irinotecan and oxaliplatin, *RR* response rate

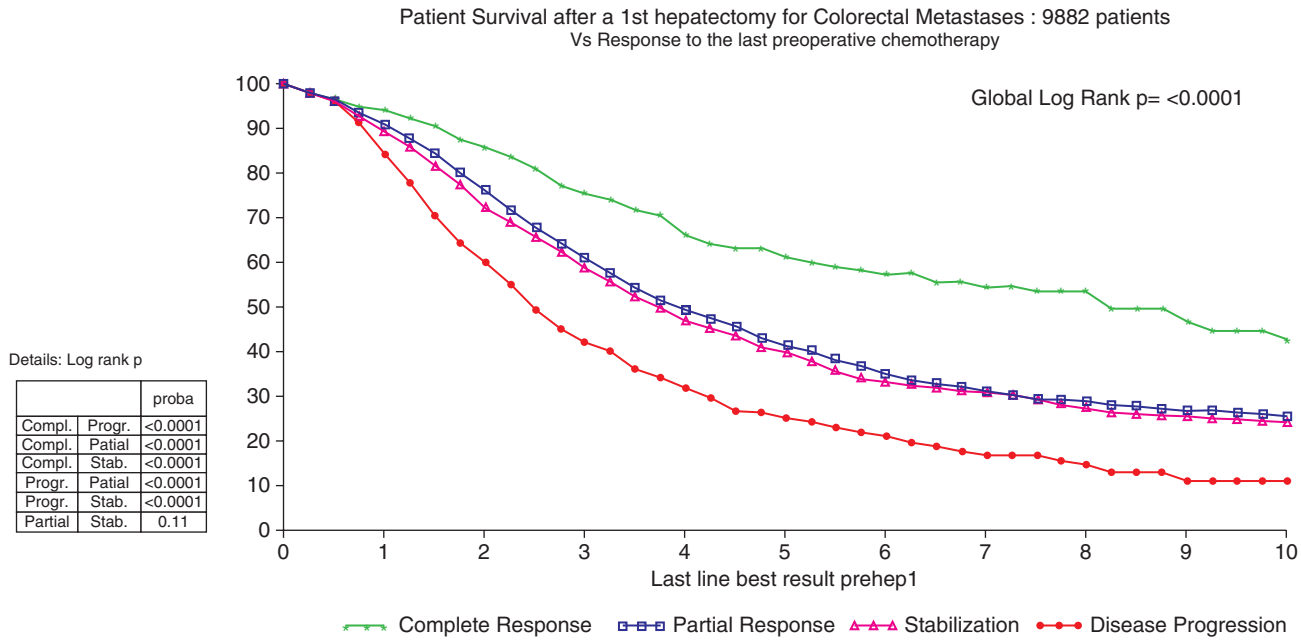
Table 24.2 Guidelines for the choice of targeted therapy combined to first-line chemotherapy, to induce resectability

JSCCR guidelines 2019 [46]		Pan Asian ESMO guidelines 2018 [47]		
Left-sided RAS wt	Right-sided RAS wt		Left-sided RAS wt	Right-sided RAS wt
FOLFOX/ FOLFIRI + cetuximab/ panitumumab	Doublet or triplet chemotherapy + bevacizumab	Disease Control	Anti-EGFR + doublet chemotherapy	Anti-VEGF + doublet chemotherapy
		Cytoreduction	Anti-EGFR + doublet chemotherapy	Anti-VEGF + doublet/triplet chemotherapy Anti-EGFR + doublet chemotherapy

JSCCR Japanese Society for Cancer of the Colon and Rectum, *ESMO* European Society for Medical Oncology, *wt* wild type

[45]. A meta-analysis reported that anti-EGFR therapy could increase the R0 resection rate by up to 60% in patients with mCRC and unresectable liver limited disease [48].

2. The second condition is a *short duration of first-line chemotherapy*. This means that preoperative treatment to induce resectability should be as short as possible because the greater the number of chemotherapy cycles given before surgery, the higher the risk of liver toxicity. Indeed, prolonged chemotherapy resulted in a "blue liver" related to the administration of oxaliplatin or a "yellow liver" related to the prolonged administration of irinotecan, and these livers were associated with a higher risk of morbidity and mortality [49, 50]. Because the aim of the approach is to achieve macroscopically complete resectability rather than a complete pathologic response to chemotherapy, we recommend to evaluate tumour response to chemotherapy every 2 months. Accordingly, at least four courses (2 months) of first-line chemotherapy should be given prior to the first evaluation for whether complete resection of liver metastases is possible. If the downsizing is not sufficient despite a good tumour response, additional four courses should be delivered. However, in case of stable disease or progression after 4 months, a second-line "salvage" "conversion intent" treatment should be considered. Overall, a total duration of 6 months of perioperative chemotherapy is recommended [4, 51]. Another drawback of prolonged chemotherapy is the possibility to induce "disappearing metastases," when some unresectable CLM are small in size. This should be considered at the time of conversion chemotherapy and some techniques including the use of a fiducial marker at the site of tumour before chemotherapy have been proposed in order to guide the resection of all metastatic sites which were initially identified [52].
3. The third condition is *to operate a patient with a "controlled" tumoural disease*. We experienced that the survival benefit is limited in patients who underwent CLM resection despite the progressive disease on chemotherapy compared to patients who experienced downsizing or stability during chemotherapy [53]. This was confirmed by the results of LiverMetSurvey (Fig. 24.4). It was not justified to unnecessarily prolong the conversion chemotherapy because the more we wait for reaching an optimal response, the higher the risk of metastatic colorectal cancer to progress within and/or outside the liver, due to acquired tumour resistance to chemotherapy.



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Compl.	Stab.	<0.0001
Progr.	Patial	<0.0001
Progr.	Stab.	<0.0001
Partial	Stab.	0.11

Survival %

Last line best result prehep1	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Complete Response	94%	85%	75%	66%	61%	58%	55%	54%	46%	42%
Partial Response	91%	76%	61%	49%	41%	35%	31%	29%	27%	25%
Stabilization	89%	72%	59%	47%	40%	33%	31%	27%	25%	24%
Disease Progression	84%	60%	42%	32%	25%	21%	17%	15%	11%	11%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Complete Response	423	306	235	172	121	96	70	56	44	27	18
Partial Response	6694	4411	2960	1903	1200	784	508	347	247	168	126
Stabilization	2042	1270	837	551	360	257	176	126	79	52	29
Disease Progression	723	467	269	158	98	64	42	24	19	10	7

Fig. 24.4 Overall survival probability after hepatic resection in relation to the objective tumoural response to preoperative chemotherapy

24.5 The Increasing Evolution of the Surgical Indications for CLM

Hepatic resection is the only treatment that can provide the possibility of prolonged survival or even cure for patients with CLM [4, 6]. The "LiverMetSurvey" International Registry showed that in patients CLM who underwent hepatic resection of CLM, the 5- and 10-year survival rates are 43% and 26%, and that of operated but nonresected patients are only 9% and 2%, respectively (Fig. 24.1). The proportion of patients with resectable CLM at the time of diagnosis is small [5]. Recent advances in surgery for CLM consist in an extension of surgical indications beyond the strict "old" criteria (e.g., less than three metastases, less than 5 cm of maximal diameter, negative resection margin, and low preoperative carcinoembryonic antigen level…) [10–12]. The resectability and curability are dependent on multiple factors, including the number and location of metastases, the volume of the future liver remnant, the presence of extrahepatic disease, and the patients' general condition. One of the expansions in the indications is the number of metastases. In the past, the presence of more than three CLM was considered as a contraindication for resection [10]. Although innovations in surgical techniques and perioperative managements have increased the chance of surgery in patients with traditional "unresectable" CLM, the oncological dogma of "no more than three CLM" has been progressively challenged [4]. The resection of multiple bilobar hepatic metastases proved to have survival benefits. A study reported that patients with more than 10 metastases have 30% of the 5-year survival after resection [13].

Another expansion is the surgical margin. The gold standard for the surgical management of CLM is complete resection with histologically negative margins (R0 resection) [54]. Several studies demonstrated that the so-called R1 resection (tumour-free margin <1 mm) was associated with worse

overall survival (OS) than R0 resection (tumour-free margin ≥1 mm) [55]. However, it is not always possible to have adequate surgical margins when tumours have a contact with vascular structures. As such, R1 resection "by necessity" may be an option. In the current era that has effective chemotherapy, surgical margin status may have less impact on survival in patients who received perioperative chemotherapy, especially in patients who showed a good response [15, 17]. The last point of the expansion is surgery for elderly patients with CLM. For patients more than 80 years old, the survival in long term is valuable [16, 18] and reached 31% at 5 years in the recently updated LiverMetSurvey results. Consequently, many factors which were regarded as a contraindication for surgery have changed and the criteria of surgical indications for CLM are expanding.

24.6 How Can We Manage Surgery of Patients Who Showed Progression during First-Line Chemotherapy?

For patients who showed progression during first-line chemotherapy and have marginally resectable disease, options are whether to propose a second-line chemotherapy or to propose surgery despite the tumour progression. The clinical decision should be made by medical oncologists and surgeons with respect to the possibility of downsizing.

1. Regarding the first option, a second-line chemotherapy may have a possibility to make diseases resectable. In that situation, liver resection is expected to provide the same survival benefit as liver resection following a first-line chemotherapy [56].

   Consequently, physicians should seek for the chance of surgical intervention, even after the failure of first-line chemotherapy.

   Another option is hepatic artery infusion (HAI) chemotherapy. Studies showed that HAI could provide a better response rate, a high rate of secondary resection with downsizing in the majority of tumours, and good survival rates [57, 58]. This was confirmed recently by a European Phase II trial using triplet infusion into the hepatic artery of 5-FU, oxaliplatin, and irinotecan with systemic cetuximab in previously treated patients with RAS wild-type CRC and a median of 10 CLM. The primary endpoint, 30% of patients undergoing R0-R1 resection was achieved, as a result of an overall 41% of the response rate, despite prior administration of one to three lines of systemic chemotherapy [59] As such, HAI may provide a second chance for better survival in patients with initially unresectable CLM.

   More recently, the efficacy of an immune checkpoint blockade for various types of cancer has been established [60]. In patients with metastatic CRC, the objective response rate of antiprogrammed death-1 antibody (anti-PD1) was 40–69% for mismatch repair deficient CRC [61, 62]. Further investigation of immune checkpoint blockade is warranted to improve the survival of patients with CLM in the future clinical practice.
2. Regarding the second option to operate patients who showed progression with chemotherapy, the following three prognostic factors were identified: three or more metastases, the largest diameter ≥ 50 mm, and a carcinoembryonic antigen (CEA) level of 200 ng/mL or more. We have shown that 3-year survival rates were 29.9% if there were less than three metastases and 19.9% if the largest lesion measured up to 50 mm, thus suggesting the potential usefulness of metastases resections in this patient group. On the contrary, the largest CLM diameter ≥ 50 mm and a number of CLM ≥ 3, or CEA ≥ 200 ng/mL were associated with less than 10% of the 3-year survival [63]. The survival benefit is limited in patients who showed progression and had poor prognostic factors compared to patients who showed partial response or stable disease during chemotherapy.

24.7 How Can we Manage Patients with Unresectable Disease after Downsizing Chemotherapy: The Development of New Surgical Procedures

In the past, patients with unresectable disease were treated with "palliative intent" chemotherapy. In the recent decades, many efforts have been made to increase the resectability of patients with unresectable CLM, and various strategies were established [25] (Fig. 24.5). Portal vein embolization (PVE) was developed for patients with extended hepatectomy to induce ipsilateral atrophy and contralateral compensatory hypertrophy in the remnant liver, thereby preventing severe postoperative liver failure [56, 64]. PVE increased the resectability rate of initially unresectable CLM [65]. Likewise, RFA combined with hepatectomy was shown to be safe and feasible, achieving comparable outcomes compared to hepatectomy alone, in patients with limited (<3) and small (<3 cm) unresectable CLM [19].

However, for patients with extensive bilateral multinodular CLM, a single hepatectomy combined with specific procedures including PVE and/or RFA is insufficient to remove all tumours. In 2000, we reported the concept of two-stage hepatectomy (TSH), based on two sequential procedures to remove multiple bilateral tumours that are impossible to remove by a single hepatectomy combined with ablation if necessary. The principle is, at the first stage, to clear the less tumour- involved hemiliver and to perform a portal embolization of the contralateral hemiliver to be further resected. With the liver regeneration obtained after the first hepatectomy, it becomes possible to perform the second hepatectomy without a risk of liver failure [20]. During the next

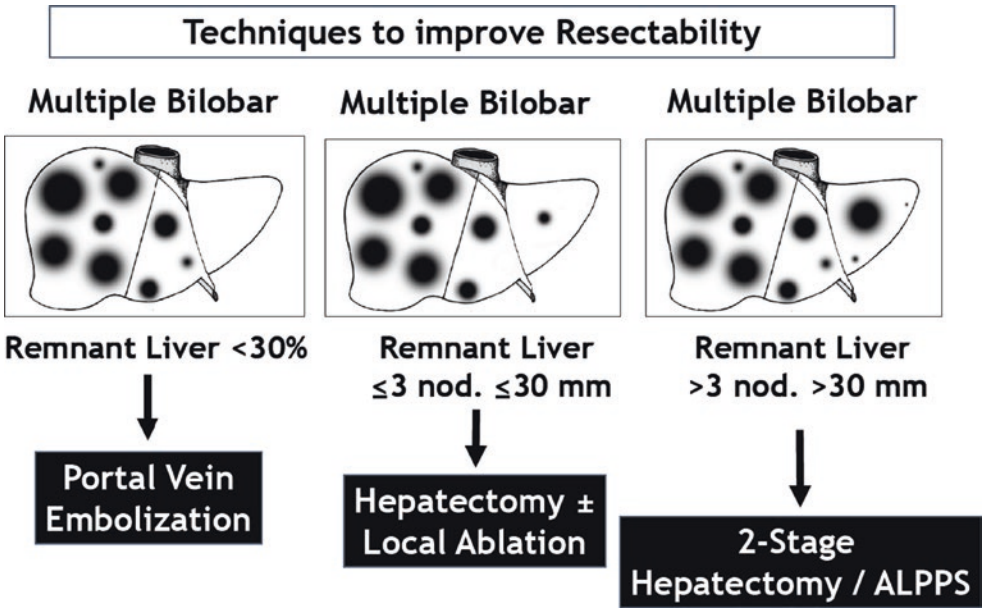

Fig. 24.5 Upfront techniques to improve the resectability of initially nonresectable patients

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 [21, 22, 66]. However, the major drawback was a dropout risk as a result of disease progression, and made resection impossible in 25% to 38% of patients who were planned to undergo TSH [67–69]. To overcome the dropout risk, a German group proposed an alternative treatment: Associating Liver Partition and Portal vein ligation for staged hepatectomy, so-called ALPPS [23, 24]. By adding TSH to a splitting of the liver in the plan of the future hepatectomy, they observed a volume increase of 74% in the remnant liver in a period of only 9 days, allowing the second stage to be performed during the same hospitalization of the patients [24]. Although the advantage of ALPPS was high feasibility, the frequency of severe complications and perioperative mortality was worrisome problems with lacking data on long-term outcomes. In the initial study, 68% of patients experienced complications and the surgical mortality rate was 12%. Although no surgical mortality was found in our initial experience, we showed that the outcome was worse in patients undergoing ALPPS than in patients undergoing TSH [70]. More recently, an RCT from a North European group evaluated the outcome between ALPPS and TSH and showed that the feasibility of ALPPS was superior to TSH, with comparable morbidity and mortality rates [69]. Because the long-term outcomes remain to be elucidated, we should be careful in widening the use of such technique.

Despite these advances in the surgical procedures, many patients with CLM are still regarded as unresectable. For such types of patients, we may reconsider the possibility of liver transplantation (LT). In the past, LT for patients with CLM was an absolute contraindication because of both organ shortage and poor patient outcomes. One- and 5-year survival following LT for CLM before 1995 was 62% and 18%, respectively, while the perioperative mortality after LT was about 30% [71]. However, in the current era, major improvements were found in the management expertise of LT, the knowledge of metastatic disease biology, and the imaging techniques allowing for proper patient selection, the efficacy of chemotherapy, and the availability of immunosuppressive drugs with antitumoural effects as sirolimus or everolimus. These dramatic progresses renewed interest in LT as a treatment option for CLM [72, 73]. Following our proposal, the group of Oslo (Norway) recently reported that the 5-year survival rate of patients who underwent LT for unresectable CLM was 60%. LT markedly increased overall survival in selected patients, compared with chemotherapy alone [74, 75]. Today, a randomized multicentric trial comparing LT with chemotherapy is running in 25 European centers, including 17 in France. The results of this ongoing RCT will be crucial in order to elucidate the role of LT in the context of the advancing oncosurge strategy for unresectable CLM.

24.8 Multidisciplinary Team (MDT) Approach for CLM

The oncosurge approach of CLM is possible with MDT and this approach is increasingly favored for cancer care. A first prospective study assessed the impact of MDTs discussion on various gastrointestinal cancers. Treatment plan before MDTs discussion changed with a proposal by a single specialty physician (i.e., an oncologist or a surgeon) in more than one-third of patients during MDTs [76]. Also, for the treatment of patients with CLM, some reports proposed that all patients with CLM should be managed by specialized hepatobiliary MDTs to select the best strategy [5, 30, 51]. MDT is a patient-centered approach performed routinely by experts oncologists, surgeons, radiologists, pathologists,

molecular biologists, and the team works together to choose the appropriate treatment with a feedback from patients and to physicians [5, 28, 29]. As such, the close collaboration between complementary expertise specialists constitutes the core of MDT success. The advantages of MDT include no dogmatic decision, a quicker decision for the strategy, a dynamic reevaluation of the patient with the good treatment at a good timing, and the synergy in the efficiency of all treatments. In order to improve patients' prognosis by MDT, the medical oncologist needs the surgeon for decision-making on the resectability and the timing of surgery. At the same time, surgeons also need medical oncologists to make unresectable patients become resectable, to control the disease before surgery, and to prevent recurrence after surgery. Another key of MDT approach is the necessity of expertise for decision-making on treatment strategies. In line with this, almost two-thirds of patients with CLM deemed unresectable by nonspecialists in a regional center were considered potentially resectable by experts of liver surgery [77]. It implies that the management of patients with CLM without the involvement of a specialist in liver surgery may derive a chance of curative-intent treatment. The population-based study of hepatic resection for CLM across England showed that the rate of hepatic resections for CLM varied significantly across hospitals [78]. Moreover, the FIRE-3 trial showed that the resectability rate among hospitals decreased from 25% in university hospitals to 16% in nonuniversity hospitals, and further decreased to only 10% in medical practice oncology or private institutions [79]. These discrepancies were caused by the lack of expertise for liver surgery in the latter centers. Consequently, multidisciplinary expertise is important to try to expand the surgical indication and to select the best strategy for patients with CLM.

24.9 Clinical Case

The patient is a 68-year-old male who underwent colectomy for sigmoid adenocarcinoma with synchronous potentially resectable bilateral liver metastases (Fig. 24.6a). After five

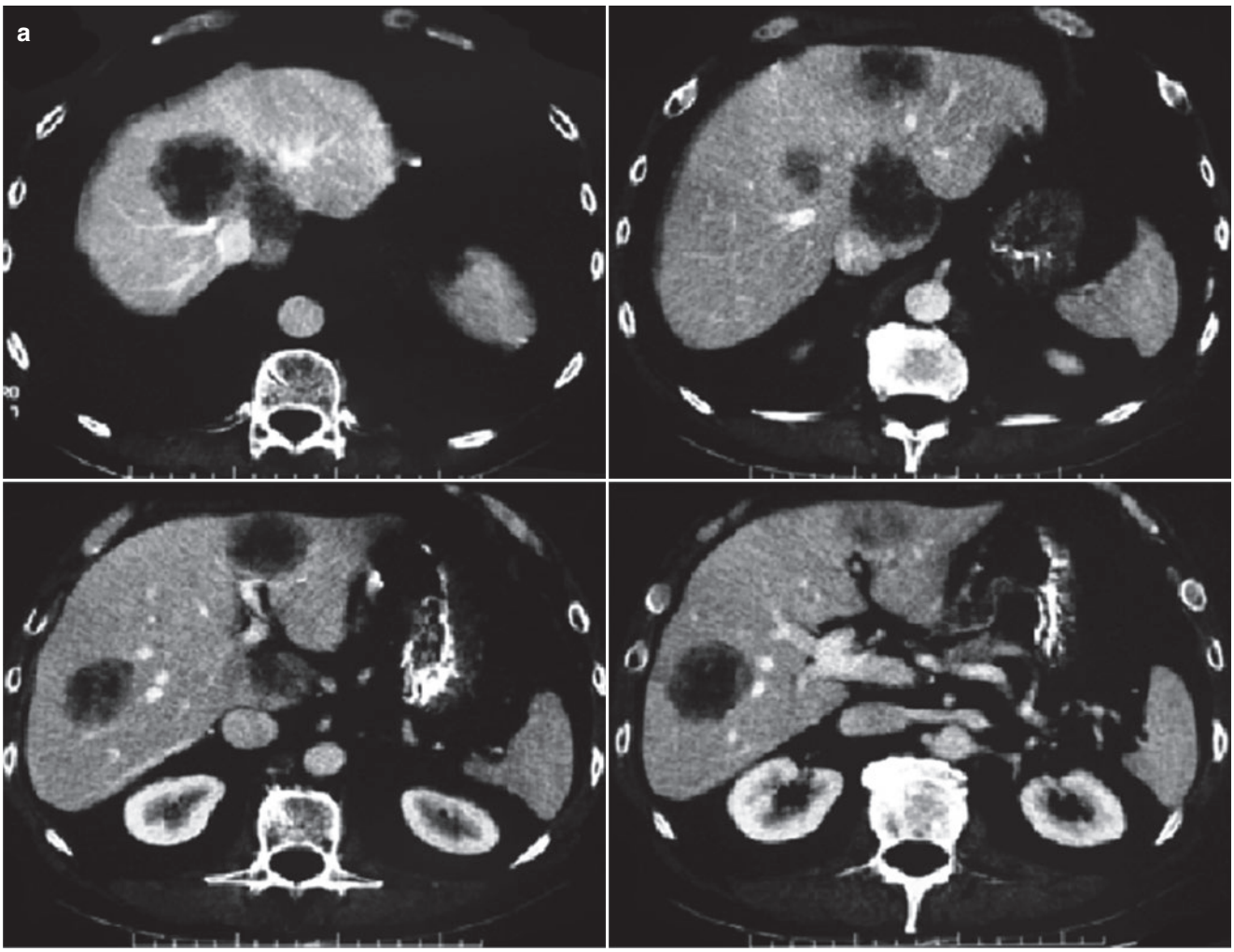

Fig. 24.6 Case of initially unresectable CLM. (**a**) Preoperative imaging. (**b**) Downsizing of liver metastases after chemotherapy. (**c**) Intraoperative gross appearance of the liver. (**d**) After right hepatectomy extended to segment 1 with partial left lateral resection

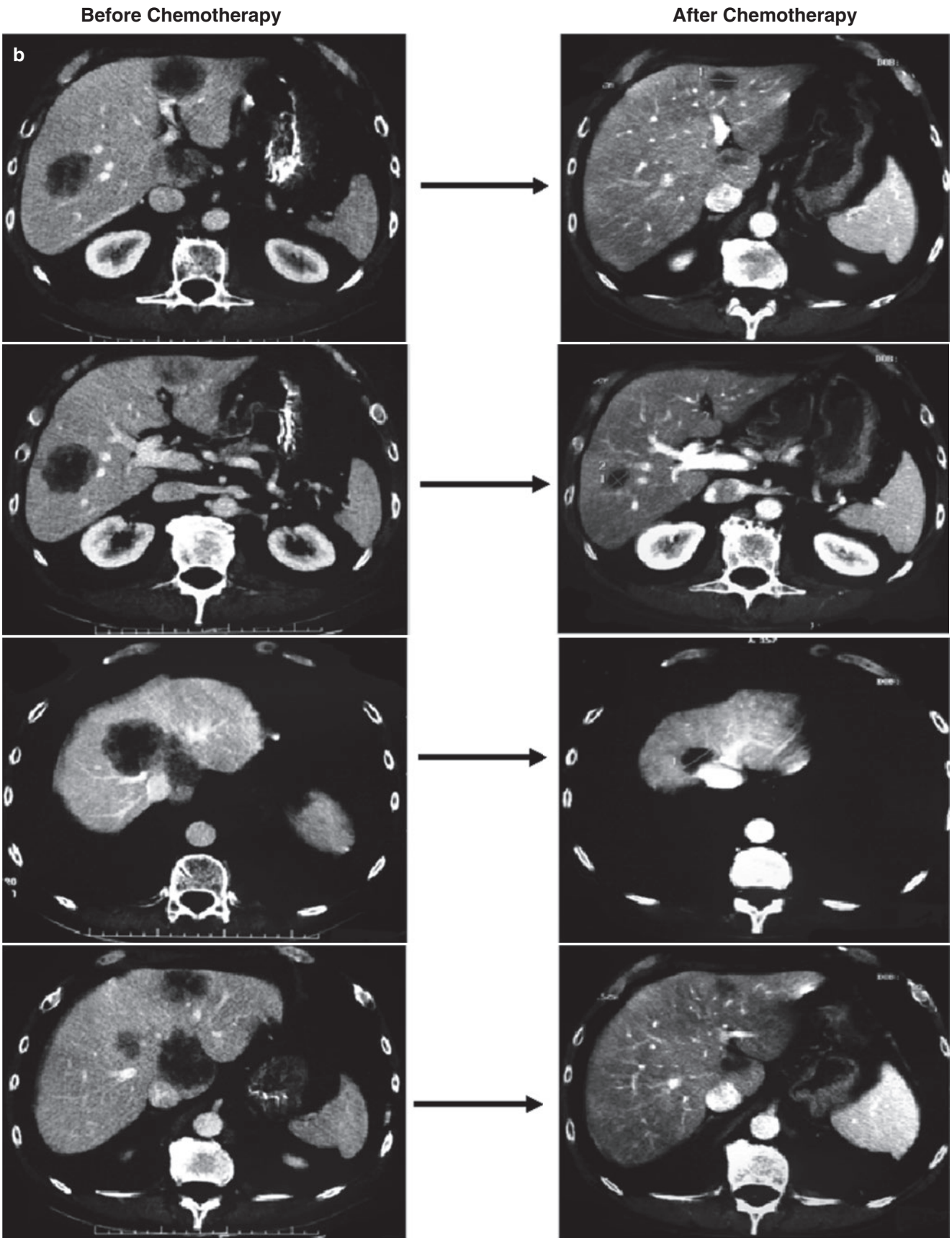

Fig. 24.6 (continued)

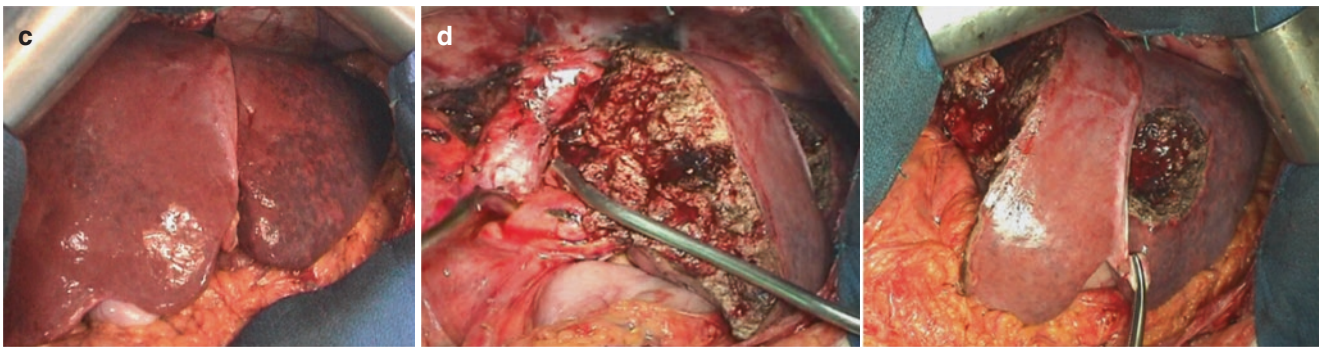

Fig. 24.6 (continued)

courses of FOLFOX therapy, tumour markers decreased (CEA: 200 → 8 ng/mL, CA 19–9: 1857 → 6.6 UI/L) and metastases were downsized (Fig. 24.6b). Surgical resection of liver disease was planned. His liver appeared to be a "blue liver" caused by oxaliplatin-based chemotherapy (Fig. 24.6c). Right hepatectomy extended to segment 1 with partial resection of the left lateral section was safely performed (Fig. 24.6d). After hepatectomy, six courses of adjuvant FOLFOX therapy were administered. Wedge resection of the lung was performed for solitary lung nodule 2 years after liver resection. The patient is alive without recurrence more than 15 years after liver resection.

24.10 Conclusions

The goal of the treatment strategy for patients with CLM is to achieve resection of CLM because this provides the best long-term outcome. Over the last two decades, the advancements in more effective chemotherapy and the development of new surgical procedures have dramatically improved the prognosis and increased the proportion of patients who undergo liver resection. However, the synergetic effect of these major advancements is achieved through the MDT management led by expert teams including at least liver surgeons, medical oncologists, and interventional radiologists who aim to increase the resectability of initially unresectable patients by integrating the up-to-date treatments. Another important feature of the CLM management is that the risk of recurrence after CLM is high, needing to reperform chemotherapy and repeat surgery. Such "reset of the clock" with repeat treatments needs motivation from all the specialists in charge of patients and patients themselves. MDT should continue to work together with a common vision for the patient: the possibility of cure and if not, the possibility of a prolonged survival. In the future, new treatment procedures (e.g., immune checkpoint blockade and LT) are likely to further improve the outcome of patients with CLM.

Conflict of Interest Statements No conflict of interest exists in this study.

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Is There a Place for Debulking?

25

Robert P. Jones

Learning Objectives

- Surgery for metastatic colorectal cancer is traditionally only offered where the macroscopic resection of all diseases, with the intention of cure, is possible.
- Despite the intention of cure, recurrence rates after surgery are very high. Irrespective, survival after recurrence is better than for those treated with initial palliative chemotherapy.
- This has led to a debate on whether localized treatment of unresectable disease should be offered in addition to palliative systemic chemotherapy.

25.1 Introduction

For patients with metastatic colorectal cancer, one of the key clinical decision points is the assessment of resectability of their disease. For patients with liver-limited metastatic disease, this decision should only be made by specialist hepatobiliary surgeons as assessment by nonspecialists may mean patients miss out on surgery with its associated long-term survival benefits and potential for cure [1]. For patients with the limited extrahepatic disease (e.g., limited lung metastases), a review by a broader multidisciplinary team is also essential in order to make a more subjective assessment of the potential benefit of localized treatments. Unfortunately, the majority of patients present with extensive multiorgan disease. In this scenario, palliative surgery **without** complete resection of all sites of disease is recognized as a potential treatment option. Palliative resection of the primary colorectal tumour in the presence of unresectable metastases has been offered based on the hypothesis that it is this primary site of disease and regional lymphatics that lead to "seeding" of the majority of additional metastatic sites [2, 3] as well as reducing the risk of future complications (such as bowel obstruction) that may interrupt effective systemic treatments. The 2020 ASCO GI Meeting saw the presentation of the randomized phase III JCOG1007 trial comparing standard of care palliative chemotherapy versus standard of care plus resection of asymptomatic primary disease for patients with unresectable metastatic cancer. After a median follow-up of 22 months, median overall survival was 25.9 (95% confidence interval [CI], 19.9–31.5) months with primary tumour resection plus chemotherapy compared with 26.7 (95% confidence interval, 21.9–32.5) months for chemotherapy alone (hazard ratio [HR], 1.10; 95% confidence interval, 0.76–1.59; not significant). These results suggest resection of an asymptomatic primary tumour in the presence of unresectable metastases should not be performed [4].

As it is metastatic disease that leads to patients' demise, it has been suggested that palliative (or debulking) surgery to metastatic sites could offer a potential survival benefit. Such an approach is already well established in ovarian cancer, where it has been recognized for over 40 years that there is a clear relationship between the volume of residual tumour left after surgery and length of survival after treatment with palliative systemic therapy [5], with maximal cytoreduction associated with the best outcome even when complete gross resection is not possible [6]. Ovarian cancer is exquisitely sensitive to systemic chemotherapy, and it has been suggested that the excellent outcomes after debulking are attributable to this. Improving outcomes for first-line systemic chemotherapy in metastatic colorectal cancer suggest a similar rationale could be adopted in this setting [7].

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25.2 Early Recurrence After Curative Intent Surgery: Inadvertent Cytoreduction?

The patterns and distribution of metastatic colorectal cancer represent a broad spectrum of disease, from small solitary liver metastases through to miliary multiorgan disease. These patterns represent a spectrum where the likelihood of surgical resection, and therefore cure, reduces as the oncological burden of disease grows. Indeed, such patterns are likely surrogates of underlying tumour biology and prognosis [8]. Even with careful patient selection, the frustratingly high rates of early recurrence after curative-intent liver surgery for colorectal liver metastases (CRLM) (~50% at 1 year [9]) mean that a significant proportion of curative-intent surgery is in fact cytoreductive. Despite this early recurrence, patients do appear to gain a prolonged survival advantage from surgery even in high-risk biological cohorts. There are further hints to suggest cytoreductive surgery may offer a survival advantage in metastatic colorectal cancer—the LiverMetSurvey group reported a 22% real-world 5-year survival for patients undergoing an R2 (macroscopically incomplete) resection of CRLM [10], figures far in excess of that seen after treatment with systemic therapy alone. It is also important to note that curative intent liver surgery for metastatic colorectal cancer is now safe with low morbidity and mortality, and increasing use of minimally invasive techniques improving functional recovery [11] mean the risk:benefit of noncurative interventions must be considered through this prism.

For patients with limited extrahepatic disease, resection is increasingly being offered with curative intent. Although widespread in clinical practice, data supporting this approach is limited to highly selected case series [12, 13] with only one small prospective study reported. This phase II study of metastasectomy for both intrahepatic and extrahepatic disease enrolled 26 patients with generally less extensive disease (median one extrahepatic organ involved with a median of two extrahepatic lesions) and reported 19% major morbidity and 4% mortality, and showed a median disease-free survival benefit of 5 months, with the implication again that such an approach is cytoreductive rather than curative [14].

It has been postulated that very early recurrence (2–3 months) after curative-intent surgery for liver metastases essentially represents unresected disease, and as such the index procedure could be cytoreductive. Tanaka et al. assessed patterns of recurrence in 165 patients from a single center and divided them into two groups based on time to recurrence after surgery (< 6 months vs. > 6 months). Unsurprisingly, those with very early recurrence had worse overall survival. However, for those patients with multiple bilobar lesions (and therefore at the highest risk of leaving behind residual disease), there was no difference in overall survival irrespective of whether recurrence was very early or late (5-year survival 39.0% vs. 42.3%, $p = 0.13$) [15]. Although a small single-center series, the authors suggested that in patients with bilobar liver disease cytoreduction was a rational treatment objective.

25.3 Localized Treatments for Unresectable Disease: Planned Cytoreduction

When surgery is not possible, thermal ablation of all sites of liver disease may be an option. The EORTC 40004 trial (CLOCC) was designed to assess the value of adding thermal ablation to systemic palliative chemotherapy for patients with liver-specialist defined unresectable disease [16]. Originally designed as a phase 3 trial, slow recruitment meant the study evolved into a phase 2 study powered to detect a difference in 30-month overall survival. Long-term data from this study are fascinating. At a median follow-up of 9.7 years, almost all patients had died of progressive disease. There was a statistically significant difference in OS in favor of the ablation/chemotherapy arm (hazard ratio [HR] = 0.58, 95% confidence interval [CI] = 0.38 to 0.88, $p = 0.01$) (Fig. 25.1). Three-, five-, and eight-year OS were 56.9% (95% CI = 43.3% to 68.5%), 43.1% (95% CI = 30.3% to 55.3%), 35.9% (95% CI = 23.8% to 48.2%), respectively, in the combined modality arm and 55.2% (95% CI = 41.6% to 66.9%), 30.3% (95% CI = 19.0% to 42.4%), 8.9% (95% CI = 3.3% to 18.1%), respectively, in the systemic treatment arm. Median OS was 45.6 months (95% CI = 30.3 to 67.8 months) in the combined modality arm versus 40.5 months (95% CI = 27.5 to 47.7 months) in the systemic treatment arm. However, some caution should be exercised—the included patient population had favorable biological characteristics and may have been considered technically resectable based on contemporary standards (e.g., 40% of patients had <4 metastases). Irrespective of these shortcomings, these results suggest that the addition of locoregional disease control strategies can improve overall survival compared with palliative chemotherapy alone.

The ORCHESTRA Trial (NCT01792934) is a Dutch randomized study designed to assess the overall survival benefit of additional tumour debulking by resection, radiotherapy, and/or thermal ablative therapy in patients with multiorgan mCRC when added to palliative systemic therapy [17]. To be eligible for inclusion, at least 80% of metastases should be treatable with surgery, curative-intent radiotherapy or thermal ablation as decided by a specialist advanced colorectal multidisciplinary team (MDT) (see Table 25.1). Patients are treated with 9 weeks of CAPOX/FOLFOX to achieve disease stabilization and assess biology. If disease is controlled, patients are then randomized.

August 2020 saw the authors report their early experience of trial recruitment [18]. One hundred patients with a median

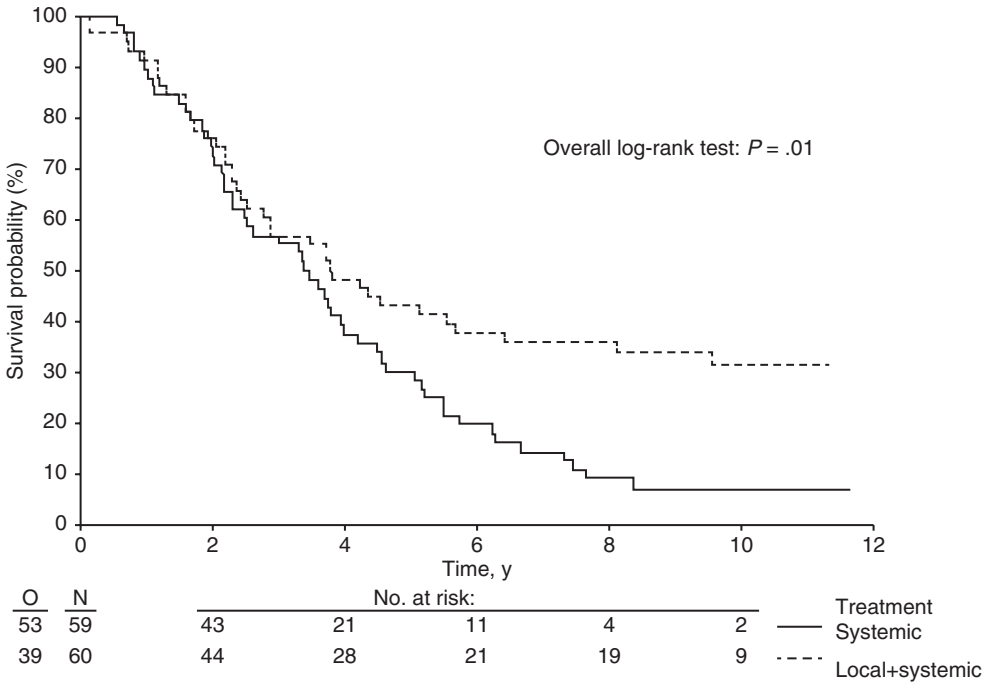

Fig. 25.1 Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or by combined modality treatment of systemic ± treatment plus aggressive local treatment by radiofrequency ablation ± resection ($p = 0.01$). (Ruers et al. [16], with permission)

Table 25.1 Main eligibility criteria for inclusion in ORCHESTRA trial

Eligible for recruitment to ORCHESTRA trial if colorectal cancer metastasis in at least two different organs if:
More than one extrahepatic metastasis ***or***
More than five hepatic metastases not located in one lobe ***or***
Either a positive Para-aortic or coeliac node, adrenal metastases, or pleural or peritoneal carcinomatosis ***or***

of six lesions were recruited over 24 months, with no patients withdrawing after randomization. This highlights both patient enthusiasm and clinician equipoise around this question and contrasts with CLOCC which struggled with recruitment because of strong prerandomization patient and clinician views on optimal treatment [19]. Debulking was performed in 82% of those randomized to the intervention arm, with 38% treated with a single modality of treatment and only four patients (11%) treated by three different debulking modalities (surgery, RFA, and radiotherapy). In 40% of patients, SAEs (serious adverse events) related to debulking were reported although only one-quarter of these were Clavien-Dindo 3 or greater (requiring surgical, radiological, or endoscopic intervention). Postoperative mortality was 2.7%, in keeping with other series of curative intent liver surgery. Crucially, after debulking systemic chemotherapy was resumed in 89% of patients suggesting minimal interruption to the existing standard of care. The median time to restart systemic treatment was 12.5 weeks after completion of the last preoperative cycle of systemic therapy, with a median interval between the last debulking event and restarting of 5 weeks. These delays compare favorably with the interval in systemic therapy in two-stage hepatectomy—an established treatment modality for bilobar disease [20].

These findings show that recruitment to a debulking trial is practical and feasible, with acceptable morbidity and mortality even after multiple cycles of systemic therapy. Importantly, debulking did not result in patients missing standard of care systemic therapy—a common argument against cytoreductive surgery. The trial continues to recruit, with a target of 478 patients to demonstrate a 6-month overall survival benefit to debulking.

Other cytoreductive studies are ongoing. LUNA is a single-center phase 2 randomized study designed to determine the overall survival benefit of liver resection in patients with unresectable lung metastases. Patients with resectable liver metastases and low-volume lung metastases (defined as solid pulmonary nodules <2 cm in size and < 15 in number) considered unresectable by a specialist thoracic surgeon are stratified by KRAS status and primary tumour location, then randomized to liver resection plus chemotherapy or chemotherapy alone. The study continues to recruit, with a target recruitment of 80 patients powered to detect a median increase in overall survival from 17 to 34 months [21].

25.4 Conclusions

Even when the intention is to deliver curative-intent surgery, high rates of early recurrence suggest a significant proportion of this surgery is in fact cytoreductive. The long-term survival benefit over palliative chemotherapy reported in patients with early postsurgical recurrence suggests that

cytoreduction may confer a potential advantage, although these findings are based on small retrospective series and so the evidence base is weak.

Noncurative ablation of limited disease has been demonstrated to offer a clear long-term survival advantage in a randomized setting and should now be considered as a standard treatment option in this setting. Surgical cytoreduction should not currently be considered a first-line treatment outside of ongoing clinical trials, the results of which will provide much-needed clarity in this area.

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Liver Transplantation

26

Pål-Dag Line and René Adam

Learning Objectives

- Liver transplantation is an option for carefully selected patients with unresectable colorectal liver metastases (CRLM).
- Application of stringent selection criteria can yield overall survival outcomes comparable to other indications for liver transplantation.
- Most common site of recurrence is lung metastases, and surgical resection is advised whenever possible.
- Liver transplantation for CRLM should preferably be done in prospective trials or reported to dedicated registries.

26.1 Introduction

Colorectal cancer is the third most common cancer, and a leading cause of cancer-related mortality, and there has been an increasing incidence during the last decennials, particularly in younger age groups [1, 2]. About 50% of the patients will develop metastases, and the liver is the most frequent location. Colorectal liver metastases (CRLM) are the most frequent secondary tumour of the liver [3]. Liver resection is the only potential curative standard of care treatment for patients with CRLM. Unfortunately, surgical resection is only feasible in around 20–25% due to factors like the extent of disease or the proximity of the metastatic lesion to vital intrahepatic structures. Thus, for the majority of patients, palliative chemotherapy is the only option. Apart from encouraging results obtained in certain sub-populations of patients like microsatellite instability high (MSI) tumours where immunotherapy can yield high survival rates [4], the 5-year overall survival on palliative chemotherapy is around 10% [5].

26.2 Transplantation for Malignant Disease

The concept of replacing the liver to treat a malignant disease is as old as liver transplantation as a therapeutic modality, and in fact some of the early liver transplants were performed for metastatic colorectal cancer [6, 7]. The first malignant liver tumour to be accepted as an indication for transplantation was, however, hepatocellular carcinoma. The initial experiences were hampered by high frequency of recurrence and inferior post-transplant survival. In 1996, the Milan group, however, was able to demonstrate that the application of strict selection criteria could yield excellent overall survival and low incidence of post-transplant recurrence [8]. This strategy of stringent patient selection based on clinicopathological features has proven to be a fundamental and valuable concept in all other areas of transplant oncology that has emerged later on [9].

The first published series exploring liver transplantation as a treatment for unresectable liver metastases from colorectal cancer and neuroendocrine tumours came from Mülbacher and coworkers in Vienna in 1991 [10]. Seventeen out of 19 patients were transplanted for CRLM, and the median survival was 13.1 months. The dismal outcomes together with other contemporaneous reports from the European Liver Transplant Registry (ELTR) led to CRLM being considered a contraindication for liver transplantation [11]. Of note, however, is that the perioperative 90-day mortality in the Vienna series was 30%, reflecting a learning curve in transplant technology. Vast improvements in imaging technolo-

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gies, oncological therapy, molecular biology, surgical technique, and intensive care medicine during the next decades made it pertinent to assume that better outcomes than those reported from the pioneering period could possibly be anticipated. Furthermore, the introduction of inhibitors against the mammalian target of rapamycin (mTORi) could theoretically confront concerns regarding a promotor effect on cancer growth and dissemination by the immunosuppression regimen utilized in transplantation that could be mitigated through the antiproliferative and partial antineoplastic properties that had been shown for this class of drugs [12–14]. This was the background for systematic studies at Oslo University Hospital from 2006 and onwards exploring the concept of liver transplantation for CRLM.

The premise of liver transplantation for secondary tumours, in general, is that the disease is limited to the liver and that the immunosuppression needed after transplant does not adversely affect post-transplant tumour recurrence and/or patient survival.

26.3 Patient Selection

All patients need to satisfy ordinary transplant criteria, that is, not having other malignancy or severe comorbidity that would contraindicate transplantation and a standard pre-transplant workup is a prerequisite. In addition, elements specific to the colorectal cancer disease must be investigated and evaluated.

A detailed and complete history from diagnosis until time of evaluation regarding the primary tumour and liver metastases with all treatment modalities as well as response to treatment is of essential importance to make a complete evaluation as to whether a patient may be a future candidate for liver transplantation.

26.3.1 Features of the Liver Metastases

The essence of patient selection for liver transplantation is to try to identify patients with "favorable tumour biology." The latter is an ill-defined term but is characterized by a set of clinicopathological features that typically indicates a less aggressive phenotype. Our current knowledge of the various features that seem to have a prognostic impact is still based on a fairly limited number of performed transplants and although they tend to be robust, more granular differentiation of risk profiles is needed before a larger population of transplanted patients is available for analysis. In this setting, the most rational definition of favorable biology could be interpreted as the *absence of clearly negative predictive factors*. It is also reasonable to assume that many of the aspects that are predictive for postoperative survival after liver resection for CRLM will have a similar impact in liver transplantation. Various scoring systems have been developed for predicting outcomes after liver resection for CRLM (Table 26.1). These scores are generally not used in clinical decision making on individual patients, most likely since they were developed before modern molecular therapy and because of the alternative strategy, palliative chemotherapy usually yields worse survival than liver resection. Most clinical scoring systems have identified tumour load in the liver as the size of the largest lesion and/or a number of liver metastases, carcinoembryonic antigen (CEA) level, and disease-free interval to be critical prognostic parameters (Table 26.1). Moreover, clinical experience clearly indicates that the failure to respond to systemic chemotherapy signifies an aggressive tumour biology and often more widely disseminated disease. These latter items form the cornerstone of individual scoring of patients considered for liver transplantation for CRLM as expressed by the "OSLO score," which was developed based on the first "proof of concept" study [15]. The patient population in this trial displayed considerable heterogeneity in clinicopathological factors considered relevant to cancer-specific survival. The study demonstrated that the following parameters at the time of transplant were closely linked to the inferior outcome:

Table 26.1 Scoring systems for prediction of disease-free and overall survival after liver resection for CRLM

	Criteria (1 point for each risk factor)	Risk groups
Fong [53]	– Disease-free interval < 12 months	Low: 0–2 points
	– Number of metastases >1	High: 3–5 points
	– Preoperative CEA level > 200 ng/mL	
	– Largest liver metastasis >5 cm	
	– Lymph node-positive primary tumour	
Nordlinger [77]	– Age > 60	Low: 0–2 points
	– Serosal invasion of the primary tumour (>pT3)	Intermediate: 3–4 points
	– Lymph node-positive primary tumour	High: 5–6 points
	– Disease-free interval < 24 months	
	– Number of liver metastases >3	
	– Largest liver metastasis >5 cm	
Nagashima [78]	– Serosal invasion of primary tumour (>pT3)	Low: 0–1 points
	– Lymph node-positive primary tumour	Intermediate: 2–3 points
	– Number of liver metastases ≥2	High: ≥4 points
	– Largest liver metastasis >5 cm	
	– Resectable extrahepatic metastases	
Konopke [79]	– Number of liver metastases ≥4	Low: 0 points
	– CEA ≥200 ng/mL	Intermediate: 1 point
	– Synchronous liver metastases	High: ≥2 points

- Diameter of largest metastatic lesion >5.5 cm.
- CEA level > 80 μg/L,
- Progression on chemotherapy.
- Time interval from diagnosis to transplant <24 months.

In scoring, each item is assigned 1 point and, thus a range of 0–4 points is possible.

An alternative method to assess hepatic tumour load is the so-called tumour burden score (TBS), which has an analogy to the metro-ticket concept in HCC. Generally, the estimated survival is hypothesized to be dependent on total tumour load, indicating that both the number of lesions as well as the maximal diameter are of significance. The latter two parameters are used to plot each individual patient in a cartesian plane, and the TBS is calculated as the two-dimensional distance from zero by utilizing the Pythagoras theorem. High TBS scores clearly lead to poor recurrence free and overall survival after liver resection [16, 17], and as such are in line with other cohort studies on a number of metastases and outcomes [18, 19]. MD Anderson Cancer Center group recently reported a contour prognostic model based on continuous diameter and number of CLM in association with *RAS* mutation status. The study showed a gradual decrease in overall survival in association with an increase in tumour largest diameter and number of CLM [19]. It is reasonable to assume that the total tumour load plays a predictive role in transplantation as well. So far, the number of lesions seems to have a far less negative impact than the size of the largest metastasis.

26.3.2 Features of the Primary Tumour

All patients considered for transplant should have undergone standard of care surgical removal of the primary with free margins prior to liver transplantation. In the ideal setting, this is done early after diagnosis of CRLM which allows a long observation time after surgery. Since many asymptomatic tumours in patients with clearly unresectable liver metastases are left in situ, this is often not the case. If the patient is considered a good transplant candidate according to predictive transplant criteria like the Oslo score, it is advisable to proceed with surgery of the primary to allow for a enough postoperative observation time before a possible transplant. There are no strict data on how long this time interval should be, but based on experience, the total time from diagnosis to transplant should be over 12 months, and if surgery of the primary is done within the last part of this interval, at least 3–6 months delay seems reasonable. Nodal status of the primary tumour is a key marker in standardized staging and is as such another prognostic factor to consider since positive regional nodes (>pN1) indicate a more advanced disease and a higher likelihood for distant spread. A pN2 is not necessarily an exclusion criterion by itself if the remaining predictive factors in the transplant evaluation are favorable. Additional observation time is, however, strongly recommended in such patients to ensure that tumour biology is favorable.

In about 70% of the colorectal cancers, the primary tumour is located on the left side, that is, distal to the splenic flexure whereas the remainder located proximally are classified as right sided tumours [20]. This distinction is of clinical relevance, since the biological properties, or "tumour biology" of right sided colon tumours appear to be less favorable than that of the distal colorectal tumours. This is related to a higher incidence of poorly differentiated tumours, signet ring cell differentiation, and BRAF mutation in right-sided cancers and reduced overall survival have been reported after liver resection for CRLM in patients with right sided primary [21–25].

Molecular profiling has been used increasingly in colorectal cancer. There is variability in terms of what is considered a standard of care test panel, but KRAS, BRAF, and MSI are usually investigated. KRAS is the most frequent RAS mutation encountered in colorectal cancer [26]. KRAS wild-type status is predictive of response to antiepidermal growth factor receptor inhibitors (EGFR) targeted therapy. Studies indicate that KRAS mutation is associated with inferior recurrence free and overall survival after liver resection for CRLM [27–29]. So far, a similar negative impact has not been convincingly documented after liver transplantation for CRLM, but it cannot be excluded due to the lack of statistical power inherent to the small sample size. On the other hand, the effect of KRAS mutation is most likely not so detrimental that this alone should preclude transplant consideration.

BRAF-V600E is a more infrequent mutation in microsatellite stable (MSS) colorectal tumours and is associated with an aggressive phenotype with poor survival compared to wild-type status. It is far more prevalent in MSI tumours and interestingly in this setting does not have the same negative impact [30]. MSI tumours account for up to 15% of all colorectal cancers [31]. The therapeutic alternative with immunotherapy yields good survival outcomes in this group [4]. This, together with the fact that immunotherapy might constitute a problem with an increased risk of allograft rejection following transplant makes patients with MSI-high status unlikely candidates for liver transplantation. Taken together, BRAF-V600E mutation is not recommended for transplant consideration.

In addition, multi-gene panels indicate that multiple mutations including TP53 and RAS comutations predict inferior survival after liver resection [32]. However, there are no data available as to whether this affects the outcome after transplantation and future studies will elucidate the significance of this and other genetic profiles in liver transplantation for CRLM.

26.3.3 Chemotherapy

All patients with extensive liver metastases should receive chemotherapy as a standard of care to ensure that whenever possible the patient can be downstaged to resection. Furthermore, response to chemotherapy contributes to the assessment of tumour biology since treatment failure is an adverse factor of outcome. All registered trial liver transplantation protocols for CRLM have a minimal required chemotherapy treatment prior to transplant consideration. There are no data or general agreement on specific regimens, but given that a prolonged observation time is advisable, it is reasonable to require at least completion of one line of standard of care chemotherapy which will usually include 5FU and irinotecan or oxaliplatin. Expected median OS from the start of first-line chemotherapy is approximately 24 months with a 5-year survival of about 10%, although longer median OS has been demonstrated with selected patients with good performance status (ECOG 0 to 1), no KRAS or BRAF mutations and left sided tumours [33–38]. The response to chemotherapy is usually expressed in percent according to the response evaluation criteria in solid tumours (RECIST) and is an important selection parameter [39]. It is reasonable to assume that the greater the response, the better the prognosis is after liver transplantation. Partial response in RECIST requires at least 30% reduction in the largest diameter of target lesions, whereas progressive disease is defined as at least 20% increase in the same parameters. Stable disease is everything in between these two categories. In Oslo, we have chosen to use a minimal response of 10% to ensure that we do not include patients with progression in transplant evaluation, and this is independent of which line of therapy is discussed.

Changes in tumour size do not always reflect the degree of pathological response particularly in the setting of biological agents [40]. RECIST criteria may therefore sometimes underestimate the response in agents that have a cytostatic rather than cytotoxic mechanism of action. The Chun criteria are based on three main characteristics: lesion attenuation, lesion–liver interface, and presence of rim enhancement. These morphological changes on CT seem to outperform RECIST criteria in predicting pathological response to chemotherapy and patient survival in patients treated with biological agents [41, 42].

There are no data on utilizing the Chun criteria for evaluation in transplant candidates, and this merits further investigation.

An unclarified question is whether patients should receive adjuvant chemotherapy after transplant. The multicentric TRANSMET trial led from Paris (study number NCT 02597348) has this as part of the protocol. In the trials of Oslo University Hospital, adjuvant chemotherapy was not part of the trial. Deciding upon a suitable regimen is difficult since more than 50% of Oslo patients had received two or more lines of chemo at the time of transplant evaluation. That means they either had progressive disease or intolerance to first-line chemo, thereby limiting the number of available chemotherapeutic options. Furthermore, there are no data indicating that an adjuvant regimen after transplant will result in a clinically meaningful survival benefit, given the absence of data after liver resection for CRLM. Perioperative chemotherapy increased 5-year survival by about 4% after liver resection in the EORTC trial where the liver tumour burden was much lower than in patients considered for transplant [43]. It cannot, however, be totally ruled out that some form of adjuvant therapy may be useful. The French TRANSMET trial may shed more light on this issue but the best approach to clarify this question would be in future multicentric randomized trials.

26.3.4 Radiology

All patients should undergo CT, MRI, and PET-CT of the thorax and abdomen as part of the evaluation process. The primary goal is to obtain a reliable assessment of liver tumour burden as well as exclude extrahepatic disease. PET-CT has a particular role in the latter aspect, but even though the combination of these three modalities will suffice in the majority of patients, a few cases of extrahepatic disease will be discovered at laparotomy after frozen section of hepatoduodenal ligament lymph nodes [44], and this should be part of the standard transplant routine for CRLM.

PET-CT can also provide functional information related to the liver metastases. High standardized uptake values (SUV) have been shown to be associated with elevated metabolic activity and tumour aggressiveness in colorectal cancer [45, 46]. Metabolic-based parameters like metabolic tumour volume (MTV) and total lesional glycolysis (TLG) are useful for increasing the predictive value of the PET parameters. MTV has in the setting of the transplant studies been defined as tumour volume with 18F–FDG uptake segmented by fixed threshold methods at 40% of maximal standardized uptake volume (SUV_{max}) in the volume of interest (VOI) [47]. When studying all PET-CT investigations performed in the SECA-1 trial, a cutoff value for MTV of 70 cm^3 separated patients with long overall survival from those with short survival [47]. Importantly, MTV pretransplant is independent of (y)pT-stage, (y)pN-stage of the primary, right versus left sided primary tumour, time from primary surgery to transplant, and KRAS mutation status [48]. Like mentioned above, there are data to support the predictive value of metabolic PET parameters in colorectal cancer. A recent study looking at liver resected patients showed a similar clear predictive property of MTV, but interestingly the cutoff value separating superior and inferior outcomes in this liver resection cohort was just

8.5% (5.98 cm^3) of that seen in liver transplantation for CRLM [49], suggesting that the acceptable tumour load is lower after liver resection than after liver transplantation.

26.3.5 Time Interval

The tumour biology, that is, true biological nature and phenotype of metastatic colorectal cancer, is as previously outlined not easily determined, dependent on an array of factors and display dynamic alterations during the progression of disease as well as treatment responses. Thus, we have to rely on close and systematic observation over time, and the interval from diagnosis to transplant therefore is a fundamental criterion in the evaluation of suitability for liver transplantation for CRLM. In the first systematic study, and other observational cohort reports this time interval has been shown to be a predictor of survival [15, 50]. The length of the observation time acts as a selection tool, filtering out patients progressing on treatment. Similar concepts have been utilized in transplantation for HCC, particularly after downstaging procedures. Theoretically, observation time may also be a double-edged sword in unresectable CRLM, since disease progression by time in patients on chemotherapy therapy alone is the rule, albeit with interindividual variations in progression rate. There is no international consensus on the ideal time interval, and it may vary according to the individual pretransplant treatment types. Patients previously resected for CRLM will often have longer time intervals, as demonstrated in the series reported by Toso et al. [50]. The cutoff value of about 24 months from diagnosis that was identified in the SECA-I trial also probably reflects that most patients were referred for transplant evaluation after longer periods of the standard of care therapy. Interestingly, the 10-year analysis of data from this study shows that the 24-month time interval was no longer a significant predictor for survival beyond 5 years. On this background, it is conceivable, that in most patients with stable response to therapy, added observation time from start of response to transplant evaluation beyond 12 months will most likely not be crucial for the predictive outcome.

26.4 Outcomes

26.4.1 Overall Survival

Currently, there are limited clinical series or case reports and only two controlled prospective trials on liver transplantation for CRLM.

In the pilot SECA-I trial, the study population was, typically for a proof-of-concept trial, heterogeneous in terms of apparent risk factors. The main inclusion criteria were a non-resectable liver-only disease, complete radical resection of primary tumour, good performance status (ECOG score 0–1), minimum of 6 weeks of chemotherapy, and absence of extrahepatic disease. There was no restriction regarding the extent of disease, nodal status of primary tumour, response to chemotherapy, or number of lines of chemotherapy given previously. The estimated survival at 5 years in the study was 60% [15].

The overall survival was linked to the presence of the four negative predictive factors constituting the aforementioned Oslo Score; maximal diameter of the largest lesion >5.5 cm, pretransplant CEA level > 80 μg/L, progressive disease on chemotherapy, and interval from diagnosis to transplant <2 years. This is similar to what clinical case series have shown [50]. Patients with Oslo score 0–1 all survived 5 years, whereas none with score 4 lived beyond 3.5 years. In a 10-year analysis of the data with a median follow-up time of 146 months (range 118–161 months), the overall 10-year survival in patients with Oslo score 0–1 was 50% (Solheim et al. 2021, submitted).

The initial results of the SECA-I study were matched to comparable patients treated with chemotherapy included in the Nordic-VII trial. The analysis indicated a substantial survival benefit for transplantation over palliative chemotherapy [51]. A substantial positive survival effect could even be clearly demonstrated when focusing only on patients that were progressing on the last line of available chemotherapy before transplantation [35].

The lessons learnt from the SECA-I study guided the protocol of the subsequent SECA-II trial to include more stringent inclusion criteria, demanding a minimal observation time of at least 12 months and a response to chemotherapy of ≥10% RECIST. Extensive tumour load was still accepted, but with an upper limit as follows: no lesion could be over 10 cm. If more than 30 lesions, the largest lesion should be less than 5 cm and a chemotherapeutic response of ≥30% RECIST was required in this latter setting. By this study protocol, all the patients included fell into the category of Oslo score 0–2, and the estimated 5-year survival rate after a median observation time of 36 months was 83% [52].

Since transplantation of deceased donor organs has to be justified by long-term survival, efforts on trying to identify predictive scoring systems have continued. In a recent publication, the Oslo score, MTV at PET CT within 90 days before transplantation and the Fong clinical risk score (FCRS) [53] were compared with respect to the prediction of long-term survival after liver transplantation for CRLM in a larger sample of patients with a median observation time of 85 months of patients alive.

Pre-transplant Oslo Score 0–2, MTV below 70 cm^3 and a FCRS of 0–2 yielded 5-year overall survival (OS) rates of 67%, 78%, and 100%, respectively [48]. Similar predictive properties were seen for disease-free survival (DFS) and survival after recurrence (SAR), (Figs. 26.1, 26.2, and 26.3).

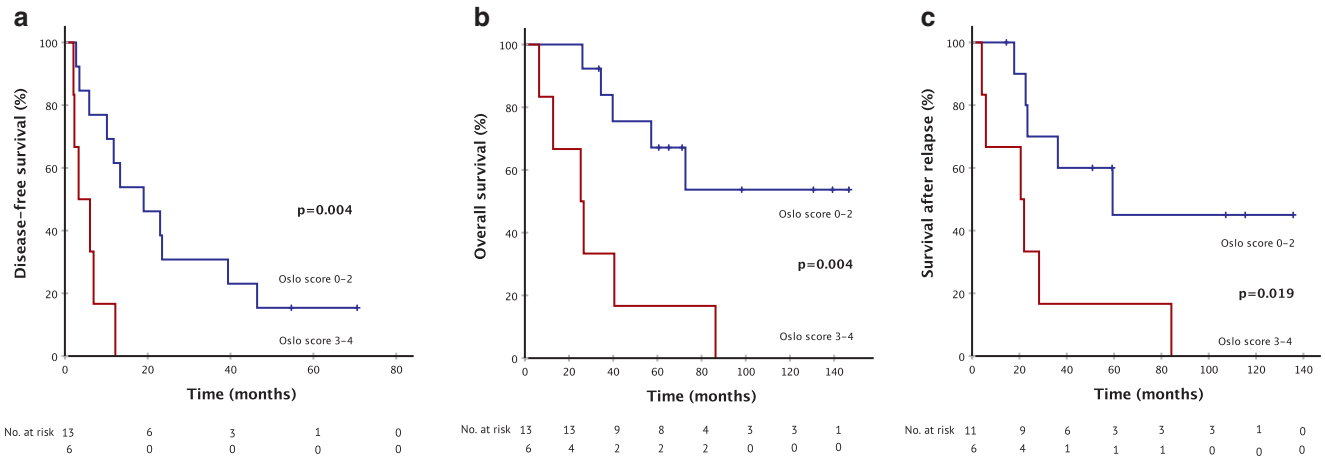

Fig. 26.1 Disease-free survival (**a**), overall survival (**b**), and survival after relapse (**c**), from time of liver transplant Blue line, Oslo Score 0–2; red line, Oslo Score 3–5. (Adapted with permission from [48])

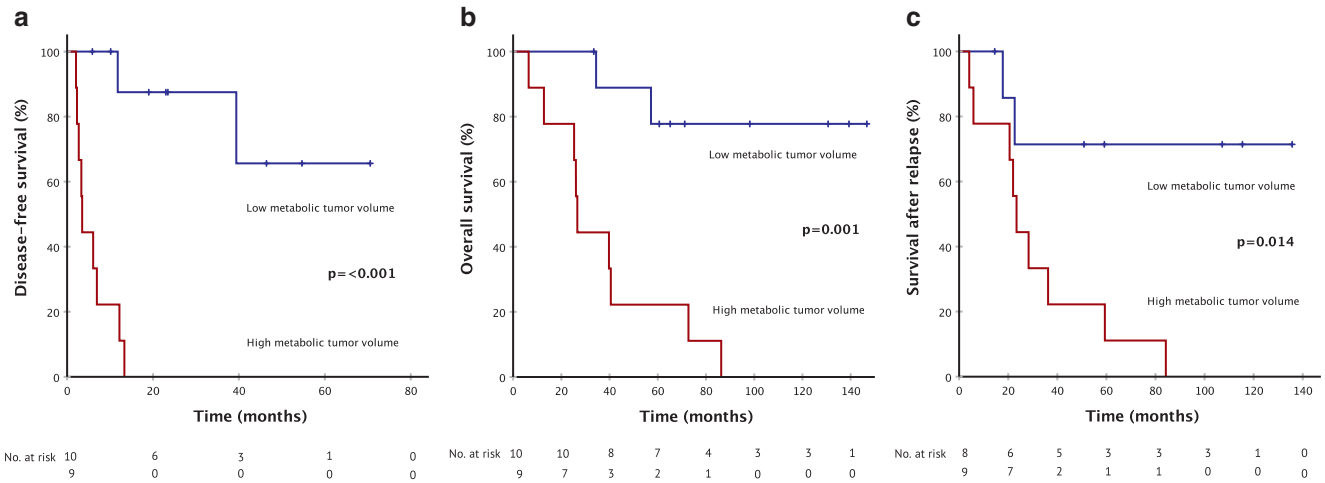

Fig. 26.2 Disease-free survival (**a**), overall survival (**b**), and survival after relapse (**c**), from time of liver transplant. Blue line, MTV < 70 cm^3; red line, MTV > 70 cm^3. (Adapted with permission from [48])

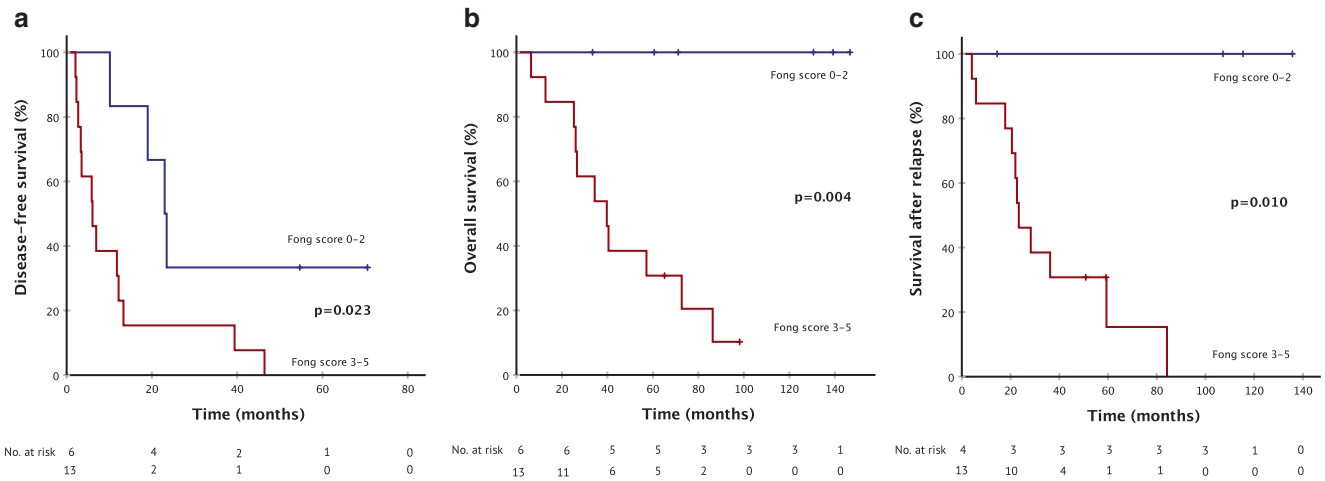

Fig. 26.3 Disease-free survival (**a**), overall survival (**b**), and survival after relapse (**c**), from time of liver transplant Blue line, Fong Clinical Risk Score 0 to 2; red line, Fong Clinical Risk Score 3–5. (Adapted with permission from [48])

All these three selection criteria are intercorrelated, meaning that most patients with low MTV have a low Oslo score and all patients with FCRS of 0–2 had low MTV. This means that a staged approach to patient selection can be utilized depending on how strict each center think is needed in order to defend transplantation for this particular indication. The caveat with strict criteria is, however, that some patients with substantial benefit from transplantation will inevitably be excluded. A calculation based on the Oslo experience indicates that applying these criteria to the whole cohort transplanted over the years would limit the volume of transplants performed for CRLM in Oslo to 60%, 50%, and 30% for Oslo score 0–2, MTV < 70 cm^3, FCRS 0–2, respectively.

A schematic approach to patient selection and evaluation based on strict selection criteria is illustrated in Fig. 26.4.

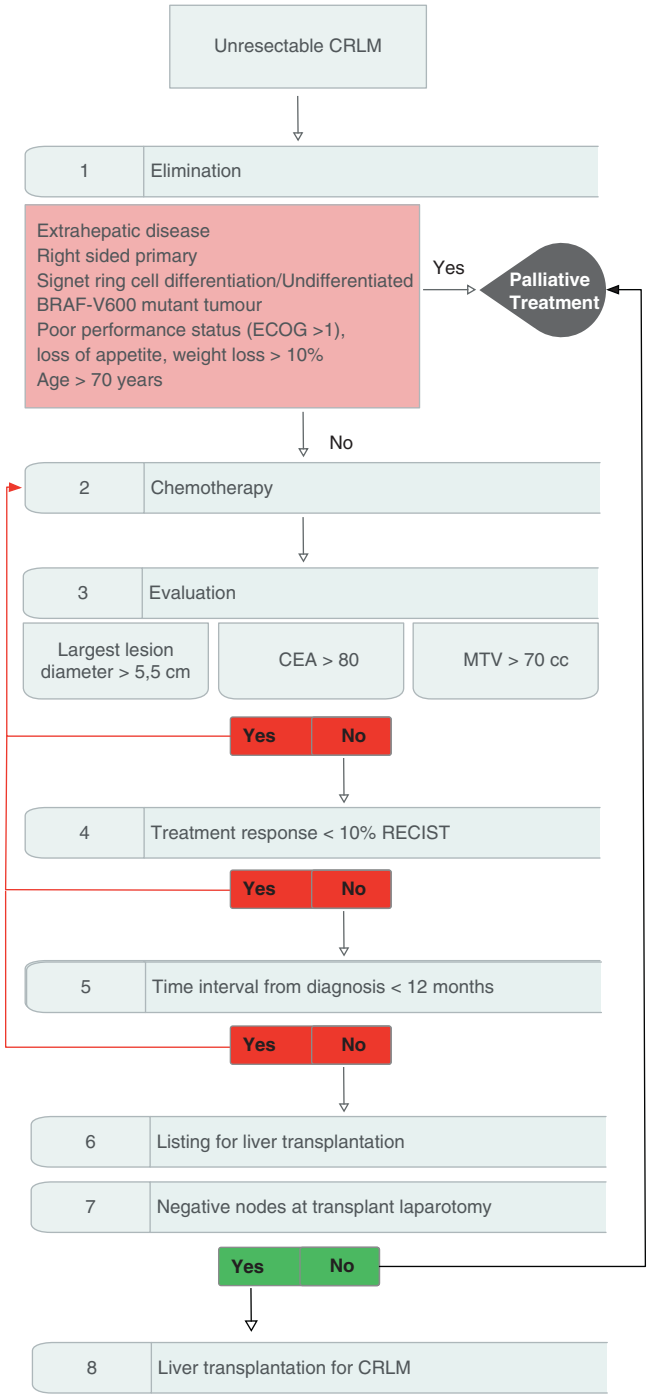

Fig. 26.4 Schematic overview of stages in the selection and evaluation process of patients with unresectable liver metastases for liver transplantation

26.4.2 Disease-Free Survival and Recurrence

Metastatic colorectal cancer is a disseminated disease, and recurrence is therefore a significant problem in all therapeutic modalities. Efficacy of treatment may be assessed by OS, DFS, and time to progression (TTP). DFS is usually a good surrogate predictor of treatment efficacy given that there is a close correlation between DFS and OS, and this is the case in many cancer forms and therapeutic modalities. The experience in liver transplantation for CRLM differs somewhat from this pattern and what is seen after liver resection and chemotherapy for CRLM.

In the SECA-I trial, all patients had recurrence within 2 years, but the overall survival was still higher than one would expect compared with chemotherapy treatment. Survival for low-risk patients (Oslo score 0–1) was better than that obtained in most liver resection studies, despite the short DFS. This paradox is most likely due to a distinctly different pattern of recurrence after transplant than after liver resection. About 60–70% of the relapses were lung metastases, that were predominantly small and growing at a slow rate. A large proportion of the patients could be resected with curative intent. Patients in the SECA-I trial who survived beyond 10 years have all been resected for lung metastases, some multiple times, and the shortest time from last lung resection in the currently surviving patients is 36 months. No evidence of disease 10 years after liver resection has been suggested as a sign of cure [54, 55]. These long-term survivors from the SECA-I trial are therefore most likely cured of their cancer.

Interestingly lung metastases in transplanted CRLM patients display a similar growth rate as in patients that are not immunosuppressed. Small pulmonary lesions after transplant can be observed without specific treatment until the diameter is about 10–15 mm and then resected [56]. The incidence of liver recurrence observed post-transplant is very low, around 5–8%, and just a smaller proportion (15–20%) of the patients experience multisite recurrence. These patients may still be offered chemotherapy, with acceptable results [57]. This is in contrast to most reports in liver resection patients. About 70% recur, and 30–50% of these represent liver recurrences. Although a proportion is amenable to

re-resection, hepatic recurrence has a clear negative impact on outcome [58–61].

Improved patient selection for transplant seems to decrease recurrence thereby improving disease-free survival [48, 52]. In the SECA II trial, 35% were without recurrence after 3 years [52]. Similar outcomes have been reported in retrospectively collected clinical case series [50]. Our policy toward recurrence is to surgically remove all resectable recurrences, and since the majority of the patients have single or a few resectable lung metastases, this translates to a high proportion of no evidence of disease (NED) in the patients treated. In the SECA-II trial, 76% of the patients had no evidence of disease at 3 years, and the 4-year survival after recurrence was 73%. Worth noting is that by retrospective examination of chest CT scans in transplanted patients, about 40% of the lung lesions were likely present at the time of transplantation [62]. Thus, one might speculate that only a portion of the lung metastases is true recurrences and that many represent initial staging failures. Unfortunately, there is a lack of sensitive and specific methods to detect and reliably diagnose small lung metastases from CRLM.

Recurrence in the setting of liver transplantation for CRLM should therefore be viewed with more nuance since the impact of recurrence deviates from what might be expected and the correlation between DFS and OS is less obvious than in chemotherapy treatment and liver resection for CRLM. Thus, the survival after recurrence for well-selected patients is substantially longer than reported following liver resection or chemotherapy [48]. This is also illustrated by a comparison with transplantation for HCC, where low-risk CRLM patients (Oslo score 0–2) have a similar overall survival despite shorter DFS compared to HCC patients transplanted within the Milan criteria [63]. The outcomes reported to date have sparked interest in many other centers. Thus, a number of trials are ongoing utilizing both deceased and living donors (Table 26.2).

26.5 The Scarcity of Liver Grafts

For most centers, the scarcity of liver grafts represents a major barrier for broader implementation of liver transplantation for CRLM. Improving access to liver grafts for these patients entails focus in two directions: stringent patient selection and expansion of the donor pool.

The goal with improved patient selection is to avoid the futile use of liver grafts and requires a good understanding of the tumour biology. The staged predictive scoring systems utilizing Oslo score, MTV, and FCRS are valuable tools in this context. Simultaneously, avoidance of clinical features associated with a negative outcome that are not part of the above-mentioned scoring systems should be taken into account (Fig. 26.4). Importantly, patients that have developed general cancer symptoms like fatigue and loss of appetite have inferior overall survival after transplantation in this setting and are not appropriate transplant candidates [64].

The need for liver grafts for CRLM can to a large extent be regulated through the choice of transplant criteria. If very stringent selection criteria are applied, calculations based on the SECA studies and the Norwegian population, suggest an eligibility rate of only 0.24–0.51 patient per 1 million people per year [48]. This represents 1–2% of yearly transplant volume (based on United States population) and would not necessarily negatively impact the rest of the waiting list for liver transplantation.

Since patients with CRLM usually do not have any signs of hepatic failure or portal hypertension, it is reasonable to assume that this cohort may tolerate the use of extended criteria donor grafts (ECD) much better than patients with chronic or acute liver failure. Thus, carefully selected ECD grafts might be a source of "surplus" liver grafts for patients with CRLM [65]. Another, potentially promising approach is based on the split liver technique and auxiliary transplantation and is called the RAPID (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy) concept [66]. This surgical technique includes a first stage operation where a segment 1–3 resection of the recipient liver is performed to provide space and optimal venous outflow for an auxiliary segment 2 + 3 graft which is transplanted following the resection. Augmented graft regeneration is facilitated by diverting portal blood flow from the liver remnant under the guidance of graft portal vein pressure and flow measurements to protect the graft from detrimental portal hyperperfusion and simultaneous registration of graft arterial flow [67, 68]. Graft size is then monitored weekly by CT or MR and when the regenerated graft volume is approaching 0.8% of body weight (or 35–40% of recipient standard liver volume), the second stage hepatectomy of the native liver remnant is completed. This is usually possible in the course of about 3 weeks. The first patients ever operated on with this technique weighed 90 kg and received a graft of 330 g. He is still without evidence of cancer, 79 months after the operation [66]. The RAPID technique has now also been further expanded in some centers by retrieving the left lateral graft from living donors [69–73]. The technical results of the RAPID technique are promising, but there is not sufficient data available to conclude that the oncological outcome is comparable to transplantation with a full-size graft. Finally, conventional living donor liver transplantation could be a future option for centers that have a well-established program offering this transplant modality and studies are currently ongoing within this area (Table 26.2).

Table 26.2 Studies on liver transplantation for CRLM registered at clinicaltrials.gov as of February 2021

Title	Status	Results	*N*	Interventions	Locations	URL
SECA-I: Liver transplantation and metastatic Colo-rectal cancer	Completed	Hagness M. et al. Ann Surg 2013, 257:800–806	23	Liver transplantation	Oslo university hospital, Oslo, Norway	https://ClinicalTrials.gov/show/NCT00294827
Living donor liver transplantation for Unresectable colorectal cancer liver metastases	Recruiting	No results available	20	Live donor liver transplantation	Toronto general hospital, Toronto, Ontario, Canada	https://ClinicalTrials.gov/show/NCT02864485
SECA-III: Liver transplantation compared to chemotherapy in patients with ColoRectal cancer	Recruiting	No results available	30	Liver transplantation | chemotherapy	Oslo university hospital, Oslo, Norway	https://ClinicalTrials.gov/show/NCT03494946
SECA-II: Liver transplantation and colorectal cancer (4 arms)	Recruiting	Dueland S. et al. Ann Surg 2020 Feb;271(2):212–218	80	Liver transplantation and liver resection	Oslo university hospital, Oslo, Norway	https://ClinicalTrials.gov/show/NCT01479608
COLT: Improving outcome of selected patients with NonresectableHepatic metastases from Colo-rectal cancer with liver transplantation	Recruiting	No results available	22	Liver transplant | chemotherapy	Ancona, Bergamo, Genova, Milano, Palermo, Pisa, Roma, Torino, Udine, Verona, Italy	https://ClinicalTrials.gov/show/NCT03803436
SOULMATE: The Swedish study of liver transplantation for NonresectableColorectal cancer metastases	Recruiting	No results available	45	Liver transplantation | best alternative care	Transplant institute, Sahlgrenska University Hospital, Gothenburg, Sweden|transplantation unit, Karolinska university hospital, Stockholm, Sweden	https://ClinicalTrials.gov/show/NCT04161092
LIVERT(W)OHEAL: Living donor liver transplantation with two stage hepatectomy for patients with isolated, Irresectable colorectal liver metastases	Recruiting	No results available	40	Living donor liver transplantation with two-staged hepatectomy	Jena University hospital, Jena, Germany|university hospital Tübingen, Tübingen, Germany	https://ClinicalTrials.gov/show/NCT03488953
TRANSMET study: Liver transplantation in patients with Unresectable colorectal liver metastases treated by chemotherapy	Recruiting	No results available	90	Liver transplantation	AP-HP, Paul Brousse hospital, Villejuif, France	https://ClinicalTrials.gov/show/NCT02597348
RAPID: Partial liver segment 2/3 transplantation with delayed 2. Stage hepatectomy	Recruiting	No results available	20	Partial liver transplantation with delayed 2. Stage hepatectomy	Oslo university hospital, Oslo, Norway	https://ClinicalTrials.gov/show/NCT02215889
TRASMETIR: Liver transplantation in patients with Unresectable colorectal liver metastases	Not yet recruiting	No results available	30	Liver transplantation	Hospital Universitario La Fe, Valencia, Spain	https://ClinicalTrials.gov/show/NCT04616495

26.6 Future Directions

This chapter has outlined the evolution and status of liver transplantation for CRLM. It is fairly well documented that high post-transplant overall survival can be obtained in well-selected patients. The whole experience with LT for CRLM has been based on patients with unresectable disease. The concept of resectability of liver tumours has, however, changed considerably during the last 20 years with portal vein/hepatic vein embolization to augment the future liver remnant and two-stage hepatectomy and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) being increasingly used, particularly in the setting of bilobar disease and multiple metastatic lesions. It is however well documented that the long-term survival probability after resection is highly dependent on hepatic tumour burden [16–18, 74, 75]. Even though the aforementioned improvements in obtaining resectability in initially unresectable or marginally resectable patients undoubtedly greatly improve the survival perspective for many patients, the overall survival rates at 5 years in a proportion of this patient category are low, and the frequency of recurrence is very high. This is illustrated by a recent publication from the international ALPPS registry, where the overall survival and recurrence-free survival at 5 years were 27% and 12%, respectively [76]. It defies logic to believe that the selection criteria for "good tumour biology" that has been documented for liver transplantation in CRLM are only predictive if the patient is nonresectable. Furthermore, technical resectability as such is not a predictive parameter of tumour biology. Hence, it is possible that future trials might include technically resectable patients with poor expected outcome after liver resection. This could for example be younger patients with a high number of metastatic lesions that concomitantly display a favorable phenotype with respect to transplant risk factors. Comparative analyses between resection and transplantation in this context are ongoing, and only future trials can elucidate whether this is a viable clinical scenario.

26.7 Conclusion

Liver transplantation is a viable option for selected patients with unresectable CRLM. The implementation of strict selection criteria and treatment protocols yield long-term survival rates that are comparable to established indications for liver transplantation. Recurrence rates are high but given proper patient selection is dominated by pulmonary metastases that can be offered lung resection with curative intent. Patients transplanted for CRLM need close, long-term follow-up. Liver transplantation for CRLM is still an evolving field within transplant oncology. It is recommended that all liver transplants for CRLM as a minimum are entered into registries, but preferably are part of prospective studies, whenever possible.

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Prognostic Models for Colorectal Liver Metastases

27

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Learning Objectives

- Morphology alone cannot determine the oncological benefit of resection in patients with colorectal liver metastases. Long-term survival can be achieved in about 30% of patients with extensive bilateral affection of the liver; thus, patients should be evaluated by expert hepatobiliary centers before unresectability is determined.
- A great number of single factors, such as numbers of metastases, size, level of carcinoembryonic antigen, disease-free time interval between the primary and the metastases and TNM-stage, have been prognostic of survival, but are losing clinical significance inversely with the availability and introduction of more effective modern chemotherapy.
- A combination of factors is pooled in prognostic models and may improve prognostication. Implementation of genetic biomarkers into these models will be important and may provide a more direct assessment of tumour biology. However, to date, no scoring system has convincingly demonstrated the power to exclude patients from surgery.

27.1 Introduction

A major and ongoing task for surgeons treating patients with colorectal liver metastases (CLM) is to refine patient selection [1, 2]. For that, prognostic models are of importance [3–6]. Patients presenting with CLM represent a heterogeneous group, where different morphological features are the most obvious. Investigators have been troubled by the fact that patients resected for a small solitary metastasis may present rapid recurrence and subsequent death, and on the contrary that patients with large or multiple bilateral lesions may achieve long-term survival after surgery. This discrepancy between tumour burden and outcome has advocated that morphology alone, cannot determine the oncological benefit of surgery and therefore a more aggressive approach toward resection [7, 8]. Currently, technical resectability is defined as an adequate volume of the future liver remnant (FLR: 20% in patients with healthy liver) with preserved vascular in- and outflow and biliary drainage [9]. Even these extensive criteria are being challenged with techniques of perioperative hypertrophy of the FLR and vascular reconstruction, and in the outermost cases, liver transplantation [10]. New prognostic models are required and welcomed to improve the selection of patients and timing of the treatment modalities available in the modern and personalized treatment of patients with resectable CLM.

In the current chapter, two major shifts in the treatment of patients with CLM will be discussed. First, the acknowledge that factors of morphology are losing significance to molecular markers that represent a better and more direct measure of tumour biology. Second, that the significance of prognostic factors to determine outcome is fluent and, therefore, needs constant revision to adapt to the changes that affect treatment and outcome.

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27.2 Prognostic Models in Colorectal Liver Metastases

27.2.1 Prognostic Factors in Patients with Resectable Colorectal Liver Metastases: A Changing Landscape

During the last decades, a large number of prognostic factors have been reported in patients who underwent resection of CLM. There are innate factors of outcome, both patient wise and disease wise, and there are treatment-associated factors. Interestingly, the significance of the different factors has not been consistently reported. It is likely that various patient selection between centers and what factors are included in multivariable analysis determines the significance level of each factor.

Lung metastases in patients with synchronous liver and lung metastases from colorectal cancer are one illustrative example of a prognostic factor with a significance level according to the context of the study cohort. In the presence of multiple and bilateral, but small lung metastases, it is unlikely these will affect overall survival in patients with unresectable liver metastases. In patients with resectable liver metastases, however, the presence of multiple bilateral lung metastases is likely to represent not curable disease, thus a factor associated with overall survival. Yet, resection of the liver metastases with lung metastases left in situ may provide prolonged survival in selected patients [11].

Prognostic factors may have changed over time due to more effective chemotherapy and the implementation of other factors better reflecting tumour biology [12, 13]. But prognostic factors also change over time during the course of treatment in patients individually. In a recent report, while *BRAF* mutation was found to be driving prognosis the first year after surgery, positive resection margin status and resected extrahepatic disease were the major drivers of prognosis thereafter [14].

Prior to the development of parenchyma-sparing hepatectomy [15] and modern chemotherapy, the dominating prognostic factors were location, numbers, and size of tumours, deciding whether or not they were resectable with a formal hemihepatectomy, in addition to presence of extrahepatic disease. The observation of long-term survivors among patients with the more extensive disease led to an evolution in liver surgery [16]. From formal hemihepatectomies to parenchyma-sparing and minimally-invasive techniques [17]. As surgical technique has developed, the definition of technical resectable disease has expanded thus allowing more patients to be candidates for surgery over the past three decades [7, 18].

Prognostic models could serve as a valuable adjunct in choosing the patients that will benefit from surgery and those who will not [19]. Identifying the patients that will not benefit from surgery may increase patient quality of life, reduce postoperative morbidity and mortality, save and potentially reduce overall costs of treatment. Furthermore, prognostic models may provide higher quality of the preoperative patient information and for patients to form a knowledge base to provide consent to treatment. Certainly, there are elderly and or frail patients that may choose not to undergo surgery or chemotherapy if we have certain measures that the probability of recurrence is almost certain.

27.2.2 From Prognostic Factors to Prognostic Models in the Era of Morphology

The readily increasing number of recognized prognostic factors reflects the heterogeneity of patients with CLM. Furthermore, implementing known prognostic factors individually in the workup of patients with CLM is simply not practically possible. Therefore, the development of clinically applicable, and accurate, prognostic models has been of interest.

Nordlinger and colleagues were among the first to introduce a prognostic scoring system in patients with CLM [19]. Their score, published in 1996, was based on age, size of the largest metastasis or CEA, stage of the primary tumour, disease-free interval, number of liver metastases and resection margin, and able to stratify patients into three risk groups according to 2-year overall survival.

In 1999 Fong and colleagues published the Clinical Risk Score (Fong score), a clinical score to predict survival after resection of CLM [3]. Fong identified five factors associated with recurrence, each assigned one point in the score: node-positive primary tumour, a disease-free interval between the primary and the liver metastases of less than 12 months, more than one liver metastasis, size of the largest metastases of more than 5 cm, and carcinogenic embryonic antigen (CEA) level more than 200 ng/mL. Thus, the score was able to stratify survival based on the combined score from 0 points (60% 5-year survival) to 5 points (14% 5-year survival). It is worth to note that the score was developed with factors associated with recurrence but used to estimate survival, which may be inaccurate, especially in modern cohorts where a number of patients undergo several liver resections with the same chance of long-term survival after each resection [16, 20]. Since Nordlinger and Fong published their scores (in 1996 and 1999, respectively), advances have been made both in chemotherapy, targeted therapy and surgical technique. The Fong score was derived from a retrospective analysis of patients from 1985 to 1998. During and since this period, many advances have been made posing the question if the CS is equally applicable today.

The Basingstoke Predictive Index, as published by Rees and colleagues in 2008, is another score developed in a

Table 27.1 Clinical, biochemical, and mutational factors reported to be predictive factors of overall and/or disease-free survival after resection of CLM

First author	Nordlinger	Fong	Iwatsuki	Minagawa	Zakaria	Malik	Rees	Kattan	Beppu	Brudvik	Margonis	Lang
N	1513	1001	305	369	663	687	929	1477	727	564	502	139
First published (year)	1996	1999	1999	2007	2007	2007	2008	2008	2012	2017	2018	2019
Reference	[19]	[3]	[26]	[27]	[24]	[25]	[21]	[23]	[22]	[4]	[5]	[37]
Factors in score												
General parameters												
Gender								X				
Age	X							X				
Disease-free interval	X	X	X					X	X			
The primary tumour												
Site colon/rectum								X				
Lymph node status primary		X		X			X	X	X	X	X	X
Differentiation grade							X					
Stage	X											
The liver metastases												
Number of metastases		X	X	X		X	X	X	X			
Size largest tumour	X	X	X				X	X	X	X		X
Tumour burden score											X	
Bilateral disease			X					X				
Number of affected lobes								X				
Resection margin (liver)	X	X	X*				X					
Regional lymph node status	X		X*	X	X							
Extrahepatic disease		X					X		X		X	
Blood transfusion					X							
Biochemical												
CEA at hepatectomy	X	X		X			X	X	X		X	
Inflammatory response						X						
Somatic gene mutations												
RAS mutations										X	X	
RAS/RAF pathway												X
SMAD family alterations												X
External validation												
N	Na	Na	Na	229	Na	Na	Na	Na	Na	608	747	Na

patient-cohort prior to modern chemotherapy [21]. A multivariable analysis was performed to determine factors of long-term cancer-specific survival, and each factor was attributed points weighted based on the individual impact on survival. The combined score could then be used to estimate survival. The investigators created one score with factors available preoperative and one score with factors only available postoperative. Even though different cutoff values for the individual factors, as for the Fong score, the factors of the Basingstoke Predictive Index were primarily those of morphology, and Rees included also primary tumour differentiation, resection margin, and the presence of extrahepatic disease, making the score somewhat complex for use in everyday practice.

Nomograms have also been suggested as prognostic models of recurrence and survival in patients with resectable CLM [22, 23]. Similarly to the Basingstoke Predictive Index, these have been criticized for their complexity, thus limited clinical value. Zakaria et al. found only preoperative blood transfusion and positive lymph nodes to be of significant importance and question the value of risk scoring systems [24]. In another interesting study, Malik et al. found an inflammatory response parameter based on plasma concentrations of C-reactive protein (CRP) or neutrophil/lymphocyte ratio of more than 5:1 to be significant markers of survival. Finally, a number of other prognostic scores based on various sized cohorts of patients resected for CLM have been published, [25–27] as summarized in Table 27.1.

27.2.3 From Morphological to Molecular Prognostication

Size, tumour number, and synchronicity have been used as surrogate markers of tumour biology in patients with CLM [3, 6]. Despite attempts to stratify patients according to acknowledged prognostic factors, still the long-term survival would vary significantly, giving us reason to believe that other prognostic factors are more specific in determining the outcome and long-term survival. With the development in

clinical genetics and tumour biology, CLM is steadily becoming a more heterogeneous and complex disease.

Somatic gene mutations are being explored to achieve a better understanding of selection and prognostication [4, 13, 28, 29]. In patients with CLM, frequently-mutated somatic genes are *TP53*, *KRAS*, *APC*, *PIK3CA*, *SMAD4*, *FBXW7, NRAS,* and *BRAF* [30]. Among these, *RAS* mutations have been of particular interest in patients with resectable CLM [13]. An important clinical implication of the *RAS* mutation is resistance to anti-epidermal growth factor receptor (anti-EGFR therapy) [31].

Additionally, *RAS* mutation has impacted the field of resectable CLM at many levels. Overall survival and recurrence-free survival have been reported worse among *RAS* mutants compared to *RAS* wild types, and mutation has been associated with a higher risk of pulmonary recurrence [32]. Independently, patients with tumours harboring *RAS* mutation have a higher risk of unfree resection margin after resecting of CLM, possibly due to a more migratory and invasive phenotype [33]. *RAS* mutation has also been linked to inferior response to perioperative chemotherapy, irrespective of treatment with anti-EGFR [34].

Based on these findings, we hypothesized that *RAS* mutation could be used to improve the performance of prognostic models in patients undergoing CLM resection [4]. The clinical risk score, as presented by Fong and colleagues in 1999, has been the most used prognostic model to estimate overall survival after CLM [3]. Based on a multivariate analysis of factors associated with survival, the following factors were attributed one point each: node-positive primary, disease-free interval < 12 months, > 1 tumour, size of the largest metastases >5 cm, and CEA > 200 ng/mL. In a more recent cohort of patients receiving the more effective oxaliplatin and irinotecan-based perioperative chemotherapy and liver resection, we performed a new multivariate analysis with the factors of Fong, but added *RAS* mutation status as the sixth factor in the analysis [4]. The inclusion of *RAS* mutation *altered* the results; disease-free interval, number of tumours, and CEA were no longer associated with survival. Thus, the modified clinical score (m-CS) was proposed using the following factors: *RAS* mutation status, node-positive primary, and size >5 cm. The m-CS outperformed the CS in the cohort and also in a large external multicenter validation cohort. The main strengths of m-CS are the fact that the score incorporates a more direct measurement of tumour biology, but also that the simplicity and few numbers of factors make it feasible in clinical practice.

Since then, there have been several attempts at improving prognostic modeling in patients with CLM with the use of genetics. A group from Johns Hopkins also aimed to refine the Fong score by adding genetics (RAS mutations), GAME-score [5]. Interestingly, they also replaced size and numbers of metastases with the Tumour Burden Score—an externally validated score that better accounts for the impact of tumour morphology on survival after resection of CLM [6]. The prognostic factors of the GAME-score were: *KRAS*-mutated tumours (1 point); carcinoembryonic antigen level 20 ng/mL or more (1 point), primary tumour lymph node metastasis (1 point); Tumour Burden Score between 3 and 8 (1 point) or 9 and over (2 points); and extrahepatic disease (2 points). The GAME-score was validated against in an external cohort and compared to the Fong score, which showed better discriminatory ability for OS.

It is likely that the prognostic scores of the future, in patients with resectable CLM, will be based primarily on molecular markers and molecular footprints rather than on morphological features. Several independent investigators have suggested that the negative impact of *RAS* mutation on prognosis may be limited to other molecular subtypes in CLM. In a report by Chun et al., concomitant *RAS* and *TP53* mutations were suggested to be an independent predictor of survival, and more importantly, the negative prognostic effect was limited to tumours harboring both mutations [30]. In another study, patients who underwent resection of CLM and concurrent extrahepatic disease, co-mutated *RAS* and *TP53* were associated with worse overall survival [35]. In a multigene examination of 507 patients, compared to *RAS* mutations alone, *TP53* and *SMAD4* mutations could be used to improve prognostic modeling after resection of CLM. Overall survival and recurrence-free survival were worse in patients with double mutated tumours compared to patients with single mutated tumours and worst in patients with triple mutated tumours [36]. In line with this, Lang et al. proposed an interesting score, the extended clinical score (e-CS), that differed from the m-CS by including *SMAD* family alterations as a prognostic factor in the score as well as replacing *RAS* mutations with all mutations in the *RAS/RAF* pathway [37]. The e-CS was based on a small retrospective series of patient, but is still interesting as it improved the established m-CS.

Recently, there has also been some interest in the less commonly mutated tumour suppressor gene *FBXW7*. While mutated in around 6% of the patients undergoing resection of CLM, *FBXW7* alterations have been found to be associated with worse survival [38].

The recognition of genetic heterogeneity has led to the increased use of more molecular markers in clinical prognostication of patients with CLM. We recently investigated the potential for improved prognostic stratification by combining *RAS/TP53* mutations and DNA copy number aberrations, thereby taking tumour heterogeneity into account. Patients with commutated *RAS/TP53* and high burden of DNA copy number aberrations identified patients with a particular poor outcome. As such, DNA copy number profiling may be used to stratify subgroups within the commutated *RAS/TP53* population [39].

27.3 Conclusion

Prognostic factors have been extensively investigated in the literature but are difficult to implement in clinical everyday practice. As such, different factors have been pooled to generate prognostic models for better stratification of good versus bad prognosis, and to render prognostication more clinically applicable. During the last decade, an increasing number of molecular markers have been proposed as prognostic factors, and also implemented into the prognostic models. With modern chemotherapy and targeted therapy, it is likely that new molecular markers will emerge. In parallel, we need continuous revision and evolution of the prognostic models to provide a better selection of the correct patient for the correct treatment, and also to determine the optimal timing of the different treatments in the ever more complex treatment algorithms.

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Personalized Prognostic Model (Contour Prognostic Model)

28

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Learning Objectives

- The practice of variables with cutoff (e.g., number of tumours, ≤ 2 vs. 3 ≤) causes substantial loss of statistical power and risk variation.
- Number and largest diameter of tumours are important prognostic variables that are always available before surgery.
- Contour prognostic model is based on the continuous number and the largest diameter of tumours and provides individualized survival probability after treatments.
- Prognostic models using continuous variables may replace categorization practice using dichotomization with an individualized risk prediction paradigm.

28.1 Introduction

Resection is an established treatment for patients with colorectal liver metastases (CLM). However, the prognosis after CLM resection differs in each patient. Some patients rapidly develop recurrence at multiple organs and die after the short interval from the resection, while others do not experience recurrence and cure from colorectal cancer. The 5-year overall survival (OS) after CLM resection widely ranges from 40% to 59% [1–5]. As such, studies reported prognostic models which categorized patients undergoing CLM resection into several groups associated with prognosis [6–17]. The concept for categorizing risk groups is considered to simplify the clinical interpretation (e.g., low risk, intermediate risk, and high risk for recurrence-free survival and OS). However, categorization of risk groups has disadvantages including loss of risk variation.

For patients with hepatocellular carcinoma (HCC), prognostic models based on the largest tumour diameter and number of tumours as continuous variables were reported for patients undergoing liver transplantation [18, 19]. and patients undergoing surgery, ablation, and trans-arterial chemoembolization [20].

Recently, our study based on an international multi-institutional cohort (derivation cohort, The University of Texas MD Anderson Cancer Center; validation cohort, Catholic University of the Sacred Heart, University of Verona, and The University of Tokyo) proposed a new prognostic model in patients undergoing CLM resection to address the issue involved in categorization of risk groups [21]. Our new personalized prognostic model (contour prognostic model) predicts individual survival probabilities in patients undergoing CLM resection on the basis of the largest diameter and number of CLMs, and *RAS* mutation status. The current chapter details how our new prognostic model is different from the previous models based on the categorization of risk groups and is useful for clinical decision-making in the management of CLM.

28.2 Use of Contour Plots for Hepatocellular Carcinoma

28.2.1 Liver Transplantation

In 2009, Mazzaferro et al. reported a model to predict the 5-year OS in patients undergoing liver transplantation on the basis of the number and the largest diameter of hepatocellular carcinoma (HCC) and the absence or presence of microvascular invasion. This report was the first to show the survival probabilities using contour plots (Fig. 28.1). They

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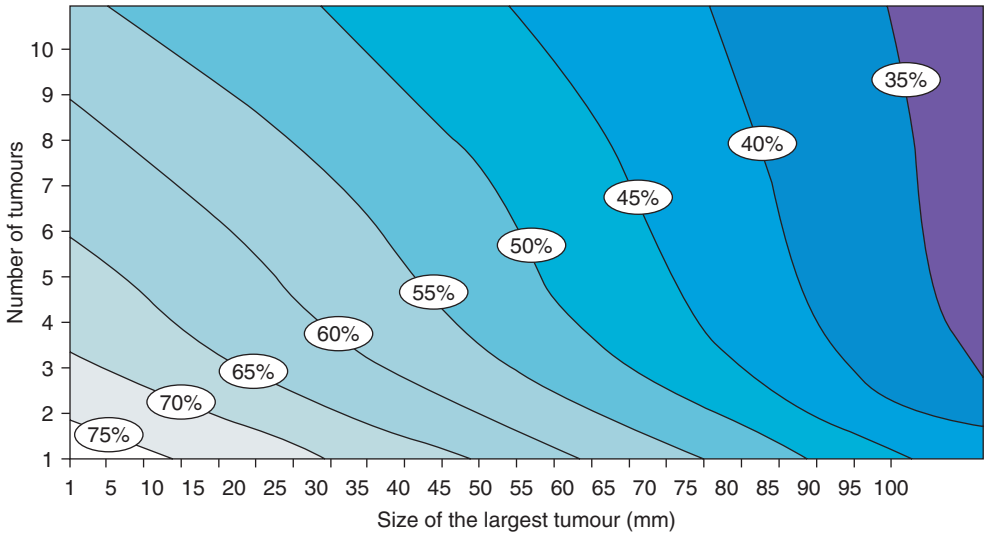

Fig. 28.1 Contour plot of the 5-year OS according to largest tumour diameter and number of tumours in patients undergoing liver transplantation for HCC. ([19], with permission)

provided a by-product tool that can calculate the 3- and 5-year OS probabilities and termed the tool as "Metroticket Calculator" because the "cost" of traveling further on the contour plot (with larger and more lesions) was decreased post-transplant survival.

28.2.2 Liver Resection, Transarterial Chemoembolization, and Ablation

Recently, the Liver Cancer Study Group of Japan and international multi-institution reported a contour prognostic model in patients undergoing resection, trans-arterial chemoembolization (TACE), and ablation. The contour prognostic model was based on the largest diameter and number of HCC (Fig. 28.2) after adjustment of covariates between the three groups (i.e., patients undergoing resection, TACE, and ablation) using inverse probability of treatment-weighted (IPTW) analyses. This finding was used to develop an online calculation tool (called Overall Survival Calculator for HCC After Resection, TACE, and Ablation). The tool is accessible at the following URL address: http://www.u-tokyo-hbp-transplant-surgery.jp/about/calculation.html. The contour prognostic model has advantages in the setting of HCC treatments. First, the diameter and number of HCC are used as indicators to select recommended treatments in the clinical practice guidelines [22, 23]. Second, the diameter and number of HCC are always available by radiological imaging before treatments and can be input in the contour prognostic model. The model showed the incremental decrease of the 5-year OS by increasing the diameter or number of HCC.

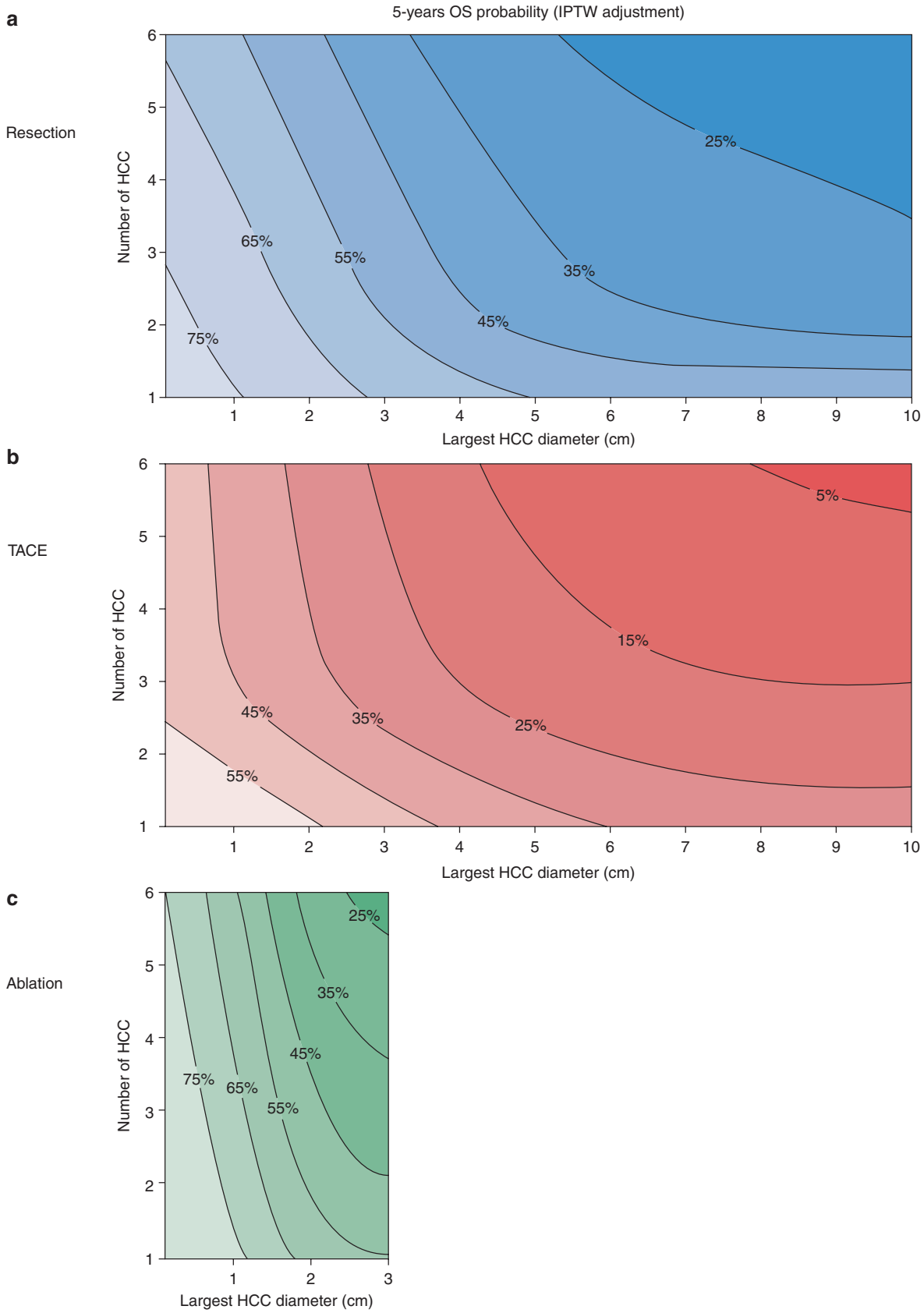

Fig. 28.2 Contour plots of the 5-year overall survival probability after the inverse probability of treatment weighting adjustment according to the largest HCC diameter and number of HCCs in patients undergoing resection (**a**), TACE (**b**), and ablation (**c**). HCC, hepatocellular carcinoma; TACE, trans-arterial chemoembolization; IPTW, inverse probability of treatment weighting ([20], with permission)

28.3 Prognostic Model for Resection of Colorectal Liver Metastases

Most prognostic models included the largest diameter and number of CLM because these factors were associated with survival in patients undergoing CLM resection [6–14, 16, 17]. It is reasonable that a larger diameter and greater number of CLM are suggestive of the spread and dissemination of cancer. However, the largest diameter and number of CLM are dichotomized around the cutoff value (e.g., number of tumours, 1 vs. ≥ 2, 1–2 vs. ≥ 3; largest tumour diameter, ≤ 5 cm vs. > 5 cm) in previous models. Dichotomization simplifies statistical analysis, but causes loss of statistical power compared with the use of continuous variables. Reported prognostic models in patients undergoing CLM resection are detailed in another chapter (Chap. 27).

28.4 Contour Prognostic Model for Resection of Colorectal Liver Metastasis: A Model Based on Continuous Number and Diameter of CLM

Our group proposed a new prognostic model termed as "a contour prognostic model." [21] Our model sought for replacing the practice of previous systems which categorize patients into risk groups with an individualized risk prediction paradigm using continuous variables. The model was developed based on a cohort including 810 patients who underwent CLM resection at MD Anderson Cancer Center and externally validated based on an international multi-institutional cohort including 673 patients who underwent CLM resection in Italy and Japan. Our model was developed in the following three steps [21].

1. A Cox proportional hazards model analysis to identify prognostic factors among 12 genetic and clinicopathological variables including largest diameter and number of CLM which were treated as continuous variables.
2. To develop a prognostic based on the largest diameter and number of CLM using three-knot restricted cubic splines [24], and diameter-by-number linear and nonlinear interaction terms.
3. To select a final prognostic model using backward selection according to the Akaike information criterion [25]. The data provided by the model were graphed using a contour plot which showed the joint effect of the largest number of CLM (the x-axis) and number of CLM (the y-axis) on 5-year OS probability.

The model development is detailed as follows.

1. A Cox proportional hazards model analysis showed that six factors were significantly associated with OS: largest diameter of CLM (continuous variable) (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.06–1.16), number of CLM (HR, 1.06; 95%CI, 1.03–1.09), *RAS* mutation vs. *RAS* wild-type (HR, 1.76; 95%CI, 1.42–2.18), age (continuous variable) (HR, 1.02; 1.01–1.03), primary lymph node metastasis (HR, 1.58; 95% CI, 1.23–2.03), and prehepatectomy chemotherapy (HR, 1.47; 95% CI, 1.04–2.08). We confirmed that the largest diameter and number of CLM as continuous variables were significantly associated with OS. Because the use of prehepatectomy chemotherapy varies widely by institution and the status of primary lymph node metastasis was not always available at the time of liver resection (e.g., simultaneous resection of synchronous primary colorectal cancer and liver metastases), these two factors were not included in the next step of the model development.
2. A prognostic model integrating the largest diameter and number of CLM and *RAS* mutation status was developed using the 3-knot restricted cubic splines together with diameter × number linear and nonlinear interaction terms because this approach improves a fit between predictors and outcomes compared with the use of linear terms alone.
3. On the basis of Akaike information criteria, the final model included a linear term for largest CLM diameter, a cubic spline for number, and the linear-by-linear interaction diameter-by-number and graphed using the contour plots (Fig. 28.3).

For example, when we group patients with *RAS* wild type by number of CLM ≤ 3 (the group with better prognosis) or not (the group with worse prognosis), we need to recognize that the 5-year OS probability of a patient group with CLM ≤ 3 widely ranges from 75% to 40% with an incremental increase of largest CLM diameter (Fig. 28.4). As such, our new contour prognostic model can avoid the underestimation of risk variation compared to the practice of categorizing risk groups and provide an individualized risk prediction based on continuous variables.

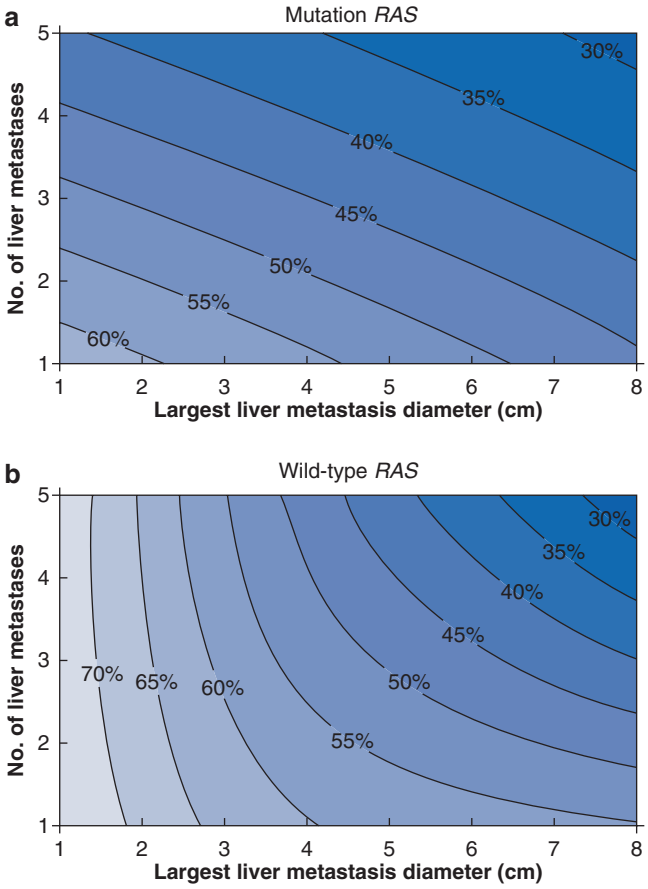

Fig. 28.3 Contour plots of 5-year OS probability based on largest diameter and number of CLM for patients with *RAS* mutation (**a**) and *RAS* wild-type (**b**). (Kawaguchi Y., et al. Contour prognostic model for predicting survival after resection of colorectal liver metastases: development and multicenter validation study using largest diameter and number of metastases with RAS mutation status. ([21], with permission)

28.5 External Validation of our Contour Prognostic Model Using an International Multi-Institution Cohort

Our contour prognostic model for patients undergoing CLM resection was validated in an international multi-institution cohort including 673 patients who underwent CLM resection at Catholic University of the Sacred Heart (Roma, Italy), University of Verona (Verona, Italy), and the University of Tokyo (Tokyo, Japan). The median duration of follow-up in the external validation cohort was 4.7 years (95% CI, 4.3–5.0 years). Figure 28.5 shows the calibration of observed versus predicted survival probabilities in this external validation cohort. The performance of the model was good, as the observed survival almost lays within a 10% margin of error around the predicted survival.

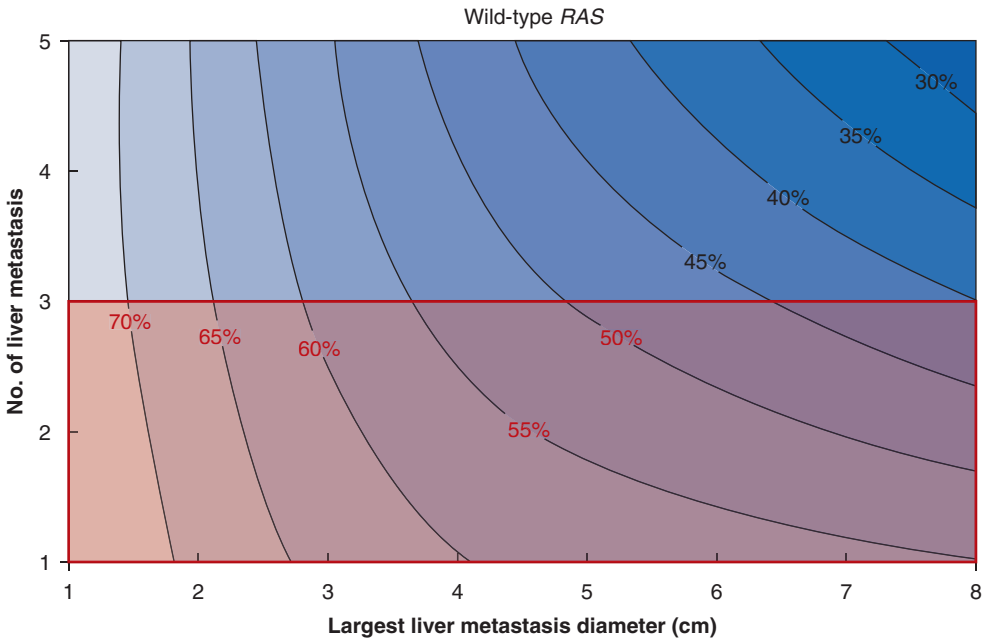

Fig. 28.4 Contour prognostic model vs. practice of categorizing risk group by cutoff value. Contour plots of the 5-year OS clearly show that the practice of categorizing risk group by cutoff value (e.g., number of CLM ≤ 3) lost the risk variation because the 5-year OS of this patient group widely ranges from 75% to 40% (the area of red square) with an incremental increase of largest diameter of CLM ([21], modified with permission)

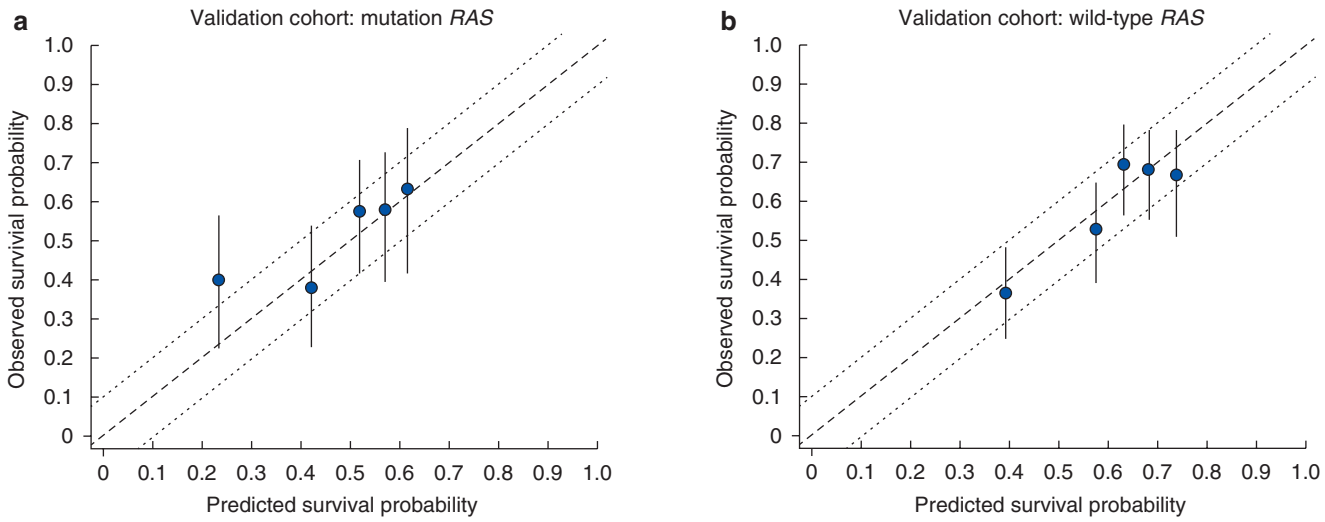

Fig. 28.5 Calibration of prognostic model by mutant and wild-type RAS in an external multi-international validation cohort. Calibration plots for mutant (**a**) and wild-type *RAS* disease (**b**) in the external validation cohort. Observed overall survival probability was measured by Kaplan–Meier analysis; error bars represent 95% CI. The dashed line represents the ideal reference line where observed survival corresponds with predicted survival, and the dotted lines indicate the 10% margin of error. ([21], modified with permission)

28.6 Conclusion

The traditional practice of assessing prognosis after resection of liver tumours is to categorize patients into several risk groups. The practice is useful for simplifying the clinical interpretation because medical care providers recognize different risk groups of patients undergoing surgery. Additionally, the practice using a cutoff of number and diameter of tumour (e.g., cutoff values of tumour number, 2 and cutoff values of the largest diameter of tumour, 3 cm) categorizes patients into four groups (i.e., groups A, number ≤ 2 and largest diameter ≤ 3 cm; group B, and number > 2 and largest diameter ≤ 3 cm). These cutoff and risk group practices cause substantial loss of statistical power and risk variation, and under−/overestimation of prognosis. We believe that our new prognostic model may replace categorization practice based on dichotomization with an individualized risk prediction paradigm.

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Conditional Recurrence-Free Survival

29

Yoshikuni Kawaguchi and Timothy E. Newhook

Learning Objectives

- Conditional survival analysis traditionally assesses overall survival stratified by a specific survival interval after surgery.
- Conditional recurrence-free survival assesses recurrence-free survival stratified by a specific interval without recurrence after surgery.
- The risk of recurrence changes over time in patients undergoing resection of colorectal liver metastases. The recurrence risk peaked approximately at 1 year after surgery.
- At the time of surgery, the 5-year recurrence-free survival was approximately 20%; however, for patients free from recurrence at 2 years, it increases approximately to 70%.

29.1 Introduction

Resection of colorectal liver metastases (CLM) remains a curative treatment option. Studies reported that 5-year overall survival (OS) after CLM resection is relatively high, ranging from 40% to 59% [1–3], whereas 5-year recurrence-free survival (RFS) after CLM resection is low, ranging from 17% to 35% [1–4]. Traditionally, survival and risk factors in patients undergoing CLM resection were assessed at the time of surgery. However, the risk of recurrence after CLM resection changes over time [3, 5]. The analyses of RFS and risks for recurrence after a predefined time without recurrence can update the changes of recurrence probability and risk factors for recurrence. The group at MD Anderson Cancer Center termed these analyses as "conditional RFS." In this chapter, we detail the assessment of conditional RFS and usefulness in clinical practice.

29.2 Conditional RFS

29.2.1 Conditional Survival and Conditional RFS

Studies reported the usefulness of conditional survival for patients who underwent resection of CLM [6, 7]. Conditional survival was traditionally defined as the probability of surviving an additional number of years for patients who have already survived a specific time interval after surgery [6], but the analysis does not take into account patients' recurrence status. Specifically, previously reported conditional survival should be clarified as conditional OS. One of the important concerns in patients undergoing curative surgery is recurrence of disease. As such, we used the concept of conditional survival for assessing recurrence (i.e., conditional RFS). To estimate recurrence-free probability changing over time, we defined conditional RFS as the recurrence-free probability after a given time interval without recurrence.

29.2.2 Changing Risk of Recurrence Over Time and Conditional RFS

In the analysis of our series [3], the risk of recurrence changes over time after CLM resection (Fig. 29.1). The peak of recurrence risk was at approximately 1 year after CLM resection. The recurrence risk decreased from 1 to 3 years, and became steadily after 4 years. The fact that the recurrence risk

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decreases with a time interval without recurrence indicates that the RFS rate is higher in patients who have a longer time interval without recurrence than in patients at the time of surgery. Indeed, the 5-year-RFS rate was 17.3% at the time of CLM resection, but it increased to 36.8% in patients free from recurrence at 1 year after CLM resection, and to 70.7% in patients free from recurrence at 2 years (Fig. 29.2). At the time of surgery, *T* stage ≥3 (hazard ratio [HR], 1.38; $p = 0.049$), extrahepatic disease (HR, 1.46; $p = 0.004$), multiple CLMs (HR, 1.27; $p = 0.029$), largest CLM diameter > 5 cm (HR, 1.78; $p = 0.049$), surgical margin (HR, 1.35; $p = 0.021$), and *RAS*/*TP53*-co-mutation (HR, 1.47; $p = 0.049$) were risk factors for RFS. However, for patients free from recurrence at 1 year after surgery, only largest CLM diameter > 5 cm (HR, 2.79; $p < 0.001$) and *RAS*/*TP53*-co-mutation (HR, 1.69; $p = 0.005$) were still risk factors. For patients free from recurrence at 2 years after surgery, *RAS*/*TP53* co-mutation (HR, 2.41; $p = 0.024$) alone was associated with a risk of recurrence. This finding implies that traditional clinicopathologic factors were risks of recurrence at the time of surgery and approximately within 1 year after surgery; however, these factors were no longer associated with recurrence in patients free from recurrence at 2 years after surgery. In contrast, biologic factors (represented by *RAS*/*TP53* co-mutation) may exert a persistent deleterious association with recurrence at least within 2 years after surgery.

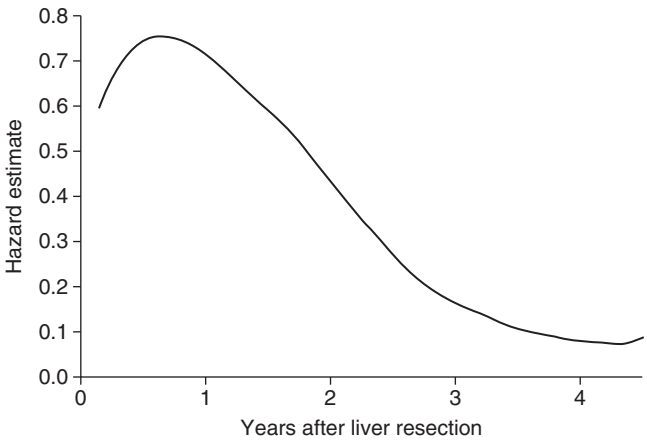

Fig. 29.1 Changing risk of recurrence over time. Changing risk of recurrence was estimated using the Kernel-smoothed hazard estimate method [11, 12]. ([3], with permission)

29.2.3 Studies of Conditional OS for CLM

Two studies reported conditional OS in patients undergoing CLM resection. Nathan, et al. showed that the 10-year OS was 22% in patients undergoing CLM resection at the time of surgery [8]. However, the 10-year OS increased to 50% in patients who survived at 5 years after surgery (this corresponds to the 5-year conditional OS estimated at 5 years after surgery). Margonis, et al. showed changes of prognostic factors in patients at the time of surgery and in patients who survived 3 years after CLM resection [9]. At the time of surgery, age, primary lymph node metastasis, extrahepatic disease, use of prehepatectomy chemotherapy, prehepatectomy carcinoembryonic antigen level, *KRAS* mutation, *BRAF* mutation, tumour number, surgical margin, and use of posthepatectomy chemotherapy were risk factors for OS. Of these risk factors, for patients who survived 3 years after CLM resection, prehepatectomy chemotherapy, *KRAS* mutation, *BRAF* mutation, and tumour number were no longer associated with OS.

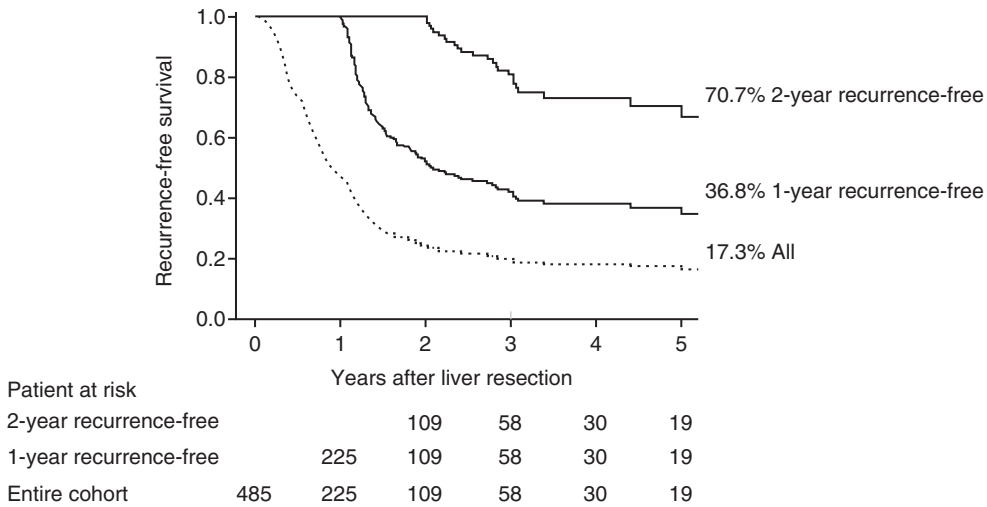

Fig. 29.2 Conditional RFS. RFS in the entire cohort, in patients free from recurrence at 1 year, and in patients free from recurrence at 2 years. ([3], with permission)

29.3 Conclusion

We may have informed patients with CLM that the recurrence rate after CLM resection was high, more than 50%. However, it is important to detail that the risk of recurrence decreases over time. If a patient visits the clinic without recurrence for 2 years after CLM resection, the probability of recurrence is half that present at the time of surgery. For example, in our recent study [3], the recurrence probability was approximately 80% at the time of surgery, but it decreases to approximately 30% in patients free from recurrence at 2 years. Conditional RFS may be useful to inform changing risks of recurrence with an interval from CLM resection and tailor surveillance frequency and intensity [10]. We believe that this information may also provide discussion for recurrence after surgical treatment to patients and health care providers.

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Repeat Hepatectomy for Colorectal Liver Metastases

30

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Learning Objectives

- To understand the rationale and principles of repeat hepatectomy.
- To evaluate the technical difficulty of repeat hepatectomy.
- To know the oncological results and main prognostic factors after repeat hepatectomy.
- To discuss the role of laparoscopy in iterative liver resection.

30.1 Introduction

The surgical odyssey of colorectal liver metastases (CLM) began in the 1980s when early reports showed that long-term survival could be obtained after resection of one or two liver metastases in selected patients [1]. Given that 5-FU was the only available chemotherapy at the time, these encouraging results provided early support for the crucial role of surgery for CLM.

Three decades later, liver resection has become the first indication of hepatectomy in western countries thanks to major improvements in systemic treatment, technical refinement of liver surgery, and molecular characterization of colorectal cancer (CRC). [2] The current management of CLM relies upon the so-called "oncosurge" approach," which associates in a sequential manner, the most efficient systemic regimen with refined surgical techniques at expert centers [3]. Despite medical and surgical improvements, the intrahepatic recurrence rate after hepatectomy remains high, even in patients with a limited and upfront resectable disease.

The management of recurrence is challenging both from an oncological and surgical point of view. Chemotherapeutical options are limited in most of these patients, who have previously received numerous cycles, and sometimes several lines of chemotherapy, thus resulting in the liver or general toxicities. Moreover, the surgical technique of re-hepatectomy is rendered more complex because of modified anatomical landmarks and hypertrophy of the remnant liver.

This chapter discusses oncological and technical aspects related to repeat hepatectomy for CLM.

30.2 Epidemiology of Recurrence After Hepatectomy

Surgical resection of CLM is associated with a high recurrence rate. Progression-free survival was 21% at 3 years in the Paul Brousse cohort [4]. In patients operated on for at least four lesions, the 3-year disease-free survival rate has been reported to be only 5%, despite modern systemic adjuvant chemotherapy [5]. The rate of recurrence also remains high in more selected patients (no more than three lesions) treated by perioperative FOLFOX with a 3-year progression-free survival of 42% [6]. At MD Anderson Cancer Center, the most favorable subset of patients (*RAS* wild type patients) experienced a recurrence-free survival (RFS) of 41% at 3 years [7]. Of 947 patients who recurred after surgical or local treatment, recurrence was confined to the liver in 43% and both extra and intrahepatic in 21% of cases [8]. *RAS* mutation was found to predict lung RFS but not liver-RFS [9].

Given the high rate of recurrence after hepatectomy for CLM, the question of repeat hepatectomy arose long before the FOLFOX/FOLFIRI era in the history of CLM treatment. The first reports of repeat hepatectomy were published at the end of the 1980s, followed by additional larger series, mentioning even cases of third hepatectomy. [10–12] These reports included highly selected patients with excellent general status and limited hepatic disease, representing less than 10% of patients who underwent a first hepatectomy and about 20% of those whose recurrence was confined to the liver.

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30.2.1 Practical Feasibility of Repeat Hepatectomy

The proportion of rehepatectomy after index hepatectomy for CLM ranged from 10% to 26% in the 1990s [12–14]. Recent reports have shown an increase in the feasibility rate of repeat resection, ranging from 14% to 50% despite a more advanced disease at the time of the first hepatectomy [15–18].

In practice, the feasibility of repeat hepatectomy is driven by technical resectability and the control of the metastatic disease. Both aspects have greatly improved over the past decades [19]. Several lines of systemic chemotherapy, targeted therapies, and molecular characterization of mCRC made it possible to control metastatic disease for a longer period. Liver surgery has gained in safety and has seen the development of mini-invasive approaches, and combined enhanced recovery programs. Combined improvements on both surgical and oncological sides likely explain the recent increased rate of repeat hepatectomy.

Concomitant extrahepatic disease (EHD) is observed at the time of liver recurrence in about 10% of patients [15, 20]. Although EHD predicts lower survival after repeat hepatectomy [13–15, 21], some recent series have shown that repeat liver surgery might be worthy in patients with pulmonary nodules controlled by chemotherapy [16, 22]. Our opinion is that the concomitant EHD, particularly pulmonary lesions, should not contra-indicate repeat hepatectomy, provided there is stabilization or response to chemotherapy.

In addition to the patient's age and its general performance status [23], the feasibility of repeat hepatectomy is governed by the location of the lesion(s) and the volume of the remnant liver and its vascular and biliary remaining structures. Peripheral lesions can be easily identified at the surface or by palpation, and sparing parenchyma hepatectomy can be achieved even without the Pringle maneuver. In contrast, deep located lesions can be difficult to find, even with intraoperative ultrasound, and require larger parenchymal resections.

The nature of the remnant liver is also crucial. The technical possibility greatly differs according to the main portal pedicle and hepatic veins and their relationship with recurrent metastases. If the previous hepatectomy has left both right and left pedicle, recurrence involving the perihilar region can still be treated by R0 resection, whereas a recurrence invading the sole remaining pedicle after major liver resection is not resectable.

Repeat hepatectomy on a two-segment-remaining liver after complex, aggressive surgery such as two-stage hepatectomy is possible (Fig. 30.1). Our group reported that among 62 patients who recurred after two-stage hepatectomy, repeat surgery was attempted in 38 patients and could be potentially curative in 31 (50%) [16]. A recent study has suggested that the feasibility of repeat hepatectomy after two-stage hepatectomy was increased after the initial laparoscopic approach compared to the open approach [24].

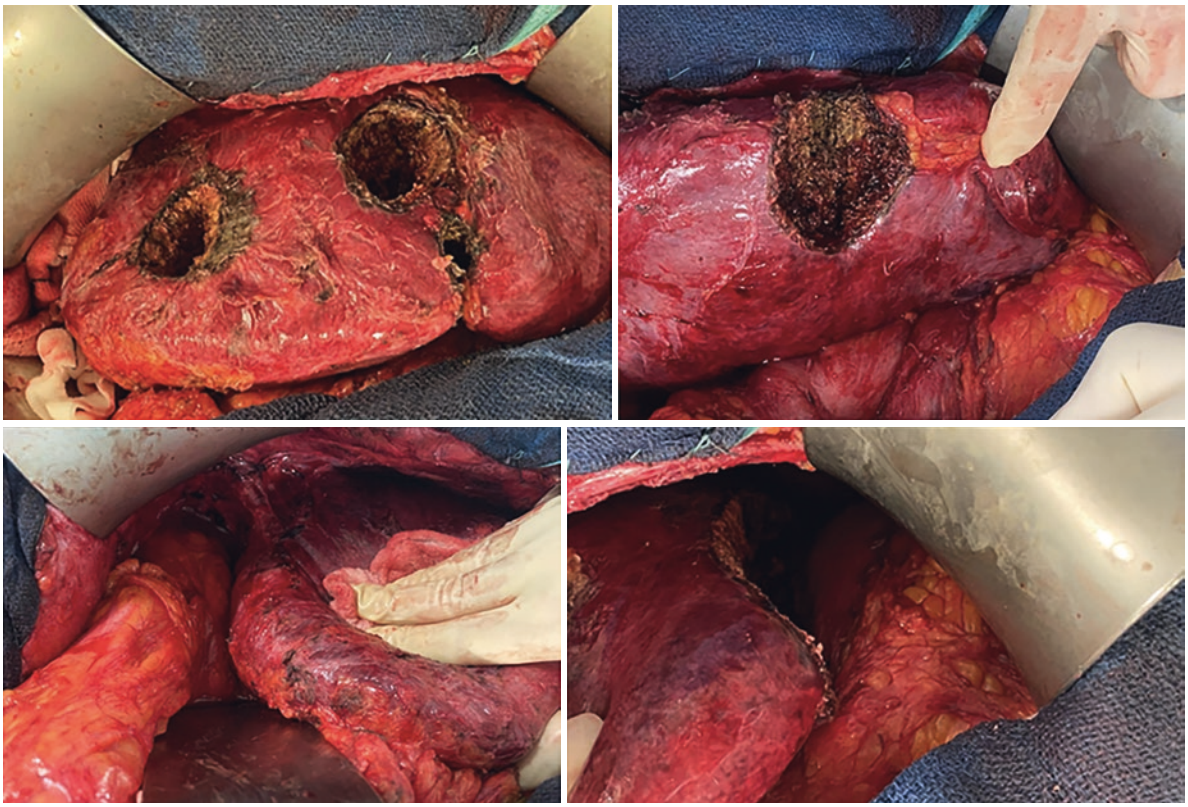


Fig. 30.1 Intraoperative view of a third hepatectomy 12 months after two-stage hepatectomy

30.3 Early and Long-Term Outcomes After Repeat Hepatectomy

There is an extensive body of literature about repeat hepatectomy consisting mainly of retrospective series and two meta-analyses [25]. These results are summarized in Table 30.1 which gives an overview of the main results from the series, including at least 100 patients, who underwent repeat hepatectomy.

The postoperative mortality remains low and compares favorably with the mortality observed after the first hepatectomy. In a meta-analysis including 22 studies, postoperative mortality after repeat hepatectomy was 1.2%. Morbidity rates were also acceptable, with a median of 23%, ranging from 12% to 71% in the same meta-analysis. The nature and the proportions of complications (biliary fistula, infected collection, hematoma, hemorrhage) remain stable across the number of hepatectomies [22].

Most of these works converge with the finding that patients undergoing repeat hepatectomy experienced better long-term outcomes compared to patients that could not undergo a second hepatectomy. In the latest meta-analysis, the median value of 5-year overall survival reported rate after the second hepatectomy was 43% (17–73%), similar to the overall survival reported after the first hepatectomy [25]. As such, repeat hepatectomy appears to reset the "oncological clock," by providing similar survival benefit as the first hepatectomy.

It could be argued that repeat hepatectomy is offered to selected patients with favorable tumour biology, thus explaining improved outcomes. No trial has ever compared repeat hepatectomy versus chemotherapy alone for resectable liver recurrence. However, the possibility to achieve re-resection at the time of recurrence has emerged as an independent factor of overall survival in several studies [15, 16, 26, 27].

The rationale of repeat hepatectomy relies on the same oncological principles underlying the first hepatectomy. The objective of hepatectomy is to remove all macroscopic visible disease, including some emerging resistant clones, whereas systemic chemotherapy aims to eradicate the microscopic disease. Repeat should be considered when complete resection of all macroscopic diseases is possible with acceptable surgical risk in patients with a stable or responsive disease under chemotherapy.

Table 30.1 Series or meta-analysis published after 2000 and including more than 100 patients undergoing repeat hepatectomy or ablation for colorectal liver metastases

Author	Study period	Country/centers	No. repeat	Mortality, %	Morbidity, %	Median OS, month	5-years overall survival from time of recurrence treatment, %
Petrowsky (2002)	1985–2001	USA-Germany, 2 centers	126	1.6	28	37	34
De Jong (2009)	1982–2008	USA, Europe, 5 centers	246	0.4	21	–	33
Adair (2012)	1993–2010	UK, Monocentric	195	1.5	20	–	29
Wicherts (2013)	1990–2010	France, monocentric	1036	3.1	34	–	54
Hallet (2017)	2006–2013	France, 39 centers	376	1.3	30.3	–	57[a]
Buisman (2020)	1992–2018	USA/Netherlands, 2 centers	374	_	_	57	47
Watanabe (2020)	2004–2015	Japan/monocentric	170	_	_	_	45[a]
Meta-analysis							
Lam (2013)	1960–2010	22 studies	1610	1.2	23 (12–57)	35 (19–56)	42 (31–73)
Wang (2019)	2000–2018	34 studies	3039	0–6	23 (8–71)	38 (19–80)	42 (17–73)

[a]Calculated from the time of first hepatectomy

30.4 Predictors of Survival After Repeat Hepatectomy

The pattern of intrahepatic recurrence has been associated with prognosis [28]. In situ recurrence, defined as either marginal or disappearing lesion after preoperative chemotherapy, seems to yield a better prognosis compared to "de novo" intrahepatic recurrence, which refers to the appearance of previously unknown liver metastases. This result is in accordance with a previous review, showing that recurrence of disappearing lesions has little impact on overall survival [29].

Several tumour-related factors associated with improved survival after repeat hepatectomy have been identified. These are not specific to repeat hepatectomy and are similar to that used for predicting outcomes after the first hepatectomy for CLM. A meta-analysis based on 34 studies (3039 patients) found that prognosis after repeat hepatectomy was governed by CEA levels, disease-free interval (<12 months vs. ≥12 months), extrahepatic disease, number of lesions (unique vs. multiple), size of lesions (<5 cm vs. ≥5 cm), and surgical margin (negative vs. positive) [25]. Response to chemotherapy which is a strong predictor before the first hepatectomy [30] is not mentioned in a series of repeat hepatectomy, likely because repeat surgery in the context of progressive disease is anecdotal.

The prognostic value of resection margin after repeat hepatectomy has been explored in several studies [15, 22, 31, 32]. Although its impact on prognosis was not significant in all series, the meta-analysis mentioned above identified resection margins at repeat hepatectomy as a predictor of survival with the highest hazard ratio [25]. These results highlight the need to achieve tumour-free margins. However, this objective remains theoretical when recurrence remains in contact with a major anatomical structure that cannot be sacrificed. An R1 resection "by necessity" may be justified based on the favorable outcomes reported after index hepatectomy [33] and the clear benefit of repeat hepatectomy on overall survival.

Not surprisingly, tumour biology also carries a major prognostic value. Recurrence-free survival is shorter in patients treated for tumours with mutations in the EGFR pathway, including *BRAF* and *RAS* genes [9]. In a series of 98 patients undergoing repeat resection, *RAS* mutation predicted overall survival after repeat surgery or ablation, independently of biological and morphological factors [34]. In another study from the same group about recurrence after two-stage hepatectomy, iterative hepatectomy was associated with better overall survival, whereas *RAS* mutation predicted worse outcomes. However, survival after repeat hepatectomy in *RAS* mutated patients remained better than in patients who did not undergo repeat resection (38% at 5-year after repeat vs. 8% at 5 years) [35].

30.5 Practical Questions Before Repeat Hepatectomy

30.5.1 Should Chemotherapy Be Given Before Repeat Hepatectomy?

This remains an open question, with no evidence. Most groups apply similar reasoning than at the time of the first resection. Favorable factors such as a single lesion occurring after a long interval from the previous hepatectomy without extrahepatic disease may be treated by upfront surgery [36]. In contrast, patients with several nodules appearing shortly after previous hepatectomy or patients with extrahepatic may benefit from chemotherapy with the rationale that previous systemic treatment and re-control of the disease will improve surgical results. Individual scenarios between these two extreme situations should be discussed at multidisciplinary meeting. The decision should take into account the chemotherapy history, its toxicity, and efficiency.

30.5.2 Diagnosis of Chemotherapy-Induced Liver Toxicity Before Repeat Hepatectomy

Most candidates for re-hepatectomy have a long history of chemotherapy, some having received several lines and numerous chemotherapy cycles. Therefore, chemotherapy-associated liver injuries should be expected before repeat hepatectomy. Two main histological and clinical entities resulting from chemotherapy toxicity have been described. Sinusoidal obstruction syndrome (SOS) is observed after a prolonged oxaliplatin-based regimen. The liver presents a typical macroscopic aspect, so-called "blue liver." Sinusoidal lesions are associated with an increased risk of intraoperative bleeding and liver failure, making it crucial for its preoperative diagnosis [37]. Some noninvasive tools are available to predict SOS. Abnormal ICG clearance or low AST/platelets ratio (APRI score) are highly suggestive of SOS [38, 39]. Preoperative diagnosis of SOS is crucial because prolonged discontinuation of oxaliplatin will help the liver function recover, given the reversible nature of SOS. Ultimately, the end stage of oxaliplatin-related lesion is known as regenerative nodular hyperplasia, which is associated with portal hypertension [40]. This condition should be suspected in the presence of indirect signs of portal hypertension such as splenomegaly, thrombocytopenia, or abnormal venous collaterals. Of note, several reports have shown that combined treatment with bevacizumab alleviates SOS [41, 42].

Steatohepatitis is the second hepatotoxic lesion induced by chemotherapy, mainly irinotecan and 5-FU in CRC [43]. Risk factors are similar to that of nonalcoholic liver fatty

disease, meaning that obese or diabetic patients are at a higher risk of developing steatohepatitis when treated with these drugs. Preoperative duration of chemotherapy (> 6 cycles) and the interval between chemotherapy and surgery (< 4 weeks) seem to increase postoperative morbidity [44, 45]. Before considering major resection, the presence of steatosis should be sought because excessive steatosis carries an almost threefold increased risk of postoperative death after major hepatectomy [46]. Steatosis can be easily detected with a low liver to spleen ratio measured on nonenhanced CT-scan phase [47].

In practice, candidates for repeat hepatectomy have often received several drugs, and histological lesions might be mixed. Therefore, a thorough assessment of the nontumoural liver with the noninvasive tools mentioned above is recommended before considering a repeat hepatectomy.

30.6 Technical Aspects of Repeat Hepatectomy

30.6.1 Surgery or Ablation

Local ablation effectively treats small lesions and preserves liver parenchyma, provided that the diameter does not exceed 2 cm. Two retrospective studies have shown that local ablation yields similar overall survival compared to repeat hepatectomy for intrahepatic CLM recurrence [48, 49]. However, local ablation was associated with shorter disease-free survival compared to repeat resection, despite smaller lesions [49]. In addition, resections of local recurrence after radiofrequency ablation carry higher morbidity and inferior survival benefit, likely explained by the tumour microenvironment favoring tumour growth and selecting aggressive clones [50]. Overall, local ablation is a valuable alternative to treat single and small recurrence, easily visualized by ultrasound or CT, and located at a distance from major vessels or biliary confluence.

30.6.2 The Technical Difficulty of Repeat Hepatectomy

The type of remnant liver, the existence of chemotherapy liver injury, and the recurrence location affect the technical difficulty of repeat hepatectomy.

Peripheral lesions represent the most favorable scenario because intraoperative localization is easier and can be guided by palpation. In addition, pedicle clamping is not imperative. In contrast, deep lesions can be difficult to find due to parenchyma remodeling and chemotherapy toxicity. Moreover, a larger surface of transection requires intermittent pedicle clamping. The aim of this section is to present technical tips to tape the hepatic pedicle safely.

After a previous hepatectomy, the hepatic pedicle is usually retracted against the inferior part of segment IV. Duodenum might also be attached to the gallbladder bed after a previous cholecystectomy. Adhesions between the portal vein and inferior vena cava with a vanishing foramen of Winslow are also possible. The risk of taping again the hepatic pedicle mainly included biliary or duodenal injury, as well as vascular injury (Figs. 30.2 and 30.3).

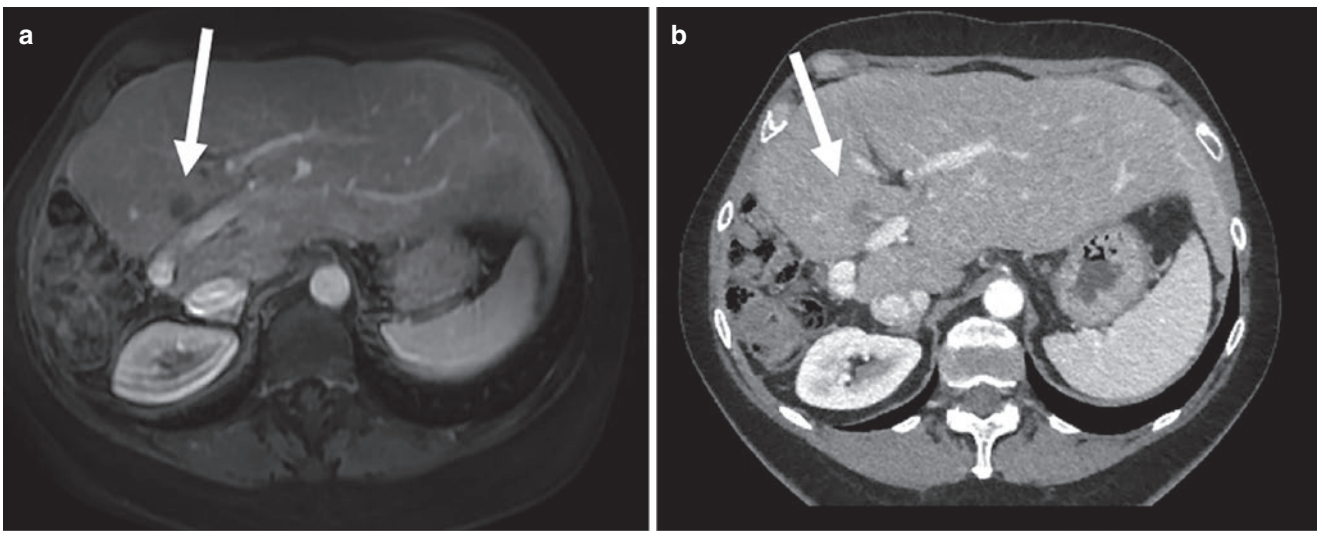


Fig. 30.2 Case illustration of problematic intrahepatic recurrence. (**a, b**) Intrahepatic recurrence in contact with the left bile duct in patient who previously underwent right hepatectomy. (**c**) Postoperative CT scan after partial hepatectomy in segment IV enabling the resection of the nodule without margins. Biliary fistula developed at postoperative day 4, but spontaneously resolved 3 weeks later. (**d**) Last CT scan (8 months after repeat hepatectomy) showing no recurrence

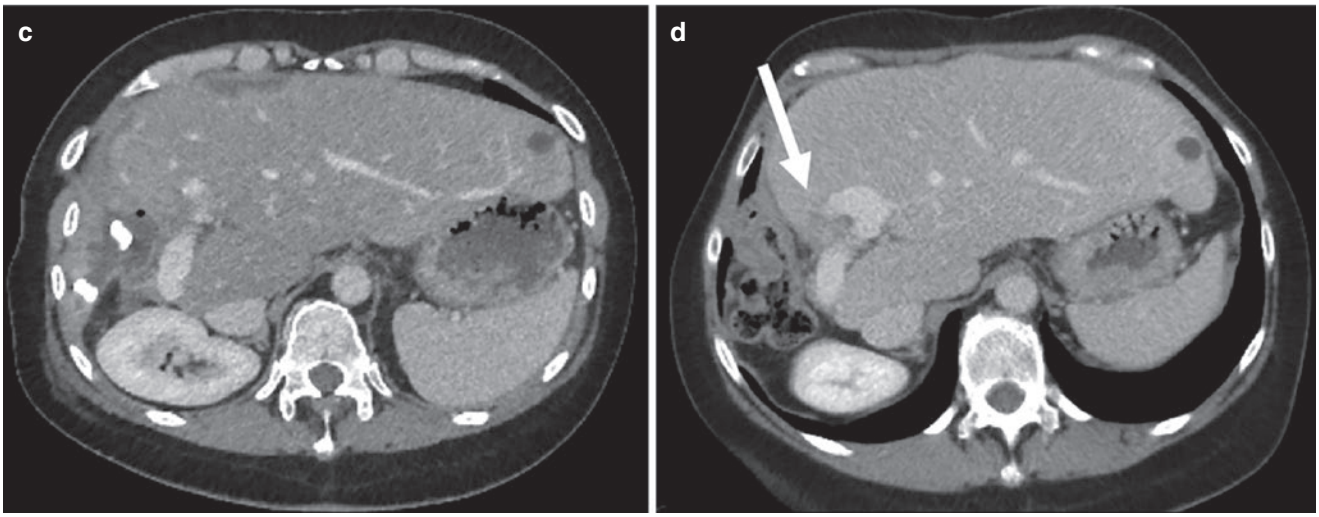


Fig. 30.2 (continued)

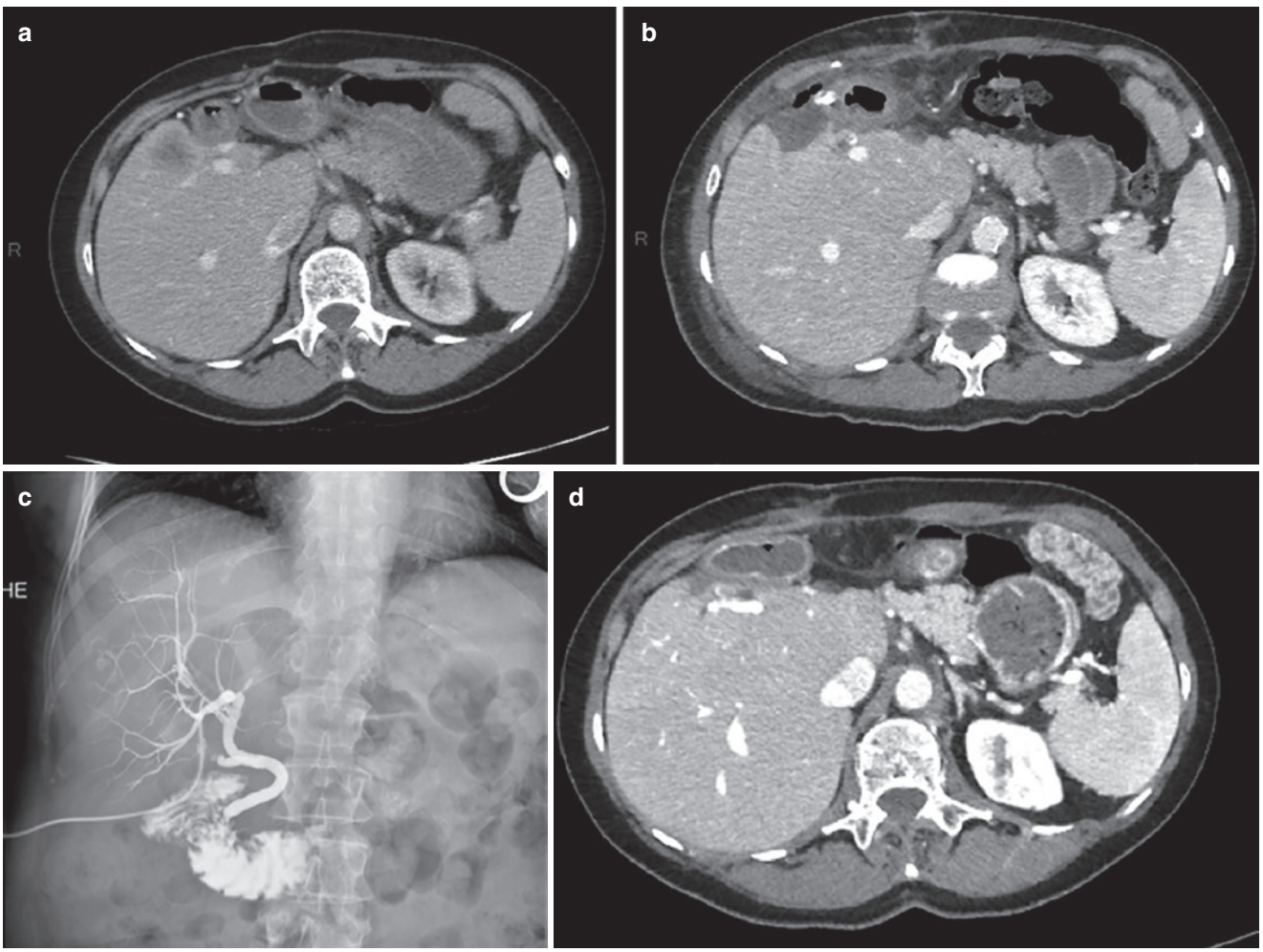


Fig. 30.3 Case illustration of intrahepatic recurrence 17 months after left hepatectomy extended to the middle hepatic vein for colorectal liver metastases. (**a**) CT scan showing intrahepatic recurrence in segment V. During repeat hepatectomy, an injury of bile of the anterior sector was made. Kehr drainage was placed intraoperatively. (**b**) Posthepatectomy CT scan showing a 2 cm collection at the site of hepatectomy. (**c**) Cholangiography before removal of T-tube drain. (**d**) Last CT scan 9 months after the second hepatectomy

A Japanese group has proposed a scoring system based on the operative videos of 66 patients undergoing repeat liver resection, focusing on the difficulty of adhesion lysis [51]. The difficulty of dissecting the hepatic hilum and liver surface is evaluated. The authors observed a correlation of their score with operative time, blood loss, and morbidity. Cholecystectomy, full mobilization of the right liver, and previous transection of segments 4 and 5 were associated with the highest degree of complexity.

30.6.3 How to "Re" Tape the Hepatic Pedicle?

To avoid injury of the duodenum, surgeons should strive to follow the dissection plane close to the liver parenchyma and to identify the duodenum that covers the common bile duct. Freeing the duodenal attachments from the liver and the common bile duct will enable to "elongate" the hepatic pedicle. At that time, dissection with scissors should be preferred to avoid thermic injury by electric coagulation. Although Intraoperative guidance with indocyanine green has been described for repeat hepatectomy in patients with hepatocellular carcinoma, the usefulness of indocyanine green for identifying the common bile duct in a previously dissected pedicle should be evaluated [52].

Finding the good plane between IVC and portal vein can be challenging, especially when portal trunk and IVC have been previously dissected. Blind dissection should be avoided as it may result in massive hemorrhage coming from IVC and portal trunk in a narrow surgical field with little possibility to place a clamp. Close contact between IVC and porta trunk should be carefully evaluated on preoperative CT scan (Fig. 30.4). A good option can be to find the right side of the IVC in an undissected area, then to pursue the dissection on the left side of the liver until finding a freeway behind the posterior part of the pedicle.

The risk of injury by controlling the pedicle should be balanced with the risk of important bleeding resulting from the parenchymal transection without clamping. The evaluation of the risk on both sides requires experience and largely contributes to the difficulty of repeat liver resection. In case of major difficulty to repeatedly dissect the hepatic pedicle, it could be wise to clamp "en bloc" the hepatic pedicle without taping it.

Several recommendations can be made to facilitate further control of the hepatic pedicle. "De principe" cholecystectomy should be avoided. The fear of ischemic cholecystitis due to intermittent pedicle clamping is unfounded and does not justify an unnecessary cholecystectomy. Intrahepatic isolation of the pedicle should be reserved for specific cases. Similarly, surgeons should refrain from the unnecessary mobilization of the liver.

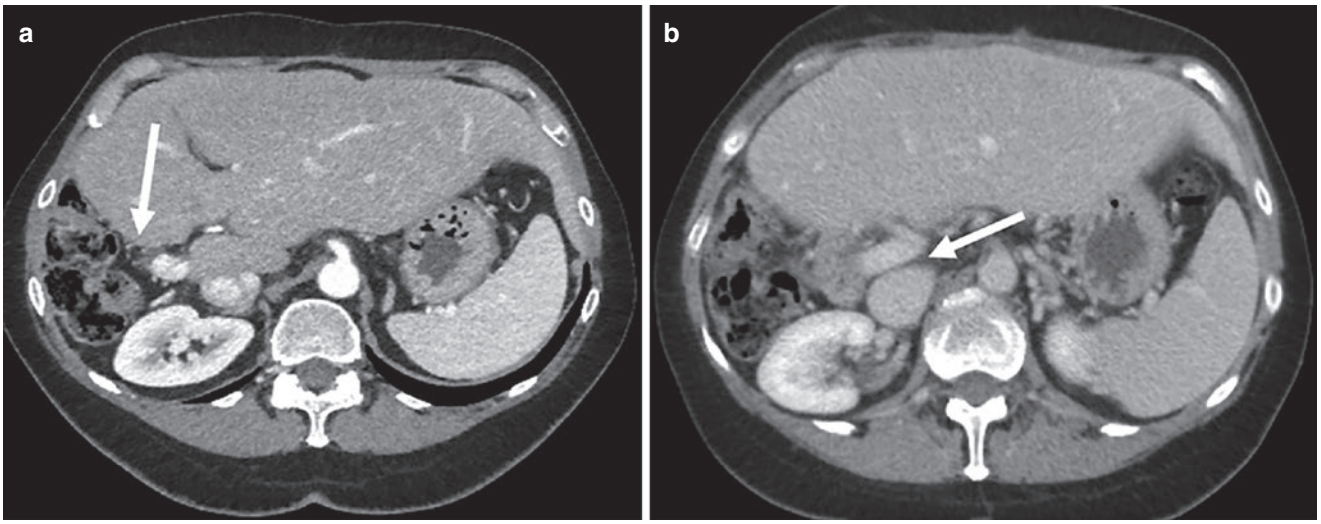


Fig. 30.4 Preoperative CT scan 2 years after right hepatectomy for colorectal liver metastases. (**a**) Close relationship between biliary confluence and the right colon. (**b**) Close relationship between portal vein and inferior vena cava

30.6.4 Laparoscopic Approach

Laparoscopy is now a validated approach to treat patients with oligometastatic disease, offering similar oncological results compared to the open approach [53, 54]. First series of repeat hepatectomy by laparoscopy have been published one decade ago, showing the technical feasibility of repeat hepatectomy by laparoscopy even after major liver resection by laparotomy [18, 55, 56].

A multicentric retrospective study has compared open (n = 164) versus laparoscopic (n = 271) repeat hepatectomy to treat intrahepatic CLM recurrence [57]. After matching on confounding, it appears that laparoscopy was associated with less blood loss, shorter duration of the operation, and shorter hospital stay, with similar oncological results. However, these findings only apply to patients with very few lesions, and the low proportion of portal clamping (14% in the laparoscopic resection group) suggests that repeat hepatectomy was mainly indicated to treat peripheral lesions.

Favorable results of repeat laparoscopic hepatectomy were confirmed by a recent meta-analysis, although the emphasis was made on the fact that this approach has been applied mainly to highly selected patients [58].

Optimal trocar placement following the triangulation principle should be anticipated by considering the modification of liver anatomy secondary to previous resection and the subsequent hypertrophy of the remnant liver. Pneumoperitoneum may also facilitate the section of adhesions around the liver and the mobilization of the liver necessary to achieve adequate resection. Most agree that slow progression or impossibility to localize the target lesion should prompt conversion and that laparoscopy is not a goal per se but a technique aiming to meet oncological imperatives.

30.7 After Repeat Hepatectomy

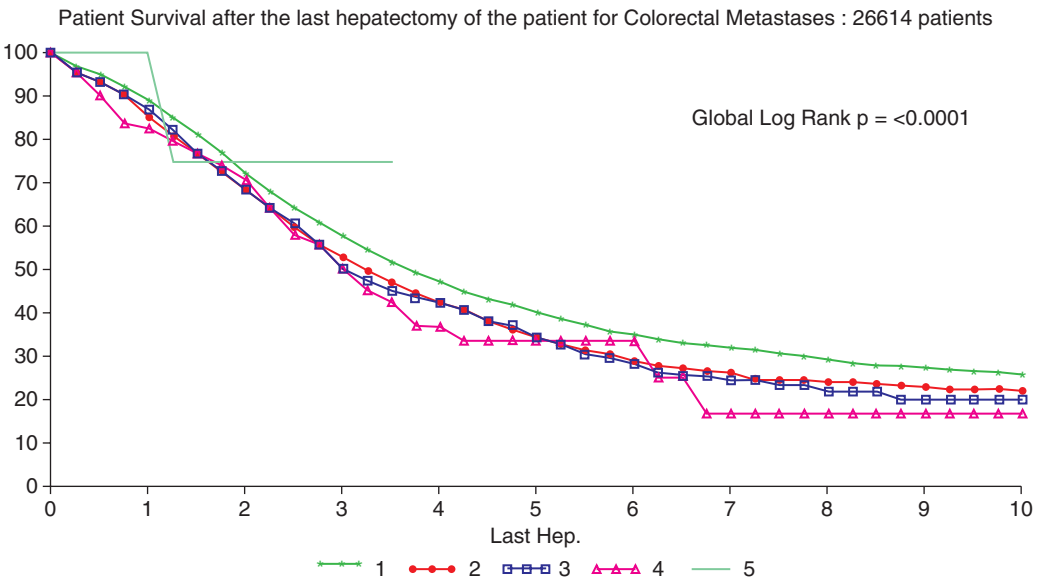
There is no evidence with regard to adjuvant chemotherapy after repeat hepatectomy. A major or complete pathological response may argue in favor of continuing preoperative chemotherapy, although this reasoning is not based on any factual data. Decisions are often taken on a case-by-case basis, considering the previous treatment administered, its toxicities, and efficiency. A bicentric study from the United States has shown that hepatic arterial infusion (HAI) after repeat hepatectomy was associated with better overall survival and hepatic disease-free survival compared to systemic chemotherapy, despite a higher number of nodules in the group treated by HAI [59]. This finding is in line with a previous report showing that adjuvant oxaliplatin HAI after the first hepatectomy for at least four CLM, offers better disease-free survival [5].

Recurrence after repeat hepatectomy is common and occurred mainly within the first 2 years. A recent bicentric study found that without adjuvant treatment, the median hepatic-disease-free survival after repeat hepatectomy for a single intrahepatic nodule in most patients was 18 months only [59]. Our group reported that 78% of patients developed a recurrence following a second hepatectomy, which involved the liver in 58% of cases [60]. We considered a third hepatectomy in patients with a resectable liver disease without the unresectable extrahepatic disease. The overall survival rate at 5 years from the third resection was 32% but reach 60% when survival time was calculated from the first hepatectomy.

Results from the *LiverMetSurvey* registry involving 26,672 patients are in accordance with previous reports. Kaplan-Meier overall survival curves since the first hepatectomy according to the number of hepatectomies are shown in Fig. 30.5. Survival probability rates correlate with the number of hepatectomies, with a 5-year overall survival increasing from 40% after a single hepatectomy to 82% after four hepatectomies.

This result underlines that long-term outcomes of patients that cannot be cured after the first hepatectomy directly rely on the possibility of achieving repeat hepatectomy.

a



Details : Log rank p

		proba
1	2	<0.0001
1	3	0.005
1	4	0.17
1	5	0.8
2	3	0.77
2	4	0.72
2	5	0.98
3	4	0.84
3	5	0.99
4	5	0.88

Survival %

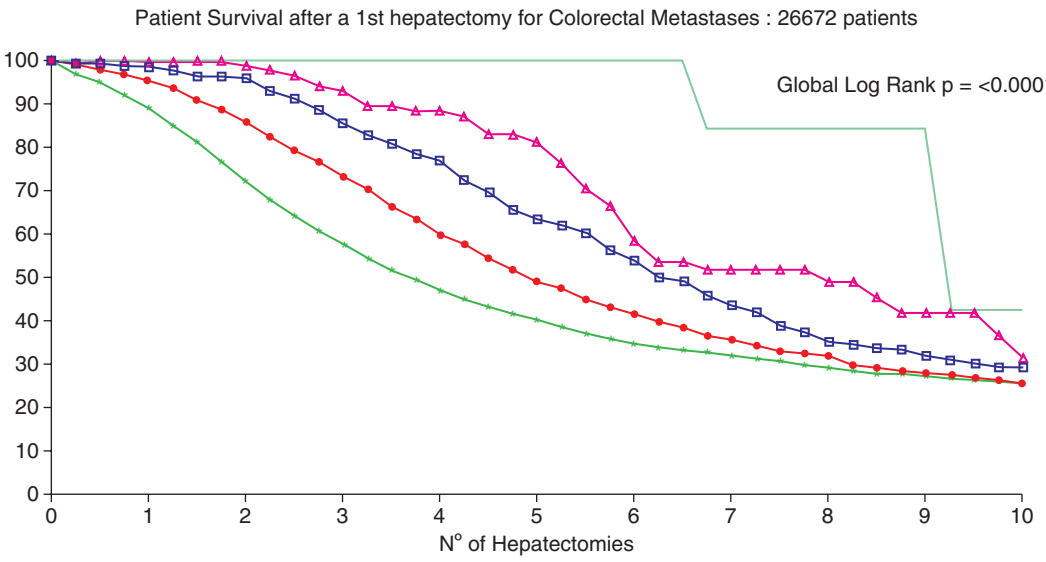
Last Hep.	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1	89%	72%	58%	47%	40%	35%	32%	29%	27%	26%
2	85%	68%	53%	43%	34%	29%	26%	24%	23%	22%
3	87%	69%	51%	42%	34%	28%	24%	22%	20%	20%
4	83%	71%	50%	37%	34%	34%	17%	17%	17%	17%
5	100%	75%	75%							

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1	22438	14431	9782	6511	4342	2999	2086	1539	1126	809	595
2	3522	2149	1437	896	596	400	246	171	127	96	65
3	553	354	231	133	92	57	33	24	13	10	8
4	92	59	41	22	11	8	4	2	2	2	2
5	9	4	2	1	0	0	0	0	0	0	0

Fig. 30.5 (**a**) Kaplan Meier overall survival from the time of the last hepatectomy, according to the number of hepatectomies, in the LiverMetsurvey registry cohort. (**b**) Kaplan Meier overall survival from the time of the first hepatectomy, according to the number of hepatectomies, in the LiverMetsurvey registry cohort

b



Details : Log rank p

		proba
1	2	<0.0001
1	3	<0.0001
1	4	<0.0001
1	5	0.008
2	3	<0.0001
2	4	0.0001
2	5	0.014
3	4	0.066
3	5	0.041
4	5	0.1

N° of Hepatectomies	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1	89%	72%	58%	47%	40%	35%	32%	29%	27%	26%
2	96%	86%	74%	60%	49%	41%	36%	32%	28%	26%
3	99%	96%	86%	77%	63%	54%	44%	35%	32%	29%
4	100%	99%	93%	89%	82%	59%	52%	49%	42%	31%
5	100%	100%	100%	100%	100%	100%	85%	85%	85%	42%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1	22438	14431	9782	6511	4342	2999	2086	1539	1126	809	595
2	3571	3068	2358	1707	1138	761	519	365	259	184	130
3	559	542	478	386	292	202	138	96	62	43	28
4	93	93	92	81	70	60	35	26	17	9	6
5	11	10	10	9	8	8	7	4	3	2	1

Fig. 30.5 (continued)

30.8 Sparing Parenchyma Policy: A Key Factor of the Strategy

The ability to achieve repeat curative resection is the cornerstone of the onco-surgical approach, thus enabling excellent long-term outcomes. This is the rationale for the sparing parenchyma policy, which aims to maintain as long as possible a high rate of feasibility for repeat hepatectomy by avoiding unnecessary sacrifices of major vascular and biliary structures. The relevance of this approach is supported by two studies showing that the feasibility of repeat hepatectomy was much lower when intrahepatic recurrence occurred after major hepatectomy because of anatomical constraints [61, 62]., thus resulting in poorer survival after recurrence. Preservation of parenchyma as much as possible makes it easier to treat intrahepatic recurrence and to "keep control" of the metastatic disease.

This has logically led to the concept of time to surgical failure, that is, the time from the first hepatectomy until the date of recurrence that is definitely beyond potentially curative therapies (local ablation or resection). The time to surgical failure proved to be more predictive of overall survival by filling the gap between disease-free survival and overall survival and was therefore proposed as a new endpoint in surgical studies about CLM [63].

30.9 Conclusion

By enabling to "reset the clock," repeat hepatectomy is a crucial component of the onco-surgical approach currently used to treat CLM patients. Cumulative evidence has demonstrated the safety, feasibility, and survival benefit of repeat hepatectomy. Allowing subsequent resection of new liver metastases should be integrated into the initial surgical

treatment strategy. Unnecessary surgical maneuvers during index hepatectomy should be avoided. A thorough evaluation of the nontumoural liver is advocated given the long history of chemotherapy of these patients in order to optimize the oncological objective and the safety of repeat hepatectomy.

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Part III

Systemic and Regional Therapy

Initial Systemic Chemotherapy for Metastatic Colorectal Cancer

31

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Learning Objectives

- To understand the landscape of treatments for initial treatment of metastatic colorectal cancer.
- To appreciate opportunities to integrate molecular and clinical biomarkers into treatment selection.
- To understand treatment tolerance and efficacy for various treatment regimens.

31.1 Introduction

Colorectal cancer (CRC) continues to remain the third leading cause of cancer-related death among both men and women in the United States. In 2021, there will be 149,500 new cases of CRC and 52,908 related deaths [1]. Globally, CRC accounts for 10.2% of all cancer cases and 9.2% of all cancer-related mortality [2]. CRCs are characterized by a number of molecular alterations that may contribute to malignant transformation. Notably, 80% of cases are sporadic, while 15% to 20% are familial and 5% are considered genetic or linked to specific genetic syndromes [3]. In recent years, a trend has been observed for an increasing incidence of early onset CRC age < 50 years; the median age of onset at diagnosis has decreased from 72 years during 2001–2002 to 66 years during 2015–2016 [4, 5]. Stage at diagnosis remains one of the most important predictors of overall outcomes; 5-year survival rate is over 90% for localized disease, but decreases to 14% for patients with metastatic disease [6]. One-fifth of CRC patients are diagnosed with synchronous metastases, and up to 70% of patients will develop metastatic disease during their disease course [7]. The liver, lung, and peritoneum remain the most common sites for metastases [8]. In a Surveillance, Epidemiology, and End Results database analysis of over 26,000 patients with stage IV colon adenocarcinoma, 73.6% of patients had hepatic involvement; of these patients, 54% were limited to the liver [9].

Improved surgical techniques, tailoring of systemic therapies based on molecular profiling, and multidisciplinary management of oligometastastic disease have led to advances in patient outcomes [3, 10, 11]. The management of liver metastases requires a multidisciplinary team including medical oncology, hepatobiliary surgery, colorectal surgery, interventional radiology, and radiation oncology. The decision-making process is complex, taking into account patients' comorbidities, performance status, presence of in-situ primary tumour, tumour biology, and molecular profile. There is no standard sequencing of perioperative systemic therapy, surgery, and other liver-directed therapies. One commonly adopted treatment strategy for patients involves administering neoadjuvant systemic therapy followed by surgical resection, and consideration of further subsequent adjuvant therapy. This chapter will focus on the first-line systemic treatment of metastatic CRC (mCRC), highlighting pertinent issues related to liver metastases.

31.2 Fluoropyrimidines: Backbone of Chemotherapy in Colorectal Cancer

31.2.1 Bolus and Infusional Fluorouracil, Capecitabine

Fluoropyrimidines, including 5-fluorouracil (5-FU) and capecitabine, make up the integral backbone of first-line therapy in the treatment of mCRC. In 1957, use on 5-FU was first published and led to objective response rates (ORR) in the range of 10–15% in mCRC; a consistent overall survival (OS) benefit was not observed. The mechanism of cytotoxicity is due to inhibition of thymidylate synthetase, and ultimately DNA synthesis. This is summarized in Table 31.1, in addition to other commonly used systemic therapy agents in mCRC. Leucovorin, also known as folinic

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Table 31.1 Summary of systemic therapy agents used in the first-line treatment of colorectal cancer [66]

Drug	Mechanism of action	Adverse reactions	Notes
Fluorouracil	Antimetabolite; pyrimidine analog antimetabolite to inhibit DNA and RNA synthesis	Myelosuppression, diarrhea, stomatitis Rare: Cardiotoxicity	Dihydropyrimidine dehydrogenase deficiency (DPD) can be present
Capecitabine	Antimetabolite; pyrimidine analog antimetabolite to inhibit DNA and RNA synthesis	Myelosuppression, hand-foot syndrome, diarrhea, nausea/vomiting, stomatitis Serious: Cardiotoxicity	Oral prodrug of fluorouracil
Oxaliplatin	Alkylator; platinum analog that inhibits DNA synthesis by cross-linking of DNA molecules	Myelosuppression, peripheral sensory neuropathy, pharyngolaryngealdysthesia	Associated with sinusoidal obstruction syndrome
Irinotecan	Topoisomerase I inhibitor; interferes with DNA replication by binding to topoisomerase I-DNA complex	Myelosuppression, diarrhea, cholinergic syndrome	Associated with hepatic steatosis Reduce dose for homozygous UGT1A1*28 allele
Bevacizumab	Anti-VEGF; recombinant humanized monoclonal antibody that binds VEGF to reduce tumour vascularization to inhibit growth	Hypertension, arterial thromboembolism, wound healing complications, proteinuria Serious: Arterial thromboembolism, gastrointestinal fistula or perforation, hemorrhage	Caution with those with in-situ primary tumours
Cetuximab	Anti-EGFR; recombinant chimeric monoclonal antibody that binds to EGFR to block EGFR signaling cascade	Infusion reactions, acneiform rash, nail changes, diarrhea, hypomagnesemia Serious: Interstitial lung disease	
Panitumumab	Anti-EGFR; recombinant human monoclonal antibody that binds to EGFR to block EGFR signaling cascade	Infusion reactions, acneiform rash, nail changes, diarrhea, hypomagnesemia Serious: Interstitial lung disease	
Pembrolizumab	Anti-PD-1; blocks PD-1 receptors on antigen presenting cells to reactivate anti-tumour immunity	Immune related adverse events including endocrine abnormalities, diarrhea, pneumonitis, rash	

acid, forms a stable ternary complex with thymidylate synthetase which leads to enhanced inhibition of the enzyme by 5-FU. Poon et al. showed that the addition of low dose leucovorin to a 5-day 5-FU bolus regimen administered every 4–5 weeks, also known as the Mayo regimen, increased OS from 7.7 to 12.0 months [12]. The Roswell Park regimen was comprised of weekly bolus 5-FU plus leucovorin, and the original trial did not demonstrate a difference in ORR and OS comparing high versus low dose leucovorin [13]. The de Gramont regimen, consisting of short-term infusional 5-FU/leucovorin, was associated with improved disease-free survival (DFS) compared to the Mayo regimen (27.6 vs. 22 weeks, $p = 0.0012$); rates of neutropenia, diarrhea, and mucositis were also lower [14]. If monotherapy 5-FU therapy is selected, infusional 5-FU is preferred. One clinical scenario where bolus 5-FU may be favored is the rechallenge of fluoropyrimidine therapy with coronary vasospasm; bolus 5-FU is associated with a decreased incidence of cardiotoxicity [15].

Capecitabine is an oral prodrug that is converted to 5-FU by thymidine phosphorylase. It was shown to have similar OS compared to bolus 5-FU/leucovorin in two large randomized trials, in the first-line mCRC setting [16, 17]. Regarding its toxicity profile, capecitabine is associated with a lower incidence of mucositis and neutropenia, whereas 5-FU was linked to a lower rate of grade 3/4 hyperbilirubinemia and hand-foot syndrome [16, 17].

31.2.2 Oxaliplatin-Based Doublet Chemotherapy

Efforts to improve fluoropyrimidine monotherapy led to landmark studies for doublet chemotherapy regimens, including FOLFOX which consists of 5-FU/leucovorin and oxaliplatin. In a phase III trial, 420 previously untreated mCRC patients were randomized to the LV5FU2 regimen (de Gramont short term infusional 5-FU/leucovorin) with or without oxaliplatin [18]. The oxaliplatin combination therapy was associated with an improvement in ORR (50.7% vs. 22.3%) and PFS (9.0 vs. 6.2 months, $p = 0.0003$), but no improvement in OS was observed (16.2 vs. 14.7 months, $p = 0.12$) [19]. The combination was associated with higher grade 3/4 toxicities including diarrhea, neutropenia, and peripheral neuropathy. The US Intergroup trial N9741 compared FOLFOX, irinotecan/oxaliplatin (IROX), and weekly bolus 5-FU/leucovorin/irinotecan (IFL) and established FOLFOX as the superior regimen for ORR, time to progression, and OS of 19.5 months [20]. This study paved the way for the approval of FOLFOX by the U.S. Food and Drug Administration for treatment of previously untreated mCRC patients. There have been variations in dosing for oxaliplatin-based chemotherapy, including FOLFOX4, FOLFOX6, modified FOLFOX6, FOLFOX7, and modified FOLFOX7 [20–24]; these regimens have not been compared head-to-head for efficacy but

modified FOLFOX6 is the most commonly prescribed in the United States.

CAPOX, also known as XELOX, replaces infusional 5-FU/leucovorin with capecitabine and is administered as 3-week cycles. Multiple phase II/III trials including TREE-1, NO16966, AIO Colorectal Study, and the Spanish Cooperative Group have demonstrated similar survival outcomes between CAPOX and FOLFOX [25–28]. However, there are differences in toxicity profiles between 5-FU and capecitabine, and the oxaliplatin dosing is higher with CAPOX due to every 3-week administration. CAPOX is an alternative regimen to FOLFOX (ref NCCN guidelines), and may be preferred in scenarios where an implanted port device and the use of an infusional pump are not desired. In a large US study evaluating first-line systemic therapy prescribing patterns for mCRC, FOLFOX remains the most commonly used first-line regimen at 70% in 2011 [29].

31.2.3 Irinotecan-Based Doublet Chemotherapy

The alternative first-line doublet regimen is FOLFIRI, composed of 5-FU/leucovorin and irinotecan. In the landmark trial by Douillard et al., FOLFIRI combination therapy compared to 5-FU/leucovorin alone was shown to improve ORR (49% vs. 31%), time to progression (6.7 vs. 4.4 months, $p < 0.001$), and OS (17.4 vs. 14.1 months, $p = 0.031$) [30]. The Irinotecan Study group trial evaluated three arms: weekly 5-FU/leucovorin and irinotecan; weekly 5-FU/leucovorin; and irinotecan alone [31]. The 5-FU/leucovorin and irinotecan arm had higher PFS, ORR, and OS whereas the irinotecan monotherapy arm performed similarly to the 5-FU monotherapy arm. In the EORTC 40986 study, the addition of irinotecan to weekly infusional 5-FU/leucovorin also improved PFS and ORR, although the improvement in median OS was not significant [32].

The combination of irinotecan and capecitabine (CAPIRI or XELIRI) is not routinely administered in place of FOLFIRI due to overlapping concerns of gastrointestinal toxicity between the two agents. The BICC-C study evaluated the three different irinotecan-based regimens, and although there was no difference in OS, the capecitabine plus irinotecan arm was associated with the highest rates of grade 3–4 gastrointestinal toxicities and dehydration [33].

Both oxaliplatin- and irinotecan-based chemotherapy continue to be used as first-line therapy for mCRC as they have shown to improve survival and choice of treatment can be determined by treating oncologists based on patient comorbidities and differences in overall toxicity profiles. Furthermore, prior receipt of adjuvant oxaliplatin-based chemotherapy in patients with metachronous metastases, duration of disease-free interval, and presence of residual neuropathy must be taken into consideration. A head-to-head comparison between FOLFIRI and FOLFOX4 showed no difference in response rates, time to progression, and OS (15 vs. 14 months, $p = 0.28$) [34]. For sequencing between the two regimens, Tournigand et al. evaluated patients who received FOLFIRI then FOLFOX6 versus FOLFOX6 then FOLFIRI; there was no significant difference in overall median OS [21].

31.3 Doublet Chemotherapy Combinations with Biologics

The incorporation of biologics into the first-line therapy of mCRC further enhanced outcomes among patients with mCRC. The decision between the addition of bevacizumab versus cetuximab or panitumumab to the chemotherapy backbone depends on multiple factors, including *RAS* and *BRAF* status, tumour sidedness, presence of primary tumour in-situ, and whether liver metastases are deemed initially resectable. Supporting data are summarized in the section *Approach to Current First-line Metastatic Colorectal Regimens*.

31.3.1 Anti-VEGF Therapy: Bevacizumab

Bevacizumab is a recombinant, humanized antivascular endothelial growth factor (anti-VEGF) monoclonal antibody that inhibits tumour angiogenesis. Hurwitz et al. demonstrated that the addition of bevacizumab to IFL led to a significant improvement in OS (20.3 vs. 15.6 months, HR 0.66, $p < 0.001$), PFS (10.6 vs. 6.2 months, HR 0.54, $p < 0.001$), and response rates (44.8% vs. 34.8%, $p = 0.004$) compared to IFL alone [35]. The addition of bevacizumab to oxaliplatin-based therapy is supported by the NO16966 trial which showed a benefit in PFS (9.4 vs. 8.0 months, HR 0.83, $p = 0.0023$), but not OS (21.3 vs. 19.9 months, HR 0.89, $p = 0.077$). In a pooled analysis of seven trials that included over 3700 patients, the addition of bevacizumab to chemotherapy was associated with increased OS (HR 0.80, $p < 0.0001$) and PFS (HR 0.57, $p < 0.0001$) [36]. This benefit was seen regardless of chemotherapy backbone, although the benefit seemed to favor irinotecan (HR 0.71) compared to oxaliplatin (HR 0.87) regimens. In the BECOME study comprised of Asian patients with *RAS* mutated mCRC with unresectable liver metastases, the addition of bevacizumab to mFOLFOX6 led to higher ORR (54.5% vs. 36.7%, $p < 0.01$), PFS (9.5 vs. 5.6 months, $p < 0.01$), and OS (25.7 vs. 20.5 months, $p = 0.03$) [37]. This highlights the importance of molecular profiling, as earlier studies did not identify the important predictive factor of *RAS* mutational status.

31.3.2 Anti-EGFR Therapy: Cetuximab and Panitumumab

Agents targeting the epidermal growth factor receptor (EGFR) and its downstream signaling cascade include cetuximab and panitumumab. EGFR is a receptor tyrosine kinase that belongs to the ErbB receptor family, which plays an important role in colorectal cancer progression. KRAS is a GTPase transductor protein encoded by Kirsten rat sarcoma viral oncogene homolog (*KRAS*) that is an essential component of the EGFR signaling cascade of extracellular growth signals. It is now recognized that KRAS and NRAS mutation testing is important for predicting resistance to anti-EGFR therapy, and mutations are present in 55% of mCRC patients [3].

In the CRYSTAL trial, mCRC patients were randomized to FOLFIRI with or without cetuximab. Patients in the treatment arm showed a modest improvement in PFS (8.9 vs. 8.0 months, HR 0.85, $p = 0.048$) and not OS (HR 0.93, $p = 0.31$) [38]. In a subsequent analysis which evaluated *KRAS* wild type patients only, OS benefit was demonstrated with the addition of cetuximab (23.5 vs. 20.0 months, HR 0.796, $p = 0.0093$) [39]. The PRIME study randomized patients to FOLFOX with or without panitumumab, and the panitumumab cohort was associated with improved PFS (9.6 vs. 8.0 months, HR 0.80, $p = 0.02$) in *KRAS* wild type patients [40]. A detrimental OS effect was observed for *KRAS* exon 2 mutated tumours that were treated with panitumumab; in a subsequent report, inferior outcomes were also seen in those with extended RAS mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2, 3, and 4 [41]. In current practice, cetuximab and panitumumab are interchangeable; as panitumumab is a humanized monoclonal antibody, it is associated with lower rates of infusion reactions with a longer half-life, although these differences are considered modest.

The toxicity profiles between bevacizumab and anti-EGFR therapy also differ significantly. Bevacizumab is associated with hypertension, thromboembolic events, wound healing complications, proteinuria, bleeding, and risk of gastrointestinal fistulation and perforation [35]. Therefore, it is generally avoided for a minimum of 4 weeks perioperatively; furthermore, precaution is taken when the primary tumour is in-situ, due to the risk of obstruction. Anti-EGFR therapy is associated with manageable dermatologic toxicity [42], which is managed pre-emptively with topical antibiotics and corticosteroids, as well as oral antibiotics [43].

31.4 Triplet Chemotherapy

Triplet chemotherapy consists of the combination of 5-FU, oxaliplatin, and irinotecan, collectively known as FOLFOXIRI. In practice, triplet chemotherapy regimens may be considered for patients with good performance status with aggressive tumours, which may include those with *RAS* or *BRAF V600E* mutations, poorly differentiated or signet ring histology, right sidedness, and a high disease burden at risk of organ dysfunction.

The TRIBE study evaluated FOLFOXIRI/bevacizumab compared to FOLFIRI/bevacizumab for 6 months followed by maintenance 5-FU/bevacizumab. This led to improvements in OS (29.8 vs. 25.8 months, HR 0.80, $p = 0.03$) [44]. The TRIBE2 study evaluated the efficacy of upfront FOLFOXIRI/bevacizumab and reintroduction after progression versus sequential FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab in the treatment of patients with metastatic colorectal cancer. The triplet arm was associated with an improved primary endpoint of PFS 2 (19.2 vs. 16.4 months, HR 0.74, $p = 0.0005$) defined as time from randomization to disease progression or death on any treatment administered after first disease progression [45].

The addition of bevacizumab and anti-EGFR therapy to the triplet backbone has been explored in multiple trials. A propensity-matched retrospective analysis of five phase II/III trials including Valentino, TRIBE, TRIBE2, STEAM, and CHARTA comparing FOLFOXIRI/bevacizumab versus FOLFOX/panitumumab showed similar PFS (13.3 vs. 11.4 months, adjusted HR 0.82, $p = 0.11$) and OS (33.1 vs. 30.3 months, adjust HR 0.80, $p = 0.14$) [46]. Rates of neutropenia were higher in the triplet group (48% vs. 26%, $p = 0.03$), but febrile neutropenia rates were similar (6% vs. 3%, $p = 0.24$). The addition of anti-EGFR therapy to triplet chemotherapy is supported by the phase II VOLFI study where the addition of panitumumab increased the ORR (87% vs. 60%, OR 4.47, $p = 0.004$) in patients with *RAS* wild type disease (PMID: 31609637). Results from PANIRINOX and TRIPLETE are pending; they are ongoing studies comparing FOLFOXIRI/panitumumab compared to FOLFOX/panitumumab [47, 48].

31.5 Approach to Current First-Line Metastatic Colorectal Regimens

Although the treatment paradigm of metastatic colorectal cancer in the first-line setting has seen modifications in the past decade, the backbone has remained unchanged. With the increasing use of next generation sequencing technology, the field moves toward a personalized biomarker-driven approach. Guidelines now have adopted treatment strategies incorporating *RAS*, *BRAF*, mismatch repair (MMR) status, and tumour sidedness. The approach to choosing a first-line regimen is summarized in Table 31.2.

Table 31.2 Approach to first-line systemic therapy, according to molecular profile and tumour sidedness

Microsatellite stable, RAS/BRAF wild type, left-sided
• Doublet or triplet chemotherapy + anti-EGFR therapy, unless resectable liver metastases then consider bevacizumab
Microsatellite stable, RAS/BRAF wild type, right-sided
• Doublet or triplet chemotherapy + bevacizumab
Microsatellite stable, RAS/BRAF mutated
• Doublet or triplet chemotherapy + bevacizumab
Microsatellite instability high tumours: Immunotherapy
• Pembrolizumab

31.5.1 Microsatellite Stable, RAS/BRAF Wild Type, Left-Sided

For left-sided tumours that are microsatellite stable (MSS) and not harboring any *RAS* or *BRAF* mutations, first-line treatment incorporates doublet or triplet chemotherapy with biologic therapy, with a preference for anti-EGFR therapy. The emergence of *KRAS* as an important prognostic and predictive marker led to re-evaluation of pivotal trials. In a posthoc analysis of the Intergroup 80,405 data by tumour sidedness, a survival advantage was seen in left-sided *KRAS* wild type tumours in patients who received doublet chemotherapy (either FOLFOX or FOLFIRI) plus cetuximab with median OS of 37.5 months, compared to those who received bevacizumab (32.1 months) [49]. Similarly, in the re-analysis of left-sided tumours from the FIRE-3 trial, the FOLFIRI/cetuximab cohort was associated with OS of 38.3 months, whereas OS was 28.0 months for the FOLFIRI/bevacizumab group [50].

In patients with resectable liver metastases, the choice between anti-EGFR therapy and bevacizumab is less clear. The New EPOC trial showed inferior OS outcomes with the addition of cetuximab compared to chemotherapy alone (81.0 vs. 55.4 months, HR 1.45, $p = 0.036$) in patients with resectable or suboptimally resectable liver metastases [51]. Translational studies are undergoing to investigate potential driving mechanisms to explain the discrepancy in outcomes between this patient population and those with more advanced disease, but this may be due to selection of more aggressive clones.

31.5.2 Microsatellite Stable, RAS/BRAF Mutated

In *RAS or BRAF* mutated tumours, systemic therapy consists of chemotherapy with the addition of bevacizumab if no contraindications are present. Anti-EGFR therapy is not recommended for *KRAS* mutated tumours, as it did not provide a survival benefit in PRIME and CRYSTAL when added to FOLFOX and FOLFIRI [38–41]. In two separate meta-analyses, *RAS* wild type but *BRAF V600E* mutated tumours did not derive a survival benefit from the addition of anti-EGFR therapy [52]. As *RAS* and *BRAF* mutated tumours confer poorer prognosis [53], consideration should be given to FOLFOXIRI/bevacizumab if patients are fit.

The standard first-line treatment for patients with *BRAF* mutated tumours consists of doublet or triplet chemotherapy and bevacizumab, and does not incorporate *BRAF* targeted agents at this time. The BEACON trial randomized patients with *BRAF V600E* mutations to encorafenib/binimetinib/cetuximab, encorafenib/cetuximab, or to investigator's choice of cetuximab plus FOLFIRI or irinotecan (control group), after progression on 1 or 2 prior regimens. In an interim analysis, the triplet regimen of encorafenib/binimetinib/cetuximab was associated with significantly longer OS (9.0 vs. 5.4 months, HR 0.52, $p < 0.001$) [54]. In a subsequent analysis, OS was similar between the triplet group and encorafenib/cetuximab (9.3 months for both groups), although ORR favored the triplet group (26.8% vs. 19.5%) [55]. To address gaps in identifying first-line therapy for *BRAF V600E* mutated mCRC, the BREAKWATER trial is currently undergoing recruitment; patients are randomized to either encorafenib/cetuximab alone or in combination therapy with doublet chemotherapy [56].

31.5.3 Microsatellite Instability High Tumours: Immunotherapy

Microsatellite instability high (MSI-H) continues to remain an important factor that impacts overall outcomes among CRC patients, and makes up approximately 5% of mCRC cases [3]. MSI-H tumours tend to have a robust immune lymphocytic response and have been considered as targets for immunotherapy agents including PD-1 and CTLA4 inhibitors. In a phase II study by Le et al. of patients with treatment refractory mCRC, patients were administered pembrolizumab [57]. Among patients with MSI-H tumours, ORR and PFS were 40% and 78%, respectively, versus 0% and 11% among patients with MSS tumours. This was later approved by the FDA as breakthrough therapy for patients with treatment refractory (MSI-H mCRC). Similar results were seen with nivolumab in later line settings, leading to its approval as well [58].

Subsequently, in the KEYNOTE 177 study, patients were randomized to pembrolizumab versus investigator's choice of chemotherapy (mFOLFOX6 or FOLFIRI +/− bevacizumab or cetuximab) [59]. Pembrolizumab was associated with improved PFS (16.5 vs. 8.2 months, HR 0.60) compared to chemotherapy; however, 30% of the patients who received pembrolizumab had progressive disease as best response compared to 12% in the chemotherapy group. Ongoing efforts to identify this subgroup of patients is

important to avoid futile therapy. CheckMate 142 is an ongoing phase II study evaluating nivolumab 3 mg/kg plus low dose ipilimumab 1 mg/kg in the first-line setting; preliminary data show a 15-month PFS rate of 75% [60]. It is unknown how dual immune checkpoint inhibition will compare to pembrolizumab monotherapy and will require further study.

31.6 Special Considerations for Liver Metastases

For those patients with resectable liver metastases, there are systemic therapy considerations that must be taken into account, including underlying liver function, possible treatment-related toxicity, and potentially inferior outcomes with anti-EGFR therapy based on the New EPOC trial.

For chemotherapy agents, fluorouracil is generally dose reduced to 50% with hepatic impairment; irinotecan is dose reduced for bilirubin up to 3 mg/dL [61]. No data are available to support dose adjustments for capecitabine, oxaliplatin, bevacizumab, cetuximab, and panitumumab. Irinotecan has been associated with development of hepatic steatosis and vascular injury, whereas oxaliplatin is linked to sinusoidal obstruction syndrome [62, 63]. It is imperative to monitor patients' liver function, and a multidisciplinary approach is required to assess optimal timing for possible surgery to minimize chemotherapy-induced hepatotoxicity and postoperative liver complications. Neoadjuvant treatment duration is recommended to be limited to 2–3 months.

The delivery of systemic therapy to try to convert liver metastases from unresectable to resectable is termed conversion therapy. FOLFOX and FOLFIRI are both effective options, and the choice between the two is based on aforementioned patient variables. The rate of attaining complete resection (R0) of metastatic disease is approximately 15–20% with triplet chemotherapy with initially unresectable disease [64, 65], and can also be considered. In the BECOME study, patients with initially unresectable *RAS* mutated liver metastases, the addition of bevacizumab to mFOLFOX6 led to higher complete resection rates compared mFOLFOX6 (22.3% vs. 5.8%) [37]. The study was limited to Asian patients, and the definition of unresectable disease was not well defined, where some patients may have had potentially resectable disease upfront.

31.7 Conclusions

Initial treatment for mCRC requires an understanding of the various treatment options and associated toxicities. Integrating these treatment decisions with a long-term perspective on patient course beyond first-line therapy is needed in order to optimize outcomes. Novel therapies are moving into first line setting, and more options for integrating biomarker directed therapies earlier require an increased utilization of molecular testing at diagnosis. Ultimately, outcomes are improving over time with these growing therapeutic options.

31.8 Future Directions

As the first-line treatment of mCRC continues to evolve and adapt a biomarker-driven approach, several questions remain unanswered. In those with MSI-H tumours, further correlative studies are required to select the one-third of patients who will have progression as best response to immunotherapy. As the uptake of combination chemotherapy and immunotherapy increases in the treatment landscape of other tumour sites, it remains unclear if this will be a better option than pembrolizumab or ipilimumab/nivolumab in mCRC. This is the subject under study in the COMMIT (SWOG-S1610) trial. Furthermore, for those patients with targetable alterations including *BRAF V600E*, *HER2* overexpression, *KRAS* G12C mutation, or *NTRK* fusions, there are data to support a targeted approach in the treatment-refractory setting, but whether these targeted approaches are better than current standard of care first-line therapy remains to be unseen. The BREAKWATER trial is one study that will be evaluating this question in *BRAF V600E* mutated tumours. Lastly, as next generation sequencing becomes more accessible in the clinic, impact of other potentially predictive alterations, such as EGFR amplification and PIK3CA mutations, will be further elucidated and potentially incorporated into future guidelines.

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Treatment Refractory Metastatic Colorectal Cancer

32

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Learning Objectives

- Sequencing of systemic therapy for metastatic colorectal cancer beyond first-line therapy is based on multiple patient and disease factors, and prior treatments.
- Molecular profiling plays a key role in systemic management of metastatic colorectal cancer in and beyond first-line therapy, specifically Mismatch repair status, *RAS and BRAF* mutations, and *HER2* amplifications.
- Regorafenib and TAS-102 are treatment options for salvage treatment of metastatic colorectal cancer refractory to other treatments.
- Survival outcomes with systemic therapy beyond first-line therapy for patients with metastatic colorectal cancer are limited, hence referral and participation on clinical trials should be encouraged.

32.1 Introduction

Patients with advanced or metastatic colorectal cancer who experience disease progression on first-line systemic therapy have multiple treatment options. Nonetheless, outcomes with these options are suboptimal and therefore clinical trial referral and participation is preferred and should be encouraged in these patients at all times. The choice of regimen among the available standard of care therapies is dependent on prior therapy and performance status among other factors. Although, over time, the distinction between various lines of therapy has blurred with various combinations of drugs across lines of therapy, evidence shows that in treatment of metastatic colorectal cancer, maximizing exposure to active drugs is more important than sequencing, as receiving more active drugs correlates with improved overall survival [1]. In this chapter, we review the main clinical trials forming the basis of key concepts in the treatment of metastatic colorectal cancer after progression of first-line therapy.

32.2 Second-Line Therapy

Biochemotherapy, defined by a combination therapy of biological agents and cytotoxic chemotherapy, is the mainstay of second-line therapy in metastatic colorectal cancer. The pivotal role of second-line chemotherapy was examined by Rothenberg and colleagues in a study of patients who had disease progression on prior fluorouracil and irinotecan [2]. Patients were randomized to receive infusional 5-FU, single agent oxaliplatin, or FOLFOX. The primary endpoint of objective response rate was 9.9% in the FOLFOX group, versus 0% in the 5-FU group. Similarly, irinotecan was initially studied as second-line therapy as a single agent in patients who experienced disease progression on 5-FU based therapy, demonstrating an overall survival benefit compared to 5-FU or placebo [3, 4].

The GERCOR study assessed the question of sequencing by randomizing patients to receive either FOLFOX then FOLFIRI versus FOLFIRI then FOLFOX [5]. The study was designed to assess the second progression-free survival. FOLFOX followed by FOLFIRI had a median progression-free survival of 10.9 months, similar to 14.2 months on FOLFIRI followed by FOLFOX. Overall survival of 20.6 versus 21.5 months was also similar, respectively. Another study assessed the question of sequencing of irinotecan and oxaliplatin-based doublets, substituting capecitabine for 5-FU, with CAPOX followed by CAPIRI having an overall survival of 17.8 months versus CAPIRI followed by CAPOX of 17.7 months [6]. Both these studies showed that either of these regimens can be used interchangeably in first-line and second-line setting. The choice of chemotherapy backbone

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used in second-line therapy therefore depends on which cytotoxic therapy was used in first-line. Guidelines generally recommend that patients who receive fluorouracil and oxaliplatin in the first-line setting be considered for irinotecan-based therapy in second-line setting and vice versa.

Reintroduction of previously used therapy (without progression) is a viable option in metastatic colorectal cancer. OPTIMOX1 trial assessed the role of intermittent oxaliplatin treatment for patients responding to front line FOLFOX by comparing a group receiving continuous FOLFOX to another receiving 3 months of FOLFOX followed by maintenance 5-FU therapy for 12 cycles then reintroduction of FOLFOX. Overall survival in the control arm was 19.3 months and similar to 21.2 months in the reintroduction arm. TRIBE2 trial also used the reintroduction of initial therapy (FOLFOXIRI plus bevacizumab) at disease progression, comparing it to FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab in sequence [7]. The primary endpoint was progression-free survival for the entire sequence and the triplet arm PFS was 19.2 months which was significantly longer compared to progression-free survival of 16.4 months in the sequential doublet arm. In contrast to reintroduction, rechallenge, defined as using a treatment on which patient has previously progressed, has also shown some activity in metastatic colorectal cancer. Retrospective studies have examined the role of oxaliplatin rechallenge in patients who had received it previously, suggesting a possible benefit with response rates between 5% and 20% [8, 9].

32.3 Anti-VEGF Therapy

Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A), inhibits angiogenesis and in combination with cytotoxic chemotherapy is mainstay of front-line treatment for all patients with metastatic colorectal cancer [10]. Continued progression of anti-VEGF therapy beyond first-line therapy has shown survival benefit. The TML trial assessed the role of bevacizumab in the second-line setting for patients with metastatic colorectal cancer who had disease progression on bevacizumab-containing chemotherapy regimen in the first-line setting [11]. Patients received second-line chemotherapy with or without bevacizumab. The study met its primary endpoint, with patients receiving bevacizumab having median OS of 11.2 months compared to those without bevacizumab of 9.8 months. Therapy was well-tolerated, and the most common grade 3 or higher events were neutropenia, diarrhea, and fatigue. Overall, 16% of patients in the bevacizumab group discontinued any treatment due to adverse events compared to 9% in the chemotherapy alone group.

Similarly, two other anti-angiogenic drugs, ziv-aflibercept and ramucirumab, have shown similar improvement in outcomes. Ziv-aflibercept is a recombinant fusion protein acting as a high-affinity ligand trap to prevent activation of VEGF receptors. Its activity was studied in the VELOUR trial, which assessed patients with metastatic colorectal cancer who had disease progression on a prior oxaliplatin-containing regimen [12]. Patients who received FOLFIRI plus ziv-aflibercept had an overall survival of 13.5 months compared to 12.1 months for FOLFIRI plus placebo. This benefit was noted to be maintained across multiple patient subgroups, including those who had received prior bevacizumab [13]. Patients receiving ziv-aflibercept had higher rates of grade 3–4 diarrhea, fatigue, stomatitis and ulceration, infections, and palmar-plantar erythrodysesthesia. Rates of discontinuation of treatment due to adverse events were 26.8% of patients in the ziv-aflibercept arm and 12.1% of patients in the placebo arm. Ramucirumab is a human IgG-1 monoclonal antibody targeting the extracellular domain of VEGF receptor 2. Its role in colorectal cancer was assessed in the RAISE trial, examining patients who had disease progression on first-line therapy with a fluoropyrimidine, oxaliplatin, and bevacizumab [14]. Patients received either FOLFIRI and ramucirumab or FOLFIRI and placebo. The FOLFIRI plus ramucirumab group had an overall survival of 13.3 months compared to 11.7 in the FOLFIRI plus placebo group. The most common grade 3–4 events in the ramucirumab group were diarrhea, fatigue, hypertension, and neutropenia. Rates of discontinuation of therapy were 29% of patients in the ramucirumab group and 13% in the placebo group.

32.4 Anti-EGFR Therapy

The role of therapy against epidermal growth factor receptor (EGFR) is changing. Anti-EGFR monoclonal antibodies (cetuximab and panitumumab) are used in treatment of patients with *RAS* wild-type and they can be used in first-line therapy for select patients, especially those with left-sided tumours [10, 15]. Patients who have not received anti-EGFR in the front-line setting can be treated in second-line with proven clinical benefits. Studies assessed the role of FOLFIRI with or without panitumumab as second-line therapy for KRAS wild-type metastatic colorectal cancer [16, 17]. Patients receiving FOLFIRI plus panitumumab had a progression-free survival of 6.7 versus 4.9 months for patients receiving FOLFIRI alone. Similarly, cetuximab has also been assessed in the second-line setting, both in combination with irinotecan and as a single agent. The EPIC study was a Phase III trial comparing cetuximab and irinotecan with irinotecan alone in patient with metastatic colorectal

cancer previously treated with fluoropyrimidine and oxaliplatin. Progression-free survival was 4.0 months for the cetuximab/irinotecan group and 2.6 months for irinotecan alone. Cetuximab was examined as a single agent in patients who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin [18]. Patients with colorectal cancer expressing EGFR who met these criteria were given cetuximab or best supportive care. The primary endpoint was overall survival, which was 6.1 months in the cetuximab group and 4.6 months in the supportive-care group. A retrospective analysis of these data showed patients with KRAS exon 2 wild type tumours had OS of 9.5 months with cetuximab compared to 4.8 months with supportive care [19]. Data exist regarding sidedness and effectiveness of EGFR inhibitors in the first-line setting and should be followed in second-line therapy [10].

32.5 Molecularly Driven Therapy

32.5.1 BRAF Mutations

Approximately 5–9% of colorectal cancers are characterized by a specific mutation in *BRAF* V600E [20, 21]. This activating mutation leads to downstream activation of *RAS* in the EGFR pathway. *BRAF* mutations are generally mutually exclusive from *RAS* mutations. Classic mutations (but not atypical non-V600 mutations) in *BRAF* have been shown to be a poor prognostic marker and patients have lower response rates to cytotoxic chemotherapy [22, 23].

In addition to prognostic implications, *BRAF V600E* mutations are a predictive marker for BRAF targeted therapy. A combination of a BRAF inhibitor, encorafenib, and a MEK inhibitor, binimetinib, with cetuximab was studied in the phase III BEACON trial for patients with *BRAF V600E* mutated metastatic colorectal cancer who had disease progression on prior systemic therapy. The trial had two investigational arms including a triplet of encorafenib, binimetinib, and cetuximab and a doublet of encorafenib and cetuximab, compared to a control arm of cetuximab with either irinotecan or FOLFIRI. Overall survival for the triplet, doublet, and control arm was 9.0 months, 8.4 months, and 5.4 months, respectively. The addition of binimetinib did not improve OS or overall response rate over the doublet. Patients in each experimental arm had a reduced risk of deterioration in quality of life compared to the control arm [24]. Other combinations of BRAF-targeting therapies have been studied. SWOG S1406 assessed irinotecan and cetuximab with or without vemurafenib in a Phase II study [25]. Progression-free survival was 4.2 months in the vemurafenib arm compared to 2.0 months in the control arm. A Phase I trial evaluated dabrafenib, panitumumab, with or without trametinib [26]. The complete response/partial response rate for the dabrafenib/panitumumab arm was 10% and for the triplet arm was 21%. However, grade 3–4 toxicities were noted in 70% of patients in the triplet arm. Combined BRAF and EGFR inhibition is now the standard of care for these patients.

32.5.2 Deficient-Mismatch Repair (dMMR) or Microsatellite Instability High (MSI-H)

Colorectal cancer with dMMR (sporadic and hereditary) comprises of 15% of all patients with colorectal cancer and about 4–5% of all patients with metastatic colorectal cancer [27, 28]. Presence of dMMR results in inability to recognize and repair spontaneous mutations and leads to high tumour mutation burden which renders these tumours susceptible to immunotherapy. Evidence suggests that dMMR metastatic colorectal cancers have poor prognosis with conventional chemotherapy [28].

Programmed death 1 (PD-1) blockade has proven clinical benefit in front-line therapy for MSI-H or dMMR metastatic colorectal cancer and has improved efficacy compared with chemotherapy as evidenced by KEYNOTE-177 trial [29]. Due to unprecedented outcomes, immunotherapy should be used in first-line therapy for these patients. For those that have not received this in first-line, second-line immunotherapy is preferred due to the favorable benefit-toxicity profile and possibility of long-term durable responses. In a phase II study, pembrolizumab (anti-PD-1 immune checkpoint inhibitor) showed immune-related objective response rate of 40% in treatment refractory patients with dMMR metastatic colorectal cancer [30]. Similarly, single agent immune checkpoint inhibition (nivolumab, anti-PD-1) and dual immune checkpoint inhibition (nivolumab plus ipilimumab, anti-CTLA4) have shown promising activity in dMMR metastatic colorectal cancer refractory to other lines of therapy. In analysis of CheckMate-142 trial, 74 and 119 patients enrolled and treated with nivolumab and nivolumab plus ipilimumab, respectively, showed investigator-assessed objective response of 31.1% and 55.0%. Median duration of response was not reached in both trials with a median follow-up of 12.0 and 13.4 months [31, 32].

32.5.3 ERBB2(HER2) Amplification/ Overexpression

HER2 amplification/overexpression is a common biomarker in breast and gastric cancer and has been successfully exploited therapeutically. In colorectal cancer only 2–3% of

all patients harbor HER2amplification/overexpression and this aberration is enriched in *RAS/BRAF* wild-type tumours where the prevalence is between 5% and 8% [33]. In *RAS/BRAF* wild-type colorectal cancer, presence of HER2 amplification/overexpression appears to predict for a lack of efficacy of second or third-line anti-EGFR therapy [34].

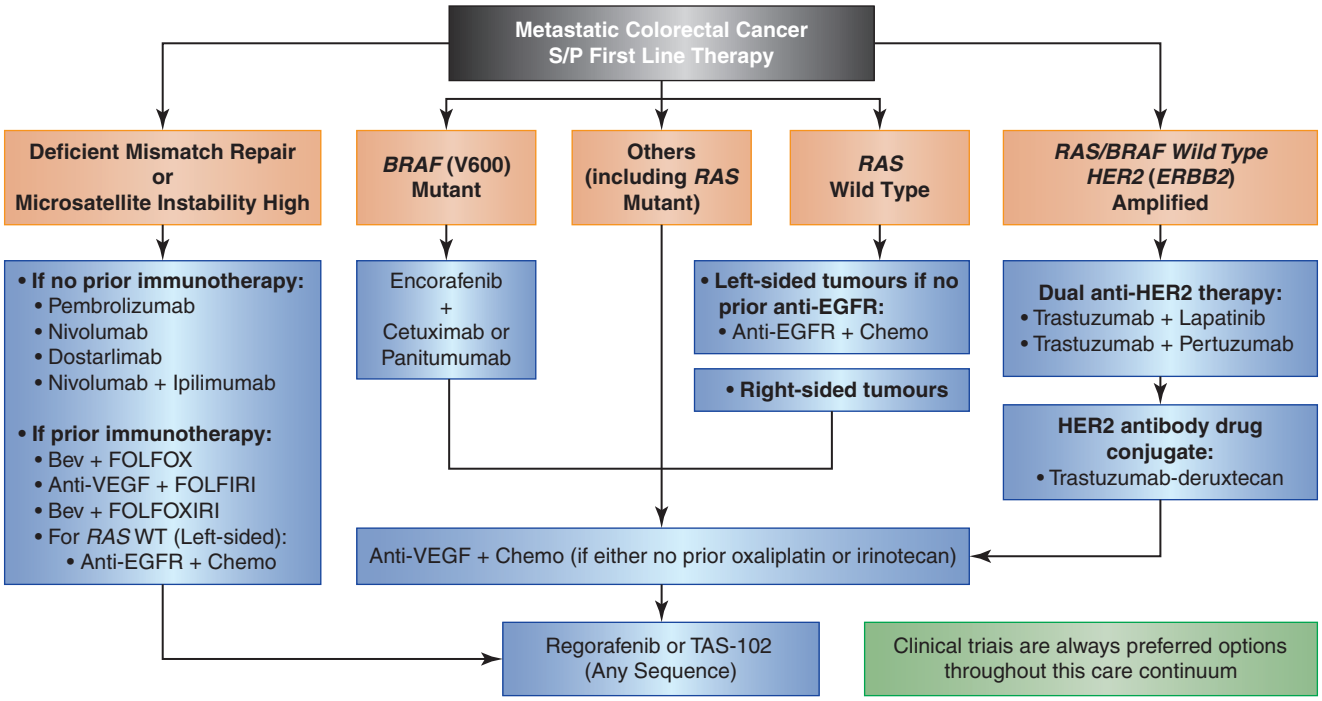
Dual anti-HER2 therapy has shown promising and durable efficacy in HER2 amplified or overexpressed metastatic colorectal cancer refractory to multiple therapies. In the phase 2 HERACLES trial, patients (N = 27) with *KRAS* exon 2 wild-type, HER2 overexpressed metastatic colorectal cancer who were refractory to standard of care therapies, and treated with trastuzumab and lapatinib, had an objective response of 30% [35]. Six (22%) patients had grade 3 adverse events, but no grade 4 or 5 adverse events were reported. Similarly, in the MyPathway phase II study, patients with HER2 amplified/overexpressed treatment-refractory metastatic colorectal cancer who were treated with pertuzumab and trastuzumab achieved an objective response of 40% in *KRAS* wild type cohort (N = 43) and 8% in *KRAS* mutant cohort (N = 13) [36]. Grade 3 or 4 treatment-emergent adverse events were reported in 37% patients. Supported by these two independent trials, guidelines now recommend dual HER2-targeted therapy as treatment option for *RAS/BRAF* wild-type, HER2 overexpressed/amplified metastatic colorectal cancer in second and third-line setting. Trastuzumab-deruxtecan, a HER2 antibody-drug conjugate with a topoisomerase I inhibitor payload, has demonstrated robust activity in treatment refractory breast and gastric cancer. The DESTINY-CRC01 phase II study in patients with *RAS/BRAF* wild-type HER2 expressing metastatic colorectal cancer that had progressed on two or more previous therapies showed promising activity in patients with HER2 positive tumours (defined as immunohistochemistry [IHC] 3+ or IHC2+ and in-situ hybridization [ISH] positive) [37]. In this cohort (N = 53), a confirmed objective response of 45.3% was reported. Grade 3 or worse treatment-emergent adverse events occurred in 10% patients with 6% having interstitial lung disease or pneumonitis.

32.6 Third-Line Therapy and beyond

Two oral drugs have shown survival benefit in treatment refractory metastatic colorectal cancer compared to placebo, regorafenib and TAS-102. Regorafenib is a novel oral multikinase inhibitor of several protein kinases (VEGFR1, VEGFR2, VEGFR3, TIE2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR). In the randomized, placebo-controlled CORRECT trial (N = 760), patients with metastatic colorectal cancer and progression after standard therapies were randomized in a 2:1 ratio to receive regorafenib or placebo with best supportive care [38]. The study met its primary endpoint of overall survival with a median overall survival of 6.4 months in the regorafenib group comparted to 5.0 months in the placebo group. TAS-102 is a combination of a thymidine analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil and causes DNA damage. With a design similar to the CORRECT trial, the RECOURSE trial randomized 800 patients to receive TAS-102 or placebo [39]. TAS-102 improved median overall survival from 5.3 months with placebo to 7.1 months. Grade 3 or higher treatment-related adverse events occurred in 54% and 69% patients in the CORRECT and RECOURSE trials, respectively. Notably, the objective response rate in both trials was 1.0% and 1.6%, respectively and the corresponding disease control rate was 41% and 44%.

32.7 Summary

Patients with metastatic colorectal cancer have multiple treatment options after progression on front-line therapy. Navigating the complex care continuum for optimal management of patients requires consideration of various patients, disease, and prior treatment factors (Fig. 32.1).



Note: Anti-EGFR (cetuximab or panitumumab); Anti-VEGF (bevacizumab, ziv-aflibercept or ramucirumab); Bev, bevacizumab; Chemo = FOLFOX/FOLFiRI/FOLFOXIRI (5-FU combined with oxaliplatin, irinotecan or both) (capecitabine can be used as 5FU interchangeably) (choice depends on whether prior therapy included oxaliplatin or irinotecan)

Fig. 32.1 Systemic therapy options for treatment of metastatic colorectal cancer after front-line therapy

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Targeted Therapy with Anti-EGFR and Anti-VEGF Therapy and Beyond

33

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Learning Objectives

- The treatment of advanced or metastatic colorectal cancer should be based on completion of molecular profiling in order to identify possible targeted therapies.
- Molecular testing should include, at the very least, MSI status, *RAS* and *BRAF* status, *HER2* amplification status, and *NTRK* fusion analysis (particularly in MSI-H patients).
- Patients with left-sided *RAS/BRAF* wild type primary tumours may be rechallenged with anti-EGFR therapy, ideally after 4–6 months off this therapy.
- Anti-EGFR therapy in combination with a backbone chemotherapy should not be used in the neoadjuvant setting prior to planned hepatectomy.
- If tissue-based molecular profiling is not feasible, ctDNA testing for alterations is a viable option.

33.1 Introduction to Targeted Therapy

Colorectal cancer (CRC) is the third most common cause of cancer-related mortality globally and in the United States [1]. Despite available systemic treatment options, overall survival (OS) of metastatic CRC (mCRC) remains poor (5-year OS < 20%). A deeper understanding of the pathways implicated in cancer cell proliferation has allowed for the development of innovative treatment strategies in patients with mCRC. Targeted therapies have been shown to improve outcomes in biomarker-selected patients with mCRC. This chapter reviews our current understanding of targeted therapy in the management of mCRC with a focus on inhibitors of EGFR and angiogenesis, and other multikinase inhibitors.

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33.2 Anti-EGFR Therapy: Cetuximab and Panitumumab

Patients with *KRAS/NRAS (RAS)* wild-type metastatic colorectal cancer (mCRC) have improved survival when treated with anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies. However, these agents do not benefit patients with oncogenic *RAS* mutations [2–5]. The EGFR is a transmembrane receptor tyrosine kinase that is stimulated by several growth factors. The EGFR signaling network results in potentiation of cellular proliferation, survival, angiogenesis, and metastases [6]. Although data have not supported the use of anti-EGFR therapy (EGFRi) for the adjuvant treatment of CRC, there is a well-established role for these agents in the metastatic setting.

33.2.1 Cetuximab

Cetuximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody specifically directed against EGFR [7]. Cetuximab has been widely studied in mCRC, both in the frontline and treatment refractory setting. There have been a number of studies that demonstrate the ability of cetuximab to enhance the anti-tumour effects of chemotherapy agents, especially irinotecan. The phase 3 randomized EPIC trial (Cetuximab Plus Irinotecan after Fluoropyrimidine and Oxaliplatin Failure in mCRC) demonstrated improved median progression-free survival (PFS) and quality of life measures [8]. Another phase 3 trial (BOND trial) also demonstrated significantly improved response rates (22.9% vs. 10.8%) with the combination of irinotecan and cetuximab versus cetuximab monotherapy in irinotecan refractory mCRC [9]. In the randomized phase 3 CRYSTAL trial, the addition of cetuximab to FOLFIRI (5-fluoropyrimidine and irinotecan) in the frontline treatment of mCRC increased the response rate by nearly 10% [5]. Given the benefit of cetuximab in advanced inoperable disease, use in the perioperative setting was explored in the EPOC trial. This was a phase 3

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randomized trial that evaluated systemic chemotherapy with or without cetuximab in patients with *KRAS* wild type resectable colorectal liver metastases. Unfortunately, there was a significant disadvantage in terms of median OS in the chemotherapy plus cetuximab group (81 vs. 55.4 months) [10]. Some experts recommend against the use of cetuximab in patients with resectable colorectal metastases based on these findings.

33.2.2 Panitumumab

Panitumumab is a fully humanized immunoglobulin G2 (IgG2) monoclonal antibody that targets the EGFR. In a randomized trial that evaluated best supportive care (BSC) versus panitumumab in patients with refractory mCRC, panitumumab had an objective response rate (ORR) of 10% versus 0% for BSC and significantly prolonged PFS in the *KRAS* wild-type group [11]. Panitumumab plus chemotherapy was approved in the frontline setting for the treatment of mCRC based on the randomized phase 3 PRIME trial that demonstrated significant improvement of PFS [12]. The phase 3 ASPECCT trial confirmed that panitumumab is non-inferior to cetuximab with similar toxicity in chemotherapy-refractory mCRC with a median OS of 10.4 versus 10.0 months, respectively [13]. Although cetuximab and panitumumab appear to have similar efficacy and toxicity in CRC, they have not been directly compared in a randomized trial.

33.2.3 Anti-EGFR Therapy and Tumour Sidedness

It is well established that right-sided primary tumours, which arise from the cecum to the hepatic flexure, carry a worse prognosis compared to left-sided tumours. Right-sided tumours are more likely to have high microsatellite instability, mucinous histology, *BRAF* mutations, and CpG island methylation [14]. Studies have shown, however, that the differences in outcomes based on primary tumour sidedness are evident regardless of mutational status or histology [14]. Two large phase 3 randomized studies (AVF2107g and NO16966) demonstrated significantly lower OS in treatment of naïve right-sided mCRC patients receiving first-line chemotherapy in combination with the VEGF inhibitor bevacizumab, whereas favorable outcomes were noted in left-sided tumours in both studies [14]. The CALBG/SWOG 80405 study evaluated the effects of first-line chemotherapy combined with either cetuximab or bevacizumab in *RAS* WT advanced or mCRC. Notably, the impact of tumour sidedness on the efficacy of treatment with cetuximab and chemotherapy was evaluated in a post-hoc analysis of CALBG/SWOG 80405, which demonstrated an OS of 16.4 months compared to 37.5 months for right versus left-sided tumours respectively [15]. The combination of bevacizumab with chemotherapy in this study resulted in an OS of 24.5 months compared to 32.1 months in right versus left-sided tumours, respectively [15]. Furthermore, post-hoc analysis for several of the anti-EGFR studies including FIRE-3, PEAK, and PRIME all confirmed that the OS and PFS benefits of cetuximab were limited to left-sided tumours. NCCN recommends avoiding anti-EGFR agents for the first-line treatment of *RAS* WT primary right-sided tumours; however, additional studies are needed to confirm whether there is potential benefit after the frontline setting.

33.3 Anti-VEGF Therapy: Bevacizumab, Ramucirumab, Aflibercept

33.3.1 Bevacizumab

Angiogenesis promotes the growth and survival of cancer cells and plays an essential role in tumour progression. Vascular endothelial growth factor (VEGF), in particular, is one of the most specific and potent angiogenesis regulators. Increased VEGF serum levels have been detected in patients with advanced CRC, especially those who are more likely to develop recurrent disease [16].

Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF that was approved by the FDA for the treatment of mCRC in 2004 [16]. In a phase 2 trial, addition of bevacizumab to fluorouracil plus leucovorin improved the response rate and median OS in patients with mCRC [17]. In the phase 3 trial that evaluated fluorouracil/leucovorin plus irinotecan (IFL) with or without bevacizumab for the frontline treatment of mCRC, the addition of bevacizumab significantly improved median OS (20.3 vs. 15.6 months) [18]. The safety and survival benefit of combining bevacizumab with fluoropyrimidine regimens and oxaliplatin was confirmed in the phase 2 TREE Study [19].

Bevacizumab in combination with FOLFOX was approved for use in the second-line setting for patients with mCRC (previously treated with FOLFIRI) based on the ECOG E3200 study, which resulted in improved median PFS (7.3 vs. 4.7 months) and survival [20]. Of note, the ECOG E3200 study also evaluated bevacizumab as monotherapy; however, this arm was closed early given an interim analysis that demonstrated inferior outcomes. Bevacizumab has not been shown to be clinically effective as monotherapy in any setting, thus should be avoided in standard of care practice. Furthermore, several studies have failed to demonstrate a significant PFS or OS benefit with the use of dual biologic therapy for the treatment of mCRC.

Bevacizumab is generally well tolerated, although it is imperative to be mindful of its potential adverse effects to

avoid use in specific high-risk cases. The most clinically significant side effects include hypertension, thrombosis, proteinuria, delayed wound healing, bleeding (usually mild), and gastrointestinal perforation. Due to these risks, administration of bevacizumab must be appropriately coordinated around surgical interventions to avoid bleeding complications.

33.3.2 Ramucirumab

Ramucirumab is a human IgG-1 monoclonal antibody directed against the extracellular domain of VEGF receptor 2. The phase 3 RAISE study evaluated the efficacy of second-line FOLFIRI with or without ramucirumab in 1072 patients with mCRC who previously progressed on frontline FOLFOX and bevacizumab. The median OS was 13.3 months for the ramucirumab group versus 11.7 months for the placebo group, and the survival benefit was consistent across all patient subgroups with manageable toxicity [21]. It remains unknown whether ramucirumab combined with chemotherapy has benefit following progression on chemotherapy plus bevacizumab in mCRC. Similar to bevacizumab, clinical benefit of ramucirumab as monotherapy or adjuvant therapy in CRC has not been proven.

33.3.3 Aflibercept

Aflibercept is a fully recombinant VEGF binding fusion protein. In the randomized phase 3 VELOUR trial, the addition of aflibercept to FOLFIRI resulted in improved PFS (6.9 vs. 4.67 months) and survival in patients with mCRC who previously progressed on an oxaliplatin-based regimen [22]. Aflibercept is FDA approved for the treatment of mCRC in combination with FOLFIRI following progression on an oxaliplatin-based regimen.

33.4 Anti-EGFR Rechallenge

Among patients with mCRC who initially respond to EGFRi, acquired abnormalities eventually develop and result in secondary resistance. Plasma ctDNA testing has allowed for the non-invasive detection of heterogeneous molecular alterations underlying the evolution of resistance to targeted therapies in mCRC [23]. Such analyses have uncovered the role of acquired subclonal *RAS* and *EGFR* ectodomain MTs in the development of acquired resistance to EGFRi [23].

Several groups have shown that in the absence of continued selective pressure from EGFR inhibition, the prevalence of *RAS* and *EGFR* mutant clones declines [24] with a half-life of approximately 4 months [25]. These data are consistent with several prospective trials demonstrating clinical benefit with anti-EGFR rechallenge. In the CRICKET single arm phase 2 study, patients with tissue-based *RAS* and *BRAF* WT tumours with a PR and PFS of at least 6 months to first-line cetuximab plus irinotecan were studied and found to have a RR, SD, and DCR rate of 21%, 32%, and 54%, respectively to anti-EGFR rechallenge. There was a statistically significant correlation between benefit from the first EGFRi and rechallenge [26]. All patients achieving a PR were ctDNA*RAS*WT prior to rechallenge with EGFRi and these patients experienced a significantly longer PFS compared to ctDNA*RAS*MT patients (4 vs. 1.9 months). There are several large-scale clinical trials currently ongoing which will hopefully better inform the rechallenge practice.

33.5 Anti-VEGF Rechallenge

Several studies have now solidified the practice of continuing anti-VEGF therapy beyond progression of the chemotherapy backbone plus anti-VEGF. For example, in the phase 3 randomized ML18147 trial, patients who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy with or without bevacizumab [27]. Patients who continued bevacizumab had a modest but statistically significant improvement in OS (11.2 vs. 9.8 months, $p = 0.0062$), a finding which was independent of *KRAS* exon 2 status [28]. Similar results were reported in the GONO group's randomized phase 3 BEPYP trials. Here, the patients who continued on bevacizumab plus a different chemotherapy backbone following progression on bevacizumab experienced a modest but statistically significant improvement in PFS and OS (6.8 vs. 5.0 months; $p = 0.001$, and 15.5 vs. 14.1 months, respectively; $p = 0.043$) [29]. Other anti-VEGF agents have also been studied in the post-bevacizumab progression setting. In a prespecified subgroup analysis of the VELOUR study, ziv-aflibercept after progression on bevacizumab resulted in an improvement in OS compared to placebo (12.5 vs. 11.7 months) [30]. Ziv-aflibercept has not shown benefit in the first-line setting. Similarly, based on results of the phase 3 RAISE trial, the anti-VEGF agent, ramucirumab is approved in the second-line setting after progression on a FOLFOX plus bevacizumab regimen, but there are no data to suggest activity of FOLFIRI plus ramucirumab in patients who progressed on FOLFIRI plus bevacizumab or vice versa [21].

33.6 Targeted Therapy Beyond Anti-EGFR and Anti-VEGF Multikinase Inhibitors

33.6.1 BRAF Inhibition

BRAF is downstream of EGFR and KRAS in the mitogen-activated protein kinase (MAPK) signaling pathway, and more than 40 somatic mutations have been identified [31]. *BRAF*^{V600E}, the most common mutation, is caused by a valine to glutamic acid substitution of the 600th amino acid resulting in subsequent constitutive activation of the EGFR signaling pathway [31]. Activation of this pathway leads to anti-apoptotic behavior and tumour cell proliferation [32]. *BRAF* mutations are most commonly mutually exclusive from *RAS* mutations [33]. *BRAF* mutations are present in roughly 10% of all mCRC cases and are associated with more aggressive biology, shorter OS, and decreased response to chemotherapy [33]. In CRC, such mutations are typically associated with right-sided T4 primary tumours, elderly females, mucinous histology, peritoneal carcinomatosis, distal nodal involvement, and sporadic microsatellite instability [34].

Historically, *BRAF* mutated mCRC has been resistant to traditional chemotherapy. In the TRIBE study, triplet chemotherapy 5-FU/oxaliplatin/irinotecan (FOLFOXIRI) plus bevacizumab was compared to FOLFIRI + bevacizumab for treatment of naive mCRC. The subgroup analysis of the *BRAF*^{V600E} patients revealed a significant improvement in OS for the triplet versus the doublet regimen (19 vs. 10.7 months) [35]. FOLFOXIRI plus bevacizumab is a reasonable upfront treatment option for patients with an adequate performance status, particularly those metastatic patients who may be converted to resectable.

Given the limited response to chemotherapy, there was a dire need for the development of targeted therapies for treatment of *BRAF* mutated mCRC. Several retrospective reviews suggested a lack of benefit of EGFRi as monotherapy or in combination with chemotherapy in the presence of *BRAF* mutations [36]. Vemurafenib, a selective *BRAF*^{V600E} inhibitor, also demonstrated limited efficacy as monotherapy for mCRC in a phase 2 study [37]. Unlike in melanoma, the ineffectiveness of *BRAF*^{V600E} inhibition alone witnessed in mCRC is primarily due to feedback upregulation of EGFR signaling [33]. However, a trial of the VIC (vemurafenib, cetuximab, irinotecan) triplet regimen was the first that resulted in improved response rates (16% vs. 4%) with a disease control rate of 67% versus 22% [38].

33.6.2 MEK and BRAF Inhibition

MEK is an enzyme that is incorporated in the MAPK pathway and a downstream effector of BRAF [39]. Inhibition of MEK stops cell proliferation and induces apoptosis, making it an ideal anticancer target. Trametinib is a reversible and highly selective MEK1/MEK2 inhibitor [39]. However, a small early phase trial of trametinib monotherapy did not demonstrate a response in patients with *BRAF* mutated CRC [40].

The BEACON study was the first randomized phase 3 trial evaluating the efficacy of encorafenib (BRAF inhibitor) plus cetuximab with or without binimetinib (MEK inhibitor) compared to irinotecan or FOLFIRI plus cetuximab in previously treated *BRAF*^{V600E} mutated mCRC. The safety lead in data from the trial revealed an ORR of 48% in the triplet regimen [41]. Overall, the BEACON study demonstrated similar survival benefit with either the triplet or doublet (encorafenib and cetuximab) regimen. The doublet arm achieved improved PFS (4.2 vs. 1.5 months) and a median OS of 8.4 versus 5.4 months compared to placebo. The FDA approved the doublet regimen for previously treated *BRAF* mutated mCRC [42].

33.6.3 Microsatellite Instability High (MSI-H)

Defects in the DNA mismatch repair process are associated with genome wide instability and the progressive accumulation of mutations resulting in microsatellite instability (MSI) [43]. MSI-high (MSI-H) is a hypermutable phenotype that promotes tumour development via dysregulation of functional DNA repair, apoptosis, and cell growth [43]. Patients with MSI-H CRC generally have a favorable prognosis compared to those with microsatellite stability (MSS), although heterogeneity within the subgroups exists that is not clearly understood [44]. Roughly 15% of stage II-III CRC patients and 4–5% of mCRC patients are MSI-H [45].

Immunotherapy has not historically shown profound responses in all patients with CRC compared to other malignancies; however, it appears to play a pivotal role in the treatment of MSI-H CRC. Pembrolizumab and nivolumab are two IgG4 monoclonal antibodies directed against PD-1 that have demonstrated promising activity. The phase 3 randomized Keynote-177 study evaluated the efficacy of pembrolizumab versus 5-fluorouracil based chemotherapy with or without bevacizumab or cetuximab for the first-line treatment of advanced or metastatic MSI-H CRC. Pembrolizumab demonstrated a median PFS of 16.5 months compared to 8.2 months for chemotherapy with manageable toxicity (HR 0.60) in Keynote-177 [46]. In the phase 2 Checkmate 142 trial, researchers evaluated the efficacy of nivolumab versus nivolumab plus ipilimumab (a monoclonal antibody targeting cytotoxic T-cell lymphocyte antigen-4) in MSI-H mCRC. The combination of nivolumab plus ipilimumab yielded an objective response rate (ORR) of 64%, a complete response (CR) rate of 9%, and a disease control rate of 84%

in an updated analysis [47]. Pembrolizumab, nivolumab, and nivolumab plus ipilimumab are all FDA approved for the treatment of mCRC. There are several ongoing clinical trials evaluating whether neoadjuvant immunotherapy has potential benefit in stage II or III MSI-H CRC.

33.6.4 HER2 Directed Therapy

The human epidermal growth receptor-2 (HER2) is an intracellular tyrosine kinase associated with multiple signal transduction pathways [48]. HER2 amplification is present in roughly 3–5% of CRC patients and is thought to be a potential mechanism of resistance to EGFRi. HER2 as a target has been successfully exploited in breast cancer via monoclonal antibodies (trastuzumab), dual kinase inhibitors (lapatinib), and antibody-drug conjugates (DS8201) which has garnered interest in exploring this target in CRC. In the phase 2 HERACLE trial, the combination of trastuzumab with lapatinib resulted in an ORR of roughly 30% in refractory HER2 positive mCRC [49]. Additionally, another phase 2 study evaluated the efficacy of dual HER2 inhibition with trastuzumab plus pertuzumab (monoclonal antibody targeting HER2) compared to cetuximab and irinotecan in HER2 amplified mCRC. In this trial, dual HER2 targeted therapy resulted in an ORR of 32% with a manageable toxicity profile [50]. The NCCN guidelines have incorporated trastuzumab/pertuzumab or trastuzumab/lapatinib as acceptable options for the treatment of refractory HER2-amplified mCRC. In the recent phase 2 Destiny-CRC01 trial, the HER2 directed antibody drug conjugate (trastuzumab-deruxtecan) demonstrated an ORR of approximately 45% with minimal toxicity for the treatment of refractory HER2 amplified mCRC [51]. The promising activity of HER2 directed antibody drug conjugate therapy in HER2 amplified CRC may also lead to future changes in the standard of care.

33.6.5 NTRK Fusion Inhibitors

The neurotrophic receptor tyrosine kinase fusion genes (NTRK) play a critical role in tumourigenesis in several cancer types [52]. NTRK fusions are quite rare in CRC, occurring in approximately 0.2–2.4% of patients [52]. Larotrectinib is a potent and highly selective inhibitor of all three TRK proteins (TRKA, TRKB, TRKC) [53]. In a study that evaluated the efficacy of larotrectinib in 55 adults and children with NTRK fusions, the ORR was 75% according to independent review and 80% per investigator assessment [53]. Three patients enrolled had CRC and two achieved an objective response. The FDA has approved larotrectinib for the treatment of all refractory solid tumours harboring an NTRK fusion. Given this potential effective treatment option, it is recommended to evaluate for NTRK fusions in mCRC.

33.7 Conclusions

In the last decade, there has been a significant advancement in our knowledge of effective targeted therapy options for specific patients with CRC. All patients diagnosed with CRC, regardless of stage, should be tested for microsatellite instability with routine IHC. This may change adjuvant chemotherapy recommendations in patients with localized disease, and will allow for frontline immunotherapy in the metastatic setting based on recent approvals. All patients with metastatic disease should also be tested at the very least for *RAS* and *BRAF* mutations, with further molecular profiling conducted if feasible. Tumours should also be evaluated for HER2 amplification by IHC, and confirmed with FISH if equivocal. These mutations, along with the site of the primary tumour, may alter therapy for patients with mCRC and have been shown to impact RR and OS. If tissue is not available for immediate molecular profiling, ctDNA testing is an acceptable alternative to assess for mutations that may impact front-line therapy decision-making.

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Adjuvant Systemic Chemotherapy

34

Van Morris

Learning Objectives

- To understand data which support use of cytotoxic chemotherapy in the adjuvant setting following resection of liver-limited metastatic colorectal cancer.
- To recognize therapies used in the clinical management of unresectable, metastatic colorectal cancer which have no proven benefit as an adjuvant treatment following resection of liver-limited disease.
- To identify emerging technologies which may accurately prognosticate patients with liver-limited metastatic colorectal cancer who are at high risk of recurrence.

34.1 Introduction

For most patients with oligometastatic, potentially resectable adenocarcinoma of the colon or rectum with concomitant liver involvement, surgery remains the most utilized approach for a curative outcome [1, 2]. Incorporation of systemic treatment options in the perioperative setting has been evaluated specifically in patients with liver-limited metastatic colorectal cancer with the goal of improving further rates of extended survival. Upfront neoadjuvant systemic therapy offers the advantages of downsizing known hepatic tumours prior to surgery [3, 4], converting resectability status from unresectable to resectable metastatic disease [5–8], and allowing providers a window of time to evaluate clinically a patient's tumour biology [9, 10], for optimal selection of surgical candidacy prior to subjecting a patient to the potential for operative morbidity. Use of adjuvant chemotherapy in the postoperative setting seeks to increase the curative fraction of patients with oligometastatic colorectal cancer by eradicating microscopic foci of minimal residual disease which may still be present after an otherwise complete resection of all identified liver metastases. This chapter will cover the seminal prospective studies (Table 34.1) which evaluated use of adjuvant chemotherapy following resection of colorectal liver metastases and propose future directions involving emerging technologies which may be applied towards improving long-term survival even further for patients with liver-limited metastatic colorectal cancer.

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34.2 Prospective Clinical Trials for Adjuvant Chemotherapy

34.2.1 FFCD ACTBTH AURC 9002 Trial: Evaluation of Single-Agent Fluoropyrimidine as an Adjuvant Therapy

In this randomized phase III international trial [11], patients with liver-limited stage IV colorectal cancer who had already completed R0 resection of both the colorectal primary tumour and all known hepatic metastases were eligible. Here, almost 70% participants had had only one liver metastasis resected. Patients were randomized after surgery in a 1:1 fashion to either observation (standard-of-care) or adjuvant chemotherapy (investigational arm). In the latter arm, patients initiated treatment before postoperative day 35 with a daily infusion of bolus 5-fluorouracil, accompanied by folinic acid, on days 1–5 of a 28-day cycle. These patients in this investigational arm received adjuvant chemotherapy for a total duration of 6 months.

The primary objective for this study was to compare median disease-free survival between the two groups. Secondary objectives sought to evaluate for differences not only in median overall survival but also for treatment-related toxicities. Patient characteristics were overall well balanced between the two arms. After a median follow-up of

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Table 34.1 Randomized, prospective trials with systemic therapy for patients with metastatic colorectal cancer involving the liver

Investigators	Intervention beyond surgery (treatment vs. control)	Site(s) of resected metastatic colorectal cancer	Planned accrual completed?	Disease-free survival (experimental vs. control)	Overall survival (experimental vs. control)
Portier et al.	5-fluorouracil/folinic acid vs. observation	Liver	No	24.4 vs. 17.6 (months)	62.1 vs. 46.4 (months)
Nordlinger et al.	FOLFOX4 vs. observation	Liver	No	18.7 vs. 11.7 (months)	61.3 vs. 54.3 (months)
Hasegawa et al.	Uracil-tegafur/folinic acid vs. observation	Liver	Yes	1.45 vs. 0.70 (years)	Not reached
Mitry et al.	5-fluorouracil/leucovorin vs. observation	Liver + lung	No	27.9 vs. 18.8 (months)	62.2 vs. 47.3 (months)
Ychou et al.	FOLFIRI vs. 5-fluorouracil	Liver	No	24.7 vs. 21.6 (months)	Not reached
Bridgewater et al.	FOLFOX/cetuximab vs. FOLFOX	Liver	No	15.5 vs. 22.2 (months)	55.4 vs. 81 (months)

87 months, trial accrual was stopped prematurely due to a lower-than-expected rate of new patient enrollment. Importantly, there were no treatment-related deaths in this study that were attributed to the administration of systemic chemotherapy. At the time of (interim) study analysis following 118 of 134 planned events, disease-free survival outcomes were improved in patients with resected liver-limited metastatic colorectal cancer who were randomized to receive adjuvant chemotherapy. Here, median disease-free survival was 24.4 months, relative to 17.6 months for the patients who were randomized to standard-of-care observation following surgery. Likewise, the percentage of patients without disease recurrence was higher at 2 (50.4% vs. 38.1%) and at 5 years (33.5% vs. 26.7%) for those patients who received adjuvant chemotherapy after surgery. Despite these encouraging improvements in disease-free survival, there was a trend towards improved overall survival as well for the patients who received adjuvant 5-fluorouracil. Median overall survival in these patients was reported at 62.1 months (vs. 46.4 months in the control arm). Slow study accrual, which prompted early end to study enrollment, likely contributed to insufficient power to detect a statistically significant difference in overall survival. Nonetheless, it is notable that the trial did satisfy its primary objective and did demonstrate a prolongation in time to disease recurrence. In doing so, this study provided important evidence from a randomized controlled trial that systemic chemotherapy may be effective in treating micrometastatic colorectal cancer following complete resection of liver metastases.

Another trial evaluated use of an oral fluoropyrimidine (uracil/tegafur) with leucovorin as a single-agent treatment option for adjuvant chemotherapy in patients with liver-limited metastatic colorectal cancer [12]. Between 2004 and 2010, this trial was able to complete its planned enrollment of 180 participants, who were randomized in a 1:1 fashion to undergo surgery alone or surgery followed by 5 cycles of uracil/tegafur and leucovorin. In this study, adjuvant chemotherapy significantly improved median recurrence-free survival (1.45 vs. 0.70 years). In a subgroup analysis, this effect was significant for those patients with ≥1 liver metastasis and with synchronous presentation of liver metastasis with initial colorectal cancer diagnosis. For the intention-to-treat analysis, adjuvant chemotherapy was not associated with an improvement in 5-year overall survival (66% vs. 67%). While toxicity data for uracil/tegafur plus leucovorin were not fully detailed, oncologists should weigh the risks versus benefits when discussing the role of adjuvant chemotherapy following resection in patients with metastatic colorectal cancer involving the liver.

34.2.2 EORTC 40983: Addition of Oxaliplatin to Adjuvant Therapy with Fluoropyrimidine

The EORTC randomized phase III trial evaluated surgery with or without perioperative chemotherapy in patients with oligometastatic colorectal cancer limited to the liver [13]. To be eligible, patients must have had 1–4 liver metastases detectable prior to study consent. The presence of extrahepatic metastases was not permitted. Patients must have also completed an R0 resection of the primary tumour, or, if still intact, must have a plan for synchronous resection of the primary tumour at the same time as liver surgery. In this study, 364 patients were randomly assigned to resection of hepatic metastases alone (control arm) or resection accompanied by FOLFOX4 (experimental arm)—5-fluorouracil plus oxaliplatin. Unlike the previously described study which evaluated chemotherapy only adjuvantly, it should be noted that the patients in the experimental arm of the EORTC 40983 trial received FOLFOX4 for 6 cycles (3 months) both in the neoadjuvant and adjuvant settings alike. Therefore, in the experimental arm, patients received a planned 6 months total of perioperative chemotherapy.

The primary objective of the EORTC 40983 trial was to compare median progression-free survival between the two

arms. Secondary objectives included comparison of median overall survival, resectability status, and pathologic treatment response at the time of surgery between these patients with liver-limited metastatic colorectal cancer who underwent surgical resection alone or in combination with perioperative FOLFOX4 chemotherapy. It is important to note that the study was powered to detect an improvement in median progression-free survival by 40%, yet it was not designed to detect a difference in overall survival. Given the avid interest by oncologists and patients alike during the time of study enrollment for the trial results, an interim analysis was performed after completion of >80% events for analysis of survival outcomes.

Progression-free survival outcomes were improved in the per-protocol analysis (but not in the intention-to-treat analysis) among those patients with liver-limited metastatic colorectal cancer who received perioperative chemotherapy relative to those who proceeded with only surgical resection. Median progression-free survival here with the addition of FOLFOX4 chemotherapy increased from 11.7 to 18.7 months. Similarly, the rate of 3-year progression-free survival improved for patients on this study from 28.1% (surgery alone) to 35.4% (surgery plus chemotherapy). With regard to comparisons to overall survival, there were trends towards improvement with the addition of systemic FOLFOX4 both for median overall survival (61.3 vs. 54.3 months) and for rates of 5-year overall survival (51.2% vs. 47.8%) [14]. There was slower accrual to this study than initially anticipated, and a failure to complete study accrual may have influenced the ability to detect a difference in overall survival. Of the 182 participants randomized for each arm, only 152 patients per arm ultimately proceeded to surgical resection. Here, the investigators analyzed survival outcomes by the per-protocol groups ($N = 152$ per arm) and by intention-to-treat groups ($N = 182$ per arm). Exercising caution in interpreting these findings given this discrepancy, the combination of a fluoropyrimidine and oxaliplatin as a perioperative treatment may offer benefit to some patients with resected liver-limited metastatic colorectal cancer.

34.2.3 Meta-Analyses for Adjuvant Chemotherapy in Liver-Limited Metastatic Colorectal Cancer

With the goal to improve upon the ability to detect a significant difference in survival outcomes using larger numbers of patients, a pooled analysis of patients with oligometastatic colorectal cancer who underwent resection with or without fluoropyrimidine monotherapy was performed [15]. These data came from the aforementioned 9002 trial ($N = 173$ patients) and the ENG 40923 trial [16] ($N = 129$ patients). The former trial included only patients with liver-limited metastatic disease, whereas the latter allowed oligometastases to the liver (~90%) or to the lung (~10%). In this pooled analysis, median disease-free survival was improved for those patients who received systemic chemotherapy in the adjuvant setting in comparison to those who underwent surgical resection alone (27.9 vs. 18.8 months). The hazard ratio (HR) for recurrence was 1.32 (95% confidence interval (CI): 1.00–1.76; $p = 0.06$). Likewise, there was a trend towards prolonged overall survival for those receiving adjuvant 5-fluorouracil (62.2 vs. 47.3 months; $p = 0.09$). Here, in a multivariate analysis, survival outcomes fared worse for patients not only who underwent surgery without receipt of adjuvant chemotherapy but also who had two or more metastatic tumours resected. Even with chemotherapy, however, in this pooled analysis, 2-year disease-free survival was 55% with adjuvant treatment, suggesting that the remaining 45% of patients did not clear all sites of microscopic disease with adjuvant chemotherapy after their macroscopic disease had been resected. This point highlights the ongoing need to offer improved therapeutic options for patients with oligometastatic colorectal cancer, as a large fraction remains at high risk of inevitable recurrence despite multimodality therapies.

Since anemic accrual to these clinical trials have limited interpretation of survival outcomes comparing complete resection versus resection with systemic chemotherapy for patients with oligometastatic colorectal cancer, a more recent meta-analysis included data from the EORTC 40983 trial (which evaluated the combination of oxaliplatin with 5-fluorouracil) to trials evaluating fluoropyrimidine monotherapy as an adjuvant option [17]. Again, a trend towards improvement in 5-year overall survival (HR: 0.83, 95% CI: 0.68–1.02; $p = 0.07$) was observed for patients who received systemic chemotherapy in combination with surgical resection.

At our institution, we interpret these findings collectively to offer perioperative chemotherapy for a total duration of 6 months—in general, 2 months neoadjuvantly and 4 months adjuvantly—using a 5-fluorouracil and oxaliplatin cytotoxic doublet chemotherapy backbone for patients with liver-limited metastatic colorectal cancer who undergo surgical resection of the primary tumour and all hepatic tumours. Based upon the randomized controlled trial data detailed here, we believe that 5-fluorouracil monotherapy as an adjuvant chemotherapy option is likewise an appropriate selection in patients with oligometastatic colorectal cancer who are not able to withstand the addition of oxaliplatin. We recommend this to our patients with the intention of treating residual micrometastases in order to delay and/or prevent development of recurrent metastatic colorectal cancer.

34.3 Agents Not Recommended as Adjuvant Therapy for Resected Liver-Limited Metastatic Colorectal Cancer

Over the past decades, therapeutic options for patients with unresectable metastatic colorectal cancer have broadened with the advent of new systemic cytotoxic and targeted biologic agents. For example, the topoisomerase inhibitor irinotecan has demonstrated safety and antitumour activity in combination with intravenous 5-fluorouracil as a cytotoxic backbone for patients with unresectable metastatic colorectal cancer [18, 19]. Antiangiogenic therapies targeting vascular endothelial growth factor (VEGF) signaling in colorectal tumours like bevacizumab [20–23], ramicirumab [24], and ziv-aflibercept [25, 26] have shown improvements in survival outcomes in the treatment of metastatic colorectal cancer when combined with chemotherapy. In addition, for the 40–50% of patients whose tumours are wild-type for the *KRAS*, *NRAS*, and *BRAF* oncogenes, antiepidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab target signaling of the MAPK pathway critical to tumour cell growth and proliferation [27], and are effective across multiple lines of treatment for unresectable metastatic colorectal cancer [28–31], especially when the primary tumour is left-sided in anatomical location [32–34]. Here, we review use of these therapies as adjuvant treatments for metastatic colorectal cancer.

34.3.1 Irinotecan

Seeking to build upon the previously detailed benefit of 5-fluorouracil as adjuvant chemotherapy for patients with liver-limited metastatic colorectal cancer, a phase III trial examined the addition of irinotecan in this context [35]. Here, patients who had undergone complete resection of both the primary tumour and all evident liver metastases were randomized in a 1:1 fashion to receive 5-fluorouracil with or without irinotecan every 14 days for a total of 6 months (12 cycles) of adjuvant therapy. Patients with a history of extrahepatic metastases were not eligible. The primary endpoint was disease-free survival. Due to slow study accrual, trial conduct was modified for an earlier-than-intended analysis, after treatment of 306 of 420 planned patients. Treatment with FOLFIRI (intravenous 5-fluorouracil plus irinotecan) was associated with no improvement in median disease-free survival relative to 5-fluororuacil (24.7 vs. 21.6 months, respectively; $p = 0.44$). There was no difference in overall survival either, with 3-year overall survival rates of 72% and 73% for patients randomized to 5-fluorouracil and FOLFIRI, respectively ($p = 0.69$). Despite no survival benefit from the addition of irinotecan in the adjuvant setting, grade $\geq$ 3 toxicities were expectedly higher in patients who received FOLFIRI, specifically with regard to increased frequencies of treatment-related neutropenia and diarrhea. These results for this trial assessing FOLFIRI as an adjuvant therapeutic option for patients with resected liver-limited metastatic colorectal cancer are consistent with similar phase III trials designed to test this combination for patients with stage II or III colorectal cancer [36–38]. In this context, the addition of irinotecan to infusional 5-fluorouracil in the adjuvant setting demonstrated has added no survival benefit but increased morbidity in patients with locoregional, nonmetastatic colorectal cancer after resection. Therefore, based upon the findings in these studies, we do not utilize irinotecan as an effective adjuvant cytotoxic chemotherapeutic for patients with liver-limited metastatic colorectal cancer after surgery.

34.3.2 Anti-EGFR Therapies

The New EPOC phase III trial sought to explore the addition of cetuximab as a biologic agent to the addition of a fluoropyrimidine and oxaliplatin perioperatively for patients with potentially liver-limited metastatic colorectal cancer. Patients were required to lack mutations in exon 2 of the *KRAS* oncogene. Patients were randomized in a 1:1 fashion to receive FOLFOX or XELOX (provider choice for chemotherapy backbone) with or without cetuximab. Treatment was administered for 12 weeks prior to resection of liver metastases (and primary tumour, if still intact) and for 12 weeks in the adjuvant setting. Approximately 15% of patients in both arms did not complete their intended duration of adjuvant chemotherapy. Both median disease-free survival (22.2 vs. 15.5 months; $p = 0.30$) and median overall survival (81.0 vs. 55.4; $p = 0.03$) were inferior with the addition of cetuximab to perioperative chemotherapy than for the use of perioperative cytotoxic chemotherapy alone [39]. Subgroup analyses revealed that detriment with anti-EGFR treatment persisted even for patients with favorable clinical and pathologic features (e.g., fewer hepatic metastases, moderately differentiated primary tumours, lower nodal involvement within the primary tumour basin, and metachronous presentation of liver metastases) [40].

Similar to the New EPOC trial for patients with metastatic colorectal cancer, the NCCTG Intergroup N0147 trial evaluated FOLFOX with or without cetuximab as an adjuvant therapy approach for patients with stage III colorectal cancer. For those with *KRAS wild-type* primary tumours, there was no improvement in 3-year disease-free survival (74.6% vs. 71.5% for FOLFOX vs. FOLFOX/cetuximab; $p = 0.08$) in this study. Based upon these findings, at our institution we do not consider anti-EGFR therapy to be an effective therapy for the treatment of colorectal liver metastases, and therefore do not

incorporate cetuximab or panitumumab in an adjuvant therapy plan following resection for patients with *KRAS wild-type/NRAS wild-type* liver-limited metastatic colorectal cancer.

34.3.3 Anti-VEGF Therapies

There have been no randomized prospective trials performed thus far evaluating the addition of an anti-VEGF therapy to cytotoxic chemotherapy in the adjuvant setting specifically for patients with stage IV colorectal cancer confined to the liver. Nonetheless, trials evaluating the addition of bevacizumab to adjuvant chemotherapy for patients with resected locoregional colorectal cancer did not show survival benefit. For example, the NSABP C-08 trial compared modified FOLFOX6 with FOLFOX6 plus bevacizumab for patients with stages II or III colorectal cancer [41]. Rates of 3-year disease-free survival were 75.5% and 77.4% for chemotherapy alone and in combination with bevacizumab, respectively ($p = 0.15$). The phase III AVANT trial randomized patients with high-risk stage II or stage III colorectal cancer following resection to adjuvant treatment with FOLFOX4 alone, FOLFOX4 with bevacizumab, or XELOX with bevacizumab in a 1:1:1 fashion [42]. No prolongation in median disease-free survival was detected by the addition of bevacizumab to adjuvant chemotherapy. Though these trials did not include patients with resected oligometastatic colorectal cancer, it does not appear that anti-VEGF therapies are effective in the treatment of colorectal micrometastases [43]. Therefore, at our institution, we interpret these findings as justification not to offer this class of agents as part of adjuvant therapy following resection of colorectal liver metastases.

34.4 Future Strategies for Adjuvant Therapies in Treatment of Liver-Limited Metastatic Colorectal Cancer: The Potential for Circulating Tumour DNA

While adjuvant chemotherapy does appear to offer some survival advantage following surgical removal of hepatic tumours, many patients still recur, suggesting the persistence of micrometastases which selectively withstand the pressures of these antineoplastic treatments. The ability to identify patients with micrometastases after surgery may allow in the future clinicians to identify patients at high risk of recurrence. Recently, the advent of circulating tumour DNA (ctDNA) technology has served as a powerful prognostic biomarker for recurrence following resection of solid tumours like colorectal cancer [44]. Tumour cells may release their cellular components, including DNA, into the bloodstream predominantly via apoptosis [45] but also following necrosis or cell secretion [46, 47]. Because tumours contain genomic somatic mutations unique from nonmalignant cells in the body, identification of tumour-specific mutations in the ctDNA can serve to illuminate the existence of tumour cells [48] which remain after surgery and continue to shed tumour-specific DNA into the circulation. Current sequencing platforms are able to detect ctDNA from the plasma at a variant allele fraction as low as 0.1% [49–51]. This very high sensitivity empowers ctDNA detection with few numbers of cells when present. Accordingly, the presence of ctDNA (in a patient with no macroscopic evidence of malignancy) serves as a surrogate for the presence of microscopic, minimal residual disease.

For patients with resected colon cancer, a postoperative ctDNA (+) status following resection confers a poor prognostic implication for inevitable recurrence. At the same time, patients with no detectable ctDNA are less likely to recur and presumably biochemically without evidence of minimal residual disease. In one series of 178 patients with stage II colon cancer who did not receive adjuvant chemotherapy, ctDNA was detected in only 8% of cases [52]. However, all patients with detected ctDNA experienced recurrent colon cancer. Interestingly, a postoperative ctDNA status in this study was associated with a higher marker prognostically for disease recurrence than traditional clinical and pathologic features like T3 versus T4 primary tumour status, tumour perforation, and number of lymph nodes examined intraoperatively, all of which are commonly used by oncologists for assessment of risk in decision making for adjuvant chemotherapy in stage II colon cancer.

Other studies for patients across all stages of colon cancer have demonstrated similar associations between ctDNA status and the risk of recurrence [53–55]. Here, the identification of ctDNA following resection precedes clinical or radiographic recurrence by an estimated median of 8–9 months. ctDNA also outperforms carcinoembryonic antigen (CEA) as a blood-based biomarker in prognosticating return of disease in patients with resected colorectal cancer [50]. For patients with stage IV colorectal cancer limited to the liver who underwent metastasectomy, this principle appears applicable based on multiple series. For example, one institution examined 54 patients with liver-limited metastatic colorectal cancer for ctDNA following complete resection [56]. Here, 44% patients had detectable ctDNA postoperatively, which was associated with a much more inferior recurrence-free survival than those with no detectable ctDNA (2-year recurrence-free survival 0% vs. 47%; $p = 0.002$). Therefore, when identified, postoperative ctDNA in the plasma likely serves as a harbinger for inevitable recurrence in patients with resected liver-limited metastatic colorectal cancer.

Despite the striking prognostic performance of ctDNA for patients with resected colorectal cancer, its relevance as a pre-

dictive biomarker that identifies patients who do (or do not) benefit from adjuvant therapies has not yet been determined in prospective, randomized trials. To date, observational series have been inconclusive that chemotherapy can definitively clear the ctDNA and improve survival outcomes. One series of patients with stages II/III colorectal cancer reported 80% recurrence for those patients with a postoperative ctDNA (+) status who completed standard-of-care adjuvant cytotoxic chemotherapy [57]. Level 1 evidence detailing predictive performance of ctDNA testing in this setting (across all stages of colorectal cancer) is highly anticipated. Novel approaches which incorporate liver-specific tumour biology may be warranted in maximizing likelihood for optimal treatment of micrometastases following liver resection in patients with a ctDNA (+) status who are at especially high risk of recurrence. For example, murine models of colorectal cancer with intact immunity have demonstrated cytotoxic T cell infiltrates present in micrometastases which become excluded from the tumour microenvironment as the liver metastases mature and enlarge [58]. Therefore, it is possible that the use of ctDNA assays to identify patients with remnant microscopic foci of colorectal cancer may offer oncologists a window to intervene on unique tumour biology with treatments like immunotherapy not otherwise responsive, over the course of tumour evolution, to radiographically detectable disease. However, clinical trials are needed to demonstrate this in patients with resected colorectal cancer. Doing so after hepatic metastasectomy would empower clinicians with an important tool in offering potentially more effective adjuvant therapies in order to improve survival outcomes further for patients with liver-limited metastatic colorectal cancer after surgery.

34.5 Conclusion

Perioperative chemotherapy with fluoropyrimidine ± oxaliplatin for a total duration of 6 months may improve survival outcomes for patients with resected liver-limited metastatic colorectal cancer. Use of irinotecan, anti-VEGF antibodies, or anti-EGFR antibodies is not recommended as an adjuvant treatment.

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Immunotherapy

35

Robert de Wilton Marsh

Learning Objectives

- Immunotherapy has a long and colorful history.
- The treatment of gastrointestinal cancers has included immunotherapy for almost a century and continues to evolve in step with other tumour types.
- The latest studies confirm the utility of immune checkpoint blockade as a major new initiative in this context.
- Evolving strategies such as adoptive T cell therapy, and newer vaccines, are set to take this to the next level.
- Parallel initiatives addressing the tumour microenvironment and the gut microbiome will be of increasing importance as knowledge develops further.

35.1 Introduction

Immunotherapy of cancer in general, and colorectal cancer specifically, is currently one of the most exciting and active areas of research in cancer therapeutics. Previously confined to research units in large academic institutions, immunotherapy is now within reach of the smallest oncology practice and the benefits for cancer patients are present and tangible. Tracing the history of this initiative from the early twentieth century until today highlights the many serendipitous discoveries as well as the structured research endeavors which have facilitated progress in this field. There is every expectation that while we currently have the means to treat less than 15% of all colorectal cancer with this approach, the number will continue to grow as new methodologies expand the understanding and application of this treatment strategy. Ancillary endeavors such as manipulation of the cancer microenvironment and the gastrointestinal (GI) microbiome, improved detection of minimal residual disease, and optimal ways of assessing both suitability for and response to immunotherapy will incrementally add to the efficacy and applicability of this technology. While immunotherapy of colorectal cancer liver metastases is in its infancy, expectations for future success are unlimited.

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35.2 Background

35.2.1 History

Immunotherapy has a long and colorful history. The beginnings of this approach to cancer therapy can certainly be debated, but many would say that the exploration of so-called Coley's toxins for sarcoma was a very early step [1]. These were actual endotoxins from erysipelas producing bacteria, Streptococcus pyogenes and Serratia marcescens, which Coley had injected into his patients. The resultant infection somehow stimulated the patients' own cells to attack the cancer [2]. Coley successfully treated more than 1000 patients but this strategy was controversial and much criticized, and ultimately was abandoned in favor of more modern treatments. A second interesting observation in the early 1900s was the apparently lower incidence of cancer at autopsy in those who had previously contracted tuberculosis (TB) compared to those who had not [3]. In a parallel endeavor, Bacillus Calmette-Guerin (BCG) had been developed in France for the prevention of tuberculosis [4], and as a result of the lower cancer incidence observed in those exposed to TB, BCG was subsequently studied as a possible treatment for cancer. The initial enthusiasm for this approach was abruptly curtailed in wake of the Lubeck disaster in 1929, when 251 infants were given three doses of BCG vaccine contaminated with *Mycobacterium tuberculosis*. One-hundred seventy three of these infants subsequently devel-

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oped radiological or clinical evidence of tuberculosis but fortunately survived; however, 72 patients died [5]. In the 1950s, interest in BCG as a possible cancer therapy was resurrected, and research was once again conducted in many tumour types. Unfortunately, there was limited success and interest eventually waned. However, a report in 1976 that intravesicular BCG was effective against early-stage bladder cancer, by evoking both a local and systemic response, was a sentinel development [6]. This treatment is still used today for this indication and has been highly successful [7]. A second report in the same year, that a combination of BCG and 5FU was effective in the adjuvant therapy of Dukes stage C colon cancer, received much attention and was notable for the fact that BCG alone seemed to be most effective when used in those with six or more positive lymph nodes ($p < 0.04$), and was ineffective in those with five or less [8].

The late 1970s and early 1980s saw the true beginnings of modern immunotherapy with the discovery of interleukin-2 (IL-2), a cytokine able to stimulate the growth of T cells in vitro [9]. IL-2 was subsequently tested in the treatment of many malignancies and the results were particularly impressive in malignant melanoma and renal cell carcinoma [10]. The cytotoxic T lymphocyte antibody 4 (CTLA-4) receptor was discovered and described in 1987 [11] and this opened the door to an understanding of the host/cancer/immune system axis, which has proven to be key in the development of immune based therapeutics. The programmed cell death protein-1 (PD-1) and PD-1 ligand were subsequently identified in 1992 and 1999, respectively [12, 13], and along with the development of CTLA-4 inhibition, these discoveries have been key to the development of effective immunotherapy via immune checkpoint inhibition (ICI). Following this work, the field accelerated at a very rapid pace with, among others, the development of chimeric antigen receptor T (CAR-T) cell therapy, cancer vaccines such as sipuleucel-T, and oncolytic viruses [14].

It is often thought that colorectal cancer is a late comer to the field of immunotherapy, following earlier and more successful results in cancers such as malignant melanoma, renal cancers, and lung cancer. Even in the realm of gastrointestinal cancers, hepatocellular carcinoma and gastric cancer look to have had more visible success. However, this is not strictly true, and in fact the treatment of colorectal cancer has benefited from immune therapy for at least four decades. In the 1960s, the successful synthesis of levamisole as an anthelminthic drug, unwittingly opened the door to an immune approach in this disease [15], complementing the work with BCG mentioned previously. While it was not until the 1980s that a report in the NEJM outlined the success of this agent, in combination with 5FU, in the adjuvant therapy of stage C colorectal cancer [16] much preclinical and clinical work had preceded this seminal study. It was initially unclear whether levamisole acted independently on the cancer cell by direct toxicity, by synergistic toxicity with 5FU, or by a so-called immunomodulatory effect [17]. However, innovative work in the lab suggested that an immune mechanism was perhaps the principle means by which this drug was able to revolutionize the treatment of colon cancer [18]. While this was very exciting, progress with an immune approach was then side-lined by the discovery that leucovorin was a more effective and tolerable addition to 5FU. Adjuvant therapy with this new combination could be completed in 6 versus 12 months, and clinicians were happy to have a less toxic regimen, which also had a more concrete biologic basis [16]. Subsequently, levamisole was ultimately taken off the market in the USA for all indications, owing to unacceptable toxicity, recently underlined by the observation that its presence in adulterated cocaine is thought to potentially cause brain damage.

35.2.1.1 Inheritance and the Lynch Syndrome

At the same time as these therapeutic advances, exciting discoveries were taking place in the field of inherited cancers in general, and colorectal cancer specifically. Perhaps the most relevant to colorectal cancer was the elucidation of the so-called Lynch syndrome [19] (also referred to initially as hereditary nonpolyposis colorectal cancer HNPCC). This syndrome had initially been recognized as a clinical entity by University of Michigan pathologist A.S.Warthin in 1913, when he astutely proposed an inherited disposition for the extensive cancer history in the family of his seamstress. Naturally, the underlying genomic and molecular abnormalities were not understood [20]. Subsequent work by him, and many others who were to follow, including Henry Lynch [21], firstly narrowed the problem to a focus on chromosome 2p and then to the 4 genes responsible for coordinating the repair of aberrant microsatellite repeats in the human genome (located on chromosomes 2p21–22 (MSH2), 3p21 (MLH1), 2q31–33 (PMS1) and 7p22 (PMS2) [22]. It was apparent that a defect in this system was an autosomal dominant condition which led to defective mismatch repair (dMMR) in dividing cells, and ultimately cancer. The predominant organs involved, and initially described, were the colon and rectum as well as the uterine endometrium. Subsequently, it became clear that other organs such as the stomach, breast, ovary, liver, kidneys, ureters, bladder, prostate, small bowel, pancreas, skin, and even the brain could be affected. Further exploration of this concept determined that certain cancers could arise from microsatellite instability unrelated to an inherited condition.

35.2.2 Errors in DNA Replication: Microsatellites, CpG Islands, and POLE/D1 Mutations

Microsatellites are regions of noncoding repeat base pair sequences in the genome, occurring at thousands of loci. During cell replication, mistakes in the paring of bases by

DNA polymerase may occur, typically about 1 in a million, and in these situations the mistakes are typically repaired by enzymes synthesized under the direction of the mismatch repair genes MLH1, PMS2, MSH2, and MSH6. However, if there is an inherited or acquired defect in this repair mechanism, the mistakes will be retained and repeated in all subsequent cell division (this is known as dMMR, microsatellite instability high [MSI-H]) [23]. These abnormalities may be detected in tumour tissue by in-situ hybridization testing for abnormal proteins produced by the mutated genes (Figs. 35.1, 35.2, and 35.3), or by polymerase chain reaction, testing for five genetic markers of dMMR. In the noninherited situations, microsatellite instability is a spontaneous event resulting from epigenetic silencing of the MLH-1 gene promoter by hypermethylation, which is related to a BRAF V600E mutation in about 30% of cases and multiple somatic mutations in the MMR genes in others. Somatic mutations in the PIK3CA gene play a role in many of these. This is a particularly common event in right-sided colon cancer where the prevalence is estimated to be up to 20%. It is now apparent that right- and left-sided colon cancers may have very different biologic behavior which not only affects the natural history of the cancers, but also the choice of appropriate therapy for both localized and metastatic disease. Very rarely, even proficient mismatch repair (pMMR) systems can miss a mutation and this error can then persist. This may lead to cancer formation by one of many possible avenues.

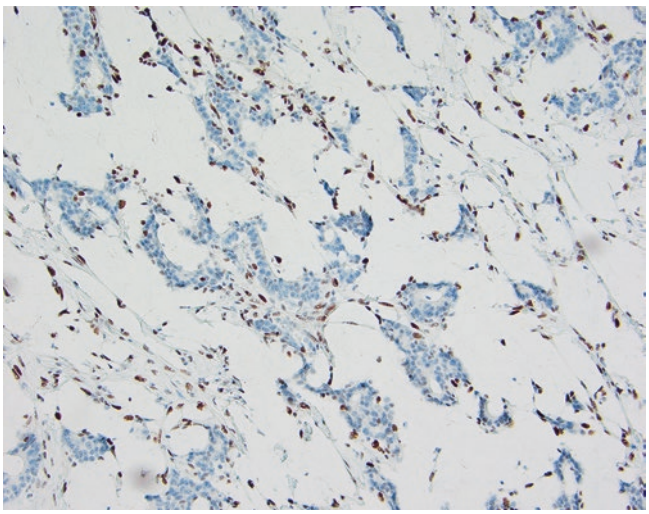

Fig. 35.3 Mucinous colorectal cancer loss of MLH1 20x

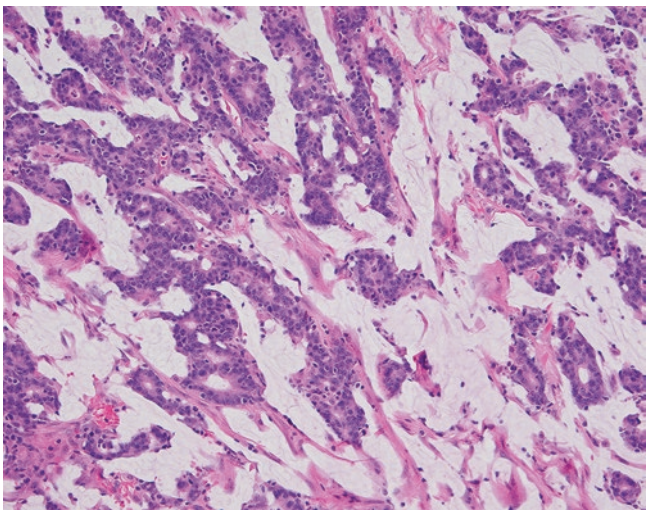

Fig. 35.1 Mucinous colorectal cancer H and E staining

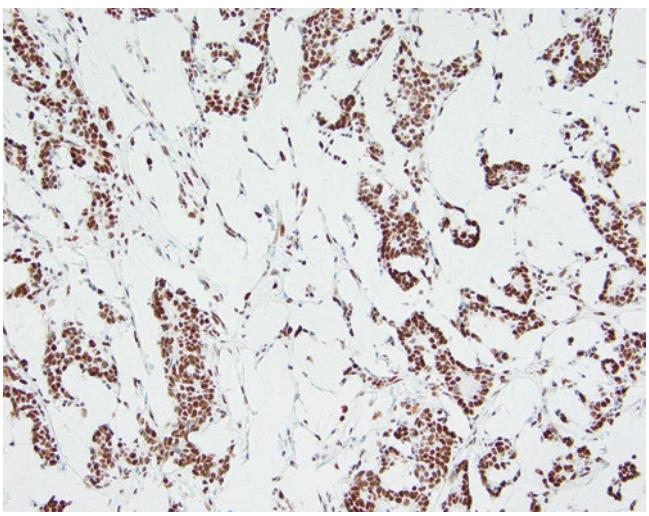

Fig. 35.2 Mucinous colorectal cancer intact MSH2 20x

A second mechanism active in the creation of MSI-H tumours involves CpG islands (in which a cytosine base is followed immediately by a guanine base linked by a phosphodiester bond), which can become hypermethylated in colorectal cancer. These cancers are then referred to as CIMP+ (CpG island methylation phenotype) tumours. The promoter region of MMR enzymes such as MLH1 and others may be affected, with silencing of gene expression resulting in an MSI-H phenotype. These cancers are somewhat unique in that they typically also have mutations in the V600 E codon of the *BRAF* gene and do not harbor mutations in the *KRAS gene* [24]. This is the diametric opposite of the genomic profile of patients with colorectal cancer related to Lynch syndrome where KRAS and not BRAF mutations are typically found.

Finally, a third mechanism implicated in the creation and persistence of errors in DNA replication is a mutation in the exonuclease region of the DNA polymerase epsilon (POLE) gene—60% of colon cancers so affected, usually MSS, or in the delta (POLD1) gene—40% of colon cancers so affected, usually MSI-H, leading to a so-called ultra -hypermutated phenotype with increased mutation number [25]. Overall incidence in colon cancer is difficult to determine but ranges from 2% to 10% depending on the study.

Table 35.1 Genomic alterations leading to an immune phenotype

dMMR	CIMP+	POLE/D1
MLH1 PMS2 MSH2 MSH6 mutations	CPG island methylation/MLH1	DNA polymerase mutations
Lynch syndrome BRAF wt RAS mutated	BRAF V600E mutated	BRAF unaffected
Non-Lynch syndrome BRAF mutated RAS wt	RAS most often wt	RAS mutations increased
MSI-H in most cases as tested by PCR or IHC	75% MSI-H cancers	Epsilon 6%—MSS
		Delta 4%—MSI-H

Cancers harboring any one of these three DNA replication errors may all potentially be responsive to immunotherapy owing to the presence of a large numbers of neoantigens (Table 35.1).

A recent international initiative to resolve inconsistencies in genome based classifications of colon cancer, which incorporates much of the above data, proposed four categories of consensus molecular subtypes (CMS): CMS1 (microsatellite instability immune 14%), hypermutated, microsatellite unstable and strong immune activation; CMS2 (canonical 37%), epithelial, marked WNT and MYC signaling activation; CMS3 (metabolic 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal 23%), prominent transforming growth factor–β activation, stromal invasion and angiogenesis [26]. It remains to be seen how widely this schema will be adopted, and further work needs to be done to validate the clinical utility of this system, but clearly CMS 1 tumours are likely to be the most responsive to immunotherapy.

35.2.3 Next-Generation Sequencing

Another major advance in the history of immunotherapy was the ability to sequence the entire exome and/or genome. Initially, the Sanger technique was the preferred option, and it may still be useful for sequencing single genes, short tandem repeats or small samples. However, this method can only reliably sequence short segments of DNA, takes a long time for more than simple tasks, and as a result is relatively expensive. Further, it is restricted to the discovery of substitutions, small insertions, and deletions. With the advent of so-called next-generation sequencing (NGS), massively parallel sequencing of thousands of genes, using much less material, could be completed less expensively and within hours [27]. Not only did this permit the identification of genomic alterations in the form of mutations, deletions, single nucleotide polymorphisms, insertions, duplications, and copy number change, but it also facilitated identification of the MSI-H phenotype and POLD1/E mutations, by assessing variation at a large number of microsatellites across the genome [28]. Further, the total mutational burden (TMB) present in a given cancer could now be quantified, which is an additional indicator of potential response to immune therapy. Despite the limitations of this technology which include the identification of clinically insignificant variants, increased personnel time for interpretation, the need for robust bioinformatics and large data storage capacity, there is no doubt that this advance has had a major impact on diagnostics and therapeutics.

35.2.4 New Approaches

The sentinel discoveries, which have resulted in truly effective immunotherapeutic options, have mostly taken place in the last 10–15 years, and are continuing at an ever-accelerating pace. Many previous initiatives with entities such as vaccines, immune stimulants, interleukins, interferons, and others directed at the treatment of various types of cancer, all had rather limited success, and it was often the case that results were obtained at the cost of excessive toxicity.

The modern era of immunotherapy was realized when the limited efficacy of these approaches was understood, and a subsequent reappraisal of the inherent immune response to cancer was undertaken. A deeper understanding of the cancer/immune system interface suggested novel opportunities for intervention, and one of these was the correction of immune paralysis, so often evident in cancers. Clearly, cancer is able to develop and grow unchecked and unrecognized in the early stages, but the fact that not everyone develops overt cancer suggests that some form of immune surveillance is at work. The immune system determines self and nonself by the binding of T cell receptors to complexes of peptides and class I major histocompatibility molecules on the cell surface of all cells, including both normal and cancer cells. Co-stimulatory and co-inhibitory signals then modulate the response of these T cells, either activating or inactivating them. Cancer cells survive by the inactivation of functional T cells, using signaling pathways which are physiologically important in the prevention of excessive immune system activity and thereby damage to self.

The cytotoxic T lymphocyte antigen 4 (CTLA-4) pathway was the first to be explored. T cell inhibitory ligands—CD80 and CD86 of the B7 family of membrane bound ligands, located on cancer cells, were observed to bind to the CTLA-4 receptors on T cells thereby inactivating their immune response. Consequently, it was postulated that antibodies which could bind to, and thereby block, these receptors could potentially interdict this interaction and allow the T cells to function once again. Similarly, the programmed cell death 1 (PD1) receptor was noted to promote T cell anergy and apoptosis when bound by the ligands PDL-1 and PDL-2. Antibodies to both receptors, and their ligands, have now

successfully been synthesized and are known as immune checkpoint inhibitors (ICIs).

The first successful treatment of a cancer based on these principles was conducted in patients with malignant melanoma [29]. This was closely followed by success in nonsmall cell lung cancer [30]. These two tumour types are distinguished by multiple mutations, thus generating many neoantigens which are presented to the T cells by the MHC 1 complexes. Other tumour types which were tested, and which do not have many mutations, such as prostate cancer and pancreatic cancer, did not respond well if at all to this approach.

In subsequent studies where colon cancer was included, patients were enrolled indiscriminately regardless of immune status, and the results were somewhat disappointing. However, with an ever-greater understanding of the underlying pathophysiology and immunology of colon cancer, researchers began to focus on those patients whose tumours were most likely to elicit an immune response and thus be prime candidates for immune modulation. These patients included those with dMMR and/or MSI-H tumours, those with a high TMB score, or those with any other reason to have multiple neoantigens such as with POLE/D1 mutations [31]. These more focused studies were considerably more promising, with the consequence that immunotherapy has challenged the hegemony of chemotherapy in this select group of patients. Results to date suggest that immunotherapy is most effective when used in the first line with a 44% response in KEYNOTE 177 [32] versus 33% response in the second line or later in KEYNOTE 164 [33]. The success of this approach has been so encouraging that much effort is now being directed to the conversion of nonimmunogenic cancers to cancers which can be recognized by the immune system as foreign, and thus a target for immune destruction. This will be discussed in more detail in a later section of this chapter.

Finally, it is important to mention that while targeted therapy, such as human epidermal growth factor receptor (HER) or epidermal growth factor receptor (EGFR) inhibition, acts principally by interdicting excessive cell signaling engendered by overexpression of the relevant genes, these interactions may indirectly involve the immune system, which could be of great importance as future therapy evolves in immunologically silent tumours.

35.3 Current Applications

35.3.1 Globally for all Colon Cancer

The successful identification of a subset of patients with colon cancer responsive to immunotherapy with ICIs has meant that this is now a very real option for this group. Because of this development, and because of the parallel development of targeted therapies in other subsets of patients, it is now essential that all colon cancers be classified not only by TNM staging, but also by molecular and genomic profiling. The extent to which this testing is carried out is dependent on the stage of the tumour and the resources available. Current recommendations suggest that all cancers beyond stage I, at a minimum, be tested for MSI-H/dMMR and BRAF/RAS expression by any one of a number of techniques [34]. Arguably, in pMMR disease, TMB should also be checked. Along with stratification for sidedness (right vs. left), this will facilitate rational choices in the adjuvant therapy of earlier disease (stages II and III) and will determine the optimal choice of therapy for more advanced cancers (stage IV) such as with liver metastases.

35.3.2 Early-Stage Disease

While adjuvant therapy is standard of care in patients with stage III disease, uncertainty and debate continue in stage II disease. Many tools and algorithms have been developed to assist in the decision regarding adjuvant therapy in stage II disease, a discussion of which is beyond the purview of this chapter. However, at this time, the issues related to the use of immunotherapy in this setting are similar to those in stage III disease. To date, the standard of care continues to be adjuvant chemotherapy with either FOLFOX (5FU, leucovorin, oxaliplatin every 2 weeks) or CAPOX (capecitabine, oxaliplatin every 3 weeks) or 5FU and leucovorin alone in the elderly and frail, for 3 or 6 months (depending on the exact staging, as per the IDEA trials and others) [35]. However, given the historically poor results with 5FU and leucovorin-based therapy in those with dMMR cancers, and the promising results with immune therapy in late-stage disease in this group, there is tremendous interest in the potential use of some form of immune therapy, either alone or in combination with chemotherapy in these patients. At present, the following studies are ongoing, and results are eagerly awaited (Table 35.2).

35.3.3 Late-Stage Disease

With the success of immune based therapy for cancers such as melanoma and nonsmall cell lung cancer, clinical studies designed to test the use of immune therapy in colorectal cancer quickly followed. At first, patients with metastatic disease who had progressed on standard chemotherapy were enrolled in studies without any selection based on immune phenotype. We now know that only around 15% of all colon cancers are MSI-H/dMMR and given the relatively low rate of metastasis in this group, only about 4% of patients with metastatic disease have cancers with this profile. It is, therefore, no surprise

Table 35.2 Immunotherapy studies in early stage disease

Study	Phase	Relevant eligibility	Outcome measures
Atomic A 021502	III	Colorectal cancer only	Primary: DFS
Adjuvant FOLFOX chemotherapy with or without atezolizumab	Target enrollment 700 patients	T1–4 N1–2 incl N1C M0	Secondary: OS and adverse events
	Opened 9/12/2017	Lynch syndrome allowed if dMMR	
NCI02912559		No prior therapy allowed	
mKRAS-targeted vaccine plus	I	Colorectal or pancreatic cancer	Primary: Number of participants with grade 3 or higher
Nivolumab and ipilimumab	Target enrollment 30 patients	T4 N1–2 M0 or totally resected M1	Study related adverse events
NCI04117087	Opened 5/28/2020	Expresses of one 6 KRAS mutations	Fold change in interferon producing mKRAS specific
		G12C, G12V, G12D, G12A, G13D, G12R	CD8 and CD4 T cells at 16 weeks
			Secondary: Months from therapy to recurrence or
			% change in interferon producing mKRAS specific
			CD8 and CD4 Tcells
Identification and treatment of micrometastatic disease in stage III colon cancer	III	Colorectal cancer T1–4 N1–2 M0	Primary: Clearance of ctDNA in all arms of the study
	Target enrollment 500 patients	Completed standard of care therapy	Secondary: Clearance of ctDNA in the arm with MSI-H cancer
	Opened 1/20/2020	MSI-H cancer for the Nivolumab arm	Cancers treated with Nivolumab (as one arm of 5)
NCT03803553		Detectable ctDNA post standard therapy	

that the initial response rates were somewhat unimpressive. However, when the data were examined further, it became apparent that those cancers with an MSI-H/dMMR profile behaved differently to the remainder and were more likely to show a response to immune therapy. Subsequent studies were designed to incorporate this critical information (Table 35.3).

KEYNOTE 016 was a phase II study conducted in three centers, in patients with colorectal cancer, both MSI-H/dMMR (11 patients) and MSS/pMMR (21 patients), who had been treated with two or more prior regimens, and also in MSI-H/dMMR noncolorectal cancer patients (nine patients) treated with one or more prior regimens [36] (Table 35.3). Patients were treated every 14 days with 10 mg/kg of pembrolizumab IV. The overall response rate for those with MSI-H/dMMR CRC was 40% with a disease control rate at 20 weeks of 78%, versus 0% and 11%, respectively, in MSS/pMMR patients. In the noncolorectal cancer patients, the corresponding numbers were 71% and 67%. Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumour in MSI-H/dMMR tumours, as compared with 73 in MSS/pMMR tumours ($p = 0.007$), and high somatic mutation loads were associated with prolonged progression-free survival ($p = 0.02$). Forty-one percent of patients had grade 3 or 4 adverse events (AEs)—lymphopenia (20%), anemia (17%), hypoalbuminemia (10%), bowel obstruction (7%), hyponatremia (7%), and increased alanine aminotransferase (ALT) (5%). These results allowed the FDA to grant accelerated approval of the use of pembrolizumab in May 2017 for patients with colorectal cancer with MSI-H/dMMR status who had progressed on standard chemotherapy, along with approval for all MSI-H or dMMR solid tumours with progression following prior treatment and with no satisfactory alternative.

CheckMate 142 was a multicohort, multicenter phase II study in patients with MSI-H/dMMR metastatic colorectal cancer. In one arm, patients were required to have progressed on or after, or been intolerant of, at least one previous line of treatment including a fluoropyrimidine and oxaliplatin or irinotecan (54% had received at least 3 or more prior therapies) and were treated with nivolumab 3 mg/kg IV every 2 weeks. In a second arm, patients were also required to have progressed on or after, or been intolerant of, at least one previous line of treatment including a fluoropyrimidine and oxaliplatin or irinotecan (76% of patients had received at least two prior therapies) and were treated with four doses of nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks, followed by nivolumab alone 3 mg/kg IV every 2 weeks until progression, death, unacceptable toxicity, or voluntary withdrawal [37, 38]. PDL-1 status did not affect the response rate in either arm. In the group receiving nivolumab only, at a median follow-up of 12.0 months, 23 of 74 patients (31.1%, 95% confidence interval [CI]: 20.8–42.9) achieved an objective response and 51 of 74 patients (69%, 57–79) had disease control for 12 weeks or longer. Median

Table 35.3 Completed immunotherapy studies

Study	Eligibility criteria	Protocol	Results				TTR	PD	mRAS/mBRAF EFFECT	
KEYNOTE 016	Progressive metastatic colorectal/other cancers	Pembrolizumab 10 mg/kg		*dMMR*	*pMMR*	*dMMR*	DMMR CRC 7 months	Not reported	Not reported	
Phase 2	Colorectal cancers with ≥2 prior therapies	IV Q 2 weeks		*Colorectal*	*Colorectal*	*Other cancer*	pMMR CRC N.A.			
	(dMMR or pMMR)		PFS at 20 weeks	78%	11%	67%	dMMR other 2 months			
	Non—Colorectal cancers ≥1 prior therapy		ORR at 20 weeks	40%	0%	71%				
	(dMMR only)		Patient numbers:	11	21	9				
CHECKMATE 142	Recurrent or metastatic colorectal cancer	Nivolumab 3 mg/kg	Disease control ≥12 weeks 69%				2.8 months	28%	Wt RAS/RAF	ORR 41%
Nivolumab only	dMMR/MSI-H	IV Q 2 weeks	ORR at 12 months 31.1%				(1.4–3.2)		mBRAF	ORR 25%
Phase 2	≥1 prior therapy		Median duration of response NR							
	54% had received ≥3 prior therapies		Patient numbers: 74							
CHECKMATE 142	Recurrent or metastatic colorectal cancer	Nivolumab 3 mg/kg	PFS at 12 months 71%				2.8 months	12%	RAS/BRAF wt or	
Nivolumab plus	dMMR/MSI-H	IV Q 3 weeks × 4 doses	ORR at 13 months 55%				(1–14)		Mutated no difference	
Ipilimumab	≥ 1 prior therapy	Then Q 2 weeks	Median duration of response NR							
Phase 2	76% had received ≥2 prior therapies	Ipilimumab 1 mg/kg	Patient numbers: 119							
		IV Q 3 weeks × 4 doses								
KEYNOTE 164	Metastatic colorectal cancer	Pembrolizumab 200 mg	PFS 2.3 months (A) 4.1 months (B)				A 4.3 months	46%	mRAS	ORR 37%

(continued)

Table 35.3 (continued)

Study	Eligibility criteria	Protocol	Results				TTR	PD	mRAS/mBRAF EFFECT	
Phase 2	dMMR/MSI-H	IV Q 3 weeks	ORR 33% both cohorts				(1.8–24.9)		mBRAF	ORR 55%
	Cohort A ≥ 2 prior therapies		OS 31.4 months to NR				B 3.9 months	40%	mRAS	ORR 36%
	Cohort B ≥ 1 prior therapy		Median duration of response NR				(1.8–12.5)		mBRAF	ORR 20%
			Patient numbers: 61, 63B							
KEYNOTE 177	Metastatic colorectal cancer	Pembrolizumab 200 mg	PFS 16.5 months (Pembrolizumab) vs. 8.2 months (chemotherapy)				P 2.2 months	29%	RAS mutated—no	
Phase 3	dMMR/MSI-H	IV Q 3 weeks	ORR 43.8% (Pembrolizumab) vs. 33.1% (chemotherapy)				(1.8–18.8)		Benefit in PFS (30%)	
	No prior therapy allowed	Or FOLFOX or FOLFIRI	Median duration of response:				C 2.1 months	12%	No RAS data	
		With our without Cetuximab	Pembrolizumab NR chemotherapy 10.6 months				(1.7–24.9)		BRAF wt and V600E	
		Or Bevacizumab	Patient numbers: 307						Mutated—equal	
		IV Q 2 weeks							Response	
		Crossover to Pembrolizumab								
		Permitted on progression								

duration of response had not yet been reached at the time of reporting; all responders were alive, and eight had responses lasting 12 months or longer (Kaplan-Meier 12-month estimate 86%, 95% CI: 62–95) [38]. The time to an objective response was 2.8 months (1.4–3.2). In the group receiving both nivolumab and ipilimumab, the overall response rate (ORR) was 55%, the disease control rate was 84%, and 7% of patients had a complete response (CR). The 12-month progression-free survival and overall survival rates were 71% and 85%, respectively. The median duration of response, median progression-free survival, and median overall survival have not yet been reached at the time of reporting. Importantly, the time to an objective response was once again 2.8 months (1–14). Grade 3–4 AEs occurred in 32% of patients in this arm. AEs leading to discontinuation included acute kidney injury, increased transaminases, colitis, sarcoidosis, dyspnea, necrotizing myositis, pneumonitis, autoimmune hepatitis, and thrombocytopenia. No deaths were attributed to therapy. This study led to approval by the FDA, in August 2017, of the use of nivolumab in MSI-H/dMMR colorectal cancer that had progressed after standard chemotherapy. Subsequent approval for the combination of nivolumab and ipilimumab was granted in July of 2018. Evaluation of this combination in the first-line setting in a current phase II study has recently been reported [39]. A total of 45 treatment-naïve patients were treated with nivolumab 3 mg/kg every 2 weeks and low-dose ipilimumab every 6 weeks until progression. At 12 months, progression-free survival (PFS) and overall survival (OS) were 77% and 83%, respectively, and ORR was 60% with 7% CR with disease control rate of 84%. Grade 3–4 AEs occurred in 16% with 7% of patients requiring discontinuation of therapy as a result. The decrease in toxicity with this regimen is notable and the response rates look very similar to those in the more intensive regimen (noting that this group was previously untreated as opposed to the more intensive group).

KEYNOTE 164 was a phase II study, conducted in 128 centers worldwide, testing pembrolizumab 200 mg IV every 3 weeks in patients with MSI-H/dMMR CRC previously treated with two or more regimens containing 5FU, oxaliplatin, irinotecan ± EGFR, or vascular endothelial growth factor (VEGF) inhibitors (cohort A, 61 patients), or one or more prior regimens (cohort B, 63 patients) [33]. The ORR was 33% in both cohorts with the median duration not reached at the time of reporting. PFS was 2.3 months in cohort A and 4.1 months in cohort B with overall survival of 31.4 months with 95% of responses ongoing in both cohorts at 12 months. Grade 3 or 4 AEs occurred in 11% of patients, including anemia, thrombocytopenia, diarrhea, pneumatosis intestinalis, arthritis, syncope, pneumonitis, and vasculitis (n = 1 each). Two patients had grade 3–4 immune-mediated AEs of colitis and pneumonitis (n = 1 each). The authors concluded that pembrolizumab conferred durable benefit in previously treated patients with MSI-H/dMMR cancers and that this was an important addition to the therapeutic options for these patients.

KEYNOTE 177 is the newest study to report results [32]. In this study, patients with untreated MSI-H/dMMR stage IV CRC were randomized to physician's choice, prior to randomization, of mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab (154 patients) every 2 weeks, or to pembrolizumab 200 mg IV every 3 weeks (153 patients). The group randomized to pembrolizumab had a much better OR (43.8% vs. 33.1%) and PFS (16.5 vs. 8.2 months; hazard ratio [HR]: 0.60; 95% CI: 0.45–0.80; p = 0.0002) than the conventional chemotherapy group. Grade 3–5 treatment-related adverse events for pembrolizumab versus chemotherapy (22% vs. 66%) were also in favor of immunotherapy. Impressively, the median (range) duration of response was not reached with pembrolizumab (2.3+ to 41.4+ months) versus 10.6 months (2.8 to 37.5+) with chemotherapy. This has now led to FDA approval for pembrolizumab in the first-line setting in patients with MSI-H/dMMR cancers. Overall survival (OS) data are yet to be presented for KEYNOTE-177, which will be complicated by the 59% effective crossover rate. One caveat not to be ignored is the fact that compared to chemotherapy, 2.5 times the number of patients on pembrolizumab had progression as their best response (29.4% vs. 12.3%). This is clearly a subgroup of patients unresponsive to PD1 blockade despite having the appropriate immune profile, but currently there is no validated method of identifying these patients. Potential strategies to mitigate this problem could be the combined use of PD1 antibodies with anti-CTLA-4 antibodies, or with chemotherapy. Finally, it is interesting to note that the dosing of pembrolizumab has evolved from 10 mg/kg every 2 weeks in KEYNOTE 016, to 200 mg every 3 weeks in KEYNOTE 164 and 177 which is more than a fourfold reduction in dose.

35.3.4 Colorectal Cancer Liver Metastases

Liver metastases are present in approximately 15% of patients at initial presentation, and in 30% to 50% of patients during the course of their disease [40]. There are several potential scenarios, all of which may require a different approach. If the liver metastases are only one facet of more widespread metastatic disease, and where there is no intent to address the liver directly in any way, treatment can clearly follow the established guidelines for stage IV disease. Systemic therapy matched to the molecular and genomic profile of the cancer is the logical choice. Conversely, if the liver metastases are the only site of metastatic disease, then a specific plan to treat these may be required. In this situation, the status of the primary tumour, the number and distribution of the metastases, and the overall performance status of the patient will determine the options. Many of these issues are addressed in

other sections of this book, but germane to this discussion is the choice of therapy when systemic treatment is needed, either by itself or in concert with liver directed therapy such as Yttrium 90 (Y90), chemoembolization, bland embolization, radiofrequency ablation, cryo-ablation, and SBRT (stereotactic body radiation therapy). In this situation, a decision needs to be made as to whether conventional chemotherapy, immunotherapy, or some combination is optimal. This decision clearly hinges on the immune profile of the cancer, and the potential for curative or only palliative therapy.

35.4 Scope of the Problem

Given the unique clinical questions posed by the therapy of colorectal cancer liver metastases, based on the results now reported for immunotherapy for colorectal cancer in general, it is important to examine what we know about immunotherapy in this specific setting. The liver is a complex organ with elements of both the innate and acquired immune systems in abundance, and with an ability to generate an inflammatory response via numerous cytokines. Immunosuppressive cells such as T-regulating cells (Tregs), N2 neutrophils, type 2 macrophages, and myeloid-derived suppressor cells (MDSCs) all contribute to immune tolerance if present. On the other hand, an increased presence of tumour infiltrating lymphocytes (TILS), dendritic cells, and N1 neutrophils are signs of an active immune response and generally correlate with improved survival [41].

The initial immune-active cells encountered by circulating cancer cells are the liver sinusoidal endothelial cells (LSECs), and the Kupffer cells (KCs), and these cells recruit and direct the subsequent immune cell activity by cytokine selection. In general, the liver microenvironment tends to be immuno-suppressive, supporting the generation of pre- and prometastatic niches which promote metastatic growth of circulating colorectal cancer cells [42]. In addition, there is evolving evidence that the liver may actually promote systemic immune tolerance by promoting systemic tumour-specific $CD8^+$ T cell loss [43]. In preclinical models, there is a suggestion that radiation therapy may abrogate this response and could be a useful adjunct to immunotherapy. It is unclear whether resection, ablation, or embolization will have the same effect. Recent data suggest that while the immune microenvironment of liver metastases is mostly homogeneous across individual lesions, these lesions not infrequently differ in their immune profile to that of the primary site [44]. Moreover, individual metastases may display notable differences in immune infiltrate one to another, presumably arising from different clones in the primary tumour. There may also be natural selection in the process of metastasis, whereby clones able to evade immune surveillance are more likely to survive in the circulation. In parallel, various mutations in genes responsible for the antigen processing machinery, such as Beta-2-microglobulin, JAK 1, and JAK 2, may become more prevalent as the cancer progresses and thus be present in liver metastases [45]. These mutations then impede the process of antigen processing and presentation and the immune system fails to act.

35.5 Optimal Sequencing of Therapy

A global question, which is as yet unanswered, is the optimal way to sequence immunotherapy, chemotherapy, and other options in those cancers (including colorectal liver metastases) where immune therapy is a possibility based on the molecular profile of the tumour. Naturally, in the practice setting, the choices may be limited by the specifics of the FDA approval for each drug. However, looking forward, it is critical to know whether choosing immunotherapy or chemotherapy or both is likely to give the best results. In addition, it is as yet unclear as to whether using immunotherapy as neoadjuvant therapy, adjuvant therapy or both optimizes the use of this modality [46]. It is possible that the optimal strategy would be to combine both neoadjuvant and adjuvant treatments as each have their advantages. As we have seen, current candidates for immunotherapy are cancers with dMMR/MSI-H phenotype, cancers with a high TMB, and cancers with POLE -like mutations, that is, CMS type 1 cancers [31]. Clearly not all of these cancers respond to immunotherapy, with an overall response rate of 15–40% depending on the study (KEYNOTE, etc.) and several resistance mechanisms have been proposed. These include mutations in Beta −2-microglobulins (B2M), important for antigen presentation, mutations in JAK 1, and JAK2 genes, which encode kinases downstream of the IFN- ϒ receptor important for IFN -ϒ signaling [47] and others including RTKs, MAPK, PI3K-AKT-mTOR, Hippo, and Wn [48]. Currently there is no way of identifying resistant tumours in advance, and thus no way to be selective in the therapy.

To objectively evaluate this issue, the three-arm phase III COMMIT study (NCT02997228) is currently examining atezolizumab (PDL-1 inhibitor) alone versus mFOLFOX6 plus bevacizumab, with or without atezolizumab, in patients with MSI-H metastatic colorectal cancer in the frontline setting. The primary objective is PFS with secondary objectives of OS, safety, duration of response, duration of stable disease, PFS at 12 months, and disease control rate at 12 months. This study is ongoing but currently suspended for interim analysis.

Clearly, if treatment is administered with the goal of shrinking the tumours and rendering them operable/ablatable, then any progression or enlargement of the lesions is highly undesirable. Based on data from the KEYNOTE 177

study, despite the fact that ORR was higher with pembrolizumab than with chemotherapy ± targeted therapy (43.8% vs. 33.1%), nearly a third of patients on pembrolizumab progressed within 2 months of starting therapy (29.4% vs. 12.3%) [32]. This is a highly problematic number, and as no more than 10% of patients in both arms have thus far received intent to cure therapy, many clinicians feel that this may preclude the use of immunotherapy in this space. Similar numbers were seen in the other studies (CheckMate 142–28% arm A and 12% arm B, KEYNOTE 164–46% arm A and 42% arm B) with CheckMate 142 arm B perhaps the most promising in this regard (nonstatistical comparison). However, toxicity must also be weighed, and in general this was notably less with immunotherapy (grade 3 or higher in 22% vs. 66% for chemotherapy). Toxicity to the normal liver from chemotherapy can lead to prohibitive perioperative complications with a plethora of data to substantiate this issue—irinotecan (hepatosteatosis), oxaliplatin (sinusoidal obstruction syndrome and noncirrhotic portal hypertension), and bevacizumab (postoperative complications, wound healing and bleeding/clotting) have all been problematic when used before surgery.

In a priori resectable disease, it is even less clear whether immunotherapy has a role. Studies to evaluate the utility of perioperative chemotherapy in this setting have not clearly demonstrated a benefit in MS-unselected patients [49] and this question has not been specifically assessed in MSI-H/dMMR cancers. Thus, the use of immunotherapy is not yet a mainstream option in the presurgical space, and limited cycles of the appropriate chemotherapy ± targeted therapy are still considered the standard of care. This will be subject to change as data continue to evolve.

Complicating the choice of therapy, a little further is the fact that the efficacy of pembrolizumab in 74 patients with RAS mutated tumours in KEYNOTE-177 looked to be less, with no benefit in PFS in RAS mutated tumours [32]. In CHECKMATE 142 the ORR with nivolumab was also lower in RAS mutated tumours versus those with both RAS and BRAF wild type (27% vs. 41%) [37]. In KEYNOTE 164, the response in BRAF mutated tumours in arms A and B was 55% and 20%, and in RAS mutated tumours was 37% and 36%, respectively [33]. However, the numbers are small, and in KEYNOTE-177 up to 30% of patients did not have RAS data available. Interestingly, response in BRAF mutated tumours in CHECKMATE 142 was 25% that is higher than the 10% seen in historical controls using standard IV chemotherapy, and the 10–16% when BRAF, MEK, and EGFR inhibitors are combined [50]. This might suggest that immunotherapy is a preferable option in these patients but will need to be confirmed with further study. PDL-1 status did not influence the response, with <1% expression having equivalent response to ≥1% expression at 28–29%.

35.6 Time to Response

If immunotherapy is chosen, it is important to understand the timeline for response such that an accurate assessment of efficacy is made. Treatment should neither be terminated prematurely, thus depriving the patient of a valuable therapy, or continued too long when there is no efficacy. In KEYNOTE 016, the dMMR colorectal cancer group receiving pembrolizumab had a time to response (TTR) of 28 weeks versus 12 weeks for the noncolorectal group. The three newest studies, which all selected patients with MSI-H/dMMR status only, are most helpful in this regard. In KEYNOTE 164, the TTR was 4.3 (1.8–24.9) months in arm A with ≥2 prior therapies, and 3.9 (1.8–12.5) months in arm B with ≥1 prior therapy [33]. In CHECKMATE 142, the TTR was 2.8 (1.4–3.2) months using nivolumab only with ≥1 prior therapy, and 2.8 months using nivolumab plus ipilimumab with aggregate ≥2 prior therapies [37, 38]. Finally, in KEYNOTE 177 where no prior therapy had been given, TTR was 2.2 (1.8–18.8) months with pembrolizumab and 2.1 (1.7–24.9) months with chemotherapy as a comparator [32]. While a statistical comparison between these studies is not possible, some general observations can be made. It appears that the earlier immunotherapy is used in treatment sequencing, the earlier a response may be seen. The operative range is from 2.1 to 4.3 months with some responses taking much longer. Secondly, the time to response specifically in metastatic disease to the liver is not reported in these studies, but given what we know about the relative resistance of disease in this location, it may possibly be longer.

35.6.1 Management of Toxicities

In general, immunotherapy is well tolerated, and most patients are able to continue their treatment with limited or no interruptions. This is especially true when a single agent is used but is more problematic with higher doses, or when two or more therapies are combined. Many patients will experience at least one of the common toxicities and a knowledge of how to manage these is key to successful continuation of treatment. In general, if the symptoms are mild, they can often be managed without interrupting treatment, but if they are severe, then immunotherapy may have to temporarily be suspended or stopped altogether. Most toxicities appear within the first 12 weeks of therapy and resolve within 12 weeks of onset with appropriate therapy, but delayed onset may occur and should be watched for. The National Comprehensive Cancer Network and the American Society of Clinical Oncology have promulgated clinical practice guidelines for the management of immune related AEs, and these are invaluable in the appropriate management of these

complications [51]. Accurate grading of the intensity of the reaction is critical to making the correct decision for therapy, and the clinician is encouraged to become familiar with these definitions and to refer to the tables as needed. Furthermore, anti-CTLA4 agents may need to be treated somewhat differently than anti-PD1 or anti-PDL-1 agents, or other therapies, as the risk of specific organ toxicity is not the same. The skin, gastrointestinal system, liver, endocrine system, and lungs are most often affected, but in aggregate, patients treated for colorectal cancer do not experience any unique or more severe symptoms than any other group. It should be noted that NSAIDs may aggravate GI toxicity and should be avoided as much as possible. Interestingly, similar to the experience with some targeted therapies, the development of an irAE (immune-related adverse event) has been correlated with response to therapy and this is currently being further evaluated [52].

Most cases are treated with topical, po and/or IV steroids, depending on location and severity, but other immunosuppressants, IVIG, plasma exchange, and Infliximab or alternative tumour necrosis factor (TNF)–blocking agents may be required in severe cases. The need to resume therapy after an interruption for toxicity is currently undergoing further evaluation, and in those patients who have already had an objective response to therapy, it is unclear as to whether resumption of immunotherapy is needed [53]. Consultation with the relevant specialists is appropriate in ≥ than grade 2 adverse events, depending on organ involvement, or at any time when the clinician is uncertain about therapy. Cardiac toxicity is somewhat unique in that holding checkpoint inhibitor therapy is recommended for all grades of complications, including grade 1 (asymptomatic biomarker elevations), with reinstitution of treatment seldom appropriate. Patients with auto-immune diseases and/or organ transplants or on any form of prior immunotherapy may be at high risk of complications and should be evaluated by a multidisciplinary team prior to starting any form of immunotherapy. Finally, emerging evidence that the patient's microbiome and personal ecology may play a role in the incidence of irAEs is the subject of intensive investigation and may lead to innovative ways to ameliorate these problems [54].

35.6.2 Evaluation of Response

35.6.2.1 Radiology

From the beginning, it was evident that response to immune-based therapies could not necessarily be judged in the same way as the response seen with conventional chemotherapy. This problem was identified in early trials of ipilimumab in melanoma where the phenomenon of pseudoprogression (apparent progression after starting therapy, followed by measurable response on subsequent imaging) was first noted [55]. Later, an equally unusual presentation of hyperprogression (actual rapid progression of disease after starting immunotherapy) was recognized [56]. This seems to be more common with anti-PD1/PD-L1 therapy. It was also realized that newly identified lesions could represent previously occult metastases that subsequently enlarged and become radiologically apparent because of immune cell infiltration and inflammation. As a result of these observations, it was clear that RECIST (Response Evaluation Criteria in Solid Tumours), developed for the assessment of response to conventional chemotherapy and subsequently upgraded to RECIST 1.1, were not always applicable to the assessment of response to immunotherapy [57]. Consequently, immune-specific-related response criteria (irRC, iRECIST, irRECIST, imRECIST) were promulgated to guide physicians and others in the assessment of response to immune based treatments [58–61]. The key adjustment to prior criteria, was to permit initial progression on the first set of images, but to follow this up with a second set of images at 4–8 weeks, at which time an assessment of response would be made. If there is an increase in the size of prior new lesions (≥5 mm for sum of new lesion target or any increase in new lesion nontarget), or if new lesions appear when none had previously been recorded, then this is deemed progression, but in a number of cases stability or regression are noted. The definition of stable disease, partial response, and complete response remained unchanged from RECIST 1.1. The differences between the new systems were mainly related to: unidimensional versus bidimensional measurements; the percentage of change in the lesions as criteria for response; and the iRECIST system did not incorporate progressive disease measurements until the second confirmatory scans. It is important also to correlate the radiologic response with the clinical status, as continued therapy in the face of initial progression is usually only countenanced if the patient is clinically stable and able to continue with therapy. Furthermore, pseudoprogression is uncommon (<3%), especially with PD1/PDL-1 based therapy, and increase in the size of metastatic lesions is far more likely to be actual progression.

A recent initiative to examine the frequency of unusual responses to immune therapy, evaluated positive responses in patients treated with immunotherapy for melanoma [62]. The authors suggest four categories of atypical response. Pattern 1 is a decrease, or less than 20% increase, in the sum of the longest dimension (SLD) without a return to below the nadir (80% of cases). Pattern 2 is a 10–19% increase in SLD, with a return to below the nadir (9% of cases). Pattern 3 is a 20% or greater increase in SLD, with a return to below the nadir (classic pseudoprogression) (1% of cases). Pattern 4 is the development of new lesions, with a decrease in SLD lasting through at least two consecutive scans (10% of cases). Patterns 2, 3, and 4 were defined as atypical response patterns. These data once again show that true pseudoprogres-

sion is indeed rare, and that other more classical patterns of response are much more common.

Most recently, guidelines for the interpretation of FDG PET/CT scans in the assessment of response to immunotherapy have also been established, as the interpretation of these tests poses a different challenge [63]. The very earliest attempt to provide a reproducible system for evaluating PET/CT in patients treated with immunotherapy proposed that a complete metabolic response (CMR) is reached when all tumour lesions are no longer detectable against adjacent background activity, whereas progressive metabolic disease (PMD) is defined as an increase in SUVmax of ≥25% from baseline imaging or the appearance of new metastatic lesions [64]. This definition has subsequently been amended in other systems, with PERCIST [65] and PECRIT [66] being two examples. Essentially, tumour response and metabolic derangement resulting from the immunotherapy must be identified and distinguished, and it is critical that results are discussed with the interpreting radiologist before any conclusions are reached. Along with interpretation of response to therapy, PET may be helpful in identifying early signs of irAEs and can alert the clinician to organs/systems of concern.

35.6.2.2 Circulating Cell-Free DNA (cfDNA) and Circulating Tumour DNA (ctDNA)

It has been known for more than 50 years that DNA exists in the circulation in a nonencapsulated form. DNA fragments enter the blood during apoptosis of normal cells, and apoptosis, active secretion, immune destruction or necrosis of cancer cells, and are typically removed by macrophages. cfDNA fragments have a very short half-life of about 2 h, and this means that they are a very dynamic marker of tumour volume. They may be more persistent when cancer is present owing to the increased turnover of cells. cfDNA derived from noncancerous cells is generally up to 200 bp in length, whereas cfDNA derived from cancer cells is often >200 bp in length. Following curative surgery, the detection of these longer fragments is suggestive of residual cancer and may be a marker for recurrence [67]. A portion of the cfDNA originates from a tumour clone and is referred to as circulating tumour DNA (ctDNA). This portion of the cfDNA contains a cancer-specific mutation in one or more of the BRAF, RAS, APC, p53, etc. coding genes. Detection of the mutation under question in the cfDNA requires knowledge of the mutations in the primary tumour, and subsequent directed assay for ctDNA containing these mutations. The identification of specific ctDNA in the blood of patients thought to be in remission, may presage and predict tumour recurrence. The detection of so-called minimal residual disease has been increasingly applied in both hematological malignancies and in sarcomas and the cancer activity discovered is thought to be the origin of disease recurrence. In stage II and III colorectal cancer there is now much interest in the use of this new technology, where both the decision to initiate adjuvant chemotherapy, and the duration thereof after primary resection, is still based on simple and often inaccurate paradigms. The specificity of ctDNA is much higher than that of CT scans, and a study in stage II colon cancer treated surgically demonstrated that 97% of patients with no detectable ctDNA postoperatively did not recur, whereas those with positive ctDNA had a recurrence risk greater than stage III disease [68]. This approach may be of particular utility in the assessment of response to immune therapy in colorectal metastases, where radiologic response may be more difficult to interpret, as noted, particularly if the tumour exhibits characteristics of pseudoprogression. This strategy has been tested in MSS refractory colorectal cancer treated with nivolumab or pembrolizumab plus regorafenib and was able to better predict early response to therapy at 4 weeks than carcinoembryonic antigen (CEA) [69]. Given the expense of immunotherapy, any improvement in the prediction of response could have a significant impact on cost. A recent summary of studies looking at this issue has concluded that the timing of the tests as well as the degree of change (complete disappearance of ctDNA at 4–6 weeks is highly predictive of a good response) is critical in drawing any reliable conclusions [70]. A joint review by the American Society of Clinical Oncology and the College of American Pathologists has raised important questions about the appropriate application and utility of this technology. They point to the fact that the data are too limited as yet to draw firm conclusions and suggest that consistency of the processes and stringency of the techniques needs to improve further before this technology can become part of routine care [71]. A parallel review reported in an NCI colon and rectal-anal task forces whitepaper is much more positive and suggests that this technology is likely to have a major impact on the assessment of disease burden in all manner of settings, including the assessment of response during immune therapy [72]. Commercial interests have rapidly espoused this approach and many tests are already in daily use.

Interestingly, ctDNA may not only be useful diagnostically and prognostically, but may potentially play a role in the actual mechanism of metastasis, a process named genometastasis [73].

35.6.2.3 CEA

CEA continues to be followed and used in concert with imaging and other blood tests, and there is certainly some value to this approach if the limitations are understood. There is often a very rapid drop in the CEA in those patients destined to have a significant response, and a falling value correlates well with outcomes (Fig. 35.4). Ultimately, a more definitive test such as an MRI of the liver will always be required, given the possibility of false positive and false negative results from the CEA, and given the fact that only about

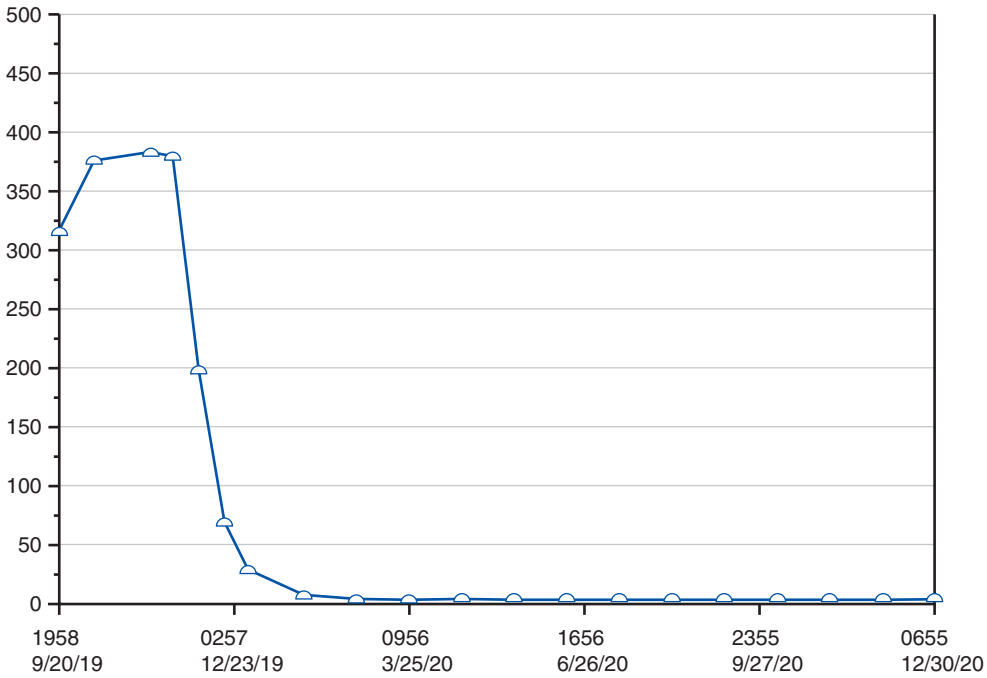

Fig. 35.4 Typical evolution of CEA (ng/mL) over 3-month intervals in a patient responding to immunotherapy

75% of colorectal cancers express this marker. Some sources feel that there is little utility from this test and a low yield on investment [74], while other believe that there is definite value and that this test still has relevance in this disease [75]. Until more advanced tests such as ctDNA have been fully vetted and firmly established, this will undoubtedly continue to be used. Interestingly, Kupffer cells express receptors for CEA and once bound, this will facilitate cytokine production which in turn will upregulate adhesion molecules and thereby protect cancer cells from the cytotoxic effects of nitric oxide. Thus, a high CEA may potentially mediate metastasis and modulate the inflammatory response in the liver [76].

35.7 Developing and Future Applications

35.7.1 New-Generation of Immune Checkpoint Inhibitors

Given that roughly 85% of colorectal cancers do not respond to immunotherapy, and that many of those that do respond often develop resistance, there is significant ongoing study to better understand this resistance and to develop strategies to address this challenge. While PD1, PDL1, and CTLA4 have been the targets of initial interest in immunomodulation, additional targets such as TIGIT, TIM-3, LAG-3, and VISTA are now being studied [45]. These receptors are notably more highly expressed on TILs (tumour infiltrating lymphocytes) as opposed to circulating lymphocytes, and when present seem to result in dysfunctional CD8 T cells and immune exhaustion. Clinical studies to evaluate the use of antibodies to these receptors, either alone or in combination with PD1 blockade, are currently in progress with very preliminary results showing some promise [77, 78].

35.7.2 Alteration of the TME

The microenvironment of metastases has been studied extensively and compared to that of the primary tumour. Interestingly, there is often a lack of concordance as previously discussed, and metastases to the liver and lungs may exhibit increased MYC signaling compared to the primary site, and are very seldom, if ever, classified as CMS3 subtype [79]. Many mechanisms which promote immune tolerance are active in the liver (-Scope of the problem above) and undoubtedly account for the overall poor response to immunotherapy in this location. Treatment strategies to abrogate these immune escape mechanisms are critically needed.

35.7.2.1 Adoptive T-Cell Therapy

This approach utilizes autologous T cells which have been harvested, expanded, and activated ex vivo by exposure to antigens, and then reinfused into patients. Trials utilizing TILs and sentinel lymph node T cells have been completed with some responses but no major improvements in DFS as yet. Chimeric antigen receptor T cell (CAR-T) therapy has been successful in hematologic malignancies, such as B-cell acute lymphoblastic leukemia, and others. The critical next steps in the transition of this technology to solid tumours such as colorectal cancer is the identification of precise target antigens, refinement of high dose lymphodepletion, and improvement of cell delivery to target tissue. If successful, this will facilitate T cell infiltration of metastases, combat T

cell exclusion, and hopefully engender a powerful immune response. Targets which have been addressed in animal models and in phase I studies in humans include GUCY2C and CEA with early indicators of efficacy [80, 81]. Toxicity is not inconsequential, however, and cost is high. A single patient with stage IV colon cancer treated with HER-2 targeted CAR-T cells, became acutely ill and subsequently died following the infusion, thought to be due to cytokine release in the lungs which expressed low levels of HER-2. This experience exemplifies the potential dangers of this strategy and subsequently tempered enthusiasm, with a suggestion that future studies should follow a dose-escalation approach [82].

35.7.2.2 Vaccines

A number of approaches have been tried in colorectal cancer, including dendritic cell therapy, viral vectors, autologous cells and peptide-based vaccines. Regardless of the technique chosen, the first sign of a positive result is the generation of appropriate antibodies or a T cell response. While this may often happen with single antigen targets such as CEA, GUCY2C, MUC-1, and TLR9, it has been difficult to demonstrate any significant improvement in PFS or OS compared to standard therapy or placebo. There is some suggestion that the use of multiple antigens may be a more productive route and up to seven antigens were used in a recent study with positive results seen in those patients who generated an immune response to all seven antigens [83]. The use of immune adjuvants and also vaccines aimed at neoantigens rather than overexpressed self-antigens is looking to be a more productive strategy in other tumours [84, 85]. Further, the combination of vaccines and ICIs is theoretically appealing as many tumours fail to respond to therapy despite the generation of a robust immune response. Examination of the tumour environment in these cases will often show immune exhaustion, making a case for the use of ICIs along with the vaccine. Numerous studies are currently examining this strategy in both MSI and MSS colon cancers.

35.7.2.3 Gut Microbiome

In the last decade, it has become increasingly apparent that the gut microbiome (GMB) plays an especially important role in the maintenance and conduct of the immune system [86]. There are trillions of bacteria in the gut and together with the mucosal barrier and local immune cells, these bacteria promote dendritic cell maturation and Th1 response, essential to both intestinal homeostasis and to systemic immune function. Many factors can affect the GMB including exercise, diet, geography, ethnicity, gender, age and co-morbidities. Antibiotics and proton pump inhibitors are particularly detrimental and can promote the risk of C diff colitis and vancomycin resistant enterococcus. These pathogenic bacteria can produce toxins and carcinogens and may also promote carcinogenesis by the induction of inflammation or immune suppression. Once antibiotics have been given, it takes at least 1 month to reconstitution of the previous status and this may actually be a negative prognostic factor [87].

Relevant to this discussion, recent work has shown that there is a significant interplay between the GMB and the efficacy of immunotherapy, which could have major implications for future treatment. There is a definite change in the GMB when immunotherapy is given, and the subsequent bacterial profile appears to influence response to therapy [88]. Further, not only may the constitution of the GMB affect the efficacy of therapy but it may also determine the development of irAEs [89]. Both in mice and in humans it has now been shown that both anti-CTLA4 and anti-PDL1 antibodies rely on the GMB for optimal activity and that Bacteroides and Bifidobacterium, amongst others, may play a key role [90, 91]. These data suggest that examination of the GMB prior to therapy could not only be predictive, by determining the likelihood of response and of toxicity, but may also be an opportunity for proactive intervention. Many strategies are being explored to this end. One approach, which has had success in mice, is the use of fecal microbial transplant (FMT). Here liquidized stool or cryopreserved microbial content from a healthy donor is introduced into the recipient's GI tract via acid resistant capsules, a nasogastric tube or per rectum. Mice with unfavorable or no GMB, who had previously been poor responders to immune therapy, were transformed into good responders by the creation of a facilitatory GMB via FMT [92]. Bacterial consortia consisting of bacteria felt to be favorable to immune activity have now been created and they may offer some advantages [93].

This is clearly an exciting area worthy of continued research and is actively being examined in ongoing clinical studies. Given the liver's significant exposure to GI microbiota and the relatively poor response of liver metastases to immunotherapy, this initiative has the potential to significantly impact future results.

35.7.3 Combination of either Chemotherapy or Radiation Therapy with Immunotherapy

With all the data pointing to the fact that neoantigen presentation is one of the key elements of a robust immune response, much effort has been directed towards the exposure of neoantigens in those cancers, such as MSS colon cancer, where this is not the case. The strategies used to date include the following:

– Combination of immunotherapy with chemotherapy. Tumour cell death secondary to chemotherapy is thought to result in neoantigen presentation with increased T cell

infiltration of the tumours [94]. A phase 2 study tested the combination of FOLFOX (5FU, leucovorin, and oxaliplatin) and pembrolizumab in 30 patients (3 patients with dMMR cancers, 22 with pMMR cancers, and 5 unknown) with an ORR of 53% and a disease control rate of 100% at 8 weeks. Dose modification of FOLFOX was required for toxicity [95]. Temozolomide plus ICIs is also being examined in studies such as MAYA, (NCT03832621) as the former is able to induce somatic mutations in pMMR cancers and may render these tumours immunoreactive. Results are awaited. A similar strategy using a combination of durvalumab plus olaparib (a poly-ADP-ribose polymerase inhibitor [PARP]) or cediranib (VEGFR inhibitor) is being examined in the DAPPER study (NCT 03851614) as PARP inhibitors prevent single strand DNA repair and thereby lead to the accumulation of neoantigens and increased TMB.

– Combination of immunotherapy with chemotherapy and EGFR or VEGF inhibitors. Interestingly, cetuximab (chimeric IgG1 antibody) leads to the formation of immune complexes and activates NK cells with increased CTL/T-reg ratio among TILs [96]. Panitumumab (fully humanized IgG2 antibody), on the other hand, does not seem to have the same capability and has less effect on the immune response when examined in head and neck cancers [97]. Studies such as NIVACOR (Nivolumab in combination with FOLFOXIRI and bevacizumab) [98], VOLFI (FOLFOXIRI, panitumumab) [99], AVETUX (FOLFOX, cetuximab, avelumab) [100], and AVETRIC (FOLFOXIRI, cetuximab, avelumab) [101] are examining these combinations with early encouraging results or results yet awaited. VEGF is perhaps a more interesting target as it inhibits the immune response in many different ways—enhanced myeloid derived stem cell infiltration, T-reg proliferation, and CTL exhaustion by the upregulation of molecules such as PD1 [102]. The VEGF antagonist bevacizumab is able to reverse many of these effects, and to normalize tumour vasculature, thereby restoring an active immune response in the tumour [103]. Examples of studies designed to examine this agent in combination with chemotherapy and immunotherapy include MODUL (FOLFOX plus bevacizumab followed by Atezolizumab plus 5FU and bevacizumab) which failed to improve either PFS or OS in pMMR cancers [104]; and ATEZOTRIBE (FOLFOXIRI plus bevacizumab +/− atezolizumab) which has completed accrual [105]. This study was based on the TRIBE and TRIBE II studies which had previously described a more favorable response when FOLFOXIRI was combined with bevacizumab versus FOLFIRI plus bevacizumab, potentially due to the increased creation of neoantigens with subsequent T cell infiltration [106, 107].
– Combination of immunotherapy with regorafenib. Tumour-associated macrophages (TAMs) cause immunosuppression in cancers when differentiated into the M2 subtype and different immune modulators may affect this process differently [108]. Regorafenib, a multitarget tyrosine kinase inhibitor, is able to reduce both the presence of TAMs and their differentiation into the M2 subtype, thereby promoting an immune response [109]. A logical strategy, therefore, would be the combination of regorafenib plus an ICI. This has been tested in pMMR chemo-refractory colorectal cancer using regorafenib and nivolumab in the Japanese REGONIVO study with ORR of 33% and PFS 7.9 months with OS not yet reached [110]. Unfortunately, the response in liver metastases, as opposed to lung metastases, was not good, with only 2 out of 13 patients responding as opposed to 8 out of 16 with lung metastases. A similar initiative in refractory pMMR colorectal cancer, evaluating regorafenib combined with avelumab in the REGOMUNE study, elicited 57% stable disease, no objective responses and PFS of 3.6 months with OS of 10.8 months. This is clearly less imprressive [111]. Interestingly, high infiltration by TAMs at baseline was associated with adverse outcome (PFS: 1.9 vs. 3.7 months, $p = 0.045$; OS: 4.8 months vs. NR, $p = 0.027$), identifying a possible biomarker for future studies.
– Combination of immunotherapy with radiation therapy. The abscopal effect in patients treated with radiation therapy was first described by Mole in 1954 [112], and subsequently recognized by others, but remains poorly understood. In this scenario radiation to one tumour site is followed by response in another nonirradiated site. One of the postulates is that the immune system is activated by neoantigens exposed by the radiation and then recognizes these in the nonirradiated site(s). Additional immune stimulation may take place such as the release of heat shock proteins, translocation of calreticulin to the cell surface membrane increasing tumour sensitivity to cytotoxic T lymphocytes, CTL recruitment and activation of dendritic cells via toll-like receptors [113]. Paradoxically, in some situations, radiation may induce immune tolerance via downregulation of cell surface receptors such as CD80 and CD86, inactivation of NK cells, and by upregulation of MDSCs and T-regs. Thus, it would seem logical to combine RT with immunomodulating agents. Two such studies with RT and either anti-CTLA4 or PD1 antibodies have been completed in melanoma with early encouraging results suggesting a response in nonirradiated lesions of between 25% and 52% [114, 115]. Recently, the PACIFIC trial tested platinum-based chemotherapy concurrent with RT followed by durvalumab, an anti-PD-L1 agent, or placebo in patients with stage III NSCLC. Median PFS was 16.8 months in the durvalumab arm versus 5.6 months in the placebo arm (HR: 0.52; 95% CI: 0.42–0.65; $p < 0.001$) leading to approval by the FDA of durvalumab in stage III,

unresectable NSCLC patients not progressing after chemoradiotherapy [116]. As of now, the optimal dose schedule and timing of RT relative to ICI therapy has not been determined and much work needs to be done. Given that many liver metastases are candidates for SBRT, it will be exciting to see how this strategy plays out in future studies in this setting.

35.8 Conclusion

The advent of tolerable and effective immunotherapy has had a significant impact on many cancers and is now a real option for a growing number of patients with colorectal cancer. As matters currently stand, the use of this modality is limited to those cancers which are MSI-H/dMMR and/or have a high TMB, but in this group an overall response rate of up to 60% with a 12-month disease control rate of up to 77% is achievable. Management of toxicities and accurate interpretation of radiologic and serologic results is key to optimal results in these patients, and multidisciplinary teams are essential. Disease in the liver continues to be a challenge, with an overall lower response in this location than in other metastatic sites, owing to the inherent immunosuppressive environment in this organ. The decision to employ immunotherapy rather than chemotherapy in this setting is a difficult one and there are no good data as yet to assist in this decision. Much still depends on the specific clinical scenario and the experience and intuition of the treating physicians, and the very real possibility of disease progression while receiving immunotherapy always warrants close attention. Exciting new initiatives aimed at the treatment of those patients with immunologically silent or nonresponsive cancers are ongoing, and the investigation of hypofractionated RT together with immunotherapy is particularly interesting in the setting of liver metastases. Modification of the total mesorectal excision (TME) by the alteration of the GMB, with vaccines, and via adoptive T-cell therapy could very well become complimentary strategies and these initiatives may possibly produce the next breakthrough. Coley would have been astounded.

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Hepatic Artery Infusion Therapy: The European Experience

36

Michel Ducreux and Francis Lévi

Learning Objectives

- Hepatic artery infusion of chemotherapy has been facilitated by the use of hepatic artery ports placed in interventional radiology thus representing a novel opportunity for a re-appraisal of HAI chemotherapy for liver metastases from colorectal cancer (LM-CRC).
- The European approach has shifted the therapeutic paradigm in patient with initially unresectable LM-CRC from tumour responses toward conversion-to-resection as a synergistic treatment resulting in a median OS of 3 years or more in patients with unresectable LM.
- Multidrug chemotherapy protocols with HAI oxaliplatin as a backbone combined with other HAI drugs and/or intravenous chemotherapy or targeted agent are highly effective, even in cases of prior progression on systemic-only chemotherapy with the same drugs.
- Upfront HAI chemotherapy should be preferred, as conversion-to-resection rates have been as high as 60% for patients receiving HAI chemotherapy as first line, 29–46% for those treated with second line and 13–18% for those receiving HAI as third or more line.
- Liver pain and catheter occlusions represent the main drawbacks of HAI chemotherapy and occur in nearly 25 and 60% of the patients, respectively, while other adverse events appear to depend upon drug extrahepatic levels. None of the adverse events significantly impacted the rates of conversion-to-resection on HAI, due to frequent early objective tumour responses (<2 months).
- Chemoembolization, in particular DEBIRI, has also shown some results, but these seem to be inferior to HAI.
- Randomized trials within the framework of onco-surgical strategies for LM-CRC are needed to validate the apparent survival benefits of modern HAI or TACE protocols in comparison with conventional intravenous and/or oral chemotherapy protocols.

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36.1 Introduction

The preferential localization of colon cancer (CCR) metastases in the liver has very quickly been at the origin of the idea of treatment by loco-regional chemotherapy. The other element justifying this type of treatment was the possibility of administering in the hepatic artery molecules highly concentrated in the liver in order to allow: high levels of active product in hepatic metastases, reduce systemic concentration, and thus lower toxicity. It therefore seemed logical to develop hepatic arterial infusion (HAI) very early on. But, HAI was particularly developed at a time when it could be a more powerful therapeutic option for the treatment of advanced colon cancer. As a result, this therapeutic modality lacks evidence-based data, but in Europe and more particularly in

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France, many trials were carried out to evaluate this technique and showed interesting results which are detailed in this chapter.

36.2 First-Line Intra-arterial Hepatic Chemotherapy in Advanced Metastatic Colorectal Cancer

Floxuridine (FUDR) has always been considered in Europe as a toxic drug for the bile ducts (probably because of its semi-continuous administration) [1]. In addition, the need to implant a pump was not in favor of this drug. Finally, the high price of the implantable pump, which had to be covered by public health systems, did contribute to the development of this technique.

36.2.1 Infusional 5-Fluorouracil (5FU)

Considering the difficulties and concerns regarding implantable pumps and FUDR, European investigators quickly turned to other drugs. Among these, 5-fluorouracil has been clinically evaluated since the 1990s for several reasons: (1) this drug was almost the only one available to treat colorectal cancers; (2) Its intra-arterial injection allowed hepatic concentrations five to ten times higher than those obtained with intravenous use. A phase II study published 30 years ago found a 60% response rate in 48 untreated patients receiving an 8-h infusion of 5FU for 7 days followed by a weekly 8-h infusion [2]. But in spite of its efficacy, this treatment was not adopted as an alternative to FUDR outside Europe. Furthermore, in a randomized trial published in 2003, 290 patients were allocated to receive either intravenous chemotherapy (combining folinic acid and 5FU: 48 h infusion: LV5FU2 schedule [3]) or HAI designed to be equitoxic (higher doses of infusional 5FU). In the HAI group, 37% of patients did not receive the treatment and 29% did not continue the planned treatment (i.e., 6 cycles) because of catheter failure. Median overall survival (OS) was 14.7 months for the HAI group and 14.8 months for the intravenous group [4]. Although a possible explanation for the lack of difference could be related to problems with the functionality of arterial catheters, the conclusion of this study was that this regimen could not be recommended in clinical practice. This trial led to the development of the use of other drugs in Europe.

36.2.2 Pirarubicin

Pirarubicin (THP)-doxorubicin is an anthracycline obtained by hemi-synthesis of doxorubicin and daunorubicin. It was demonstrated to be active on CCR liver metastases (LM) usually unresponsive to doxorubicin in animal models especially when it was directly infused in the liver (high extraction during the first hepatic passage) [5, 6]. A prospective phase II study including 64 evaluable chemotherapy naïve patients was performed to determine the feasibility, efficacy, and safety of HAI with pirarubicin combined with intravenous administration of 5FU and folinic acid. The response rate was 32%, times to hepatic progression and extrahepatic progression were 8.3 and 15 months, respectively, and median OS was 19 months [7]. After this relatively promising results, the combined use of HAI with pirarubicin and systemic therapy, 5FU and irinotecan (FOLFIRI) was tested. Thirty-one patients were included in a phase II trial. The objective response rate was 38%. The median PFS was 9.1 months, and the OS was 20.5 months [8]. The trial concluded that this approach deserved further investigation but the clinical development of this molecule was stopped for industrial reasons.

36.2.3 Oxaliplatin

In Europe, the "revolution" in HAI came with the demonstration of the efficacy and acceptable toxicity profile of intra-arterial administration of oxaliplatin. Oxaliplatin was administered by HAI to rabbits. The tissue concentrations were significantly higher in tumours than in healthy hepatic tissue with a ratio of 4.3 [9]. The first phase II study evaluating the efficacy of HAI with oxaliplatin combined with LV5FU2 systemic therapy was conducted in France. Twenty-eight patients were included and 26 patients were treated. Two hundred courses of therapy were administered, and the median number of courses was 8 (range, 0–20 courses). The main toxicity related to HAI was neutropenia and pain. The intent-to-treat objective response rate was 64% (95%CI, 44–81%; 18 of 28 patients). With a median follow-up of 23 months, the median overall and disease-free survival were 27 and 27 months, respectively [10]. After this first experience, further studies tried to improve results by combining HAI with intravenous LV5FU2 and cetuximab. In an open non-randomized study, involving 35 LM-CRC patients, the results were even better. Thus, objective response rate was 88%, median PFS and OS were 19.5 and 43 months, respectively [11]. Following the encouraging result, a randomized trial evaluating the role of HAI with oxaliplatin was planned. The design of the trial was simple: patients received an oxaliplatin-based doublet chemotherapy combined with bevacizumab when the tumour harbored RAS mutation and with anti-EGFR when the tumour was RAS wild-type. Oxaliplatin was administered intravenously in one group and by HAI in the other one (NCT 02885753? 180/284 patients included).

36.3 Conversion to Surgery and Rescue HAI Chemotherapy

Achieving tumour shrinkage is an important goal of chemotherapy of LM-CRC, as it can offer successful partial hepatectomy as a "synergistic" therapeutic option in patients considered unresectable at presentation [12–14].

Aggressive liver-specific medico-surgical strategies can shrink LM and enable macroscopically complete liver resection (R0-R1) resulting in consistent long-term survival, and even cures [15–17]. However, hepatectomies with curative intent could typically be performed in only 15% of all patients with initially unresectable LM, following downsizing through systemic conventional or chrono-modulated chemotherapy [16]. Thus, it was necessary to further reinforce the existing hepatic treatment strategies. In this field, systemic treatments have improved and made HAI even more complex to implement. However, the benefit of HAI in terms of response rate allows to restore situations in particular when a standard systemic first line fails.

36.3.1 HAI Protocols for Previously Treated Patients

In this specific context of patients pretreated with chemotherapy, an attempt has been made to restore sensitivity to these molecules by giving all or part of the usual intravenous multidrug intra-arterial therapies. The results of six studies evaluating this approach in 288 patients are detailed in Table 36.1 [18–23]. Oxaliplatin is the cornerstone HAI drug, and the dose ranges from 130 to 80 mg/m^2 in five studies. HAI oxaliplatin is delivered at a constant infusion rate over 2–6 h or as fractionated daily chrono-modulated infusions over 4 days, using a programmable-in-time pump. HAI-based courses are repeated every 2–3 weeks. In three observational studies, HAI oxaliplatin was combined with intravenous administrations of modified LV-5FU2 or FOLFIRI, with or without antiangiogenic or anti-EGFR antibodies [18]. In a fourth observational salvage study, patients failing on HAI oxaliplatin for toxicity or progression after receiving HAI mitomycin C or 5-FU [23]. A randomized Phase II trial evaluated the efficacy of HAI raltitrexed in addition to HAI oxaliplatin (RalOx), with PFS as a primary endpoint [22]. In the European Phase II OPTILIV trial, triplet HAI, combining oxaliplatin, 5-FU, and irinotecan, were administered jointly with intravenous cetuximab in patients with RAS wild-type.

36.3.2 Expected Efficacy Outcomes

The studies have further documented the efficacy of HAI-based chemotherapy, using both standard endpoints such as response rates, PFS and OS, and the rates of conversion-to-resection. Such endpoint was prospectively determined in the European Phase II OPTILIV. The feasibility and impact of completing the medical-surgical strategy for disease-free and OS was also evaluated in second line as compared to third or more line settings.

Despite most patients receiving a median of 2 prior systemic chemotherapy lines in the 6 studies (range 1–4), objective response rates were 34–55% (43.8% in the RalOx trial and 40.6% in OPTILIV trial). Such high response rates were achieved in previously treated LM-CRC patients. Moreover, median PFS ranged from 4.5 to 6.7 months, being 6.7 months in the combined HAI arm in the RalOx trial, and 9.3 months in OPTILIV. Most importantly, median OS ranged from 11.2 to 25.8 months, and this data largely exceeded intravenous or oral chemotherapy. Median OS were 11.2 months in the RalOx trial and 25.5 months in OPTILIV (Fig. 36.1a).

The R0-1 surgical resection rates following HAI chemotherapy were 13–26.9% in the observational studies and reached 29.7% in OPTILIV. This international Phase II trial confirmed the primary endpoint. Case reports highlighted tumour downsizing using HAI triplet despite acquired resistance to intravenous oxaliplatin-5-fluorouracil (Fig. 36.2) or weak activity of intravenous irinoteacan-5-fluorouracil (Fig. 36.3). Both in the largest single-institution observational study [21] and in OPTILIV, the median OS of those patients who reached the conversion-to-resection was approximately 3 years (Fig. 36.1b). These figures are unprecedented for previously treated LM-CRC patients.

36.3.3 Timing of Administration of HAI Chemotherapy Along the Course of LM-CRC Management

This issue was carefully analyzed in the OPTILIV trial, whose patient characteristics were similar to the groups of patients included after a single or two to three prior chemotherapy protocols (ECOG performance status = 0: 61 vs. 64%; median number of LM: 10 vs. 9; median diameter of largest LM: 41 vs. 57 mm; bilateral LM: 86 vs. 83%; median number of segments involved: 6 vs. 6; extrahepatic disease: 36 vs. 44%) [20]. First, the incidence of severe adverse events did not differ according to the number of prior chemotherapy lines, except for a trend toward less abdominal pain in those receiving OPTILIV as second line rather than as third to fourth line (15% vs. 34% of the patients, $p = 0.10$). Second, the rate of R0-1 LM resections was nearly three times higher among the 28 patients receiving OPTILIV as second line compared to 36 patients receiving the protocol as third or fourth line (46% [19.3–73.5] vs. 17 [13.1–46.5]; $p = 0.014$). Single stage hepatectomy was performed in 78.9% of the operated patients. Median time from OPTILIV onset to LM surgery was 5 months [2.6–19.4]. Neither the type of hepatectomy nor the time to surgery was significantly influenced by the number of prior chemotherapy lines.

Table 36.1 Results of phase II studies evaluating the use of the main molecules tested in HAI treatment in Europe

HAI drug(s) (doses and schedule)	Other drugs (route, dose and schedule)	Study design dates	N of pts. N of prior chemo lines (median, range) % prior PD	Prior drugs % of pts	Five main Grade 3–4 toxicities, % pts. Catheter dysf, % pts	% ORR [95% CI] % R0-R1 [95% CI]	Median PFS & OS, mo [95% CI] Median OS in R0-R1 pts. [95% CI]	Refs.
Oxaliplatin (100 mg/m^2)	Iv LV-5FU2	Observational Monocentric *2000–2004*	44 pts. Prior lines, 2 (1–5) *70% prior PD* −34% extrahepatic disease	5-FU-LV, 98% oxaliplatin, 77% irinotecan, 84%	Neutropenia, 44% Sensory neuro., 16% Abdominal pain, 14% Thrombocytopenia, 9% Diarrhea, 0% Catheter dysf., 41%	55% [40–69] 18% [*NR*]	7 [*NR*] 16 [*NR*] R0-R1, [*NR*]	Boige Ann Surg Oncol 2008 [18]
Oxaliplatin (80 mg/m^2) Irinotecan (160 mg/m^2) 5-Fluorouracil (2.4 g/m^2) *Chronomodulated* (5d)*	None q-3 weeks	Salvage Monocentric *2000–2006*	29 pts. Prior lines, 3 (1–8) *100% prior PD*	5-FU-LV, 100% oxaliplatin, 100% irinotecan, 89%	Abdominal pain, 14% Diarrhea, 10% Fatigue, 10% Neutropenia, 3% Sensory neuro., 3% Catheter dysf., 31%	34.5% [*NR*] 14% [*NR*]	All pts. 4.5 [2.4–6.5] 18 [5.8–30.2] R0-R1 27+, 35, 77+	Bouchahda Cancer 2009 [19]
Oxaliplatin (85 mg/m^2) Irinotecan (180 mg/m^2) 5-Fluorouracil (2.8 g/m^2) *Chronomodulated* (4d)* *or Conventional (2d)*	Iv Cetuximab (500 mg/m^2) q-2 weeks	Phase II Multicenter International *2008–2012*	64 pts. (RAS wt) Prior lines, 2 (1–3) *48% prior PD* -median, 10 LM −41%, extra-hepatic disease	FU-LV, 95% oxaliplatin, 63% irinotecan, 78%	Neutropenia, 42% Abdominal pain, 26% Fatigue, 18% Diarrhea, 16% Sensory neuro., 3.3% Catheter dysf., 42%	40.6% [28.6–52.3] 29.7% [18.5–40.9]	ITT population 9.3 [7.8–12.3] 25.5 [18.8–32.1] R0-R1 35.2 [32.6–37.8]	Levi Ann Onc 2016 [20]
Oxaliplatin (100 mg/m^2, 2–6 h day 1)	Iv mLV-5FU2/FOLFIRI and Iv Cetuximab/Panitumumab/Bevazucimab q-2 weeks	Retrospective Monocentric *2005–2016*	89 pts. Prior lines, 1 (0–5) *43% prior PD* −34% extrahepatic disease	FU-LV, 93% oxaliplatin, 78% irinotecan, 73% antiEGFR,33% bevazucimab, 67%	Abdominal pain, 43% Neutropenia, 40% Sensory neuro., 12% Thrombocytopenia, 8% Diarrhea, 1% Catheter dysf., 54%,	42% [*NR*] 26.9% [*NR*]	9 [8–11] 20 [15–24] R0-R1 36 [26–59]	Boileve Eur J Cancer 2020 [21]
Raltitrexed (3 mg/m^2, 1 h) Oxaliplatin (130 mg/m^2, 2 h)	Control arm, Standard treatment	Randomized Phase II Multicenter *2010–2016*	HAI, 38 pts. Std tt., 19 pts) Prior lines, 2 (2–4) −31% extrahepatic disease	FU-LV, 100% oxaliplatin, 100% irinotecan, 100% antiEGFR,37% bevazucimab, 94%	Abdominal pain, 37% Neutropenia, 6% Sensory neuro., 12% Thrombocytopenia, 12% Diarrhea, 6% Catheter dysf.,12%,	43.8% R0-R1 *NR*	PFS HAI, 6.7 [3.9–7.2] Std, 2.2 [1.2–4.3] *(P = 0.01)* OS HAI, 11.2 [4.8–17.6] Std., 11.9 [2.8–14.3]	Ghiringhelli J Cancer Res Clin Oncol 2019 [22]
5-FU (0.6–1.2 g/m^2, 4 h) q2-weeks, or Mit-C (7 mg/m^2) q4-weeks	Iv mLV-5FU2/FOLFIRI and Iv Cetuximab/Panitumumab/Bevazucimab q-2 weeks	Retrospective Monocentric *2010–2016*	24 pts. 5-FU, 17 pts. Mit-C, 7 pts. *63% prior PD* - > 8 LM, 75% −42% extrahepatic disease	Prior HAI oxaliplatin, 100% FU-LV, 100% irinotecan, 92% antiEGFR,25% bevazucimab, 67%	Abdominal pain, 0% Neutropenia, 0% Sensory neuro., 0% Thrombocytopenia, 4% Diarrhea, 0% Catheter dysf.,12%,	42% 13%	5.6 25.8	Pernot Clin Res Hepatol Gastroenterol 2018 [23]

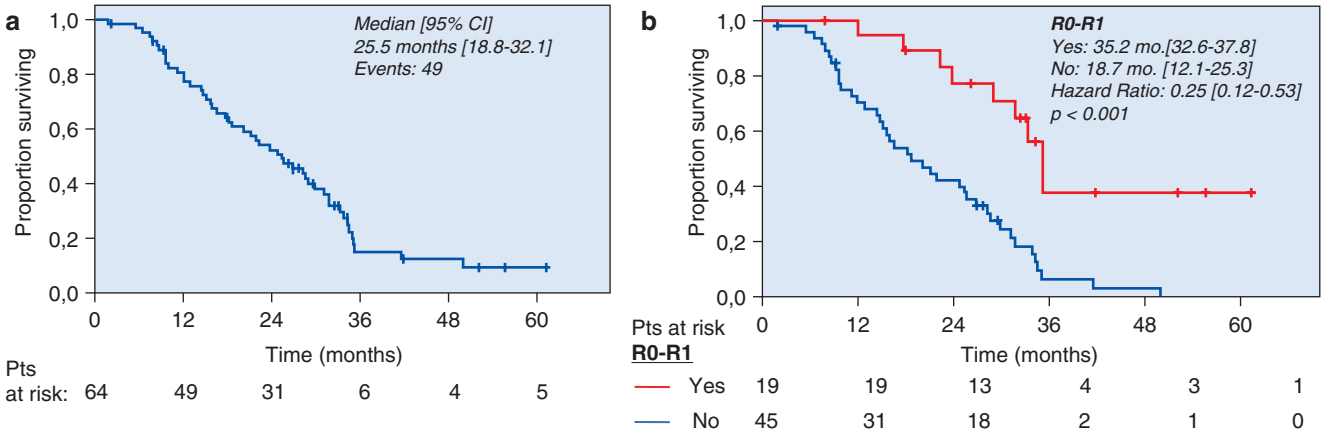

Fig. 36.1 Overall survival in international Phase II trial OPTILIV. (**a**) Intent to treat overall survival curve in the 64 patients with initially unresectable LM and a median of two prior systemic chemotherapy protocols. (**b**) Overall survival according to the reach of conversion-to-resection (R0-R1). *After Lévi* et al. *Ann Oncol 2016*

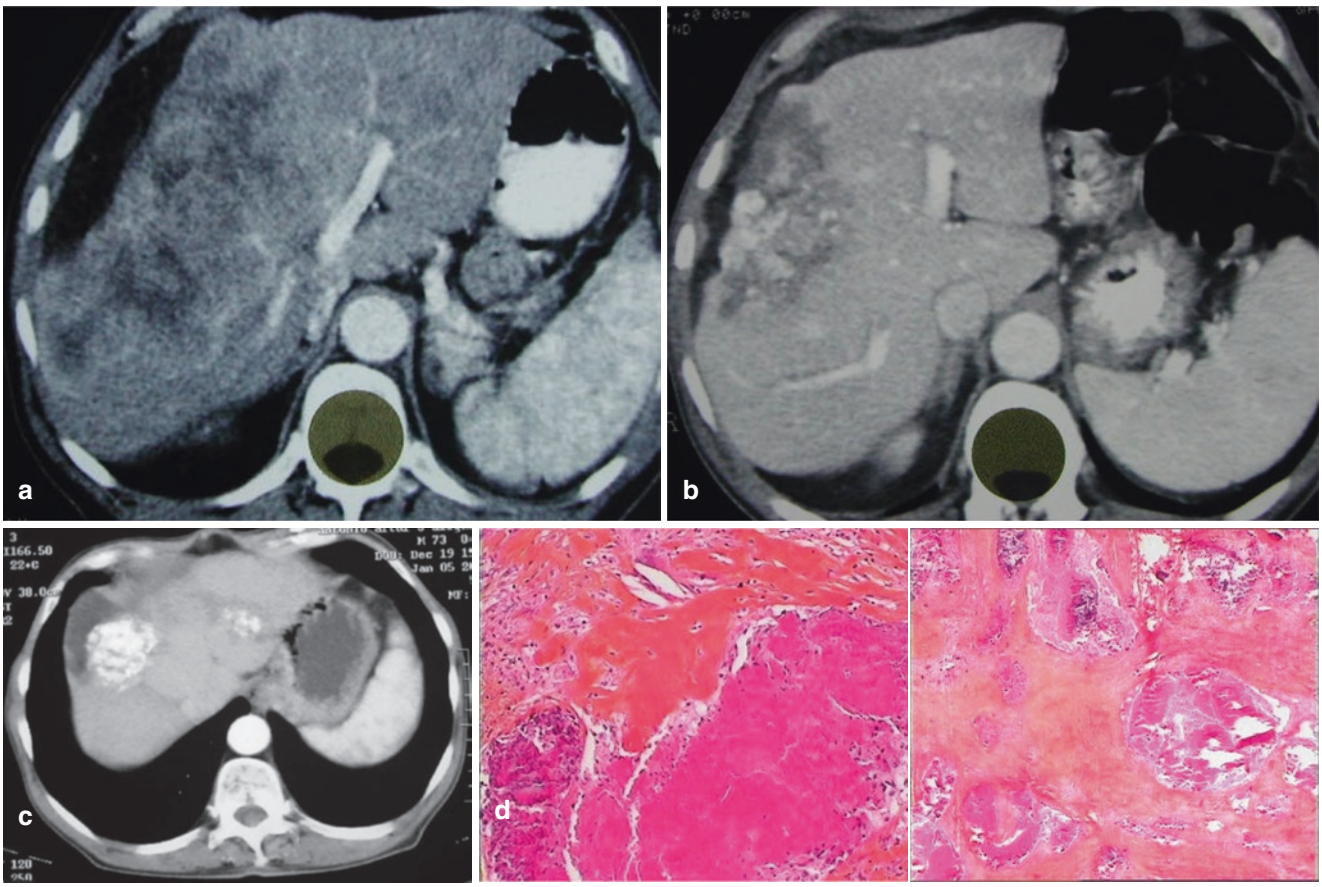

Fig. 36.2 Case report in a 72-year-old man with PS = 0 who presented with a poorly differentiated colon adenocarcinoma and ill-placed synchronous liver metastases (**a**). He had painful hepatomegaly measuring 7 cm below costal margin. Baseline plasma CEA was 140 ng/mL. Primary tumour was not resected initially. (**b**) Instead, he received 10 courses of intravenous chrono-modulated 5-fluorouracil, leucovorin, and oxaliplatin which achieved a major response with CEA dropping down to 27 ng/mL after 7 courses. Unfortunately, the tumour marker then rose up to 125 ng/mL thus suggesting acquired resistance to oxaliplatin-5-fluorouracil. As a result, the planned LM resection was deferred. The patient underwent sigmoidectomy and HAI catheter placement. (**c**) He received 5 courses of chrono-modulated HAI triplet, which shrunk and calcified the liver metastases, and reduced plasma CEA down to 7 ng/mL. The patient underwent partial hepatectomy (segments IV, V, and VIII). (**d**) Pathology revealed massive necrosis, fibrosis, and calcifications amounting ~95% of the metastases size. Patient remained disease-free for 13 years, i.e., until 16.5 years after initial LM-CRC presentation. Thus, while being 86.5 years old, he displayed a single LM-CRC recurrence that was resected and relapsed 1 year later. The patient refused further treatment and died at age 88

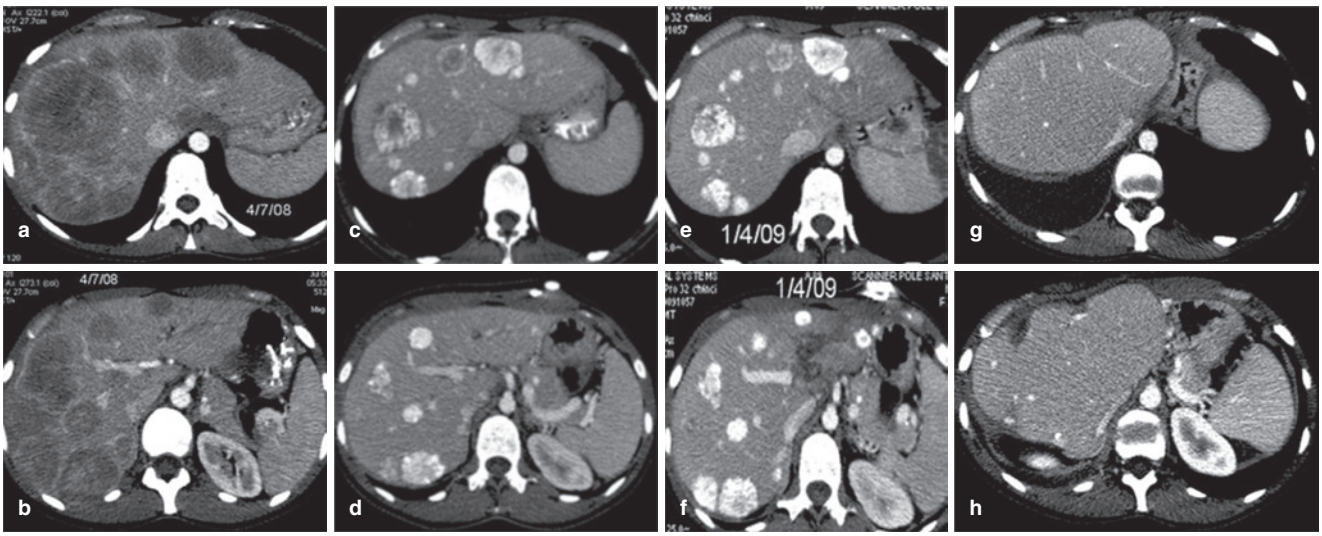

Fig. 36.3 Case report in a 33-year-old patient illustrating exceptional outcome on OPTILIV as second-line treatment for multiple synchronous LM-CRC. (**a** and **b**) Abdominal CT illustrating occurrence of multiple nonresectable synchronous liver-only metastases from sigmoid cancer ($n = 27$); (**c** and **d**) Minor response with partial calcification of metastases after nine courses of first-line intravenous FOLFIRI; nonresectable at laparotomy; sigmoidectomy and surgical placement of HAI catheter; (**e** and **f**) Major response after four courses of intravenous. Cetuximab and HAI of chrono-modulated triplet; three-stage hepatectomy; pathologic complete response (necrosis, fibrosis, and calcifications) in 26 of 27 LM, with only a few possibly active remaining cancer cells in a single lesion; (**g** and **h**) Liver CT scan 3 years after third stage of hepatectomy. As of May 2021, patient is disease-free and treatment-free, with PS = 0 and no residual toxicity 12.5 years after initial presentation and 11 years after last treatment. *After Lévi* et al. *Ann Oncol 2016*

The improved rates of R0-1 resection almost doubled with median OSin favor of an earlier HAI treatment line (second vs. third to fourth lines: 32 months [26–37.6] vs. 15.6 [10.1–21.2]; $p = 0.001$). Logistic regression and multivariate analysis validated HAI treatment line as a predictive factor for conversion-to-resection ($p = 0.006$), and a prognostic factor for OS ($p < 0.0001$).

Similar trends were reported in a single institution observational study where HAI oxaliplatin + iv chemotherapy was administered as second line for 45 patients and as third to fifth line for 38 patients [21]. The rates of R0-1 resections were 25% in second line and 21% in third to fifth line, respectively, but median OS was not reported in this series. The number of prior chemotherapy lines was a significant predictor for R0-1 LM resections, PFS and OS.

Taken together, these results strongly supported HAI chemotherapy as the second rather than third or fourth line to patients with initially unresectable LM from colorectal cancer. In the second-line HAI setting, R0-1 LM resections may be expected for nearly half of the patients, with a median OS of 3 years and a chance for cure for the operated patients. Potential mechanisms to reach such efficacy are discussed below.

36.3.4 Toward Precision HAI Chemotherapy in Individual LM-CRC Patients

Several factors or parameters were investigated in order to best predict, track, and optimize HAI chemotherapy. The studies usually involve a limited number of patients. However, strikingly large and statistically significant effects have been reported. Prospective translational studies are expected to move this field toward precision and personalized medicine for LM-CRC patients.

36.3.4.1 Early Tumour Response

The predictive value of an early response on HAI chemotherapy was first shown in OPTILIV [24]. Indeed, an early tumour response to systemic chemotherapy was found to predict improved survival in LM-CRC patients on cetuximab-based systemic chemotherapy [25], but this was unknown for HAI chemotherapy. In OPTILIV, an early objective response occurred at 6 weeks for 28% of the evaluable patients, and later for 17.5% of them. R0-1 LM resection was performed for 43.8% of the early responders, despite having initially unresectable LM and failure on prior systemic chemotherapy. Moreover, the median OS of early responders was 35.1 months, compared to 20.2 months in the non-early responders ($p = 0.01$). Multivariate analyses confirmed that early tumour response was an independent predictor for both R0-1 liver resection (OR = 11.8; $p = 0.024$) and a prognostic factor for OS (HR = 0.39 [0.17–0.88]; $p = 0.023$) [20].

36.3.4.2 Pharmacokinetics

The extrahepatic passage of HAI chemotherapy accounts for non-liver-specific adverse events of HAI chemotherapy, and plays a role in the control of extrahepatic disease.

While such mechanisms may have little relevance for the therapeutic index of FUDR, which has a very high extraction ratio at the first liver pass, plasma pharmacokinetics may be relevant for those drugs with low liver extraction ratio, which are used in "modern" HAI chemotherapy protocols. To investigate this issue, plasma pharmacokinetics were determined for irinotecan, 5-FU, and oxaliplatin in 11 LM-CRC patients receiving triplet chrono-modulated HAI jointly with intravenous cetuximab in OPTILIV [26]. Consistent trends were found between the area under the plasma concentration-time curve (AUC) values of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN38; a bioactive metabolite), total oxaliplatin, and platinum ultrafiltrate (P-UF), on the one hand, and subsequent leukopenia severity, on the other hand. Moreover, the maximum plasma concentration (C_{max}) and the AUC of platinum ultrafiltrate significantly predicted grades of diarrhea (p = 0.004 and 0.017, respectively) and anemia (p = 0.001 and 0.008, respectively) after the first course. Thus, systemic drug exposure could explain both the adverse events and the low rate of extrahepatic progression—a usual drawback of HAI chemotherapy. Indeed, no extrahepatic progression compromised outcomes in patients with responding or stable LM-CRC, despite documented extrahepatic disease in 40.6% of the OPTILIV population.

36.3.4.3 Pharmacogenetics

Although most LM-CRC patients benefit from HAI chemotherapy despite failure of one prior systemic chemotherapy line, this rate decreases after failure of two or more prior systemic lines. Pharmacogenetics may help in identifying single-nucleotide polymorphisms (SNPs) that would predict favorable outcomes in LM-CRC patients for HAI chemotherapy. This issue was addressed in OPTILIV [27]. Circulating mononuclear cells were analyzed for 207 single-nucleotide polymorphisms (SNPs) from 34 pharmacology genes in 52 LM-CRC patients. SNP's passing stringent Hardy-Weinberg equilibrium test was evaluated for their association with outcomes in 52 patients. Striking pharmacogenetic predictors of patient outcomes were identified. VKORC1 SNP (rs9923231) T/T achieved more early responses than C/T (50% vs. 5%, P = 0.029) and showed 4-year OS (46% vs. 0%, P = 0.006). N-acetyltransferase-2 (rs1041983 and rs1801280) were associated with up to sevenfold more macroscopically complete hepatectomies. PFS was the highest in ABCB1 rs1045642 T/T (P = 0.026) and rs2032582 T/T (P = 0.035). Associations were found between toxicities and gene variants (P < 0.05), including neutropenia with ABCB1 (rs1045642) and SLC0B3 (rs4149117 and rs7311358); and diarrhea with CYP2C9 (rs1057910), CYP2C19 (rs3758581), UGT1A6 (rs4124874), and SLC22A1 (rs72552763) [27]. Further confirmation of the relevance of VKORC1, NAT2, and ABCB1 variants for predicting HAI efficacy and tolerability are needed in order to personalize liver-targeted medico-surgical therapies for LM-CRC patients.

36.3.4.4 Circulating DNA

The prognostic and predictive value of cell free DNA (cfDNA) was investigated in plasma samples from 62 LM-CRC patients included in a single-arm Phase II trial involving HAI oxaliplatin (100 mg/m^2) and oral capecitabine (3500 mg/m^2) every 2 weeks for 12 weeks [28]. Low baseline levels of plasma cfDNA significantly predicted for objective responses (p = 0.02) and survival (p = 0.02) and suggested that cfDNA could represent a useful predictor of patient outcomes on HAI oxaliplatin chemotherapy.

36.3.5 Antitumour Immunity

Experimental and clinical studies have revealed that the antitumour efficacy of oxaliplatin among a few other chemotherapy agents involved a strong stimulation of dendritic cells. The latter resulted from signaling through TLR4 and its adaptor MyD88 for efficient processing and cross-presentation of antigen from dying tumour cells [29].

A translational study investigated the possible role of oxaliplatin-induced antitumour immunity for the long-term survival of LM-CRC patients undergoing hepatectomies after HAI oxaliplatin and oral capecitabine, within the previously mentioned Phase II trial [30]. The serum concentration of fms-related tyrosine kinase3 ligand (FLT3LG), a marker of intra-tumoural immune activity, was determined in 55 LM-CRC patients at baseline and every three courses of HAI oxaliplatin. Among the 34 resectable LM-CRC patients in this study, the serum FLT3GL had doubled over the initial 6 treatment weeks in those 9 patients who were apparently cured from their disease beyond 8.5 years, as compared to the other 24 whose FLT3GL levels remained unchanged and died before this date. Thus, early activation of antitumour immunity could also help the identification of those individual patients who may have a survival benefit from HAI oxaliplatin chemotherapy.

36.3.6 Chemotherapy Schedule

36.3.6.1 HAI Oxaliplatin or Triplet

While HAI oxaliplatin has become the cornerstone of "modern" HAI protocols for LM-CRC, there have been concerns regarding extrahepatic progression, OS, as well as treatment tolerability. As such, overall benefits of such cumbersome treatment modality have been questioned.

In order to minimize the risk of extrahepatic progression, HAI oxaliplatin has been combined with a variety of intravenous chemotherapy protocols including modified LV-5FU2 [10], modified FOLFIRI, or oral capecitabine [21], as well as

anti-EGFRs or antiangiogenics [11]. Four single-institution studies showed that limited extrahepatic disease was rather well-controlled with such combined HAI-IV or oral chemotherapy protocols, because median PFS ranged from 4.5 to 9 months (median, 6.3 months), and median OS ranged from 16 to 25.8 months (median, 19 months) (Table 36.1) [18, 19, 21, 23].

An alternative approach was followed in OPTILIV under the reasoning that maximal antitumour efficacy should target LM, where the disease predominates, in order to achieve a high enough conversion-to-resection rate and long-term survival. Triplet HAI combining oxaliplatin, irinotecan, and 5-FU were thus administered, with intravenous administration of cetuximab in 64 patients with KRAS wt primary CRC [20]. Despite its detection in 46% of the patients, minimal extrahepatic disease was neither a predictor of R0-1 LM resections nor an independent prognostic factor for PFS or OS in multivariate analyses. This may be due to the efficacy of the documented extrahepatic passage of the three drugs [26], with the intravenous administration of cetuximab.

36.3.7 HAI as Conventional or Chrono-modulated Delivery

Conventional HAI delivery has involved infusion schemes similar to those used for the intravenous administration of the same drugs. Thus, oxaliplatin was infused over 2–6 h, irinotecan over 60–90 min, and 5-fluorouracil over 46 h in most studies (Table 36.1). Electronic pumps were used, as they develop higher and controlled pressure, compared to elastomeric ones. Chrono = modulated HAI protocols (chronotherapy) mostly involved triplet delivery through administration schedules mimicking those given intravenously. The rationale for HAI chronotherapy is based on the demonstration that molecular circadian clocks usually remain functional in nonmalignant liver cells, but they are disrupted in the LM cancer cells (Fig. 36.4a). Molecular circadian clocks involve 15 specific "clock" genes and proteins that generate 24-h rhythmic oscillations within each cell through three transcription/posttranscription feedback loops [31]. The genetic clocks rhythmically drive cell cycle, DNA repair, apoptosis, and autophagy, as well as Phase I, II, and III drug metabolism over the 24 h [32]. In cancer cells, molecular clocks are often disrupted, resulting in the loss of circadian clock control of cellular proliferation and metabolism in cancer cells, as shown for LM-CRC both in experimental models and in cancer patients [33, 34] Thus, chrono-modulated chemotherapy represented a potential approach for improving the therapeutic effect of HAI for LM-CRC patients, when using the same timing specifications as those in the intravenous protocols (Fig. 36.4b) [35]. In a first salvage study, chrono-modulated HAI of irinotecan–5-FU–oxaliplatin enabled R0-1 liver resection in 14% of 29 patients with initially unresectable LM following the failure of a median of

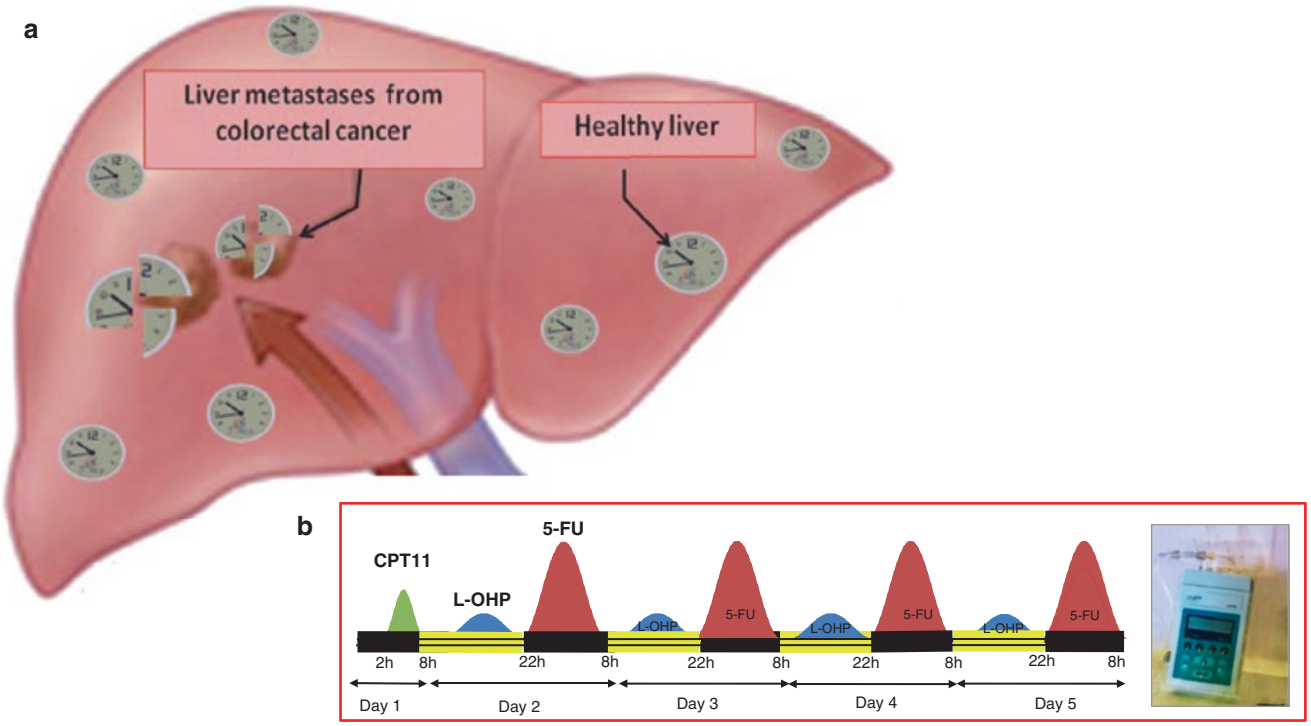

Fig. 36.4 Schematic rationale for HAI chrono-modulated chemotherapy. (**a**) The hypothesis, based on mouse and human study results [33, 34], is that circadian clocks are robust in healthy liver cells and disrupted in LM-CRC cells. (**b**) A scheme of the chrono-modulated HAI triplet is given as an example, using a programmable-in-time external multichannel pump [19, 20]. Note: *CPT11* irinotecan; *l-OHP* oxaliplatin; *5-FU* 5-fluorouracil

four prior systemic chemotherapy protocols and achieved a median OS of 18 months (Fig. 36.2) [19]. In OPTILIV, triplet chemotherapy was administered as a conventional infusion for 46 patients and as a chrono-modulated one for 18 patients, according to cancer institution experience [24]. Early responses occurred in 44% of the patients undergoing chronotherapy, as compared to 22% of those undergoing conventional chemotherapy. As a result, all the R0-1 LM resections after an early response occurred after HAI triplet chronotherapy, as compared to 5% of those on conventional HAI delivery, with a significant impact on OS. Further mathematical modeling of PK-PD data of patients on chrono-modulated HAI triplet revealed the need for (i) specific HAI programs in the chronotherapy pump to take into account a nearly 2-h delay in the detection of plasma drug levels in peripheral veins and (ii) the personalization of chronotherapeutic delivery to reduce interpatient variabilities in pharmacokinetics [36].

36.4 Adjuvant Intra-arterial Hepatic Chemotherapy for Resected Liver Metastases

The rationale of adjuvant HAI chemotherapy after resection of CRLM is that initial recurrences involve the liver in half of the patients. The first attempts concerning HAI as an "adjuvant" treatment after resection of liver metastases were done in the US using FUDR regimen. The meta-analysis of these trials did not show a major advantage in favor of HAI [37]. European experience used 5-FU in the past and did not show better results. In a German trial conducted in the 1990s, 226 patients with LM-CCR were randomized to resection of the liver metastases followed by adjuvant HAI of 5-FU (1000 mg/m^2 per day for 5 days as a continuous 24-h infusion) plus folinic acid (200 mg/m^2 per day for 5 days as a short infusion), or liver resection only. The first planned intention-to-treat interim analysis showed a median OS of 34 months in the adjuvant therapy group versus 41 months in the control group. The median time to progression was 14.2 months in the adjuvant therapy group versus 13.7 months in the control group [38]. The results of the trial conducted later using HAI with oxaliplatin showed promising outcome with respect to the efficacy. To date, there are no randomized trials to recommend this type of approach. However, there is recent indirect published support in favor of this treatment. From January 2000 to December 2009, 98 patients, who had undergone curative resection of at least four colorectal liver metastases, were selected from a prospective database. Among them, 44 (45%) had received postoperative HAI combined with systemic 5-FU (HAI group) and 54 (55%) had received "modern" systemic chemotherapy (IV group). The two groups were similar in terms of age, sex, the stage of the primary, and the administration of preoperative chemotherapy. Twenty-nine patients (66%) had received at least six cycles of HAI including oxaliplatin, and 22 patients (50%) had received the full planned treatment. For the remaining 22 patients (50%), HAI chemotherapy had been discontinued because of toxicity ($n = 8$), HAI catheter dysfunction ($n = 6$), an early recurrence ($n = 6$), and patient's refusal ($n = 2$). After a median follow-up of 60 months (51–81 months), 3-year OS was slightly higher in the HAI group (75% vs. 62%, $P = 0.17$). The 3-year disease-free survival was significantly higher in the HAI group than in the IV group (33% vs. 5%, $P < 0.0001$). In the multivariate analysis, adjuvant HAI chemotherapy and an R0 resection margin status were the only independent predictive factors for prolonged disease-free survival [39]. Technically, the catheter placement may be a risk after liver surgery. Fifty-seven patients who underwent major hepatectomy for CRLM resection were selected from a prospective database. Among them, 22 had had a catheter insertion during surgery. Both groups were similar in terms of age, body mass index (BMI), ASA score, and the average number of preoperative courses of systemic chemotherapy The rate of overall complications was slightly higher after catheter insertion (63% vs. 51%), although the difference was not statistically significant. Two patients had died postoperatively from liver insufficiency; both had undergone catheter insertion after a major hepatectomy associated with contralateral procedures resulting in a small remnant liver volume with low outflow capacity. Thrombosis of the common hepatic artery and portal venous gas were found on both CT scans. Thus, in case of extended and complex hepatectomy, with a higher risk of postoperative complications, the catheter placement may have to be placed later [40].

Following these results, an adjuvant clinical trial was conducted comparing surgery of liver metastases followed by intravenous chemotherapy with surgery of liver metastases followed by intra-arterial chemotherapy with oxaliplatin. This trial, named PACHA, has completed its inclusion period and results are expected by the end of 2022 [41].

36.4.1 Adverse Events of HAI

Taken together the clinical studies reviewed have revealed that the combination of HAI oxaliplatin with intravenous chemotherapy and/or additional HAI drugs was rather well tolerated. Most adverse events were those known for the intravenous administration of the drugs, including neutropenia, thrombocytopenia, diarrhea, fatigue, and sensory neuropathy. Their incidence was similar to or less than those reported for the intravenous administrations of the same drugs: i.e., grade 3–4 neutropenia for approximately 40% of the patients, grade 3 sensory neuropathy for approximately 15%, and grade 3–4 thrombocytopenia or diarrhea for approximately 10%. Two adverse events specific to HAI were observed. Severe abdominal pain was reported for

14–43% of the patients. Catheter dysfunction including hepatic artery occlusion was encountered in 12–54% of the patients, without any apparent impact on symptoms, liver function or even liver surgery. The incidence of severe adverse events varied according to the study protocol (Table 36.1).

36.5 Trans-arterial Chemoembolization (TACE)

Trans-arterial chemoembolization (TACE) is the most widely used treatment for patients with unresectable hepatocellular carcinoma (HCC), because it improves tumour responses and OS [42]. TACE has been further investigated for LM-CRC. In a single-center study, 564 patients (mean age, 60.3 years) with liver metastases of CRC refractory to standard chemotherapy were repeatedly treated using TACE [43]. In total, 3384 TACE procedures were performed (mean, six sessions per patient). The trans-arterial chemotherapy protocol consisted of mitomycin C alone (43.1%), mitomycin C with gemcitabine (27.1%), mitomycin C with irinotecan (15.6%), or mitomycin C with irinotecan and cisplatin (15.6%). Embolization was performed with lipiodol and starch microspheres. Evaluation of local tumour control showed partial response in 16.7% of the patients, stable disease in 48.2%, and progressive disease in 16.7%. Median survival time from the start of chemoembolization treatment was 14.3 months. These results seem to be inferior to those obtained with HAI in refractory patients [43]. However, the same team suggested that these modalities of treatment could be useful in potentially resectable liver metastases allowing secondary resection or radiofrequency ablation and better survival in these patients [44].

The technology of chemoembolization has been constantly improving. This includes drug-eluting beads which is a relatively novel drug delivery embolization system. LC/DC Beads (Biocompatibles, UK Ltd) were originally developed for the treatment of HCC with combination of doxorubicin, and are also used for LM-CRC with combination of irinotecan (DEBIRI). In a single-arm open trial, 55 patients who had received prior systemic chemotherapy and who underwent a total of 99 DEBIRI treatments were reviewed. The median number of DEBIRI treatments was 2 (range 1–5), with total hepatic treatment of 200 mg (range 200–650 mg), with 86% of treatments performed as lobar infusion and 30% of patients treated with concurrent simultaneous chemotherapy. Adverse events occurred in 28% of patients with median grade of 2 (range 1–3) with no deaths at 30-day post procedure. Response rates were 66% at 6 months and 75% at 12 months. OS in these patients was 19 months, with PFS of 11 months [45]. In a multi-institutional study, 74 patients were randomly assigned to receive DEBIRI versus systemic FOLFIRI [46]. Median OS was 22 months (95% confidence interval [CI], 21–23 months) for DEBIRI and 15 months (95% CI, 12–18 months) for FOLFIRI. PFS were 7 months (95% CI, 3–11 months) in the DEBIRI group compared to 4 months (95% CI, 3–5 months) in the FOLFIRI group. The differences between groups were statistically significant (p = 0.006, the log-rank test). The median duration of improvement in quality of life were 8 months (95% CI, 3–13 months) in the DEBIRI group and 3 months (95% CI, 2–4 months) in the FOLFIRI group (p = 0.00002, the log-rank test). A study added bevacizumab to DEBIRI in a preliminary study including only a small number of patients [13] and showed promising results [47].

A more recent beads' formulation, the drug-eluting beads (LifePearl®, Terumo, Tokyo, Japan) that can be loaded with irinotecan (LIFIRIR) or doxorubicin (LIFDOXR) was released. The innovation of this new formulation is that it guarantees more compressibility, elasticity and maximizes beads' suspension time. First experience was promising especially with irinotecan against LM-CRC refractory to chemotherapy [48].

After these encouraging results of DEBIRI in refractory LM-CRC patients, a study suggested to use the same treatment in neoadjuvant setting to replace neoadjuvant FOLFOX in frontline resectable LM-CRC [49]. The trial had a primary endpoint of tumour resectability (R0 resection). Forty patients received DEBIRI, with a median dose of 103 mg irinotecan (range 64–175 mg). Morbidity was low with no evidence of systemic chemotoxicity. All patients proceeded to surgery, with 38 undergoing resection (95% of the patients, with an R0 resection rate of 74%). The 30-day postoperative mortality was 5% (n = 2), without death associated with the use of TACE. A total of 66 lesions were resected, with histologic major or complete pathologic response documented for 77.3% of targeted lesions. At median follow-up of 40.6 months, 12 patients (34.3%) died from the recurrent disease after a median OS of 50.9 months.

Finally, chemoembolization showed encouraging results in some European teams. Nonetheless, this technique should be still considered as a secondary treatment option of LM-CRC.

36.6 Conclusion

The European experiences nicely complemented the American experiences in the field of locoregional medical treatment for LM from colorectal cancer. The efficacy of liver-targeted protocols, particularly HAI, has not been completely proven in phase III studies. The published results of phase II studies or retrospective studies in high volume centers support the efficacy of HAI and the rate of conversion-to-resection, with survival improvements. This is especially true for HAI with systemic chemotherapy using oxaliplatin-containing regimen or triplet systemic chemotherapy with

FOLFIRINOX. HAI with systemic chemotherapy appears to be effective, particularly in terms of conversion to liver resection, compared to chemoembolization.

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Infusional Therapy: American Experience

37

Greg D. Sacks, Michael D'Angelica, and Nancy E. Kemeny

Learning Objectives

- Infusional chemotherapy is effective in the treatment of colorectal liver metastases using a hepatic artery infusion (HAI) pump, typically placed in the gastroduodenal artery.
- When used in the adjuvant setting, HAI chemotherapy improves recurrence-free survival and overall survival.
- In the setting of unresectable liver disease, HAI chemotherapy is associated with very high response rates and conversion to resection in up to 50% of patients.

37.1 Introduction

In the United States each year, approximately 135,000 people are diagnosed with colorectal cancer [1]. Of these, approximately 25% will present with synchronous liver metastases and overall, of those who develop metastatic disease, more than 50% will develop liver metastases during their lifetime [2]. Liver-directed therapies therefore can play an integral role in controlling the disease and prolonging life. While the systemic therapies available to treat metastatic disease have improved over time, successful resection of colorectal liver metastases (CRLM) remains the only chance for a patient to be cured of the disease [3, 4]. To supplement the backbone of systemic therapy and surgery, multiple locoregional treatments are also available for the treatment of CRLM. These include ablation (cryoablation, microwave, radiofrequency ablation, irreversible electroporation), trans-arterial embolization (bland, trans-arterial chemoembolization (TACE), radioembolization with ytrrium-90 [Y90]), and liver-directed chemotherapy via a hepatic artery infusion pump. This chapter focuses on this latter treatment strategy and reports on its use in the United States over the past several decades.

The need for additional treatment options for patients with CRLM is evident by the historically poor outcomes and the limits of surgery and systemic chemotherapy alone. Prior to the widespread use of systemic chemotherapy, survival for patients with unresected CRLM ranged from 5 to 9 months, with no patients living to 5 years [5]. Even for patients with resected liver metastases, according to a report from 1990, the median survival was only 14.9 months [6]. In the subset of patients with resected tumours with negative margins, the median survival during this era was 30 months and a 5-year survival of 38%.

Over time, outcomes for patients with CRLM have improved, mirroring simultaneous improvements in chemotherapy, evolution of surgical technique and its more widespread use, and greater use of salvage chemotherapy, surgery, and/or ablation in the setting of recurrence. In more modern series, the 5-year survival after complete resection of CRLM ranges from 30 to 60% [3, 7, 8] In fact, as many as 20% of patients undergoing complete resection of their metastases can expect to be cured of their disease, living beyond 10 years with no evidence of disease recurrence [3, 4]. Advances in systemic chemotherapy have also translated to improvements in outcomes. Treatment with cytotoxic chemotherapy—typically with 5-FU, leucovorin, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) in the first-line setting—offers response rates of 35–50% with median survival in the range of 16–20 months [9]. Furthermore, newer biologic agents, such as those that target VEGF, EGFR, or mutated BRAF, when combined with cytotoxic chemotherapy, yield response rates as high as 60% and median survival in the range of 26–28 months [10–12]. However, treatment with chemotherapy alone has its limits and, without surgery, 5-year survival is uncommon and long-term cure is exceedingly rare [6, 10, 13]. A combination of surgery and systemic chemotherapy, when possible therefore constitute the backbone of modern treatment for CRLM.

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Cure for patients with CRLM is limited by two features of the disease epidemiology and biology. The first is that only 15–20% of patients with CRLM are resectable at the time of presentation [14–16]. The second is that among those who do undergo resection, at least 70% will recur after resection, most within 2 years of surgery, and most of these patients are only treatable with palliative chemotherapy [17–19]. Central goals in the treatment of the disease are therefore to convert unresectable disease to resectable and to prevent recurrence in the liver after resection.

Unfortunately, systemic chemotherapy has proven to be relatively ineffective in achieving both goals. In conversion to resectable (CTR), systemic chemotherapy alone is only effective in a minority of patients (10–30%) [20, 21]. And after failing first-line chemotherapy, patients can expect very low response rates (in the range of 10–35%) from second–line systemic chemotherapy, further lowering the likelihood of CTR [22–25]. In preventing disease recurrence after resection, results from multiple randomized controlled trials have been equally disappointing for systemic chemotherapy [26–28]. In the most recent trial comparing the combination of perioperative chemotherapy and surgery to surgery alone, the EORTC Intergroup trial 40,983 demonstrated a significant improvement in early PFS in patients undergoing resection (33.2% vs. 42.4% at 3 years; $p = 0.025$) in the per-protocol analysis [29] that did not translate into an improvement in overall survival (5-year overall survival 51.2% vs. 47.8%) [30]. Most relevant here, the incidence of recurrence in the liver was comparable between the two groups ($n = 49$ in the perioperative chemotherapy group vs. $n = 60$ in the surgery alone group) [29]. Regional chemotherapy via hepatic artery infusion (HAI) aims to target these two shortfalls of systemic chemotherapy by increasing the likelihood of CTR and lowering the likelihood of liver recurrence after resection.

37.1.1 Rationale for Intra-arterial Chemotherapy

The rationale for intra-arterial, liver-directed chemotherapy stems from the dual blood supply of the liver. While normal hepatocytes derive approximately two-thirds of their blood supply via the portal vein and one-third of their blood supply from the hepatic artery, the blood supply for CRLM arises almost entirely from the hepatic artery [31, 32]. As such, injection of chemotherapeutic agents into the hepatic artery has been shown to concentrate the drug in tumour 15-fold relative to normal liver parenchyma [33]. This effect is not observed however when the drug is injected directly into the portal vein [34]. Additionally, certain chemotherapeutic agents undergo up to 99% first-pass metabolism by the liver, [31] and thereby allowing the use of higher dosing and little concern for systemic toxicity.

Over the past decades, several different chemotherapeutic strategies have been used [35]. Today, the most widely used regimen in the United States is 5-Flouro 2-deoxyuridine (FUDR), owing to its short half-life (10 min) and high first pass extraction in the liver (94–99%) followed by rapid clearance. These properties allow for drug delivery that results in a 400-fold concentration of drug in the liver with minimal systemic exposure to the drug [31]. Successful trials in the 1970s and 1980s established a way to deliver the drug using a subcutaneous pump attached to a catheter secured in the hepatic artery [36, 37]. Since then, the operative technique has been refined to its modern version outlined below. This operation is typically performed after completion of the liver resection or, in the setting of unresectable disease, it can be performed alone. In either scenario, the operation can safely be performed in conjunction with (typically preceding) a colorectal operation to remove the primary tumour.

37.2 Technique

Prior to performing an operation to place the HAI catheter and pump, it is critical to obtain cross-sectional multiphasic imaging to delineate the arterial anatomy of the liver and make note of any accessory or replaced vessels. The imaging should also confirm the patency of the gastroduodenal artery (GDA), which is the preferred vessel for catheter placement. Due to redundancy between the celiac and superior mesenteric artery blood supply, the GDA can be catheterized and ligated distally without causing ischemia.

The operation can be divided into three steps: (1) dissection of the GDA for catheter placement, (2) skeletonization of hepatic artery and its branches to limit the possibility of extrahepatic perfusion, and (3) creation of a subcutaneous pump pocket and fixation of the pump in place. Access to the abdomen is achieved via either an upper midline, right subcostal, or limited hockey-stick incision. The operation can also be done laparoscopically [38, 39] or robotically [40]. The hepatic artery and its branches are dissected, skeletonized, and all small vessels and lymphatic channels are divided to avoid subsequent perfusion of the stomach, pancreas, and duodenum with chemotherapy. The entire extra-pancreatic GDA is dissected and fully mobilized to allow maximal length for catheter placement. When extrahepatic perfusion is present, the majority of cases arise from within 2 cm of the bifurcation of the proper hepatic artery (PHA) [41]. Therefore, the right and left hepatic arteries are dissected for at least 2 cm from their origin. The right gastric artery is ligated and divided. Cholecystectomy is performed since perfusion of the gallbladder with chemotherapy (via the cystic artery) can result in severe chemical cholecystitis.

Once the dissection is complete, the GDA is ligated as distal as possible at the level of the pancreas. The common

hepatic artery (CHA) and PHA (or the origin of the GDA) are clamped and a transverse arteriotomy is made in the distal GDA. The pump catheter is then introduced into the vessel, taking care to avoid the creation of an intimal flap and propagating an arterial dissection. The catheter is advanced until its tip is at the level of the GDA origin, where it is secured in place using permanent ties. Placement of the catheter tip too far into the PHA can result in thrombosis, while placement of the catheter tip within the GDA exposes the frail wall of the GDA to high doses of chemotherapy, possibly resulting in vessel injury and pseudoaneurysm formation.

The pump itself is placed in the lower abdominal wall, typically on the left side to allow for a possible future right subcostal incision. Large ventral hernias, existing or prior ostomies, and large body habitus may necessitate alternate siting of the pump pocket. Other options include the right abdominal wall or the chest wall, the latter option having the added benefit of limiting the potential for the pump to flip in very obese patients. The pump is secured to the fascia with permanent sutures through loops attached to the pump. The catheter is then tunneled through the abdominal wall into the peritoneal cavity. Despite theoretical risks of contamination, this operation can safely take place at the same time as a colorectal operation. Typically, placement of the pump is performed first, the pump pocket incision is closed and protected prior to initiation of the colorectal operation.

37.2.1 Special Anatomic Considerations

Prior to ligating the GDA, the GDA should be temporarily occluded to ensure a persistent pulse in the hepatic artery. In the setting of celiac stenosis, arterial blood supply to the liver may be dependent on the superior mesenteric artery (via retrograde flow through the GDA). If a hepatic artery pulse is not present after test-clamping the GDA, the arcuate ligament may be released to restore flow from the celiac artery. If that maneuver is unsuccessful, the GDA should be left intact and the catheter can be placed instead in the common hepatic artery. The common hepatic artery is ligated proximal to the catheter insertion site, allowing for hepatic arterial supply to arise from the SMA, via retrograde GDA flow to the proper hepatic artery.

Special consideration is required in the case of aberrant arterial anatomy, which occurs in 34% of patients [42]. The aberrant anatomy should be identified on the preoperative CT angiogram and the operative plan adjusted accordingly. If left unaddressed, parts of the liver supplied by aberrant arteries will not be adequately perfused, rendering the treatment less effective. In most cases, the aberrant anatomy can safely be addressed by ligating any accessory or replaced vessel(s) as cross perfusion of the liver is extremely reliable. With the pump catheter in the GDA, the liver will, in the majority of cases, be perfused throughout by chemotherapy [43].

If the GDA is not available due to prior surgery or anatomic variation, an alternate vascular conduit is necessary, preferentially the right or left hepatic artery with ligation of the vessel proximal to the catheter insertion site. In rare instances, a vascular graft—typically a segment of saphenous or gonadal vein—can be connected to a hepatic artery branch to secure the pump catheter in place. It should be noted however that use of a vessel other than the GDA is associated with higher incidence of pump-related complications and less durability [43].

37.2.2 Confirming Appropriate Catheter Function

After securing both the pump and the pump catheter, half-strength methylene blue (alternatively, fluorescein with Wood's lamp) is injected via the side port of the pump to check for bilobar perfusion and to ensure the absence of extrahepatic perfusion. If extrahepatic perfusion is detected—most commonly in the duodenum, stomach, or head of the pancreas—care is taken to identify and ligate any perfusing vessel or lymphatic branch and the test is repeated. At the end of the operation, the catheter is flushed with heparinized saline and the incisions are closed.

Prior to discharge, liver perfusion is assessed by a radionuclide pump flow study using technetium 99 m (^{99m}Tc) sulfur colloid and ^{99m}Tc-labeled macroaggregated albumin (MAA). In 5–7% of cases, extrahepatic perfusion is detected and can usually be salvaged by angiographic intervention [44, 45]. Incomplete perfusion of the liver may also occur but typically resolves spontaneously on a repeat scan performed a few weeks later. In some instances, angiography may be necessary to embolize a persistent accessory vessel missed at the initial operation [41, 45].

37.2.3 Complications

Complications following pump placement occur in 12–41% of cases [44, 46–48].

Complications relating to the catheter itself include arterial thrombosis (6%), extrahepatic perfusion (3%), incomplete hepatic perfusion (2%), and hemorrhage (0.02%). Pump pocket complications can also occur and include pump pocket infection (3%) and pump migration (1%). Most complications (63%) occur more than 30 days after surgery. In addition to these perioperative complications, approximately 9% and 16% of patients experience a pump failure at 1 and 2 years, respectively [45].

While systemic complications (nausea, vomiting, mucositis, myelosuppression) from pump chemotherapy are rare (owing to the high extraction rate of drug in the liver), regional complications can and do occur. Historically, extrahepatic perfusion to the GI tract caused complications, including gastroduodenal ulcers, pancreatitis, or diarrhea [49]. Fortunately, with modern approaches and careful assessment of extrahepatic perfusion, these complications are now rare. The most common adverse event related to pump chemotherapy is biliary sclerosis, which occurs in up to 5% of patients [50]. but can be mitigated by concurrent administration of dexamethasone via pump and careful dosing regimens [51, 52]. This complication is more likely to occur when HAI is used in the adjuvant setting after complete resection in comparison to when it is used in the setting of unresectable disease [50].

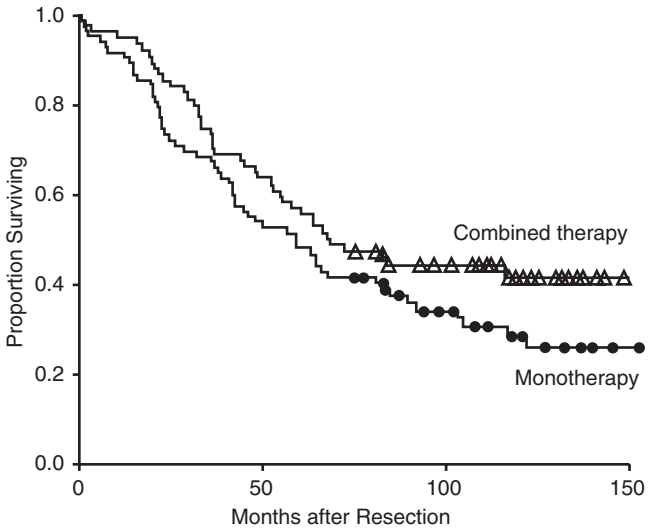

Fig. 37.1 Overall survival at 10-year follow-up in patients with colorectal cancer liver metastases randomized to combined therapy (pump chemotherapy plus systemic chemotherapy) or systemic therapy alone. (Adapted with permission from Kemeny and Gonen [57])

37.3 Infusional Chemotherapy in the Adjuvant Setting

Recurrence after complete resection of CRLM occurs in at least two-thirds of patients and half of these recurrences will be limited to the liver [17, 53–55]. This pattern of recurrence inspired early investigations in the use of HAI chemotherapy in the adjuvant setting, with the goal of targeting residual micrometastastic disease in the liver, reducing the likelihood of hepatic recurrence, and thereby prolonging survival.

A landmark trial from Memorial Sloan Kettering Cancer Center (MSKCC) offers some of the most compelling evidence for the use of infusional chemotherapy in the adjuvant setting. In this phase III trial, 156 patients who underwent complete resection of hepatic metastases were randomly assigned to receive either six cycles of hepatic arterial infusion with FUDR and dexamethasone plus intravenous 5-FU with or without leucovorin or 6 weeks of similar intravenous chemotherapy alone. After 2 years, patients who received HAI plus systemic chemotherapy experienced significantly higher rates of survival free of hepatic progression (90% vs. 60%, $p < 0.001$) and significantly higher rates of actuarial overall survival (86% vs. 72%, $p = 0.03$) [56]. The long-term follow up (median follow-up: 10.3 years; Fig. 37.1), demonstrated that patients receiving both HAI and systemic chemotherapy experienced significantly longer overall progression-free survival (31.3 vs. 17.2 months, $p = 0.02$) and dramatically higher rates of survival free of hepatic progression (not reached vs. 32.5 months, $p < 0.01$). Furthermore, the overall survival among patients with high clinical risk scores were more than twice as likely to be alive if they were treated with HAI plus systemic chemotherapy (38.7 vs. 16.3%) [57]. Similar findings were corroborated by another multicenter, intergroup phase III trial, which also demonstrated an improvement in recurrence-free survival and survival free of hepatic metastases (the study was not powered to detect a difference in overall survival) [58].

Another randomized trial performed at MSKCC offers insight into the effectiveness of HAI in the adjuvant setting. In a phase II trial, patients were randomized after liver resection to HAI plus systemic therapy with or without bevacizumab. Although the addition of bevacizumab did not increase RFS or OS and led to higher rates of biliary toxicity, 4-year overall survival was extremely high in both arms (85% and 81%) [59].

Several additional randomized trials have investigated the use of infusional pump chemotherapy in the adjuvant setting after complete resection of CRLM (Table 37.1) [60–64]. In 2004, a Cochrane review compiled the results from 7 of these trials, conducted between 1990 and 2002, including a total of 592 patients [65]. The meta-analysis concluded that there was no benefit in overall survival conferred by HAI chemotherapy. There are however important limitations to this analysis. For example, the review included a variety of different HAI regimens, including FUDR, 5-FU, 5-FU/leucovorin, 5-FU/mitomycin, and IL-2, and several of the trials included did not combine HAI therapy with systemic chemotherapy. Nevertheless, the review did demonstrate a lower rate of recurrence in the liver, although, due to heterogeneity in study data reporting, the investigators were unable to determine whether this finding was statistically significant.

It is difficult to apply the results of these trials to current-day practice, where FUDR is the preferred HAI therapy in the United States and 5-FU is no longer the preferred regimen for adjuvant systemic chemotherapy. More modern sys-

Table 37.1 Summary of randomized trials on hepatic artery infusional therapy after complete resection of colorectal liver metastases

Authors, Year	Intervention	Control	N	Liver-PFS	DFS	OS
Kemeny, N 1999	HAI FUDR/dexamethason + systemic 5-FU ± leucovorin	Systemic 5-FU ± leucovorin	156	90% vs. 60% ($P < 0.001$)	57% vs. 42% ($P = 0.07$)	Actuarial OS 86% vs. 72% ($P = 0.03$)
Kemeny, MM 2002	HAI FUDR + systemic 5-FU	Observation	75	67% vs. 43% ($P = 0.03$)	46% vs. 25% ($P = 0.04$)	63.7 vs. 49 months ($P = 0.60$)
Lorenz, 1998	HAI 5-FU/leucovorin	Observation	226	33% vs. 37% ($P = 0.72$)	14.2 vs. 13.7 months	34.5 vs. 40.8 months ($P = 0.15$)
Lygidakis, 1995	(HAI and systemic) mitomycin C/5-FU/leucovorin/IL-2	Systemic mitomycin C/5-FU/leucovorin/IL-2	143	82% vs. 49% ($P < 0.001$)	58% vs. 34% ($P = 0.002$)	73% vs. 60% ($P = 0.05$)
Rudroff, 1999	HAI mitomycin C/5-FU	Observation	42	54% vs. 50% (P=NS)	15% vs. 23% (P=NS)	25% vs. 31% (P=NS)
Tono, 2000	HAI 5-FU + systemic 5-FU	Systemic 5-FU	19	11% vs. 60%	67% vs. 20% ($P = 0.045$)	78% vs. 50% ($P = 0.27$)
Kusano, 2017	HAI 5-FU	Systemic 5-FU	91	68% vs. 45% ($P = 0.037$)	20% vs. 44% ($P = 0.038$)	35% vs. 59% ($P = 0.164$)

Abbreviations: *NS* not significant

temic therapy regimens, such as oxaliplatin or irinotecan, have not been compared to HAI chemotherapy in a randomized trial. However, several observational and single-arm prospective studies out of MSKCC have offered some compelling evidence for the benefit of HAI chemotherapy after successful resection of all liver metastases [66, 67].

One noteworthy example of such a study analyzed 2368 patients who underwent complete resection of CRLM between 1992 and 2012 and compared those who received HAI to those that did not. The authors found a significant association between median overall survival and treatment with HAI (67 vs. 44 months, $p < 0.001$), despite the presence of more advanced disease in the HAI group (more likely to have advanced nodal disease, higher number of tumours, greater use of two-stage resections and use of intraoperative ablation). When limited to only those patients who received modern systemic chemotherapy (containing oxaliplatin or irinotecan), this association remained favorable to patients treated with HAI chemotherapy. Furthermore, this association was still significant after adjusting and matching for a patient's propensity to be treated with HAI chemotherapy [68]. As a result of this study, the use of HAI chemotherapy is further being studied in the adjuvant setting with a randomized trial currently being conducted in the Netherlands [67].

The use of adjuvant HAI chemotherapy in the setting of extrahepatic disease, such as the presence of lung or peritoneal involvement is controversial. For these patients, liver progression may not be the primary driver of survival and therefore the importance of controlling disease in the liver becomes a slightly lower priority. However, in carefully selected patients with minimal extrahepatic disease and a substantial burden of metastatic disease in the liver, HAI chemotherapy can still be considered and may offer some benefit [69].

37.4 Treatment of Unresectable Disease

The vast majority of patients (>80%) with CRLM present with liver disease that is not amenable to up-front resection [14–16]. While systemic chemotherapy has been the mainstay of treatment and response rates have improved significantly, few patients can expect long-term survival from systemic chemotherapy alone. One of the primary goals in treating patients with unresectable liver metastases is to shrink the tumours in the liver to make liver resection feasible. There is now ample evidence demonstrating that if the burden of disease in the liver can be diminished and the patient is able to undergo resection, these patients experience favorable outcomes similar to those who present with liver disease that is resectable at initial presentation [15, 70–73]. Towards the goal of improving tumour response in the liver, improving overall outcomes, and allowing more patients with unresectable disease to undergo liver resection, HAI chemotherapy has evolved as an effective treatment option.

37.4.1 Hepatic Artery Infusion Chemotherapy Alone

Initial trials in the 1980s and 1990s tested the effect of HAI chemotherapy alone in the treatment of patients with unresectable liver metastases. These trials demonstrated significantly higher response rates to HAI chemotherapy alone (either 5-FU or FUDR; ranging from 42 to 62%) compared to standard systemic chemotherapy (5-FU at the time) (ranging from 0 to 21%) [64, 74–77]. Yet, despite the higher response rates observed, these trials failed to demonstrate a survival benefit to HAI chemotherapy. The results of these trials were summarized in a 2007 meta-analysis by Mocellin et al. Although this study confirmed the higher response rates

conferred by HAI chemotherapy (42.9% vs. 18.4% for systemic chemotherapy; $P < 0.0001$), the authors reported no difference in overall survival between the two groups (15.9 months vs. 12.4 months). The results of this study prompted many to abandon the use of HAI chemotherapy in the setting of unresectable liver disease [78].

However, in subsequent years, this meta-analysis has been criticized for failing to account for several limitations that may cumulatively explain why the analysis failed to detect a survival benefit to HAI chemotherapy [79, 80]. The most important of these limitations is the fact that several of the trials included in the meta-analysis were permissive of cross-over between treatment groups, allowing those who progressed on systemic chemotherapy to later undergo treatment with HAI chemotherapy. Crossover, in this setting, would thereby diminish the ability to detect a difference in overall survival should it actually exist.

In part to address this specific limitation of prior studies, the CALGB 9481 trial was performed. This multi-institutional trial randomized 134 patients to either systemic 5-FU/LV or HAI (consisting of FUDR, leucovorin, and dexamethasone), explicitly forbidding crossover between treatment groups. Dexamethasone was added because prior data had shown decreased biliary toxicity with its addition to HAI FUDR [51]. Confirming prior findings, the CALGB 9481 trial reported significantly higher response rates with HAI compared to systemic chemotherapy (47% vs. 24%; $P = 0.012$) and longer time to hepatic progression (9.8 vs. 7.3 months, $P = 0.034$). Contrary to previous trials however the study also found a significant benefit in overall survival (24.4 months vs. 20 months; $p = 0.0034$), as well as an improvement in quality-of-life scores for patients treated with HAI chemotherapy [81].

37.4.2 HAI Chemotherapy Combined with Systemic Chemotherapy

Despite the promising improvements seen in overall survival, the CALGB 9481 trial also identified a potential shortcoming of HAI chemotherapy. While the trial did demonstrate a longer time to progression in the liver (9.8 vs. 7.3 months, $P = 0.034$), the authors also noted that patients in the HAI chemotherapy arm experienced earlier progression outside of the liver (7.7 vs. 14.8 months, $P = 0.029$). This finding, which mirrored the results in the use of HAI chemotherapy in the adjuvant setting, [56] inspired efforts to combine HAI chemotherapy with systemic chemotherapy to simultaneously treat metastatic disease both within and outside the liver (Fig. 37.2).

In fact, by the time the CALGB 9481 trial was published, several phase I and II trials combining HAI and systemic chemotherapy had already begun to enroll patients. The first of these trials evaluated 46 patients with unresectable liver metastases treated with HAI FUDR/dexamethasone combined with systemic irinotecan. In addition to confirming the safety and feasibility of combining HAI and systemic chemotherapy in the setting of unresectable liver metastases, this trial demonstrated a promising 74% response rate in the liver [82]. Similar results were subsequently seen in another phase I trial combining HAI chemotherapy with oxaliplatin-based chemotherapy. This trial of 36 patients, the majority of whom had been previously treated with chemotherapy, demonstrated response rates of 90% and median survival of 36 months [83].

To date, there have been no randomized trials comparing modern systemic chemotherapy to combination HAI and systemic chemotherapy in the treatment of unresectable CRLM. However, at least two observational studies offer some insight into how the two treatment options compare. One used a case-control design to demonstrate a significant improvement in overall survival associated with HAI plus systemic chemotherapy compared to systemic chemotherapy alone (32.8 vs. 15.3 months; $p < 0.001$) [84]. The second is a study that analyzed 110 patients with unresectable CRLM that had failed treatment on at least three standard systemic therapies (including fluorouracil and leucovorin, irinotecan, oxaliplatin with or without bevacizumab, and anti-EGFR therapy for *RAS* wild-type tumours) and were then treated with HAI plus systemic chemotherapy. For this refractory population of patients, response rates to further attempts at systemic chemotherapy would be exceedingly low. However, when treated with HAI FUDR and best systemic chemotherapy, response rates were as high as 29% for those with isolated liver metastases and 36% for those with limited extrahepatic metastases. And for patients with isolated liver metastases, median survival was 17.2 months [85]. Therefore, combination of HAI and systemic chemotherapy offer a very effective treatment strategy to augment response rates and extend life in patients with unresectable CRLM. It should be noted however that the systemic chemotherapy given together with HAI needs to be tailored accordingly. One important example is that the addition of bevacizumab to HAI FUDR is not a viable treatment option since it leads to more biliary toxicity with no improvement in response rates or conversion rates to liver resection [86].

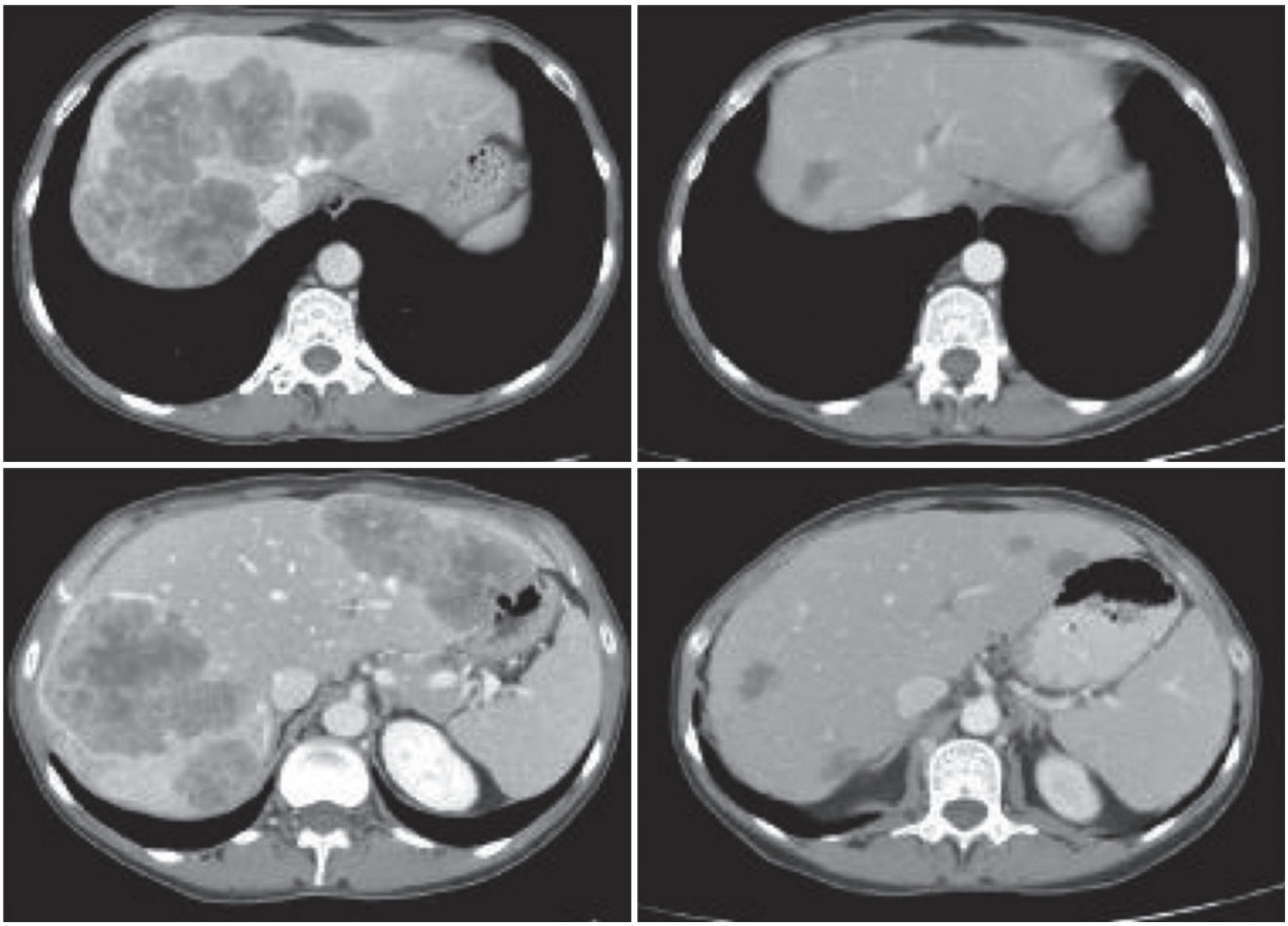

Fig. 37.2 Conversion to resectability with hepatic artery infusion (HAI) and systemic chemotherapy. (Adapted with permission from Kemeny et al. [8])

37.4.3 Conversion to Resectable

Since complete resection offers the only chance for patients with unresectable liver metastases to experience long-term survival or cure, determination of resectability is a critical assessment in patients with CRLM. For the majority of patients who present with initially unresectable CRLM (IU-CRLM), improving response rates to facilitate resection is therefore a foremost goal. Systemic chemotherapy has some efficacy and 10–30% of patients might be converted to resection (CTR) with this treatment alone [87–89] (some trials report conversion rates as high as 59% with systemic chemotherapy [90] however on closer reading, these studies include patients with initially resectable disease [91]). Given the limitations of systemic chemotherapy alone in this setting, HAI chemotherapy can be added to increase the likelihood of CTR.

There are currently no randomized trials comparing HAI to systemic chemotherapy specific to the outcome of CTR. But given the documented higher response rates seen with HAI chemotherapy, one might assume that the CTR rates would also be higher. In fact, the observational studies on this topic seem to support that conclusion. In 2013, a study from MSKCC summarized a decade's experience from their institution in using HAI chemotherapy to treat unresectable liver metastases. Of the 373 patients included, 93 (25%) eventually underwent complete resection and/or ablation, which translated into a median survival of 59 months [92]. But these and other observational data were limited by the fact that unresectable liver disease was defined subjectively and may vary between providers and/or institutions.

To address this limitation, a phase I trial was conducted at MSKCC in which strict definitions for resectability were used. In this study, 49 patients were enrolled, half of whom had previously been treated with systemic chemotherapy [8]. The patients included had extensive liver disease: 73% had more than 5 liver lesions, 98% had bilobar disease, and 86% had ≥6 liver segments involved. The response rate to

combined HAI and systemic chemotherapy was impressively high at 92%. Overall, 47% of all patients and 57% of chemotherapy-naïve patients were converted to resection, translating into a median overall survival of 35 and 51 months, respectively. This study was followed up by a phase II trial that specifically evaluated the CTR rate of HAI FUDR plus best systemic therapy in 49 patients with unresectable liver metastases. These patients had a higher burden of disease in liver (median tumours 14) and were heavily pretreated (65% with prior chemotherapy). Nevertheless, the authors reported a response rate of 76% and 47% of patients were successfully converted to resectable, eventually undergoing resection and/or ablation to clear the liver of disease [93]. This trial was subsequently updated with an expanded cohort of 64 patients and a final CTR rate of 52% with a median overall survival of 38 months and 5-year survival of 36%. Furthermore, nine patients were free of disease at median follow-up of 86 months from initiation of treatment [94].

In sum, there are now extensive data demonstrating that in the setting of unresectable CRLM, HAI chemotherapy is associated with response rates higher than systemic chemotherapy. Even for patients who have failed multiple lines of systemic chemotherapy, HAI chemotherapy yields high response rates. Furthermore, these high response rates allow for both local tumour control in the liver, as well as converting many patients to resectable disease, allowing them to undergo potentially curative liver resection.

37.5 Conclusion

For patients with resectable CRLM, liver resection is the most effective treatment option and can lead to long-term survival and cure in approximately 20% of patients. In order to reduce the high rates of tumour recurrence in the liver, HAI chemotherapy has demonstrated promising results. Particularly when used in combination with modern systemic chemotherapy, HAI chemotherapy reduces the likelihood of tumour recurrence in the liver, improves progression-free survival, and prolongs overall survival. For the majority of patients who present with unresectable liver metastases, HAI combined with systemic chemotherapy yields high response rates, offering patients the best chance to have their disease downstage so they can eventually undergo potentially curative resection. Future trials that compare modern systemic chemotherapy alone to HAI combined with systemic chemotherapy in both the adjuvant and unresectable setting will offer important data to demonstrate which patient populations benefit most from this therapeutic strategy.

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Part IV

Radiology, Interventional Radiology and Radiation

Optimal Diagnostic Imaging of CLM for Surgical Candidates

38

Maïté Lewin

Learning Objectives

- Establishing MR imaging sensitivity using a combined hepatobiliary contrast agent with diffusion-weighted imaging in the detection and characterization of CLM.
- Assessing response to treatment of CLM, based on the size as the most clinically meaningful response biomarker, knowing that new criteria are currently under investigation.
- Drawing attention to chemotherapy-induced liver injury for CLM.

38.1 Introduction

The diagnostic imaging of colorectal liver metastases (CLM) for surgical candidates should address different points: (a) precise assessment of the extent of the disease including the number, localization, and vascular relationships of CLM, (b) detection of any extrahepatic disease [1]. For this purpose, different imaging techniques are available, but no consensus has emerged so far on the optimal imaging strategy for preoperative staging. This chapter aims to provide evidence on diagnosis accuracy of ultrasonography (US), computed tomography (CT), magnetic resonance (MR) imaging, and ^{18}FDG FDG-PET in the detection and staging of liver metastases as well as in imaging assessment of CLM response to systemic therapy.

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38.2 Different Modalities for Detection and Staging of Liver Metastases

38.2.1 Ultrasonography (US)

US has a limited role in the preoperative evaluation due to its low sensitivity, estimated at 63% in a per-patient meta-analysis, compared with other imaging methods [2]. Contrast-enhanced ultrasonography (CEUS), which has a better sensitivity than US, estimated at around 80–90%, is not a good tool either, because it fails to offer the complete information required for surgical planning such as the presence or not of extrahepatic metastases [3].

38.2.2 Multidetector Computed Tomography (MDCT)

Contrast-enhanced MDCT is the imaging modality that is the most commonly used in the workup of patients with CLM and it is also widely available. MDCT offers the advantage of volumetric acquisition with isotropic voxels, which enables high-quality reformatted images in various planes to better visualize the tumour and its contact with adjacent vascular structures. Most CLM are visualized as hypovascular lesions. On CT, they appear hypodense with continuous peripheral enhancement in the portal venous phase which is the most reliable phase for the detection of CLM [4]. CLM have various degrees of heterogeneity according to their size and previous treatment (Fig. 38.1). Calcium degeneration is relatively common in patients with a primary mucinous tumour or following chemotherapy. Since the main differential diagnosis is intrahepatic cholangiocarcinoma when in doubt, a liver biopsy puncture should be performed with an immunohistochemical analysis which will confirm or refute the diagnosis. According to a meta-analysis on CLM, the mean sensitivity of CT performed in the portal phase is 74.4% on a per-lesion analysis and 83.6% on a per-patient basis [5]. One of the limitations of CT is the inability to

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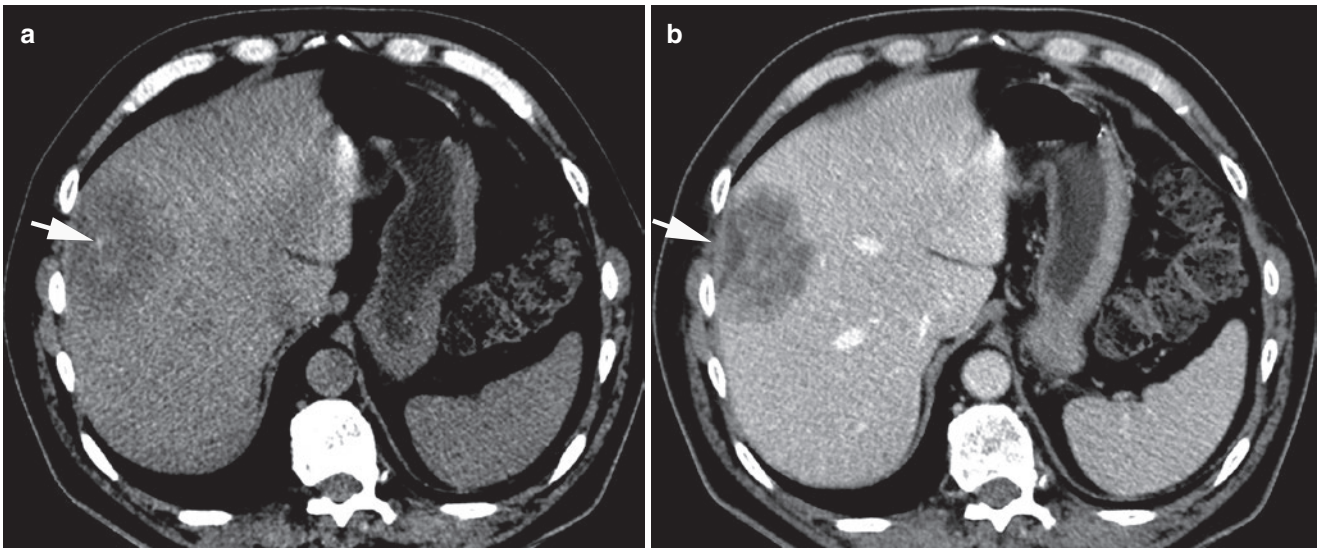

Fig. 38.1 Liver Metastasis in a 53-year-old man with sigmoid colon cancer. (**a**) Pre-contrast CT shows a hypodense lesion in the right liver with calcifications (arrow); (**b**) Contrast-enhanced CT image shows a hypoattenuating liver lesion with early capsular retraction (arrow)

investigate a lesion less than 10 mm in diameter because it is too small to characterize. In such case, the sensitivity on a per-lesion basis is 47.3% [5]. Another limitation of CT is the presence of a fatty liver which is common after chemotherapy and may interfere with the detection of liver metastases.

38.2.3 Magnetic Resonance (MR) Imaging

In comparison to CT, MR imaging has a better soft tissue contrast resolution, which is helpful for detecting and characterizing CLM, particularly lesions smaller than 10 mm in diameter [5]. CLM are typically hypointense on T1-weighted imaging while mildly hyperintense on T2-weighted imaging. The use of in-phase and out-of-phase gradient-recalled echo imaging offers an advantage over CT in the case of the fatty liver (Fig. 38.2) [6]. After extracellular contrast injection of gadolinium, liver metastases were visualized with heterogeneous continuous peripheral enhancement in the arterial, venous, and delayed phases [6]. Several studies have already shown that MR imaging with conventional sequences is significantly more sensitive for detecting liver metastases on a per-lesion basis than CT, its sensitivity ranging from 78.2 to 80.3% [5, 7].

Recently, the sensitivity of MRI for detecting CLM increased using diffusion-weighted imaging (DWI) and hepatocyte-specific contrast agents. DWI measures the mobility of water molecules in tissues which can be affected by pathological conditions. Apparent diffusion coefficient (ADC) values are quantitative estimates of diffusion restriction. On DWI, CLM restricted diffusion due to their hypercellular nature and was visualized as high signal intensity lesions with low ADC values [6]. A meta-analysis showed that addition of DWI improved sensitivity and specificity for detecting and characterizing lesions with a sensitivity of 87.1% on a per-lesion basis [8]. Two hepatocyte-specific contrast agents are used: gadobenate dimeglumine (MultiHance, Bracco) and gadoxetate disodium (Eovist, Bayer). They are preferentially taken up by hepatocytes and excreted into the bile duct. In the delayed phase (10–120 min after intravenous administration), CLM appeared hypointense compared to the normal surrounding liver parenchyma (Fig. 38.3) [6]. A recent meta-analysis showed that hepatocyte-specific contrast-enhanced MR imaging helps detect more metastatic lesions than does conventional MR imaging with a sensitivity of 90.6% on a per-lesion basis [8]. Similar results have been reported in a randomized multicenter trial which demonstrated the superiority of hepatocyte-specific gadoxetic acid-enhanced MR imaging over contrast-enhanced-MDCT and even over MR imaging with extracellular contrast medium for establishing a surgical plan [9]. The combination of hepatobiliary phase imaging with DWI showed a high detection rate, particularly for small liver metastases which may not have been seen in other sequences with a sensitivity of 95.5% on a per-lesion basis [8]. Similar results have been reported in a prospective study with a sensitivity of 98% on a per-lesion basis for detecting CLM [10]. The multiparametric approach of MRI, with multiple tests (T1- and T2-weighted imaging, DWI) in one MR imaging protocol liver, explains better results.

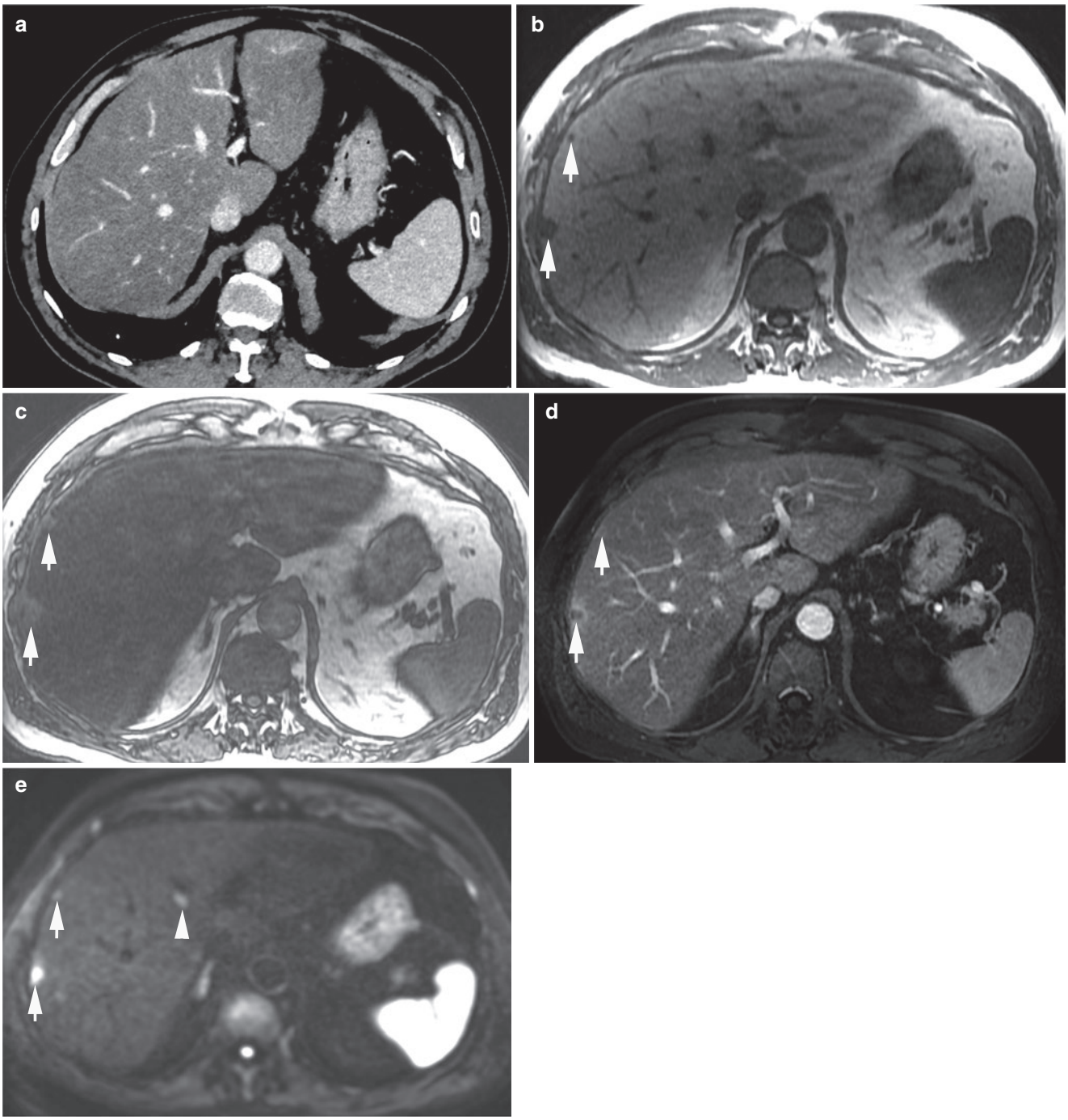

Fig. 38.2 Liver metastases in a 69-year-old man with rectum cancer. The patient had undergone rectal surgery and adjuvant systemic chemotherapy using 5 Fluoro-uracile and Oxaliplatine. One year later, the patient presented an elevated carcinoembryonic antigen level. (**a**) Contrast-enhanced CT image shows hepatic steatosis but no lesion; On axial in-phase (**b**) and out-of-phase (**c**) MR images, two lesions in the right hepatic lobe are more clearly detected (arrows) with a signal drop in the surrounding liver parenchyma in out-of phase image due to diffuse steatosis; (**d**) Axial gadolinium-enhanced fat-suppressed T1-weighted MR image shows two lesions with a peripheral rim enhancement in the right hepatic lobe (arrows); (**e**) Axial diffusion-weighted image (b = 800 s/mm^2) demonstrates diffusion restriction of the same lesions as well as an additional subcentimeter lesion near the median hepatic vein (arrow head)

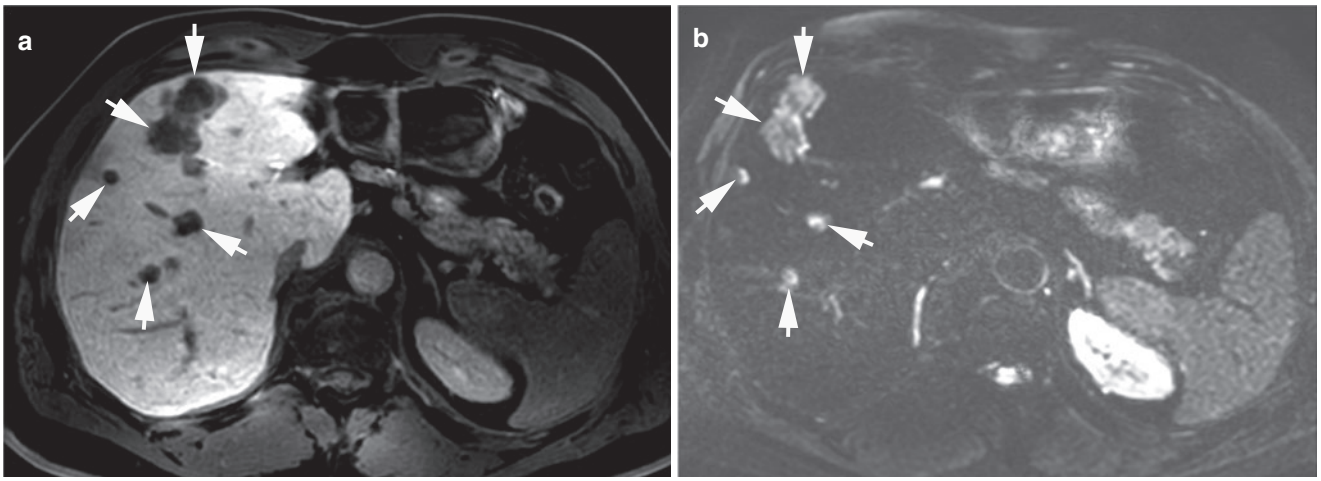

Fig. 38.3 Liver metastases in a 63-year-old-man with left colon cancer. (**a**) Axial gadolinium-enhanced fat-suppressed hepatocyte phase T1-weighted MR image, obtained with gadoxetate disodium after a 20 min delay, shows no uptake in the metastases lesions which appear as dark signals (arrows); (**b**) Axial diffusion-weighted image ($b = 900$ s/mm^2) demonstrates diffusion restriction on the liver metastases which appear as bright signals (arrows)

38.2.4 Positron Emission Tomography (PET) Combined with CT or MR Imaging

The role of ^{18}FDG PET-CT is evolving, mainly due to its ability to detect extrahepatic metastases. It is highly sensitive for the detection of CLM on a per-patient basis (93%), but less accurate on a per-lesion basis (60%) [11]. Its sensitivity drops to 36% for lesions of less than 1 cm [6]. In addition, false-negative results may occur in case of tumour necrosis or mucinous content [6]. The benefit of ^{18}FDG PET-CT in addition to standard imaging of CT chest, abdomen and pelvis, and MR liver in presurgical patients has not been proved yet [12]. However, in metachronous hepatic disease and in high-risk patients, ^{18}FDG PET-CT should be considered as a means to identify extrahepatic metastases prior to hepatic surgery.

Recently, integrated PET/MR imaging was introduced into oncologic imaging. Per-lesion sensitivity of PET/MR with the liver-specific contrasts agent in the diagnosis of CLM was found to be ranged from 88 to 89% and per-patient sensitivity around 85% [13]. The diagnostic performance of PET/MR imaging proved to be significantly better than multidetector CT performance. However, there was no significant difference in the performance between diagnosis of PET/MR imaging and liver-specific contrast-enhanced MR imaging, in the detection of CLM [13].

38.3 Algorithm for the Pretreatment Staging of CLM

The preoperative radiological assessment of patients with hepatic metastases is absolutely required to select the patients who will benefit from surgical excision and those for whom surgery is not necessary. There are three possible scenarios: (a) patients with hepatic metastases which are immediately resectable, (b) patients whose liver metastases will be potentially resectable following response to chemotherapy, and (c) patients whose lesions cannot be resectable. For these three groups of patients, thoraco-abdominopelvic MDCT is the key examination for detecting liver lesions, identifying extrahepatic lesions, and also analyzing the primary lesion.

However, while MDCT is sufficient for the evaluation of patients who cannot be resectable, it is not the case for the other two groups of patients for whom hepatic MR imaging and ^{18}FDG PET-CT combined with MDCT are also recommended. Indeed, MR imaging is more accurate than CT for detecting CLMs and ^{18}FDG PET-CT for ruling out extrahepatic disease [12]. The key objective is that all lesions identified at pretreatment imaging must be mapped at the preoperative stage to achieve complete resection with negative margins (R0 resection). But, due to chemotherapeutic success, disappearing metastases (i.e., non-visualization of CLMs at follow-up imaging due to their small size) may occur. Furthermore, because a "complete radiological response" does not indicate a complete pathological response, with the presence of viable tumours at the site of the lesions, in most cases, the resection of the target lesions is necessary [14]. This implies the necessity to accurately detect as many liver metastases as possible prior to treatment planning. The recent consensus report from the 9th International Forum for Liver MR imaging stated that the combination of hepatobiliary phase images with DWI provides the highest sensitivity for detecting CLM and therefore should be used systematically in patients who are potentially resectable [15].

38.4 Evaluation of Treatment Response of CLM

Chemotherapy is commonly used in patients with potentially resectable CLM. The evaluation of radiologic response to treatment is usually based on imaging biomarkers.

38.4.1 Imaging Biomarkers

The first biomarker that is widely accepted is a set of size-based criteria called RECIST1.1 (Response Evaluation Criteria in Solid Tumours) which defines treatment response by a 30% decrease in unidimensional measurement (Fig. 38.4) [16]. This biomarker reflects tumour growth but there are limitations in only using size measurement to assess response. That is why other imaging biomarkers have been explored.

Since the introduction of antiangiogenic agents, the changes in tumour density on MDCT have been proposed as another imaging biomarker. Chun et al. have reported three patterns of morphologic response with or without changes in tumour size on MDCT in patients treated with a bevacizumab-containing regimen [17]. In their study, metastases that are characterized by homogeneous attenuation with a sharp tumour-liver interface, represent a good or even optimal morphologic response treatment. The disappearance of a peripheral rim of enhancement, that was present at pretreatment scanning, is also interpreted as a good response. The absence of any of these changes has been defined as absent morphologic response [6, 17]. The authors found a significant correlation between the three morphologic patterns of response previously identified and both pathologic response and long-term survival of the patients.

Instead of using morphological criteria, the use of functional imaging appears as a novel approach to evaluate treatment response in the targeted therapies. Dynamic contrast-enhanced (DCE) imaging allows for the quantification of physiologic changes in tumour vascularity. DCE-MDCT and DCE-MR imaging provide parametric maps of perfusion data and have been shown to be innovative and reliable tools in monitoring perfusion changes in response to antiangiogenic agents [18]. For example, antivascular agent trials used the K_{trans} volume transfer constant parameter as one of the preferred DCE-MRI endpoints [18]. An early decrease in the biomarker K_{trans} has been repeatedly demonstrated following administration of antivascular agents, which suggests that this parameter may help determine the biologically active dose, optimal timing, and therapeutic window of drugs [18]. Similar changes can be observed with DCE-CT in terms of response biomarkers with a decrease in hepatic arterial perfusion parameter [19, 20]. DWI, a marker of cellularity, can also help monitoring physiologic treatment response to various therapies. An increase in the ADC values post-therapy in metastatic lesions at DWI has several times been reported as a potential response biomarker [21, 22]. However, the main limitation of these imaging biomarkers is the lack of standardization of the technique and parameters.

Another aspect of the functional imaging concerns the metabolic tumour response assessment with ^{18}FDG PET-CT. Many therapies reduce glucose uptake, including established cytotoxic chemotherapy agents and antiangiogenic agents. For such therapies, a decline in metabolic activity (i.e., ^{18}FDG PET-CT signals) during treatment is

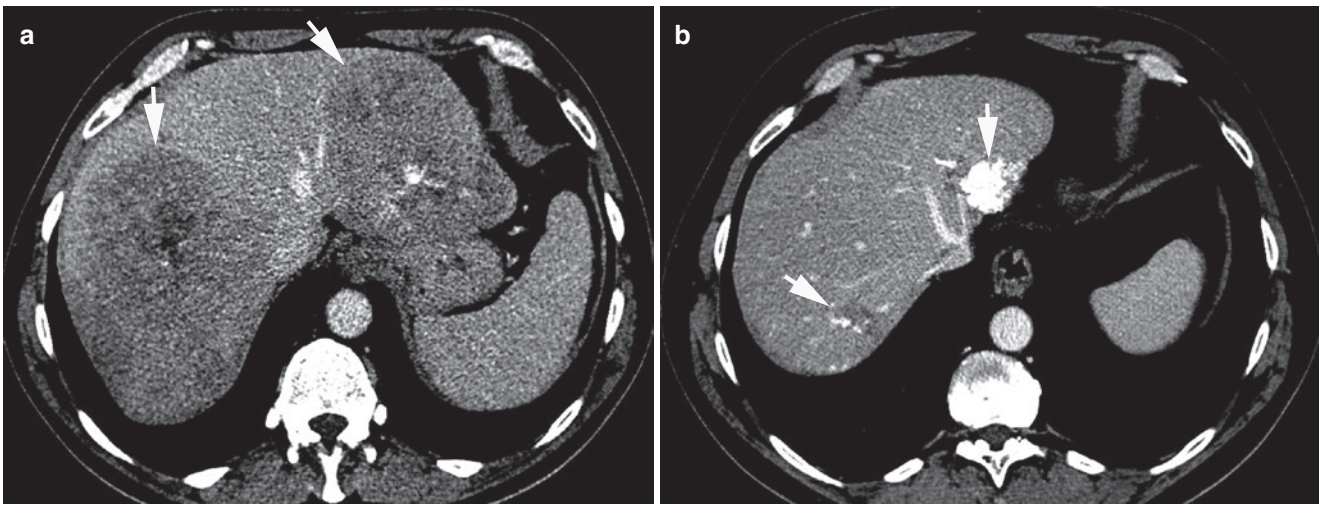

Fig. 38.4 Liver metastases in a 54-year-old man with rectum cancer. (**a**) Contrast-enhanced CT image shows liver lesions in both hepatic lobes (arrows); (**b**) Contrast-enhanced CT image, obtained 6 months after chemotherapy, demonstrates reduction in size and calcifications of liver metastases (arrows)

indicative of a favorable treatment response [23]. More recently, the quantitative analysis called PET Response Criteria in Solid Tumours (PERCIST, version 1.0) has been proposed as a nonspecific imaging biomarker for monitoring treatment response [24]. However, complete resolution of metabolic activity is not always indicative of pathologic complete response. Furthermore, a recent meta-analysis found that the sensitivity of ^{18}FDG PET-CT for detecting liver metastases after neoadjuvant chemotherapy dropped from 71% to 52%, most likely due to the small size of the treated lesions and to central necrosis [25]. Therefore, the role of ^{18}FDG PET-CT in evaluating treatment response in CLM is under investigation because of the false negatives (necrotic lesions) and false positives (inflammation and surgery) after treatment, [6].

38.4.2 Liver Injury Associated with Chemotherapy of CLM

There are three specific injuries of the liver parenchyma due to chemotherapy: steatosis, steatohepatitis, and sinusoidal obstruction syndrome (SOS) [12].

Steatosis: The administration of 5-fluorouracil is known to cause steatosis, a mild form of nonalcoholic fatty liver disease (NAFLD). The reported incidence of steatosis in patients who received chemotherapy for CLM varied from 30–47% [26]. On CT, hepatic steatosis, which results in a diffuse decrease in liver attenuation, may obscure metastasis lesions (Fig. 38.2a) [6]. Quantification of hepatic steatosis can be performed with chemical shift MR imaging. Steatosis is associated with increased complications postliver resection, though not increased mortality [12].

Steatohepatitis: The use of irinotecan is associated with nonalcoholic steatohepatitis (NASH), a more severe form of NAFLD with hepatic inflammation. Steatohepatitis may lead to cirrhosis; early signs of such transformation include abnormal enhancement and restriction of diffusion on DWI [6]. In terms of its impact on liver surgery, studies have shown that patients with steatohepatitis have an increased risk of postoperative morbidity and mortality [6, 26].

SOS: Oxaliplatin is the predominant drug known to cause endothelial injury resulting in SOS. Up to 78% of patients receiving oxaliplatin show evidence of sinusoidal injury [12]. SOS can lead to diffuse or focal hepatopathy and to focal nodular hyperplasia-like nodules. At imaging, hepatosplenomegaly, portal hypertension, and decrease portal venous flow are noted [6]. Gadoxetic acid-enhanced MRI typically identifies SOS as a diffuse hypointensity on HBP imaging, with a high specificity (96–100%) and good interobserver agreement [15]. This led the European Society of Gastrointestinal and Abdominal Radiology to recommend gadoxetic acid-enhanced MRI for the diagnosis of SOS in patients with chemotherapy-treated CLM [15]. SOS is linked to increased postoperative morbidity [12].

38.5 Conclusion

Imaging plays a critical role in the management of patients with CLM. MDCT has proven to be a robust tool in the detection of CLM but MRI and PET-CT are increasingly used when the surgical indication needs to be discussed. Indeed, MR imaging combining hepatobiliary delayed images with DWI is the most accurate modality for detecting and characterizing CLM, particularly lesions less than 1 cm in diameter. Furthermore, ^{18}FDG PET-CT is useful to rule out extrahepatic disease when hepatectomy is being considered. Imaging evaluation of CLM response after systemic therapy relies on changes in tumour size, as defined by RECIST criteria but, there is growing evidence that response to systemic therapy is best assessed with alternative treatment response imaging criteria. Chemotherapy-associated liver injury can be detected when imaging studies are appropriately interpreted.

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Prevention of Postoperative Hepatic Insufficiency

39

Junichi Shindoh

Learning Objectives

- Systematic volumetry of future liver remnant (FLR) stratifies the risk of postoperative hepatic insufficiency (PHI) and selects patient population requiring portal flow modulation procedure and/or two-stage hepatectomy.
- FLR volume is a strong predictor of PHI and death from liver failure. Minimum requirement of FLR volume should be determined based on the quality of underlying liver parenchyma.
- Dynamic measures in liver function test and volumetric parameters after portal vein embolization independently predict the risk of PHI. Maximum extent of hepatectomy should be determined considering both static and dynamic measures for hepatic functional reserve.

39.1 Introduction

With advances in surgical strategy and perioperative care in the field of hepatobiliary surgery, there is an increasing need for extended hepatectomy for patients with advanced hepatobiliary malignancies. At the same time, however, this increases the risk of postoperative hepatic insufficiency (PHI), a critical state associated with death from liver failure, because of an increasing number of expanded resections for patients with injured underlying livers. Given that resection of a hepatic malignancy has two primary goals: complete removal of the tumour and safe surgery, ~~and~~ prediction and prevention of PHI are of most importance to secure the safety of major hepatectomy.

39.2 Definition of Postoperative Hepatic Insufficiency and Risk Factors

PHI is manifested by nonobstructive jaundice, ascites, coagulopathy, and increased susceptibility to complications. However, there has been no standardized definition of PHI. The International Study Group of Liver Surgery (ISGLS) defines post-hepatectomy liver failure (PHLF) as "a postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5." [1] However, these criteria are partly subjective and difficult to quantify. Among the various definitions of PHI reported in previous studies, 50–50 criteria [2] (prothrombin time <50% and serum bilirubin >50 μmol/L on postoperative day 5) and Mullen's definition [3] (peak total bilirubin >7 mg/dL) are simple and objective criteria that have been used in various studies looking at the risk of PHI. Because the primary objective to define PHI is to sensitively predict death from liver failure, the definition should exclude clinical outcomes or ongoing treatment, and preferably use simple and objective measures.

Reported risk factors for PHI include small future liver remnant (FLR), excessive intraoperative blood loss, prolonged operation time, underlying liver disease, male gender, advanced age, malnutrition, and infection, etc. [4]. Among these, small FLR is the most important factor that is "modifiable" with several portal flow modulation procedures. Thus, systematic volumetry of the liver is essential as the first step in the preoperative workup for patients scheduled to undergo liver resection.

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39.3 Preoperative Risk Assessment

39.3.1 Volumetry

A previous anatomic study [5] reported that the left lateral section (segment II + III) accounts for only 17.6% of total liver volume in median (Table 39.1). Therefore, routine volumetry is recommended especially for patients undergoing extended right hepatectomy to predict the risk of PHI. Recently, various three-dimensional (3D) simulation software for liver surgery has become available (Fig. 39.1) and its clinical usability has been reported [6]. On volumetry, FLR should be calculated as "full functioning" part of the liver (i.e., the part of the liver that will have both adequate arterial/portal inflow and venous/biliary drainage) because ischemic part of the liver does not function and congestive area is reportedly associated with decreased hepatic function, followed by delayed atrophy [7, 8].

39.3.2 Static Functional Measures for Risk Assessment

In many centers in Western countries, risk of PHI is estimated by preoperative clinical information including basic laboratory data and measurement of FLR volume. Vauthey et al. proposed a formula estimating total liver volume (TLV): TLV (cm3) = −794.41 + 1267.28 × BSA (m^2) [9] and adopts the standardized FLR (sFLR) that is calculated as the ratio of the FLR volume to the estimated TLV for surgical risk assessment. Estimated minimum requirement of sFLR is reported to be ≥20% in patients with normal liver to avoid PHI or death from liver failure, [10] while at least 30% is required for patients who underwent extensive chemotherapy (≥3 months) [11] and at least 40% should be preserved for patients with cirrhosis [12]. Another means to prevent PHI after extended hepatectomy has been reported to rely on the ratio between the remnant liver volume (RLV) and the body weight. Patients with an anticipated RLV ≤0.5% of body weight are at considerable risk for hepatic dysfunction and postoperative mortality [13].

Table 39.1 Volume proportions of each liver segment in the whole liver. (Adopted from Shindoh J, et al. Ann Surg 2010 [5] with permission)

	Volume (mL)	Percentage (vs. TLV)
Segment I	84 (55–123)	7.6% (5.4–9.9%)
Segment II	99 (15–181)	8.2% (1.6–15.8%)
Segment III	107 (35–232)	9.4% (2.6–19.8%)
Segment IV	131 (55–231)	11.7% (5.1–18.5%)
Segment V	135 (28–247)	12.0% (3.0–24.8%)
Segment VI	134 (46–371)	11.7% (3.4–29.8%)
Segment VII	151 (60–341)	13.8% (5.1–29.1%)
Segment VIII	270 (113–515)	24.2% (11.1–44.8%)
Total liver volume	1103 (781–2034)	100%

Figures represent median (range). *TLV* total liver volume

Although the most common disease referred for hepatectomy is colorectal liver metastases (CLM) which is not associated with underlying liver disease, many patients undergo preoperative chemotherapy and increasing number of cases present chemotherapy-associated liver injury in the era of multidisciplinary treatment. It is well known that there is a specific correlation between chemotherapy regimens and histopathological damages on the underlying liver. Sinusoidal injury related to oxaliplatin [14, 15] and steatohepatitis induced by irinotecan particularly in patients with high body mass index [16] are two major chemotherapy-associated hepatotoxicity. While it is difficult to accurately predict the presence of chemotherapy-associated hepatic injury before surgery, it has been reported that the duration of chemotherapy is significantly associated with the incidence of hepatic atrophy, a morphological phenotype of sinusoidal injury, and impaired hepatic functional reserve [17, 18]. Given such observations and increased risk of PHI among patients with prolonged preoperative systemic therapies, [11] care should be paid for those who are scheduled to undergo extended hepatectomy after more than 3 months of chemotherapy.

39.3.3 Dynamic Functional Measures for Risk Assessment

Indocyanine green (ICG) clearance test is widely used in Japan to precisely estimate the functional reserve of the liver. The conventional safety criteria for the maximum extent of hepatectomy based on the ICG retention rate at 15 min (ICG-R15) (Makuuchi's criteria) was originally established to secure the safety of hepatectomy for patients with cirrhosis [19]. These criteria determine that up to 2/3 hepatectomy (e.g., right hepatectomy or trisectionectomy) is acceptable for the patients with ICG-R15 of <10%, up to 1/3 hepatectomy (e.g., left hepatectomy or sectorectomy) for those with ICG-R15 of 10–19%, up to 1/6 hepatectomy (e.g., segmentectomy) for those with ICG-R15 of 20–29%, and only limited resection or enucleation is acceptable for patients with ICG-R15 of 30% or greater. By strictly following these criteria, the University of Tokyo group achieved zero mortality in more than 1000 consecutive hepatectomies in the late 1990s [20].

39.3.4 Combination of Dynamic and Static Measures for Expanding Surgical Indication

In the era of 3D simulation for surgical planning, much sophisticated criteria based on the combination of ICG disappearing rate (ICG-K) and meticulous 3D volumetry have been adopted [21, 22]. At Toranomon Hospital, Tokyo,

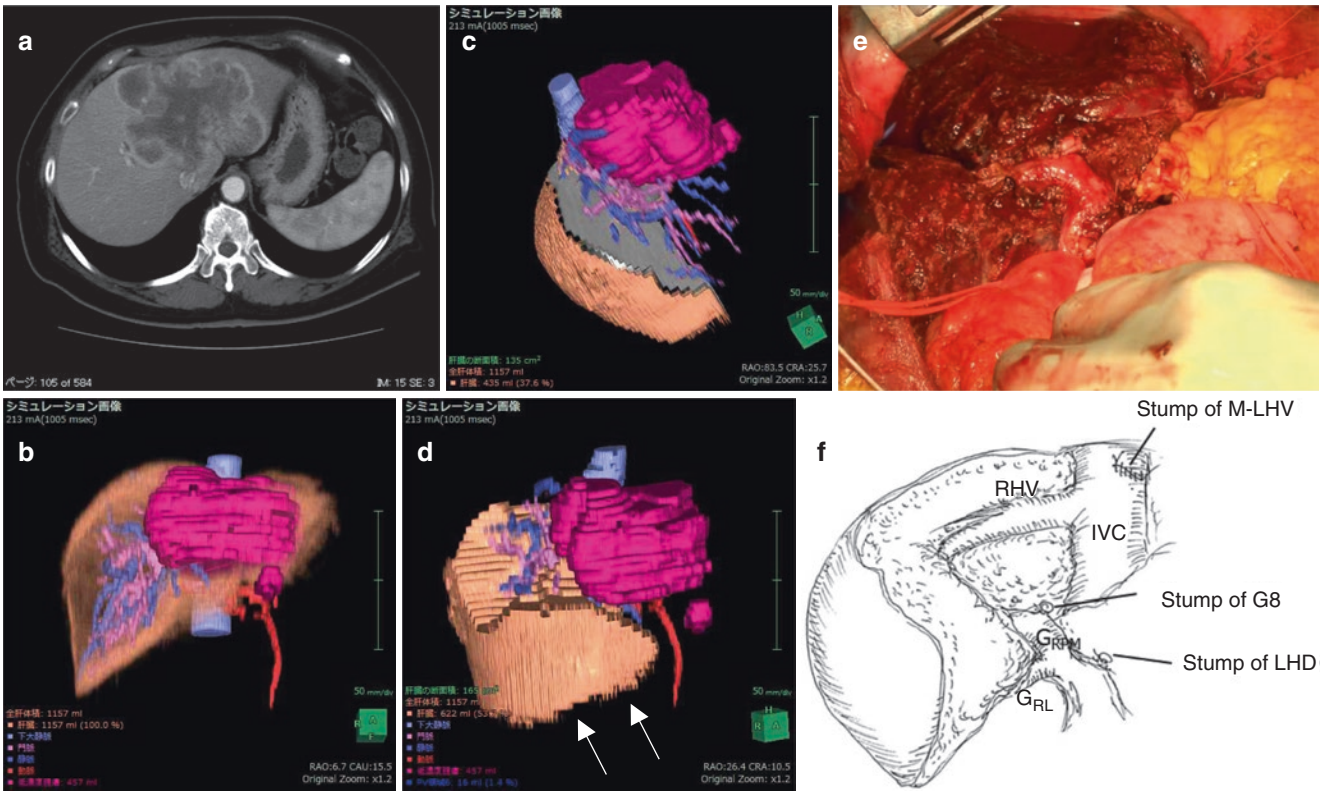

Fig. 39.1 3D simulation of the liver for surgical planning. A case of huge intrahepatic cholangiocarcinoma (**a**) and its 3D simulation for surgical planning (**b**). This patient had an impaired underlying liver due to steatohepatitis and at least 50% of the liver needed to be preserved according to the safety criteria based on the indocyanine green clearance. On volumetry, the estimated FLR volume after left trisectionectomy was only 37.6% (**c**), while 53.7% of the liver could be left when segment V is preserved (arrows in **d**). This patient achieved R0 resection by extended left hemihepatectomy and postoperative course was uneventful (**e**, **f**). Abbreviations: *M-LHV* middle-left hepatic vein; *LHD* left hepatic duct; *RHV* right hepatic vein; *IVC* inferior vena cava

JAPAN, we have used expanded criteria using estimated ICG-K of full functioning part of the FLR (ICG-Krem) in patients with serum total bilirubin level of <2.0 mg/dL and none or controllable ascites.

ICG clearance rate (ICG-K) is measured by sampling at three time points; 5, 10, and 15 min after injection. Three points are plotted on a semi-logarithmic graph using a non-logarithmic scale for time (x-axis) and a logarithmic scale for ICG concentration (y-axis). The three points are connected and a line is created by the least-squares method and the initial concentration of ICG (C_0) is determined from y-axis intersection. The half-valued period ($t_{1/2}$) of ICG concentration ($C_0/2$) is also determined from this graph. ICG-K is calculated by the following formula:

$$\mathrm{ICG-K} = \left(\log C_0 - \log C_t\right) / t = \left(\log C_0 - \log C_0 / 2\right) / t_{1/2} = 0.693 / t_{1/2}$$

ICG-Krem is then calculated using the ratio of FLR to total liver volume (TLV) as follows:

$$\mathrm{ICG-Krem} = \mathrm{ICG-K} \times \mathrm{FLR} / \mathrm{TLV}$$

By strictly keeping ICG-Krem of ≥0.05 in patients undergoing hepatectomy, it has been shown that postoperative peak total bilirubin level never exceeds 7.0 mg/dL (Fig. 39.2) and we have not experienced death from liver failure in more than 1200 consecutive hepatectomies performed during the last 7 years (year 2014–2020) (unpublished data).

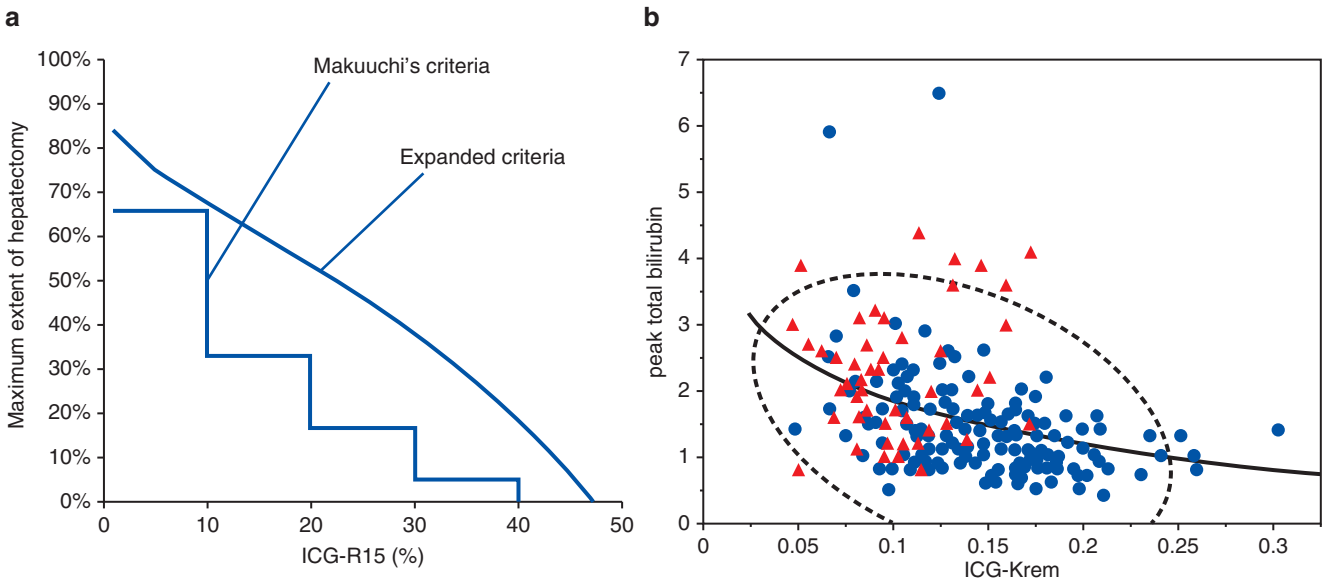

Fig. 39.2 Maximum extent of hepatectomy according to the indocyanine green clearance rate and postoperative peak serum total bilirubin level. (**a**) Proposed maximum extent of resection according to the indocyanine green retention rate at 15 min (ICG-R15). This graph visually compares the conventional criteria (Makuuchi's criteria [19]) and the expanded criteria based on the ICG disappearing rate of future liver remnant (ICG-Krem) of ≥0.05 [22]. (**b**) Correlation between ICG-Krem and postoperative peak serum total bilirubin level. Blue dots represent the cases fulfilling the Makuuchi's criteria and red dots represent the cases beyond the conventional criteria. Regression curve revealed that estimated postoperative peak serum total bilirubin level is less than 3.0 mg/dL as long as ICG-Krem exceeds 0.05 after surgery. (Adopted from Kobayashi Y, et al. HPB 2020 [21] with permission)

39.4 Strategy to Prevent Postoperative Hepatic Insufficiency

39.4.1 Portal Vein Embolization

Portal vein embolization is the most common portal flow modulation procedure performed preoperatively to reduce the risk of extensive liver resection in patients with a small anticipated FLR [23–26]. By redirecting portal blood flow to the intended FLR, PVE produces a shift in hepatic functional reserve resulting from atrophy of the embolized liver and compensatory hypertrophy of the FLR. Several cohort studies from high volume centers have shown that PVE can be safely performed with minimal morbidity and contribute to safer extended hepatectomy with minimized mortality rate [27, 28].

It has been reported that death from liver failure can be minimized when a patient achieves sufficient regeneration of FLR after PVE and meets the criteria for minimal requirement of sFLR volumes [10]. In addition, it has also been known that regenerative capacity of the liver independently predicts surgical outcomes regardless of the absolute sFLR volume achieved by PVE. Kinetic growth rate (KGR) [29] defined as the degree of hypertrophy of sFLR divided by number of weeks elapsed after PVE sensitively predicts the risk of postoperative hepatic insufficiency. KGR >2.0%/week is strongly associated with low risk of postoperative morbidity and mortality irrespective of the sFLR volume [29, 30].

39.4.2 Two-Stage Hepatectomy (Including ALPPS)

For patients with bilateral multiple CLMs, two-stage hepatectomy is sometimes required to safely achieve R0 resection when one-stage hepatectomy is thought to be not feasible even after PVE. There are various types of two-stage hepatectomy in combination with PVE or portal vein ligation plus in situ splitting (i.e., ALPPS: the associating liver partition with portal vein ligation for staged hepatectomy [31]). Figure 39.3 shows our surgical strategy based on the distribution of CLMs for patients with too small FLR. Major hepatectomy and partial resection of the remaining part of the liver is a reasonable strategy when the distribution of CLMs is right-side dominant or left-side dominant (Fig. 39.4), while combination of parenchymal-sparing hepatectomies is preferable for patients with multiple lesions on both sides of the liver to reduce the risk of PHI and to increase the salvageablity at future resection for recurrence.

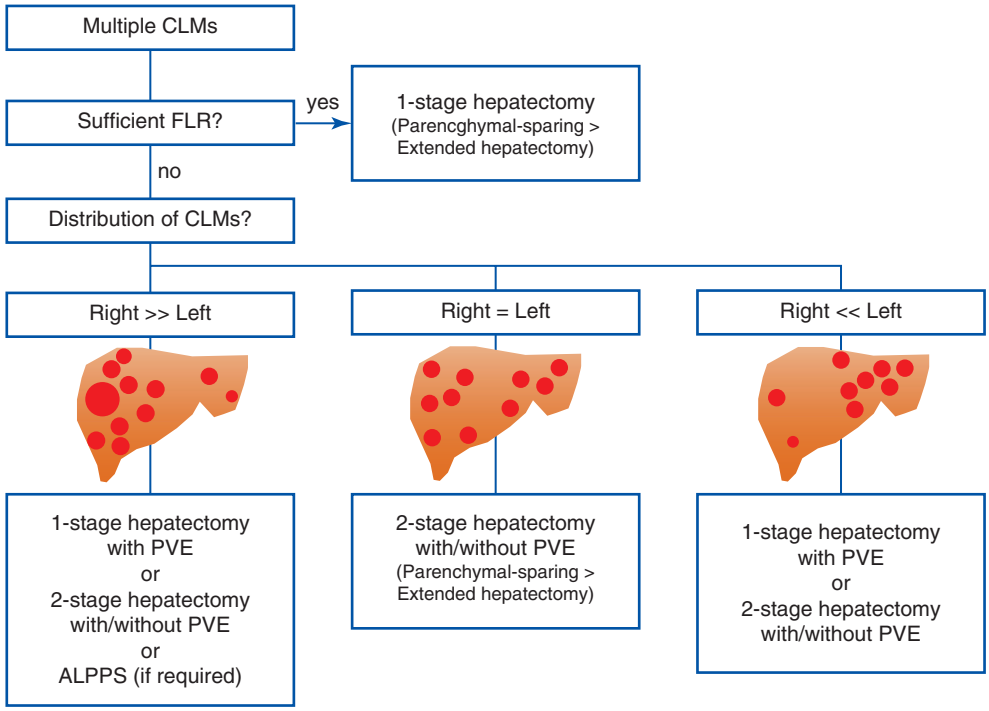

Fig. 39.3 Surgical strategy based on the FLR and distribution of tumour in patients with multiple colorectal liver metastases

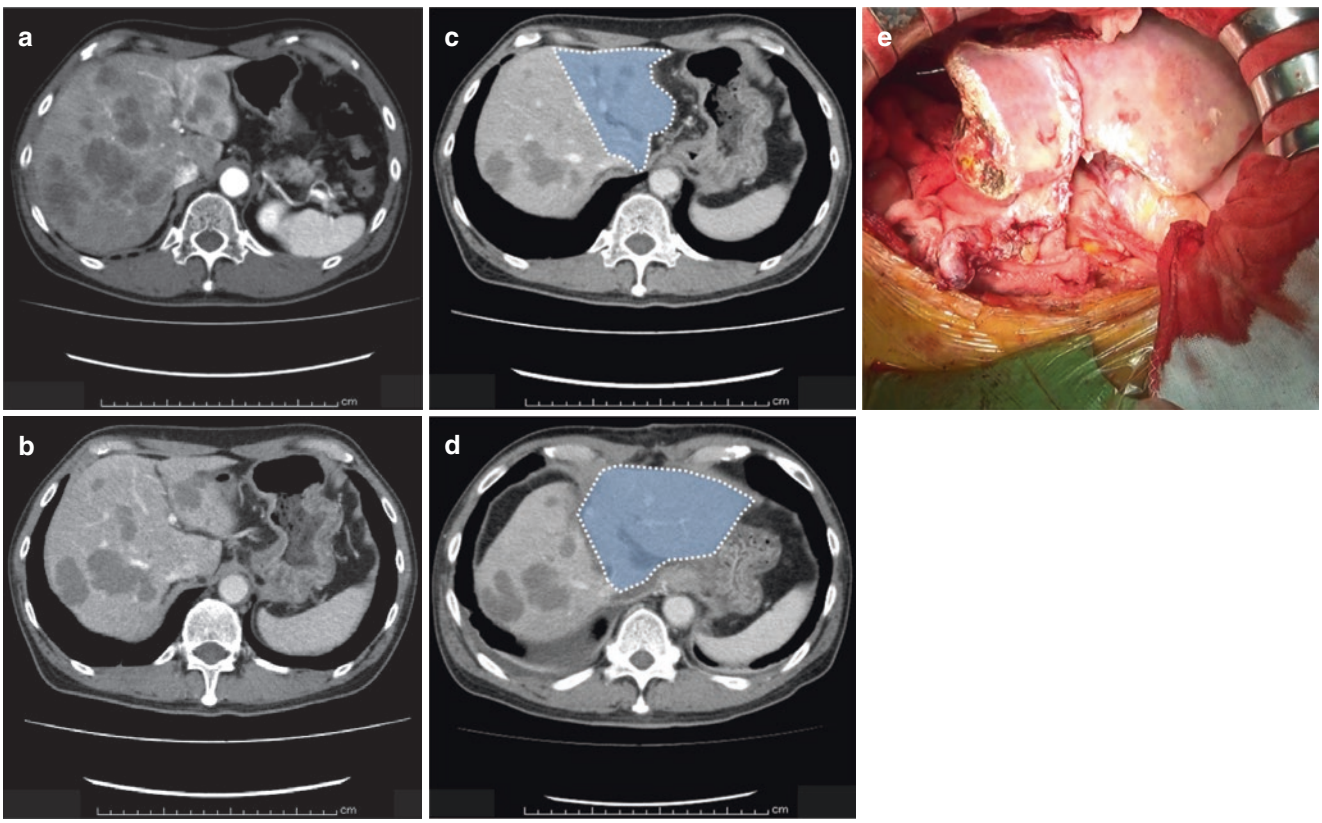

Fig. 39.4 An example of two-stage hepatectomy. The patient presented synchronous multiple liver metastases (21 nodules) (**a**) and underwent 6 cycles of FOLFOX + bevacizumab (**b**). Although good response was observed (RECIST PR and optimal morphologic response), future liver remnant volume after extended right hemihepatectomy and partial resection of the left hemiliver was estimated as 19.5% (**c**). Because safe access route for portal vein embolization cannot be secured due to the presence of multiple metastatic lesions, two-stage hepatectomy with portal vein ligation was scheduled in this case. At initial hepatectomy, all the metastatic lesions in the left hemiliver (7 nodules) were enucleated and right portal branch was ligated. By adding *in situ* splitting (i.e., ALPPS), sufficient increase in future liver remnant was observed (from 19.5 to 40.3% at 16 POD) (**d**) and safe removal of the right hemiliver was achieved (**e**). This patient survived for 40 months after surgery

39.4.3 Duration of Chemotherapy

Association between the duration of chemotherapy and risk of postoperative morbidity is well recognized [32]. Prolonged preoperative chemotherapy is reportedly correlated with an increased risk of decreased hepatic functional reserve and PHI [11, 18]. Two volumetric studies have confirmed that normal liver parenchyma tends to shrink with impairment of hepatic functional reserve as the duration of chemotherapy is prolonged [17, 18]. Given that patients who require preoperative chemotherapy frequently undergo major hepatectomy, duration of chemotherapy should be balanced with the risk of impairment of underlying liver. A previous report has demonstrated that >3 months of chemotherapy with modern cytotoxic regimen predicts increased risk of PHI [11]. Therefore, initial assessment during preoperative chemotherapy should be performed 2–3 months after induction of chemotherapy and surgical intervention should be considered when surgical indication criteria [33] are fulfilled.

39.5 Conclusions

PHI is associated with insufficient FLR volume and systematic volumetry should be routinely performed before major hepatectomy. Minimal requirement of FLR volume is dependent on the degree of functional injury in underlying liver, and several perioperative strategies including PVE or two-stage hepatectomy are used to avoid the risk of PHI when the FLR volume does not meet with safety criteria for hepatectomy.

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Portal Vein Embolization with and without Hepatic Vein Occlusion

40

Kosuke Kobayashi, Nicolas Villard, Alban Denys, and Emmanuel Melloul

Learning Objectives

- Portal vein embolization induces hypertrophy of the future liver remnant.
- About 20% of patients undergoing portal vein embolization cannot proceed to surgery due to disease progression or insufficient liver hypertrophy.
- Hepatic vein embolization contributes to safer and effective major hepatectomy.
- Ipsilateral portal vein embolization with hepatic vein embolization is associated with superior kinetic growth compared to portal vein embolization alone.

40.1 Introduction

Globally, colorectal cancer is a growing cause of cancer-associated death; about 30% of patients with colorectal cancer develop liver metastases [1–3]. Although chemotherapy regimens have improved in recent years, liver resection is the main curative treatment for colorectal liver metastases (CLM) [4]. However, liver failure remains a serious postoperative complication associated with high mortality after major liver resection [5]. After major hepatectomy, the 30-day and 90-day all-cause mortality rates were 3.2% and 4.7%, and 2.8% of 90-day mortality was associated with liver failure [5].

Future liver remnant (FLR) volume is an important factor predicting postoperative liver failure [6]. When the remnant liver volume is insufficient on the basis of the preoperative volumetric assessment using computed tomography (CT), portal vein embolization (PVE) is one of the methods used to induce hypertrophy of the FLR in patients planned for a major hepatectomy. Subsequently, simultaneous or sequential embolization of the portal vein and the hepatic vein was reported in the 2010s [7]. Ipsilateral hepatic vein embolization, also termed liver venous deprivation (LVD) [8–10] together with PVE, or radiological simultaneous portohepatic vein embolization (RASPE) [11] increases the FLR hypertrophy. This chapter describes procedures of both PVE and PVE with hepatic vein embolization (HVE) and their outcomes.

40.2 Portal Vein Embolization

Use of PVE for humans was first described by Kinoshita et al. [12] and Makuuchi et al. [13], in 1980s. In 1994, Kawasaki reported the use of PVE for bilateral CLMs [14]. Since then, PVE has been widely used to induce hypertrophy of the FLR in patients planned for a major hepatectomy [15–17]. Two techniques of PVE are used: percutaneous transhepatic portal vein embolization (PTPE) [18–20] and transileocolic portal vein embolization (TIPE) [21, 22]. The TIPE is a surgical procedure performed under general anesthesia. PTPE can be achieved via an ipsilateral approach [18] or contralateral approach [19].

40.2.1 Indication for PVE

The percentage of FLR is used to evaluate the efficacy of PVE. A cut-off value of less than 25–30% of FLR in normal liver and less than 35–40% of FLR in diseased liver

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(e.g., chemotherapy-associated steatohepatitis, cholestatic liver) are indications for performing PVE [23, 24]. In many studies, FLR calculated by pre-procedural CT is used (%FLR ratio = FLR volume/total liver volume) [18–21, 25–29]. Other studies have used the standardized FLR (sFLR) calculated dividing FLR volume by standardized liver volume (SLV) (SLV = −794.41 + 1267.28 × body surface area) [30]. However, generalization of safety limit of FLR in patients with diseased liver is still controversial. Indocyanine green (ICG) retention rate at 15 min [31] or liver scintigraphy with 99mTc-mebrofenin [32, 33] have also been reported for predicting liver dysfunction and postoperative mortality. One drawback of the ICG retention rate is that it cannot predict FLR function, while liver scintigraphy does [34].

40.2.2 Hypertrophy

The increase in FLR volume after PVE can be calculated using two methods:

1. %FLR volume increase = (% Post-FLR − % Pre-FLR) × 100/% Pre-FLR, and
2. the degree of hypertrophy = Post-FLR − Pre-FLR volume.

However, regeneration rate of the FLR after PVE varies among individuals and its clinical significance is unknown. For that purpose, the kinetic growth rate, defined as the degree of hypertrophy at initial volume assessment divided by number of weeks elapsed after PVE (KGR) has been used [35]. KGR seems to be a better predictor of postoperative morbidity and mortality after liver resection for small FLR than conventionally measured volume parameters (i.e., sFLR volume and degree of hypertrophy).

A systematic review showed that the mean increase of FLR volume was 37.9% ± 0.1% (range: 20.5–69.4%) in mean time interval of 25.9 days ± 10.1 days (range: 14–42 days) after PVE [36]. Although patients with chronic liver disease showed less hypertrophy response than patients with normal liver parenchyma, chemotherapy seems to have no influence on the hypertrophy response [26–29].

40.2.3 PVE Safety

A meta-analysis including 37 studies with a total of 1088 patients showed that the overall morbidity of PVE was 2.2% [16]. The complication after PVE divided into minor and major is shown in Table 40.1. Minor complication such as fever or abdominal pain appears in 45.7% and major complication rate is 0.4%. The procedure-related mortality was reported to be very low. In a study of 146 patients by Giraudo et al. [19], only one patient died 20 days after PVE due to lethal pulmonary embolism. In addition, overall mortality rate was 0.1% in a systematic review including 1791 patients in 44 studies [36].

Table 40.1 Comparison between PVE alone and PVE with HVE

	PVE alone [16, 35]	PVE with HVE [7–11, 38–40, 42–44]
Technique of embolization	TIPE/PEPE (ipsilateral or contralateral)	TJ/TH (simultaneous or sequential)
Technical success rate, %	99.3% (86.6–100%)	100%
Morbidity after embolization, %	2.2%	0% (hemobilia[a] [10], hemoperitoneum[a] [11])
Mortality after embolization, %	0.1%	0%
Degree of hypertrophy, %	37.9% ± 0.1% (20.5–69.4%)	27–67%
Dropout rate, %	20.0% (358/1791)	14.4% (28/194)
Time from embolization to surgery, days	36.9 (21–84)	23–49
Morbidity after hepatectomy	21.7%	10.3% [41]
Mortality after hepatectomy	3.3%	5.1% [41]

Data are presented as mean (range) or n (%)
Abbreviations: *PVE* portal vein embolization; *HVE* hepatic vein embolization; *TIPE* transileocolic portal embolization; *PTPE* percutaneous transhepatic portal embolization; *TJ* transjuglar approach; *TH* transhepatic approach
[a]PVE-related complication

40.2.4 PVE and Liver Resection

Up to 20% of patients undergoing PVE cannot proceed to surgery [36]. Main causes of cancelation are (1) intrahepatic tumour progression or newly developed metastases in the FLR, (2) extrahepatic tumour spread, or (3) others such as insufficient liver hypertrophy or complication of PVE.

According to a systematic review including 1791 patients, more than 70% of patients can undergo a right hepatectomy or extended right hepatectomy, on average 36.9 days (range 21–84 days) after PVE. The overall morbidity and mortality after liver resection is reported to be 21.7% and 3.3%, respectively [36]. The causes of mortality are acute liver failure, liver failure in combination with multiple organ failure, portal vein thrombosis, abdominal/liver bleeding, cholangitis, cardiac failure, or unknown cause.

40.3 Portal Vein Embolization with Hepatic Vein Embolization

One drawback of PVE is the risk of progression of the tumour during the waiting period, mainly in patients with bilobar CLM [37]. Hwang et al., reported the efficacy of sequential bi-embolization, PVE followed by HVE, and this technique resulted in superior FLR volume than PVE alone [7]. Ipsilateral HVE with PVE was named liver venous deprivation (LVD), or radiological simultaneous portohepatic vein embolization (RASPE). Several groups have reported that ipsilateral LVD contributes to safer and effective major hepatectomy [8, 9, 38–40] and one systematic review showed its safety [41]. Recently two large retrospective cohorts of simultaneous HVE and PVE showed superior KGR after LVD compared to PVE alone [10, 11].

40.3.1 Technique of HVE

Two HVE techniques have been reported: (1) the transjuglar approach [7, 10, 38–40] and (2) the transhepatic approach [8, 9, 11, 42, 43]. The transjugular method consists of selective catheterization of the different hepatic veins and deployment of multiple plugs placed from the periphery down to the central portion of the vein. The transhepatic approach uses a percutaneous access to the main right hepatic vein. From this access, a vascular plug is deployed in the distal portion of the vein. Immediately after, N-butyl cyanoacrylate is injected to occlude the rest of the vein. If multiple veins are present, multiple large-bore access are needed. Figures 40.1, 40.2, 40.3, 40.4, 40.5, 40.6, and 40.7 summarize the LVD procedure in a clinical case.

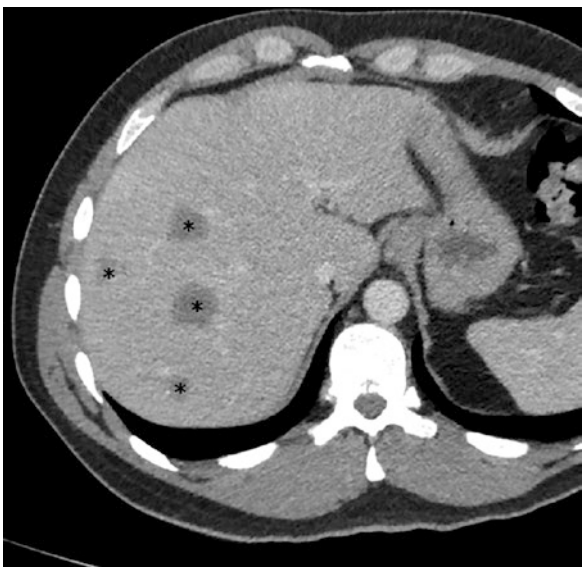

Fig. 40.1 A 43-years-old male patient with sigmoid adenocarcinoma and liver metastases (pT4a pN2b pM1c) presented after response to preoperative systemic chemotherapy (FOLFOXIRI) and right hepatectomy was planned. Asterisks: liver metastasis in the right liver

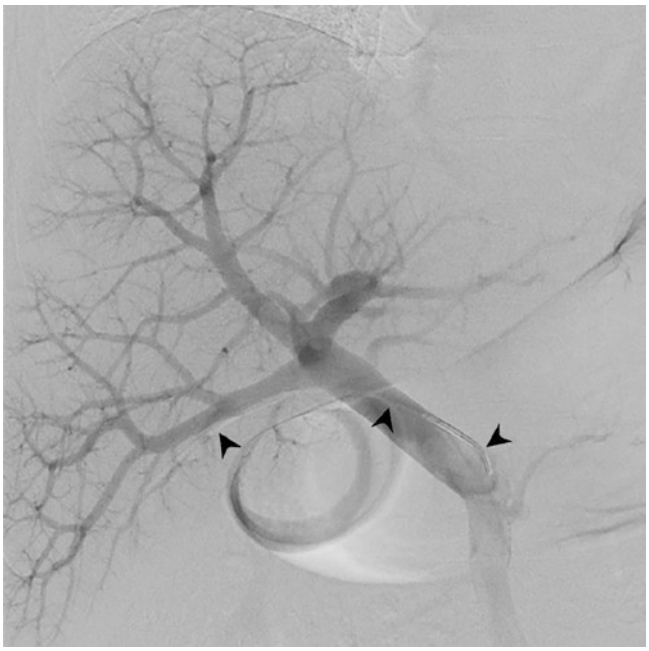

Fig. 40.2 Ipsilateral 5F portal venous system access is gained with US and fluoroscopic guidance. Portography was performed with portal venous pressure measurement. Arrowheads: catheter with tip positioned in portal trunk

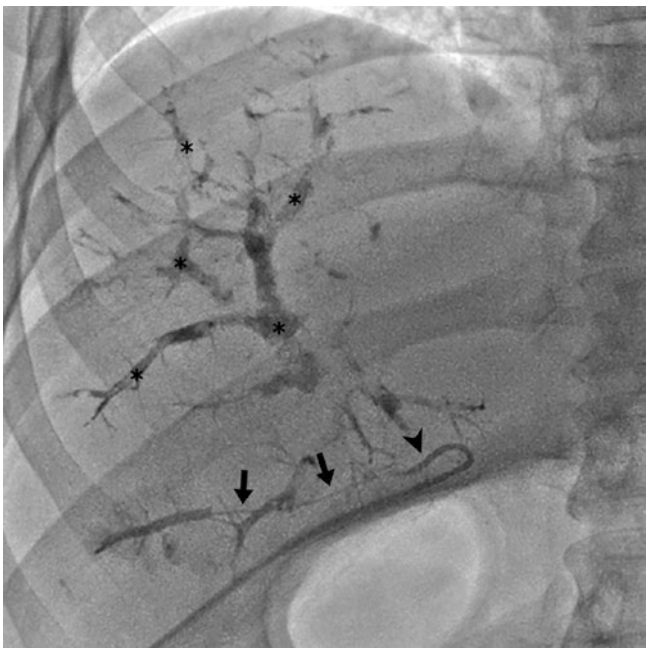

Fig. 40.3 Right portal vein branches were catheterized and microcatheterized and then embolized using glue (histo-acryl mixed with lipiodol). Aarrowhead: catheter; arrows: microcatheter injecting glue; asterisks: embolized portal veins branches

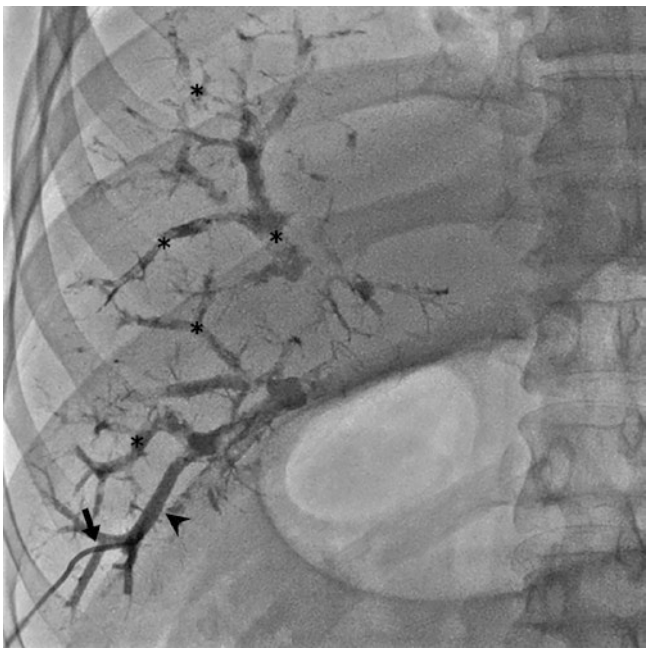

Fig. 40.4 Access was closed by injecting glue during sheath and catheter removal. Arrow: catheter; arrowhead: glue in the branch used for the access

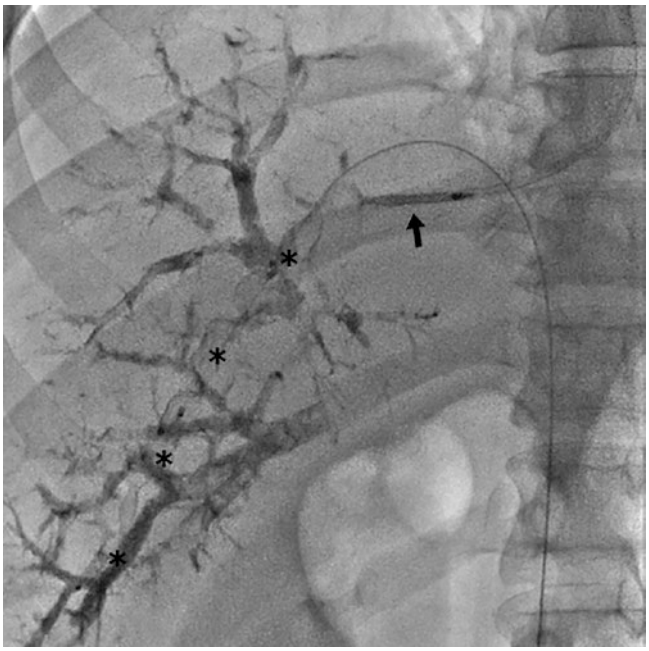

Fig. 40.6 The two major branches of the right hepatic vein are then selectively catheterized and occluded using plugs Arrow: plug placement through the femoral catheter; asterisks: plugs placed in the main right hepatic vein

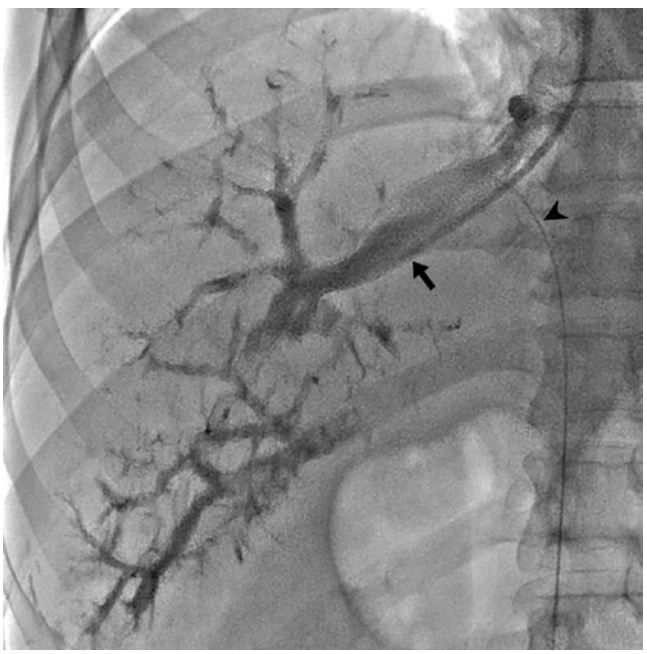

Fig. 40.5 Because of anatomical consideration (early division of the right hepatic vein), right internal jugular and right femoral vein 6F accesses are gained under US guidance. Arrow: catheter from jugular access injecting contrast in the main right hepatic vein; arrowhead: guidewire from femoral access positioned into the early superior division of the right hepatic vein

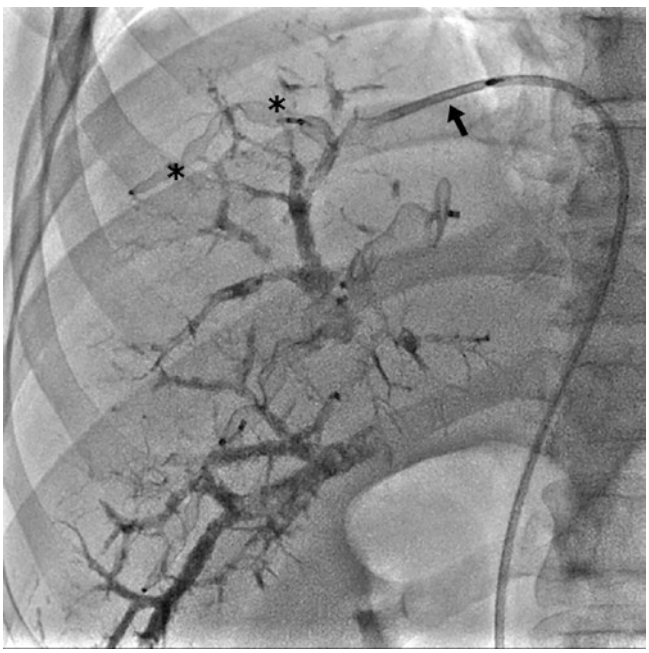

Fig. 40.7 The two major branches of the right hepatic vein are then selectively catheterized and occluded using plugs. Arrow: plug placement through the jugular catheter; asterisks: plugs placed in the early superior division of the right hepatic vein

40.3.2 Hypertrophy

According to 12 studies, the degree of FLR hypertrophy range from 27 to 67% after ipsilateral PVE with HVE [7–11, 38–40, 42–44]. In two studies comparing ipsilateral LVD (or RASPE) and PVE alone, ipsilateral LVD had a greater degree of hypertrophy of the FLR [10, 11]. The KGR was calculated by the following formula: KGR = degree of hypertrophy (%)/time elapsed since PVE (weeks) at first post-PVE volume assessment [45]. Our group showed that LVD had superior KGR (2.9% vs. 1.4%) compared with PVE alone, confirming that LVD triggers a greater and faster hypertrophy of the FLR [10]. In addition, other studies demonstrated that future liver remnant function, measured by 99mTc-mebrofenin scintigraphy, significantly increased after LVD compared to PVE alone [46].

40.3.3 Procedure-Related Morbidity

HVE-related major complication (e.g., pulmonary embolization) was not reported. Complications such as hemobilia [10], hemoperitoneum, and embolization of the wrong portal branches [11] were reported. There are no significant differences in the liver enzymes profile after embolization with LVD or PVE alone [10].

40.3.4 Liver Resection After LVD

Dropout due to disease progression or insufficient FLR hypertrophy occurs in up to 18% of patients (0–18%) following ipsilateral PVE with HVE after a median interval of 23–49 days from embolization and planned surgery [7–11, 38–40, 42–44]. The intra- and postoperative outcomes, including liver enzymes profile did not significantly differ between LVD and PVE groups in two retrospective cohort studies [10, 11]. Of note, the time to scheduled surgery may differ from one center to another, which may add a bias in the analysis of the results, in particular for the risk of dropout due to disease progression.

40.3.5 Comparison Between PVE Alone and PVE with HVE

The comparison between PVE alone and LVD is shown in Table 40.1. Despite the success rate of embolization, morbidity and mortality after embolization/hepatectomy were similar between PVE alone and LVD. Dropout rate was lower and interval from embolization to surgery was shorter in LVD.

40.4 Conclusion

Simultaneous ipsilateral HVE with PVE before major hepatectomy is safe and might induce a faster FLR hypertrophy than PVE alone. One RCT that aims to investigate ipsilateral HVE with PVE versus PVE in patients who had colorectal liver metastases and FLR <30% is ongoing (NCT03841305) and one international registry on LVD was launched (https://eurolvd.ch). These studies will provide additional data to validate the technique.

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Radiofrequency Ablation, Electroporation, and Microwave Ablation

41

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Learning Objectives

- Ablation is indicated for a limited number (1–3 optimal, <5 preferable) of small-sized (<3 cm preferable) colorectal liver metastases.
- Ablation with or without systemic chemotherapy is recommended as the treatment of choice for patients with limited unresectable colorectal liver metastases.
- Ablation is recommended as the treatment of choice for patients with unresectable colorectal liver metastases due to inadequate liver reserve or recurrence after surgery.
- Ablation is recommended as the treatment of choice for patients with unresectable colorectal liver metastases due to medical comorbidity.
- Irreversible electroporation is applied for selected tumours in proximity to bile ducts or vessels when thermal injury to such structures could cause liver failure or significant toxicity from bile or vascular injury.

41.1 Introduction

Ablation techniques such as radiofrequency ablation (RFA), microwave ablation (MWA), and irreversible electroporation (IRE) are curative-intent locoregional therapies widely utilized in clinical practice for patients with small tumours that are not eligible for liver resection or present with recurrence after resection [1–4]. Thermal ablation can also be considered for patients as a stand-alone first-line local therapy for small colorectal liver metastases (CLM) that can be eradicated with margins and close follow-up [5]. The evolving knowledge of tumour biology along with improvements in ablation and imaging technology have improved patient selection and ablation efficacy, ultimately enhancing the role of this treatment in the management of patients with CLM [6–10].

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41.2 Liver Ablation

41.2.1 Ablation Technologies

RFA and MWA are thermal ablation modalities that are widely used as the standard of care to treat unresectable small CLM [11]. The thermal ablation shows the advantage of parenchyma-sparing features which reduces the morbidity of treatment and allows the possibility of sequential locoregional treatment for recurrent tumours, a common theme in the metastatic setting [4, 11]. Prior studies have demonstrated that when thermal ablation can be used to treat local tumour progression (LTP) or new tumours, survival is much improved compared to patients that cannot be ablated [12]. More recently, IRE, a nonthermal technology, has been applied for patients who present with CLM not amenable to thermal ablation due to the higher risk of thermal injury to vital structures in proximity to the ablation zone such as those near a central bile duct [13–16].

41.2.1.1 Radiofrequency Ablation

RFA uses an interstitial electrode to produce an alternating electric current to the target tissue. The electric current oscillates tissue ions rapidly and creates frictional heating. When the temperatures of the target tissue are between 60 and 100 °C, protein denaturation, immediate cell death, and coagulative necrosis occur within the tumour [17]. If the temperatures are above 100 °C, the water vaporizing and tissue carbonizing adjacent to the electrode will degrade the

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electrical conductance, limiting the amount of energy delivered to the tumour, therefore resulting in a suboptimal ablation zone. A major limitation of RFA is the heat-sink effect that occurs if the target tumour abuts a blood vessel 3 mm or larger. Another drawback of RFA is heat injury to vital structures adjacent to the ablation zone. For this reason, treatments for the tumours in the proximity of large vessels or vital structures are challenging and sometimes contraindicated [18].

RFA has been used to treat CLM in selected patients who are not eligible for surgery [2, 19, 20]. It has shown that repeat ablations of CLM can be achieved without compromising long-term outcomes [21]. The benefit of RFA over systemic chemotherapy alone was suggested by one randomized controlled study. The study reported that RFA ± resection combined with systemic chemotherapy improved the overall survival of unresectable CLM compared to systemic chemotherapy alone, disclosing the 8-year survival rate of 35.9% and 8.9%, respectively [22]. Furthermore, RFA prolonged the median progression-free survival compared with systemic chemotherapy alone (16.8 months vs. 9.9 months, $P = 0.005$).

Comparing the effectiveness of RFA to resection, some retrospective nonrandomized studies have reported that RFA has similar outcomes to resection with 5-year survival rates of up to 55% [21, 23–25]. Other meta-analysis studies have reported that liver resection was significantly superior to RFA in overall and disease-free survival, although RFA showed a significantly lower rate of complications [11, 26–28]. All comparisons are limited due to lack of stratification of outcomes by the ability to treat with sufficient margins. Prior studies that compared resection, laparotomy, and RFA showed no difference in progression-free survival and overall survival when complete resection (R0) or ablation with margins (A0) was achieved [29]. The lack of randomization, heterogeneous patient population, and the fact that patients undergoing RFA usually have additional comorbidities limit the generalization of such results.

Several factors have been recognized as independent factors associated with local recurrence at the ablation site, which is defined as local tumour progression (LTP), such as tumour size and minimal ablation margins [2, 30–32]. Minimal ablation margins greater than 5 mm are considered critical for optimal local tumour control, and LTP rates of 15–18% were reported once such margins were obtained. Additionally, the LTP rates were 0–5% for minimal ablation margins greater than 10 mm [2, 31, 33]. A prospective study found that the 2-year cumulative LTP rate was 3% for minimal ablation margins greater than 5 mm with negative biopsy findings at the margins [34]. The result was comparable to marginal recurrence rates after resection of CLM [35, 36].

41.2.1.2 Microwave Ablation

MWA creates an electromagnetic spectrum with frequencies from 900 to 2450 MHz creating heat by agitating surrounding water molecules [37]. MWA generates greater heat and less heat-sink effect than RFA, creating larger areas of ablation zone in a shorter period, which comes at an expense of more complications for peribiliary lesions [38]. Retrospective data have reported lower rates of overall LTP with MWA than RFA (MWA: 6–10% vs. RFA: 20–20.3%), and a lower cumulative LTP rate at 2-year reported in one study (7 vs. 18%; $P = 0.01$) [39–41]. Another study that stratified outcomes by margins, found no difference in the LTP rates between RFA and MWA (3 vs. 7%; $P = 0.47$) and the 2-year cumulative LTP rates were 36% and 38%, respectively ($P = 0.84$) [33]. Of interest, there was no LTP after RFA or MWA for tumours ablated with margins >10 mm [33]. The same study indicated that MWA performed equally well in perivascular as non-perivascular tumours unlike RFA that was associated with higher LTP rate for perivascular tumours, negatively impacted by the heat-sink effect [33]. Regarding overall survival and ablation-related complications, there was no significant difference between MWA and RFA [33, 39–41]. A meta-analysis of primary and metastatic liver tumours reported that there was no significant difference in 1-year and 5-year overall survival, disease-free survival, adverse events, and LTP rates between MWA and RFA [42]. The subgroup analysis according to two studies that included only liver metastases suggested a lower LTP rate for MWA, although the comparison was not stratified by minimal ablation margins [42]. However, no randomized studies are comparing MWA to RFA, and it may be that the two techniques have complementary rather than competing roles.

Comparing MWA versus liver resection, a small randomized trial of 30 patients published during the early experience with intraoperative MWA found equivalent 3-year overall and disease-free survival, and the ablation-related complication rates were similar between the groups [43]. Recently, a case-matched study of 271 patients reported no difference in 3-year overall survival between patients submitted to MWA and hepatectomy as the first intervention for CLM (76 vs. 76%; $P = 0.253$) [1]. However, randomized studies and long-term survival analysis are still lacking.

41.2.1.3 Irreversible Electroporation

IRE is a novel modality of non-thermal ablation. The mechanism of IRE is based on the high-voltage electrical pulses that cause irreversible cellular membrane disruption, leading to cell death while remaining underlying connective tissue scaffold intact. This results in intact vulnerable structures such as blood vessels and bile ducts while still ablating tumours. The potential safety of IRE ablation close to major

bile ducts has been reported in a small case series. After ablation within 1 cm adjacent to the bile ducts, luminal narrowing was noted in 14.8% (8/54) of bile ducts, while the laboratory values remained normal 1–2 months later [44]. Because IRE does not use heat to eradicate the tumours, its efficacy is not impeded by the heat-sink effect by neighboring blood vessels [45]. Therefore, the application of IRE is best for small tumours in proximity to major vascular structures where RFA-associated heat-sink effect can occur [13, 46, 47]. The major limitation of IRE is that the ablation zone is created between at least two parallel electrodes with space approximately 1–1.5 cm apart, which is relatively small as compared with other modalities. The larger the tumour size the more electrodes are required for ablation. Precise placement of multiple electrodes with appropriate space is challenging and time-consuming [48, 49]. Furthermore, it has been reported that the post-IRE imaging response may be inaccurate in the reflection of the histopathologic appearance of the ablation zone [50, 51], which limits the analysis of treatment endpoints and efficacy. Several studies of IRE have demonstrated the primary efficacy of 66–100% for primary or secondary hepatic tumours in proximity to major vascular or biliary structures [13, 15, 52–54]. A pilot study evaluated 10 CLM lesions treated with IRE who underwent resection approximately 84 min later and showed absence of viability and irreversible cell damage in all the lesions [55]. Two retrospective studies found a 2-year overall survival rate up to 62% in CLM treated with IRE, while the 2-year progression-free survival rates were reported from 18 to 40.5% [16, 56]. Another study of 24 patients with unresectable CLM reported the 3-year and 5-year overall survival rates were 25% and 8.3%, respectively [54]. Recently, a phase II prospective study (COLDFIRE-2) using IRE to treat CLM unsuitable for partial hepatectomy and thermal ablation reported the 1-year LTP free-survival was 79% and the overall complication rate was 40% [57]. Although the current evidence is encouraging, these studies reflect a small and heterogeneous population with short-term follow-up. Therefore, RFA and MWA are still considered the ablation modalities of choice in clinical practice, with IRE being reserved for patients presenting with CLM where such thermal ablative modalities are considered risky.

41.2.2 Patient Selection

Although ablation has a favorable local curative potential for CLM, its use has been associated with a relatively higher risk of local recurrence (defined as LTP) [4, 58]. Studies have shown that LTP is associated with tumour size, number, and location and especially the lack of creation of sufficient ablation margins [2, 4, 33]. Analysis of local recurrence rates and survival showed an advantage for small tumours that can be ablated with margins [2, 30]. The most commonly used cutoff maximal diameter is 3 cm [2, 4, 11, 59, 60]. A tumour sizes up to 3 cm is an independent predictor of overall and LTP-free survival and has been shown in retrospective studies to provide similar oncologic outcomes to resection [2, 61–63]. For tumour size 3–5 cm, ablation is considered with multiple overlapping approaches to achieve complete tumour coverage [4]. For tumour sizes larger than 5 cm, thermal ablation is generally not recommended for a curative intent because of the high LTP rates [64, 65]. However, ablation of CLM up to 5 cm can be performed with adequate planning and monitoring in selected cases to achieve acceptable outcomes [66, 67].

Universally, a solitary tumour under 3 cm is ideal for thermal ablation; however, patients with up to five tumours are eligible [4, 68]. Several patient and disease characteristics predicting the clinical outcomes after thermal ablation could be used for patient stratification. A modified ablation clinical risk score adapted from surgical clinical risk score, including the nodal status of the primary tumour, the time interval from primary resection to CLM diagnosis, carcinoembryonic antigen level, number of tumours, and size of the largest tumour, is associated with LTP and overall survival rates [2, 69]. Moreover, RAS mutation status has been shown to have earlier LTP after thermal ablation [8, 9, 70]. In patients with RAS mutant type, larger minimal ablation margins of at least 10 mm in all dimensions should be aimed to offer the appropriate local tumour control.

Contraindications to ablation include uncorrectable coagulopathy, no safe pathway of ablation needle to the tumour, and anticipated damage to the vital structures adjacent to the target lesion. The location of the tumour affects LTP and complications. Using the thermal ablation modalities adjacent to the major bile duct increases the risk of bile duct injury, causing subsequent complications such as cholangitis or liver abscess [71]. Thermal ablation close to large vessels (the heat-sink phenomenon) increases the risk of residual tumour and LTP [72–74]. Nonthermal ablation techniques such as IRE can be applied on tumours abutting the bile duct and the large vessel [13, 44, 57].

Although the optimal patients for ablation are those with disease limited to the liver, patients with limited extrahepatic liver disease can also benefit from liver tumour ablation [75–77]. In a study of 162 patients undergoing liver ablation, the patients with lung-only metastases had the highest median overall survival compared with more than one site of metastases (35 months and 14 months, respectively) [2]. The result was similar to a multi-institutional surgical study that in patients who underwent liver and extrahepatic disease resec-

tion, patients who had only lung metastases had the highest median overall survival compared with multiple metastatic sites (46 months and 15 months, respectively) [78]. A similar result was found in another study that 5-year overall survival rates of patients with resection of CLM and lung metastases were better than those with CLM resection only [79]. In patients with an extensive distribution of CLM, it is difficult to approach curative-intent resection at the time of diagnosis and ensure sufficient function for future liver remnant. The hepatectomy combined with intraoperative or postoperative ablation and two-stage hepatectomy can achieve a cure and preserve the future liver remnant in these patients [80–83]. A case-matched study reported no significant difference in 5-year overall survival in two-stage hepatectomy and one-stage hepatectomy combined with RFA (29 vs. 35%; $P = 0.6$) [84]. In another case-matched study comparing patients treated with hepatectomy combined with RFA and hepatectomy alone, there was no significant difference in 5-year overall survival (57 vs. 61%; $P = 0.573$) and disease-free survival (19 vs. 17%; $P = 0.865$) [80]. A study reported a sequential treatment strategy, postoperative percutaneous completion ablation following liver resection for intentionally untreated lesions. Results demonstrated that such approach may provide better local tumour control comparing with intraoperative ablation (5-year LTP rate: 31.7 vs. 62.4%; $P = 0.03$), with no significant difference in overall survival (5-year overall survival: 53.2 vs. 41.8%; $P = 0.407$) [82].

For patients with post-resection recurrence, the image-guided ablation is considered as an alternative salvage treatment to liver resection. The ablation can be repeated to treat recurrence with less destruction of liver tissue and can achieve survival similar to patients without recurrence [67, 69, 85–87]. Repeat ablation can delay liver resection with the test-of-time strategy, sparing unnecessary surgery because it is disease-free after ablation or develops multifocal liver disease during the waiting time [69]. A retrospective study of 64 patients with liver-limited recurrence after hepatectomy reported the 4-year overall survival rates were 30.4% for patients who underwent ablation and 43.5% for resection ($P = 0.447$) [86]. However, the ablation was associated with worse progression-free survival when compared to surgical resection (median hepatic progression-free survival: 11.8 vs. 5.4 months; $P = 0.008$) [86].

41.2.3 Preablation Imaging and Imaging Guidance Modalities

41.2.3.1 Preablation Imaging Modalities

Optimal preablation imaging plays a critical role in patient selection and treatment planning [88, 89]. A baseline intravenous contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis is commonly used in the workup of patients considered for ablation [90]. A whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan can provide additional information for liver and extrahepatic metastases and may change the management [91]. Magnetic resonance imaging (MRI) is the most accurate imaging for the detection and characterization of hepatic metastases, especially with the hepatocyte-specific MRI contrast agent such as gadobenate dimeglumine (Gd-BOPTA; Multihance, Bracco Diagnostics, Princeton, NJ, USA) or gadoxetate disodium (Gd-EOB-DTPA, Eovist or Primovist; Bayer Healthcare Pharmaceuticals). It has a high sensitivity for the detection of smaller tumours that may not be easily detected by CT and PET [92].

41.2.3.2 Imaging Guidance Modalities

Imaging guidance is an essential component of ablation success. Modalities include ultrasound, CT, MRI, or PET alone or in combination. Each modality used depends on the application environments and has its strengths and weakness. Imaging fusion combines multiple modalities have also been developed for tumour targeting.

41.2.3.3 Computed Tomography

The advantages of CT are the wide availability, less operator dependence, and ability to provide three-dimensional spatial imaging. The intravenous contrast agent can be administered at the time of applicator placement to better assess the localization of the lesion. Using CT fluoroscopy can provide a near real-time visualization of applicator placement. A post-ablation contrast-enhanced CT can be used to provide a rapid evaluation of residual tumour and the ablation zone. The disadvantages of CT guidance include the ionizing radiation and the limitations of guidance planes.

41.2.3.4 Ultrasound

Ultrasound provides real-time monitoring applicator placement without ionizing radiation. However, it is occasionally difficult to delineate the lesion because of its limited sensitivity and operator-dependent nature. Also, spatial resolution is significantly limited when compared to CT. Using the intravenous contrast can improve the sensitivity similar to the CT [93, 94]. However, the gas bubbles generated during the RFA or MWA can obscure the visualization of the applicator and lesion. A post-ablation contrast-enhanced ultrasound can be used to detect the residual unablated tumour [95].

41.2.3.5 Positron Emission Tomography/Computed Tomography

The advantage of PET/CT during ablation guidance is it can offer metabolic information during the procedure. However, there are challenges in the registration of images due to the morphologic distortion after the ablation.

Additionally, tumour FDG activity is not dissipated by thermal ablation and the ablation-related inflammatory changes can lead to the difficulty of assessment for residual tumours [96, 97]. A split-dose technique for FDG PET/CT guidance and a nitrogen 13 ammonia perfusion PET combined with FDG PET/CT have been developed for tumour targeting and immediate post-ablation assessment to overcome these limitations [98, 99].

41.2.3.6 Magnetic Resonance Imaging

The limitations of MRI guidance are the complexity of the procedure due to the only use of MR-compatible devices, limited availability, and relatively high cost. However, the advantage of MRI guidance is nonionizing radiation, higher contrast resolution, and multiparametric imaging. Moreover, MRI is currently the only modality with well-validated techniques for near real-time temperature monitoring during the ablation, which is useful to delineate the ablation margins [100].

41.2.4 Studies on CLM Ablation

Although comparable overall survival rates for thermal ablation versus resection of small CLM were reported in some of the existing literature [21, 23, 80, 84, 101], most meta-analyses and systemic reviews have suggested the overall survival rates of thermal ablation were inferior to liver resection [28, 102–105]. These conflicting results increase the necessity to confirm tumour eradication with margins by thermal ablation, especially when using thermal ablation instead of hepatectomy for smaller CLM. A recent meta-analysis indicated that MWA had similar outcomes with limited hepatic resection and that ablation should be offered for eligible patients and that is no longer appropriate to treat this population with chemotherapy alone [5]. Additionally, several publications have demonstrated the importance of genetic biomarkers (e.g., TP53, RAS, and SMAD4) on surgical outcomes [106–108]; however, evidence of these genetic biomarkers on ablation is lacking. An ongoing randomized controlled trial to compare thermal ablation and liver resection for CLM (the COLLISION trial) will add evidence for these topics [109].

Several studies have demonstrated the ablation margin is a key factor associated with local tumour control [2, 30–32]. The minimal ablation margin larger than 10 mm was reported to achieve the best local tumour control (whereas a 5 mm margin is the absolute minimum required) when using a manual measurement with anatomic landmarks on post-ablation contrast-enhanced CT [2, 30, 32, 33]. A panel of experts has recommended minimal ablation margins on a three-dimensional plane larger than 10 mm as a procedure goal for patients with CLM [4]. This 10 mm ablation margin can correspond to the surgical resection margin R0 and a study reported that margins 10 mm or larger are associated with no LTP after thermal ablation within a 24-month follow-up period [33]. This conventional method was limited by the misalignment of the liver due to the different patient position and variations on the respiratory phases, tissue structural changes after ablation, and the image resolution, especially in vertical or oblique dimension. There have been reports using a volumetric quantitative method with the fusion of pre-and post-ablation images, fusion imaging with preablation images and post-ablation contrast-enhanced US, and perfusion PET to improve the accuracy of ablation margin assessment [99, 110–113]. However, the currently available imaging and ablation technologies do not provide reliable intraprocedural information regarding the ablation zone, warranting further investigations. Recent papers have proposed intraprocedural methods of ablation zone assessments that can help optimize thermal ablation as local curative therapy for CLM [114, 115]. The current evidence supports the use of thermal ablation in selected patients that may be resectable, when the ablation can be offered with 10 mm ablation margin and within the test-of-time strategy. With a reliable method for ablation planning, intraprocedural evaluation, and margin measurement, we are moving toward the goal of ablation as a curative alternative to a surgical procedure.

Regarding the IRE, no randomized controlled trials compare IRE with standard therapy currently. Although the result of a phase II, single-arm clinical trial reported the local control rate following repeat procedures was 74% of participants unsuitable for partial hepatectomy and thermal ablation, the overall complication rate was 40% [57]. This is substantially higher than most reports of complications for the thermal ablation of CLM in less challenging locations. A further prospective study with a large patient population is encouraged. A list of the most relevant publications published in the last 5-years on the use of ablation for CLM (Table 41.1) and in combination with surgical resection (Table 41.2) is presented.

Table 41.1 Relevant published studies on survival following ablation of colorectal liver metastases within 5 years

Author/year	Type of study	Intervention	Approach	Number of patients/ lesions	Mean/ median tumour size (cm)	Mean/ median tumour number	Median follow-up period in months	Local tumour progression rate in %	3 years OS in %	5 years OS in %	8 years OS in %
Meijerink/2021 [57]	Prospective (Phase II Trial)	IRE	Percutaneous or surgical	50/76[a]	2.2	1.2	23.9	38	n/a	n/a	n/a
Han/2021 [30]	Retrospective	RFA	Percutaneous	365/512[b]	5[c]	n/a	43.1	24.6	58	41	n/a
Shi/2021 [116]	Retrospective	MWA	Percutaneous	210/505[b]	2.7	2.4	48	23.8	53.3	32.9	n/a
Kurilova/2020 [31]	Retrospective	RFA and MWA	Percutaneous	286/415[b]	n/a	3[d]	31	45.1	53	37	n/a
Tinguely/2020 [1]	Retrospective	MWA	Percutaneous or surgical	82/n/a[e]	3[c]	n/a	25.2	n/a	69.1	n/a	n/a
Zimmermann/2020 [85]	Retrospective	RFA	Percutaneous	23/29[f]	3[c]	1.3	26	13	57	24	n/a
Schullian/2020 [67]	Retrospective	RFA[g]	Percutaneous	64/217[f]	2.7	2	21	11.5	46.2	34.8	n/a
Cornelis/2020 [56]	Retrospective	IRE	Percutaneous	25/29	n/a	n/a	25	58.6	26.8	n/a	n/a
Schicho/2019 [54]	Retrospective	IRE	Percutaneous	24/n/a[e]	2	2	26.5	n/a	25	8.3	n/a
Odisio/2018 [117]	Retrospective	RFA, MWA, and Cryoablation	Percutaneous	49/59[f]	1.4	5[d]	28	6.1	78	n/a	n/a
Ruers/2017 [22]	Prospective (Phase II Trial)	RFA ± resection	Percutaneous or surgical	60/237[e]	4[c]	4	116.4	15	56.9	43.1	35.9
Dupré/2017 [86]	Retrospective	RFA, MWA, and IRE	Percutaneous or surgical	33/n/a[f]	2	2	36.2	n/a	30.4	n/a	n/a
Shady/2016 [2]	Retrospective	RFA	Percutaneous	162/233[b]	1.8	n/a	55	48	48	31	n/a

Abbreviations: *IRE* Irreversible electroporation; *MWA* microwave ablation; *n/a* not available; *OS* overall survival; *RFA* radiofrequency ablation

[a]The lesions are unresectable and unsuitable for thermal ablation

[b]The lesions are unresectable or recurrent colorectal liver metastases

[c]Maximal diameter

[d]Maximal tumour number

[e]The lesions are unresectable colorectal liver metastases or refused surgery

[f]The lesions are recurrent colorectal liver metastases after liver resection

[g]Stereotactic radiofrequency ablation

Table 41.2 Relevant published studies on survival following ablation plus surgery versus surgery alone of colorectal liver metastases within 5 years

Author/year	Type of study	Modality	Number of patients	Mean/median tumour size (cm)	Mean/median tumour number	Median follow-up period in months	3 years DFS in %	5 years DFS in %	Statistical significance	3 years OS in %	5 years OS in %	Statistical significance
van Amerongen/2019 [118]	Retrospective	RFA + resection	18	2.7	3	28	0	n/a	Yes	43	n/a	No
		Resection	63	3.2	1	28	16	n/a		72	n/a	
Mizuno/2018 [119]	Retrospective	1S ± RFA	101[a]	4	5	39	n/a	n/a		n/a	24[b]	Yes
		2S	126	3.4	7	39	n/a	n/a		n/a	35[b]	
Hof/2018 [24]	Retrospective	RFA ± resection	35[c]	1.9	n/a	36.1	n/a	39.1	No	n/a	49.2	No
		Resection	35	2.2	n/a	36.1	n/a	30.1		n/a	56.3	
Imai/2017 [80]	Retrospective	RFA + resection	31	1.4 (RFA) 3 (resection)	2 (RFA) 5 (resection)	35.6	n/a	19	No	n/a	57	No
		Resection	93	3.3	5	35.6	n/a	17		n/a	61	
Sasaki/2016 [120]	Retrospective	RFA + resection	86	2.2	5	30.9	n/a	n/a		52.6	37.2	Yes
		Resection	399	2.5	2	30.9	n/a	n/a		73.8	58.7	

Abbreviations: *1S* one-stage hepatectomy; *2S* Two-stage hepatectomy; *DFS* disease-free survival; *n/a* not available; *OS* overall survival; *RFA* radiofrequency ablation

[a]Of the 101 patients, 29 (29%) underwent hepatectomy only

[b]On an intention-to-treat basis

[c]Of the 35 patients, 9 (25.6%) patients underwent RFA only

41.3 Conclusion

The role of ablation in the management of CLM is evolving, and it is well recognized as a modality that can provide adequate local tumour control for small CLM. The novel non-thermal ablation IRE technique is evolving and further study and understanding of the electric properties of different tumour types are necessary. The importance of genetic mutations in patients undergoing ablation of CLM was demonstrated in several publications. It may be useful for risk stratification of local tumour progression. In patients with a genetic status of higher risk of LTP, precise intraoperative evaluation of ablation margins becomes critical. However, it is challenging to evaluate the ablation margins depending on imaging alone and the methods are still under investigation. In the not distant future, further randomized controlled trials will hopefully shift the paradigm in this field.

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Radiation Therapy

42

Julia E. Douglas and Eugene J. Koay

Learning Objectives

- Communicate the technical aspects of radiation delivery using SBRT.
- Share the results of SBRT in the clinical setting for colorectal liver metastases.
- Point to future directions for SBRT in the management of patients with metastatic colorectal cancer.

42.1 Introduction

SBRT emerged in the 1990s, due to advances not only in the radiation linear accelerator treatment technology itself, but also due to the addition of onboard linear accelerator imaging, improvements in the quality of the onboard imaging, advancements in the immobilization of patients, and refinements of treatment algorithms (calculations to deliver high doses of radiation accurately) [1]. The past decade has seen increased use of SBRT because it is a well-tolerated and effective treatment in selected patients with early-stage and metastatic cancers, including liver metastases [2–7].

Prior to SBRT, radiation therapy was rarely utilized in the treatment of liver metastases due to the liver being a radiosensitive organ. For example, conventional radiation of the whole liver posed a high risk of radiation-induced liver disease (RILD), which is irreversible liver injury that can lead to organ failure and death [6, 7]. As seen in Fig. 42.1, SBRT differs from whole liver radiation in that SBRT applies fewer fractions (3–5) and higher doses of radiation (8–20 Gy) focally and precisely to the tumour, whereas the antiquated approach of whole liver radiation applied more fractions at conventional doses of radiation (1.5–2 Gy per day) to the entire liver volume. The Radiation Therapy Oncology Group (RTOG) carried out studies in the 1970s and 1980s to evaluate the effect of whole liver radiation on hepatic metastases [8]. In an RTOG Phase I/II dose-escalation trial of whole liver radiation in 1.5 Gy twice-daily fractions, no patient developed classic RILD after treatment with 27–30 Gy, while 10% of patients developed classic RILD after treatment with 33 Gy [9]. When the whole liver was treated with 30 Gy in 2 Gy per fraction, the risk of classic RILD was estimated to be 5% [10, 11].

Important studies from the University of Michigan showed that the use of focal high doses of radiation to the liver could be done safely and effectively [12, 13]. These studies paved the way for more modern radiation trials that showed good rates of local control for liver metastases. Here, we review the role of SBRT for colorectal liver metastases.

In the 1970s, whole liver radiation was tested as a treatment for liver metastases but resulted in unacceptable rates of RILD. In the 1990s, it was demonstrated that focal high doses of radiation using 3D conformal technique was safe and effective. The advents of SBRT and IMRT have resulted in additional treatment options for patients with unresectable liver metastases [10, 11].

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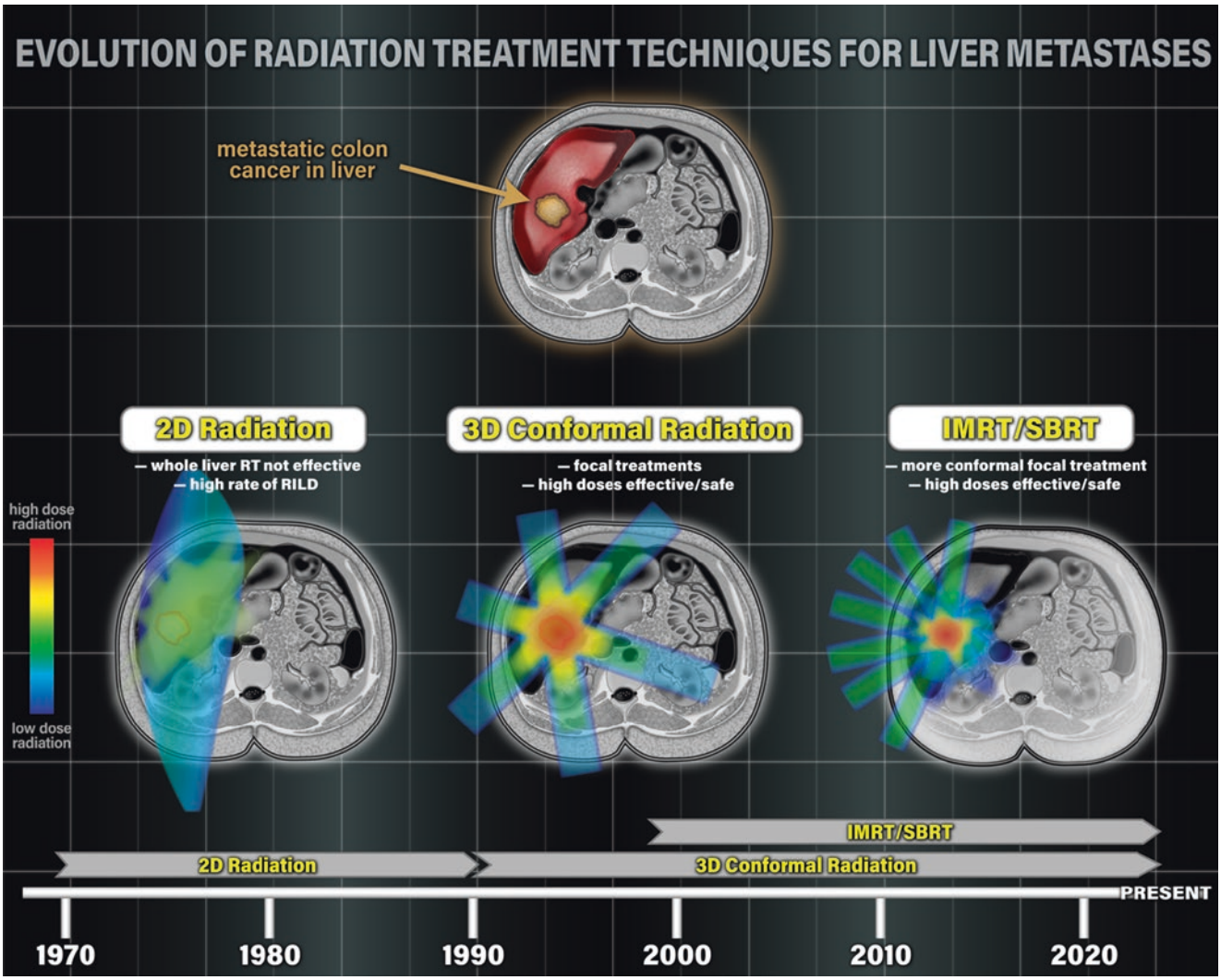

Fig. 42.1 Evolution of radiation treatment techniques for liver metastases

42.2 Radiation Therapy for Colorectal Liver Metastasis

A limited number of high-dose precision ablative radiation treatments are used for SBRT. The term "stereotactic" refers to the relationship of the tumour target position with known fiducials that provide a series of reference points to designate a coordinate system. This can be used to identify the target tumour, direct the treatment planning process, and guide the treatment toward the target location in the body intended for therapy. Liver metastases are challenging to treat due to the sensitivity of the liver parenchyma to radiation, respiratory motion, and intra- and inter-fraction motions of the surrounding bowel. To overcome these challenges, SBRT fundamentally relies on controlling respiratory motion to avoid variability in treatment delivery, and fractionation to achieve ablative radiation doses [14].

Accounting for internal organ motion during radiotherapy is an inherent challenge since the liver follows the motion of the diaphragm during respiration. Although the general parameters of movement have a degree of predictability [15], this amplitude of motion can vary greatly between patients which necessitates unique attention to each patient's respiratory pattern. The motion also depends on the location of tumour, whether within the liver or biliary tree, as well as near the dome of the liver or more inferiorly [14]. Differences in day-to-day bowel position and shape are other variables that must be monitored and taken into account to ensure safe and consistent treatment. Image-guided radiation therapy (IGRT) has made considerable advancements in recent years. Numerous options for target verification and motion control [14] enable greater certainty in target alignment, which can help reduce dose to normal tissues and escalate dose to tumours. Common IGRT strategies include tracking liver tumour targets using

implanted fiducials [16], CT-on-rails, cone beam CT, and magnetic resonance linear accelerators. Motion management can be achieved with breath hold [17–20], respiratory gating [21, 22], and abdominal compression [23].

Administering SBRT treatment safely to large liver tumours (>6 cm) has been challenging. Use of an SBRT technique with control of organ motion and high-quality image guidance is an essential starting point. Nevertheless, even with the assistance of these technologies, safe delivery of ablative doses in 3–5 fractions without overdosing the liver, GI mucosa, or main bile ducts often proves difficult. An SBRT technique coupled with the time-honored principle of fractionation permits ablative doses to be given (90–100 Gy BED) and leads to a substantial survival benefit for patients with large liver tumours [14]. For most large central tumours (>6 cm), giving 15–25 fractions with an SBRT technique may be necessary to deliver an ablative dose and stay within the tolerance of the OARs (organs at risk). The alternative is to give five fractions and reduce the dose, which may no longer be ablative (Fig. 42.2) [14].

Clinical studies using SBRT to treat CRLM are ongoing. Results of phase I and II studies demonstrated promising local control and occasional long-term survivors [6, 24, 25]. Petrelli F et al. [26] performed a systematic review in 2018 of published trials to evaluate the efficacy of SBRT as a primary modality therapy for CRC liver oligometastases. This review covered a comprehensive search of the Cochrane Central Register of Controlled Trials, Pubmed, and EMBASE for publications regarding SBRT for CRC liver metastases. The results can be seen in Table 42.1, along with updated information to reflect recent advances.

Although SBRT has not been directly compared with other liver-directed treatments in prospective randomized studies, the outcomes from the reported studies to date compare favorably to other types of liver-directed treatments. Local-regional treatment with RT consists of conventional RT, SBRT, TARE, and brachytherapy [27]. Alternative methods of delivering high doses of radiation focally to the target area while limiting dose to surrounding normal liver tissue include TARE and brachytherapy. Early trials on the addition

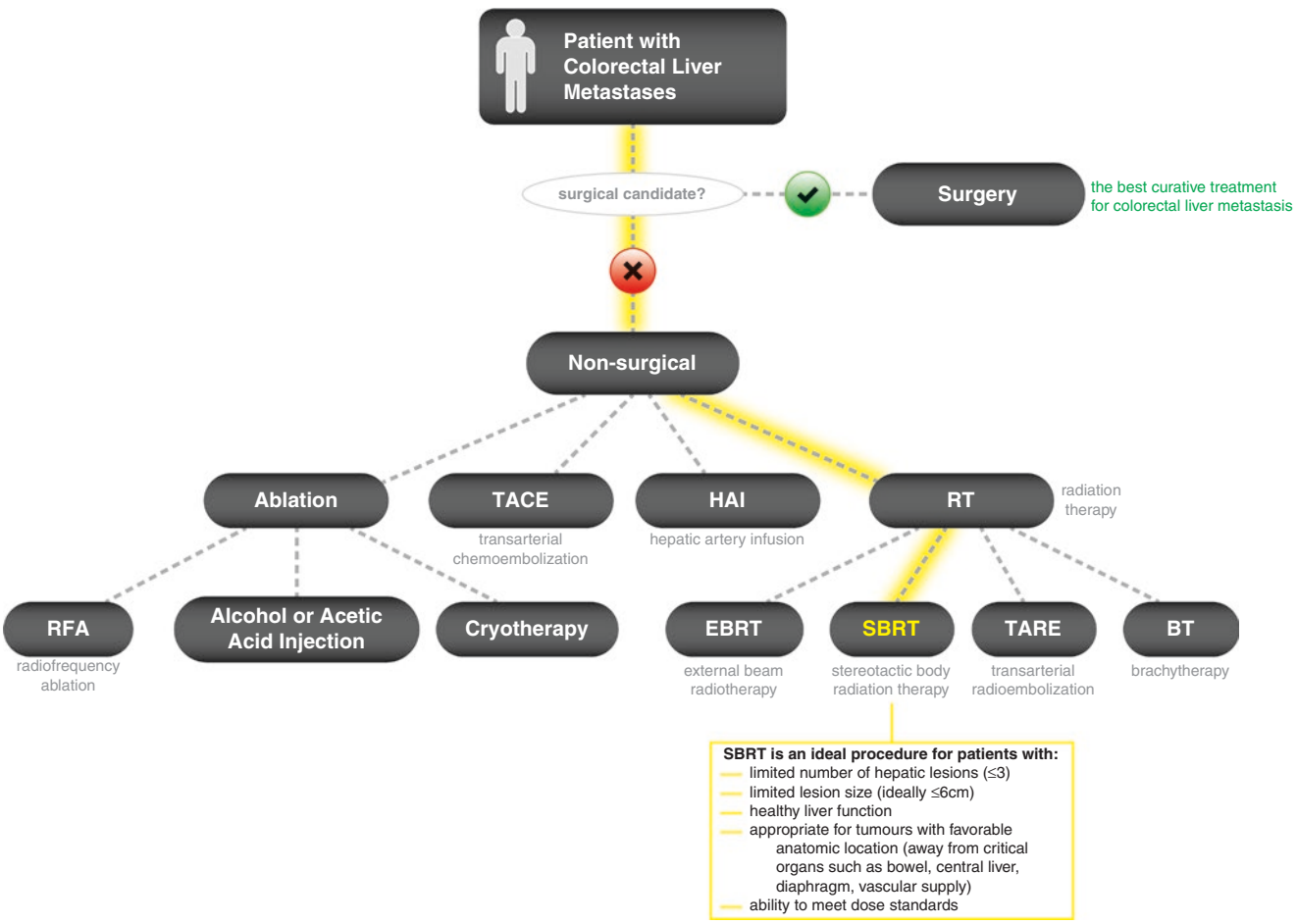

Fig. 42.2 Treatment algorithm for selecting loco-regional modalities for patients with colorectal liver metastases. Please note that this algorithm depends greatly on available resources and institutional practice and expertise. Patients with tumours >6 cm can receive EBRT in ablative doses using 15–25 fractions [14]

Table 42.1 Studies on SBRT for colorectal liver metastases

	Characteristics of studies on SBRT for colorectal liver metastases					Outcomes					
Author/year	Type of study	Total number of treated liver metastases	Lesion sizes (range) (cm)	Dose: range Gy/n° fxs (BED 10 Gy)	Median follow up (months)	Median OS (months)	1 year LC (%)	1 year OS (%)	2 years LC (%)	2 years OS (%)	Median PFS (months)
Chang/2011	Retrospective cohort (pooled analysis)	65	1–2 (80%)	22–60 Gy/1–6 fxs (40.5–180 Gy)	14	–	62	72	45	38	–
Vautravers-Dewas/2011	Retrospective	30	–	40 Gy/4 fxs (80 Gy) 45 Gy/3 fxs (112.5 Gy)	14.3	–	79	–	86	58	–
Liu/2013	Retrospective	24	1–4	24–60 Gy/1–5 fxs (81.6–132 Gy)	18	25.2	86	–	67	–	–
Berber/2013	Retrospective	53	1.6	41 Gy/3 fxs (96.76 Gy)	17	–	60	56	–	–	–
van de Voorde/2015	Retrospective	17	–	EQ2 62–150 Gy/3–10 fxs (NR)	21	25	–	–	–	–	–
Goodman/2016	Retrospective	54	–	32–60 Gy/3–5 fxs (52.48–180 Gy)	33	38	93	95	88	78	10
Ahmed/2016	Retrospective	22	2 (0–5)	50–60 Gy/5 fxs (100–132 Gy)	20.5	–	–	100	59	73	–
Mendez Romero/2016	Retrospective	40	1–2 (95%)	50.25 Gy/3 fxs (134.42 Gy) 37.5 Gy/3 fxs (84.38 Gy)	25 and 26[a]	43 and 35[a]	90 and 96[a]	94 and 95[a]	90 and 74[a]	81 and 69[a]	–
Doi/2017	Retrospective	24	1 (75%)	45–72 Gy/8 fxs (71.7–115.5 Gy)	16	45	67.2	82.3	35.9	67.1	16 (LC time)
Joo/2017	Retrospective	70	1–2 (86%)	45–60 Gy/3–4 fxs (58–180 Gy)	34.2	–	–	–	92 (BED ≥ 112) 61 (BED < 112)	75	–
Ambrosino/2009	Prospective series	11	1.8	25–60 Gy/3 fxs (45.83–180 Gy)	13	–	–	–	–	–	–
Kim/2009	Prospective series	10	14	36–51 Gy/3 fxs 79.2–137.7 Gy)	12	25	80	53	60	40	–
van der Pool/2010	Prospective series	20	2.3	37.5–45 Gy/3 fxs (93.6–112.5 Gy)	26	34	–	100	74	83	11
Stintzing/2013	Prospective series	30	1 (86%)	24–26 Gy/1 fxs (81.6–93.6 Gy)	23.3	34.4	85	–	80	–	–
Lee/2009	Phase I	40	2 (1–8)	27.7–60 Gy/6 fxs (40.44–120 Gy)	10.8	15	71	63	–	–	3.9
McPartlin/2017	Phase I & II	60	1 (1–6)	22.7–62.1/6 fxs (31.28–126.37 Gy)	28.1	16	50	63	32	26	–
Hoyer/2006	Phase II	44	3.5	45 Gy/3 fxs (112.5 Gy)	52	19.2	–	–	78	38	6.5 (TTP)
Scorsetti/2015/2018	Phase II	42	1 (81%)	75 Gy/3 fxs (262.5 Gy)	73	27.6	95	85.2	91	65	12
Hong/2017	Phase II	89	2.5 (0.5–11.9)	30, 40, 50 GyE/5 fxs (48, 72, 100 GyE)	30.1	18.1	71.9	66.3	–	35.9	3.7

SBRT stereotactic body radiotherapy; *LINAC* linear accelerator; *pts* patients; *BED* biologically equivalent dose; *M+* metastases; *CT* chemotherapy; *Gy* gray; *GyE* gray equivalent; *fxs* fractions; *NR* not reported; *OS* overall survival; *LC* local control; *PFS* progression-free survival; *G* grade

Scorsetti [7, 30], Stintzing [31], van de Voorde [32], van der Pool [33], Vautravers-Dewas [34], Ahmed [35], Ambrosino [36], Berber [37], Chang [38], Mendez Romero [39], Doi [40], Goodman [41], Hoyer [42], Joo [43], Kim [44], Lee [25], Liu [45], McPartlin [46], Hong [47]

[a] Two different dose levels

of TARE to first-line systemic therapy suggested a role in selected patients, but additional data is needed to clearly define the role of TARE in different settings (surgically resectable, unresectable, salvage treatment [28]). Although infrequently used, brachytherapy represents an additional method of conformal radiotherapy that can offer patients with CLM moderate rates of liver control [27].

More broadly, aggressive local treatment of liver oligometastases may be an effective option with encouraging survival rates. In a 2017 randomized phase II trial [29], 119 patients with unresectable colorectal liver metastases ($n < 10$ and no extrahepatic disease) received systemic treatment alone or systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection. The long-term overall survival (OS) results showed that there was a statistically significant difference in OS in favor of the combined modality arm compared to systemic treatment alone. Median OS was 45.6 months (95% CI = 30.3–67.8 months) in the combined modality arm vs 40.5 months (95% CI = 27.5–47.7 months) in the systemic treatment arm.

This was the first randomized study to demonstrate that aggressive local treatment can prolong OS in patients with unresectable CLM. This trial had limitations. However, most notably the small sample size and selection of patients are considerations for wider applicability. Although the study's results show promising impacts on LC and OS, definitive validation in larger randomized studies is warranted. The extension of this concept to SBRT in patients with oligometastatic disease.

In addition to aggressive liver-directed therapies that may include SBRT, future prospective trials will test the impact of molecular characteristics, radiation dose, and novel systemic and immune-based therapies [48]. A 2017 phase II single-arm study evaluated the efficacy and safety of risk-adapted, proton-based SBRT for liver metastases from solid tumours [47]. This is the largest prospective study of liver SBRT for hepatic metastases to date with protons. Proton beam therapy utilizes charged particles as opposed to high-energy photons. Protons can offer a clinical advantage over photon-based radiation in certain patients, particularly those with tumours on the right side of the liver [49, 50].

Protons were well tolerated and proved effective even for metastases that were greater than or equal to 6 cm. Radioresistant subgroups were identified based on genotype. Mutation in the KRAS oncogene was found to be a strong predictor of poor LC ($P = 0.02$). Tumour with both mutant KRAS and TP53 were particularly radioresistant, with a 1-year LC rate of only 20.0%, compared with 69.2% for all others ($P = 0.001$). This stresses the need for tumour genotyping prior to SBRT and treatment intensification in this patient subset. Future efforts will investigate how to achieve more durable local control in KRAS- and TP53-mutant tumours [47]. Future studies may select patients for proton radiation based on molecular characteristics or in combination with other novel therapies to overcome resistance.

There is also potential for future investigation into the role of liquid biopsies to guide the field of radiation oncology. Liquid biopsies are characterized by the isolation of cancer-derived components and provide a rich source of non-invasive tumour-specific biomarkers. These biomarkers could have a substantial impact on cancer treatment by categorizing patients into risk groups, tracking radiation therapy impacts before, during, and after treatment, and identifying patients with radioresistant tumours. The liquid biopsy is a minimally invasive, inexpensive, and easily repeatable technique that can enable efficient screening and early diagnosis [51]. The concept of this type of personalized medicine is becoming more readily incorporated into clinical practice and research studies and could serve as a solution to the much-needed predictive biomarkers to guide therapeutic management [52].

Patients should be considered for participation in randomized clinical trials when possible because the efficacy of liver metastasis SBRT has not yet been fully established. SBRT can treat liver metastases safely; studies have shown that radiation doses >47 Gy (3–6 fxs) can improve local control. The optimal fractionation has yet to be clearly defined [25, 53, 54].

42.3 Conclusion

Currently, the best curative treatment for colorectal liver metastasis is surgical resection. However, many patients are not viable surgical candidates. Stereotactic body radiotherapy (SBRT) is a well-established alternative treatment option for patients with liver metastases that are unsuitable candidates for surgical resection. Advancements in technology have allowed SBRT to deliver high dose radiation precisely to the tumour, sparing surrounding normal liver tissue. Numerous recent studies have shown evidence of encouraging local control and OS rates after treatment with SBRT, without increased rates of RILD. The safety and success of liver SBRT rely heavily on ensuring appropriate patient selection and attention to normal tissue dose tolerances.

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Yttrium-90 Radioembolization for Metastatic Colorectal Cancer

43

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Learning Objectives

- Yttrium-90 emits β-radiation; it is loaded onto non-resorbable microparticles, which are then injected via the hepatic artery. The radiation dose delivered will depend on the distribution and amount of particles/radioactivity administered.
- The absorbed cut-off dose to achieve a metabolic response for metastatic colorectal carcinoma to the liver is likely approximately 60 Gy, while an absorbed dose cut-off to achieve a complete response is likely approximately 100–120 Gy.
- It is important to understand the limitations involving the various dosimetry calculation methods used to plan selective internal radiation therapy with Yttrium-90.
- Phase 3 clinical trials have not shown improved overall survival when Yttrium-90 is used in conjunction with first-line chemotherapy. However, improvement in liver progression-free survival was observed.
- Potential uses of Yttrium-90 for the surgical patient include simultaneous induction of ipsilateral tumour control and contralateral future liver remnant hypertrophy as well as downstaging patients to resection.

43.1 Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the fourth most common cancer in the United States. The backbone of modern systemic therapy is formed by a combination of systemic chemotherapy with or without targeted biological agents. First- and second-line systemic therapies include a fluoropyrimidine combined with either oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI regimen). Biologically targeted agents include vascular endothelial growth factor inhibitors and epidermal growth factor inhibitors [1]. This current regimen of systemic therapy has extended the median overall survival (OS) for patients with metastatic CRC (mCRC) to 31 months [2]. Historically, surgical resection for liver-dominant mCRC is the preferred method of treatment as it results in a 5-year OS of up to 58% [3–6]. Unfortunately, up to 85% of patients with liver-dominant mCRC are not candidates for surgical resection. Selective internal radiotherapy (SIRT) is a therapeutic alternative in selected patients with liver metastases from CRC. While phase III clinical trials have reported negative results with regards to OS benefit in patients with liver-dominant mCRC who received both first-line systemic therapy and Yttrium-90 (Y-90), the role of Y-90 in the management of mCRC in select patient cohorts is still evolving. The purpose of this chapter is to review the proposed mechanism of Y-90 therapy for patients with liver-dominant mCRC, dosimetry considerations, tumour assessment, and results of published data. An emphasis will be placed on the potential impact of Y-90 in surgical patients.

43.2 Principles of Y-90

Y-90 undergoes predominantly β-decay emitting a high-energy photon with limited soft tissue penetration [7]. The maximum energy of the β-particles is 2.27 MeV with a mean of 0.93 MeV. The half-life of Y-90 is 64.1 hours meaning that 94% of the radiation is delivered in 11 days following admin-

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istration with eventual decay into stable zirconium-90. The mean penetration of the β-radiation is 2.5 mm with a maximum penetration of approximately 11 mm. SIRT via Y-90 is performed by selective injection of the radioactive microspheres into the hepatic artery. The particles are then preferentially distributed into the tumour by making use of the fact that blood supply to liver tumours is primarily via the hepatic artery; whereas, hepatocytes receive blood supply primarily from the portal vein. Currently, there are two commercially available Y-90 products, SIR-Sphere® resin microspheres (Sirtex Medical Limited, Woburn, MA, USA) and TheraSphere™ glass microspheres (Boston Scientific, Marlborough, MA, USA). No head-to-head prospective trials comparing the safety and efficacy of these two devices have been performed. Table 43.1 details the differences between the two devices.

An important consideration when administering Y-90 is the number of particles administered and the activity per particle. In practice, as the number of particles administered increases so does the relative embolic load. On the other hand, a potential theoretical benefit of using more particles is that the distribution of particles can be more uniform, which can be relevant for patients in whom there is considerable heterogeneity in tumour perfusion or in whom there is a large intended territory for treatment [8]. Both products available provide flexibility to tailor the dose delivered and embolic potential to suit the clinical scenario. In studies performed on SIRT of mCRC, similar survival rates were reported with SIR-Sphere® and Therasphere™ [9, 10].

Table 43.1 Comparison of Yttrium-90 containing devices used for selective internal radiation therapy

Characteristic	SIR-Sphere®	TheraSphere™
Material	Resin	Glass
Size of particle	Mean, 32 μm; range, 20–60 μm	Range, 20–30 μm
Activity per sphere at calibration	68 Bq	2500 Bq
Number of spheres per vial	44 million	1–28 million
Indication approved by the United States Food and Drug Administration	Treatment of unresectable metastatic liver tumours from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy of floxuridine	Local tumour control of solitary tumours (1–8 cm in diameter), in patients with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status

Common adverse events of Y-90 include fatigue, nausea, abdominal pain, gastrointestinal ulcers, and elevation of liver enzymes [11–17]. In a review of the adverse event profile for SIRT, Kallini JR et al. reported on 2317 patients with hepatocellular carcinoma (HCC) treated with glass microspheres (Therasphere™, $n = 1597$ patients) versus resin microspheres (SIR-Sphere®, $n = 720$ patients) [18]. The authors found the following adverse event rates of grade 3 or higher: gastric ulcer (0.4% for Therasphere™ and 1.4% for SIR-Sphere®), ascites (6.1% for Therasphere™ and 2.3% for SIR-Sphere®), cholecystitis (1.9% for Therasphere™ and 5.0% for SIR-Sphere®), hepatic encephalopathy (2.8% for Therasphere™ and 8.0% for SIR-Sphere®), pleural effusion (0.5% for Therasphere™), nausea (1.5% for Therasphere™ and 0.4% for SIR-Sphere®), fatigue (1.9% for Therasphere™ and 2.3% for SIR-Sphere®), and abdominal pain (1.9% for Therasphere™ and 1.2% for SIR-Sphere®). This review encompassed published results from 2004 to 2014. Important improvements have since been implemented into clinical practice which have further improved the safety profile of Y-90. In particular, intra-procedural Cone Beam or Fan Beam CT imaging with intra-arterial contrast is now commonly performed to evaluate for extrahepatic arterial supply as well as perfusion to the liver tumours. During the arterial mapping study, ^{99m}Tc-labeled macroaggregated albumin (^{99m}Tc-MAA) is also injected into each artery in which Y-90 microspheres are planned to be administered. Evaluation of ^{99m}Tc-MAA distribution is now performed with single-photon emission CT, which has been shown to be more effective than planar imaging for identifying extrahepatic uptake [19].

Radioembolization-induced liver disease (REILD) is a serious complication following Y-90 microsphere administration. REILD should be suspected with elevated liver function tests and ascites in the absence of obvious tumour progression. REILD may occur 4–8 weeks after SIRT although delayed hepatotoxicity may occur. In severe cases, there is histologic evidence of venoocclusive disease [20]. The incidence of REILD ranges from 0.8 to 20% [20, 21]. Reported risk factors include prior chemotherapy, younger age, low body mass index, non-HCC pathology, low tumour volume, higher bilirubin level, and whole-liver radioembolization [22].

43.3 Dosimetry Considerations

Dosimetry calculation is critically important to ensure an adequate dose of radiation to the tumour. There are multiple methods employed to determine dose, each with its own advantages and disadvantages. The following methods are used in clinical practice:

43.3.1 Empirical Methods

With the empirical method, a standard amount of radioactivity is administered based on the tumour burden in the liver. For tumour involvement of more than 50% of the liver, 3.0 GBq of activity is recommended. For 25–50% tumour involvement, 2.5 Gbq is recommended. For tumour involvement less than 25%, 2.0 GBq is recommended. For the body surface area (BSA) method, the BSA is calculated from the patient's weight and height and incorporated into the percentage of involved liver (tumour and non-tumour bearing liver), Eq. (43.1).

$$D_C\left[\text{GBq}\right] = \left(\text{BSA} - 0.2\right) + \left(\%\text{tumour invovlement} \div 100\right) \tag{43.1}$$

where D_c is the radioactivity in GBq and *BSA* is the body surface area measured in m^2/kg.

Overall activity in dosimetry loosely correlates with the degree of tumour infiltration within a target volume. The drawback of the BSA equation is that it does not consider the actual activity (or distribution) deposited into the liver versus tumour. Despite this limitation, the BSA method has been effectively utilized for resin microspheres in randomized controlled trials [23, 24].

43.3.2 MIRD Method

The Single Compartment MIRD methodology utilizes liver volume (and corresponding liver mass), which can be calculated using cross-sectional imaging, Eq. (43.2). The compartmentalization and preferential uptake of particles in tumour are not accounted for in this model. As a result, the method of activity determination results in high variations in calculating a priori the dose reaching the tumour compared to normal liver parenchyma (e.g., cases of low tumour burden or hypovascular lesions).

$$D\left[\text{Gy}\right] = \frac{49.67 \times A\left[\text{GBq}\right]}{M\left[\text{kg}\right]} \tag{43.2}$$

where D is the radiation dose in Gy, A is the activity of Y-90 administered in GBq, and M is the mass of the perfused liver in kg.

43.3.3 Partition Model

The partition model, which was originally developed in the 1990s, represents the theoretically most accurate method in estimating activity to the partitioned volume by accounting for variables such as tumour volume, liver volume, relative tumour uptake, and lung shunt fraction, Eq. (43.3).

$$A\left[\text{GBq}\right] = \frac{D_T\left[\text{Gy}\right] \times \left(M_N\left[\text{kg}\right] + M_T\left[\text{kg}\right] \times r\right)}{49.67 \times r \times \left(1 - L\right)} \tag{43.3}$$

Where A is the activity of Y-90 administered in GBq, D_T is the dose to the tumour, M_N is the mass of the normal liver within the treatment area in kg, M_T is the mass of the tumour within the treatment area in kg, and L is the lung shunt fraction, Eq. (43.4)

$$L = \frac{\text{total counts in lungs}}{\text{total counts in lungs} + \text{total counts in liver}} \tag{43.4}$$

And r the tumour to normal liver ratio (T/N), Eq. (43.5):

$$r = \frac{\text{average counts per mL in tumour}}{\text{average counts per mL in non} - \text{tumour liver}} \tag{43.5}$$

One of the advantages of the BSA and MIRD methods is that the methods can be performed quickly with the assistance of third-party software to assist in liver and tumour volume calculations. While the variables measured in the partition model should make it the most accurate of the dosimetry calculation methods, it is also subject to the limitation that compartments within the tumour receive a uniform and homogenous dose, which is often not the case in heterogeneous, hypovascular tumours. In order to mitigate the limitations posed by the clinical absorbed dose calculations for SIRT, an area of active research is the use of voxel-level dosimetry models for tumour dose calculations, which would more closely mimic the methods used in radiation oncology [25]. The goal of Y-90 dosimetry should be to base treatment on the predicted tumour versus normal liver dose and then evaluate posttreatment effects by a similar dose delivered criteria which would allow for an assessment of treatment efficacy and early retreatment, if necessary. O'Doherty J et al. reviewed the current generation of three-dimensional dosimetry techniques for Y-90 SIRT (i.e., direct Monte Carlo, dose kernel convolution, and local deposition method) [26]. While the dosimetry models are promising, there are limitations with respect to image reconstruction (i.e., energy window choice, collimator choice, detector specifications, and reconstruction algorithm) and voxel resolution with single-photon emission CT (SPECT) and positron emission tomography (PET). Despite these limitations, voxel-based dosimetry will likely gain traction as hardware and software improvements are made [27].

When evaluating studies reporting on the efficacy of Y-90 SIRT, it is important to consider the dose delivered to the tumour, as prior studies have indicated a particular dose-response relationship for patients with mCRC [28]. In a retrospective analysis of 57 evaluable mCRC liver lesions in patients with progressive disease who were given FOLFOX chemotherapy, a post-SIRT tumour absorbed cut-off dose of

60 Gy predicted a metabolic response with a positive predictive value of 96% and a negative predictive value of 63% using the partition model [29]. Additional retrospective studies have corroborated that improved responses were observed for tumour doses >40–60 Gy using the BSA dosimetry model and doses >50 Gy using the mBSA method [30, 31]. Furthermore, based on an international recommendation from a multidisciplinary expert panel on the use of SIRT for primary and metastatic liver diseases, a minimum absorbed dose cut-off of 100–120 Gy is recommended to achieve a complete response for patients with mCRC [28].

43.4 Treatment Assessment

Treatment assessment response following SIRT for hypovascular tumours is generally performed with RECIST version 1.1, which is based on changes in tumour size [32]. A partial response is defined as a greater than 30% decrease in the sum of the longest diameters of target lesions while progressive disease is defined as a greater than 20% increase in the sum of the longest diameters of target lesions. However, when assessing post-SIRT efficacy, it should be noted that partial response can be achieved without changes in tumour size. In 2012, Tochetto SM et al. compared post-SIRT contrast-enhanced CT imaging with volume-weighted standard uptake values (SUV) of target lesions from 18F-FDG PET studies [33]. The authors evaluated patients with mCRC at baseline and 3 months following Y-90 and found a 15% decrease in tumour attenuation measured at pre and posttreatment portal venous phase CT imaging may serve as an early response marker when compared to corresponding SUV measurements. In a larger series of 80 patients with mCRC, Fedler WP et al. evaluated several PET-derived parameters for predicting survival following Y-90, specifically metabolic tumour volume (i.e., metabolically active volume of tumour segmented using FDG PET), total lesion glycolysis (product of mean SUV and metabolic tumour volume), and change in SUV. 18F-FDG PET was performed at baseline and 3 months after the procedure [34]. The authors found that decreases in metabolic tumour volume and total lesion glycolysis predicted survival, while no correlation was found for changes in SUV and RECIST criteria. Thus, when evaluating mCRC patients following SIRT, it is important to consider the assessment tool being used by the interpreting physician.

43.5 Results

43.5.1 Y-90 as an Adjunct to First-Line Chemotherapy in Patients with mCRC

The SIRFLOX trial was a phase III randomized controlled trial comparing Y-90 resin microspheres with FOLFOX chemotherapy +/− bevacizumab versus FOLFOX +/− bevacizumab alone in 530 patients [24]. Although the primary end point of PFS at any site was not met, the liver PFS was prolonged in the study arm (20.5 months for the Y-90 plus FOLFOX arm versus 12.6 months for the FOLFOX alone arm; HR 0.69; 95 CI 0.55–0.90; $P = 0.002$). The authors point out the discrepancy between the SIRFLOX study in which improved liver PFS did not translate into improved OS in comparison with the Chemotherapy + Local Ablation Versus Chemotherapy (CLOCC) study, which evaluated combined radiofrequency ablation plus FOLFOX-based chemotherapy in patients with liver-only mCRC. The authors of the CLOCC study found improved liver PFS and an increased OS from 45.6 months in the combined modality arm versus 40.5 months in the systemic treatment only arm though the primary objective of the prospective study was to exclude a 30-months OS rate less than or equal to 38% for the radiofrequency ablation plus chemotherapy arm [35, 36]. Unlike the SIRFLOX study, all patients in the CLOCC study had a low burden of disease in the liver, no extrahepatic disease, and all patients had their primary CRC resected.

The FOXFIRE and FOXFIRE global studies were additional phase III trials performed in a similar manner to SIRFLOX to assess the efficacy of Y-90 as adjunctive first-line therapy for mCRC [37]. The compilation of data from the SIRFLOX, FOXFIRE, and FOXFIRE global studies was analyzed to assess oncologic outcomes in a larger cohort with a primary outcome measure to assess improvement in OS. The pooled data involved 549 patients randomly assigned to FOLFOX alone and 554 patients assigned to FOLFOX plus SIRT. There was no significant difference in OS with a median OS of 23.3 months for the FOLFOX alone arm and 22.6 months for the FOLFOX plus SIRT arm, $P = 0.61$. While there was no difference in OS, the combined study further confirmed the finding in SIRFLOX of a decreased cumulative incidence of radiological progression within the liver when SIRT was added to FOLFOX chemotherapy (HR 0.51 95% CI 0.43–062, $P < 0.001$). The findings from SIRFLOX, FOXFIRE, and FOXFIRE global suggest that the early use of SIRT in conjunction with oxaliplatin-based chemotherapy in *unselected* patients with mCRC should not be recommended. A fundamental limitation of pooled analyses of patients who undergo Y-90 SIRT is the lack of consistency with dosimetry planning. Y-90 SIRT exerts its tumoricidal effect by emission of β-radiation so accurate dose calculation and accounting for differences among the different dosimetry models must be appreciated [38].

In a subsequent retrospective pooled analysis of patients included in the SIRFLOX and FOXFIRE global trials, Gibbs P et al. reported on the change in OS for patients treated with FOLFOX plus SIRT compared to FOLFOX alone based on the side of the primary tumour [39]. It has been demonstrated that patients with right-sided primary tumours have a poorer

prognosis with standard chemotherapy [40, 41]. From a molecular point of view, right-sided and left-sided colon cancers are different entities. Right-sided colon cancers are associated with defective mismatch repair genes, mutations in *KRAS* and *BRAF*, and microRNA-31, whereas left-sided colon cancers are associated with chromosomal instability, p53, *NRAS*, microRNA-146a, microRNA-147b, and microRNA-1288 [42]. The mechanism by which SIRT may impact the molecular underpinnings of right-sided versus left-sided colon cancer is unknown. Nonetheless, the findings reported by Gibbs P et al. suggest a role for SIRT as part of first-line therapy in patients with right-sided CRC with liver-only or liver-dominant metastases.

43.5.2 Y90 for Patients Refractory to First-Line Chemotherapy in Patients with mCRC

Limited data suggests that there may be a role for Y-90 SIRT in patients with liver-dominant mCRC who have failed previous oxaliplatin- and irinotecan-based systemic chemotherapy regimens. In this clinical setting, median OS ranges from 8 to 13 months for patients who undergo SIRT along with additional systemic agents as salvage therapy [9, 23, 43, 44]. While Y-90 is generally regarded as safe in this clinical setting, key limitations remain regarding the role of SIRT in this patient population. In particular, the published data is limited to small patient cohorts, retrospective nature of some of the studies, and heterogeneous patient population (e.g., lines of prior chemotherapy, presence or absence of extrahepatic disease, intrahepatic disease burden, and Y-90 dosimetry plans). The EPOCH trial is an open-label, prospective, multicenter randomized, phase 3 trial utilizing Therapshere® Y-90 being conducted in the US, Canada, Europe, and Asia. Eligible patients will have mCRC involving the liver and disease progression after first-line chemotherapy consisting of either an oxaliplatin- or an irinotecan-based regimen. Patients will be randomized to either the SIRT plus chemotherapy arm or the chemotherapy-alone arm. The primary end points are PFS and hepatic PFS [45].

43.5.3 Y-90 Radiation Segmentectomy for mCRC

Radiation segmentectomy is a technique that involves delivery of high-dose radiation to treat tumours in a limited territory of the liver (i.e., tumours involving one to two segments of the liver). While there have been no studies describing the technique for mCRC, Vouche M et al. evaluated a multi-institutional cohort of 102 patients with unresectable, solitary HCC less than or equal to 5 cm not amenable to ablative therapies [46]. All patients were treated with Theraspehere® prescribing an intended lobar dose of 120–150 Gy into a sublobar volume of the liver. Segmental doses were higher than the prescribed dose by the ratio of lobar to segmental volumes. The actual ablative dose delivered to the targeted portion of the liver was calculated by using the MIRD method. Modified RECIST complete response, partial response, and stable disease were 47/99 (47%), 39/99 (39%), and 12/99 (12%), respectively. Including all 102 patients, 53 of 102 (52%) patients exhibited adverse events (all grades). Among Y-90-related clinical adverse events, the following were observed: fatigue 45%, pain 10%, nausea 8%, fever 3%, appetite loss 2%, dyspnea 1%, vomiting 1%, and weight loss 1%. Importantly, no major complications were identified, and no patients required readmission following Y-90 administration. While the data for Y-90 segmentectomy in the setting of mCRC is still immature, it is a promising technique for use as an ablative modality in patients who are not surgical candidates with tumours not amenable to thermal ablation (Fig. 43.1).

43.5.4 Induction of Future Liver Remnant [FLR] Hypertrophy in Surgical Patients

There is emerging evidence that SIRT can be used to induce hypertrophy of the FLR. While portal vein embolization (PVE) is generally regarded as the gold standard for induction of FLR hypertrophy, a major drawback is that tumour growth may occur while awaiting hypertrophy. In one case series, 76 (21.2%) of 358 patients with liver tumours who underwent PVE in anticipation of liver resection did not undergo definitive hepatectomy. The most common reason for not proceeding to curative surgery was disease progression from intrahepatic tumour growth ($n = 25$ of 76 patients, 32.9%) [47]. In contrast to PVE, SIRT has the theoretical benefit of providing tumour control and downsizing while also increasing the size of the FLR. In a review of 284 patients following SIRT to the right liver with HCC ($n = 215$ patients), intrahepatic cholangiocarcinoma ($n = 12$ patients), and liver metastases ($n = 85$ patients), Teo JY et al. found that SIRT resulted in FLR hypertrophy ranging from 26 to 47% at 44 days to 9 months [48]. It is important to note that all studies included in the review were retrospective, contained heterogeneous patients with variable tumour types, variable times from SIRT to measurement of the FLR, and nonuniform doses of Y-90 delivered to the right liver. In a retrospective matched pair cohort analysis, Garlipp B et al. evaluated 26 matched pairs of patients with right liver metastases. The authors found that FLR volume increases from baseline were greater following PVE compared with Y-90 (61.5% versus 29%, respectively, $P < 0.001$). Increases in the size of the FLR were measured at a median of 33 (range, 24–56) days after PVE and 46 (range, 27–79) days following SIRT [49]. Figure 43.2 (1079330) depicts FLR hypertrophy which can be observed following right lobar Y-90 treatment in a patient with mCRC.

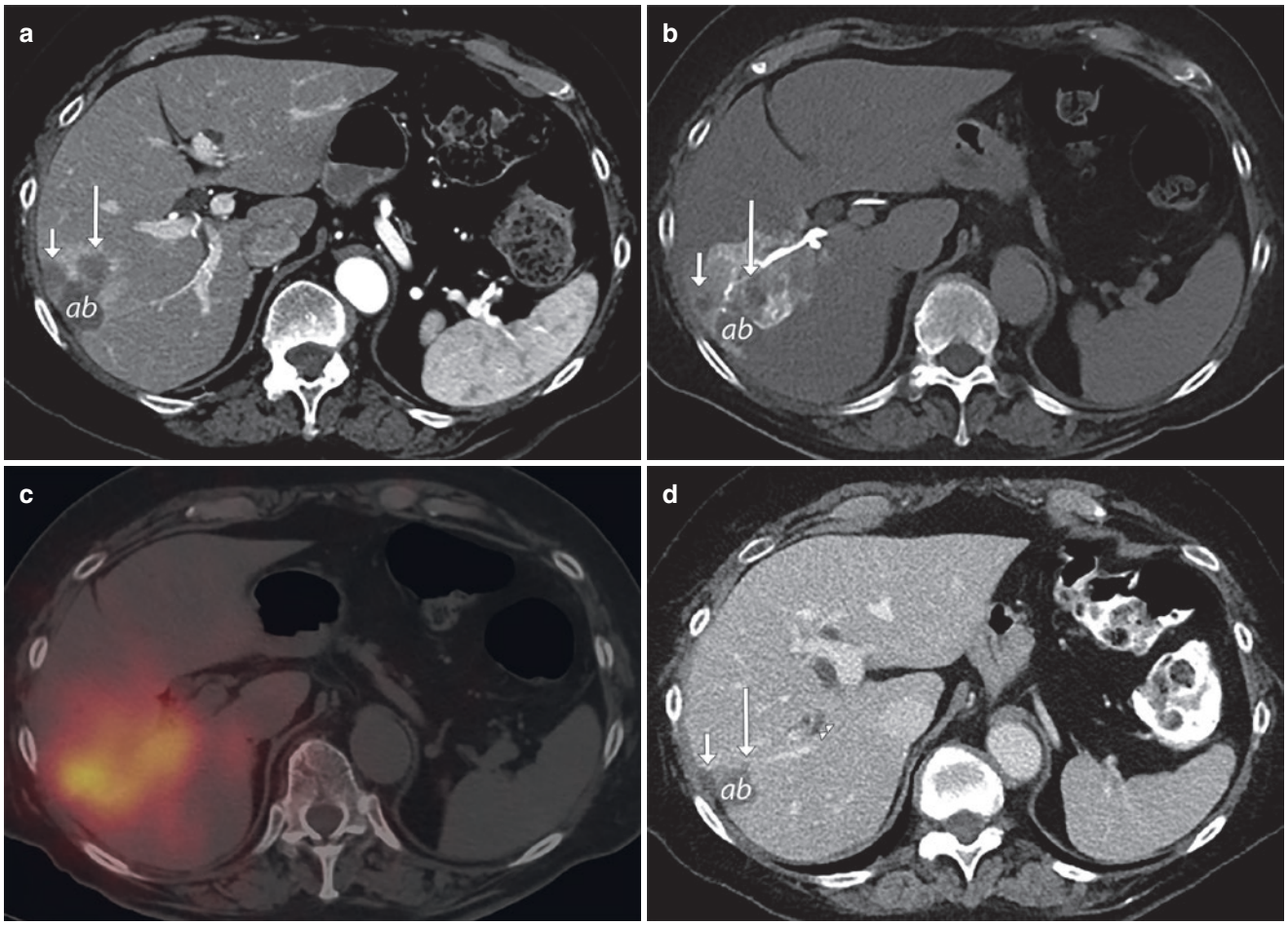
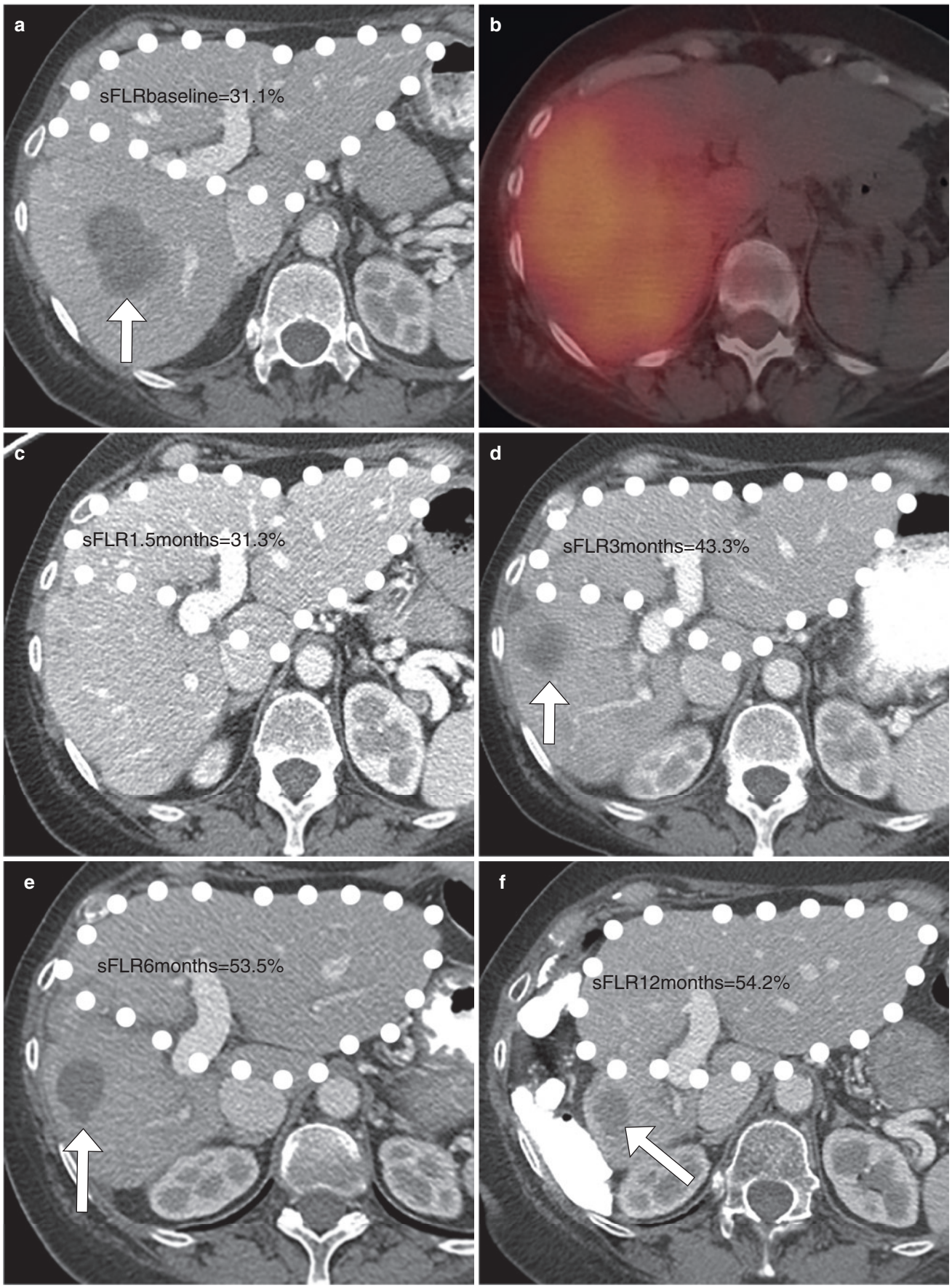


Fig. 43.1 SIRT segmentectomy. 67-year-old female with two segment six marginal recurrences 1 year after thermal ablation for metastatic colorectal cancer. (**a**) Axial CT image of the liver demonstrates the prior ablation (*ab*) and two areas of marginal recurrence (*long and short arrows*). Given the large territory of recurrence, the patient was treated with radiation segmentectomy. (**b**) Axial CT image of the liver with intra-arterial contrast during the Y-90 mapping study demonstrates heterogeneous arterial perfusion to the two areas of marginal recurrence (*long and short arrows*). (**c**) Fused axial CT and Bremsstrahlung image following intra-arterial Y-90 administration into a branch of the segment six hepatic artery. (**d**) Axial CT image of the liver approximately 1 year after Y-90 administration demonstrates the prior ablation (*ab*) with a significant interval decrease in size of the two areas of marginal recurrence (*long and short arrows*). Incidental asymptomatic segment six biliary ductal dilatation is noted (*double arrowheads*)

Fig. 43.2 Hypertrophy involving the left liver following Y-90 treatment to the right liver. (**a**) Axial image from a CT scan demonstrates one of the multiple right-sided hypovascular metastases in the right liver (*arrow*). The patient was not a surgical candidate. Decision was made to treat the right liver with 50 mCi of Y-90. The baseline standardized future liver remnant (*sFLR*) is represented by the area within the white dots and measured 31.1%. (**b**) Fused axial CT and Bremsstrahlung image following intra-arterial Y-90 administration into the right hepatic artery. (**c**) Axial image from a CT scan obtained 1.5 months following Y-90 administration demonstrates no significant change in the *sFLR*, which measured 30.1%. (**d**) Axial image from a CT scan obtained 3 months following Y-90 administration demonstrates interval increase in the *sFLR* to 43.3%. A right-sided hepatic metastasis (*arrow*) is partially visualized. (**e**) Axial image from a CT scan obtained 6 months following Y-90 administration demonstrates interval increase in the *sFLR* to 53.5%. A right-sided hepatic metastasis (*arrow*) is partially visualized. (**f**) Axial image from a CT scan obtained 12 months following Y-90 administration demonstrates interval increase in the *sFLR* to 54.2%. A right-sided hepatic metastasis (*arrow*) is partially visualized. Atrophy of the right liver is noted


a
sFLRbaseline=31.1%
b
c
sFLR1.5months=31.3%
d
sFLR3months=43.3%
e
sFLR6months=53.5%
f
sFLR12months=54.2%

As data become available to better quantify FLR hypertrophy induced by Y-90, underlying patient characteristics and technical details of the procedure (e.g., quality of the underlying liver parenchyma, which may be impacted by steatohepatitis from irinotecan administration or sinusoidal obstruction syndrome from oxaliplatin administration, usage of resin versus glass microparticles, and dose of radiation delivered) should be described.

43.5.5 Combination of SIRT and First-Line Chemotherapy to Improve Resectability in Surgical Patients with Unresectable Liver-only mCRC

A retrospective analysis was performed on the SIRFLOX study patients to assess whether the addition of SIRT to first-line chemotherapy for mCRC compared to patients who underwent first-line chemotherapy only led to an increased rate of technical resectability of liver metastases [50]. Technical resectability was defined by majority consensus from a pool of liver surgeons after a review of CT imaging. Addition of SIRT to first-line therapy led to an increase in technical resectability of disease ($n = 93$ [38.1%] of 244 SIRT patients *versus* $n = 66$ [28.9%] of 228 of chemotherapy-only patients) $P < 0{\cdot}001$. Of note, disease burden in the liver appeared to impact whether adding SIRT to first-line chemotherapy resulted in successful down staging to technical resectability. On the follow-up imaging for patients who had a baseline tumour burden in the liver greater than 25%, the authors found no significant difference between the rate of downstaging to technical resectability for patients who were treated with SIRT and chemotherapy versus chemotherapy alone (12% versus 13%, respectively).

43.5.6 Safety of Surgical Resection After Y-90

Surgical complications following Y-90 therapy to the liver have been evaluated. Wright GP et al. reported on patients who underwent surgical resection of liver tumours following Y-90 in 12 patients [51]. The diagnoses included colorectal adenocarcinoma ($n = 6$), neuroendocrine tumour ($n = 1$), ocular melanoma ($n = 1$), and HCC ($n = 4$). The median time from Y-90 treatment to surgery was 9.5 months (range, 3–20 months). The type of liver surgery included right hepatectomy ($n = 3$), extended right hepatectomy ($n = 5$), extended left hepatectomy ($n = 1$), segmentectomy with ablation ($n = 2$), and segmentectomy with liver perfusion ($n = 1$). The median operating time was 225 min (range, 147–393 min) with an estimated blood loss of 700 mL (range, 400–1500 mL). Intraoperatively, there were 3 portal venous injuries which required blood transfusion and primary repair. The 90-day morbidity rate was 42% ($n = 5$ of 12 patients). Four patients experienced bile leak and an intra-abdominal abscess. The 90-day mortality rate was 8% ($n = 1$ of 12 patients). The authors described technical challenges posed by liver resection following Y-90. Specifically, the authors cited radiation-induced fibrosis and scarring involving the non-tumour bearing liver and hepatic hilum. The authors postulated that the liver fibrosis may have led to difficulty in manipulating the liver parenchyma during resection causing a higher incidence of postoperative bile leak in their study. The authors also posed that the scarring in the hepatic hilum may have led to the three observed incidents of intraoperative portal venous injury.

Melstrom LG et al. performed a multi-institutional analysis which included 47 patients who underwent hepatectomy following Y-90 therapy [52]. Malignancies treated included HCC ($n = 14$), mCRC ($n = 11$), cholangiocarcinoma ($n = 8$), neuroendocrine tumour ($n = 8$), and other tumours ($n = 6$). The median time to resection from Y-90 was 196 days (range 13–947 days). The 90-day complication rate was 43% and mortality was 2%. The type of liver surgery was predominantly right or extended right hepatectomy ($n = 30$, 64%). Of note, 13 patients (27.7%) had a Clavien-Dindo Grade 3 or higher complication which were associated with the following risk factors: prior liver resection ($P = 0.058$), greater than one lobe treated with Y-90 ($P = 0.032$), extent of surgery ($P = 0.041$), and duration of operation ($P = 0.009$).

43.6 Conclusion

While phase III clinical trials have failed to show an improvement in OS with Y-90 in the setting of first-line chemotherapy, SIRT continues to serve an important role within the armamentarium of locoregional treatment options for patients with mCRC to the liver. Ongoing studies are being performed to evaluate the effectiveness of Y-90 as an adjunct to second-line therapy. Additional uses may also include adjuvant therapy for patients with right-sided colon cancer, downstaging to resection, and induction of FLR hypertrophy while also achieving local tumour control.

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Part V

Surgical Pathology and Molecular Pathology

Hepatic Injury from Chemotherapy

44

Laura Rubbia-Brandt

Learning Objectives

- Hepatoxicity is an expanding field in hepatology with an interest in chemical-driven liver damage.
- Patients with advanced colorectal cancer receive chemotherapy and develop a chemotherapy-associated liver injury.
- The common chemotherapy-associated liver injury in patients with colorectal cancer are steatosis, steatohepatitis, and sinusoidal obstruction syndrome.

44.1 Introduction

Hepatotoxicity is an expanding field in hepatology and implies chemical-driven liver damage [1–3]; it includes toxicity notably related to conventional drug medications, as well as illicit drugs, herbal medicine, and dietary supplements. Drug-induced liver injury (DILI) is responsible for 5% of all hospital admissions and 50% of all acute liver failures [2]. Drugs can affect all liver tissue structures, including hepatocytes, cholangiocytes, and hepatic vessels.

While different modalities (as laboratory testing or standard imaging modalities) have been studied and showed their utility, liver histology remains the gold standard for most types of DILI and is most helpful for the diagnosis. The pattern of histologic lesions contributes to identifying the causative drug and is particularly helpful when interpreted together with clinical presentation [1–3].

Patients with advanced colorectal cancer (CRC) have largely gained these last decades in long-term survival rate from advances in multimodal treatment and standardized multidisciplinary approach [4–10]. In the context of colorectal liver metastases (CLM), surgical resection with curative intent is a key treatment and preoperative (neoadjuvant) systemic chemotherapy has a substantial role notably by allowing improved resectability rates (notably by decreasing tumour burden or by converting prior unresectable CLM into potentially resectable disease). Postoperative adjuvant systemic chemotherapy may also be included in the treatment modality.

Linked to their established high efficacy, (notably by tumour response rates evaluated by imaging or by pathological regression grade scoring), most CLM chemotherapy regimens administered commonly in this setting today include drugs such as oxaliplatin with 5-FU and leucovorin, known as FOLFOX protocol, and irinotecan plus 5-FU and leucovorin, known as FOLFIRI [4–10]. However, as a drawback, numerous reports have well shown that several modern systemic chemotherapy-based treatments cause liver injury. These are qualified under the term chemotherapy-associated liver injury (CALI).

These non-tumoural liver tissue injuries are responsible for potential significant postoperative complications [11–19]. Chemotherapy-induced hepatotoxicity may have an impact on longer surgery and hospital stay, risk of infections, increase risk of preoperative hemorrhage, and on impairment in the accuracy of metastasis detection on post-chemotherapy imaging and postoperative impaired liver function and regeneration (i.e., poor liver functional reserve and postoperative liver failure after major hepatectomy, portal hypertension and ascites, a rare case of death).

Identification of CALI is thus important to optimize care and taken into account management strategy and surgical risks because it can engender significant morbidity and mortality, i.e., when evaluating before surgery liver remnant volume, time of surgery after the last chemotherapy, number of cycles of preoperative chemotherapy to be applied and possibly prevention.

This chapter will go mainly through an overview of the spectrum of pathological liver lesions related to the individual drugs such as 5-FU, irinotecan, and oxaliplatin.

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44.2 Patterns of Hepatic Lesions and Their Association to Specific Chemotherapy Drug Regimens Used for CLM Treatment

44.2.1 Steatosis

Hepatic steatosis or fatty liver is a common histological lesion nowadays, observed in the spectrum of injury observed in fatty liver disease and is related to various etiologies [20–22]. It is defined today as at least 5% of hepatocytes containing lipid triacylglycerol (TAG)-rich macrovascular and/or microvascular lipid droplets within the cell cytoplasm, in the absence of inflammation or other liver injuries (Fig. 44.1). Liver microvacuolar steatosis is usually graded based on the percentage of fat within the hepatocytes: grade 0 (healthy, <5%), grade 1 (mild, 5–33%), grade 2 (moderate, 34–66%), and grade 3 (severe, >66%).

Simple hepatic microvacuolar steatosis is a reversible lesion. Some steatosis is thought by some studies to be possibly hepatoprotective. However, what is established is that significant excess intrahepatic lipid storage (when in addition it is prolonged) is a risk factor for disease and may lead to liver metabolic dysfunction, progression to inflammation, and advanced forms of fatty liver disease.

Under normal physiologic conditions, lipid is metabolized by the liver but does not accumulate within it. Its pool results in a balance between free fatty acids (FFAs) influx within the liver (derived from the diet, and adipose tissue lipolysis, and/or de novo lipogenesis) and intrahepatic FFAs clearance (through hepatocellular β-oxidation or through hepatocellular FFAs esterification into TAG, followed by TAG assemblage into very-low-density lipoprotein (VLDL) and secretion into the blood).

Thus, several mechanisms have been involved in steatosis development and are prevalent according to etiologies, among which increased flux and excessive import of FFAs to the liver, increased de novo lipogenesis, and/or reduction of clearance through impaired mitochondrial β-oxidation of FFAs or diminished hepatic export of TAG via impairing in very-low-density lipoprotein secretion, that become stored as lipid droplets in hepatocytes.

Hepatic steatosis is correlated notably with obesity, type 2 diabetes, dyslipidemia, and several genetic defects or factors such as excess alcohol intake, viral infection (i.e., HCV), or drug treatments.

44.2.1.1 Chemotherapy Associated Steatosis (CAS) by 5-Fluorouracil (5-FU)

An association between 5-FU and steatosis was first observed initially by radiologic studies [23–27]. Several different mechanistic pathways have been studied and proposed for the development of 5-FU-induced steatosis. Experimental studies on primary human hepatocytes in vitro culture showed that 5-FU administration resulted in a significant increase of intracellular FFA and triglyceride levels by impairing mitochondrial FFA beta-oxidation through mitochondria membrane injury. Mitochondrial membrane injury seems to be due to an increase of reactive oxygen species (ROS) notably by cytochrome P450 of the smooth endoplasmic reticulum, increase in the expression of acyl-coenzyme A oxidase 1 ACOX1 expression by peroxisome or induction of pro-inflammatory genes.

Two other possible pathways for 5-FU induced steatosis development are the reduction of capacity of hepatocytes to metabolize liver fat and export lipid by catabolites of 5-FU which remain long in hepatocytes and aggravation by chemotherapy of preexisting steatosis in patients at risk of metabolic syndrome.

The impact of metabolic disorders rather than 5-FU has been also outlined by some authors.

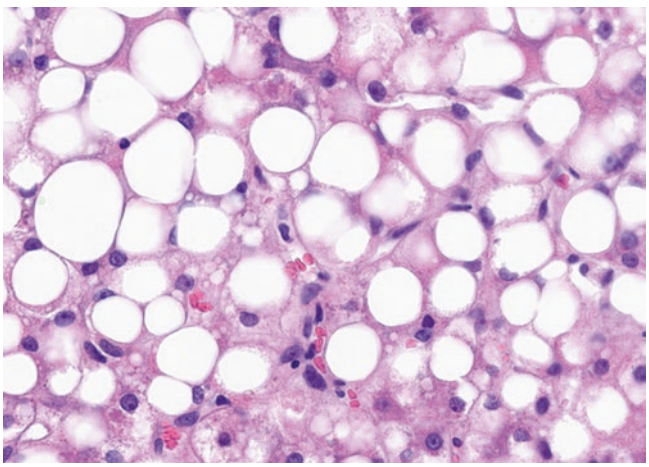

Fig. 44.1 Image of hepatic steatosis

44.2.2 Steatohepatitis

Steatohepatitis (SH) refers to a specific form of hepatic fatty liver injury characterized by three mandatory histological lesions: steatosis (mainly macrovacuolar) (Figs. 44.2 and 44.3), hepatocellular ballooning (Fig. 44.2), and inflammation (polymorphonuclear neutrophils (PMN) rich) (Fig. 44.2b), which may be accompanied by intrahepatocellular Mallory-Denk body inclusion (Fig. 44.2). SH may then lead to pericellular fibrosis. It can significantly impair acutely normal liver function and lead to chronic lesions with fibrosis and cirrhosis and liver failure in a number of patients. Numerous causes may induce SH an overlap with steatosis [20–22, 28].

Pathogenesis is multifactorial), but inflammation is considered the key element of disease progression. The liver har-

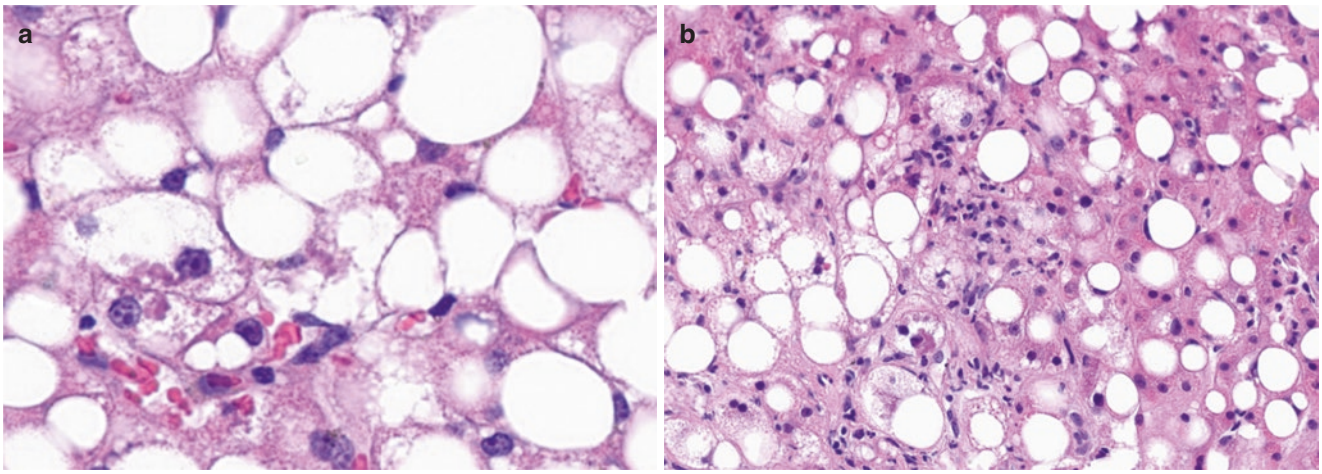

Fig. 44.2 Images of steatohepatitis (**a**) macrovesicular steatosis and ballonned cells with Mallory-Denk hyaline inclusion (**b**) polymorphonulear rich inflammation organized in satelitosis

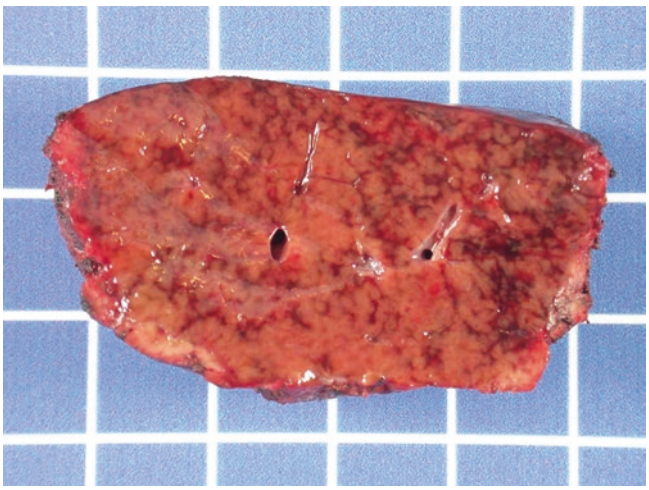

Fig. 44.3 Gross appearance of blue liver

bors numerous resident immune cells, in combination with recruited immune cells, which have a major role in the development of SH.

Several generalized postulated models are available to explain SH pathogenesis. One of them is based: on the "two-hit" process, which says that SH occurs in response to two sequential events; the first steatosis followed by a second injury that induce ballooning (in response to oxidative stress caused through mitochondria DNA, essential for cell respiratory chain (ATP production) and inflammation [29]. The second model says that SH is a systemic inflammatory disease. Here steatosis, ballooning, and inflammation occur simultaneously [30]. The capability of drugs to simultaneously stimulate the accumulation of lipids and reactive oxygen species (ROS) is of importance for SH development while drugs that solely induce lipid accumulation provoke simple steatosis but rarely SH.

44.2.2.1 Chemotherapy Associated Steatohepatitis (CASH) by Irinotecan

CASH induced by Irinotecan has been investigated in vitro in human hepatocytes, in vivo in mice model, and human in resected liver specimens from irinotecan-treated patients [31–37].

Irinotecan seems to induce the development of SH, in a dose-dependent manner, by notably hepatic lipid accumulation and pro-inflammatory gene expression, mainly through its toxicity to hepatocyte mitochondria (by binding to mitochondrial DNA/topoisomerase-1 complexes) and cause their injury such as inhibition of beta-oxidation of FFAs, inhibition of mitochondrial respiration (decrease the synthesis of enzymes involved in electron transport), mitochondrial DNA injury (preventing DNA recoiling), and topoisomerase and/or oxidative phosphorylation. Inhibition of oxidative phosphorylation and mitochondrial respiration is toxic to the mitochondria and can lead to the release of reactive oxygen species (ROS). Other proposed mechanisms comprise disruption of phospholipid metabolism in lysosomes, prevention of lipid outflow from hepatocytes, decreasing intestinal barrier function and role of gut microbiota and that bacterial translocation may participate in the development of CASH, activation of the adenosine pathway, increasing fatty acid synthesis, and sequestration of coenzyme. However, the precise mechanisms by which irinotecan effects these pathways have to be still more detailed.

The impact of metabolic disorders rather than irinotecan has been also outlined by some authors.

44.3 Sinusoidal Obstruction Syndrome and Associated Lesions

Hepatic sinusoidal obstruction syndrome (SOS) was formerly known as hepatic veno-occlusive disease (VOD), in reference to histologically characteristic centrilobular vein occlusion. Previously, these hepatic centrilobular venous lesions were mandatory for the diagnosis. Subsequently, the development of an experimental monocrotaline-based animal model in rodents has elucidated its pathogenesis and revealed that centrilobular vein involvement is not crucial to the development of SOS and that the main injury occurs at the level of the hepatic sinusoids [38–43]. In human pathological studies, occlusion of the centrilobular veins occurs only in 50–75% of patients who develop SOS after hematopoietic stem cell transplantation and around 50% of patients with SOS after oxaliplatin-based chemotherapy. This has led to a general acceptance of the use of the term SOS in preference to VOD. The diagnosis is presently based on the presence of sinusoidal lesions, independently of hepatic venous lesions, the latter being a sign of severity.

First reports are from 100 years with causative agents being senecio poisoning in South Africa, consumption of pyrrolizidine alkaloids rich herbal bush tea in Jamaica, inadequately winnowed wheat or herbal traditional remedies in countries such as India or Egypt. Then it comes to be a well-established complication of myeloablative high-dose chemo-irradiation treatment in the context of hematopoietic stem cell transplantation. Today SOS has been associated with more than 20 drugs including conventional doses of some immunosuppressive and chemotherapeutic agents.

In relation to any cause, hepatic sinusoidal obstruction syndrome (SOS) commonly results from toxic injury to a hepatic specific vascular structure: sinusoidal endothelial cells (SECs), resulting in a loss of sinusoidal wall integrity with consequent sinusoidal congestive obstruction and is occasionally associated with perisinusoidal fibrosis, centrilobular hepatic vein fibrotic obstruction, nodular regenerative hyperplasia (NRH) or peliosis [44–48].

Macroscopically, a liver with SOS has a typical bluish-red marbled appearance, commonly named as “blue liver” (Fig. 44.3). SOS may occasionally prevail in the subcapsular region or be accompanied by hemorrhagic lakes similar to peliosis hepatitis. Microscopically, SOS is characterized by lobular zones (predominately centrilobular) with large dilated sinusoids occupied by plugs of erythrocytes intermingled with zones of intact parenchyma. In severe SOS, dilated sinusoids appear as a form of bridging congestive bands (Fig. 44.4). Because of sinusoidal wall rupture, perisinusoidal hemorrhage is observed characterized by extravasation of erythrocytes into the perisinusoidal space along the dilated sinusoids (Fig. 44.5). From time to time, centrilobular veins display focal endothelial cell rounding and/or intimal hemorrhage; venular inlets are dilated and easily discernable where they connect to centrilobular veins (Fig. 44.6). Along dilated sinusoids, hepatocellular plates are occasionally atrophic and/or intermingled with focal hepatocellular necrosis (Fig. 44.7). At ultrastructural level, sinusoids may be denuded of SECs or when present, round-shaped and protruding into the lumen of the sinusoid. Sinusoidal lumen is filled with cytoplasmic blebs and erythrocytes.

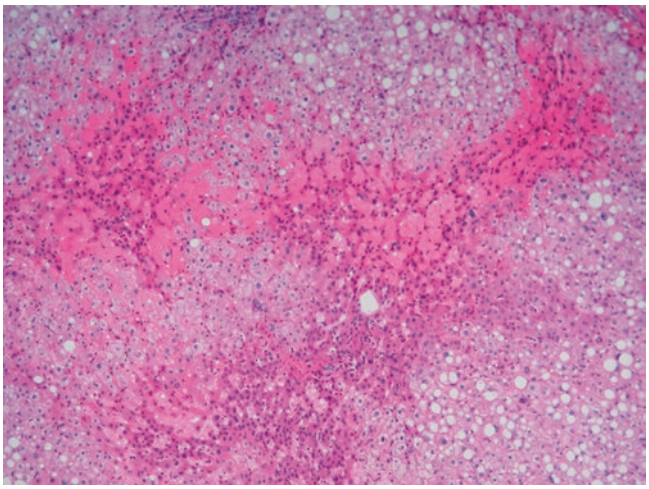

Fig. 44.4 Microscopic image of sinusoidal obstruction syndrome

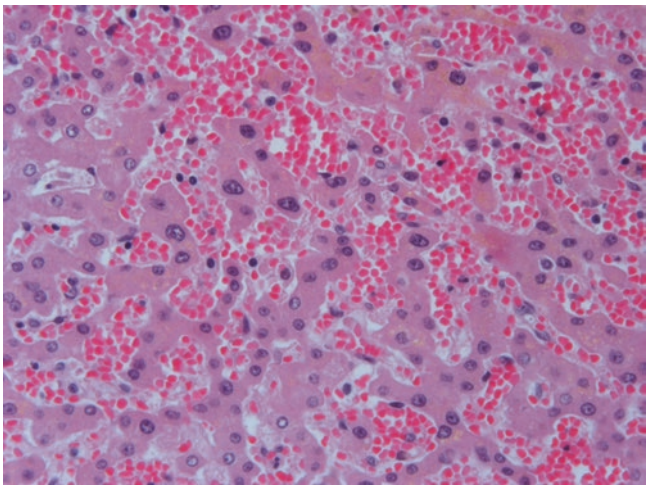

Fig. 44.5 Perisinusoidal hemorrhage of sinusoidal obstruction syndrome

SOS may be accompanied by one or more other lesions such as centrilobular perisinusoidal and venular fibrosis, peliosis, and nodular regenerative hyperplasia (NRH). Morphologically distinct from sinusoidal changes, these additional lesions are related to SOS severity itself. Perisinusoidal fibrosis frequently concerns only areas of centrilobular zone and may extend occasionally to centrilobular vein with subsequent variable degrees of lumen occlusion, only rarely complete. NRH is characterized macroscopically

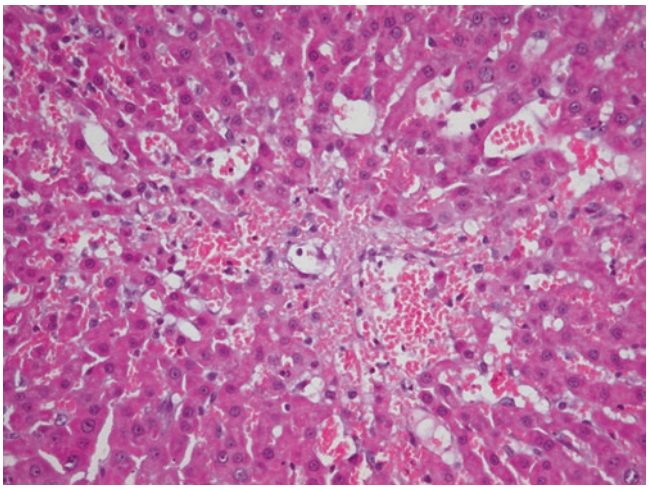

Fig. 44.6 Dilatation of venular inlets in sinusoidal obstruction syndrome

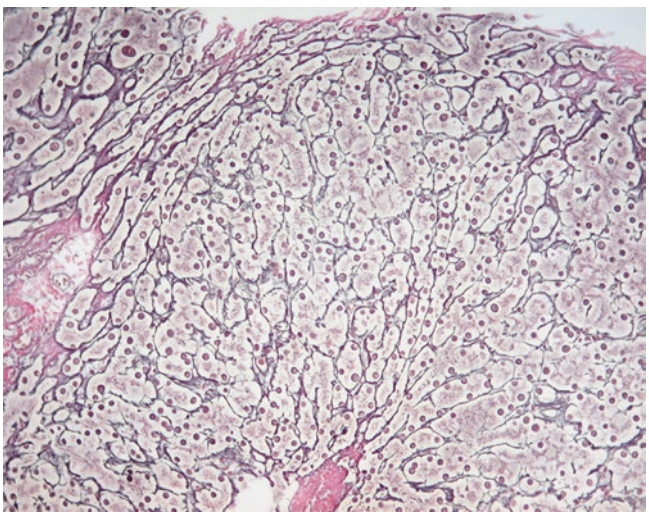

Fig. 44.7 Focal hepatocellular necrosis in sinusoidal obstruction syndrome

by small bulging nodules usually less of 3 mm wide without fibrosis; at microscope, they are composed of enlarged regenerative hepatocytic plates (Fig. 44.7). These may be centered on portal tracts and delineated at their periphery by atrophic hepatocytes or dilated sinusoids (Fig. 44.7). NRH is responsible for non-cirrhotic hypertension [49].

The major target of SOS is thus the sinusoid [50]. The latter is a peculiar vessel lined by fenestrated endothelium and lacking a basement membrane. It is surrounded by the perisinusoidal space of Disse which contains a slight collagen network. It is the main structure involved in the exchange between blood and hepatocytes (oxygen and nutrients). It plays a role in clearing toxins and foreign bodies from the bloodstream. Its functions rely on distinct sinusoidal cells, i.e., Küpffer cells (KS), SECs, and hepatic stellate cells (HSCs).

A number of SEC functions are connected to their morphological characteristics. SECs are flattened with processes such as fenestrae that occupy 6–8% of the endothelial surface. Fenestrae are structured in groups of 10–50 pores, measuring 150 nm in diameter that are unequally spread along the sinusoid. Highest concentration is confined in centilobular zone. Fenestrae are dynamic structures that contract and dilate functioning as a selective sieving barrier to control the exchange. The absence of a basement membrane around SEC also facilitate the exchanges. SECs have a scavenger role, eliminating a range of macromolecules from the blood by receptor-mediated endocytosis and an antigen-presenting function similar to dendritic cells. In cooperation with KC and hepatic dendritic cells, they contribute to the immunoregulatory functions in the liver.

Sinusoids have a key role in regulating hepatic blood flow through the regulation of sinusoidal blood flow (balance between vasoconstrictive and vasodilatative factors). In normal liver, nitric oxide (NO) is mainly synthesized by SECs constitutive NO synthetase (eNOS) located in large vessels and sinusoids. NO controls the blood flow of hepatic microcirculation by acting on HSC contraction. Besides this role on vascular tone, SECs' NO also have an impact on extracellular matrix remodeling by inhibiting matrix metalloprotease (MMPs) expression and maintaining HSC in a quiescent state [51].

VEGF produced by hepatocytes and HSC and NO released by SEC themselves in response to VEGF stimulation has the main role in conserving SEC differentiation, especially fenestration preventing the capillarization of sinusoids. In addition, SECs express MMP-9 and MMP-2, enzymes responsible for extracellular remodeling. Activation of SEC exerts pro-inflammatory and pro-adhesive as well as pro-coagulant properties.

SECs are a major cellular target for several toxins. One cause is their location and direct exposure to drugs absorbed by the intestinal tract and transported to the liver by portal venous blood. Moreover, both hepatocytes and SECs are rich in cytochrome P450 and thus activate drugs and export their toxic metabolites into the perisinusoidal space.

Animal model of SOS: Rat model based on monocrotaline (a pyrrolizidine alkaloid) gavage by Deleve et al. [52–59] clarified SOS pathogenesis. Lesions appear in centrilobular zones of hepatic lobules within 48 h after monocrotaline administration. Monocrotaline binds to actin filaments of the cytoplasmic cytoskeleton of SECs and causes their depolymerization. As a consequence, SECs round up, lose their fenestration, detach and pack within the sinusoidal lumen. This rupture of the sinusoidal endothelial barrier, allows erythrocytes to penetrate into the perisinusoidal space and dissect sinusoidal lining. An increase in expression of matrix metalloprotease MMP-9 (and to a lesser extent MMP-2) from SEC also occurs simultaneously and induces

perisinusoidal extracellular matrix degradation which further contributes to SECs detachment. Upregulation in MMPs activity is due both to actin depolimerization itself and to the removal of NO-related inhibition of MMPs synthesis due to the decline in NO synthesis after the loss of SECs. Monocrotaline also depletes cellular glutathione inducing an increase in ROS production and oxidative stress contribute also to SEC injury. Sloughed SECs, cytoplasmic blebs, and Kupffer cells intermingled with erythrocytes subsequently embolize downstream within the sinusoid lumen towards venular inlet and centrilobular vein and contribute to sinusoidal obstruction and causes a reduction of blood flow in hepatic microcirculation.

Three to five days after monocrotaline exposure, because of the tight link between intact microcirculation and the viability of parenchymal cells, hepatocyte necrosis and centrilobular hemorrhagic zones appear,

Lastly, on days 6–7, fibrosis appears as sinusoidal collagen deposition; fibrosis may also occur in centrilobular venular lumens leading to centrilobular venular occlusion and inlet vein occlusion. MCT-related SOS according to Deleve's protocol is not associated with NRH development.

SEC injury possibly induces a procoagulant condition. Overexpression of MMP-2 and MMP-9 is associated with increased platelet adhesion to sinusoidal cells. Nevertheless, the role of clotting abnormalities in the experimental SOS model is under debate.

It results in hepatomegaly, hyperbilirubinemia, and ascites. It increases portal pressure and delays liver regeneration after major hepatectomy in an experimental animal model [6, 60, 61].

In a murine chemotherapy model of FOLFOX-induced SOS, there was confirmation of endothelial damage that led to a pro-thrombotic state within the liver [62, 63]. This was concomitant with the upregulation of plasminogen activator 1 (PAI-1) and von Willebrand factor and factor X.

Human: The mechanisms involved in human SOS are not yet conclusively established. Morphologically, the lesions observed in chemotherapy-related SOS are similar to the MCT rat model and the molecular causes might be similar [64, 65].

SEC toxic injury in human may result in NRH a lesion that is morphologically distinct from SOS. The pathogenesis of NRH is poorly understood. It is known to result in changes in intrahepatic blood flow, that lead to atrophic hypoperfused areas interspersed with hyperperfused regenerative areas.

44.3.1 Chemotherapy Associated SOS (SOS) by Oxaliplatin

Oxaliplatin-based regimens are associated with various types of microvascular hepatic lesions, which may all occur in various combinations [44–49]. Sinusoidal alterations including sinusoidal dilatation and SOS are the most frequently reported between 8 and 49% of patients treated with oxaliplatin. Perisinusoidal fibrosis was reported in 30% of the patients. Occlusion of the centrilobular veins, which is considered to be a criterion for increased SOS severity, is found in 50% of oxaliplatin-related SOS. In addition to sinusoidal lesions, NRH occurs in up to 12–20% of the patients treated with oxaliplatin. Peliosis may occur. The classification of SOS groups patients into mild (less than 1/3 of lobule), moderate (1/3–2/3 of lobule), and severe changes (extending into lobule).

In humans, oxaliplatin and other platinum compounds lead to depolymerization of F-actin in sinusoidal endothelial cells, increased expression of matrix metalloproteinase (MMP)-9 and MMP-2 by sinusoidal endothelial cells, generation of ROS, and glutathione depletion in SEC resulting in SEC injury. Oxaliplatin also activates hepatic stellate cells, resulting in the deposition of a collagen matrix in the perisinusoidal spaces and centrilobular veins. Patients with SOS show increased serum VEGF that is synchronized with the development of SOS. HSC activation has been reported in patients with SOS.

Studies in pathway analysis in humans [63, 64] revealed molecular signatures characterized by high gene upregulation in six pathways in SOS compared with controls: acute phase response (notably interleukin 6), coagulation system (Serpine1, THBD, and VWF), hepatic fibrosis/hepatic stellate cell activation (COL3a1, COL3a2, PDGF-A, TIMP1, and MMP2), and oxidative stress. Angiogenic factors (VEGF-C) and hypoxic factors (HIF1A) were upregulated. The most significant increase was seen in CCL20 mRNA. Activation of VEGF and coagulation (vWF) pathways could partially explain at a molecular level the clinical observations that bevacizumab and aspirin have a preventive effect in SOS.

44.4 Reversibility of Chemotherapy-Related Liver Injury

CALI histological lesions persist for a long time after chemotherapy. SOS and NRH regress only after 9 months without chemotherapy, whereas steatosis and steatohepatitis persist [66].

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor that increases the efficacy of systemic chemotherapy in patients with metastatic CRC, has shown to have a protective role in SOS appearance [45, 67–69], the incidence of SOS of any grade being significantly lower in patients treated with bevacizumab compared with those patients not treated with bevacizumab.

44.5 Conclusion

Current management of colorectal cancer largely relies on the usage of effective systemic adjuvant or neoadjuvant chemotherapies. One of their major and well-accepted drawbacks is hepatotoxicity. Several regimen-specific histological characteristics have been reported. Steatosis is associated with the use of 5-FU and irinotecan, steatohepatitis is associated with irinotecan, and SOS is associated with oxaliplatin-containing regimens. In SOS, the target of drug toxicity is sinusoidal endothelial cells resulting in hepatic microcirculation alterations. Several open questions are today the object of intense study, its pathogenesis, diagnosis, reversibility, and prevention.

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Imaging Response Evaluation

45

Sireesha Yedururi, Usama I. Salem, Rony Avritscher, and Evelyne M. Loyer

Learning Objectives

- Emphasize the role of high-quality baseline study for accurate response assessment of colorectal liver metastases.
- Understand the response assessment criteria that are most relevant to routine clinical practice, i.e., size and morphological criteria.
- Understand disappearing liver metastases and strategies to mitigate the problem.
- Recognize the imaging findings of chemotherapy-induced liver toxicity.

45.1 Introduction

Noninvasive evaluation of treatment response is a critical task in oncology whose aim, is first to determine as early as possible the impact of treatment to avoid unnecessary exposure to side effects and undue costs. The quality of the response informs on the outcome and indirectly on the tumour biology. Clinical symptoms and tumour markers can serve as indicators of response but for the most part, the response is judged on imaging. With the optimized technique, imaging can provide a simple, noninvasive, often quantifiable, and early indication of treatment efficacy. Imaging response to systemic chemotherapy in colorectal liver metastases (CLM) rely mainly on anatomic criteria. Criteria however continuously evolve with the therapeutic and technological advances. Ongoing research on functional and quantitative imaging will further expand the available methods of response assessment.

Until recently, anatomic criteria were strictly focused on tumour size. These size-based criteria are not specific for tumour type or treatment and remain the most widely used but their accuracy varies with the mechanism of action of the drugs being used. Systemic therapy for CLM includes cytotoxic chemotherapy, drugs targeting vascular endothelial or epidermal growth factors and immunotherapy, often used in combination. As expected, the impact on the radiographic appearance of tumours varies with the type of drug. Tumour shrinkage induced by cytotoxic chemotherapy is well evaluated with size-based criteria, but tumour shrinkage is not always present with targeted therapy or immunotherapy. This issue was initially recognized in trials exploring targeted therapy in CLM where treatment benefit on overall survival was found to be independent of the presence of objective tumour response on imaging [1]. The risk of discrepancy between outcome and objective response by RECIST is now well known, and has led in the past 15 years to a reappraisal of the size criteria and to the development of anatomic criteria that do not rely exclusively on size.

In this chapter, we focus on the imaging criteria that are currently used in clinical practice (size and non-size-based criteria) to assess response to systemic chemotherapy in CLM. We briefly review functional imaging and the assessment of response after locoregional therapies. We also review the imaging findings of side effects of chemotherapy on the liver parenchyma, as the detection of therapy-induced liver injury and extrahepatic side effects is an integral part of assessing response.

45.2 Importance of Baseline, Pretreament Imaging

Before any discussion of response, one cannot stress enough the importance of optimal baseline staging before the administration of any treatment. It is not uncommon for patients to

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present to a tertiary cancer care facility after initiation of chemotherapy at another institution with a baseline study, CT, or MRI that is not optimized to detect small lesions or with PET/CT only as the baseline exam. These situations preclude accurate staging and expose the patient to the risk of early recurrence in the event of resection. This is a common issue since hepatic resection for CLM has become the standard of care for an increasing number of patients. Optimized baseline scan is also important for accurate characterization of all liver lesions prior to surgical resection. Indeterminate small liver lesions that do not change with neoadjuvant chemotherapy are likely benign while those that decrease in size or change morphology with treatment are likely metastases. Conversely, posttreatment changes after targeted therapy can be confused with a benign disease in the absence of a reliable baseline for comparison. In addition to the lack of high-quality baseline images, the long delay between the baseline study and chemotherapy initiation can lead to inaccurate response assessment.

45.3 Imaging Response After Systemic Chemotherapy

About 25% of colorectal cancer patients present with synchronous metastases and about 50% will develop liver metastasis in the course of the disease. Surgical resection is the best treatment option for long-term survival but is possible in only a small fraction of patients (10–30%) before chemotherapy [2]. Response assessment for CLM is performed with CT or MRI. CT is favored at our institution due to its patient-centric qualities, ease of detection of peritoneal involvement, and simultaneous acquisition of chest imaging to evaluate for lung metastases, which obviates the need for two separate imaging appointments. While change in tumour size on CT or MR examinations remains a key marker of response, regardless of the type of treatment, response needs to be always judged from two different perspectives, size and morphological changes that may or may not be accompanied by a change in size.

45.4 Size-Based Criteria

45.4.1 Definition

Objective measurements are used in daily practice and the optimal choice in the context of clinical trial. The WHO criteria, introduced in 1979, are based on changes in bidimensional measurements (longest diameter multiplied by the greatest perpendicular diameter) of the target lesions. The change in tumour area (product of diameters) is categorized into four groups: complete response (CR), partial response (PR) (50% decrease in target lesions, without a 25% increase in any one target lesion), progressive disease (PD) (25% increase in the size of measurable or unequivocal progression of non-target lesions), and stable disease (SD) (neither PR nor PD) [3, 4].

RECIST criteria were introduced in 2000 by the European Organization for Research and Treatment of Cancer, the National Cancer Institute of the United States and the National Cancer Institute of Canada to increase standardization and simplify data collection [4]. RECIST criteria rely on unidimensional measurement of the tumour's largest diameter. The sum of the longest diameters of target lesions is calculated and classified into the same four categories as for the WHO criteria, but since it uses unidimensional measurement of diameter compared to bidimensional measurement of areas, the cutoff values for PR and PD are different at 30% decrease in the sum of the longest diameters of target lesions for PR and 20% increase in the sum of the longest diameters of target lesions, appearance of new lesions, or unequivocal progression of non-target lesions for PD. RECIST criteria were revised in 2009 to clarify the evaluation of nodal disease, refine the definition of PD, and further simplify data collection [5].

45.4.2 Limitations/Pitfalls

While the size-based criteria are strong, simple, and objective indicator of treatment effect, their simplicity draws on postulations that undermine accuracy. With these criteria, the assumption is that tumours are spherical and change in diameter is an accurate reflection of the change in volume, but tumours are far from being always spherical. Not infrequently, tumours may shrink into a linear or band-like area with a disproportionate decrease in the longest diameter compared to other two dimensions. Direct measurement of tumour volume has been proposed to alleviate the incertitude in measuring tumour burden [6, 7]. These volumetric methods rely on various segmentation tools that are yet to be standardized and although volumetric RECIST criteria have been developed, the use of volumetric response assessment is still limited [8].

Another and more serious issue with RECIST is the arbitrary choice of the cutoff values used to define the response categories. PR response by RECIST requires a 30% decrease in size at any point in time exposing to the risk of long delay before the impact of a drug regimen can be objectively measured. New ways of categorizing change in size have been explored looking at both alternate cut-off values and alternate time points. Of those, early tumour shrinkage (ETS) assesses the percentage of size decrease at first restaging (8 weeks) with a cutoff value for response at 20% and depth of response (DpR) quantifies the maximal tumour shrinkage 4–6 months after the

start of chemotherapy. Both have been shown to strongly correlate with long-term outcome in patients treated with cytotoxic chemotherapy alone or in combination with Cetuximab [9, 10]. In the FIRE-3 trial assessing FOLFIRI (5-Flurouracil and Irinotecan) plus bevacizumab versus FOLFIRI plus Cetuximab, response rate by RECIST did not correlate with the improved survival observed for the Cetuximab arm but post hoc analysis using ETS and DpR showed the new metrics to correlate with the survival benefit of Cetuximab in the RAS wild type subgroup [11]. Another recent study has confirmed the value of these new metrics [12].

Finally, size-based criteria presume that the change in size reflects a change in the number and viability of tumour cells. This of course is not valid when for example, there is necrosis or with drugs that have a dominant cytostatic effect; consequently, criteria that focus on the estimation of residual viable tumour tissue rather than size have been developed and are discussed below.

Another less common issue with the measurement of CLM has to do with peripheral enhancement of the metastasis that may vary due to variations in timing of image acquisition or changes in volume/rate of contrast administration and make the metastasis appear smaller. Figure 45.1 illustrates an example of underestimation of tumour size on portal venous phase images compared to pre-contrast phase images, leading to inaccurate response evaluation. Assessing size changes in pre-contrast phase in addition to portal venous phase prevents such misinterpretation. This pitfall needs to be kept in mind. A multiphasic liver protocol or at least adding a non-contrast phase at follow up is helpful in a small subgroup of patients where significant, rapid, peripheral enhancement is noted at baseline.

45.4.3 Disappearing Liver Metastasis

For patients with colorectal liver metastases who are potentially eligible for surgical resection, it is critical to identify and take note of small liver metastases that may disappear with initial chemotherapy (Fig. 45.2). Complete radiographic response (CR) by RECIST, also termed "disappearing" liver metastasis (DLM) on CT or MRI is not a reliable indicator of complete pathological response. Depending on the series, viable tumour is present in 34–83% of the lesions that disappear. The effectiveness of current chemotherapy and the growing number of patients undergoing resection of CLM, make DLM an important issue because of the risk of early recurrence after resection. Of course, the incidence of DLM after neoadjuvant chemotherapy is affected by the technical quality of imaging and has been shown to vary

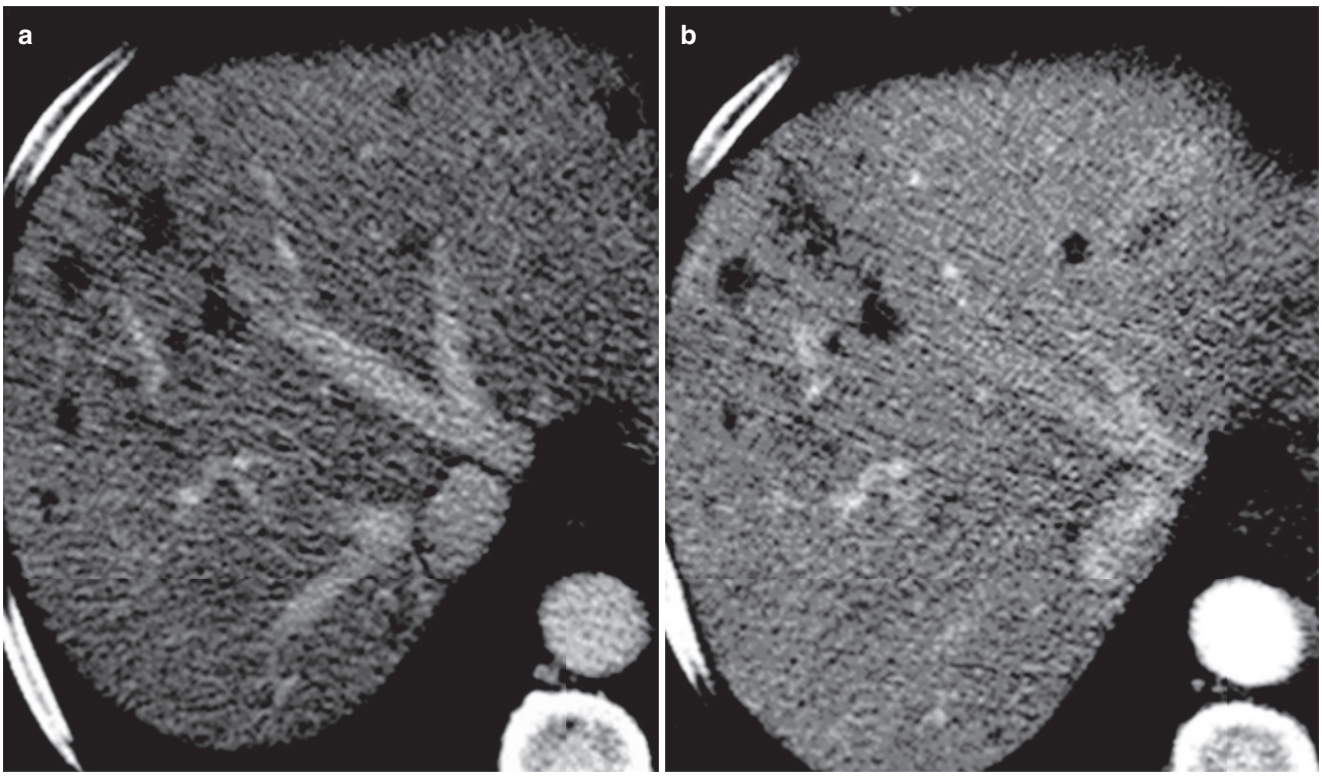

Fig. 45.1 Pitfall in size measurement: Contrast-enhanced CT images in portal phase (**a** and **b**) and non-contrast phase (**c** and **d**) before treatment (**a** and **c**) and after treatment (**b** and **d**). On the portal phase, the metastases are similar in size before and after treatment. On the non-contrast scan, progression is evident, metastases are larger in (**d**), (*arrows*) but cannot be appreciated on the portal phase

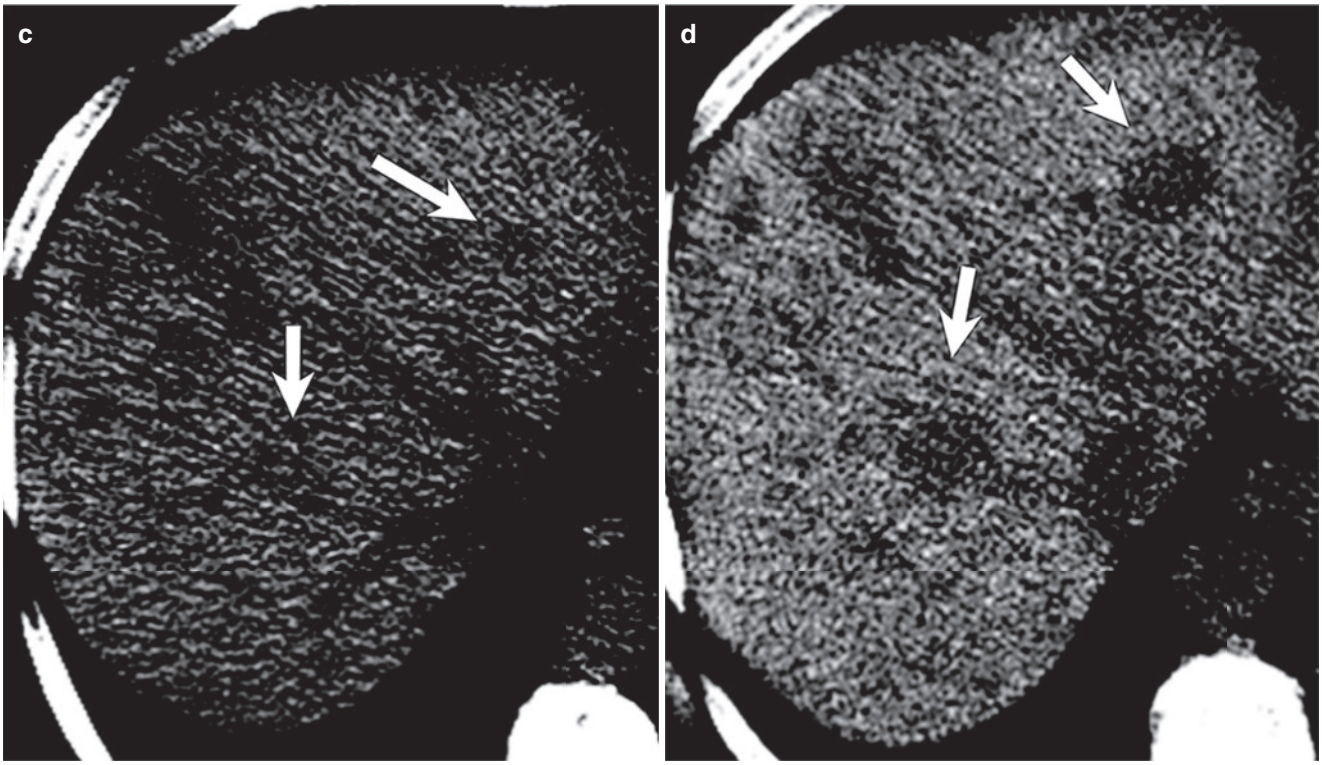

Fig. 45.1 (continued)

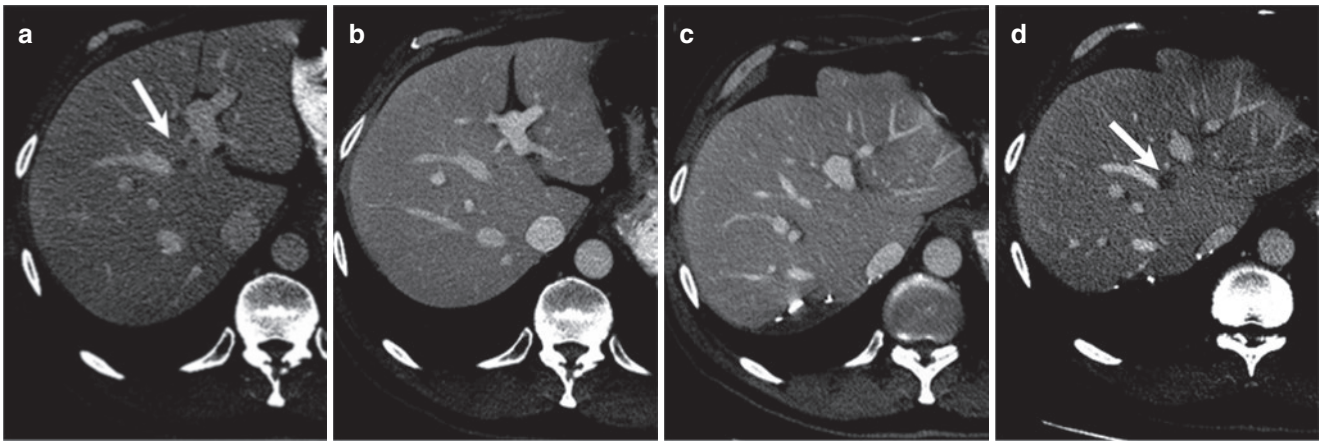

Fig. 45.2 Disappearing CLM: Serial CT images at baseline (**a**), preoperatively after 5 months of neoadjuvant chemotherapy (**b**), after surgery at 10 months (**c**), and 14 months (**d**). There is a sub-centimeter segment 4 metastasis at baseline (*arrow* in **a**) that has disappeared post-chemotherapy on the presurgical CT scan (**b**) but recurred postoperatively (*arrow* in **d**). This metastasis was not mentioned at baseline

between 5 and 38% of metastases [13–16]. A recent study by Tani et al. [17] using up-to-date imaging techniques reports finding DLM in 20 out of 82 patients. 619 liver metastases were identified in their patient population and 111 became undetectable after treatment. Of those 58.5% had residual disease [17].

To limit the risk of DLM, radiologists need to be aware of the frequency of this issue and be particularly attentive when interpreting follow-up scan in potentially surgical patients. Tiny metastasis can disappear at first restaging (Fig. 45.2); consequently, comparison needs to systematically refer to the baseline scan obtained before any treatment, as it is the scan that provides the most accurate depiction of the extent of disease. Short of this habit, the risk is of "forgetting" metastases that disappear early in the course of the treatment and not being commented upon on follow-up examinations.

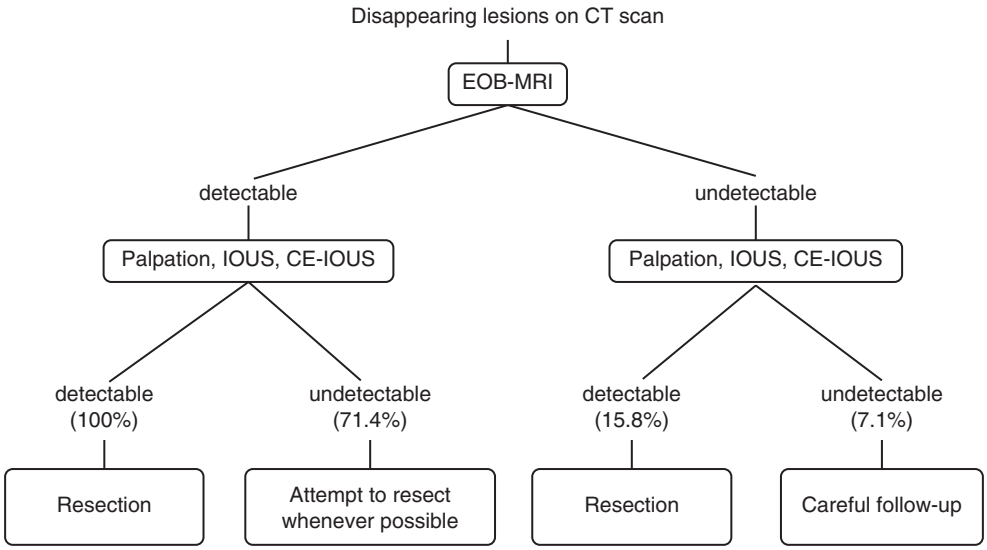

Fig. 45.3 Reprinted from Tani et al., J Surg Oncol. 2018. Algorithm for the management of DLMs. Presented numbers indicate the percentages of residual tumours obtained from this study

Another approach to limit the risk of DLM is to use fiducials. Tiny metastases identified at baseline outside the field of resection and at risk of disappearing with chemotherapy can be marked with fiducials. At our institution, indications for fiducial marker are metastasis <2 cm that are located >1 cm deep in the liver parenchyma. This procedure is safe and allows localization for resection or ablation [18]. Finally, one can gauge the risk of viable residual tumour in DLM on CT with Eovist MRI. Failure to detect treated metastasis at MRI correlated with a higher probability of complete response in the series by Auer et al. and Tani et al. [16, 17] subsequently confirmed that DLM identifiable on Eovist MRI had a higher probability of incomplete response even if they could not be identified by CE-IOUS. They proposed an algorithm (Fig. 45.3) for the management of DLM.

45.5 Non-size-Based Morphological Criteria

The introduction of targeted therapy confronted investigators with a paradoxical observation. Restaging scans did not show objective response based on size and yet patient's outcome was much improved. With increased experience of these new drugs, a new pattern of imaging response was recognized. These changes concerned mostly the degree of heterogeneity of the tumours and the sharpness of the tumour-normal liver interface (TNI). These changes did not correlate with response by RECIST but indirectly reflect the amount of residual viable tumour. They were first observed with Imatinib in the treatment of gastrointestinal stromal tumours [19]. It was quickly established that similar patterns of response occurred with other drugs and other tumour types including CLM [20]. Interestingly this pattern could also be observed with traditional cytotoxic therapy but at a much lower rate, probably explaining why it had not been recognized earlier [21].

45.5.1 Radiographic Observation After Bevacizumab

Phase III clinical trial evaluating the efficacy of bevacizumab (BEV) in the treatment of CLM concluded that the addition of BEV improved outcome. As with Imatinib, patients were doing better in the absence of objective response by RECIST [1]. Although there was no meaningful size reduction, the CT appearance of the metastases in some patients was dramatically changed from the pretreatment pattern.

The systematic comparison of pre and posttreatment CT scans in an initial cohort of 50 surgical patients treated with first-line BEV-containing chemotherapy showed that changes in the tumour appearance were characterized by a tendency for the tumour content to become more homogenous and of lower attenuation, while the interface with the normal liver became sharper. These changes could be broadly grouped into three categories [20].

In this analysis, it is important to keep in mind that the morphologic classification is made exclusively on changes in the content and contours of a given tumour. CLM before treatment are most often characterized by heterogeneous tissue of variable attenuation that is enhancing and centered over a core of low attenuation. Rarely untreated metastases are of low uniform attenuation. The margins are most often nodular and ill-defined but can be infiltrative or rarely smooth and relatively well-defined (Fig. 45.4). Morphologic assessment relies on both the analysis of the content and the analysis of margins. Change in tumour size is neither taken into consideration for classification nor is the degree of enhancement.

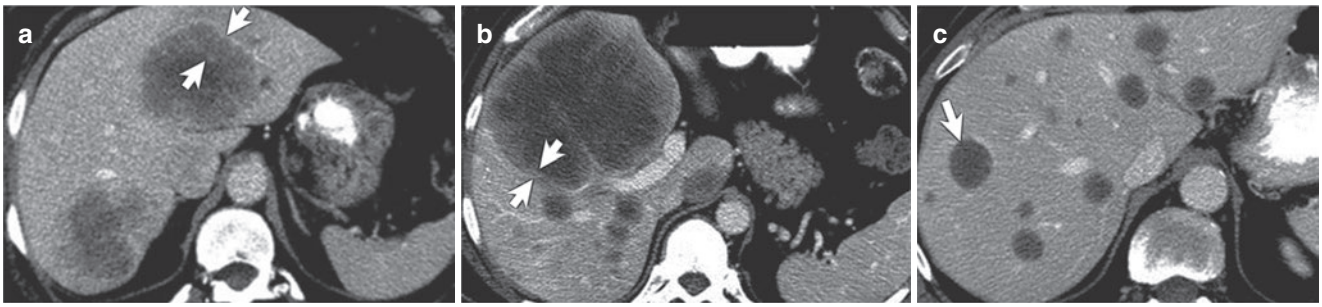

Fig. 45.4 Distinctive appearances of CLM at baseline. Reprinted from Piyaporn B et al. AJR 2011. 50-year-old man, 39-year-old woman, and 65-year-old woman, all presenting with CLM. Contrast-enhanced CT scans performed before treatment show three distinctive appearances. (**a** and **b**) Images show metastases of heterogeneous attenuation with a central zone of low attenuation surrounded by thick (**a**) or thin (**b**) rim of soft tissue (*arrows*, **a** and **b**) of relatively higher attenuation. (**c**) Image shows metastasis (*arrow*) of uniform low attenuation

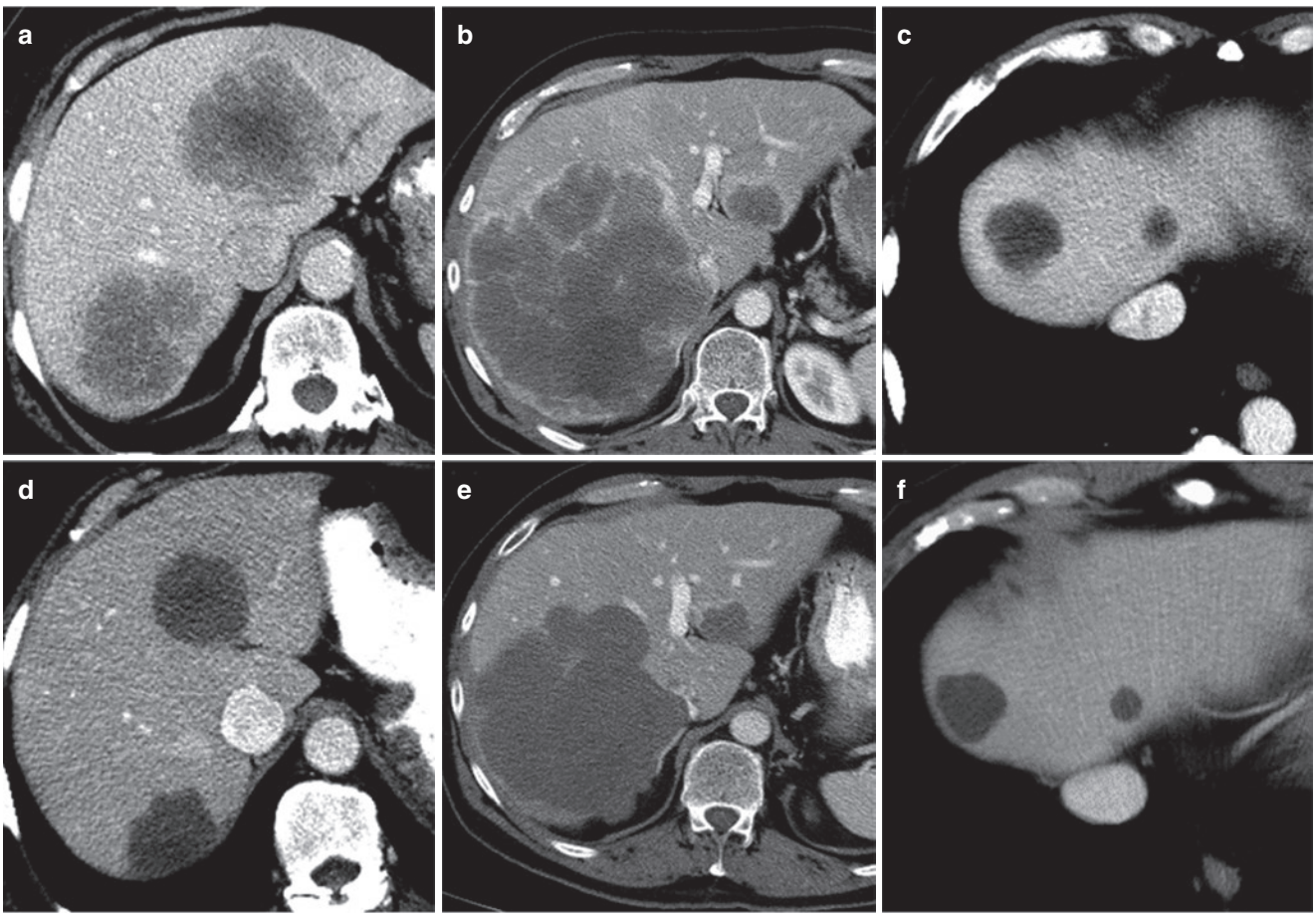

Fig. 45.5 Morphological changes characteristic of group 1. Baseline CT in three patients with CLM, from left to right, show a thick (**a**) or thin (**b**–**c**) peripheral rim of soft tissue centered over a central zone of low attenuation and ill-defined interface with the normal liver. Posttreatment scans obtained after 6 cycles of FOLFOX/bevacizumab (**d**), 8 cycles of FOLFIRI/bevacizumab (**e**), and 6 cycles of XELOX/bevacizumab (**f**), respectively show the same pattern in all patients: homogeneous tumour of low attenuation with a sharply defined interface with the normal liver. The peripheral rim of soft tissue has disappeared

After BEV-containing regimen, the changes observed fit the three-following scenarios [20].

Group 1 is characterized by dramatic, very easily recognizable changes in content and contours becoming homogeneous, hypoattenuating, and well marginated, basically mimicking a cyst in the portal phase (Fig. 45.5). The recognition of this pattern is very simple, and the learning curve is very short. These changes are best observed on multiphasic CT. In the pretreatment studies owing to

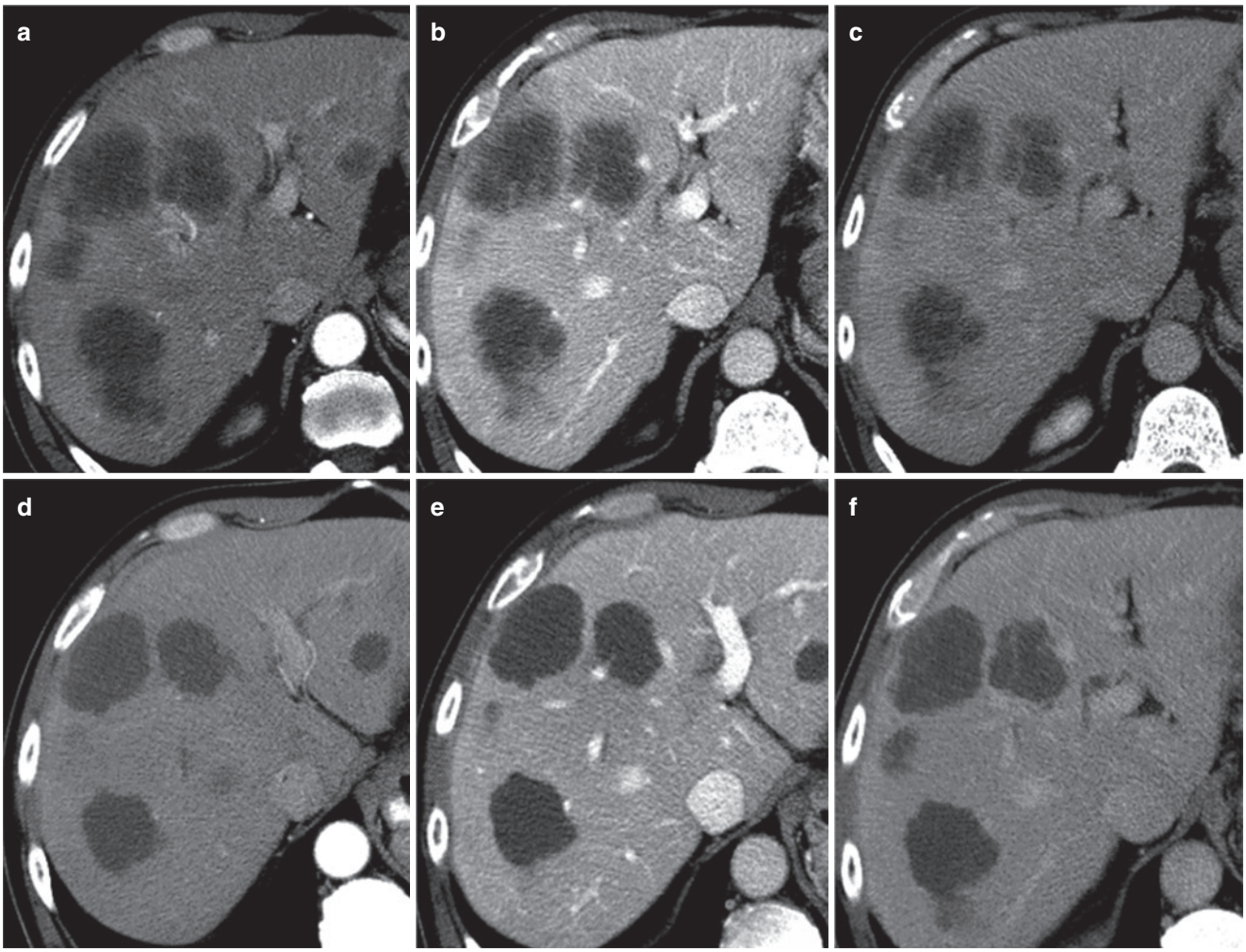

Fig. 45.6 Morphological changes characteristic of group 1. Multiphasic contrast-enhanced CT scan—in arterial (**a**, **d**), portal (**b**, **e**), and delayed phase (**c**, **f**). Please note that (**a**–**c**) are images obtained before chemotherapy and (**d**–**f**) are images after 8 cycles of FOLFIRI/bevacizumab. (**a**–**c**) Before treatment, the peripheral rim of soft tissue further enhances over time making the metastases appear slightly smaller on the delayed phase than the portal phase. (**d**–**f**) After treatment, the rim of soft tissue is not identified any longer, and the size and appearance (homogenous content and sharp margins) of the metastases are stable on all phases

delayed enhancement of colorectal liver metastases, these tend to appear smaller in delayed phase. On the posttreatment scans, the size tends to remain stable in all phases (Fig. 45.6).

Group 2 is characterized by decreased heterogeneity and improved margination but to a lesser degree than group 1 so that a pseudocyst appearance was not achieved in any phase (Figs. 45.7 and 45.8). Again, the residual enhancement can be better depicted on delayed images and the value of delayed imaging in further assessment of morphologic response is illustrated (Fig. 45.8).

Group 3 is defined by the absence of change in the appearance of the tumour (Fig. 45.9). Group 3 tumours like the other groups could be smaller than baseline but had none of the morphologic change described above.

Enhancement is not part of the evaluation but evidently plays an important role in the analysis as response is judged on contrast-enhanced scans and active disease enhances notably on delayed imaging. With optimal morphologic response, evidence of any tumour enhancement disappears including delayed enhancement (Fig. 45.6).

45.5.2 Rad-Pathologic Correlation

Pathologic response to neoadjuvant chemotherapy is an independent predictor of long-term outcome providing important insights into the tumour biology [22, 23]. Untreated tumours are characterized by the intermingling of viable tumour cells and necrosis that is replaced mostly by fibrosis

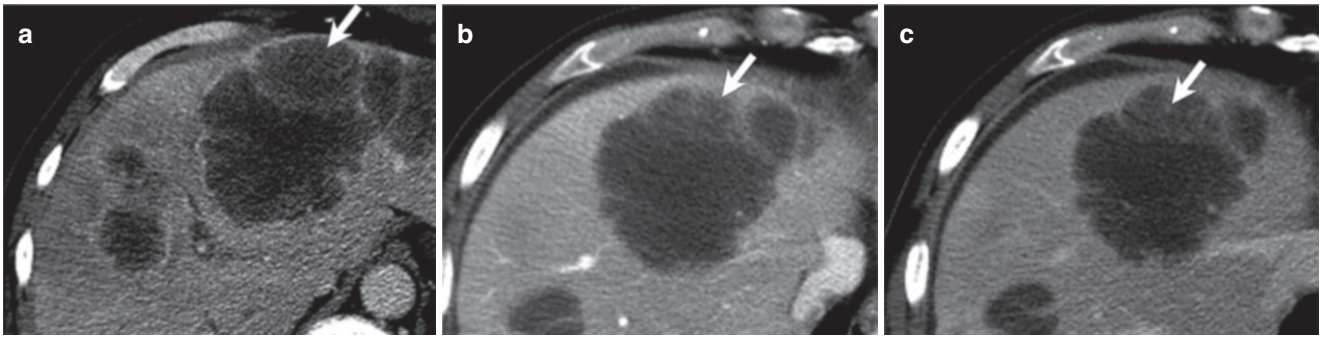

Fig. 45.7 Morphological changes characteristic of group 2 in a 68-year-old woman with CLM. Baseline (**a**) and posttreatment CTs after 4 cycles of FOLFOX/bevacizumab in the portal and delayed phase (**b** and **c**) show decreased but persistent peripheral soft tissue in the treated metastases, best seen in the anterior aspect of the metastasis (*arrows* in **a**–**c**)

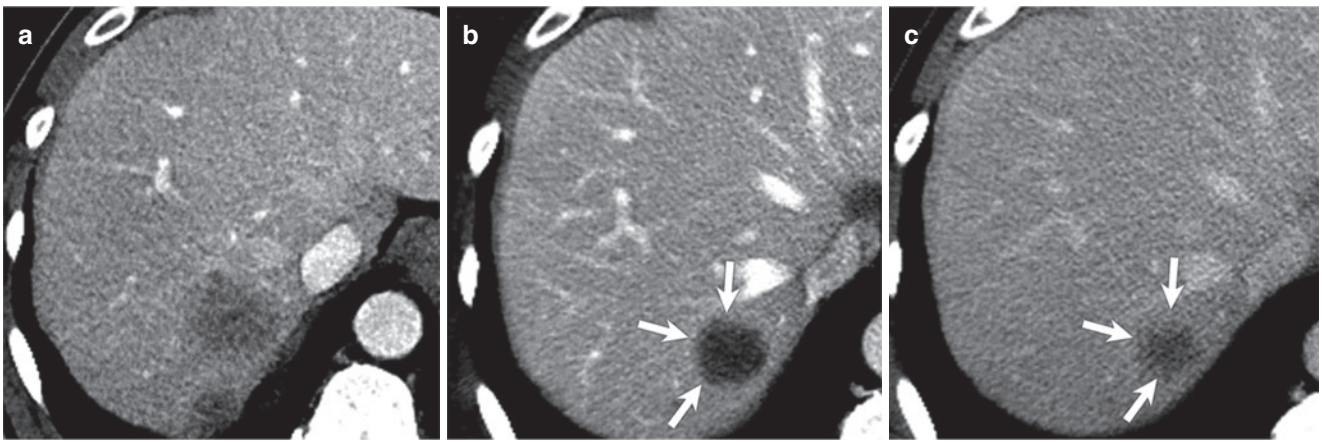

Fig. 45.8 Morphological changes characteristic of group 2. Baseline (**a**) and posttreatment CTs after 4 cycles of FOLFIRI/bevacizumab in portal and delayed phase (**b** and **c**) show a decrease in the amount of soft tissue but margins remain ill-defined with a subtle peripheral rim of higher attenuation than the center (*arrow* in **b**). Delayed images, unlike the case in Fig. 45.6, show increased enhancement and apparent decreased size of the metastasis with a more obvious peripheral enhancing rim (*arrow* in **c**)

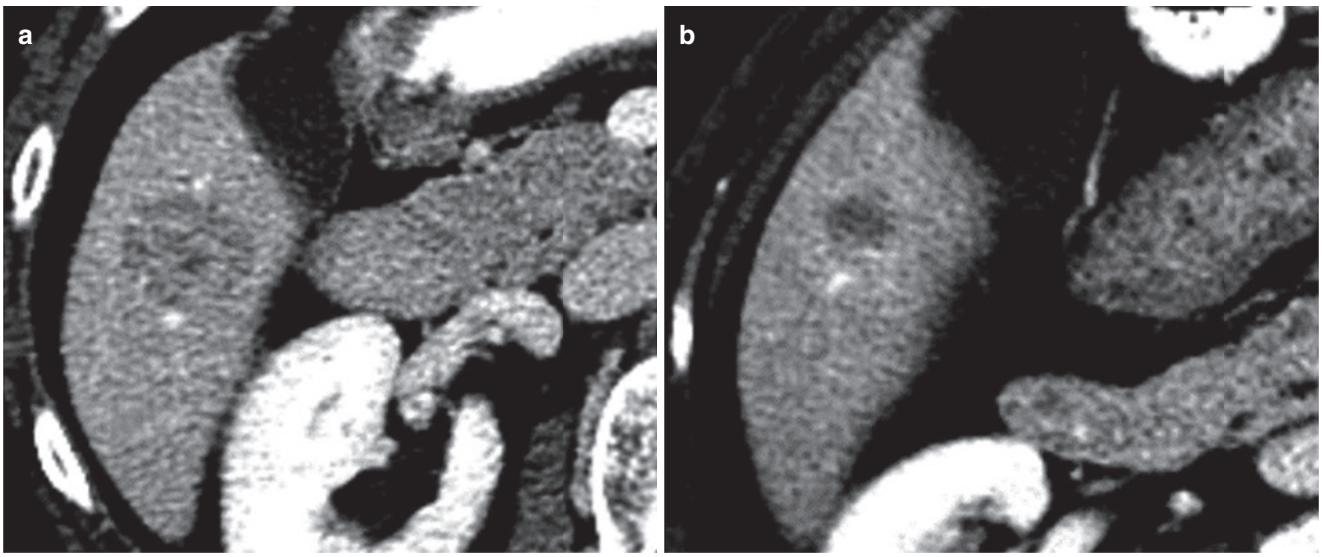

Fig. 45.9 Morphological changes characteristic of group 3. Baseline (**a**) and posttreatment CT after 6 cycles of FOLFIRI/bevacizumab (**b**) show decreased size but no morphologic change in the content or contours of the tumour. There is a response by size but not by morphology

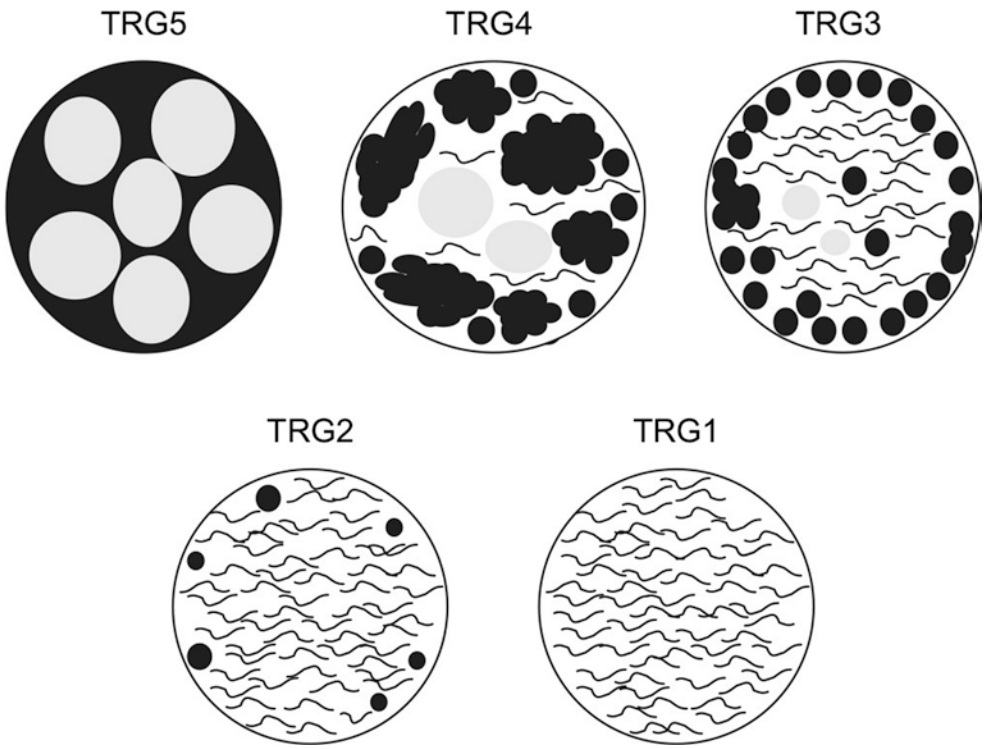

Fig. 45.10 Pathologic response: Tumour regression grade (TRG) scoring system. Reprinted from Rubbia-Brandt et al., Ann Oncol. 2007. *TRG1* absence of residual cancer and large amount of fibrosis; *TRG2* rare residual cancer cells scattered throughout the fibrosis; *TRG3* more residual tumour cells but fibrosis predominates; *TRG4* residual cancer cells predominate over fibrosis; and *TRG5* no signs of regression. Black area: tumour cells; gray area: necrotic area; fibrils: fibrosis. Optimal morphologic response corresponds to TRG1 or 2

and acellular mucin in responding CLM [24]. Consequently, pathologic response in CLM can be assessed either by an estimation of the percentage of viable residual tumour cells [23], by an estimation of the ratio of fibrosis/viable cells or tumour regression grade (Fig. 45.10) [25], or by measuring the tumour thickness at the tumour-normal liver interface (Fig. 45.11) [26, 27].

After treatment, residual viable tumour cells are seen predominantly at the tumour-normal liver interface [25, 26, 28]. Tumours in group 1 were shown to be replaced by fibrosis and have a very small amount of residual tumour cells at the tumour-normal liver interface at pathology compared to tumours in group 2 or 3 (Fig. 45.10).

Using a semi-quantitative assessment the percentage of residual tumour cells ranged from 10 to 30% for tumours in group 1 in Chun et al. study [20]. The median viability of the tumour was 10% (interquartile range [IQR], 8–20%) in group 1, in a study by Nishioka et al. [29]. The median tumour thickness at the tumour-normal liver interface measured 0.5 mm (IQR, 0.5–1.5 mm) in group 1, 3 mm in group 2 (IQR, 1.4–6 mm), and 6.3 mm in group 3 (IQR, 4.3–10 mm) [26]. Figure 45.11 illustrates the radiology-pathology correlation between morphologic response on imaging and tumour thickness at the tumour-normal liver interface at pathologic assessment in patients with poor and good morphologic response.

Both RECIST and morphologic response correlated with the pathologic response. Major pathologic response (<50% of residual tumour cells) was more sensitively predicted by morphologic response. Semi-quantitative assessment in a cohort of 209 surgical patients showed the rate of major pathologic response to be 92% for patients with optimal morphologic and 59% for suboptimal morphologic response while by RECIST the rate of major pathologic response was 83% with PR and 66% with SD or PD [20, 21].

45.5.3 Definition and Validation of the Criteria

Patients with the group 1 morphology are classified as optimal responders for morphologic response. Patients with group 2 morphology are suboptimal responders and patient in group 3, non-responders.

Surgical cohorts: In a cohort of 209 patients who underwent hepatic resection for CLM, Shindoh et al. showed that CT morphologic response was observed in 47% of the 108 patients treated with BEV and only 12% of 102 patients that did not receive BEV, indicating that morphologic response is not specific to BEV, but less likely to occur in the absence of antiangiogenic therapy [21]. They determined that optimal morphologic response correlated with improved outcome (Fig. 45.12), both in recurrence-free (21.1 months vs. 11.8 months, $p = 0.004$) and overall survival (114.2 months vs. 49.0 months, $p = 0.0009$). Multivariate analysis confirmed that the optimal morphologic response was a significant prognostic factor for recurrence-free survival and correlated with a twofold increase in overall survival. In a smaller cohort of 86 surgical patients, Nishioka et al. con-

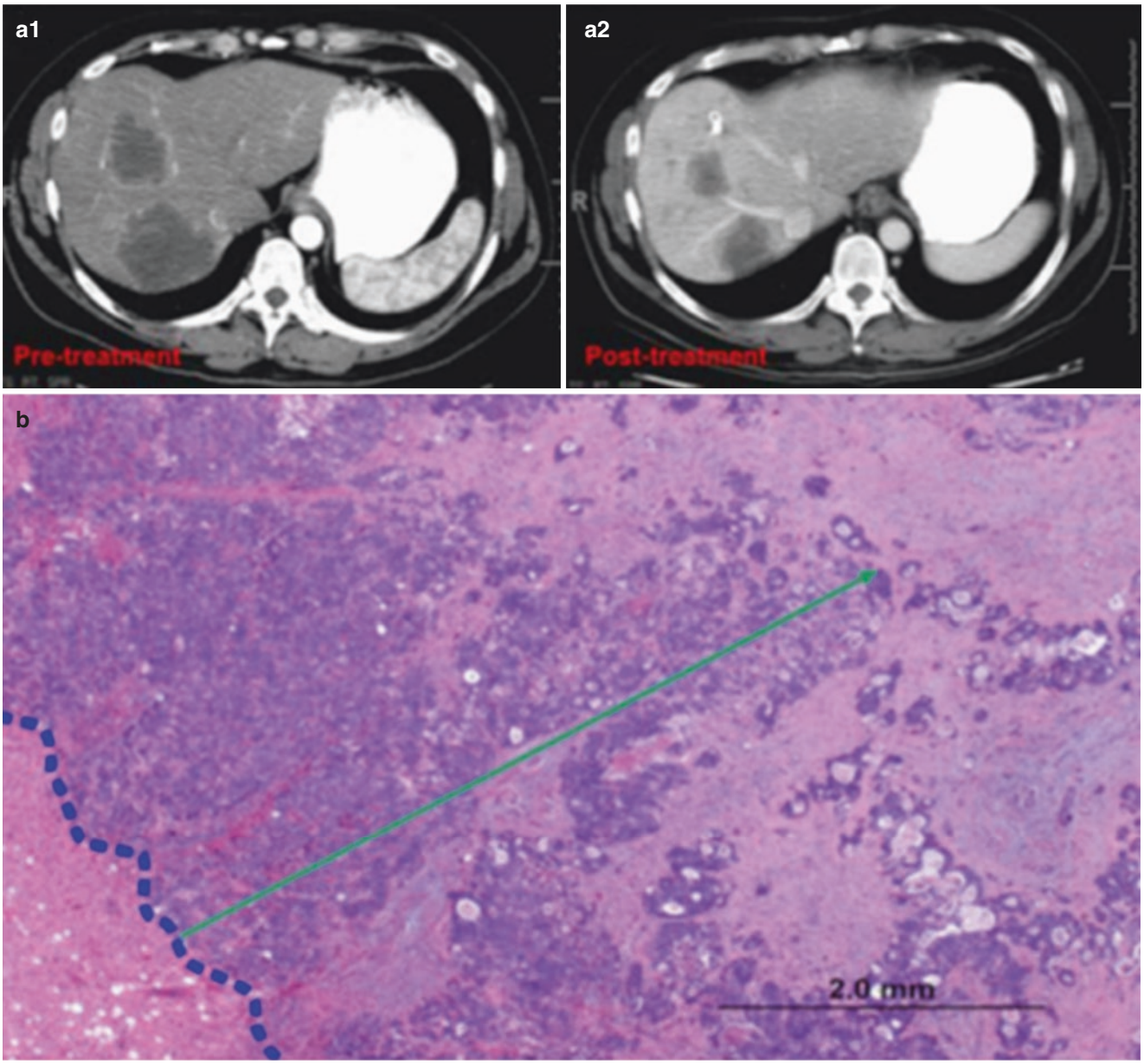

Fig. 45.11 Pathologic response illustrating: tumour thickness at the tumour-normal liver interface. Reprinted from Maru et al., Am J Surg Pathol 2010. Examples of pretreatment and posttreatment CT scan and HE-stained section of tumour from a patient with a poor response (**a1**, **a2**, **b**) and a patient with a good response (**c1**, **c2**, **d**)

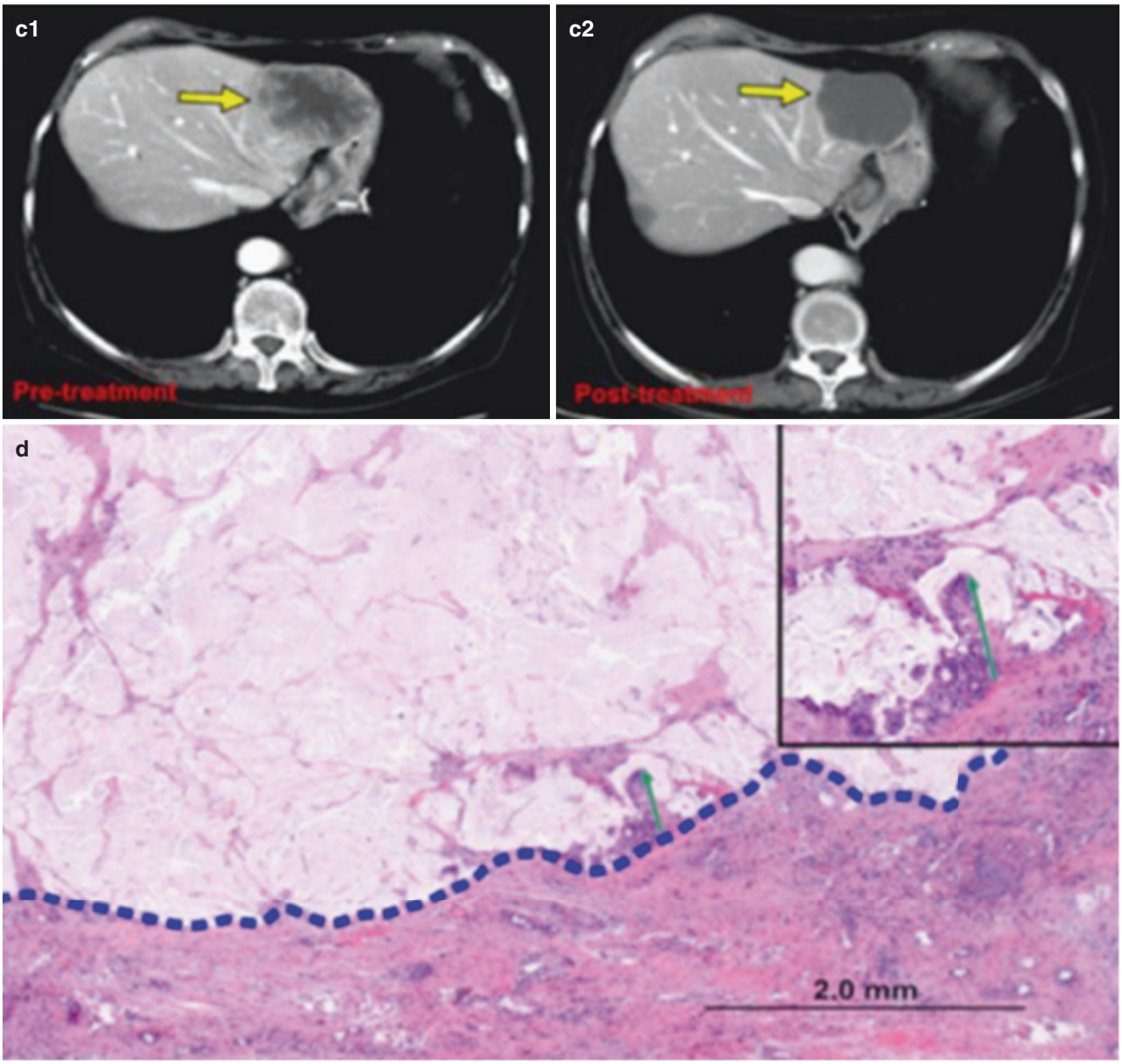

Fig. 45.11 (continued)

firmed these results [29]. Optimal morphologic response was seen in 22.8% of their patients and associated with a significant increase in OS and DFS. In both series, suboptimal response and no response were predictive of tumour recurrence [21, 29].

Medical cohort: In a cohort of 283 patients with unresectable CLM, half of them were treated first with BEV and the other half from a randomized study evaluating the addition of BEV to oxaliplatin-based chemotherapy. Optimal morphologic response at first or second restaging was strongly predictive of prolonged PFS in both groups. Optimal morphologic response at second restaging in the non-randomized cohort was significantly associated with OS (Fig. 45.13a) but not in the randomized cohort (Fig. 45.13b). Patients in the randomized cohort had advanced disease with extrahepatic metastases in 82 patients and only 29% received BEV, this may partially explain the lack of impact on OS in this group. In this study, patients who received BEV were 6.2 times more likely to achieve an optimal morphologic response [30].

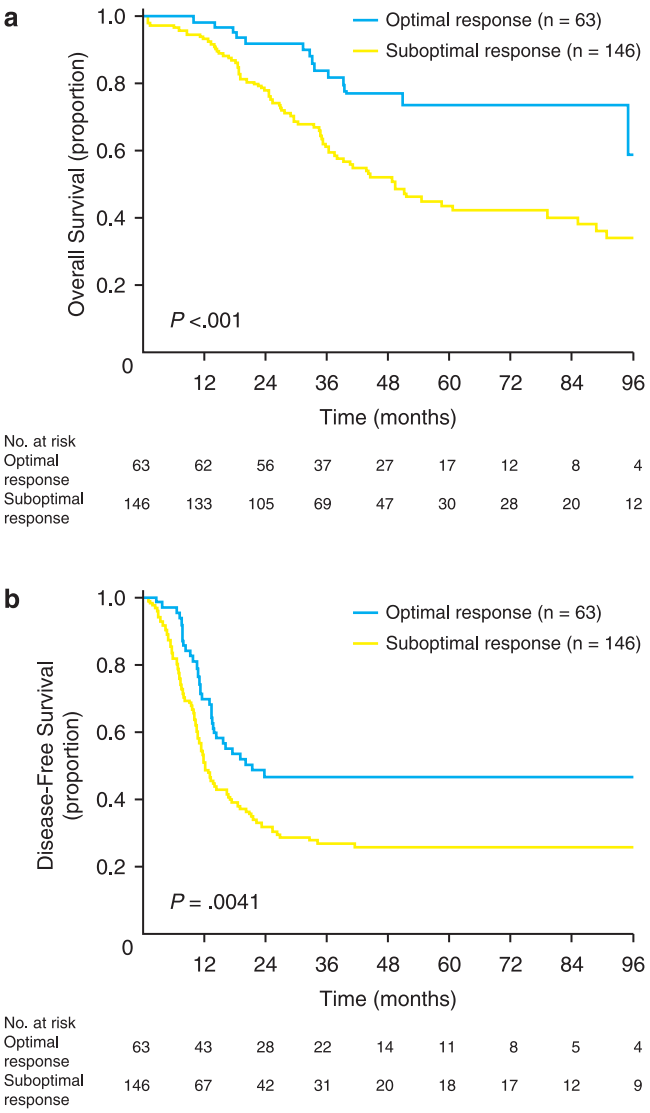

Fig. 45.12 Morphologic response and outcome in surgical patients. Reprinted from Shindoh et al. J Clin Oncol, 2012. (**a**) Overall survival and (**b**) disease-free survival by morphologic response in 209 patients undergoing resection of colorectal liver metastases after preoperative chemotherapy

In both medical and surgical patients, the morphologic response was evident at first restaging and did not correlate with RECIST response. The median time to achieve an optimal or suboptimal response was 2.5 months in the medical cohort [30]. Change in size is not a parameter assessed with morphologic response; however, morphologic response following BEV is associated with some degree of shrinkage and never associated with an increase in tumour size [31]. In patients with multiple metastases, the pattern of response is usually uniform (Figs. 45.5, 45.6, and 45.7) and mixed changes are rare (Fig. 45.14) [20, 21, 25].

Morphologic criteria are reliable early indicator of response and predictor of outcome. In practice, what matters most is the recognition of the optimal responder (group 1 pattern) as it is the pattern of response with potentially the largest impact on management. Notably, group 1 response to preoperative regimen has been shown to correlate with the decrease of micro metastases beyond a width of 1 mm from the tumour. Nishioka et al. found no difference between R0 and R1 resection in patient with group 1 response, similar results were reported by Andreou et al. These results support that for this subgroup of patients, surgery should not be denied even if a close margin is anticipated [32, 33].

45.5.4 Additional Points Regarding the Morphologic Criteria

Applicability to MRI: Although morphologic response assessments have been validated using CT, the principles are equally applicable to MR.

Image quality: The only obstacle to the application of these criteria is the image quality. Spatial and contrast resolution must be optimized for the assessment of small structure as noise interferes with the definition of the interface between normal liver and tumour, a key parameter of response. In addition, the availability of delayed images is helpful in difficult cases (Figs. 45.6 and 45.8). There is to this day no valid data supporting cancer risk from CT imaging nor data supporting the validity of the Linear Non-Threshold Model for radiation risk assessment. Hence, there is no reason not to optimize the radiation dose in these patients and use multiphasic CT when indicated [34].

Nonspecificity: These criteria are not specific to the type of therapy but are most frequently observed with drug that have an antiangiogenic activity. They are seen in 25–40% of patients receiving BEV-containing therapy. They have been used successfully with regorafenib [35–37]. They are also accurate marker of response albeit at a much lower rate in patient receiving exclusively cytotoxic chemotherapy (Fig. 45.15) [21, 30].

Subjectivity: In spite of their simplicity, short learning curve and strong interobserver agreement [20, 29, 36], morphologic criteria are underused possibly because of hesitancy to use a subjective method and limitations encountered with suboptimal CT technique. Attempts have been made to quantify objectively the morphologic response but unlike the Choi criteria, simple density measurement using ROI does not correlate reliably with response in CLM, probably because CLM have a more complex pathology and available treatment options than GIST [20, 36, 37]. Computer analysis of the heterogeneity of the tumours however is possible with the advancement of radiomics. Radiomics is a new method of analysis of imaging studies that is going beyond visual interpretation. In this process, images are converted into

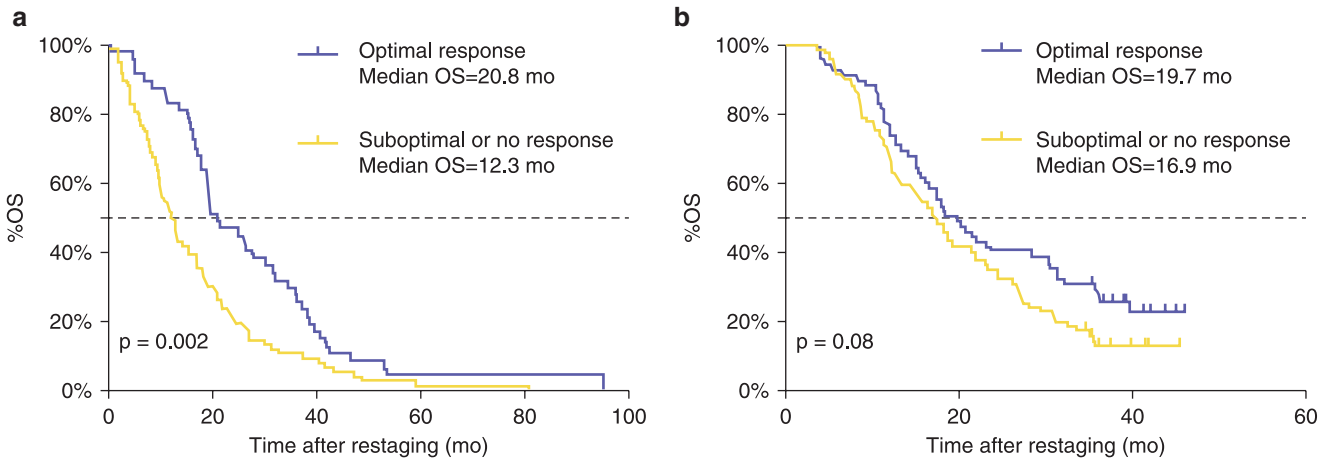

Fig. 45.13 Morphologic response and outcome in medical patients. Reprinted from Mazard et al. Gut 2018. (**a**) OS in the non-randomized population, receiving BEV-containing chemotherapy, in responders and non-responders by morphological criteria at second (16 week) restaging. (**b**) OS in the population randomized to receive BEV or placebo with cytotoxic chemotherapy in responders and non-responders by morphological criteria at second (12 week) restaging. *OS* overall survival

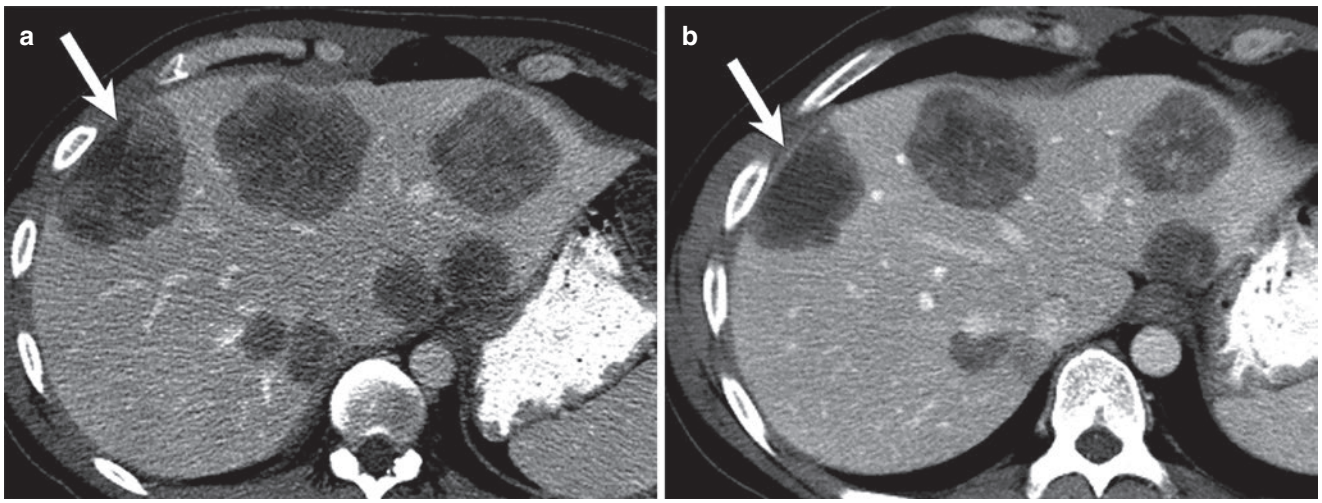

Fig. 45.14 Morphological changes characteristic of group 3 and group 2. Baseline (**a**) and posttreatment CT after 5 cycles of FOLFIRI/bevacizumab (**b**) show group 2 response in segment 8 liver metastasis, note decrease in the amount of soft tissue (*arrows* in **a** and **b**) and group 3 response in the other metastases

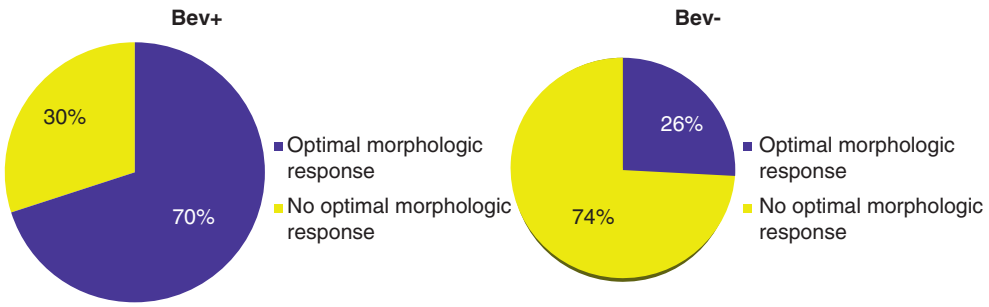

Fig. 45.15 Correlation between Bevacizumab-containing chemotherapy and optimal morphologic response. Optimal morphologic response is not specific to antiangiogenic therapy, it is also seen with cytotoxic chemotherapy at a lower frequency. Courtesy Dr. Mazard, based on data presented in the article by Mazard et al. Gut 2018

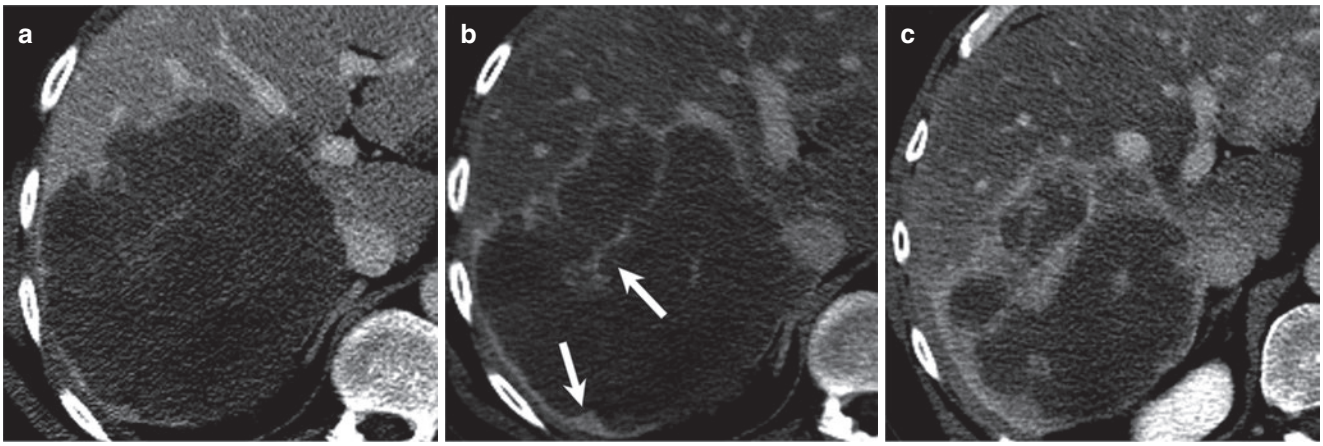

Fig. 45.16 Progression after optimal morphologic response with reversal to the pretreatment pattern. CT scan after 8 cycles of FOLFIRI/bevacizumab show optimal morphologic response (**a**). Serial follow-up CT 4 months after treatment change to FOLFIRI and panitumumab (**b**) shows subtle increased peripheral soft tissue thickening, increased thickness, and nodularity of internal septations (*arrows* in **b**). Follow-up CT 3 months after **b** (**c**) shows further progression. Reversal to the pretreatment pattern (seen in Fig. 45.5b) is an early sign of progression

minable data that can be analyzed [38]. Recently Dohan et al. have defined a radiomics signature predicting early poor outcome at 2 months in patients treated with FOLFIRI and BEV as first-line treatment, and hence breaking the ground for a possible objective measure of morphological response. They developed a radiomics nomogram that combines a measure of the tumour size, measure of the attenuation, and measure of kurtosis. Kurtosis reflects the degree of heterogeneity of the tumour. Regions of high kurtosis correlate with a larger distribution of tissue types, while a decrease in kurtosis reflects the tendency of the tumour to become more homogeneous [31].

45.5.5 Progression After Morphologic Response

Imaging features of progression after response to a BEV-containing regimen are distinctive and may early on, be limited to a reversal of the pattern of response without change in size. Metastases tend to evolve from a pseudocystic configuration back to the heterogeneous poorly marginated appearance of untreated metastases. These changes often precede tumour growth and are observed predominantly at the tumour-normal liver interface as new areas of increasing soft tissue thickening (Figs. 45.16 and 45.17) or as nodules that grow into the adjacent liver parenchyma (Fig. 45.18). Finally, the development of new lesions (Fig. 45.19) among stable treated metastasis can be observed. In contrast to tumour response, which is most often uniform, early recurrence often occurs in only one or a few lesions. Therefore, the detection of early recurrence requires an evaluation of each treated lesion and an active search for new nodules in the intervening parenchyma. In a medical cohort, Mazard et al. showed that morphologic progression preceded progression by RECIST by approximately 2 months [30].

45.5.6 Correlation of Imaging Response and Histologic Growth Pattern

Resistance to antiangiogenic therapy in CLM has been linked to the histological growth pattern of the metastasis. Metastases gain their vascular supply through angiogenesis but can also do so by vessels co-option where instead of inducing new vessels growth they incorporate preexisting vessels from surrounding tissue. Frentzas et al. have demonstrated that patterns of growth supported by neoangiogenesis were prevalent in optimal responder on imaging while vessel co-option was the prevalent mechanism in patients that responded poorly to BEV and in patients that progressed following response to BEV-containing chemotherapy [39].

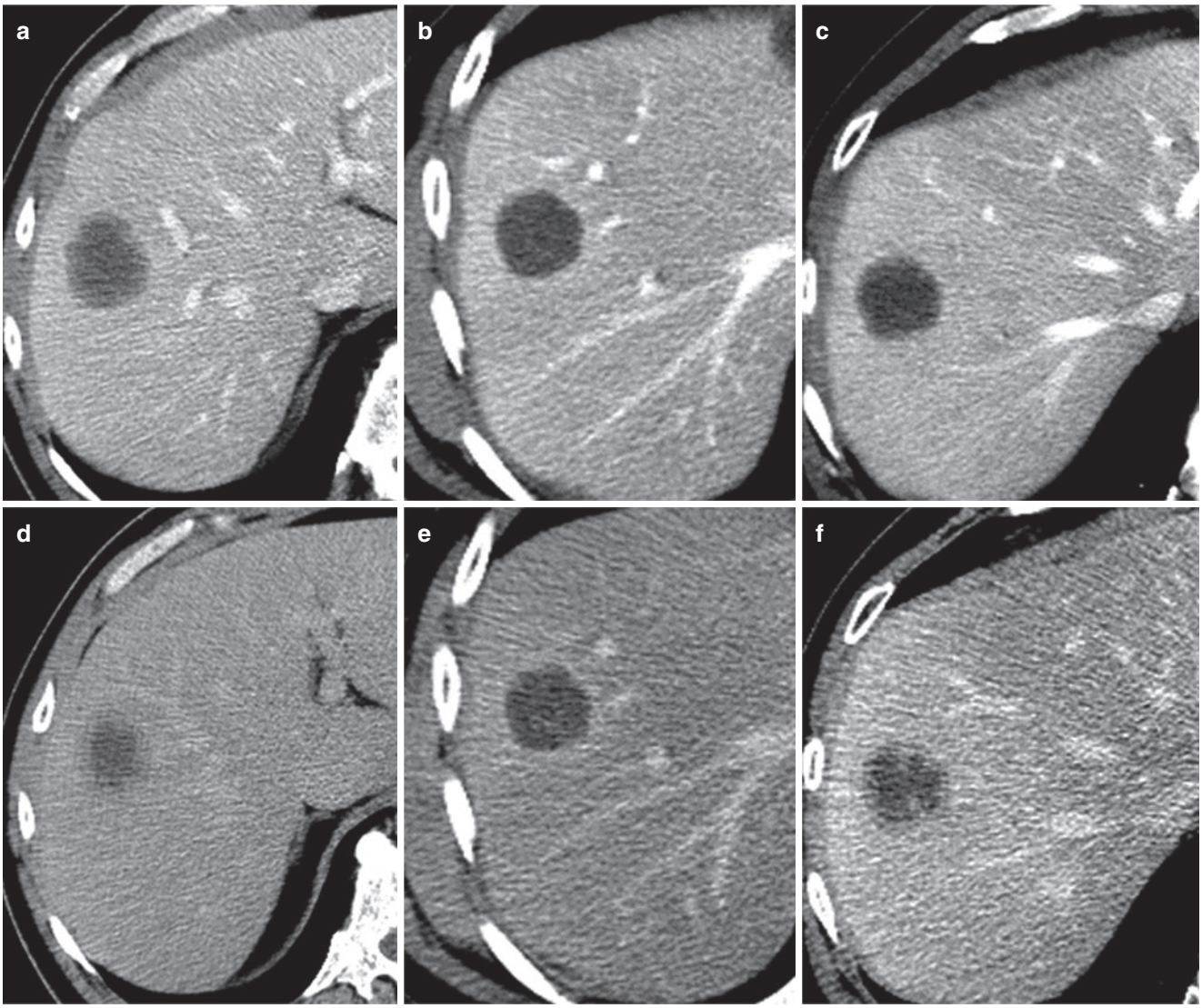

Fig. 45.17 Value of delayed images to confirm recurrence. Baseline CT Portal phase (**a**–**c**), delayed phase (**d**–**f**) at baseline (**a**, **d**), after 6 cycles of FOLFOX/bevacizumab (**b**, **e**) and follow up after treatment interruption (**c**, **f**). Immediate posttreatment images (**b**, **e**) show optimal response of liver metastases. After treatment interruption, increased peripheral soft tissue thickening consistent with progression is more evident on delayed phase (**f**) than the portal phase (**c**)

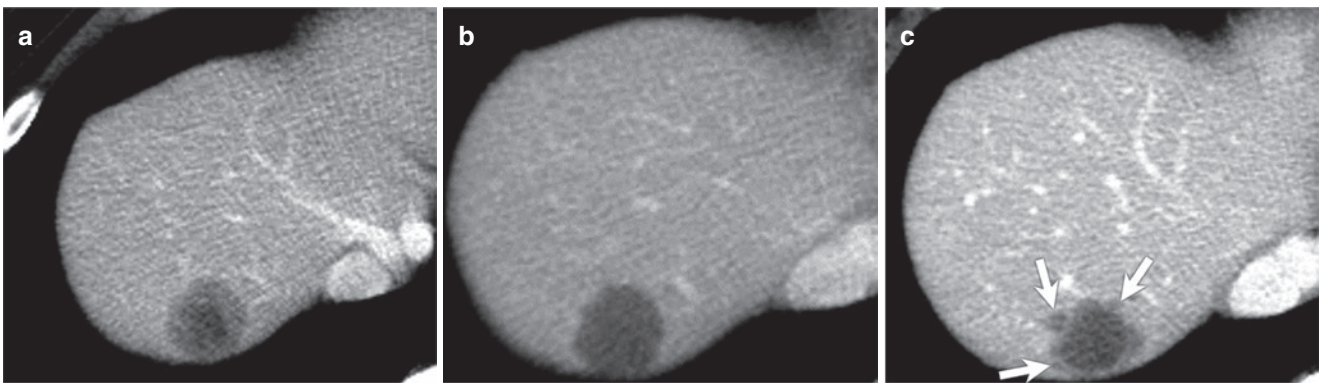

Fig. 45.18 Progression after optimal morphologic response: new peripheral nodules. Baseline (**a**) and serial posttreatment scans (**b** and **c**) show initial optimal morphologic response (**b**) followed by early progression in the form of new nodularity at the tumour/normal liver interface (*arrows* in **c**)

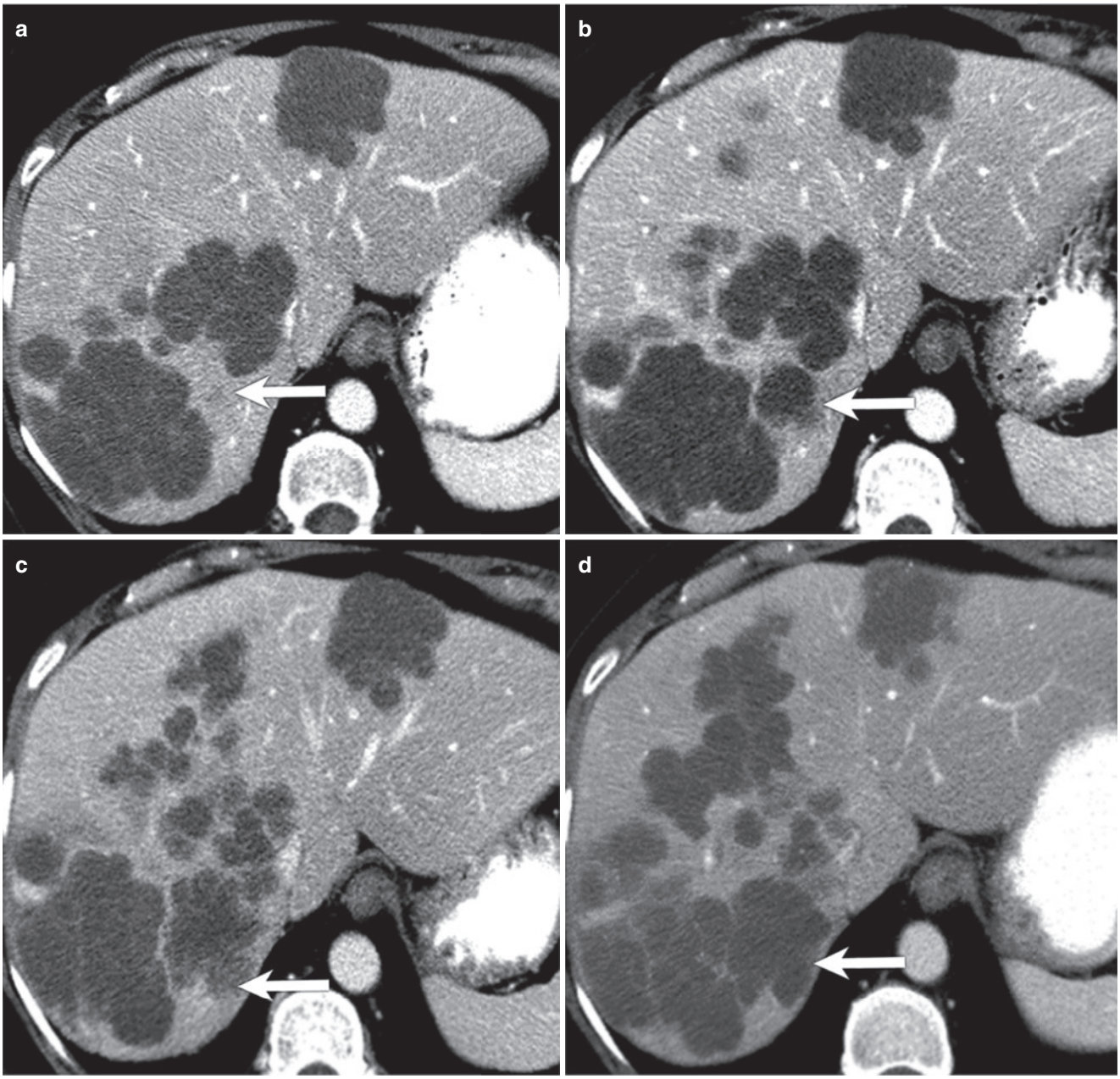

Fig. 45.19 Progression after optimal morphologic response: new liver metastasis. Optimal morphologic response to FOLFOX and BEV (**a**). Serial follow-up studies after Irinotecan for 8 months show a subtle new lesion (*arrow* in **a**) and progression on follow-up scans (*arrows* in **b** and **c**). The patient then received FOLFIRI and bevacizumab with optimal response in this new metastasis that has become homogeneously hypoattenuating and well marginated (*arrow* in **d**)

45.6 Imaging Response After Immunotherapy

Approximately 5% of patients with metastatic colorectal carcinoma have tumours that are mismatch-repair deficient, also called microsatellite instability-high (MSI-H). These tumours are generally poorly responsive to conventional cytotoxic chemotherapy, but immunotherapy using immune checkpoint inhibitors (ICI) significantly improves the outcome. There are currently three ICI approved: pembrolizumab, nivolumab, and ipilumab for colorectal carcinoma; these molecules block the activation of immune checkpoints that impair the host immune response to tumour cells consequently reactivating the normal immune response against tumour cells [40, 41]. Strategies to expand the benefit of immunotherapy to the more common, proficient mismatch-

repair, carcinoma is being explored in an effort to expand the indication for immunotherapy [42].

Response after ICI therapy differs from the patterns of response previously discussed and can be difficult to assess. The response may not be evident until after long delays and can continue over prolonged periods (even after the agent is no longer administered). In a small subset of patient tumour growth may accelerate, this is called hyper progression and is associated with poor survival outcome [43]. Immunotherapy has also been associated with pseudo progression, defined as improvement in spite of tumour growth or the development of new lesions at the beginning of therapy. Pseudo progression's main risk is to be misclassified as progression. Pseudo progression is not well understood and may be explained by inflammation, infiltration of T cells into tumours, or the delay between the start of treatment and efficacy. One needs to keep in mind that pseudo progression is rare and increased tumour burden is more likely due to disease progression [41, 44–47]. Early Tumour Shrinkage (ETS) and Depth of Response (DpR) may be of value in assessing response in patients receiving ICI [48].

New response imaging criteria to assess immunotherapy have been developed but data for tumour other than melanoma are still limited. Immune-related Response Criteria (irRC), developed in 2009, uses bidimensional measure of tumour size and requires confirmation of progression on two consecutive studies at least 4 weeks apart; the Immune-modified Response Evaluation Criteria in Solid Tumours (imRECIST) use unidimensional measurement to unify the method with RECIST criteria, finally Immune-related Response Evaluation Criteria in Solid Tumours (irRECIST) introduces the notion of "unconfirmed progression" [41].

Discrepancy between radiological and pathological response has been observed in a small series indicating that residual tumour on imaging may not indicate active disease following response to anti-PD1-based therapy. However, larger prospective studies are warranted [49].

Patients treated with ICI develop abnormal radiographic findings of immune-related adverse effects. The mechanism is presumed to be autoimmunity secondary to drug-induced misdirected stimulation of the immune system. They can involve various organs, are of variable severity and commonly manifest during the first 3 months. They can mimic progression or infection. Colitis is a common event, either diffuse or focal and associated with diverticulitis. Pneumonitis is rare but potentially life-threatening. Hepatitis is uncommon and associated with hepatomegaly and periportal edema in severe cases [41, 45, 50, 51].

The place of PET/CT in response assessment remains to be defined. Interim PET/CT examinations could aid as an early response assessment and help to identify atypical response patterns, especially hyper progression or pseudo progression. PET/CT for ICI therapy response assessment is not yet ready for a broader application [52].

PET/CT is sensitive for the detection of immune-related adverse effects [51, 53]. There is ongoing research to use functional, molecular imaging and radiomics notably to identify imaging biomarkers predicting the response to immune therapy and to develop more specific tracers than F18 FDG [51–53].

45.7 Role of Functional Imaging

Techniques that aim to evaluate the physiological characteristics of the tissues rather than their morphology can also be used to assess response. Response assessment with diffusion weighted MRI, perfusion imaging, and the use of radiotracers are under investigation [44]. So far, response assessment with these techniques has not been integrated into routine clinical practice. Of these techniques, diffusion weighted (DW) imaging including apparent diffusion coefficient (ADC) images is widely available on modern scanners and seems to be inching closer towards integration into clinical practice [54]. However, wide variations exist in the imaging technique (e.g., the b values used) and assessment of changes in ADC (e.g., measuring whole lesion versus periphery versus single representative slice) interfering with standardization. Typically, highly cellular tumours show higher signal on DWI images and lower signal on ADC map images. Decrease cellularity with response can be measured. Liu et al. analyzed 126 patients with CLM receiving bevacizumab containing chemotherapy in the neoadjuvant setting. A decrease in arterial enhancement and increased ADC value were seen on posttreatment MRIs compared to baseline and used to define optimal cutoff value to differentiate responders and non-responders. The method was tested on a validation cohort and newly developed RECIST (D-RECIST) criteria that have significant prognostic value were defined [55]. Boraschi et al. evaluated posttreatment ADC changes in 24 patients with CLM undergoing surgical resection after neoadjuvant chemotherapy and also concluded that ADC changes are reliable biomarkers of response [56]. Donati et al. analyzed ADC values of 106 liver metastases after neoadjuvant chemotherapy and showed significantly higher ADC values in lesions with good response and lower in lesions with poor response [57]. In our institution, due to predominant use of CT for response assessment, DW MRI is not routinely used for response assessment and is mainly for further characterization of lesions identified on other MR sequences or CT.

A multitude of methods has been proposed with respect to response assessment with PET/CT. Lastoria et al. analyzed with 50% decrease in total lesion glycolysis and maximum

SUV before and after one cycle of chemotherapy in 33 patients with CLM treated preoperatively with FOLFIRI plus bevacizumab. They compared PET/CT results with standard RECIST and concluded that PET/CT assessment is superior to CT RECIST to predict long-term outcomes [58]. Lau et al. evaluated semi-quantitative PET/CT parameters including proportional changes in max SUV, metabolic tumour volume, and total glycolytic volume (TLG) and correlated with CT RECIST and tumour response grade in 80 patients with CLM treated preoperatively. They concluded that change in SUVmax was predictive of recurrence-free survival and overall survival [59]. Nemmeth et al. introduced new PET/CT parameters: standardized added metabolic activity (SAM) and normalized SAM, also correlating with OS and PFS and performing better than SUV max and TLG [60]. In our institution, PET/CT is not routinely used for response assessment but is used as a problem-solving modality.

In addition to early detection of response, these techniques may allow to predict treatment response based on the pretreatment characteristics of the tumours, a potential also explored with the radiomics technique [31, 44].

45.8 Assessment of Chemotherapy-Induced Liver Toxicity

Improvement in chemotherapy has increased survival for patients with CLM and combined with development in surgical techniques has expanded tremendously indication for liver resection. Preoperative chemotherapy can allow conversion to resectability for patients who were deemed unresectable at baseline. Unfortunately, chemotherapy can result in parenchymal injury that affects liver function and regeneration. Surgical candidates are exposed to an increased risk of perioperative morbidity and mortality [61, 62].

The type of injury is regimen-specific. Irinotecan-based chemotherapy has been shown to be associated with nonalcoholic steatohepatitis (NASH) with an increased risk of postoperative mortality notably in patients with high BMI. The diagnosis of NASH cannot be done on CT but the development of fatty changes during treatment are important to report particularly in the preoperative setting [63].

Oxiplatin-based chemotherapy induced an injury of the hepatic sinusoids and occurs between 50 and 80% of the patients [64]. Variable degree of portal hypertension can be recognized on imaging. An increase in the size of the spleen has been shown to correlate with an increasing grade of sinusoidal injury [65]. The change in the size of the spleen can be very subtle and sometimes appreciated only by comparison to the baseline images (Fig. 45.20). In addition to the evaluation of the spleen, screening for varices should also be systematic (Fig. 45.20).

Both hepatic steatosis and sinusoidal injury have been reported to rarely manifest as a focal lesion that can be confused with metastasis [66]. A long-term consequence of chemotherapy-induced sinusoidal obstruction is the development of focal nodular hyperplasia. These vascular lesions can develop after the sinusoidal injury has resolved, sometimes several years after completion of chemotherapy. Recognition is important to avoid unnecessary biopsy. If needed confirmation can be obtained with Eovist MRI [67]. Finally, long-term chemotherapy (7 cycles) has been shown to induce a decrease in the total liver volume [68].

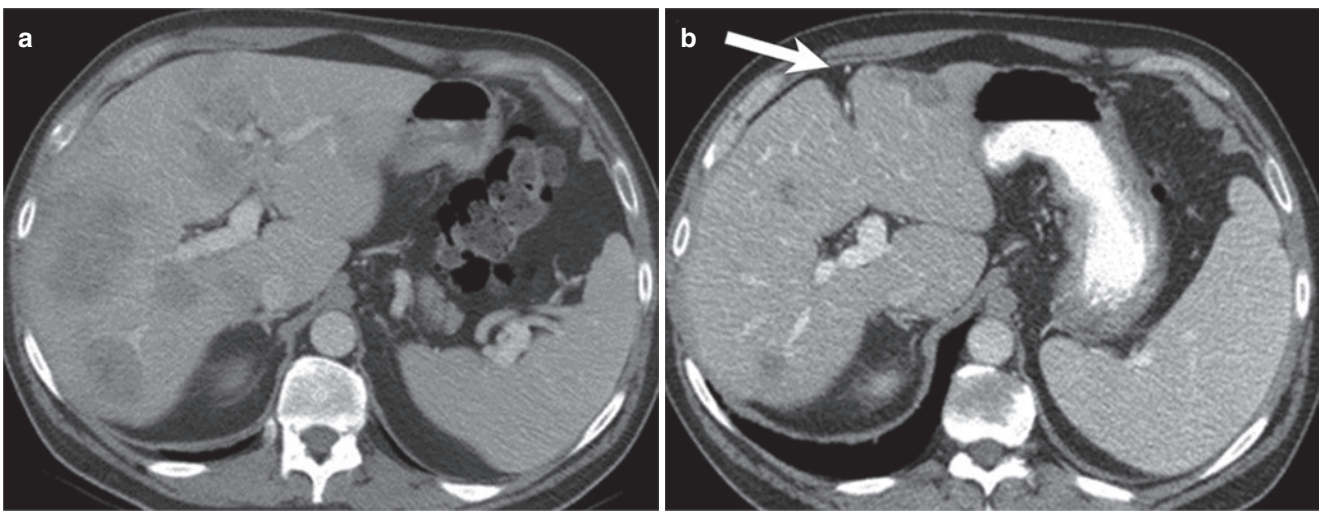

Fig. 45.20 Chemotherapy-induced liver sinusoidal injury in two patients: Patient 1 (**a** and **b**): Baseline CT (**a**) and follow-up CT after 6 months of chemotherapy with FOLFOX and bevacizumab (**b**) show decreased size of multiple liver metastases but increasing splenic size and recanalization of paraumbilical vein consistent with portal hypertension. Patient 2 (**c** and **d**): Baseline CT (**c**) and follow-up CT after 8 months of chemotherapy with FOLFIRI and bevacizumab (**d**) show improved liver metastases and subtle periesophageal collaterals (*arrow* in **d**) in addition to increased splenic size (not shown) consistent with portal hypertension

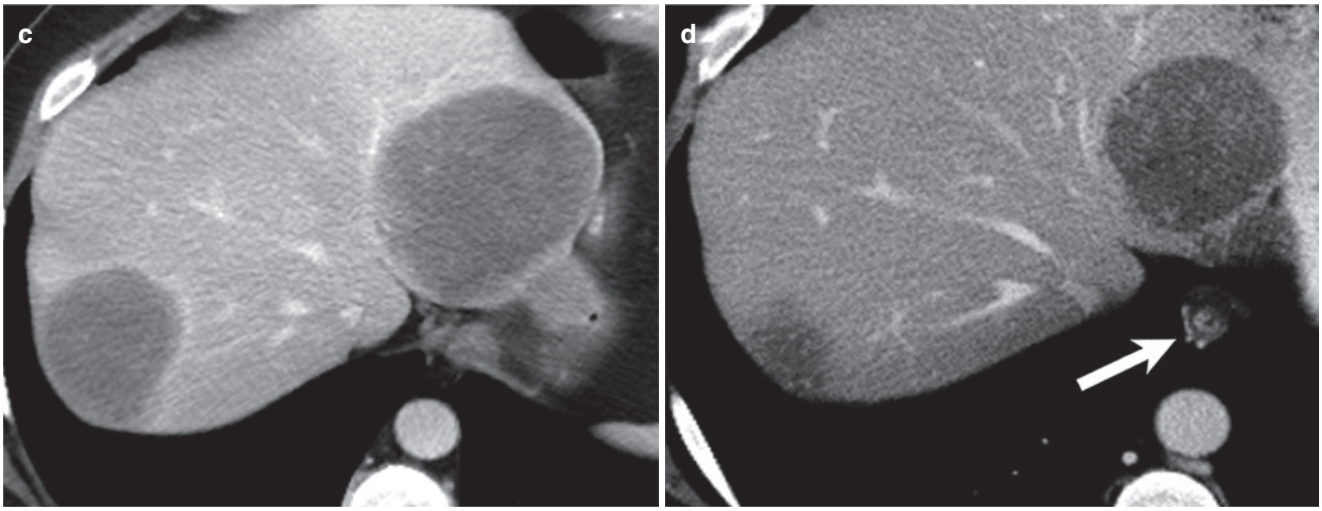

Fig. 45.20 (continued)

45.9 Response Assessment After Locoregional Therapy

45.9.1 Ablation

Liver ablation is used routinely to treat unresectable CLM that are smaller than 5 cm. The main difficulty with ablation is accurately estimating the completeness of ablation during the procedure and at follow up. The width of the ablative margin, defined as the thickness of the normal peritumoral parenchyma included in the ablation zone is the best predictor of successful ablation. Local recurrence occurs with a high concordance rate at sites of insufficient ablative margin. A margin of at least 5 mm has been shown to be associated with the best local control in colorectal carcinoma [69–71].

At imaging follow up, efforts should be made at appraising the width of the ablation margin. This can be done subjectively or objectively comparing the peri-lesional vascular network before and after ablation [70]. The width of normal parenchyma that has been included in the ablation zone (i.e., the ablative margin) can be inferred by comparing the distance between the point of reference in the liver parenchyma (i.e., vessels) and the tumour edge with the distance between the same point and the edge of the RFA defect (Fig. 45.21). For each RFA defect, several reference points are used. The assessment requires an optimal technique with good vascular opacification and multiplanar reformat [69, 70].

More recently, nonrigid registration software that enables image fusion of pre and post-ablation CT studies are being developed to provide accurate registration during and after the procedure. These provide a more accurate volumetric assessment of the ablation margin and improve accuracy and effectiveness of ablation [72].

45.9.2 Transarterial Radioembolization

Transarterial radioembolization (TARE) is the transcatheter intra-arterial injection of embolic agents loaded with radionuclides, such as iodine-131 (^{131}I) or rhenium-188 (^{188}Re)-labeled lipiodol or yttrium-90 (^{90}Y)-labeled microspheres. The rationale for radioembolization is based on the unique characteristics of blood flow to liver tumours, which receive 80–100% of supply from hepatic artery, once they reach 3 mm in diameter. Thus, intra-arterial delivery of these therapeutic agents targets preferentially tumour tissue, while sparing the surrounding normal liver parenchyma, which derives the majority of blood flow from the portal vein [73]. In addition, normal hepatocytes are highly sensitive to radiation greatly limiting the use of external beam radiotherapy in these patients. Tumour response to ^{90}Y-TARE or other radioembolotherapies is assessed by changes in tumour size and reduction in tumour vascularity after treatment. In responding patients, the median time to radiological response using a combination of size and vascular enhancement is 29–30 days. Based on this timeline, early imaging 4–6 weeks after treatment is critical to assess therapeutic failures identified primarily by unchanged contrast-enhanced patterns, when compared to the pretreatment scans. Using size measurements alone to determine treatment adequacy leads to much longer response times, due to the presence of confounding intra-lesional hemorrhage and edema. Treatment-related edema leads to an increase in lesion size and has been reported 19–75 days (mean 31 days) after TARE. Thus, increase in lesion diameter cannot be trusted, in isolation, to determine response during this period. After that, patients should be followed every 3 months with the cross-sectional modality of choice [74–77].

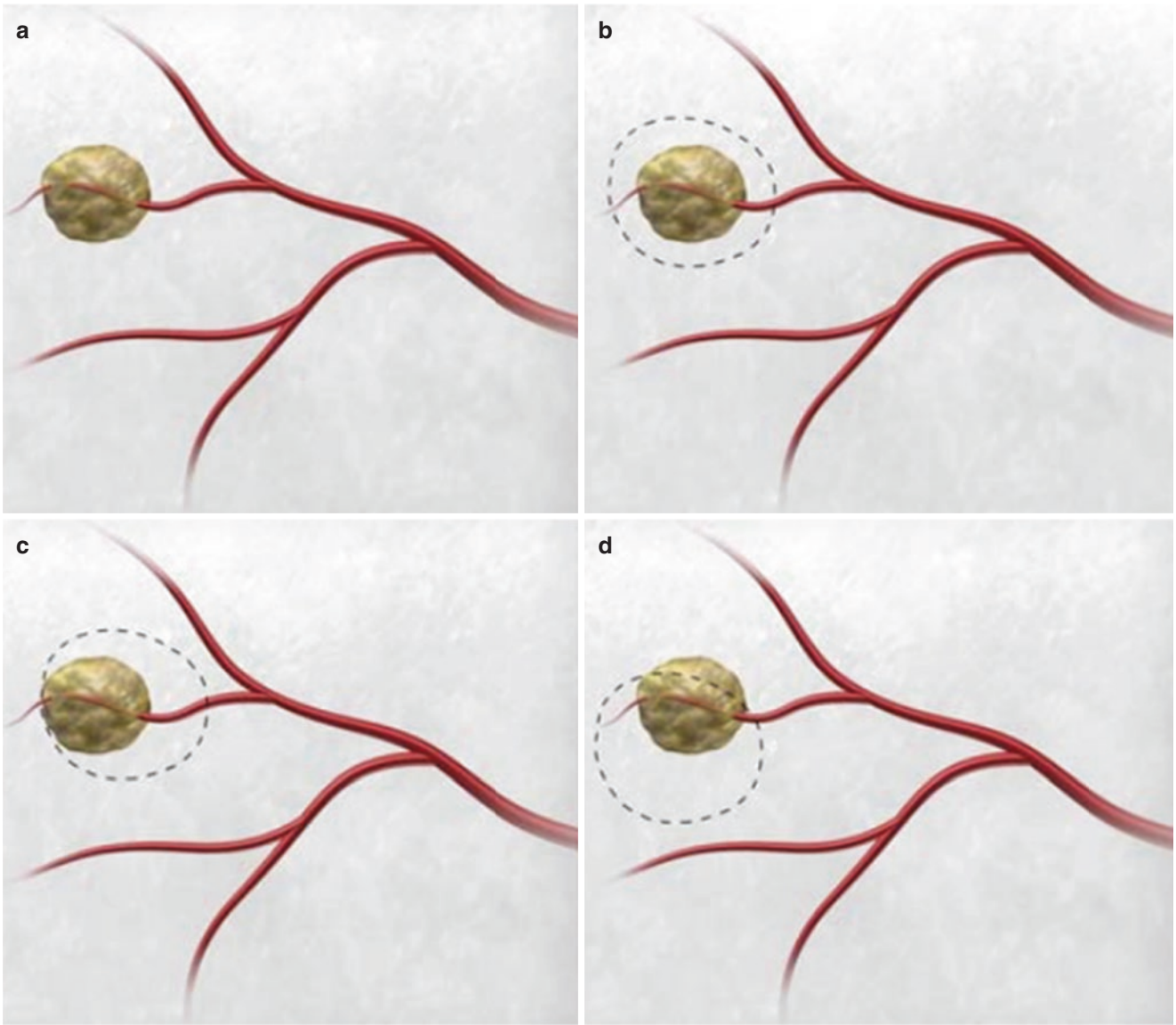

Fig. 45.21 Schematic representation of the scoring of the ablation margin. Reprinted from Yedururi et al. JCAT 2017. Schematic representation of an index liver lesion with normal vessels around the lesion (**a**). Schematic representation of the RFA defect (*dotted line*) superimposed on the index liver lesion illustrates a wide ablation margin (**b**). Schematic representation of the RFA defect (*dotted line*) superimposed on the index liver lesion illustrates a close ablation margin (**c**). Schematic representation of the RFA defect (*dotted line*) superimposed on the index liver lesion illustrates an incomplete ablation margin with a gross residual tumour (**d**)

Multiphasic MR and CT are the primary imaging modalities used to follow up patients undergoing TARE. Due to the shortcomings described above, different imaging tools, as well as novel MR sequences have been tried to improve diagnostic accuracy and enable earlier detection of treatment failures. PET and more recently PET/CT, and diffusion weighted MRI are emerging as surrogate methods for determining early response to TARE [74–76, 78]. Barabasch et al. evaluated response using size, contrast enhancement, SUV changes, and ADC changes in 35 patients who received ^{90}Y TARE for liver metastases (of which 20 had colorectal liver metastases). These patients underwent PET/CT and MRI within 6 weeks before and 6 weeks after radioembolization. They used RECIST for size response, subjective assessment for contrast enhancement, and an increase of minimal apparent diffusion coefficient (ADC min), or decrease of maximum standard uptake value (SUVmax) by at least 30% as a positive response on MRI and PET/CT. They did not observe statistically significant changes in size and contrast enhancement before and after treatment but did observe statistically significant changes in SUVmax and ADCmin in that context. They reported sensitivity, positive and negative predictive values to predict response of 96%, 96%, and 92% for MRI and at 65%, 88%, and 56% for PET/CT. These findings sup-

port the potential superiority of DW MRI over PET/CT for early response assessment in patients with hepatic metastases treated with TARE [78], as residual restricted diffusion suggests persistent viable disease. For those patients undergoing TARE with lipiodol-based therapies, the use of MR is recommended since this agent causes substantial beam-hardening artifact on CT.

The impact of ^{90}Y TARE is not limited to the targeted tumour, but also to the normal liver parenchyma in the treated segments and an adequate evaluation must include the assessment of the remaining liver. Persistent peripheral enhancement up to several months following treatment has been attributed to preferential flow to the periphery of the tumour and induced radiation changes in the surrounding liver. Transient perivascular edema representing post-radiation changes in a perivascular distribution has also been described [74, 75, 79]. Areas of ischemia in the vascular territory of the treated tumour results in geographic areas of hypoattenuation devoid of mass effect and vessels, best seen in portal venous phase. Eventually, ipsilateral hepatic lobar volume loss, contralateral hypertrophy, hepatic fibrosis, and capsular retraction will be seen in the remaining liver parenchyma and expose to the risk of portal hypertension [74, 75, 79, 80].

45.10 Conclusion

Accurate imaging response is contingent on optimal image quality, baseline scan of excellent quality, and adequately timed in relation to the beginning of treatment. Suboptimal images expose to the risk of inaccurate staging which decreases the chances of R0 resection for patient that may be resectable. Response assessment implies a review of not only the immediately preceding scans but of as many scans as necessary to accurately document the evolution of all malignant lesions, intra and extrahepatic, from the baseline to the current scan with particular attention to the small volume disease that may undergo a complete radiographic response in potentially resectable patients.

Tumour size remains the most common measure of response. In the past 15 years however imaging response for CLM has evolved from a simple, uniform method based exclusively on changes in tumour size and codified by the RECIST criteria to a method where both size and appearance of the tumour content and contours are evaluated in order to determine response to evolving modern therapies that combine diverse mechanisms of action. The introduction of immunotherapy is changing once again the therapeutic landscape. Investigation is ongoing to properly define criteria that will address the effect of immunomodulating drugs.

Research in functional, quantitative imaging and deep learning suggests a future where technological progress will expand the field of response allowing to predict early outcome and possibly anticipate response to a given therapy based on the tumour appearance at baseline.

Finally, a systematic search for radiographic evidence of chemotherapy-induced toxicity needs to be concomitant to the evaluation of response.

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Pathological Response Criteria

46

Dipen M. Maru

Learning Objectives

- Pathologic response predicts survival and improves understanding of the biology of colorectal liver metastases.
- Tumour regression grade is based on the relative proportion of extent of fibrosis and presence of residual tumour cells.
- Tumour cell thickness at tumour-normal interface is measured as an uninterrupted layer of tumour cells without admixed fibrotic stroma, acellular mucin, or nonneoplastic liver parenchyma.

46.1 Histopathology Evaluation of Resected Colorectal Metastases After Neoadjuvant Chemotherapy

Histopathological examination, an essential component of multidisciplinary care of patients who undergo surgical resection of colorectal liver metastases (CLM), entails macroscopic and microscopic examinations that provide predictive and prognostic information including response to preoperative medical therapy, completeness of resection, and effects of preoperative therapy on the nonneoplastic liver. A number of groups have identified and validated histopathologic parameters of response to neoadjuvant chemotherapy/targeted therapy in resected CLM. However, there is a lack of standardized guidelines for pathology reporting of these specimens, requiring pathologists to be familiar with the published literature and work closely with the operating surgeon, so that optimal histopathology information can be generated from these specimens. This approach contributes to high-quality postoperative management of the patients and to a better understanding of the biology of response to neoadjuvant therapy in CLM.

46.2 Macroscopic Examination and Sampling

Macroscopic examination of resected CLM includes the type of specimen, number of lesions, size of the lesions, perihepatic extension of the tumour, the distance of the lesion/tumour from the nearest liver parenchymal, soft tissue, and other margins (e.g., vessels or hilar plate). The specimen can be examined and sampled immediately or after fixation. However, immediate intraoperative macroscopic assessment of the resected specimen is frequently requested by surgeons to confirm the number and size of the nodules and determine the distance of the tumour from the liver resection margin. The immediate gross assessment also helps to confirm the removal of the lesions seen on preoperative imaging or intraoperative sonography. The specimen should be serially sectioned perpendicular to the liver resection margin in thin (5 mm thick) slices so that small lesions cannot be missed. The CLMs are grossly circumscribed nodules with yellow-white, yellow, and yellow-gray cut surfaces with granular necrotic debris. It is not unusual to see variations in the gross appearance of different lesions in the same specimen due to variable responses to preoperative chemo and targeted therapy with and without portal vein embolization. The gross examination should include the presence or absence of vascular invasion, biliary invasion, or extension into the perihepatic and hilar soft tissue with measurement of the distance from other margins, i.e., soft tissue, hilar vessels, and bile duct.

Although there is a lack of consensus on the exact number of nodules associated with poor survival outcomes, several studies and a meta-analysis with a large sample size have shown that four or more tumour nodules are associated with shorter disease-free and overall survival in patients who

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undergo surgery without neoadjuvant therapy [1–5]. In the neoadjuvant setting, non-solitary CLMs are associated with shorter recurrence-free and overall survival as compared to solitary CLM, in more than one study with a multi-institutional study showing three or higher number of tumour nodules as an independent prognostic factor of recurrence-free survival [6, 7].

Similar to the number of tumours, tumour size correlates with the survival outcome of patients who undergo curative resection for CLM with or without preoperative chemotherapy and targeted therapy. Several studies showed tumour size larger than either 5 or 8 cm was associated with shorter recurrence-free and overall survival in patients who undergo resection without neoadjuvant chemotherapy [2, 8, 9]. A cut-off size after neoadjuvant chemotherapy and/or targeted therapy has not been determined yet. However, reduction in tumour size after neoadjuvant therapy on pathology specimen as compared to preoperative imaging is an indication of the efficacy of neoadjuvant therapy. Benign liver lesions including bile duct adenoma, focal nodular hyperplasia, and focal fibrosis are in differential diagnoses on macroscopic examination with less than 1 cm lesion and adequate sampling for microscopic examination is necessary to confirm the diagnosis of these lesions.

Macroscopic negative margin is one of the best predictors of recurrence-free survival. Optimal negative margin is defined as a 10 mm rim of nonneoplastic tissue around a visible tumour. However, in a large number of specimens, a 10 mm margin is not possible to achieve and it is important to document the exact distance of nearest liver parenchymal and other margins on gross examination.

Given the heterogeneity of response within and across different lesions, it is essential to extensively sample the CLM for optimal assessment of the response to preoperative therapy. All lesions that are smaller than 15 mm should be entirely submitted for histopathologic examination. For tumours larger than 15 mm, one section per 5 mm is recommended. The sampling should equally include center and periphery of the tumour. One of the approaches to optimally sample center and periphery is to submit alternate slices in their entirety for histopathologic examination. Given the importance of changes at the tumour-normal liver interface, it is important to include a rim of adjacent liver parenchyma in the sections.

46.3 Microscopic Examination

46.3.1 Histopathologic Response to Neoadjuvant Therapy

Two major quantitative/semi-quantitative methods of assessing histopathologic response to neoadjuvant chemotherapy and targeted therapy have been described based on the review of Hematoxylin and Eosin stained sections of the CLM.

46.3.1.1 Pathologic Response Defined as Residual Tumour Cell Burden

The extent of residual carcinoma is assessed quantitatively by estimating the proportion of residual cancer cells in relation to the total tumour area. The tumour area includes areas of chemotherapy-related tissue injury, tumour necrosis, fibro-collagenous proliferation, and other reparative changes [6, 7, 10]. The sum of the percentage of residual cancer cells on each section/slide is calculated and the mean of the percentage of residual tumour cells is derived by dividing the sum by the number of slides for each tumour. In patients with multiple tumour nodules, the mean of the values for the various tumour nodules is used to define the pathologic response. The response is classified into the three semi-quantitative subsets: no residual cancer cells or complete response, 1–49% residual cancer cells remaining or major response, and 50% or more residual cancer cells remaining or minor response (Fig. 46.1). In a study of 305 patients treated with fluoropyrimidine and oxaliplatin with or without bevacizumab or fluoropyrimidine and irinotecan with or without bevacizumab, the complete pathologic response was associated with 100% of overall survival 1 year after CLM resection, 100% at 3 years, and 75% at 5 years. The major pathologic response was associated with 95% of overall survival at 1 year after CLM resection, 69% at 3 years, and 56% at 5 years. The minor response was associated with 91% of overall survival at 1 year after CLM resection, 58% at 3 years, and 33% at 5 years. Independent predictors of complete or major pathologic response included preoperative serum CEA $\leq$ 5.0 ng/mL, tumour size $\leq$3.0 cm, and chemotherapy with fluoropyrimidine plus oxaliplatin and bevacizumab. Subsequently, this approach to assess pathologic response has been validated in a multicenter study of retrospectively collected samples. In this study of 163 patients, 3-year and 5-year disease-free survival rates, respectively, by categories of response were: complete response, 77% and 77%; major response, 32% and 31%; and minor response, 26% and 18%. Tumour size was the only predictor for pathologic response in this study. The high interobserver agreement for the category of pathology response was observed among pathologists from more than one institution with a kappa of 0.82 (almost perfect agreement) [7].

Another method that combines tumour size and percentage of tumour cells was shown to be of prognostic relevance in a study of 223 patients with resected CLM, who were treated with preoperative chemotherapy without bevacizumab or cetuximab [11]. The prognostic value of residual tumour tissue is calculated using $\sum_{n=1}^{N}\left(\%(n)\times s(n)\right)$, where n is each separate nodule, % is the percentage of remaining

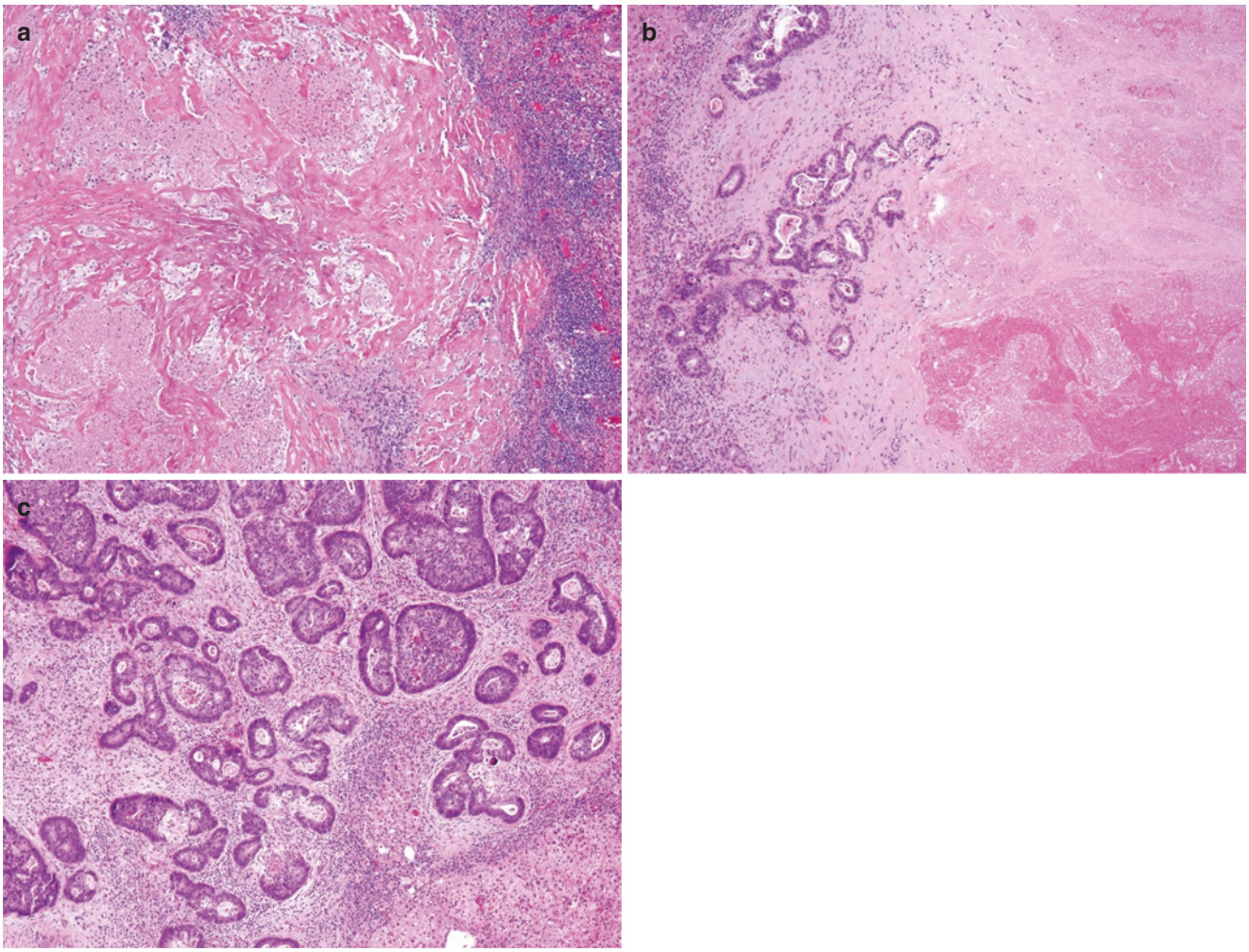

Fig. 46.1 Photomicrographs of representative examples of complete (**a**), major (**b**), and minor pathologic response (**c**). (**a**) shows tumour bed with necrotic debris, hyalinized/collagenized tissue, and inflammatory cells with no tumour cells, (**b**) shows neoplastic glands occupying less than half of the tumour bed, and (**c**) shows neoplastic glands occupying the majority (>50%) of the tumour bed admixed with a minor component of fibrocollagenous stroma with inflammation

tumour cells within nodule n (%) and s is the size of nodule n (cm). A significant difference in overall survival was observed using the cutoffs of 0–6 cm residual tumour tissue, and >6 cm residual tumour tissue when two groups were compared at a given time ($P = 0.055$, $P = 0.006$ and $P = 0.005$, respectively).

46.3.1.2 Tumour Regression Grade (TGR)

Tumour regression grade in CLM is scored as per the scheme described for esophageal carcinoma and modified for the CLM [12]. This modified scheme identified five TRGs on the basis of the relative proportion of extent of fibrosis and the presence of residual tumour cells [13]. TRG1 is defined as the absence of tumour cells replaced by abundant fibrosis; TRG2 is defined as rare residual tumour cells scattered throughout abundant fibrosis; TRG3 is defined as more residual tumour cells throughout predominant fibrosis; TRG4 is defined as a large amount of tumour cells predominating over fibrosis; and TRG5 is defined as tumour cells without fibrosis. Patients with multiple CLM with different TRG are categorized according to the highest TRG-tumour with least response. Patients with TRG 1 and TRG2 are classified as major responders, patients with TRG 3 are classified as partial responders, and patients with TRG4 and TRG5 are classified as non-responders. This categorization has shown to be of prognostic significance in a study of 106 patients who underwent surgical resection of CLM after preoperative chemotherapy regimens composed of fluoropyrimidine with and without oxaliplatin or irinotecan. In patients with major response, the 1-, 3-, and 5-year disease-free survival rates were 78%, 49%, and 38%, respectively. In patients with partial response, the 1-, 3-, and 5-year disease-free survival rates were 58%, 37%, and 37%, respectively. In patients with no response, the 1-, 3-, and 5-year disease-free survival rates

were 53%, 18%, and 15%, respectively. Major or partial response was observed in >80% of patients who were treated with oxaliplatin and fluoropyrimidine with or without irinotecan as compared with 31% of patients treated with irinotecan and fluoropyrimidine and with 27% of patients treated with only fluoropyrimidine.

46.3.2 Histologic Growth Patterns

Morphologic changes at the periphery of CLM particularly at tumour-normal liver interface have been recognized for their prognostic and predictive relevance and potential impact on a better understanding of the tumour biology.

46.3.2.1 Tumour Cell Thickness at the Tumour-Normal Interface

Tumour thickness at tumour-normal interface is measured as a focus composed of uninterrupted layers of tumour cells without admixed fibrotic stroma, acellular mucin, or nonneoplastic liver parenchyma (Fig. 46.2). The thickness was measured perpendicular to the tumour-normal interface by a ruler or ocular micrometer at more than 1 focus, and the greatest thickness was reported in mm or cm. In specimens with multiple tumours, tumour thickness was measured separately for each tumour nodule and the average thickness was reported in mm or cm. The study that originally described this feature included 93 patients who underwent CLM resection after oxaliplatin- or irinotecan-containing chemotherapy with or without bevacizumab [6]. The median thickness at the tumour-normal interface was 2.8 mm [interquartile range (IQR), 0.5–6 mm]. At 4 years from CLM resection, the recurrence-free survival was significantly better with lower tumour thickness at tumour-normal interface: 70% for the group having tumour thickness less than 0.5 mm, 51% for the group having tumour thickness equal to or more than 0.5 mm and less than 5 mm and 35% for the group having tumour thickness equal to or more than 5 mm. For every twofold increase in TNI, the risk of recurrence or death increased by 14%. The tumour thickness at the tumour-normal interface correlated with pathologic response (Spearman $r = 0.80$, $P < 0.0001$), radiologic response on CT categorized by CT morphology criteria and response evaluation criteria in solid tumour (Spearman $r = 0.35$, $P < 0.001$) and preoperative medical therapy that included bevacizumab ($P = 0.03$) or oxaliplatin ($P = 0.02$). The prognostic significance of tumour thickness at tumour-normal interface was validated in a multi-institutional study of 171 patients who underwent resection of CLM after preoperative chemotherapy with and without bevacizumab [7]. The 3-year and 5-year disease-free survival rates, respectively, by categories of tumour thickness at the tumour-normal interface were: <0.5 mm, 58% and 58%; 0.5 to <5 mm, 31% and 24%; and ≥5 mm, 15% and 11%. In this study preoperative treatment with oxaliplatin-based regimen or bevacizumab-based regimen was associated with lower tumour thickness at the tumour-normal interface.

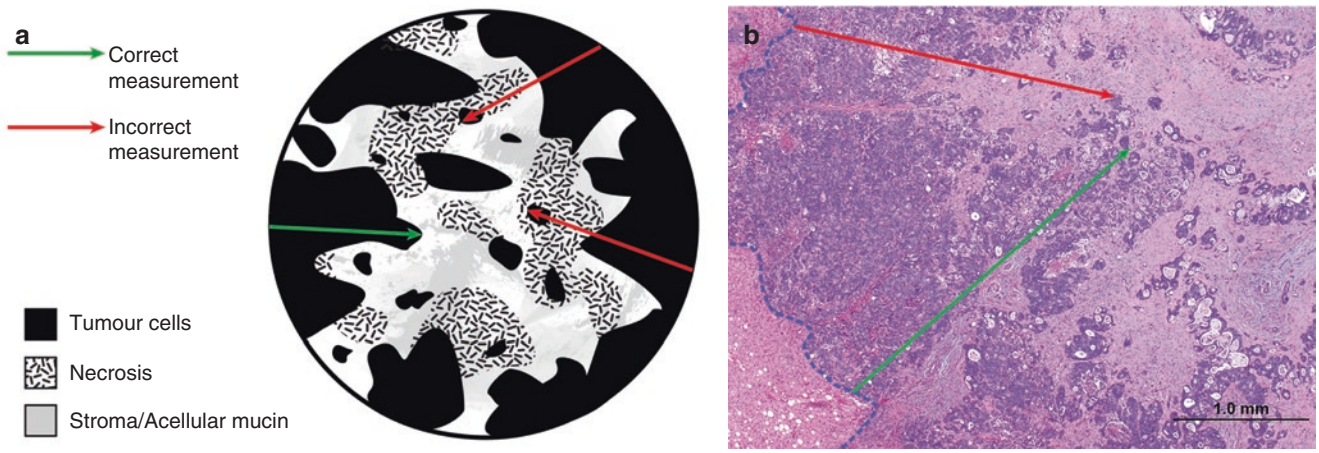

Fig. 46.2 Cartoon (**a**) and photomicrograph (**b**) demonstrating correct and incorrect methods of measuring tumour thickness at the tumour-normal liver interface. (**a**) shows tumour cells/neoplastic glands as a homogenous dark area of the tumour bed. Different stromal components are shown with other symbols. The outer layer of the circle represents the tumour-normal liver interface. (**b**) Hematoxylin and eosin-stained section showing normal liver parenchyma in the left lower corner, tumour-normal liver interface highlighted with blue interrupted line. In both (**a**) and (**b**) the green arrow shows the longest area of tumour cells without admixed stroma, necrosis, or inflammation. Red arrow indicated focus with layer of tumour cells interrupted by fibrosis/necrosis

46.3.2.2 Histologic Pattern at the Tumour-Normal Liver Interface

Histologic patterns at the tumour-normal interface are indicative of tumour cells-hepatocytes and tumour cells-liver microenvironment interactions including vessel co-option with normal liver sinusoids vs. tumour-induced angiogenesis. The histologic patterns include (i) a pushing growth pattern, in which the CLM compresses the surrounding liver parenchyma, pushing the liver cell plates aside, pushing the liver plates parallel to the CLM circumference; (ii) a desmoplastic growth pattern, in which a fibrous rim or pseudo capsule separates the metastasis from the liver parenchyma. The rim frequently has a high density of lymphocytes and other mononuclear immune cells. Bile ducts, capillaries, and at times tumour cells clusters are identified in the desmoplastic rim (iii) a replacement growth pattern, in which tumour cells infiltrate the liver cell plates, either replacing or in close contact with the hepatocytes and frequently co-opting the hepatic sinusoids, and (iv) mixed-growth pattern has been defined as where at least two growth patterns are present, both appearing in at least 20% of the tumour-normal interface [14, 15]. The prognostic relevance of these growth patterns on survival outcome of these patients is not yet clear. A study of 205 patients with resected CLM failed to demonstrate the clear significance of growth pattern with patient survival outcome, although at 2-year follow up, the lower survival was observed in patients who had pushing or mixed histologic pattern. Another study of 217 patients demonstrated poor survival outcomes for patients with replacement growth pattern. However, the study's impact is limited by the exclusion of preoperative chemotherapy in the survival analysis. The replacement growth pattern is also shown to be associated with poor response to bevacizumab with pathologic response as the end-point. In preclinical models, vessel co-option predominantly observed with replacement pattern was shown to be a resistance mechanism against antiangiogenic therapy [16]. These findings strongly support additional studies focused on a better understanding of genotypic and phenotypic underpinnings of the tumour cells and associated microenvironment to improve understanding biology of CLM and identify early markers of progression of liver metastases within or beyond the liver.

46.4 Conclusion

In conclusion, pathology changes after preoperative chemotherapy in resected CLM predict patients' survival outcome and contribute to understanding the biology of CLM. Macroscopic and microscopic pathologic parameters including pathology response to preoperative chemotherapy and tumour regression grade should be routinely included in the pathology report to help oncologists and surgeons assess the risk of recurrence in these patients.

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Histopathological Patterns of Progression and Vessel Co-option

47

Eve Simoneau and Peter Metrakos

Learning Objectives

- Two main distinct histopathological patterns exist in colorectal liver metastasis: replacement and desmoplastic patterns.
- Vessel co-option is a well-described non-angiogenic mechanism by which primary or metastatic tumours obtain their blood supply by hijacking ("co-opting") the mature vessels already existing in the host organs, as opposed to using neovascularization.
- Replacement histopathological pattern is mainly using vessel co-option, while desmoplastic pattern is angiogenic.
- Vessel co-option was shown to mediate the resistance to antiangiogenic therapy in patients undergoing resection for colorectal liver metastasis.
- The histopathological patterns—effectively characterized using international validated pathological guidelines—are strong independent prognostic factors, suggesting a role in decision-making in the adjuvant setting.

47.1 Introduction

Colorectal cancer represents a significant disease burden and unfortunately up to 25% of patients will present with metastatic disease [1, 2]. Expanding the understanding of disease biology with an optimized systemic regimen is crucial to confer the best possible outcomes for these patients. Patients will undergo multimodal therapy including systemic perioperative chemotherapy and when resectable can potentially achieve a 5-year overall survival of close to 60% [3–5]. The use of certain biologic agents is now part of the standard regimen, combined with cytotoxic chemotherapy, although the magnitude of the clinical benefit has been questioned. The challenge in the surgical management of metastatic disease lies in the understanding of the relationship between the tumours and the host organ.

In this scenario, the host microenvironment is exploited by the tumour, and a key player here consists of its vascular niche. How tumour vascularization, notably by a process called vessel co-option, can potentially explain the lack of clinically significant overall survival benefit for patients with CRLM will be summarized in this chapter.

47.2 Utilization of Antiangiogenic Therapy for Patients with CRLM

One of the main cancer hallmarks is the ability of tumours to create new blood vessels, a process well-identified as angiogenesis [6]. Two main mediators of angiogenesis are hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF), and they have been shown to be key regulators in colorectal cancer progression. In fact, VEGF expression is promoted by HIF-1α, which itself is upregulated in states of tumour hypoxia, for instance when tumour growth outpaces the rate of angiogenesis [7]. This mechanism instigated the development of therapies directed at VEGF blockade, for instance with bevacizumab. Contemporary regimens now include oxaliplatin and/or irinotecan-based chemotherapy with the addition of bevacizumab [8–12] as first line for patients with metastatic colorectal cancer, which has been also validated as perioperative treatment. Although this targeted therapy has been used in metastatic colorectal cancer [12], the overall survival benefit in clinical trials has been limited, measured in months

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only. Efforts to understand the modest benefit of antiangiogenic therapy have emerged and focused on tumour vascularization processes.

47.3 Histopathological Growth Patterns in Liver Metastasis

47.3.1 Vessel Co-option

It appears that some metastases located in highly vascularized organs such as the liver may resort to different vascularization to obtain their blood supply, instead of relying solely on angiogenesis. In fact, vessel co-option is a mechanism whereby tumours hijack the existing mature vasculature of the host organ [13]. It was shown to be mediating resistance to antiangiogenic therapy in hepatocellular carcinoma, lung metastases, as well as some brain tumours [14–19]. For CRLM, tumour vascularization has been studied with regards to histopathological growth patterns, which provided key insights to understanding some mechanisms of resistance to antiangiogenic therapy.

47.3.2 Three Distinct Growth Patterns

Liver metastases have been shown to grow according to three distinct histopathological growth patterns (HGP): a replacement growth pattern, a desmoplastic growth pattern, and finally a (less common) pushing pattern (Fig. 47.1). First described by Vermeulen et al. [20, 21] these growth patterns are defined by the tumour and liver interface characteristics as well as the immune cells infiltration. Replacement pattern consists of the tumour cells replacing the liver parenchyma and an absence of desmoplastic stroma and immune cells infiltrating—also called an immune desert. A desmoplastic pattern is characterized by a desmoplastic rim separating the tumour cells from surrounding hepatocytes, in addition to having strong immune cell infiltrates [22]. Pushing pattern resembles replacement as is it characterized by metastatic tissue pushing the liver plates; however, there is no invasion of the normal liver parenchyma. The latter has been described to be far less common (3–7%) and its clinical implication has yet to be defined; it has even been suggested that it may represent a "transitory" pattern. All those can be distinguished with H&E staining using detailed and validated histopathological guidelines [21].

47.3.3 Vessel Co-option in Replacement Pattern Mediates Resistance to Antiangiogenic Therapy and Progression in CRLM

The two main HGP—replacement and desmoplastic—have been shown to harbor different vascularization processes; replacement being the co-opting pattern and desmoplastic being the angiogenic one [23–26]. The prognostic and therapeutic implications of these two HGP have been evaluated for patients undergoing preoperative chemotherapy for resectable CRLM. Several concepts are established: (1) *HGP are associated with pathological response*. (Fig. 47.2) In validated cohorts evaluating lesions scored by HGP and pathological response independently, the co-opting replacement pattern was shown to have a lower probability of obtaining a good pathological response (OR = 0.06, 95% CI 0.03–0.15, $p < 0.0001$) for patient treated with bevacizumab-containing chemotherapy. Of note, Frentzas et al. also demonstrated that the prevalence of replacement and desmoplastic patterns in chemo-naive patients is relatively equally distributed, eliminating HGP being histopathological findings related to treatment effects. (2) *Patients with a predominance of replacement patterns have less clinical benefit from antiangiogenic therapy*. In fact, in the same study, patients specifically receiving cytotoxic chemotherapy with bevacizumab had lower survival than those with non-co-opting patterns. (3) *Inhibiting co-option in addition to angiogenesis may be more effective* than the current treatment modality with cyto-

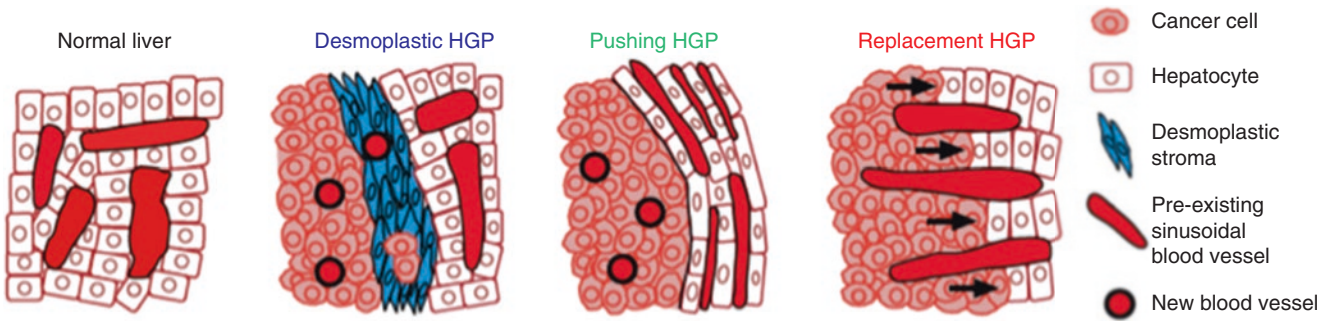
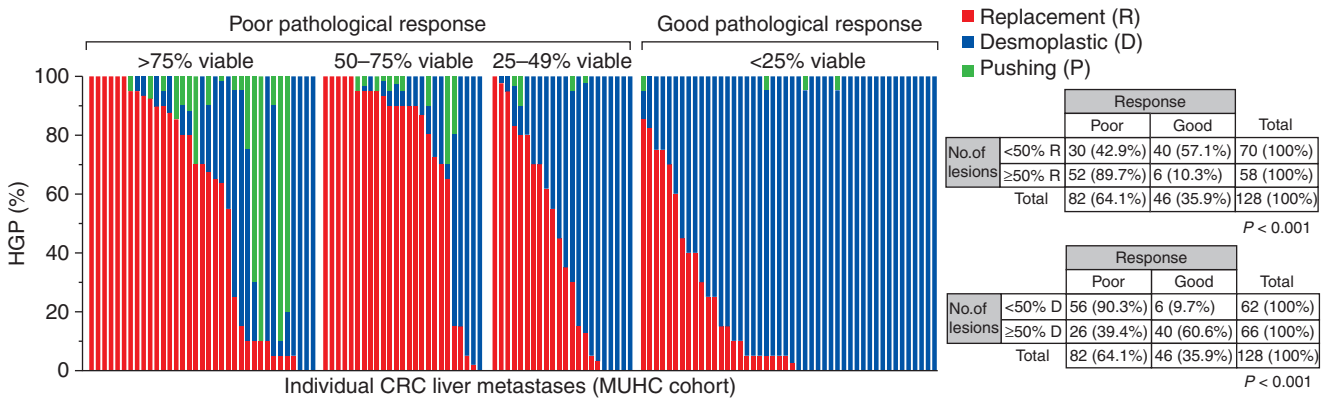


Fig. 47.1 Representation of the three histological growth patterns (desmoplastic, pushing, and replacement) described in colorectal liver metastasis, distinguished by their respective tumour-liver interface, in addition to distinct immune infiltrate and tumour vascularization processes [23]



		Response		
		Poor	Good	Total
No.of lesions	<50% R	30 (42.9%)	40 (57.1%)	70 (100%)
	≥50% R	52 (89.7%)	6 (10.3%)	58 (100%)
	Total	82 (64.1%)	46 (35.9%)	128 (100%)

$P < 0.001$

		Response		
		Poor	Good	Total
No.of lesions	<50% D	56 (90.3%)	6 (9.7%)	62 (100%)
	≥50% D	26 (39.4%)	40 (60.6%)	66 (100%)
	Total	82 (64.1%)	46 (35.9%)	128 (100%)

$P < 0.001$

Fig. 47.2 Individual liver metastasis lesions, scored independently by three blinded pathologists, are represented based on pathological response. Lesions with a predominance of desmoplastic (angiogenic) pattern, represented in blue, were present in the good pathological response group, whereas the replacement (co-opting) pattern was significantly enriched in lesions showing poor pathological response [23]

toxic chemotherapy and antiangiogenesis. In *in vivo* models, ARPC3-knockdown tumours—which lead to desmoplastic lesions by inhibiting cell motility and not proliferation—responded significantly better to a combination of anti-VEGF inhibitory antibody and capecitabine, providing a strategy that might optimize treatment response and outcomes for patients with CRLM.

47.4 Clinical Implications of Histopathological Growth Patterns in CRLM

At the moment, vessel co-option has been shown to have a strong prognostic value, which could be helpful in adjuvant settings for patients undergoing surgery [23, 27–31]. A study including 732 patients with CRLM confirmed that the angiogenic desmoplastic pattern, specifically in untreated chemonaive patients, was the strongest positive prognosticator of disease-free and overall survival [28]. In addition, Bohlok et al. recently showed that a predominance of desmoplastic HGP was an independent predictor of postoperative recurrence and that the prognostic value for overall survival was further enhanced by combining the histopathological data to a validated clinical risk score, with desmoplastic HGP and a low-risk score reaching a 5-year survival of 83% [32]. On the contrary, it was well-established that replacement HGP has a significant lower survival especially when treated with antiangiogenic therapy in the neoadjuvant setting. In the same context, patients exhibiting disease progression with new lesions while on systemic chemotherapy combined with bevacizumab had those developing lesions scored almost entirely as replacement co-opting patterns [23]. Despite the significant therapeutic and prognostic potential of vessel-co-option, the limitation in clinical practice so far lies in the ability to determine with certainty the HGP (and therefore whether a tumour is angiogenic or co-opting), without biopsy or surgical intervention. Models that correlate noninvasive data, such as radiological criteria and/or serum biomarkers, with tumour vascularization are currently the focus of ongoing research, as decisions to administer tailored treatments should be based on the likelihood of response.

47.5 Conclusion

Vessel co-option is now a recognized mechanism by which metastatic or primary tumours can obtain their blood supply and targeting cell motility and invasion was shown in preclinical models to maximize anti-tumour effects, although this has yet to be translated in clinical trials. Moreover, insights and detailed characterization of the distinct immune microenvironments of the two main histopathological growth patterns are also needed, particularly with an expanding field of immunotherapy. Taken together, the data existing so far has shed light on an important mechanism of resistance to antiangiogenic therapy that is commonly used for patients with colorectal liver metastasis.

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Colorectal Liver Micrometastases

48

Guillaume Passot, Alexendros N. Flaris,
and Yujiro Nishioka

Learning Objectives

- Liver micrometastases are defined on pathological examination as microscopic lesions separated from the gross tumour by a rim of nonneoplastic liver parenchyma.
- Preoperative chemotherapy decreases the risk of developing micrometastases.
- RAS/TP53 co-mutation is associated with an increased rate of micrometastases.
- Liver micrometastases are associated with worse recurrence-free and overall survival.

48.1 Introduction

The natural history of cancer involves growth at the primary site followed by spreading to distant sites. Primary or metastatic tumours can only be diagnosed once they reach a size that allows for detection. Like icebergs, the largest tumour burden could remain hidden at the time of diagnosis. The current standard of care for potentially curative treatment of metastatic solid cancers involves complete removal of any macroscopic disease—usually by surgery—and treatment of any residual microscopic disease with systemic therapy, such as chemotherapy.

In colorectal cancer, the liver is the most common site of metastasis [1]. Despite complete surgical macroscopic tumour resection, 60% of patients will recur within the liver. These recurrences are due to the persistence of microscopic disease and can be divided into remote recurrences and recurrences at the resection site. The former ones are due to circulating tumour cells [2] which would be controlled by perioperative chemotherapy, whereas the latter ones are due to residual tumour cells at the resection site following surgery which would be controlled by appropriate margin width. Micrometastases surrounding the main tumour are thought to play a role in local recurrence after resection of colorectal liver metastases (CLM) [3]. In this chapter, we describe liver micrometastases and their impact on surgical management.

48.2 Micrometastases

48.2.1 Pathology Description

Liver micrometastases are defined on pathological examination as microscopic lesions separated from gross tumour by a rim of nonneoplastic liver parenchyma, and include vascular, biliary, and lymphatic infiltration along with satellite nodules [4, 5].

To identify liver micrometastases within the specimen, 5 mm thickness slices are obtained and radial samples including the edge of the main tumour and 2 cm of adjacent normal liver parenchyma are collected and sent to formalin fixation and staining (Fig. 48.1) [3, 6, 7]. In order to avoid overdiagnosing micrometastases, immunohistochemical staining for both tumour and normal hepatocytes should be performed (Fig. 48.2).

The main limit for pathological evaluation of micrometastases is shown in Fig. 48.3; if the main tumour mass has polypoid extensions then, depending on the depth of the

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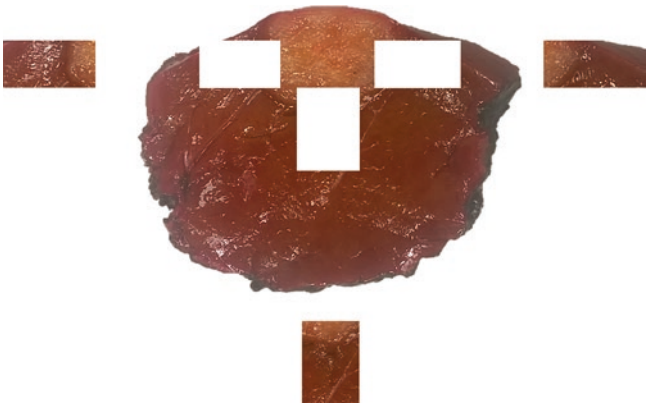

Fig. 48.1 Slice sampling for pathological analysis of micrometastases

slice, these extensions might resemble micrometastases when it is not (i.e., false positive).

48.2.2 Risk Factors for Developing Micrometastases

In 2012, Wakai et al. reported the presence of micrometastases in 81% of patients that were not on chemotherapy and in 24% of patients that were on chemotherapy. Recent studies have confirmed that chemotherapy decreases significantly the incidence of micrometastases [7].

Furthermore, in a recent series of 138 patients, the addition of bevacizumab to conventional chemotherapy was

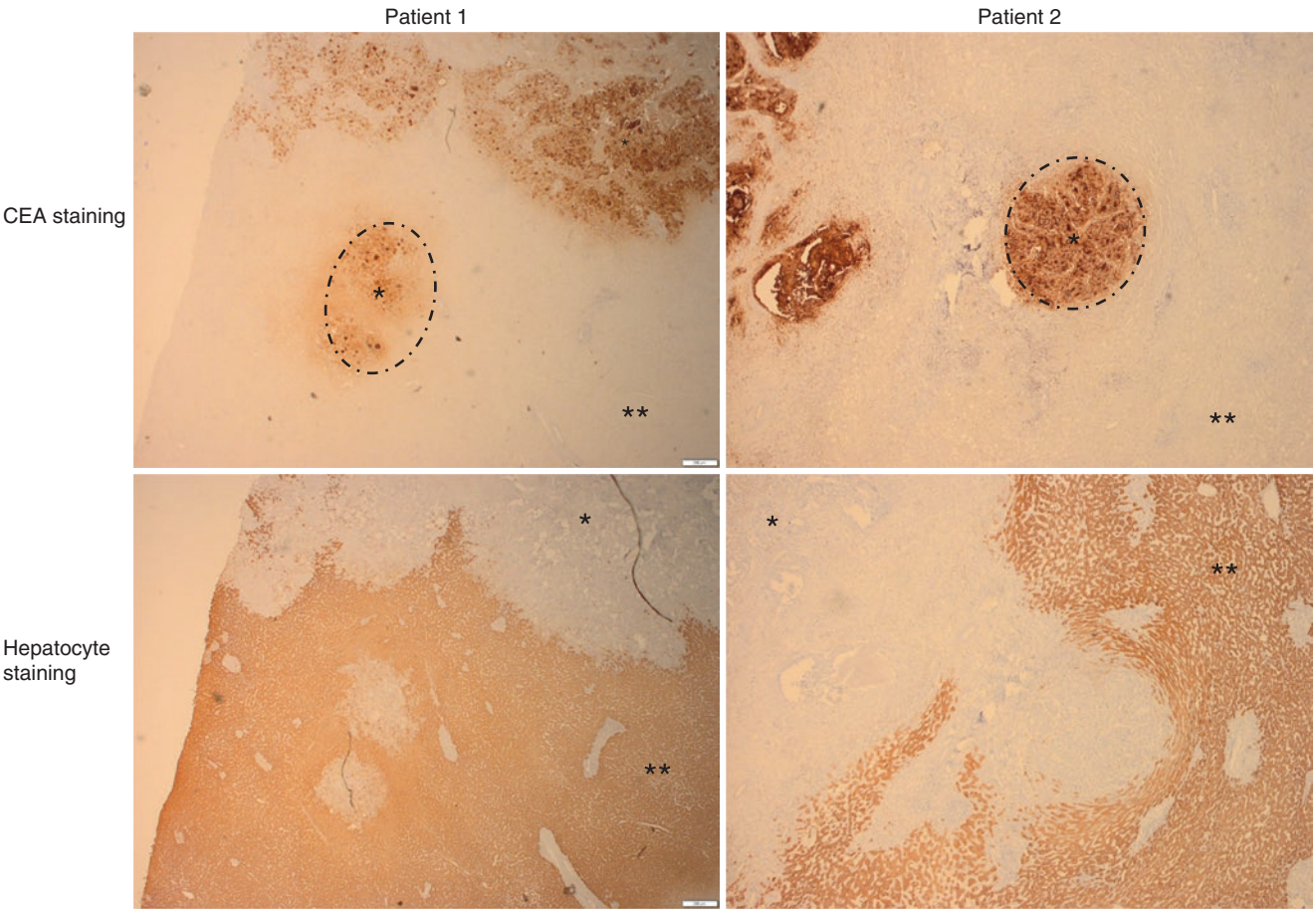

Fig. 48.2 Evaluation of Micrometastases using Immunohistochemical staining (Carcinoembryonic Antigen Tumour Marker) and Hepatocytes; * Tumour; ** Normal Liver Parenchyma; Both patients were suspected to have micrometastases after CEA staining. After hepatocyte staining though, patient 2 had no normal liver (dark staining) between gross tumour and suspected micrometastases

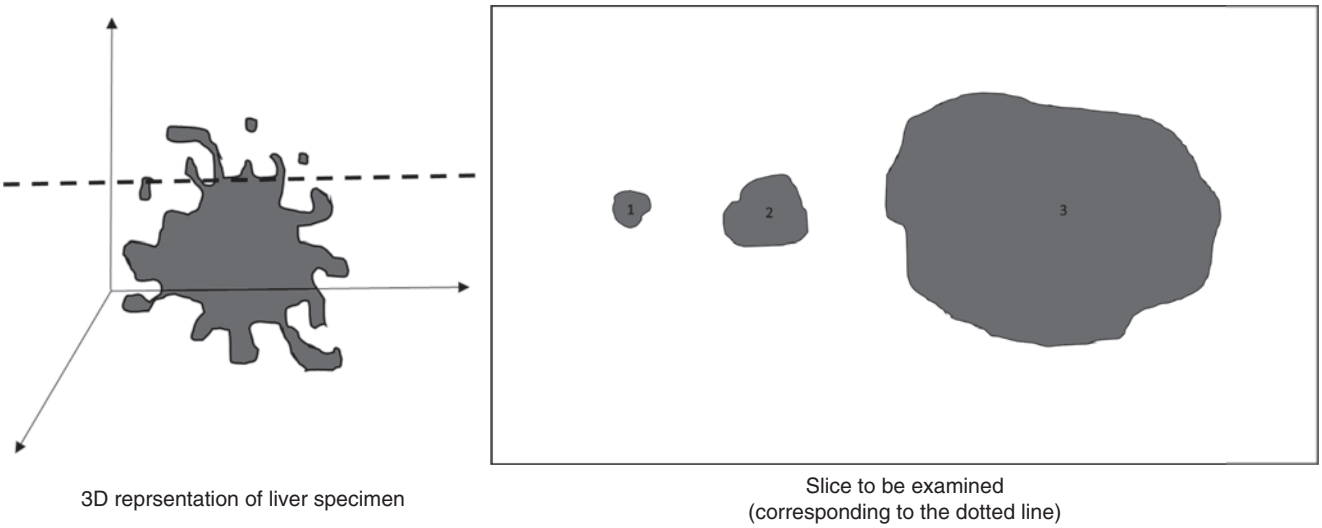

Fig. 48.3 Pathological slice of infiltrating colorectal liver metastasis (3), representing polypoid extension (2) and micrometastases (1)

associated with a decreased incidence of micrometastases. In this study, the authors also reported that the RAS/TP53 co-mutation was associated with an increased rate of micrometastases development [8]. Of note, Chun et al. had already reported that the RAS/TP53 co-mutation was associated with a worse prognosis, which could be explained by more infiltrating liver metastases within liver parenchyma as a form of micrometastases [9].

48.2.3 Impact on Survival

Vigano et al. investigated the impact of the microscopic vascular and biliary invasion of CLM on survival. Microscopic vascular invasion was associated with worse overall survival (OS) (hazard ratio [HR] 2.004, 95% Confidence Interval [95% CI] 1.133–3.543, p = 0.017) as well as microscopic biliary infiltration (HR 2.371, 95% CI 1.075–5.229) [10].

An analysis in our institutions among 138 patients, also showed that micrometastases was significantly associated with worse recurrence-free survival (RFS), worse hepatic recurrence-free survival (hRFS) and worse OS [8]. (Fig. 48.4) In this study, the presence of micrometastases was an independent factor for worse RFS (HR, 1.67, 95% CI, 1.09–2.58; p = 0.020), worse hRFS (HR, 1.86, 95% CI, 1.10–3.14; p = 0.021), and worse OS (HR 3.97, 95% CI 1.69–9.33; p = 0.002). In the same study, the authors also looked at the combined effect of margin status (R0 vs. R1) and the presence of micrometastases on OS. They found no statistically significant difference in OS between patients who had undergone R1 resection for CLM without micrometastases compared to patients that had undergone R0 resection for CLM with micrometastases. (p = 0.510). In patients with micrometastases, R1 resection was independently associated with worse OS compared to R0 resection (3y-OS 19.4% vs. 69.0%; p = 0.047). (Fig. 48.5).

48.3 Surgical Management

Perioperative chemotherapy has become the standard of care for patients presenting with resectable CLM [11]. Several studies have reported the importance of the radiological response following chemotherapy (based on the RECIST criteria), in predicting survival after CLM resection [12]. Sindoh et al. used an alternative criteria (the morphological criteria) based on three findings from CT scans: tumour homogeneity, tumour-liver interface smoothness, and attenuation [13]. Tumours presenting "optimal" response with homogeneous low attenuation with thin, sharply defined tumour-liver interface were associated with better survival, compared to heterogeneous poorly defined tumour-liver interface tumours. Chemotherapy and bevacizumab improved morphological response [13, 14]. Similar data was suggested for micrometastases, as chemotherapy and bevacizumab were associated with lower risk of micrometastases, and CLM morphological response can predict micrometastases occurrence [7]. When effective, chemotherapy leads to homogenization of CLMs, smoothing of the tumour-liver interface, and a decrease in the number/size of

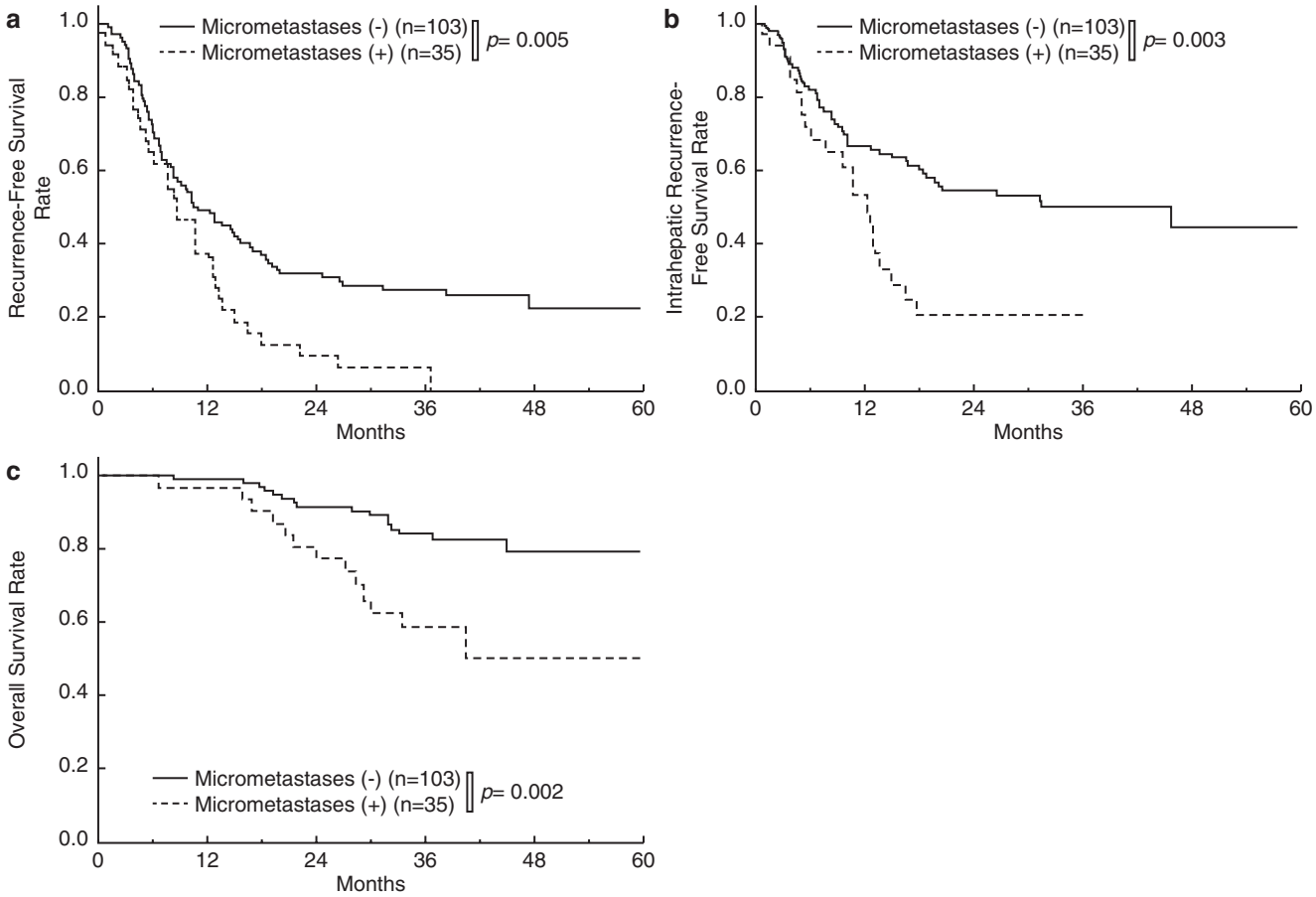

Fig. 48.4 Impact of micrometastases surrounding CLM on (**a**) recurrence-free survival (RFS), (**b**) intrahepatic recurrence-free survival (hRFS), and (**c**) overall survival (OS)

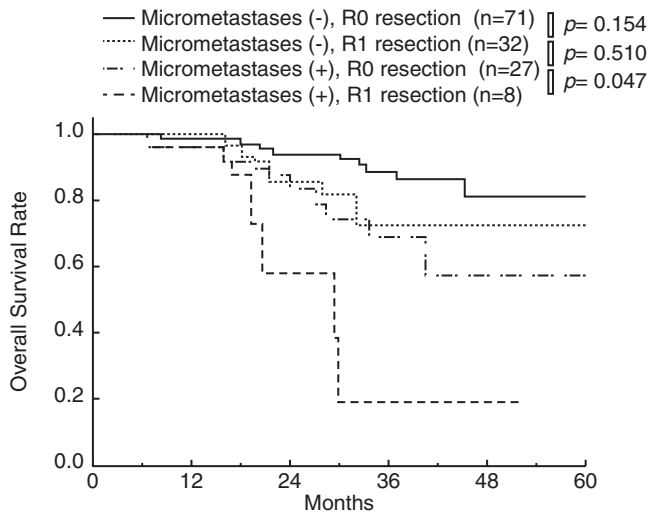

Fig. 48.5 Overall survival stratified by surgical margin status and the presence of micrometastases

micrometastases (Fig. 48.6). They also reported that surgical margin status did not affect survival in patients with an optimal morphological response.

The standard of care remains complete resection of all visible CLM. Complete resection is considered as R0 resection with a negative surgical margin; however, ideal width of surgical margin is still controversial and considering the incidence of micrometastases could help in which may help in deciding the ideal surgical margin width. Without chemotherapy, CLMs show infiltrative characteristics with an elevated risk for developing micrometastases leading to a high risk of local recurrence after resection [4]. For these patients, the surgical margin should be as wide as possible in order to achieve good oncologic outcomes. On the other hand, patients who did receive preoperative chemotherapy, with good response on imaging, have a lower risk of micrometastases [7], and narrower surgical margins may be potentially permitted.

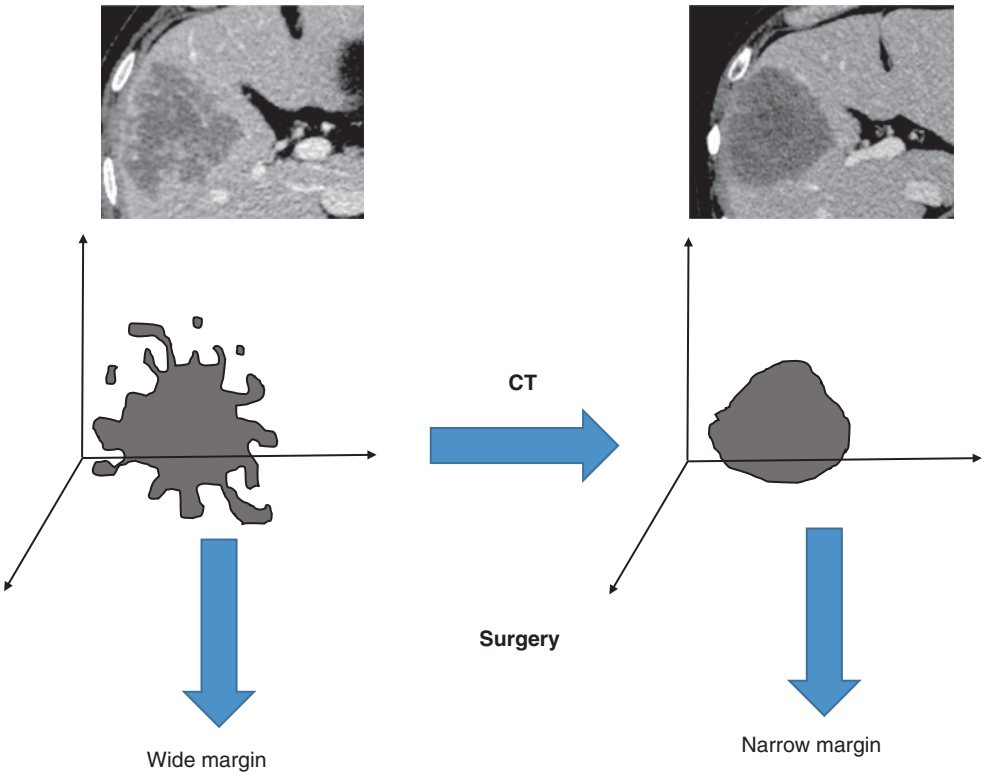

Fig. 48.6 Impact of tumour morphology on surgical margins: CT aspect and schematic representation

48.4 Conclusion

Despite the scarcity of research focusing on micrometastases surrounding CLMs, micrometastases appear to be crucial when it comes to surgical margins. Micrometastases are associated with CLMs that are more infiltrating and more aggressive, increasing thus the risk of local recurrence following resection. Chemotherapy is an effective treatment for micrometastases. The morphological response on CT imaging can predict the presence of micrometastases, which may help in deciding the ideal surgical margin width.

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Liquid Biopsy

49

Rebecca A. Snyder, Arvind Dasari, and Y. Nancy You

Learning Objectives

- Assays to detect and isolate ctDNA in patients with metastatic colorectal cancer can be performed using either PCR or next-generation sequencing (NGS) techniques.
- In a randomized trial, patients with colorectal liver metastases (CRLM) treated with chemotherapy who had detectable ctDNA levels had a lower rate of margin-negative resection and worse overall survival compared to patients without detectable ctDNA.
- Prospective studies have demonstrated an association between postoperative ctDNA and recurrence-free survival and overall survival in patients with CRLM.
- In the future, detection of ctDNA following curative-intent liver resection may be used to identify patients at greatest risk for recurrence and to identify patients most likely to benefit from postoperative chemotherapy.

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49.1 Introduction

Liquid biopsy is an emerging technique with the potential promise of enabling noninvasive characterization of cancer, as well as monitoring for early detection of recurrent disease. The term "liquid biopsy," can refer to the detection of circulating tumour elements, including circulating tumour cells (CTC), circulating tumour DNA (ctDNA), or cellular components such as exosomes. This chapter will primarily focus on ctDNA, as there is growing evidence to support the use of this technique in colorectal cancer.

Cell-free DNA (cfDNA) is DNA that can be isolated from plasma and can be released from both malignant and nonmalignant cells. Circulating tumour DNA (ctDNA) is cell-free DNA that is derived from apoptotic or necrotic tumour cells and is typically comprised of fragments of DNA with a predictable length (typically between 140 and 170 base pairs) of DNA [1–3]. Assays to detect and isolate ctDNA from cfDNA can be performed using either PCR or next-generation sequencing (NGS) techniques (Fig. 49.1). PCR-based assays rely on the detection of specific mutations enriched in the tumour, such as *KRAS, NRAS,* or *BRAF*. Although highly sensitive, PCR-based assays are limited to detection based on a small number of known mutations. NGS-based techniques enable sequencing of the entire circulating genome and can be classified as targeted or non-targeted. Targeted NGS-based approaches are often limited to a panel of genes commonly present in cancers, or to specific mutation hotspots within several hundred genes that are specific to the particular cancer of the patient [4]. Non-targeted NGS-based approaches employ whole exome or whole genome sequencing and require significant time and bioinformatics expertise [5]. All detection techniques require strict quality control to avoid contamination with genomic DNA from lysed immune cells and for DNA integrity to ensure accurate and optimal sequencing [4]. To date, significant variation in specimen collection, DNA extraction, assay platforms, and subsequently application to clinical practice exists. Improved standardization of assay techniques will be critical to the conduct

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CONSENSUS STATEMENT

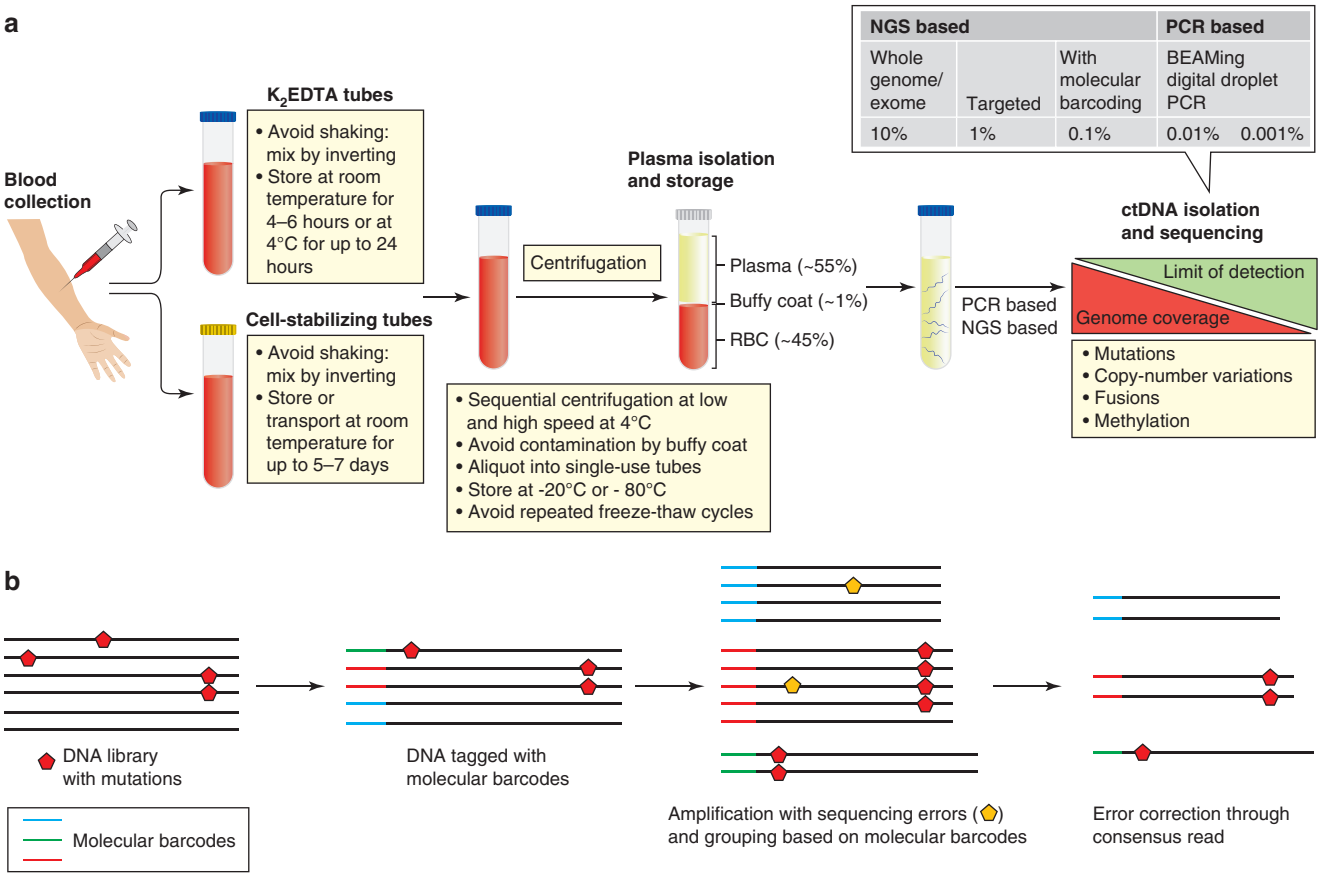

Fig. 49.1 ctDNA isolation and analysis. (**a**) Circulating cell-free DNA of which circulating tumour DNA (ctDNA) is a part of, is isolated from plasma samples after serial centrifugation of blood collection in either K, EDTA, or cell-stabilizing tubes. ctDNA is subsequently isolated from cell-free DNA using library preparations and analyzed for the presence of various genetic aberrations, including mutations, copy-number variations, fusions, and/or other alterations such as changes in DNA methylation. (**b**) Molecular barcoding: prior to PCR and sequencing, each DNA fragment can be labeled with unique DNA barcodes; subsequently, reads that share the same barcode (typically in thousands) can be grouped together because they all originate from the same ctDNA fragment. This approach enables sequencing errors (orange pentagon, seen in the minority) to be distinguished from true mutations (red pentagon, seen in the majority). Molecular barcoding also helps correct potential biases in amplification and thus assists in the precise quantification of mutations or amplification frequencies. NGS, next-generation sequencing; RBC, red blood cells. (Reprinted from: Dasari A, Morris VK, Allegra CJ, et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. *Nat Rev Clin Oncol.* 2020;17(12):757–770. Used with permission by creative commons license (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/)

of further scientific studies and to allow for meaningful implementation of ctDNA into clinical practice [4].

Interest in the role of ctDNA in colorectal cancer has been growing rapidly, as it has a number of potential applications along the cancer care continuum (Fig. 49.2). ctDNA detection may allow for early detection prior to clinical presentation or radiographic evidence of disease, identification of minimal residual disease (MRD) following curative-intent resection of locoregional disease, earlier detection of recurrent disease, or monitoring of treatment response in the neoadjuvant or metastatic setting.

Evidence to date indicates that the proportion of patients with detectable ctDNA varies based on the extent of disease, ranging from 50% among patients with locoregional CRC to 90% in patients with stage IV disease [6]. The focus of this chapter will be on the role of ctDNA as a measure of disease burden and treatment response in patients with colorectal liver metastases, particularly as it pertains to selection of patients who might be optimal candidates for surgical resection with curative intent.

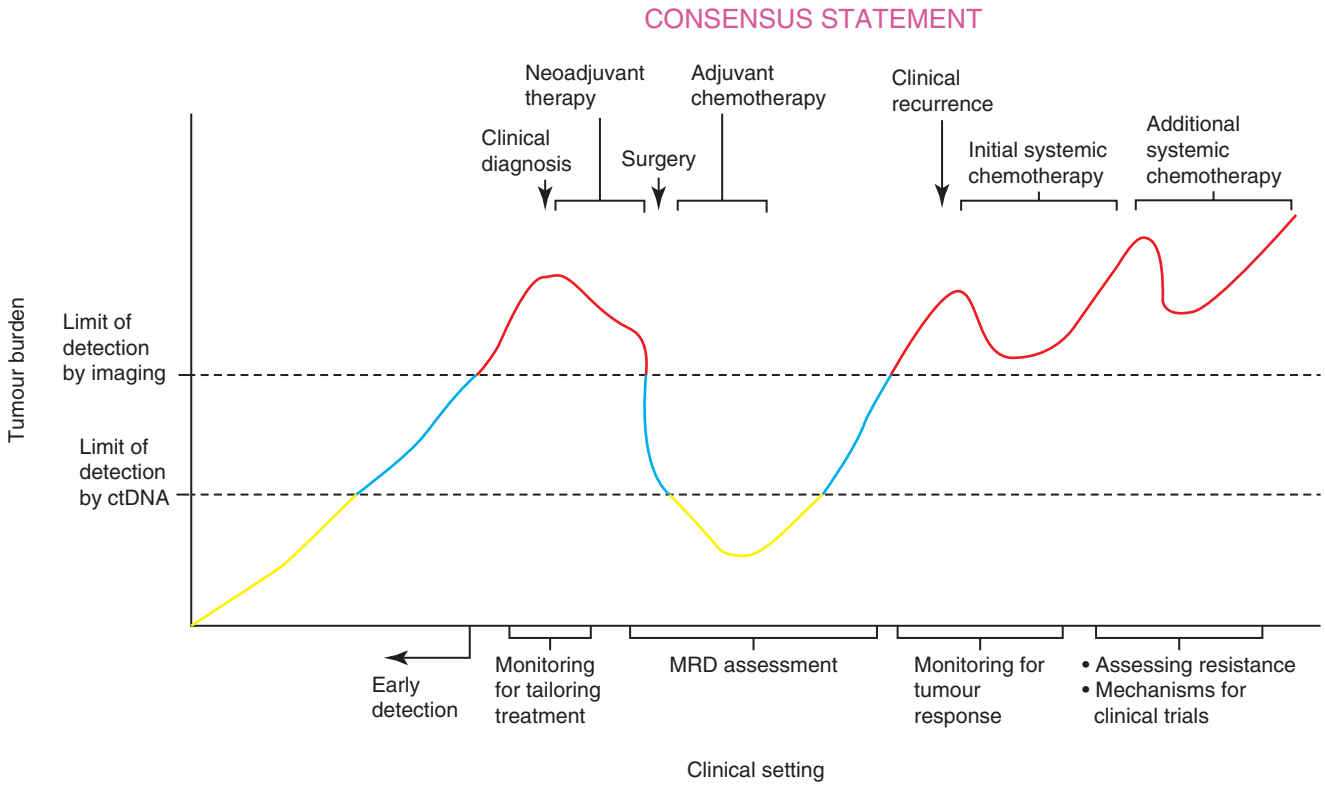

Fig. 49.2 Clinical applications of ctDNA. Circulating tumour DNA (ctDNA) provides a more sensitive method of detecting malignancies than imaging or other conventional approaches. This sensitivity can be exploited in several ways: early diagnosis of colorectal cancer prior to the emergence of clinical or radiological manifestations and in the detection of minimal residual disease (MRD), defined as the detection of ctDNA with no other clinical evidence of disease recurrence in patients who have completed all potentially curative therapies. In patients with radiographically evident disease, ctDNA also seems to be more sensitive to changes in tumour burden and might assist in tailoring the intensity of therapy in the neoadjuvant setting and in monitoring for tumour response in patients requiring palliative treatment. Furthermore, qualitative assessments of the types of aberrations and their subsequent alterations might assist in assessments of tumour evolution and heterogeneity that lead to the emergence of resistance as well as in the selection of the most appropriate therapies. (Reprinted from: Dasari A, Morris VK, Allegra CJ, et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. *Nat Rev Clin Oncol.* 2020;17(12):757–770. Used with permission by creative commons license (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/)

49.2 ctDNA and Resection of CRLM

Currently, resectability of colorectal liver metastases (CRLM) is determined based on multidisciplinary evaluation and careful consideration of the anatomic extent of tumour(s) in combination with the patient's underlying liver function. Patients with acceptable performance status who can undergo margin-negative resection with preservation of an adequate future liver remnant are considered surgical candidates. However, despite curative resection of CRLM, most patients develop recurrent disease. Within the EORTC 40893 randomized clinical trial of perioperative chemotherapy for resectable colorectal liver metastases, 3-year disease-free survival ranged from 29.9 to 39.0% across study arms [7].

The identification and selection of patients with favorable biology most likely to benefit from curative-intent resection would be advantageous and would allow for avoidance of futile surgery in patients at risk for early postoperative disease relapse. To date, although tumour mutational analysis provides some prognostic information, its role in the surgical selection of patients with CRLM has remained limited.

Emerging data have demonstrated an association between postoperative ctDNA levels and early disease recurrence in patients with locoregional CRC [4, 8–10]. This has sparked interest in evaluating the utility of ctDNA in the metastatic setting, specifically the association of baseline ctDNA or post-chemotherapy ctDNA and clinical outcomes, such as margin-negative resection, recurrence, and overall survival rates.

Only one phase II randomized clinical trial in patients with colorectal liver metastases (CRLM) that has included circulating tumour DNA (ctDNA) analysis has been reported to date [11]. The PRODIGE-14 trial randomized patients with potentially resectable CRLM to a first-line triplet

(FOLFIRINOX) or doublet chemotherapy [(5-FU, leucovorin, and oxaliplatin (FOLFOX) or 5-FU, leucovorin, irinotecan (FOLFIRI)] combined with targeted therapy (bevacizumab in RAS mutated tumours, cetuximab in RAS wild-type tumours). *KRAS* ctDNA analysis was performed by polymerase chain reaction (PCR) in all patients ($n = 125$) at baseline prior to treatment initiation. Analysis was performed again after 1 month of systemic therapy ($n = 35$) and prior to surgical resection ($n = 21$) in the subgroup of patients with *KRAS* exon 2 mutations in the primary tumour. *KRAS* ctDNA levels decreased significantly during chemotherapy ($p = 0.0001$). At baseline, 91% of patients with KRAS mutant tumours had detectable ctDNA, which decreased to 63% at 4 weeks, and 19% prior to surgery. Patients with persistently detectable ctDNA levels after 4 weeks of therapy had a lower R0/R1 resection rate than patients with no ctDNA detected (36% vs. 85%, $p = 0.01$) (Fig. 49.3). Additionally, among patients who underwent R0/R1 resection, patients with detectable ctDNA levels prior to surgery had a worse overall survival ($p < 0.001$) (Fig. 49.4). This suggests that the presence of detectable ctDNA after 4 weeks of systemic chemotherapy or at the completion of preoperative therapy could play a role in patient selection for resection of CRLM. The authors of this study suggest that the absence of detectable ctDNA levels during chemotherapy may ultimately become a selection criterion for metastasectomy.

Several smaller series have been reported with similar results. A prospective series of 60 patients with CRLM from Memorial Sloan Kettering Cancer Center demonstrated that detection of ctDNA (specifically *APC* and *TP53* mutant DNA) was associated with larger CRLM tumour size [12]. Additionally, pre-resection detection of *TP53* ctDNA in a peripheral blood sample was associated with worse disease-specific survival (DSS) compared to patients without *TP53* ctDNA detection; however, the presence of preoperative *APC* ctDNA or any ctDNA was not associated with DSS. A small, prospective study of 20 patients undergoing resection of CRLM found that presurgery ctDNA levels had a predictive value for relapse ($p < 0.001$), and that patients with low presurgery ctDNA were more likely to experience prolonged progression-free survival ($p < 0.001$) [13].

Similarly, in a single-center retrospective study of 40 patients who underwent resection for CRLM, ctDNA was detected in 80% of patients prior to surgery [14]. Recurrence-free survival (RFS) was significantly shorter in patients positive for ctDNA compared to patients without detectable

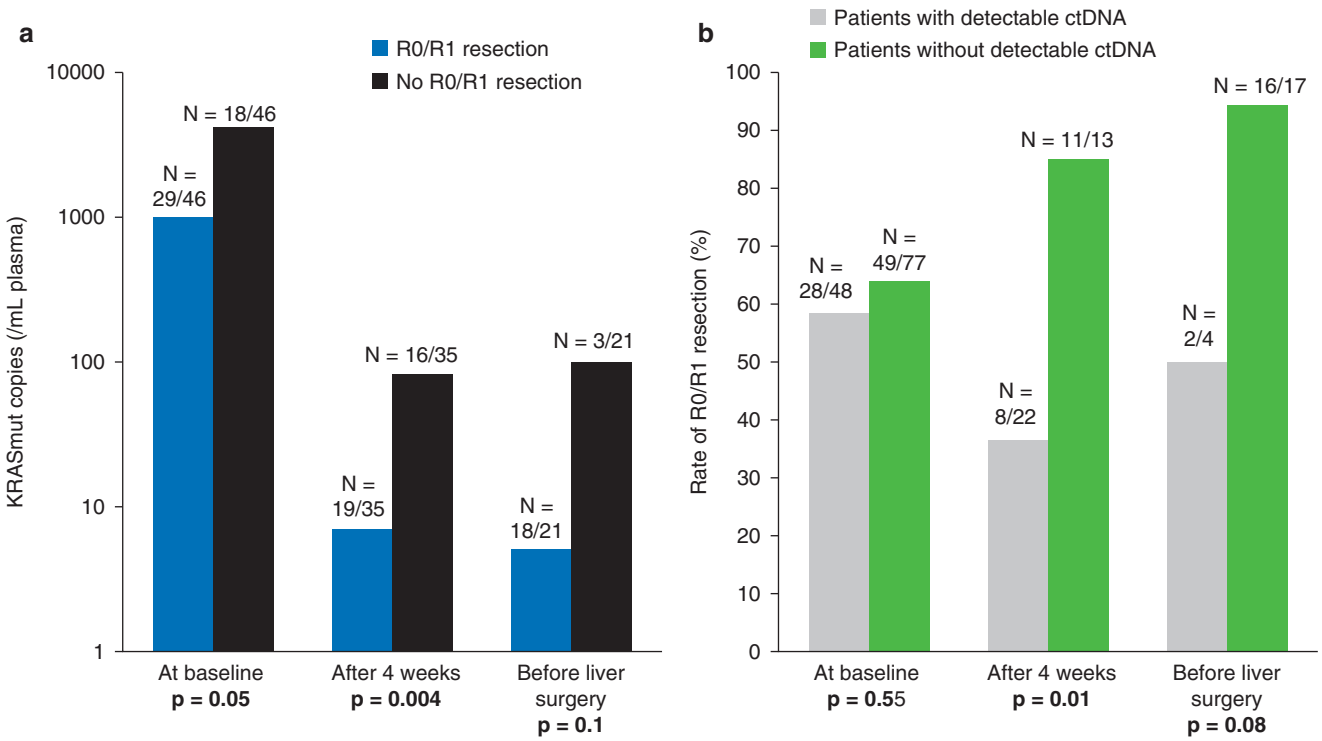

Fig. 49.3 (**a**) Mean number of KRAS mutated copies per mL of plasma at baseline, after 4 weeks, and prior to liver metastasis resection. N indicates the number of patients who achieved or did not achieve R0/R1 resection, among patients (with a KRAS mutated tumour) Available for KRAS mutation assessment at each timepoint. (**b**) Rate of R0/R1 resection for patients with or without detectable ctDNA (dichotomized variable). N indicates the number of patients who achieved R0/R1 resection according to their ctDNA detection status, among patients who underwent the ctDNA detection assay at each timepoint. (Reprinted from: Bidard FC, Kiavue N, Ychou M, et al. Circulating Tumour Cells and Circulating Tumour DNA Detection in Potentially Resectable Metastatic Colorectal Cancer: A Prospective Ancillary Study to the Unicancer Prodige-14 Trial. *Cells*. 2019;8 (6):28. Used with permission by creative commons license (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/)

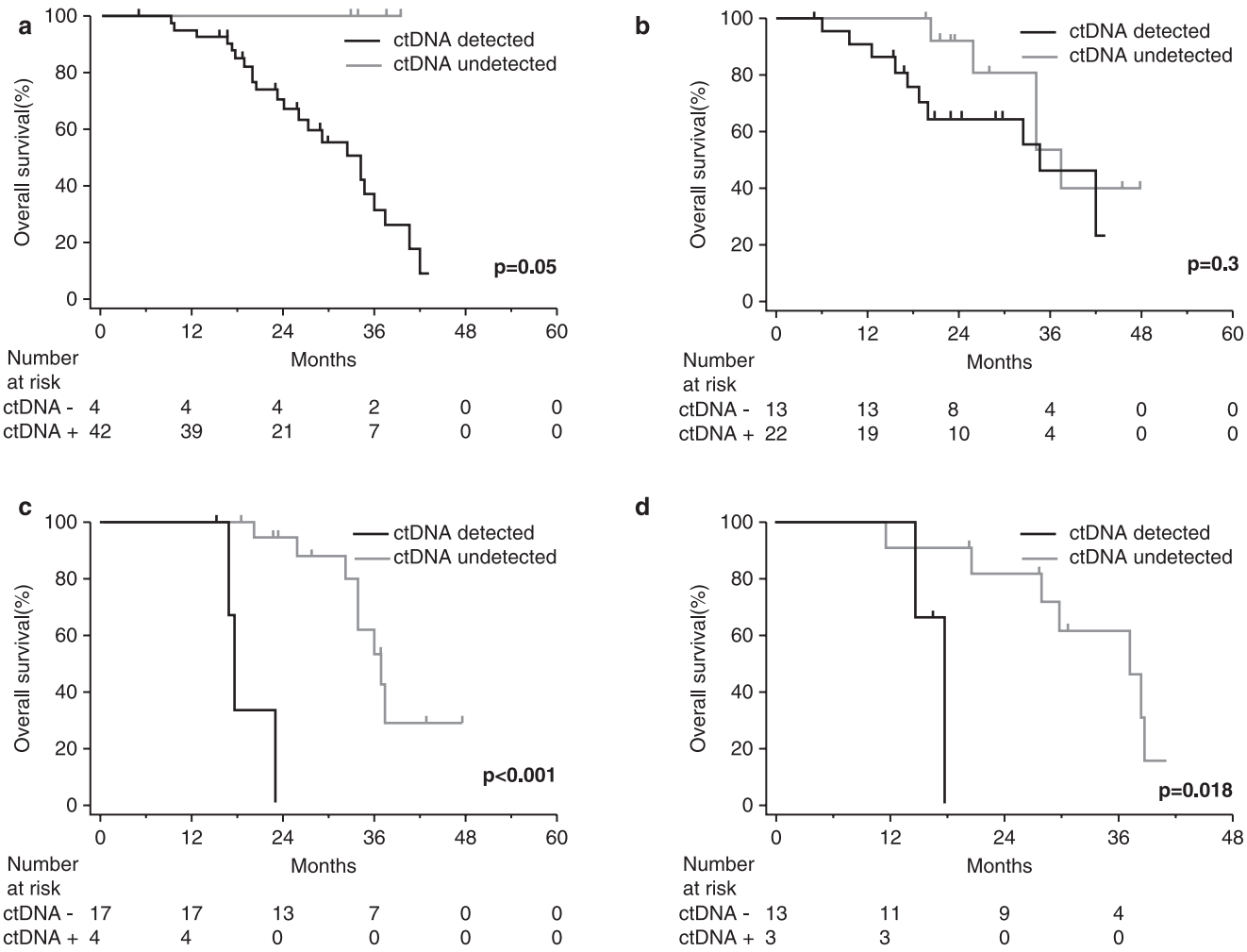

Fig. 49.4 Kaplan-Meier curves for Overall Survival according to ctDNA detection. (**a**) at baseline, (**b**) at 4 weeks, (**c**) before liver surgery, and (**d**) Kaplan-Meier curve for postoperative Overall Survival according to ctDNA detection before liver surgery. (Reprinted from: Bidard FC, Kiavue N, Ychou M, et al. Circulating Tumour Cells and Circulating Tumour DNA Detection in Potentially Resectable Metastatic Colorectal Cancer: A Prospective Ancillary Study to the Unicancer Prodige-14 Trial. *Cells.* 2019;8(6):28. Used with permission by creative commons license (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/)

ctDNA prior to hepatectomy (median 12.5 months vs. not reached (NR); $p = 0.02$). Finally, in a study of 41 patients who underwent hepatectomy for CRLM, patients with a decreased long-fragment cell-free DNA to Beta-globulin ratio had a significantly longer recurrence-free survival compared with patients with an increased ratio (366 days vs. 100 days, $p < 0.001$), suggesting that cell-free DNA to Beta-globulin ratio may serve as an effective marker of early recurrence following resection of CRLM [1].

49.3 ctDNA and Liver Directed Therapy

There are also several studies evaluating the role of ctDNA in patients undergoing nonsurgical treatment of CRLM, including hepatic arterial infusion (HAI) and chemoembolization. In a phase II study of 52 patients treated with HAI, patients with baseline ctDNA higher than the 75th quartile had shorter overall survival (2.4 years; 95% CI 0.7–2.8 years) compared to patients with baseline ctDNA lower than the 75th quartile (3.9 years; 95% CI 2.8–5.9 years, $p = 0.02$) [15]. A second phase II study of 14 patients treated with transarterial chemoembolization with irinotecan loaded beads (DEBIRI-TACE) reported a similar association between baseline ctDNA levels and prognosis, as well as improved OS among patients with a more significant decline in ctDNA levels following treatment [16]. This study closed early due to toxicity and lack of feasibility; therefore, due to the small study size, study findings did not meet statistical significance.

49.4 Residual Disease

Similar to the locoregional setting, it has been hypothesized that ctDNA could serve as a measure of MRD following curative-intent hepatectomy and could ultimately inform post-resection treatment planning, intensity of surveillance testing, and long-term prognosis.

In a series of 54 patients who underwent resection of CRLM at MD Anderson Cancer Center, ctDNA mutations were detected using a 21-gene panel in 80% of patients prior to surgery and 44% of patients following resection [17]. The sensitivity of postoperative ctDNA for recurrent disease was 58% (95% confidence interval (CI) 41–71%) and specificity 100% (95% CI 66–100%). Postoperative ctDNA detection was associated with worse recurrence-free survival (RFS) (0% vs. 47% 2-year RFS; $p = 0.002$), and ctDNA allowed for detection of recurrence a median of 5.1 months prior to radiographic evidence of recurrence. A follow-up study of 63 patients who underwent resection for CRLM at MD Anderson detected ctDNA in 67% of patients following resection using a 70-gene panel, with mutations most commonly identified in *APC* (76%), *TP53* (74%), and *KRAS* (38%) [18]. Two-year OS was worse in patients with detectable ctDNA after resection (70% vs. 100%, $p = 0.005$), and was worse for those with 4 or more mutations detected by liquid biopsy (41%).

In a small study of 28 patients with detectable preoperative ctDNA who underwent resection for CRLM, 26 (93%) were negative for ctDNA following surgery [19]. The remaining patients ($n = 2/28$) with positive ctDNA following metastasectomy developed recurrence within 6 months. Of the 7 patients who underwent R1 resection, 57% ($n = 4/7$) were positive for ctDNA, and all developed early disease recurrence within 3–7 months. Finally, in a cohort of 23 patients with CRLM who underwent curative-intent resection, recurrence occurred in 100% of patients with detectable ctDNA 3 months post-resection, but in only 50% of patients without detectable ctDNA [8].

Another study of 35 patients with CRC metastatic to the lungs or liver assessed total cfDNA and ctDNA following local therapy to the metastatic site [including resection, radiofrequency ablation (RFA), stereotactic beam radiotherapy (SBRT)] and found that ctDNA positive patients ($n = 5$) had a significantly shorter median time to recurrence (273 days) compared to ctDNA negative patients (median time to recurrence not reached) [20].

49.5 ctDNA and Treatment Response

In the metastatic setting, investigators have explored the association between changes in ctDNA levels and response to therapy, progression, and survival. A recent prospective study of 82 patients found that reductions in ctDNA concentrations of more than 80% after first- or second-line chemotherapy correlated with more favorable objective response rates (47.1% vs. 0%, $p = 0.03$), longer progression-free survival (8.5 months vs. 2.4 months, $p < 0.0001$), and improved overall survival (27.1 months vs. 11.2 months, $p < 0.001$) [21]. In another prospective study of 30 patients with metastatic colorectal cancer, ctDNA predicted more disease progression events than CEA levels (80% ($n = 16$) vs. 30% ($n = 6$), and the rise in ctDNA occurred significantly earlier than an increase in CEA in patients with increases in both ($p = 0.046$) [22].

49.6 Limitations

A number of limitations to the use of ctDNA for disease monitoring have been identified [4]. First, the reported studies have utilized a heterogenous mix of ctDNA detection methods, and the optimal technique is not yet established. Assays may be unreliable in patients without detectable somatic variants in ctDNA, either due to the absence of a detectable somatic mutation within the tumour or due to low disease burden. The sensitivity of most assays is approximately 85% and can vary depending on the extent of disease burden and tumour location. Secondly, the cost of ctDNA assays should be considered when determining how to integrate this testing into routine clinical practice. Careful consideration of cost coverage will be necessary to avoid exacerbating existing socioeconomic and insurance-based disparities in colorectal cancer care and outcomes. Thirdly, while ctDNA may be valuable for disease detection and monitoring, it remains unclear what clinical intervention should take place based on the ctDNA result. Furthermore, the impact of such clinical intervention on both ctDNA levels as well as on long-term oncologic outcomes is currently undefined.

49.7 Future Directions

Given the growing evidence regarding the role of ctDNA for the detection of recurrence after curative resection for locoregional CRC, it is plausible to expect that ctDNA will also prove to be a meaningful prognostic biomarker in the metastatic setting. Future studies are warranted to determine if detection of ctDNA following curative-intent liver resection may be used to identify patients at greatest risk for recurrence and to guide treatment decisions regarding the use of postoperative chemotherapy. Further, ctDNA may provide information regarding patient response to systemic chemotherapy, both in the preoperative and palliative settings. Finally, additional studies are necessary to determine if ctDNA can result in improved surveillance strategies following resection of CRLM (Table 49.1).

Table 49.1 Summary of studies of ctDNA detection and association with outcomes in patients with resectable colorectal liver metastases

Authors	Year	Study design	Cohort size (n)	Percent of patients with detectable ctDNA at clinical timepoints	Association of ctDNA detection with clinical outcomes
Bidard FC et al. [11]	2019	Phase II randomized clinical trial	125	Baseline: 91% • After 4 weeks of chemotherapy: 63% • Preoperative: 19%	• Lower R0/R1 resection rate in patients with persistently detectable ctDNA levels after 4 weeks of therapy (36% vs. 85%, $p = 0.01$) • Worse OS in patients with detectable ctDNA levels prior to resection ($p < 0.001$)
Narayan RR et al. [12]	2019	Single-institution prospective study	60		• Pre-resection detection of *TP53* ctDNA associated with worse DSS • Detection of preoperative *APC* ctDNA or any ctDNA not associated with DSS
He Y et al. [13]	2020	Single-institution prospective study	20		• Pre-surgery ctDNA levels associated with recurrence ($p < 0.001$) • Low pre-surgery ctDNA levels associated with prolonged PFS ($p < 0.001$)
Kobayashi S et al. [14]	2021	Single-institution retrospective study	40	• Preoperative: 80%	• RFS shorter in patients positive for ctDNA (median 12.5 months vs. not reached (NR); $p = 0.02$)
Iwai T et al. [1]	2020	Single-institution prospective study	41		• Decreased long-fragment cell-free DNA to Beta-globulin ratio associated with longer RFS compared to an increased ratio (366 days vs. 100 days, $p < 0.001$)
Overman MJ et al. [17]	2017	Single-institution prospective study	54	• Preoperative: 80% • Post-resection: 44%	• Sensitivity of postoperative ctDNA for recurrent disease 58% (95% CI 41–71%) and specificity 100% (95% CI 66–100%) • Postoperative ctDNA detection associated with worse RFS (0% vs. 47% 2-year RFS; $p = 0.002$)
Benesova L et al. [19]	2019	Multi-center prospective study	28	• Post-resection: 7%	• Patients ($n = 2/28$) with positive ctDNA following metastasectomy developed recurrence within 6 months • 57% of patients who underwent R1 resection ($n = 4/7$) were positive for ctDNA, and all developed early disease recurrence within 3–7 months
Scholer LV et al. [8]	2017	Single-institution prospective study	23		• Recurrence occurred in 100% of patients with detectable ctDNA 3 months post-resection vs. 50% of patients without detectable ctDNA
Boysen AK et al. [20]	2020	Single-institution prospective study	35		• Shorter median time to recurrence in ctDNA positive patients ($n = 5$; median 273 days) compared to ctDNA negative patients (median NR)
Mason MC et al. [18]	2021	Single-institution retrospective study	63	• Post-resection: 67%	• 2-year OS worse in patients with a positive liquid biopsy (70% vs. 100%; $p = 0.005$) • Presence of ≥4 mutations associated with worse 2-year OS (41%, $p < 0.001$)

Circulating tumour DNA (ctDNA); overall survival (OS); progression free survival (PFS); disease specific survival (DSS); recurrence free survival (RFS)

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Part VI

Genetic Sequencing and Clinical Implication

Multigene Testing for Prognostication and Therapeutic Actionability

50

Federico Oppliger, Wai Chin Foo, and Yun Shin Chun

Learning Objectives

- Molecular alterations in colorectal liver metastases are increasingly used to evaluate tumour biology and direct targeted therapy.
- *RAS* mutations are established as an adverse prognostic factor after resection of colorectal liver metastases and predict resistance to treatment with anti-epidermal growth factor receptor therapy.
- Double mutation in *RAS/TP53* and triple mutation in *RAS/TP53/SMAD4* are more powerful predictors of prognosis after resection of colorectal liver metastases than *RAS* mutation alone.

50.1 Introduction

The heterogeneity of cancer metastasis has been recognized for decades, but the underlying biology has remained elusive until the advent of high-throughput, cost-effective molecular testing [1]. Today, rapid developments in molecular profiling and targeted anticancer therapy have led to the identification of distinct molecular subtypes of colorectal liver metastases (CLM) and effective, novel treatment strategies. In the 1990s, DNA mismatch repair (MMR) deficiency leading to microsatellite instability-high (MSI-H) tumours was identified as an important factor resulting in colon carcinogenesis [2]. In 2020, the United States Food and Drug Administration (FDA) approved immunotherapy for first-line treatment of patients with metastatic MSI-H colorectal cancer. However, MSI-H tumours affect <2% of patients undergoing resection of CLM. In contrast, somatic gene mutations, particularly driver mutations in *RAS* and *BRAF,* have emerged as key biologic factors in CLM that determine prognosis and response to therapy. Furthermore, co-occurring mutations in doublet and triplet combinations have been found to have a greater impact on prognosis than an isolated, single gene mutation.

50.2 Multigene Testing Technology and Analysis

Technology for multigene testing of CLM has evolved from sequencing a limited number of genes and exons to rapid, high-throughput sequencing of hundreds of genes (Fig. 50.1). The workflow for multigene testing entails DNA extraction from formalin-fixed, paraffin-embedded tumour tissue, followed by preparation of a sequencing library of amplified DNA fragments. The nucleic acid sequence is then determined by a DNA sequencing machine, and data are analyzed using specialized software. In CLM, the mutation status of *RAS, BRAF,* and *TP53* has been shown to be >90% concordant between primary colorectal cancer and liver metastasis [3]. Thus, genotyping can be performed from tissue obtained from the primary tumour or liver metastasis.

A potential drawback of large gene panels is alterations of unknown significance. Determining whether a genetic alteration is pathogenic or a benign polymorphism depends upon comparison with publicly available and institutional databases of somatic mutations in cancer [4]. Parallel sequencing of tumour specimens with paired normal tissue or blood improves the accuracy of distinguishing somatic mutations from germline variants. An additional challenge with the analysis of large multigene panels is differentiating clinically significant driver mutations from bystander passenger mutations.

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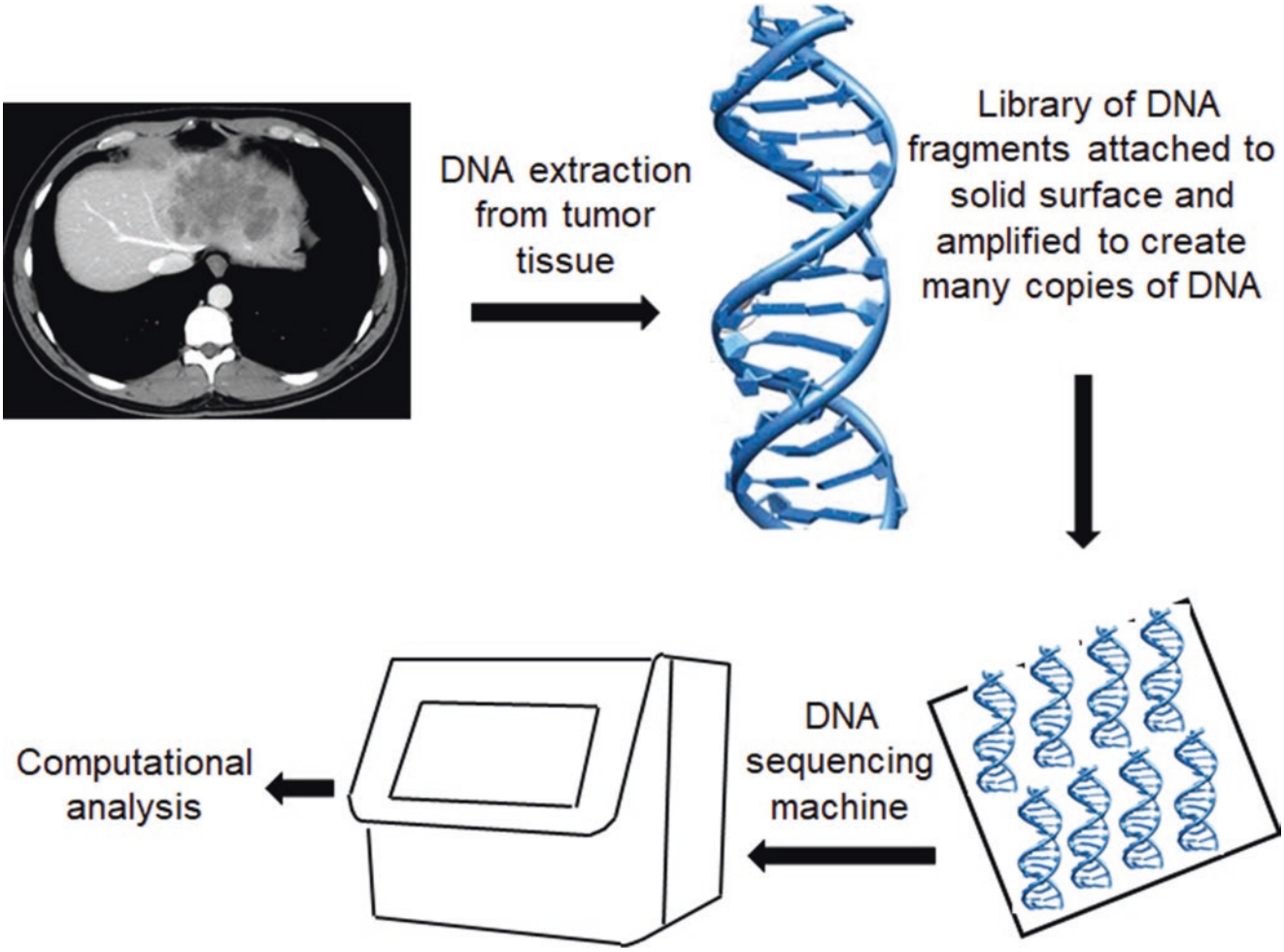

Fig. 50.1 Workflow of next-generation sequencing

50.3 Mismatch Repair

The MMR system repairs errors in complementary base pairing that occur during DNA replication, recombination, or from exogenous carcinogens. The main proteins in the MMR system are MLH1, MSH2, MSH3, MSH6, and PMS2 [2]. In colorectal cancer, deficient MMR (dMMR) occurs from silencing of the MLH1 gene or, less commonly, a germline mutation in one of the MMR genes in patients with Lynch syndrome. Microsatellites are short tandem repeats of DNA that are prone to mismatch errors. Colorectal cancers with dMMR are characterized by high microsatellite instability, with numerous microsatellite insertions and deletions.

A practical, cost-effective method to detect MSI-H colorectal cancer is immunohistochemical staining for loss of one or more of the MMR proteins (Fig. 50.2). The polymerase chain reaction (PCR)-based MSI test compares a panel of microsatellite loci between tumour and normal tissue. A tumour is classified as MSI-H if the number of repeats in tumour versus normal tissue differs in ≥2 microsatellite loci. Next-generation sequencing of dozens to hundreds of microsatellites can also be performed.

Colorectal cancers with dMMR are characterized by a high tumour mutation burden and tumour-specific neoantigens at the surface of cancer cells that are recognized by the immune system. Clinical trials of immunotherapy in metastatic colorectal cancer have shown favorable objective response and survival rates in dMMR tumours (see Chap. 35). For metastatic colorectal cancer that is not MSI-H, clinical trials, thus far, have not shown a benefit with immunotherapy. Among patients undergoing CLM resection, < 2% have MSI-H tumours. Thus, the prognostic effect of dMMR after CLM resection is not well-established.

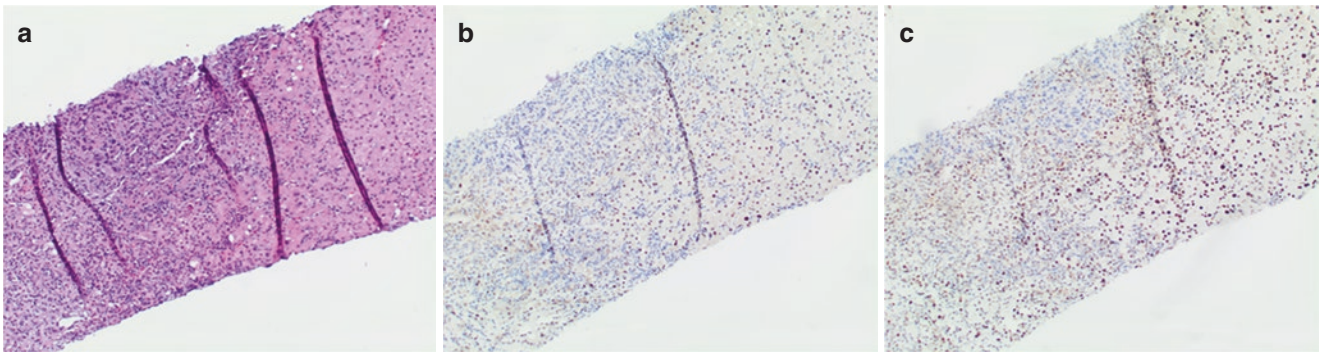

Fig. 50.2 Biopsy of liver metastasis from a patient with microsatellite instability-high colorectal cancer. (**a**) Hematoxylin-and-eosin-stained slide. (**b**) Immunohistochemistry showing loss of MSH2. (**c**) Loss of MSH6

50.4 Primary Tumour Sidedness

The location of the primary tumour in the left (splenic flexure to rectum) and right colon (cecum to hepatic flexure) has been shown to be a prognostic and predictive factor in metastatic colorectal cancer [5, 6]. Right-sided tumours have a higher prevalence of *BRAF* mutations and worse survival after CLM resection. Primary tumour sidedness is predictive of response to anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer. In clinical trials of *RAS* wild-type tumours, anti-EGFR therapy in the first-line setting was not beneficial for patients with right-sided primary tumours [7]. In contrast, primary tumour sidedness did not affect the efficacy of bevacizumab [8].

50.5 Somatic Gene Mutations

50.5.1 RAS

The *RAS* genes encode the proteins KRas, NRas, and HRas, which are members of the family of small GTPases in the mitogen-activated protein kinase (MAPK) signaling pathway (Fig. 50.3) [9]. The MAPK pathway transmits extracellular signals to the nucleus to regulate cell growth and apoptosis. EGFR lies upstream of Ras in the MAPK pathway. In colorectal cancer, a somatic mutation in *KRAS* or *NRAS* leads to constitutive activation of the encoded Ras protein and, importantly, resistance to therapies that target EGFR.

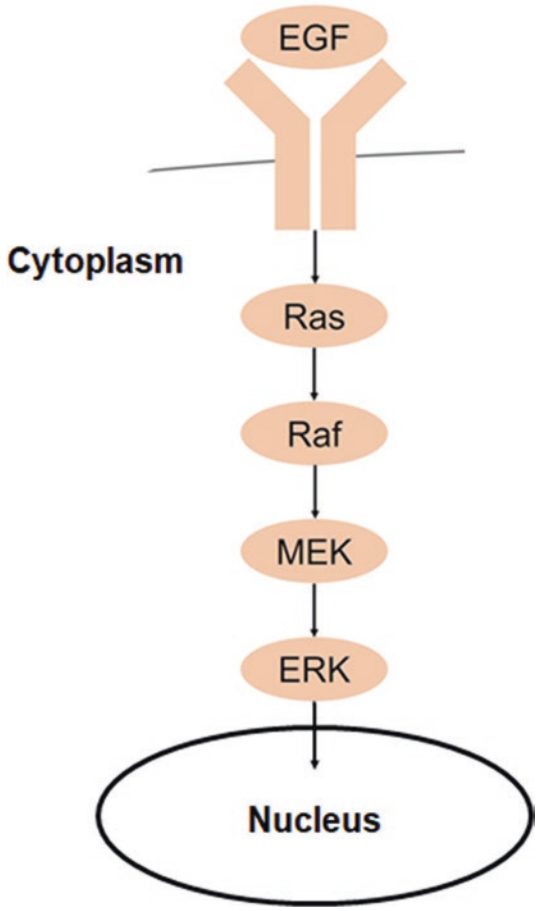

Fig. 50.3 Signaling between epidermal growth factor receptor, Ras, and Raf in the mitogen-activated protein kinase signaling pathway [33]

Among patients undergoing CLM resection, *RAS* mutations are the most well-established prognostic biomarker and identified in approximately 40–50% of patients (Fig. 50.4). In a study published in 2013 of 193 patients undergoing CLM resection, *RAS* mutations predicted significantly lower overall survival (OS), with 3-year OS of 52.2% with a *RAS* mutation, compared with 81% *RAS* wild-type ($P = 0.002$) [10]. Pattern of recurrence after CLM resection was also impacted by *RAS* mutations, which were associated with higher rate of recurrence in the lungs (3-year lung recurrence-free survival, 34.6% vs. 59.3%, $P < 0.001$). A meta-analysis of 1181 patients confirmed the poor prognostic effect of *RAS* after CLM resection [11].

Historically, *RAS* has been difficult to target pharmacologically due to the smooth structure of the protein, which

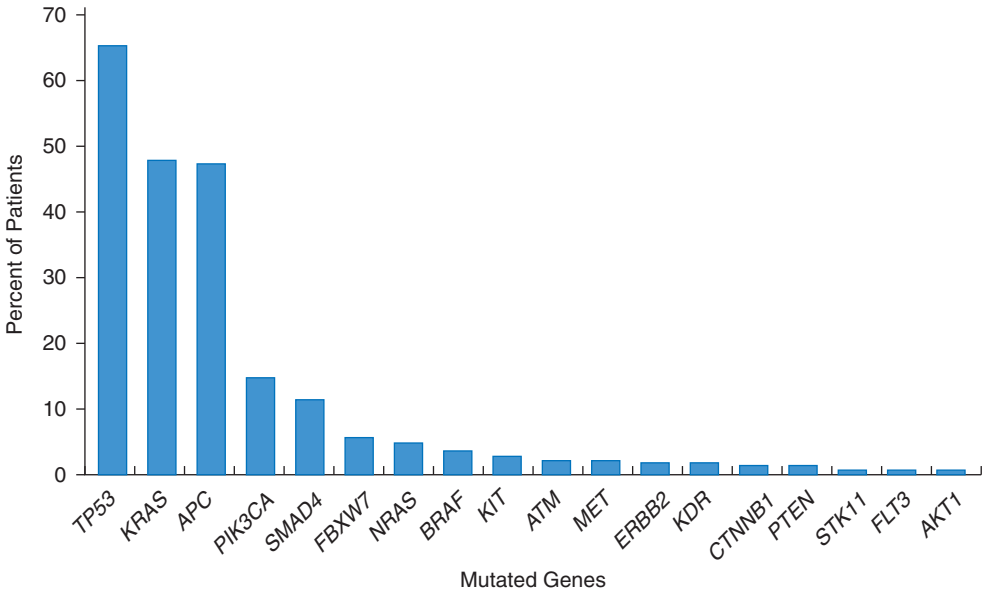

Fig. 50.4 Distribution of somatic gene mutations among patients undergoing resection of colorectal liver metastases [28]

lacks surface grooves for inhibitors to bind [12]. Recently, sotorasib, an allele-specific covalent inhibitor of the specific *KRAS* mutant, G12C, demonstrated a 37.4% objective response rate and median progression-free survival (PFS) of 6.7 months in patients with non-small-cell lung cancer (NSCLC) [13]. Based on these results from the registrational phase II CodeBreak 100 trial, sotorasib received FDA approval for *KRAS* G12C-mutated NSCLC. Unlike NSCLC, *KRAS* G12C mutations are uncommon in metastatic colorectal cancer, identified in only 3.1% of patients [14]. In patients with *KRAS* G12C-mutated metastatic colorectal cancer treated with at least two previous lines of systemic therapy, the objective response with sotorasib was only 7.1% [15]. The lack of response to *KRAS* G12C inhibition in colorectal cancer is hypothesized to result from pathways other than *RAS* that mediate oncogenic signaling.

50.5.2 BRAF

BRAF, a member of the rapidly accelerated fibrosarcoma (Raf) family of protein kinases, leads to activation of the MAPK signaling pathway downstream of Ras (Fig. 50.3). In metastatic colorectal cancer, *BRAF* mutations are present in 8–12% of patients and associated with a poor median OS of only 12 months [16]. Patients with *BRAF* mutations are less likely to present with metastases confined to the liver, and, hence, comprise <5% of the population in hepatectomy series. In a multicenter study of 1497 patients undergoing CLM resection, median OS and recurrence-free survival (RFS) rates were significantly shorter with a *BRAF* mutation, compared with *BRAF* wild-type (OS, 40 vs. 81 months; RFS, 10 vs. 22 months; both $P < 0.001$) [17].

The most common *BRAF* mutation is V600E, leading to a change in amino acid from valine (V) to glutamic acid (E) at codon 600. Up to a quarter of *BRAF* mutations in colorectal cancer encode non-V600E mutations. A pooled analysis of metastatic colorectal cancer patients showed that non-V600E *BRAF* mutations are associated with a favorable prognosis, with a median OS rate of 60.7 months, compared with 11.4 and 43.0 months with V600E mutation and *BRAF* wild-type, respectively ($P < 0.001$) [18]. However, series of CLM resection have not demonstrated improved survival with non-V600E mutations, likely due to the small number of patients.

BRAF inhibitors have demonstrated clinical activity in other cancers harboring *BRAF* V600E mutations, including melanoma, thyroid cancer, and NSCLC. However, in colorectal cancer, single-agent BRAF inhibitors do not yield a clinical benefit because of feedback upregulation of signaling through the EGFR pathway. Clinical trials combining BRAF inhibitors with blockade of EGFR and/or MAPK kinase (MEK) for *BRAF* V600E-mutated metastatic colorectal cancer have shown promising results (see Chap. 33) [19, 20].

50.5.3 ERBB2/HER2 Amplification

ERBB2, commonly referred to as *HER2*, encodes a member of the EGFR family of receptor tyrosine kinases. *HER2* amplification leads to constitutive activation of HER2-dependent intracellular signaling and increased tumour growth in many cancer types. For HER2-positive breast and gastric cancers, HER2 blockade has led to significant improvements in survival.

In metastatic colorectal cancer, *HER2* amplification is identified in 2–6% of patients and confers resistance to anti-

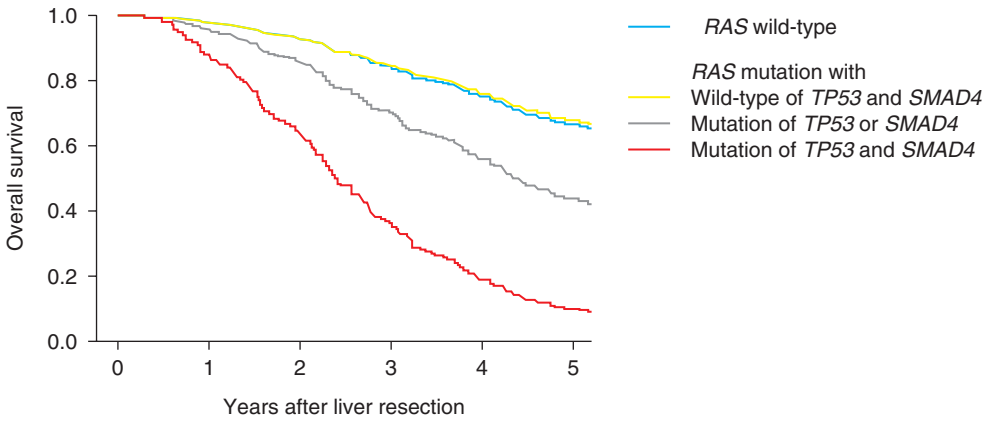

Fig. 50.5 Overall survival after resection of colorectal liver metastases, stratified by *RAS, TP53*, and *SMAD4* mutations [30]

EGFR therapies [21]. Phase II trials of HER2 inhibitors in patients with treatment-refractory metastatic colorectal cancer have demonstrated objective response rates of 28–32% (see Chap. 33) [21, 22]. Importantly, *RAS* mutations are associated with resistance to HER2 inhibition in metastatic colorectal cancer [23].

50.5.4 SMAD4

SMAD4 is a tumour suppressor gene in the transforming growth factor-β signaling pathway. In colorectal cancer, *SMAD4* mutations are associated with resistance to chemotherapy and poor prognosis. *SMAD4* mutations have been identified in 13% of patients with both resectable and unresectable CLM, suggesting that unlike *BRAF*, *SMAD4* does not affect the rate of liver-limited metastases [24]. In a study of 278 patients undergoing CLM resection, patients with mutated-*SMAD4* had significantly lower 3-year OS of 62%, compared with 82% for *SMAD* wild-type ($P < 0.001$) [25].

50.5.5 FBXW7

FBXW7 is a tumour suppressor gene that encodes a protein that regulates degradation of many oncoproteins, such as mTOR and Notch. After CLM resection, *FBXW7* mutations, identified in approximately 6% of patients, have been shown to significantly affect survival (5-year OS, 29.7% vs. 61.2%, with and without *FBXW7* mutation, $P = 0.005$) [26].

50.5.6 Concurrent Mutations

Concurrent mutations in oncogenes and/or tumour suppressor genes in doublet or triplet combinations are increasingly recognized as stronger determinants of tumour biology than a single gene mutation. The most frequently mutated gene in CLM is *TP53*, which in isolation, does not affect prognosis (Fig. 50.4). Preclinical studies in colorectal cancer have shown that cooperation between mutated *TP53* and *RAS* activation is critical for malignant transformation [27]. In a study of 401 patients undergoing CLM resection, double mutation in *RAS/TP53* was an independent predictor of worse OS and PFS [28]. The negative prognostic effect of *RAS* and *TP53* mutations was restricted to patients whose tumours carried both mutations. Double mutation in *BRAF* and *TP53* has also been correlated with poor survival [29].

Triple mutation in *RAS, TP53*, and *SMAD4* has an even greater adverse effect on survival than double mutation after CLM resection [30]. In a study of 507 patients undergoing CLM resection, patients with *RAS* mutation and wild-type *TP53* or *SMAD4* had similar survival rates as those with *RAS* wild-type tumours (Fig. 50.5). Survival was significantly shorter with double mutation in *RAS/TP53* or *RAS/SMAD4*, and this decrement in survival increased with triple mutation in all 3 genes. On multivariable analysis, *RAS/TP53/SMAD4* triple mutation was an independent predictor of worse OS, with a hazard ratio of 8.61, compared with wild-type for the 3 genes (95% CI 3.80–19.5, $P < 0.001$).

In a recent analysis of a multigene liquid biopsy panel, the presence of ≥4 mutated genes in circulating tumour DNA was an independent predictor of worse OS after CLM resection [31]. The worse survival with multiple concurrent mutations is partly attributable to increased tumour heterogeneity and evolution of subclones resistant to therapy. In addition, tumours harboring multiple mutations driving different signaling pathways cannot be arrested by agents that block a single pathway.

50.6 Implications of Gene Mutations for Surgical Practice

Patients with adverse gene mutations, including *RAS/TP53/SMAD3* triple mutation or *RAS/TP53* double mutation, should be assessed for response to systemic therapy or disease stability before considering liver resection. On the other

hand, patients with traditionally poor prognostic factors, such as limited extrahepatic disease, can be considered for surgery if their mutational status is favorable. *RAS* mutation status affects short- and long-term risks of disease recurrence after CLM resection and can guide postoperative surveillance algorithms (see Chap. 59) [32].

50.7 Conclusions

Rapid advances in molecular diagnostics and interpretation are revealing new insights into CLM biology and tumour heterogeneity. These insights have led to the development of biomarkers that not only predict response to treatment and survival but also serve as actionable targets for anticancer therapy. Patients undergoing CLM resection should undergo evaluation for dMMR, *HER2* amplification, and mutations in *KRAS, NRAS, TP53, SMAD4,* and *FBXW7*. Further studies are needed to elucidate mechanisms for cooperativity between multiple mutations that drive malignant progression and resistance to therapy.

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Cancer-Related Signaling Pathway and Prognosis

51

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Learning Objectives

- For patients with colorectal liver metastases, the following seven cancer-related signaling pathways are frequently altered: (1) p53, (2) Wnt, (3) RTK-RAS, (4) PI3K, (5) TGFβ, (6) Notch, and (7) cell cycle pathways.
- Pathway alterations in the chapter were mostly attributable to one predominant gene or gene group: (1) p53 (*TP53*), (2) Wnt (*APC*), (3) RTK-RAS (*RAS/BRAF*), (4) PI3K(*PIK3CA*), (5) TGFβ(*SMAD4*), (6) Notch (*FBXW7*), and (7) cell cycle (*RB1*) pathways.
- Four signaling pathways (p53, RTK-RAS, TGFβ, and Notch) and corresponding predominant member genes (*TP53, RAS/BRAF, SMAD4,* and *FBXW7*) were associated with worse survival in patients undergoing resection of colorectal liver metastases.
- Alterations of the Wnt pathway and *APC* were associated with better OS.
- Pathway-centric risk classification is useful for finer prognostication in patients undergoing resection of colorectal liver metastases.

51.1 Introduction

Colorectal liver metastases (CLM) develop in 15–30% of patients with colorectal cancer [1]. Advancements in medical therapy including oxaliplatin- and irinotecan-containing regimen and molecular targeted therapy have contributed to expand surgical indication and to improve survival in patients undergoing CLM resection and patients with unresectable CLM [2]. Nonetheless, liver resection remains an effective curative-intent treatment in patients with CLM and provides approximately 40–59% of the 5-year overall survival (OS) [3–6]. Prognosis after CLM resection widely varies depending on risk factors for survival: e.g., number of CLM, largest CLM diameter, primary lymph node status, primary T factor, extrahepatic metastases, and R0 resection status [7, 8]. Recently, studies reported that information on somatic gene alteration of CLM is useful for prognostication after CLM resection [9–11], finer stratification of recurrence risk [6], decision-making of postoperative surveillance intensity [12], and potential for guiding future therapy in patients undergoing CLM resection. Most studies assessed specific single somatic gene alteration (especially, *RAS* and *BRAF*) in patients undergoing CLM resection. Our study at MD Anderson Cancer Center showed that alterations of multiple somatic genes (e.g, double alteration of *RAS* and *TP53*, and triple alteration of *RAS*, *TP53*, and *SMAD4*) stratified prognosis in patients undergoing CLM resection, rather than single somatic gene alteration [6, 11, 13]. We expanded this approach to understand molecular biology of metastatic colorectal cancer in the context of cancer-related signaling pathway [14], as shown by The Cancer Genome Atlas (TCGA) project [15]. This chapter details multiple somatic gene alteration and cancer-related signaling pathway in patients with metastatic colorectal cancer to improve understanding of clinical heterogeneity of this patient group.

51.2 Alterations in Pathways and Member Genes in Patients Undergoing CLM Resection

TCGA grouped hypermutation status and recurrent alterations in the following 5 signaling pathways: (1) p53, (2) Wnt, (3) receptor-tyrosine kinase (RTK)-RAS, (4) phosphatidylinositol-3-Kinase (PI3K), and (5) transforming growth factor beta

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(TGFβ). Our recent study added (6) Notch pathway and (7) cell cycle pathway on the basis of another study which produced a list of candidate member genes for 10 canonical signaling pathways (Fig. 51.1) [16]. Figure 51.2a shows the frequency of seven cancer-related signaling pathways in the analysis of 579 patients who had genetic sequencing data and underwent CLM resection [14]. The alteration of p53 pathway was the most frequent (73%) followed by the alterations of Wnt pathway (59%), RTK-RAS pathway (58%), PI3K pathway (19%), TGFβ pathway (11.2%), Notch pathway (7.1%),

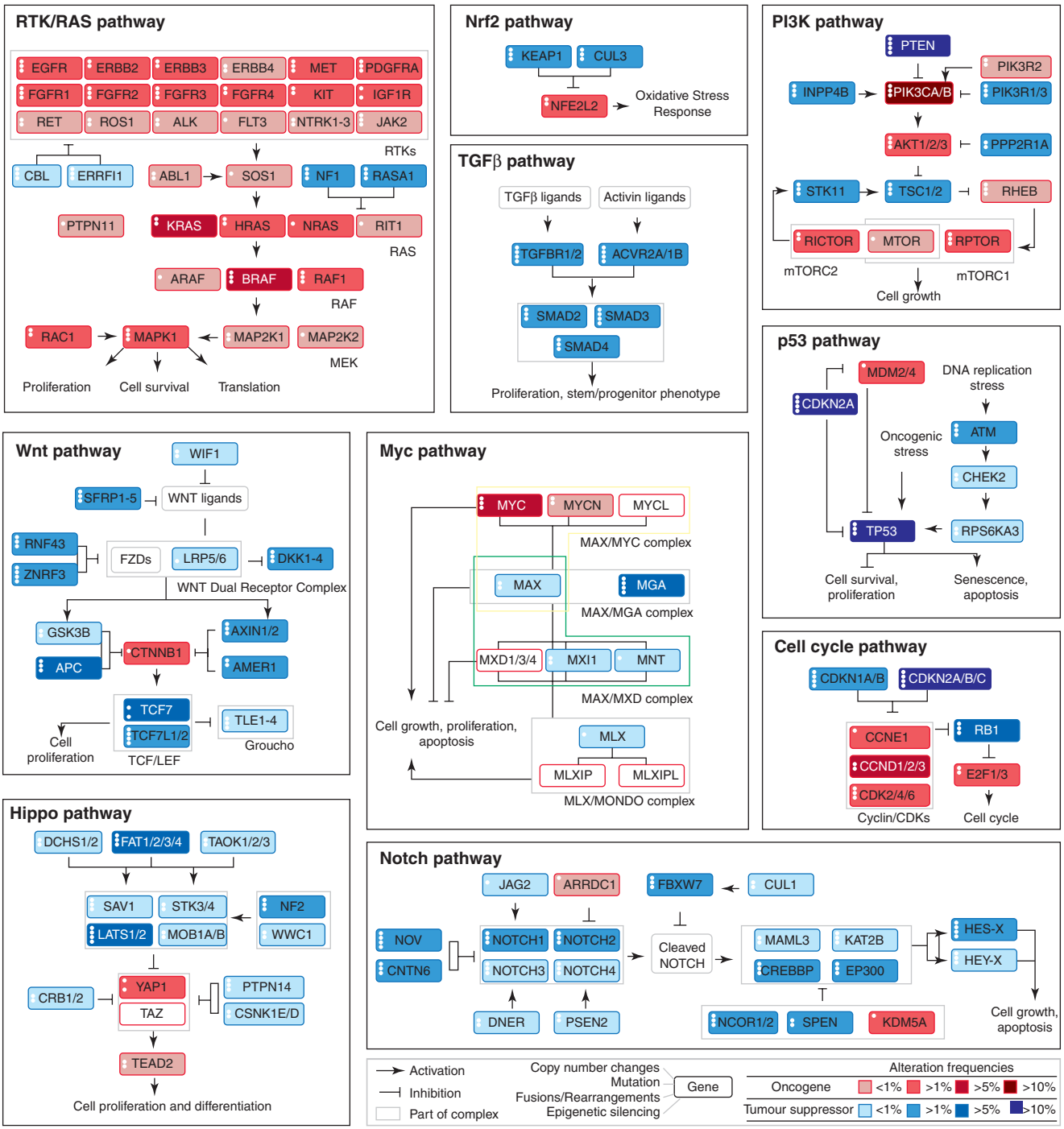

Fig. 51.1 Cancer-related signaling pathways. (Sanchez-Vega, F., et al. Oncogenic Signaling Pathways in The Cancer Genome Atlas. (Sanchez-Vega, F., et al. (2018). "Oncogenic Signaling Pathways in The Cancer Genome Atlas." Cell 173(2): 321–337 e310., with permission [16])

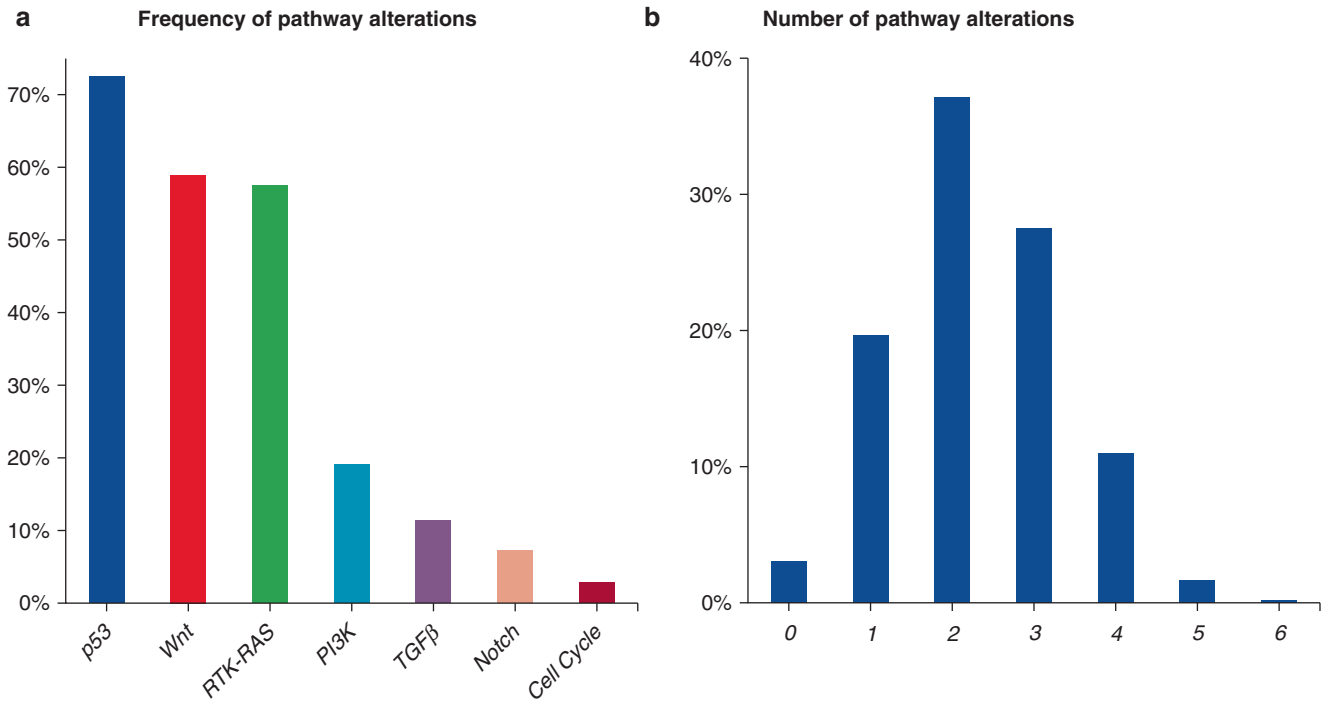

Fig. 51.2 Frequencies of alterations in seven cancer-related signaling pathways (**a**) overall and (**b**) frequencies of specific numbers of pathway alterations. (Kawaguchi Y, et al. "Genomic Sequencing and Insight into Clinical Heterogeneity and Prognostic Pathway Genes in Patients with Metastatic Colorectal Cancer." J Am Coll Surg. 2021 Jun 3:S1072-7515(21)00412-9. https://doi.org/10.1016/j.jamcollsurg.2021.05.027. Online ahead of print, with permission [14])

and cell cycle pathway (2.6%). Figure 51.2b shows the number of alterations found in 579 patients. These data clearly show that metastatic colorectal cancer is genomically heterogeneous. Approximately 80% of patients with metastatic colorectal cancer had 1–3 alterations in signaling pathways whereas 5% of patients had no pathway alteration and 15% of patients had four or more pathway alterations.

51.3 Cancer-Related Signaling Pathway and Member Genes

The analysis of the same 579 patients showed the proportion of member genes in each signaling pathway (Fig. 51.3) [14]. Interestingly, most pathway alterations were attributable to one predominant gene or gene group. *TP53* was a dominant somatic gene, accounting for 97.4% of alteration in the p53 pathway; *APC*, for 97.9% of the Wnt pathway; *RAS/BRAF* for 92.8% of the RTK-RAS pathway; *PIK3CA* for 84.5% of the PI3K pathway; *FBXW7* for 92.7% of the Notch pathway; *RB1* for 73.3% of the cell cycle pathway. In the TGFβ pathway, alteration of only one gene, *SMAD4* was tested according to the 46-gene panel used (Fig. 51.3e).

51.4 Pathway/Predominant Member Gene and Clinical Heterogeneity

In the same cohort (579 patients undergoing CLM resection), a Cox proportional hazards model analysis showed that alterations of four pathways (p53, RTK-RAS, TGFβ, and Notch) and corresponding predominant member genes (*TP53, RAS/BRAF, SMAD4,* and *FBXW7*) were significantly associated with worse OS, and alterations of the Wnt pathway and *APC* were associated with better OS (Table 51.1). Clinicopathologic factors including age, primary lymph node metastases, number of CLM, and largest CLM diameter were associated with OS. Adjusted hazard ratios of signaling pathways and corresponding predominant member genes are shown in Table 51.1. According to the results of the Cox proportional hazards model analysis, the prognosis after CLM resection was estimated as the worst in patients who had tumours with alterations of p53 (*TP53*), RTK-RAS (*RAS/BRAF*), and TGFβ (*SMAD4*), and wild-type of Wnt (*APC*). The pathway-centric risk scores (from 0 to 4) of OS in patients undergoing CLM resection were generalized as follows: 1 + (number of alterations of *TP53, RAS/BRAF,* and *SMAD4*) − 1 (if *APC* is altered). The final pathway-centric

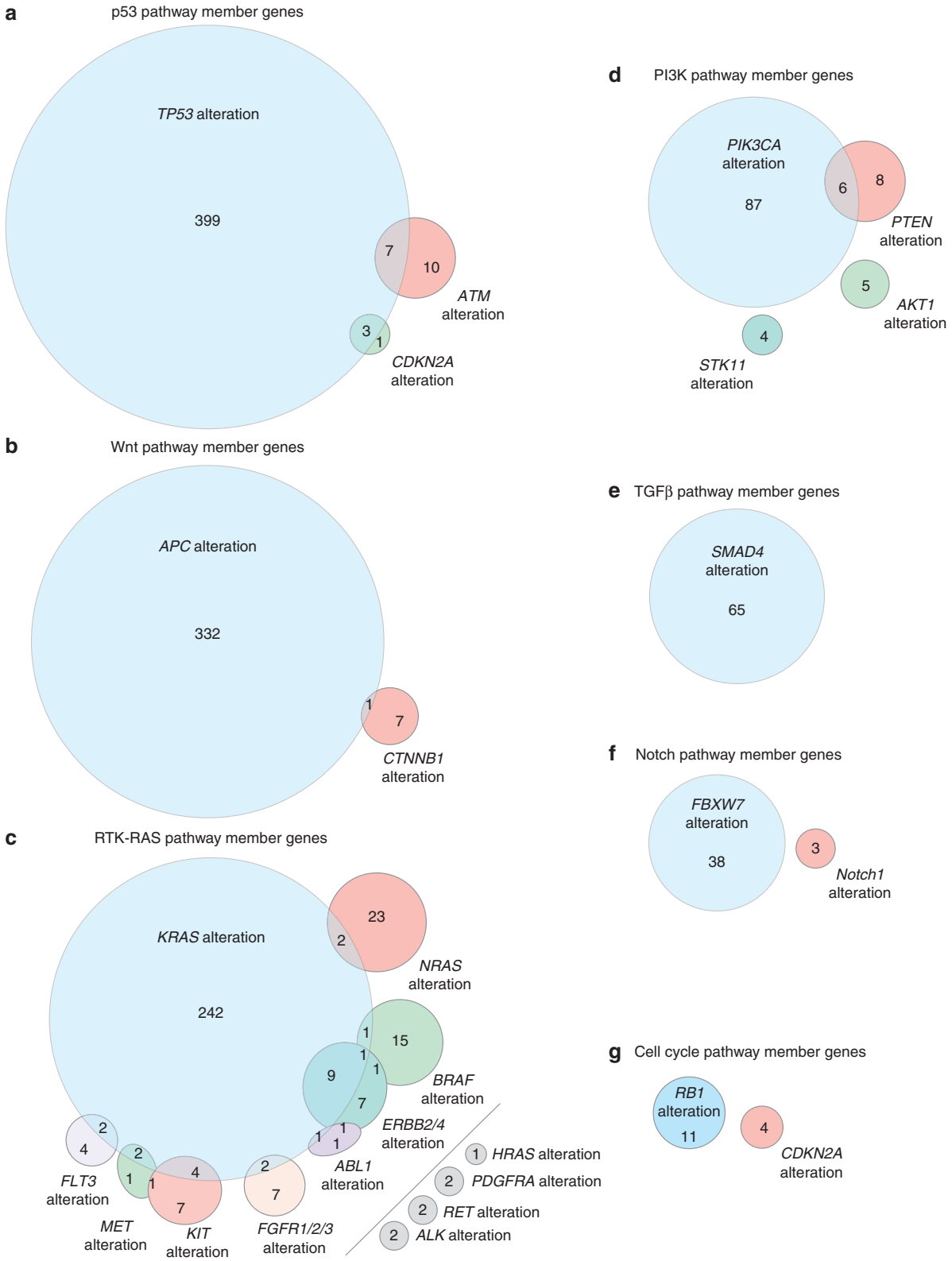

Fig. 51.3 Frequencies of alterations in genes in the (**a**) p53, (**b**) Wnt, (**c**) RTK-RAS, (**d**) PI3K, (**e**) TGFβ, (**f**) Notch, and (**g**) cell cycle pathways. Circle sizes correspond to sample sizes. (Kawaguchi Y, et al. "Genomic Sequencing and Insight into Clinical Heterogeneity and Prognostic Pathway Genes in Patients with Metastatic Colorectal Cancer." J Am Coll Surg. 2021 Jun 3:S1072-7515(21)00412-9. https://doi.org/10.1016/j.jamcollsurg.2021.05.027. Online ahead of print, with permission [14])

Table 51.1 Multivariable HRs for OS for signaling pathways and member genes in 561 patients

Factor	No. of patients	No. of events	Multivariable HR[†]	95% CI	*p*-value
Altered pathway[a]					
p53	404	134	1.73	1.19–2.51	0.004
Wnt	333	87	0.64	0.48–0.87	0.005
RTK-RAS	325	114	1.82	1.31–2.52	< 0.001
PI3K	105	23	0.80	0.51–1.28	0.354
TGFβ	63	29	1.68	1.11–2.53	0.014
Notch	41	16	1.93	1.13–3.27	0.016
Cell cycle	13	4	1.15	0.42–3.19	0.781
Altered gene[b]					
TP53	395	133	1.88	1.30–2.74	< 0.001
APC	326	86	0.66	0.49–0.89	0.007
RAS/BRAF	297	105	2.20	1.58–3.05	< 0.001
PIK3CA	88	21	0.86	0.53–1.39	0.528
SMAD4	63	29	1.64	1.08–2.48	0.019
FBXW7	38	16	1.80	1.06–3.07	0.031
RB1	11	3	0.91	0.28–2.94	0.880

Of the 579 patients, 561 were analyzed because data were unavailable for lymph node metastasis in 18 patients

HR hazard ratio; *OS* overall survival

(Kawaguchi Y, et al. J Am Coll Surg. 2021 Jun 3:S1072-7515(21)00412-9. doi: 10.1016/j.jamcollsurg.2021.05.027. Online ahead of print, with permission [14])

[a]Multivariable HR was assessed after adjustment for the following factors: alterations in p53, Wnt, RTK-RAS, PI3K, TGFβ, Notch, and cell cycle pathways; age; primary lymph node metastasis; number of CLM; and largest CLM diameter

[b]Multivariable HR was assessed after adjustment for the following factors: alterations in *TP53*, *APC*, *RAS/BRAF*, *PIK3CA*, *SMAD4*, *FXXW7*, and RB1; age; primary lymph node metastasis; number of CLM; and largest CLM diameter

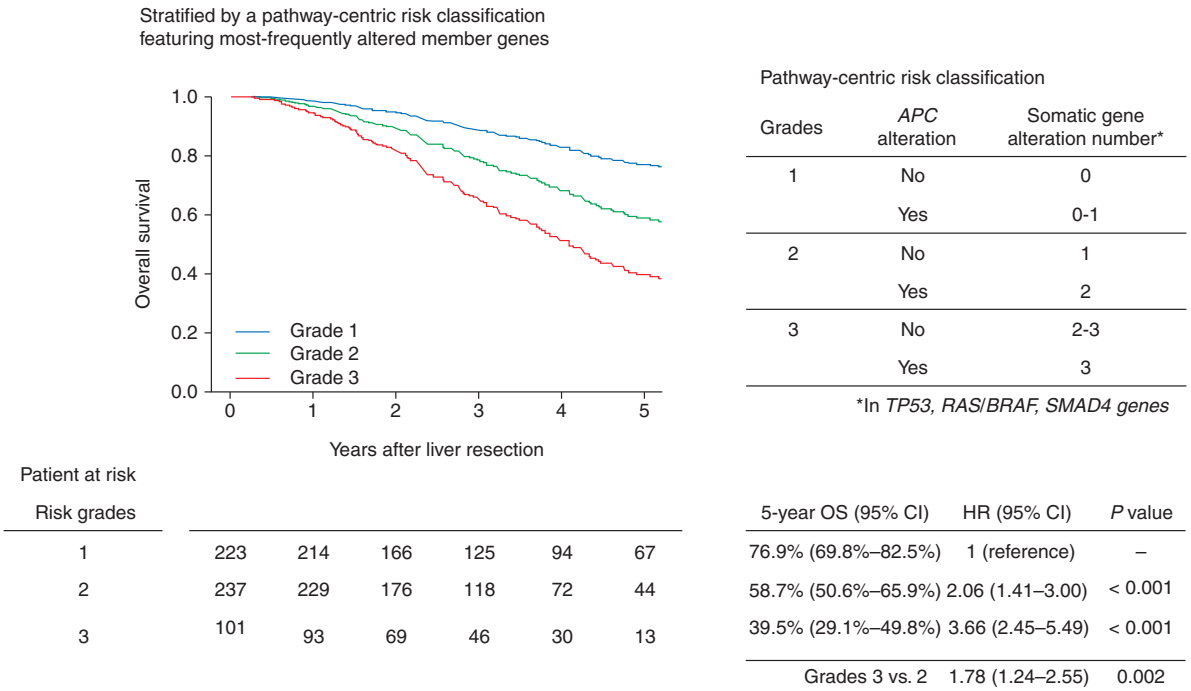

Fig. 51.4 Overall survival (OS) by a pathway-centric risk classification based on alteration status in four driver genes in 561 patients who underwent resection of CLM (cohort from MD Anderson Cancer Center). OS curves after adjustment for age, primary lymph node metastasis, number of CLM, and largest CLM diameter. (Kawaguchi Y, et al. "Genomic Sequencing and Insight into Clinical Heterogeneity and Prognostic Pathway Genes in Patients with Metastatic Colorectal Cancer." J Am Coll Surg. 2021 Jun 3:S1072-7515(21)00412-9. https://doi.org/10.1016/j.jamcollsurg.2021.05.027. Online ahead of print, with permission [14])

risk classification included three grades: grade 1 (scores 0–1), grade 2 (score 2), and grade 3 (scores 3–4). The pathway-centric risk classifications including four pathways (or corresponding predominant member genes/gene groups) clearly stratified OS in patients undergoing CLM resection after adjustment for other prognostic factors (Fig. 51.4). The

covariates-adjusted OS was significantly higher in patients with favorable tumour biology (i.e., pathway-centric risk grade 1) than in patients with worse tumour biology (i.e., pathway-centric risk grades 2 and 3): the 5-year OS, 76.9% (grade 1) vs. 58.7% (grade 2) vs. 39.5% (grade 3).

51.5 Risk Stratification of Resection and Liver Transplantation for CLM

Traditionally, risk stratification of resection and liver transplantation for CLM were made based on clinicopathologic factors. Fong et al. reported a risk stratification in patients undergoing CLM resection with the following 5 factors: positive primary lymph node, a disease-free interval between colorectal cancer and CLM <12 months, multiple liver metastases, the largest CLM diameter >5 cm, and carcinogenic embryonic antigen (CEA) level >200 ng/mL. Dueland et al. reported a risk stratification in patients undergoing liver transplantation for unresectable liver-only colorectal metastases with the following four pretransplant factors: largest CLM >5.5 cm, CEA levels >80 mg/L, time from surgery of primary tumour to LT <2 years, and progressive disease on chemotherapy at the time of transplantation. Most recently, for patients undergoing CLM resection, a risk stratification model which integrates clinicopathologic factors with somatic alteration was reported [17]. Given that the association of multiple somatic gene alterations with prognosis in patients with metastatic colorectal cancer has been increasingly reported [2, 14, 18], the pathway-centric risk classification may be useful as a criterion for selecting candidates of liver transplantation for unresectable liver-only colorectal metastases. Particularly, it may be reasonable to exclude patients who have CLM with worse tumour biology (e.g., pathway-centric risk grades 2 and 3) from liver transplantation candidates.

51.6 Conclusion

Prognosis in patients undergoing CLM resection was assessed using clinicopathologic factors. However, the association of somatic gene alteration with prognosis has been increasingly reported. For this analysis, single somatic gene alteration (e.g., *RAS*, *BRAF*) was typically assessed. The drawback of this approach is that *RAS* and *BRAF* belong to the same signaling pathway (RTK-RAS pathway) and that alterations of *RAS* and *BRAF* are almost always mutually exclusive. It should be noted that when comparing *RAS* mutant patients with *RAS* wild-type patients, *RAS* wild-type patients have a possibility of including *BRAF* alteration. This may underestimate the deleterious association of *RAS* alteration because we may compare survival in patients with *RAS* alteration and patients with *RAS* wild-type (but including *BRAF* alteration). As such, the pathway-centric assessment may be useful as follows. First, the concept of pathway-centric analysis for prognosis may accurately evaluate the association between somatic gene alteration and prognosis. Second, pathway-centric understanding of tumour biology may indicate key nodes downstream of altered genes as potential therapeutic targets.

In conclusion, the current pathway-centric risk classification based on four pathway driver genes, *TP53*, *APC*, *RAS*/*BRAF*, and *SMAD4* may be useful for better prognostication, clinical decision-making, and risk stratification of patients in future clinical trials.

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Part VII

Ultrasound and Operating Room Settings

Intraoperative Ultrasound

52

Guido Torzilli

Learning Objectives

- Background of intraoperative ultrasound.
- Basics of ultrasound anatomy.
- Principles of ultrasound liver exploration.
- Principles of ultrasound-guided resections.
- Other guidance techniques: alternatives or complimentary?

52.1 Introduction

Initially used in patients with liver cirrhosis intraoperative ultrasonography (IOUS) has been used in hepatic surgery since the early 1980s [1]. Ultrasound guidance has then been progressively applied to complex cases to assist in performing "radical but conservative" resections [2–4] as a reliable alternative to major hepatectomy [5, 6]. For this purpose, precise identification of the tumour-vessel relationships is important for planning this type of resection [7]. IOUS allows surgeons to recognize whether a tumour is away from the hepatic vessel and helps for estimating the circumferential extent of the tumour-vessel contact; in other words, whether a vessel wall invasion exists. These benefits opened a new surgical era (see Chap. 18—Torzilli et al.) [6, 8].

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52.2 Equipment

52.2.1 Probes

IOUS probes need to be sterilizable because this enables a better contact with the targeted organ and avoids the artifact caused by an ultrasound sterile cover. Efficient systems for sterilizing IOUS probes, such as hydrogen peroxide gas-plasma technology (Sterrad; ASP, Rome, Italy), are now available.

High-frequency echo probes (7.5–10 MHz) are often recommended to perform IOUS because they allow a higher spatial resolution than those with lower frequency (3.5–5 MHz). However, lower frequency probes are also useful, at least for the initial exploration, providing a better panoramic view, despite a lower spatial resolution. In case a superficial nodule is slightly visible on IOUS but is not palpable, particularly in a cirrhotic liver, a surgical glove filled with deaerated sterile water can be positioned between the probe and the liver surface and may help in visualizing the lesion. Indocyanine green fluorescence imaging (ICG-fluorescence) provides further helpful insights which may reduce the role of IOUS in visualizing superficial lesions [9] (Fig. 52.1).

The shape and volume of an IOUS probe is crucial. The following probe type presents the best compromise: [1] size should be small enough to facilitate handling in deep and narrow spaces, [2] the large scanning window should be large enough to enable the widest area of exploration at once, and [3] the adherence with the surface of the target organ, should be good enough to enable adequate stability during handling and avoids gas interposition and artifacts.

The most frequently used probes are the T-shaped (Fig. 52.2a), interdigital, and microconvex probes (Fig. 52.2b). The microconvex probe is the most suitable for liver surgery among all the previous requirements. The T-shaped probe is also stable and is associated with higher image resolution, but it has an unfavorable ratio between lateral length and US scanning window than the microconvex

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probe. Recently, small linear transducers with enlarged scanning windows have been developed. They have the stability of the linear probes and the image resolution is high (Fig. 52.2c). Another aspect that should be considered is the suitability for surgical maneuvers, as the selective intrahepatic vessel compression for visualizing the segmental border [10] and the nodule compressions for differential diagnosis of new lesions at IOUS.

Unique aspects of ultrasound probes for laparoscopic exploration of the liver are shown below. Laparoscopic transducers are available in several configurations that can fit through the 10–12 mm laparoscopic port. The simplest transducer configuration is the rigid, linear array. However, because they have a rigid shaft, they need to be frequently moved from ports to ports. They cannot follow the curve of the liver in the upper segments. This drastically limits the field of exploration. Flexible tip with hidden cables controlled by knobs provided at the proximal end of the shaft (Fig. 52.3) allows ultrasound exploration in transverse and longitudinal. This reduces the need for moving to different trocars, and allows following the curvature of the liver, making feasible its exploration for the upper segments. Laparoscopic ultrasound (LUS) probes operate at a frequency of 2–13 MHz and are equipped with linear or convex array.

Recently, probes dedicated to robotic liver surgery have become available. They feature a cable as probes for open abdomen IOUS (indeed usable with this approach), and a grip to grab with the forceps used in the robotic or laparoscopic setting (Fig. 52.4).

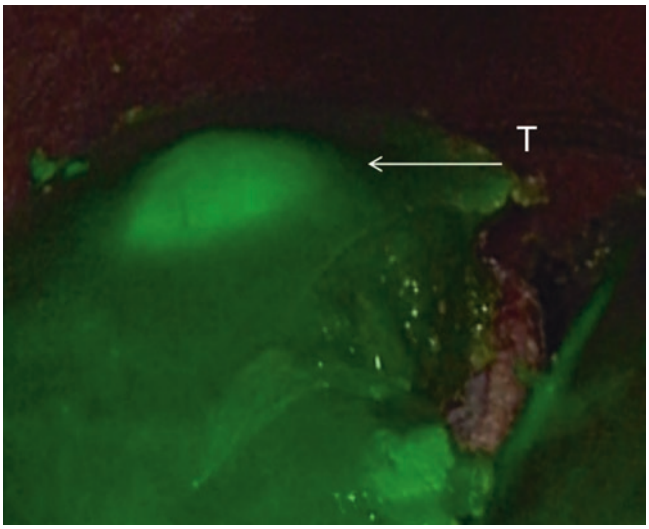

Fig. 52.1 ICG-fluorescence at laparoscopy showing the appearance of a superficial tumoural lesion (*arrow*)

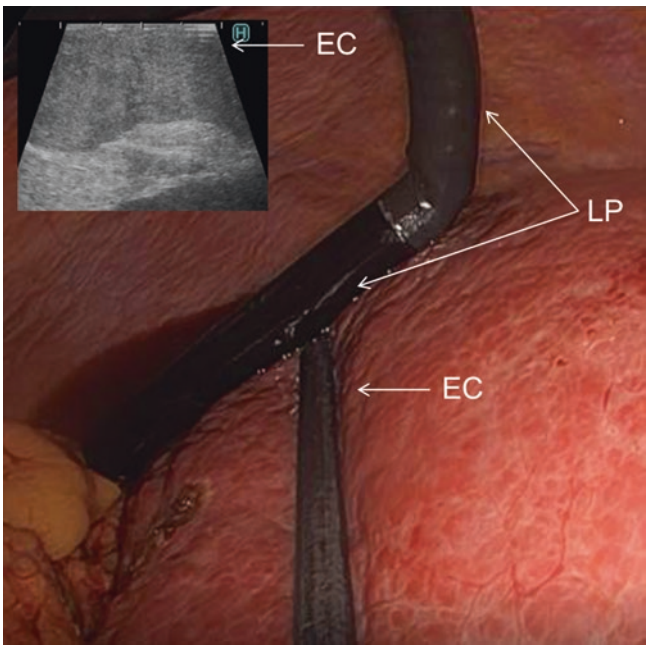

Fig. 52.3 Laparoscopic probe (*LP*) with linear and flexible transducer; on the upper left side of the picture the IOUS image with a trapezoidal scanning showing the appearance of the electrocautery (*EC*) positioned between the probe and the liver surface

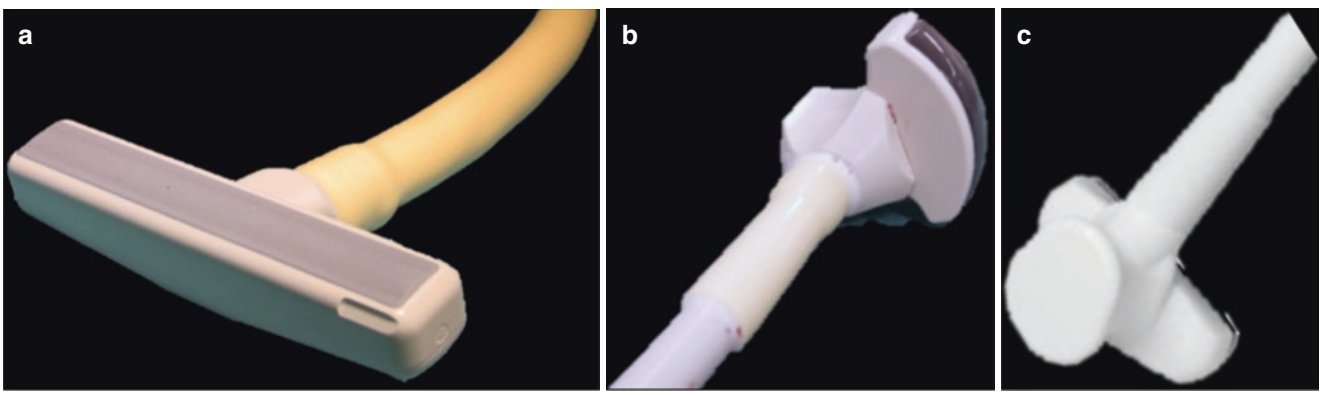

Fig. 52.2 (**a**) T-shaped IOUS probe; (**b**) microconvex IOUS probe; (**c**) IOUS probe with mini T-shaped transducer and ergonomic finger handling

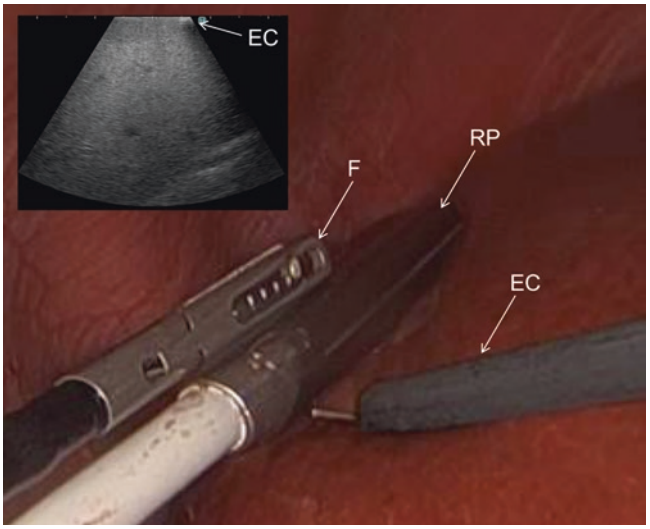

Fig. 52.4 Robotic probe (*RP*) with linear transducer handled in a laparoscopic setting by a forceps (*F*); on the upper left side of the picture, the IOUS image with a trapezoidal scanning showing the appearance of the electrocautery (*EC*) positioned between the probe and the liver surface

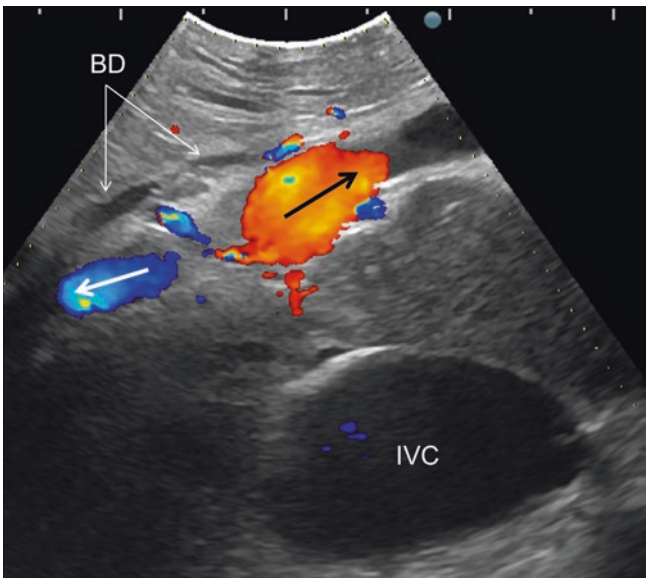

Fig. 52.5 Color-flow analysis should feature any US system. Herein is represented the portal bifurcation at color-flow in which the flow is represented in red once its direction is toward the probe (*black arrow*) and in blue (*white arrow*) when in the opposite direction. *BD* bile duct; *IVC* inferior vena cava

Color Doppler imaging, and, particularly, more sensitive color-flow modes, have greater roles in the intraoperative evaluation of liver inflow (Fig. 52.5) and outflow (Fig. 52.6). This provides crucial information about flow changes induced by tumours or by surgical maneuvers. This information enables various surgical strategies [7, 8] (see Chap. 18—Torzilli et al.).

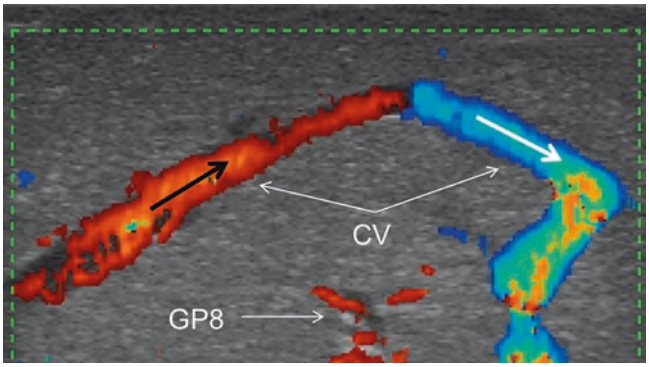

Fig. 52.6 Color-flow disclosure of a communicating vein (*CV*) between the middle and the right hepatic vein: the flow is represented in red once its direction is toward the probe (*black arrow*) and in blue (*white arrow*) when directed oppositely. GP8, glissonean pedicle to segment 8

Contrast-enhanced IOUS and LUS is now an established application of US [11], and intraoperative ultrasound systems should be equipped accordingly (Fig. 52.7).

A useful function allows to perform fusion imaging which shows the preoperative imaging in the US system merged with the preoperative imaging. This facilitates the guidance and aids in the detection of lesions which are not well visualized by IOUS (Fig. 52.8).

52.3 Liver Exploration

First, a surgeon in charge of the surgical procedure should carry out the IOUS. This provides the most meaningful benefit for the patient and finalizes the surgical strategy. IOUS and US-guided maneuvers should be performed by the same person.

The US system should be positioned to enable surgeons to simultaneously view both the screen and the operative field. A transparent, sterile covering pad should be available to handle the keyboard directly.

After the abdominal cavity is entered either in open or minimal access surgery, the division of the round and falciform ligaments, and the dissection of adhesions to free the anterosuperior and inferior surfaces of the liver should be performed before liver exploration with IOUS. Adhesions from the tumour to other organs or structures should not be dissected because they may represent tumour infiltration; in this situation, IOUS can help exclude or confirm tumour invasion and may change the surgical strategy.

For wide exposure of the liver surface, the round ligament can be pulled for traction, allowing tracing of the portal branches and the hepatic veins. The probe should be managed by using enough pressure to ensure good contact with the liver surface, but not that much as to compress the intrahepatic vascular structures, particularly the hepatic veins.

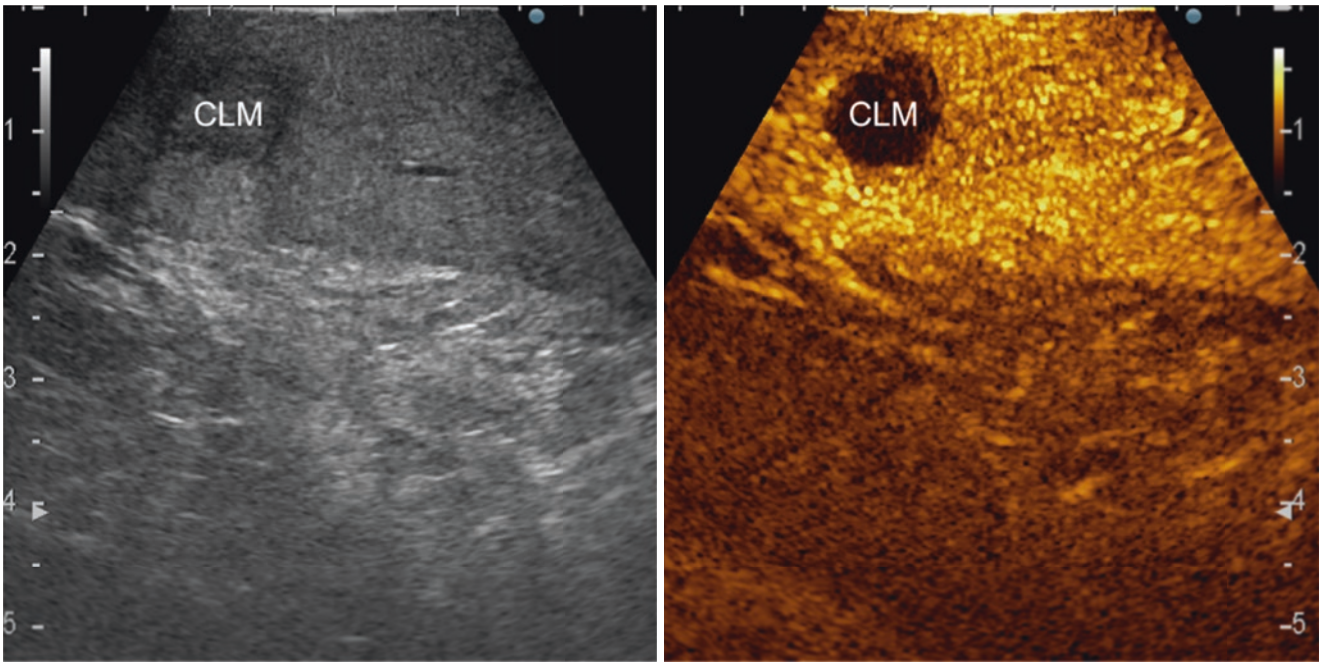

Fig. 52.7 Contrast-enhanced IOUS (CEIOUS): on the left the b-mode (IOUS) and on the right CEIOUS of a colorectal metastases (*CLM*): the black-hole effect is quite evident

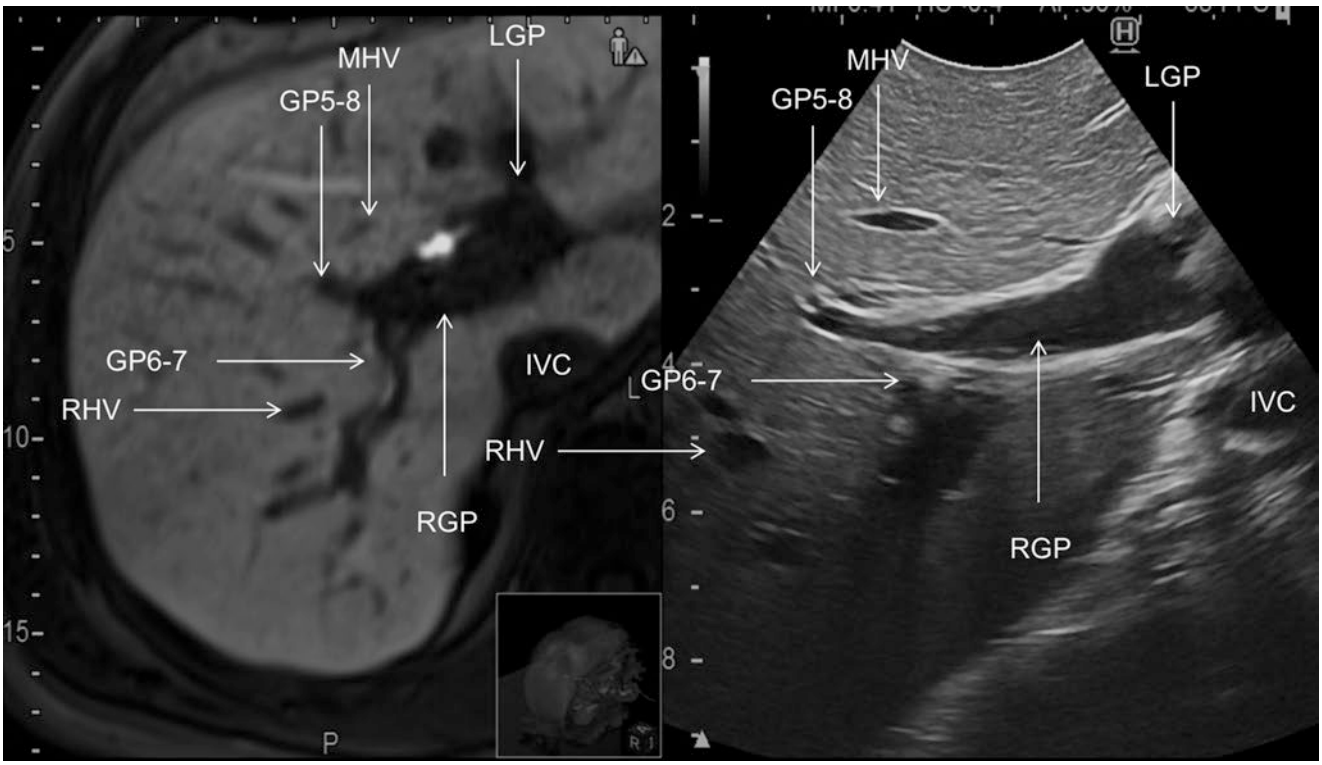

Fig. 52.8 Fusion imaging merging preoperative MRI (uploaded on the US machine) and IOUS. The scan is quite symmetric both showing the left glissonean pedicle, (*LGP*), the right (*RGP*) and those to segment 5 and 8 (*GP5-8*) and 6 and 7 (*GP6-7*), the right hepatic vein (*RHV*), the middle hepatic vein (*MHV*), and the inferior vena cava (*IVC*)

52.3.1 IOUS Semiology

For surgical anatomy, the Brisbane terminology is considered [12].

52.3.1.1 Glissonean Pedicles

Exploration starts from the Glissonean branches following the portal pedicles at the sectional, segmental, and subsegmental levels, then defining precisely the anatomical location of the IOUS target. Initially, Glissonean pedicles can be followed by positioning the probe horizontally, grossly between the cross-margin of segments 4, 5, and 8, to visualize the first-order bifurcation (Fig. 52.9). In open approach, the first-, second-, and third-order Glissonean branches can be followed in a right-to-left clockwise manner (right Glissonean pedicle, right anterior, right posterior, left Glissonean pedicle, pedicle to segment 4 superior/inferior, segment 3, and segment 2) (Fig. 52.10), just tilting the probe upward and downward, and/or rotating it on its perpendicular axis (Fig. 52.9). Because of the existence of the Glisson capsule, the Glissonean pedicles, which include portal vein branches, arteries, and bile ducts, have thick vessel walls compared with the hepatic veins. Therefore, in IOUS imaging, Glissonean pedicles appear as multiple echo-free zones surrounded by a thicker, hyperechogenic layer, while the hepatic veins appear as single echo-free zones surrounded by a thin hyperechoic layer (Fig. 52.11). In principle, the distinction between hepatic veins and portal branches should be based not only on their appearance but mainly on their anatomy since in some conditions they are mistaken such as in the cirrhotic liver or in some cross-sectional scans (Fig. 52.11).

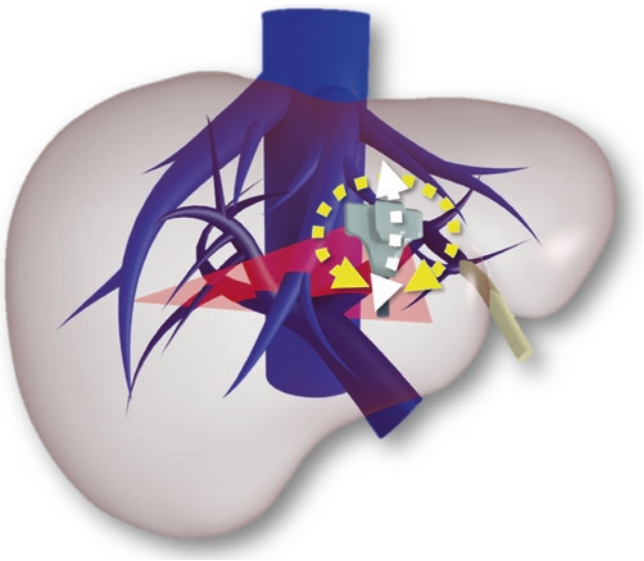

Fig. 52.9 Schematic representation of the probe positioning and movements (on the perpendicular axis in yellow dotted-line and on the vertical axis in white dotted-line) for the entire liver exploration

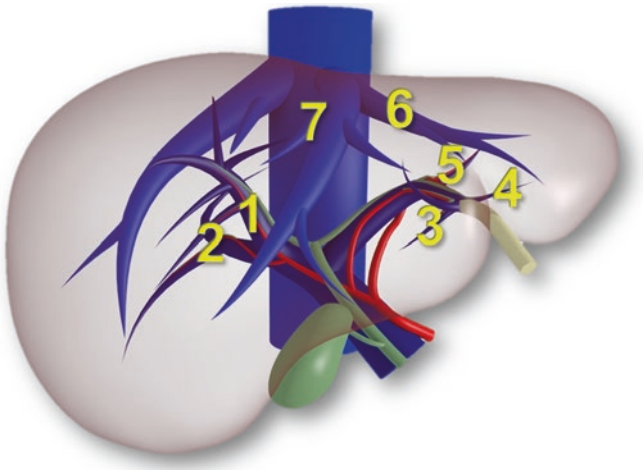

Fig. 52.10 Schematic representation of the sequence (from 1 to 7) used for liver exploration following initially the second-order glissonean pedicles and then the hepatic veins. (1) glissonean pedicle to segments 5–8; (2) glissonean pedicle to segments 6–7; (3) glissonean pedicle to segment 4; (4) glissonean pedicle to segment 3; (5) glissonean pedicle to segment 6; (6) moving the probe upward from the left hepatic vein to the caval confluence; (7) moving the probe downward from the caval confluence of the hepatic veins to explore the entire segment 1 located posterior to the hepatic veins

The appearance of the bile ducts on IOUS is worth to be better disclosed. Once the bile ducts are dilated, the bile ducts appear as more evident echo-free zones with a serpiginous path (Fig. 52.12). Furthermore, the confluence of sectional and segmental ducts is closer to the hilum compared to the bifurcation of the portal branches. As a result, it is possible to visualize more than one segmental bile duct with one scan, and with enough US background. IOUS can allow exact definition of the bile duct anatomy not only in pathologic conditions but also in the normal state (Fig. 52.13). This ability is crucial for assessing variations in the normal anatomy, such as the confluence of the right posterior sectional bile duct into the left hepatic duct, a critical issue in case of left hepatectomy.

During hepatectomies, it is necessary to confirm biliary tree integrity to check when the bile duct injury is suspected. This can be done by using a simple, self-made contrast agent that can be visualized on IOUS thereby providing a real-time intraoperative cholangio-ultrasound (IOCUS). The contrast agent consists of a compound of air and saline. The respective amount varies from pure air to the combination of saline and air. The latter is a preferred method for examining anatomic detail, although similar anatomic information can be provided with the injection of pure air. Indeed, once the air is injected slowly, its progressive mixture with the bile juice provides anatomic details (Fig. 52.14). In contrast, when the air is injected under pressure, a parenchymatous effect is obtained (Fig. 52.15), which is useful for checking the proper drainage of a specific portion of the liver. Nonetheless, the

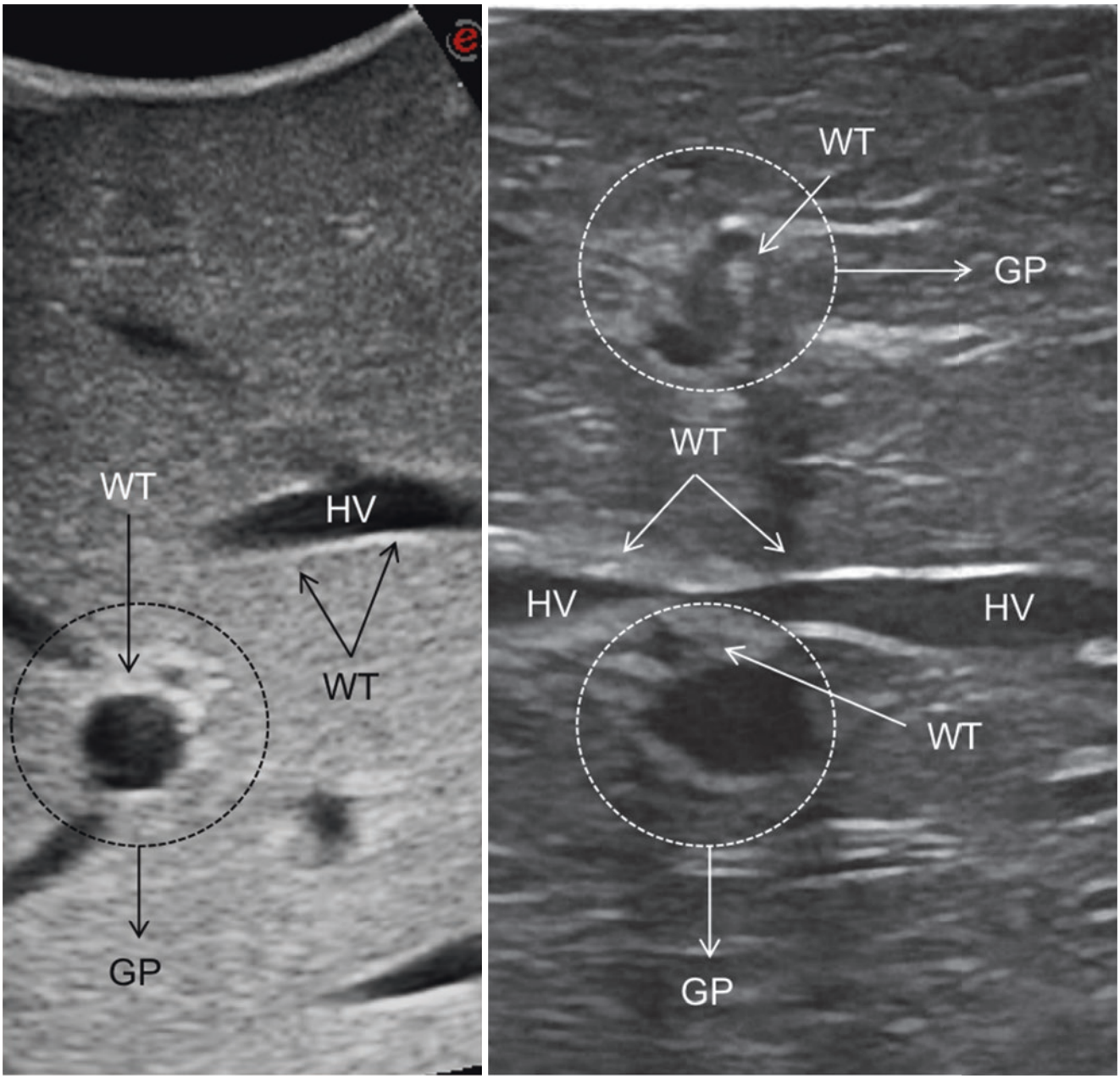

Fig. 52.11 The glissonean pedicle (*GP*) is represented by at least two anechoic (*black*) structures, representing the artery and the portal vein; the bile duct is always seen in the case of the first- and second-order branches, and often disclosed, particularly when dilated, in the case of a more peripheral GP. On the left GP and hepatic vein (*HV*) in a normal liver showing a different wall thickness (*WT*) on IOUS; on the right, a cirrhotic liver, where often HVs have a thickened wall that mimics the wall of a GP: the anatomic landmarks and the inclusion of various structures together allow for their proper differentiation

injection of the air in the biliary tree is anyhow useful for ruling out the presence of bile leaks on the cut surface: the so-called air-leak test [13].

52.3.1.2 Hepatic Vein

The three main hepatic veins are readily identified at their junction with the inferior vena cava (IVC), as visualized once the portal tree has been entirely explored. The left hepatic vein (LHV) appears in between the Glissonean pedicles for segment 2 and 3. Following it upward, the LHV at the hepatocaval confluence is visualized, and when the probe is gently withdrawn, the hepatic vein paths can be traced into the liver (Fig. 52.10).

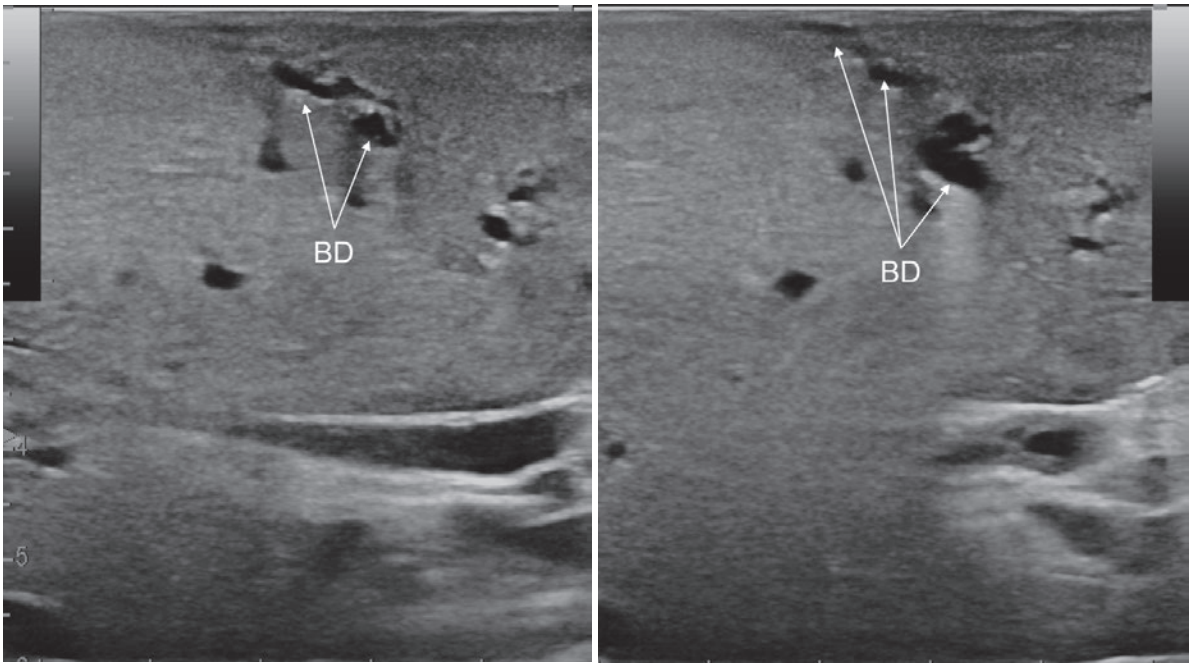

Fig. 52.12 IOUS showing subsegmental bile duct (*BD*) dilation, which assumes a serpiginous path (*arrows*)

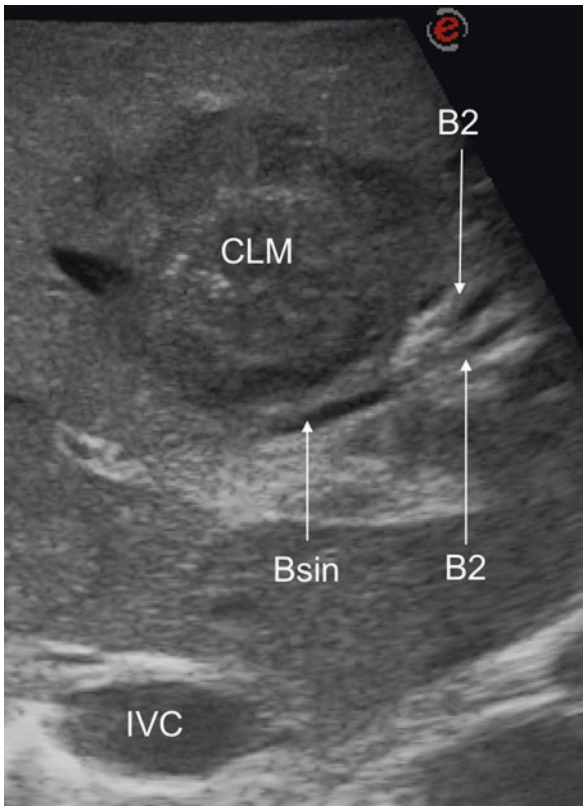

Fig. 52.13 IOUS may provide anatomical details of the intrahepatic biliary tree even if non-dilated, with the main anatomical feature being a centripetal bifurcation pattern. In this picture, IOUS shows non-dilated bile ducts first and second-order bile ducts: left bile duct (*Bsin*), bile duct draining segment 2 (*B2*), and segment 3 (*B3*). *CLM* colorectal liver metastases; *IVC* inferior vena cava

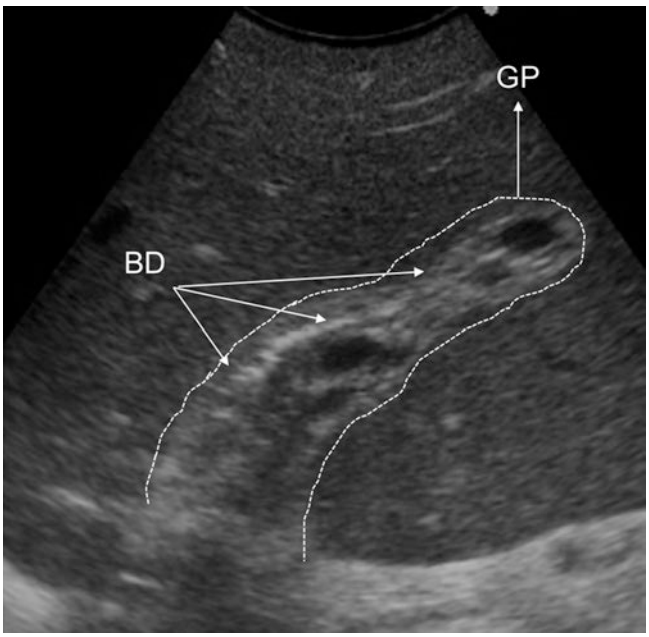

Fig. 52.14 Slow injection of air in the biliary tree allows its mixture with the bile juice enhance the anatomical details of the bile ducts (*BD*) within the glissonean pedicle (*GP*) and allows to perform intraoperative cholangio-ultrasonography (IOCUS)

52.3.2 Diagnosis and Staging

Despite the improvement of preoperative imaging [14], IOUS remains the gold standard for detection and differentiation. Studies reported that more than 10% of patients had additional intraoperative findings provided by laparoscopic or intraoperative ultrasound [15]. In the setting of CLM, the problem is sometimes the disappearance of lesions which are anyway frequently not visible but will become viable [16]**.** In this sense, real-time intraoperative fusion imaging represents relevant progress (Fig. 52.7) [8]. The possibility to combine the real-time IOUS scans with, in real time, the previously uploaded images of the CT or MRI performed before the systemic therapies enables the detailed recognition of the areas in which the disappeared lesions were located.

Characterization of any new lesion detected intraoperatively remains crucial. The only nodule that can be easily visualized using IOUS is the small hemangioma since it displays a typical US pattern, and when compressed, it changes in shape given its compressibility (Fig. 52.16). Elastography allows the differentiation of lesions based on tissue stiffness expressed on the IOUS screen by different colors may further help in this sense (Fig. 52.17) [17, 18].

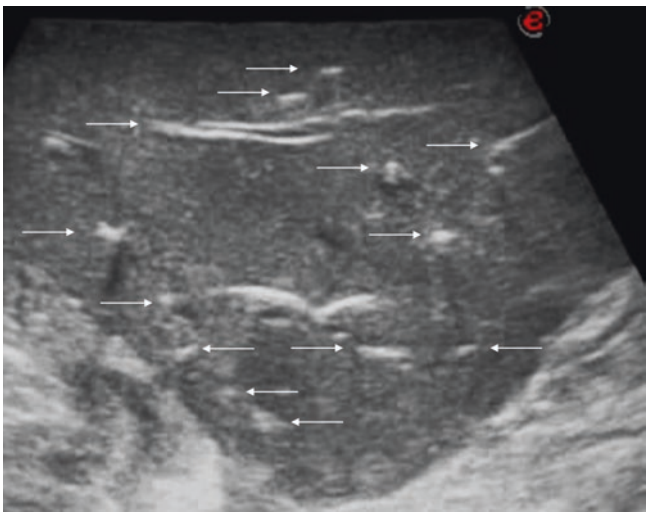

Fig. 52.15 Forced injection of air in the biliary tree displacing the bile juice allows disclosure of the peripheral harboring of the biliary tree (*arrows*) thus performing a parenchymal IOCUS

52.3.2.1 Contrast-Enhanced IOUS

In 2004, contrast-enhanced intraoperative ultrasound (CEIOUS) has been introduced both for characterizing newly detected focal liver lesions [19]. After that, several studies with different contrast agents have shown that it enhances tumour detection, despite the progress of preoperative imaging [14], and the preventive IOUS exploration [19–27]. Two contrast agents are commonly used: vascular (Sonovue®—Bracco Imaging SpA, Maderno, Italy) and post-vascular (Sonazoid®—GE Healthcare, Oslo, Norway). The latter has the advantage of a prolonged

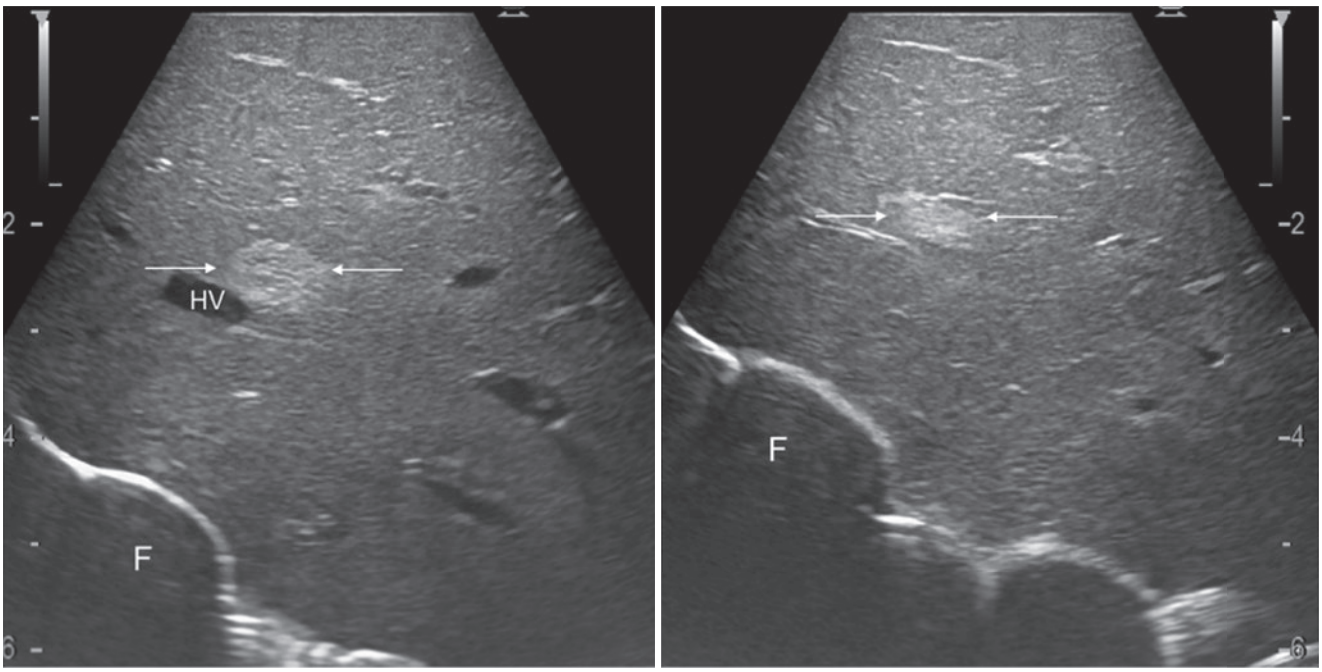

Fig. 52.16 Test for diagnosing a hemangioma. On the left, hemangioma (*arrows*) at IOUS, typically bright (hyperechoic), and located next to a hepatic vein (*HV*). On the right, once compressed by the surgeon's fingertip (*F*) under IOUS guidance, its shape changes (*arrows*); this finding along with its echogenicity confirms the diagnosis of hemangioma

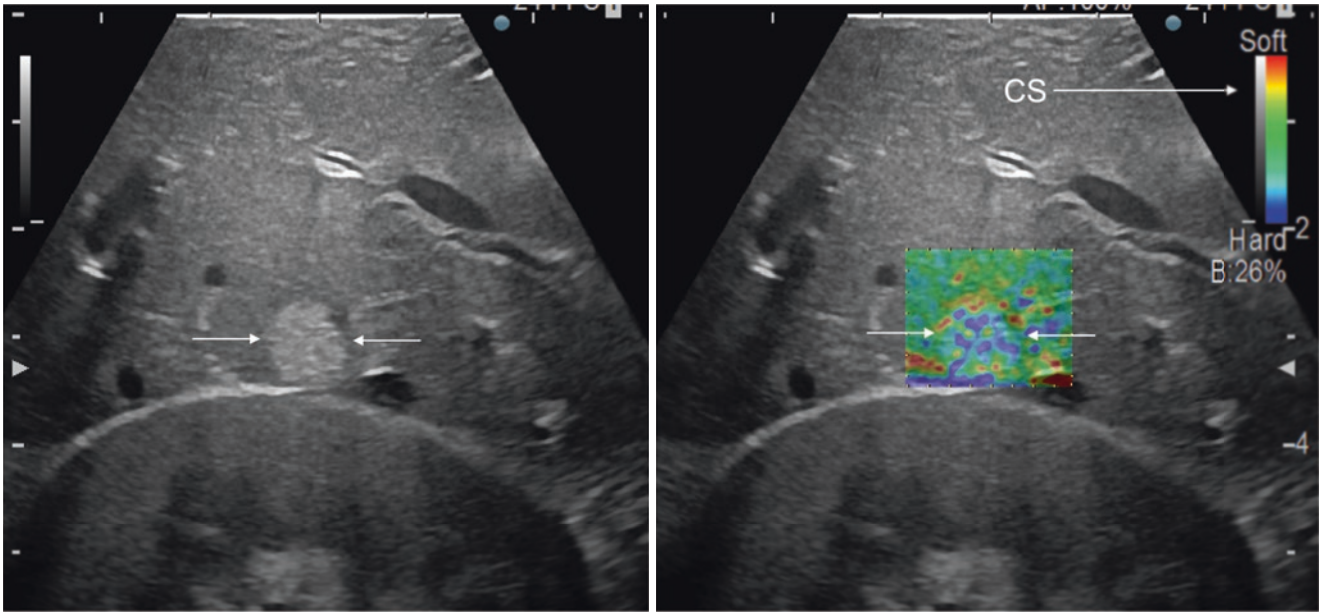

Fig. 52.17 Potential value of elastography in estimating tissue stiffness, using a color scale (*CS*). A hemangioma (*arrows*), typically bright (hyperechoic) and rounded at IOUS (on the left), at elastography (on the right) shows a greenish-yellowish pattern according to its mid-low stiffness

duration of the contrast effect which behaves as a hepato-specific contrast agent.

Focusing the attention to CEIOUS for the CLM, it improves the detection as initially sustained [19–21, 23–25], and thereafter confirmed [28]. Indeed, CLM, in the vascular phase, which lasts from 2 to 5 min after injection, remains unenhanced and black in comparison with the surrounding enhanced liver parenchyma: the so-called black-hole effect (Fig. 52.7). CEIOUS allowed us to detect 9% additional nodules in the author's experience [23]. This increment in sensitivity appears to be relevant in the absence of a bright liver [29], and in the presence of multiple isoechoic CLM [30]. Indeed, the existence of multiple isoechoic CLM can be missed by IOUS without contrast. In contrast, for those presenting with hypoechoic CLM in a bright liver, visibility is generally optimal on IOUS. Also, CEIOUS with Sonazoid proved to increase CLM detectability [31].

Both, Sonovue and Sonazoid have proven to increase the detectability of those CLM disappearing after chemotherapy at preoperative imaging [32, 33] despite the improvement of the preoperative imaging with the advent of hepato-specific MRI [34]. CEIOUS and hepato-specific MRI are rather complementary: a recent analysis showed that CLM disappearance both at preoperative hepato-specific MRI and CEIOUS with Sonazoid is associated with a high probability of CLM truly disappeared [35].

Caution should be used in patients with CLM who have coexisting liver cysts. This may appear similar to CLM along with the delayed phases of contrast enhancement. The cysts should have been already screened based on the preoperative imaging and identified at exploration with conventional IOUS. The liver cysts at IOUS have an anechoic content and a posterior echo in contrast which CLM does not have such feature (Fig. 52.18).

The impact of CEIOUS in modifying the surgical strategy is strongly influenced by the attitude of the surgeon [36]. Given the capability of CEIOUS to improve tumour detection, for the liver clearance, the confirmation of the predicted strategy depends on the possibility to include the new lesions within the planned resection area or not: this is often a subjective decision based on the surgical expertise [30]. Despite new findings by CEIOUS it is not obvious to assist in modifying surgery; however, this element does not diminish the value of this specific diagnostic tool.

On a technical standpoint of view, visual effects could last up to 5 min after injection, which could be repeated for reassessment or to assess the arterial phase enhancement of identified lesions for their characterization. With vascular and post-vascular phase agents, detection of malignant lesions can appear up to 20–25 min post-injection in the hepato-specific phase [26, 31, 37, 38]. Irrespective of the contrast agent used, high doses should be avoided because this limits US penetration in all phases.

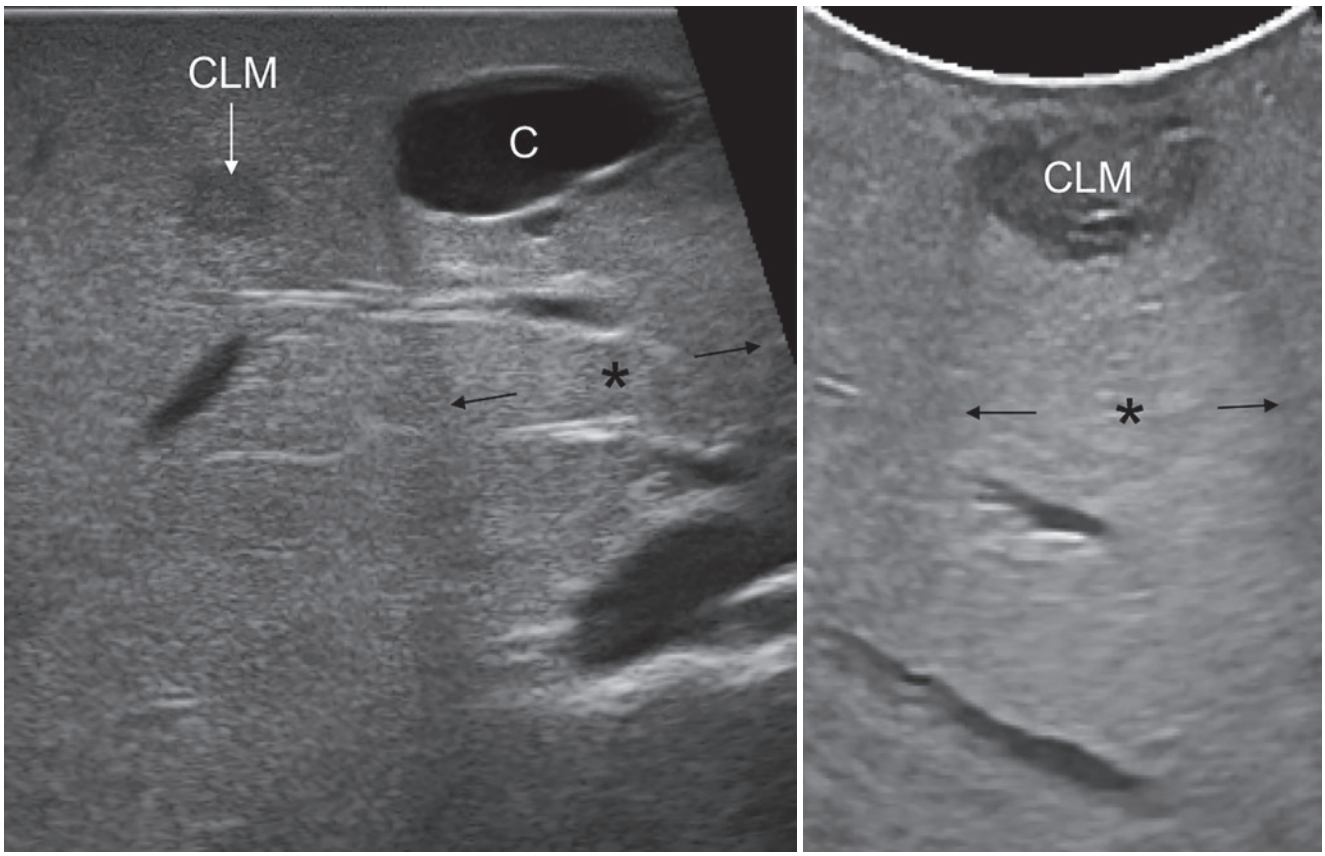

Fig. 52.18 On the left a hypoechoic metastatic lesion (*CLM*) at IOUS without any significant posterior hyperechoic echo beside a typical pattern of a liver cyst (*C*) inversely showing the posterior hyperechoic echo (*). On the right, a hypoechoic CLM showing nonetheless a posterior hyperechoic echo (*) like a liver cyst

52.4 Resection Guidance

52.4.1 Definition of the Resection Areas

Limited resection is commonly accepted as an oncologically proper approach for CLM [39]. In this context, IOUS guidance plays a fundamental role. IOUS guidance allows tailoring the resection area based on liver anatomy and oncological requirements. In practice, once the tumour is identified using IOUS, the surgeon can mark the border of the lesion and that of the area to be removed on the surface of the liver with electrocautery under IOUS control. The superficial projection of the anatomical landmark as the main intrahepatic vessel could be marked with electrocautery according to the IOUS images. Such modality enables figuring where a vessel is with good approximation, although it does not identify the anatomical plane separating segments or subsegments. For demarcation or targeting structures, the flat and thin tip of the electrocautery device is positioned between the probe and the liver surface. This results in a shadow on the IOUS image that runs deeply just below the electrocautery (Fig. 52.19). In this way, it is possible to define the position of the electrocautery device in relation to the tumour edge, and consequently to mark with the electrocautery itself the resection area.

Additionally, when the resection area involves two different surfaces of the organ, the frontal landmark is marked with the electrocautery as described, while the posterior one is defined by positioning the surgeon's fingertip under IOUS control, visualizing its position in relation to the tumour and the frontal surface. The structures between the fingertip, the frontal marker, and the tumour edge can be precisely estimated, the resection area can be marked posteriorly, according to the planned dissection plane (Fig. 52.19). Once the resection area is drawn on the liver surface, the main target is finalizing a tumour-free smooth and regular cut surface. All these maneuvers could be done in a minimal access environment using dedicated probes and instead of the fingers the forceps (Figs. 52.3 and 52.4).

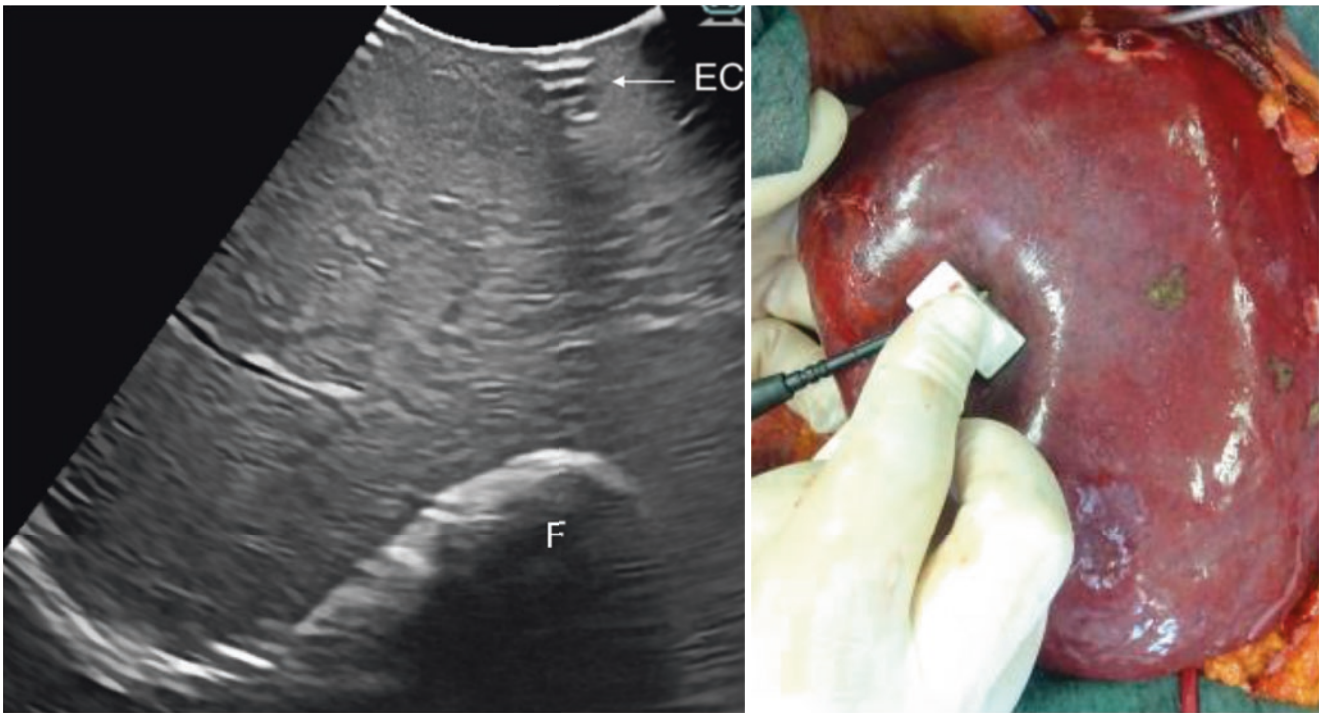

Fig. 52.19 On the left, both the shadow generated by the electrocautery (*EC*) and the profile of the surgeon's finger (*F*) are visualized, and the surgeon can draw an ideal dissection plane (*arrows*) that can be followed as shown on the right once the resection area is marked using these landmarks

52.4.2 Liver Parenchyma Dissection

The main advantage of IOUS-guided resection is the possibility to proceed in dissecting the liver according to more complex trajectories other than the vertical planes or the curved but peripheral ones. Furthermore, IOUS allows surgeons to follow the dissection plane in real time, to see it constantly in relation to the tumour edge, and then to modify its direction when needed. This is because the dissection plane can be visualized on the IOUS image, which appears as an echogenic line as a result of the entrapment of air bubbles and clots between the facing cut surfaces (Fig. 52.20). If the dissection plane is not clearly visible, it can be better visualized by inserting a gauze (Fig. 52.20) between the facing surfaces. In this way, it is possible to carry out a rounded trajectory of the dissection plane around the tumour, avoiding tumour exposure, its eventual disruption, and potentially cancer seeding other than allowing surgeons to spare important vascular structures. This results in more conservative but radical treatments, minimizing the rate of major hepatectomies.

The artifacts that may appear on IOUS sometimes mask critical structures to the dissection plan, such as portal branches, which should be either ligated or preserved. For this reason, to better visualize the targeted point where the portal branch should be divided, the "hooking technique" has been devised [40]. When the glissonean pedicle is exposed, it is encircled with a stitch. Under US control, the

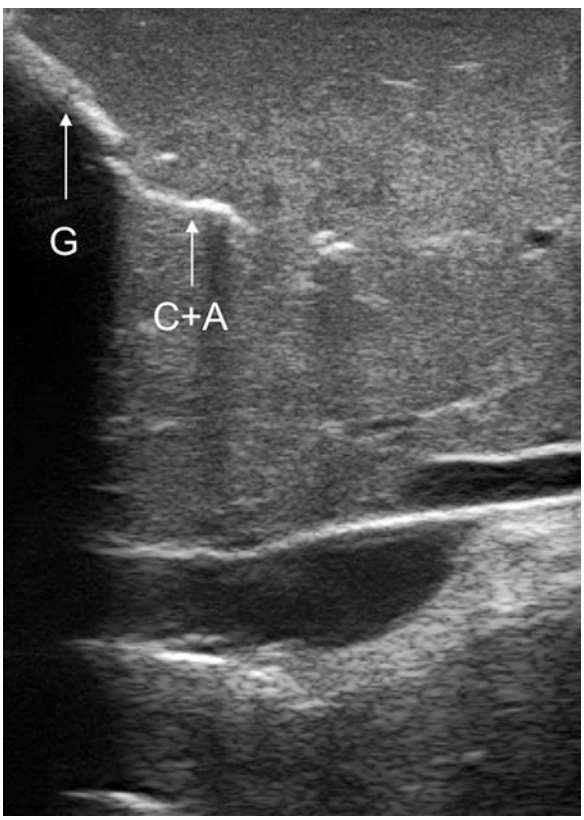

Fig. 52.20 Appearance at IOUS of the dissection line once faced the cut surfaces with a gauze interposition (*G*) or without when the hyperechoic line is caused by clots and air trapped in it (*C* + *A*)

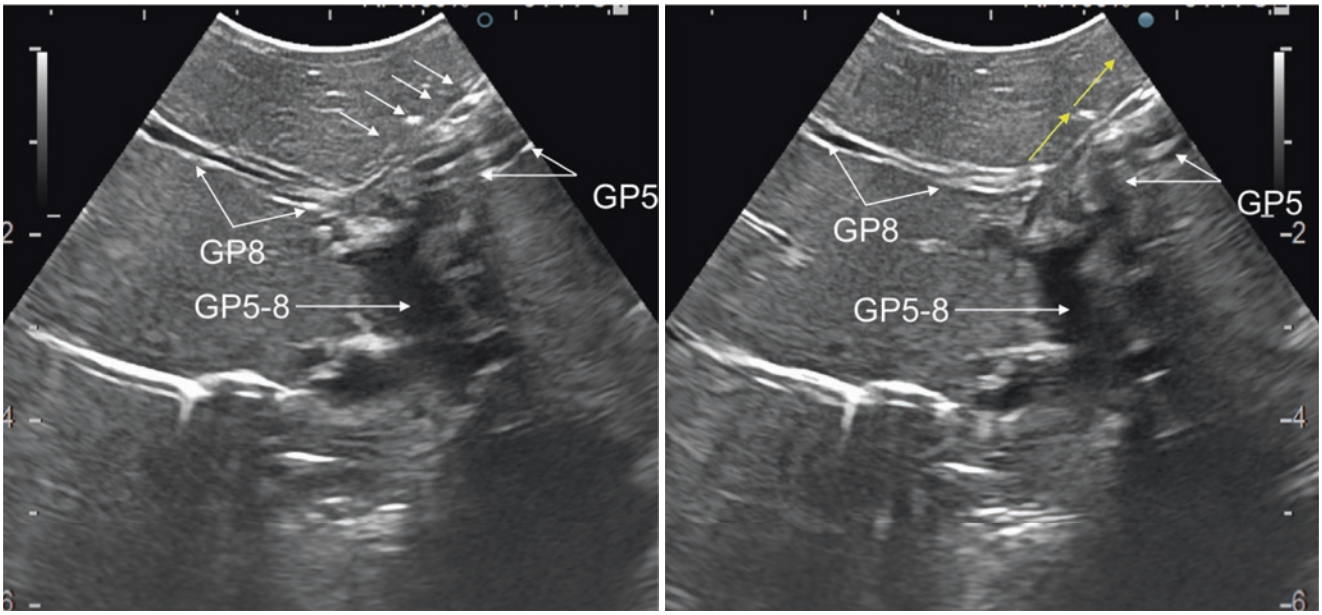

Fig. 52.21 Hooking technique: arrows are indicating on the left the dissection plane used to reach the glissonean pedicle to segment 8 (*GP8*) encircled with a stich; on the right the *yellow arrows* are showing the traction applied to GP8 through the stich: the evident shifting of GP8 confirms that GP8 is the pedicle encircled. *GP5-8* glissonean pedicle to segments 5 and 8, *GP5* glissonean pedicle to segment 5

stitch hooking the encircled vessel is then gently pulled up, then slightly stretching the portal branch; this traction point is demonstrated clearly at IOUS (Fig. 52.21). If the exposed portal branch is not clearly visible because it has collapsed, the portal triad is unclamped. If the target site is correct, the portal branch is ligated and divided, and resection is completed under IOUS guidance. Conversely, if the exposed vessel was not the targeted one, it is spared, and unnecessary sacrifice of further liver parenchyma is avoided.

A practical example of using the hooking technique is during ventral or dorsal subsegmentectomy of segment 8. The portal trunk to this segment may show bifurcation in its dorsal branch and ventral trunk near the origin of the portal vessel to segment 5. In this situation, there is the risk of ligating and dividing the portal branch of segment 5, instead of the planned subsegmental branch of segment 8. Under IOUS control, the hooking technique enables the identification of the branch, which was encircled, and then the surgeon can decide with certainty whether to ligate it or not.

The hooking technique is also useful when tumour thrombi occupy portal branches [41]. Once the portal branch is skeletonized, it is encircled with a stitch, which is gently pulled up under IOUS control; this traction stretches the portal branch slightly, and the traction point is demonstrated clearly by IOUS. If the traction point is not at the level of the tumour thrombus, it is possible to ligate the portal branch and proceed with the liver resection, ensuring that the thrombus will not migrate because of surgical manipulation.

Recently, the hooking technique has been introduced also in the minimal access setting with the same criteria of utilization: in this approach where the tactile feeling is absent, a further correlation between IOUS and surgical field is of utmost relevance [42].

During liver dissection, the backflow bleeding from the hepatic veins is an important source of blood loss, then its limitation is a priority in liver resections. A US-guided technique is simple and effective for backflow bleeding control [43]. Once the hepatocaval confluence is exposed anteriorly, dissection proceeds until the surgeon's fingertip can compress the targeted hepatic vein at its caval confluence; the effectiveness of this maneuver is checked by color-flow ultrasound.

52.4.3 Postresection Evaluation

After nodule removal, IOUS offers two options for specimen handling. The "water bath" technique consists of real-time control of the proper resection of the targeted nodule, verifying its complete inclusion in the specimen removed from the liver (Fig. 52.22) [44]. The second option involves checking the cut surface, which is refreshed with saline to avoid the artifacts generated by the residual air bubbles and clots.

In patients who require major resection, color Doppler IOUS allows the proper positioning of the remnant liver such that there is no partial occlusion or turbulence of the inflow and outflow in terms of velocity and waveform [45].

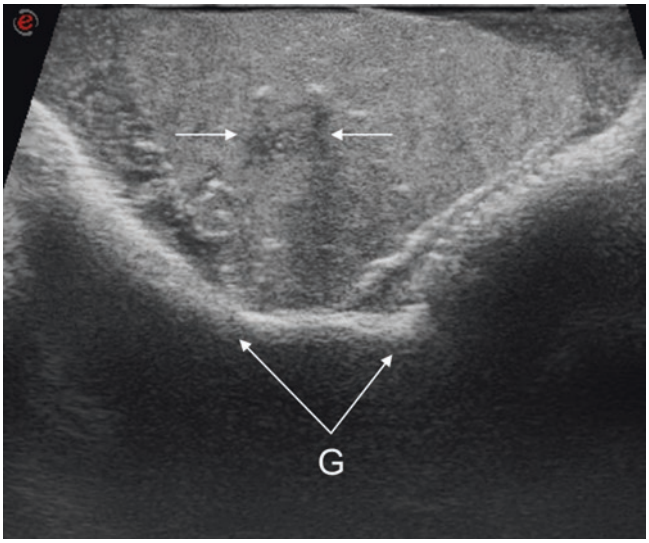

Fig. 52.22 From left to right the water bath technique for checking the surgical specimen: the inclusion of the targeted nodule (*arrows*) is confirmed at IOUS. *G* gauzes

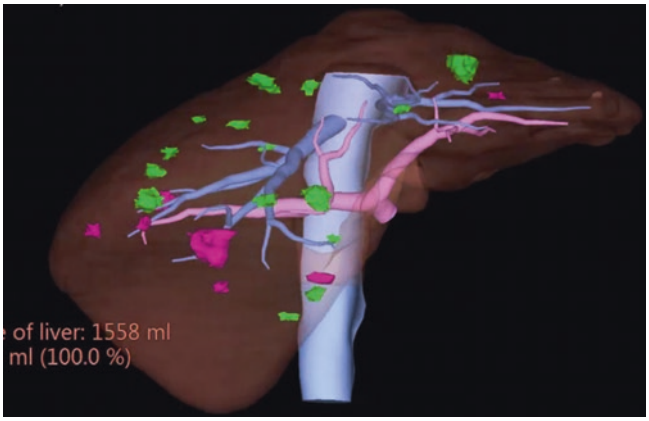

Fig. 52.23 A liver cast of a patient with multiple bilobar colorectal liver metastases: in green those CLM still visible; in pink those that have disappeared

52.5 Complementary Guidance Modalities

In recent years, tracking systems that combine the position of the dissecting instruments and the three-dimensional (3D) liver reconstruction, based on software elaboration of the preoperative CT or MRI or the 3D US images themselves, have been proposed for dissection guidance [46]. This approach is mainly used to offer real-time and continuous guidance of the liver dissection, rather than the one warranted by IOUS guidance. IOUS guidance can be done repeatedly but is not providing information anyway if dissection is not interrupted for the IOUS check. System which is also trying to overcome the need for training in IOUS image interpretation. The unresolved problem of organ shifting, costs, and lack of data proving their superiority have kept the dominance of IOUS in surgical practice [47–50].

In expert hands, IOUS guidance enhances parenchyma-sparing and results in new hepatectomies, while keeping adequate oncological results. Therefore, IOUS guidance should be considered as the gold standard in terms of "navigation" for liver surgery. On the other hand, merging the information provided by IOUS with those of a 3D cast available in the operating room and/or by fusion imaging remains a promising future improvement.

In the case of complex resections featured by multiple parenchymal-sparing resection for multiple bilobar CLM, preoperative estimation of liver volume provided by 3D liver cast is undoubtedly an improvement [51] (Fig. 52.23).

Once surgery is planned for multiple bilobar CLM a precise definition of the liver involvement should be recommended before neoadjuvant therapy. Measurement of the treatment response and finding of any CLM disappearance are the most relevant issues to be defined after systemic treatment and prior to surgery. CLM disappearance at the preoperative imaging does not compulsorily mean a real vanishing of any vital residual tumoural tissue. When surgical strategy would consist of a single session parenchymal-sparing major hepatectomy the identification of the clusters' compass points represents one of the pillars [52, 53] (see Chap. 18—Torzilli et al.). That becomes essential in those conditions featured by multiple CLM disappeared after chemotherapy. For this reason, pre-chemotherapy imaging assumes a crucial role since it may act as a standard of reference for showing the distribution of all CLMs. The fusion imaging featuring most of advanced US systems can match pre-chemo CT or MRI with the real-time IOUS finding in a simplified and low-cost solutions for intraoperative navigation in these circumstances (Fig. 52.7). Fusion imaging provides a further advantage for surgeons. Indeed, IOUS scans are simultaneously shown on the same screen with the corresponding CT or MRI of a given patient. This facilitates the surgeon's interpretation of IOUS images and may help in speeding up his/her learning curve.

52.6 Conclusions

IOUS still remains the best method for staging the liver involvement by the tumour. The aid of CEIOUS, ICG-fluorescence imaging, and fusion imaging have further increased its role. Furthermore, IOUS remains the best method for the surgeon to understand the liver anatomy and the relations between tumours and intrahepatic vessels. In this perspective, 3D liver cast, and fusion imaging have facilitated the role. IOUS remains crucial for planning the resection and guiding the surgeon's hand in real-time during the liver parenchyma dissection. The methods for performing

IOUS-guided resection guarantee a radical intent in a conservative manner whenever doable. This has positive consequences either for the effectiveness of the surgical treatment than for its safety. For CLM, the use of IOUS provided relevant insights (i.e., the R1vascular surgery [53, 54], the role of the communicating vein in case of partially occluded outflow [55–57], and the radical but conservative IOUS-guided policy) opened surgical options for cases which were previously considered unresectable (see Chap. 18—Torzilli et al.). The parenchymal-sparing major hepatectomies [53] is used as an alternative to the staged approach for multiple bilobar CLM [6, 54, 58].

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Hybrid Room for Combined Procedures

53

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Learning Objectives

- Hybrid rooms are fully equipped surgical operating rooms in combination with medical imaging based on 3D coordinate systems (CT, MR, CBCT) in association with other techniques (ultrasound, fluoroscopy) and/or guidance systems.
- Hybrid rooms allow a combination of interventional radiology and surgical procedures in the same setting, and therefore improving patients' workflow.
- The use of cross-sectional and angiography imaging during local therapies for colorectal liver metastasis improves outcomes after the treatment.

53.1 Introduction

In the last few decades, significant advancements in surgical technique, equipment technology, the understanding of tumour biology, multidisciplinary therapy, and systemic therapy have improved the outcomes of patients with colorectal liver metastasis (CLM). Multidisciplinary care has become the cornerstone for the management of patients with CLM. For those patients who are deemed candidates for surgical resection, interventional radiology plays a critical role in their longitudinal care. Pre-, peri-, and postoperative image-guided procedures are routinely applied in a variety of clinical situations.

Hybrid rooms that combine the equipment used in interventional radiology suites and operating rooms have recently emerged as an appealing avenue for facilitating multidisciplinary care of patients with CLM. Thanks to the relevant improvements in technology and equipment ergonomics, imaging equipment that previously required a dedicated room and extensive footprint area can now be installed in the operating room. This convergence has also provided the ability to combine interventional radiology and surgical procedures to be performed simultaneously, and has successfully reduced several of the workflow-related burdens experienced by patients. In this chapter, we discuss definitions of equipment in interventional radiology and image-guided surgery, and its current clinical application in the management of patients with CLM.

53.2 Image-Guided Minimally Invasive Procedures

Minimally invasive procedures have advanced with the progress of technology and are considered a safe and effective alternative when compared to traditional nonminimally invasive approaches. The development and advances of novel imaging technology techniques contributed to a large part of the progress experienced by minimally invasive procedures in the last three decades. These techniques enhance the understanding of the target organ anatomy, facilitating procedure planning, guidance, and treatment assessment, ultimately improving procedural outcomes.

Image-guided techniques require a multi-professional collaboration of physicians from different specialties, as well as engineers and computer scientists. Meanwhile, the terminology used in the field of image-guided minimally invasive procedures has become divergent. Therefore, some research-

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Fig. 53.1 Hybrid room at MD Anderson Cancer Center. (**a**) Patient table; (**b**) C-arm fluoroscopy; (**c**) Computed tomography on rails

ers proposed and reached a consensus agreement on the following definitions to image-guided minimally invasive procedures [1]. On such consensus, a hybrid operating room (Fig. 53.1) is defined as a facility equipped with full surgical capabilities, including medical imaging based on coordinate systems (CT, MR, Cone-Beam CT) in association with other techniques (ultrasound, fluoroscopy) and/or guidance systems. Through different types of human-machine interfaces, the planning, guidance, and control stages can be performed intraoperatively in a dynamic fashion.

53.3 Equipment Definitions

53.3.1 C-Arm Fluoroscopy

A C-arm is a fluoroscopic system that is based on x-ray technology. The name derives from the C-shaped arm used to connect the x-ray source and x-ray detector. Initially, the C-arm fluoroscopy was historically used for simple examinations and procedures, but gradually it was applied to more complex ones. In recent decades, C-arm fluoroscopy has been widely used for angiography and therapeutic studies, where flexibility in the examination process is needed. The use of fluoroscopy has contributed greatly to combined procedures, and therefore is critically important for the procedure's success. This system provides real-time imaging with considerable temporal anatomical information and high-resolution X-ray images, allowing the physician to monitor the situation at any point and make any rapid adjustments.

The combination of angiography and subtraction of pre- and post-contrast fluoroscopic images has given rise to digital subtraction angiography (DSA), which allows improved visualization of vascular structures and tumour enhancement in real time. In addition, digital technology allowed the development of fluoroscopic system with a flat panel detector (FPD) instead of the x-ray image intensifier system. For fluoroscopy, FPDs are smaller in volume, lighter, more durable, and have much less image distortion than the x-ray image intensifier system. Thereby, FPDs offer significantly improved contrast and spatial resolution. The use of C-arms equipped with FPD allows the acquisition of C-arm cone-beam CT (CBCT) images, which provide 3D cross-sectional CT-like images. This single unit solution allows the acquisition of real-time fluoroscopy, angiography, and CT-like cross-sectional images and is now widely used in various interventional procedures.

53.3.2 CT Angiography and Angio-CT Suite

CT angiography is an invasive imaging technique used to increase imaging quality by acquiring a true CT image during interventional radiology (IR) procedures. In this technique, a catheter is placed in the celiac or hepatic artery (CT hepatic angiography [CTHA]) or in the superior mesenteric (CT during arterial portography [CTAP]). These techniques have been used for preoperative studies and several interventional procedures [2–4]. However, CT angiography in a conventional IR suite equipped only with a fluoroscopic system requires transferring the patient between the CT room and the C-arm IR suite.

In order to eliminate the need for transportation between two distinct rooms, a hybrid angiography-computed tomography (angio-CT) suite was developed in the 1990s [5]. This system combines a fully functional C-arm unit with a helical sliding-gantry CT attached to a common patient table in the same IR suite. A patient table is used for both CT and C-arm units without patient transportation while performing CT scans, fluoroscopy, and angiography. This solution provides robust cross-sectional imaging in the angiography suite while decreasing the risk of catheter dislodgement and complications due to patient transportation.

53.4 Clinical Applications for Liver Surgery

53.4.1 Procedure Planning

The use of computer-assisted preoperative planning and intraoperative guidance has allowed surgeons to perform more complex and extensive liver surgeries [6, 7]. The optimal surgical strategy includes the determination of the exact course of hepatic parenchymal resection, the planning of vascular or biliary reconstruction, and the choice of laparoscopic or open approach. Computer-assisted surgical planning has facilitated better patient selection, appropriate liver volumetry, identification of anatomical risks, and evaluation of surgical strategies in liver tumour resection [8, 9]. Today, a wide range of computer systems for preoperative liver surgery planning is becoming increasingly available in clinical practice.

Segmentation of medical images is a processing technique in which different anatomical structures are individually marked and analyzed for a posteriori reconstruction into a 3D model [10]. The segmented 3D model is suitable for preoperative planning in liver surgery. Understanding the patient's anatomy through segmentation can reduce the incidence of postoperative complications such as bile leak, segmental vascularization, or venous drainage failure, which in turn can reduce the functional capacity of the remaining liver. In a study by Radtke et al. reporting 202 consecutive hepatectomies, information gathered from additional 3D preoperative planning, compared to conventional axial data, changed the surgical strategy in 33% of patients [11]. The changes in preoperative planning included increased extent of resection, planning for intrahepatic vascular reconstruction, and complete planning changes. In particular, 3D preoperative planning is useful in planning extended left hepatectomy and repeat hepatectomy.

53.4.2 Navigation

Parenchymal-sparing hepatectomy is considered the standard surgical strategy for the treatment of colorectal liver metastasis (CLM). Precise surgical planning by means of preoperative simulation and intraoperative navigation are critical steps to achieve precise CLM resection while preserving sufficient functional liver parenchyma. Such strategies are discussed in detail in Chap. 5.

53.4.3 Fast-Track Two-Stage Hepatectomy

Synchronous and metachronous CLM occur respectively in about 15 and 30% of patients with colorectal cancer [12]. Liver resection has been proven to be the safe and effective local therapeutic approach, with 5-year overall survival rates ranging from 40 to 58% [13–15]. Moreover, recent advances in the understanding of tumour biology along with the use of routine preoperative chemotherapy have expanded resection criteria thus increasing the number of patients with advanced CLM eligible for curative resection.

In spite of such expansion, there are still a significant number of patients deemed unresectable. For instance, patients with inadequate future liver remnant (FLR) may not fulfill the resection criteria. In order to ensure sufficient FLR, a variety of local strategies has been implemented, such as portal vein embolization (PVE) [16–18], two-stage hepatectomy (TSH) [19], and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) [20].

PVE was first reported in the 1980s to deal with FLR insufficiency. Thereafter, TSH for multiple bilobar CLM was reported as the safe and effective technique to improve resectability in 2000 by Adam et al. [19]. In the first stage of hepatectomy, partial hepatectomies (generally the left liver) are performed to remove the FLR lesions. One to three weeks after the first hepatectomy, PVE is often required to promote hypertrophy of the FLR. After approximately 3–4 weeks following PVE, once sufficient FLR is con-

firmed, a second-stage hepatectomy is performed. One of the major issues with patients undergoing TSH is dropout of patients between the first and second stages. The reason for the dropout may be caused by inadequate FLR or worsening of the disease [21, 22]. The progression is due to a prolonged period without chemotherapy during the time course. Some suggested that interval chemotherapy can reduce the risk of disease progression without affecting FLR hypertrophy, while others questioned the efficacy of chemotherapy between the first and second stages of TSH in reducing the dropout rate.

In order to shorten the time interval between stages and reduce the dropout rate, the ALPPS and fast-track TSH methods were proposed. In the fast-track TSH using a hybrid room, the first-stage hepatectomy and PVE are performed in the same surgical setting. The first-track TSH improves patient workflow process by consolidating several encounters (first-stage hepatectomy, PVE, and postoperative CT) in a single event, and therefore reducing costs and shortening the time between first- and second-stage hepatectomies to only 4 weeks, instead of 8–16 weeks [23–26] (Fig. 53.2).

53.4.4 Intraoperative Ablation Under Cross-Sectional Imaging Guidance

Ablation has been widely adopted as a minimally invasive technique for small CLM. However, the impact of ablation on survival remains controversial [15, 27]. Studies reported that the combination of ablation and hepatic resection achieved outcomes comparable to hepatic resection alone in appropriately selected patients and tumour conditions [28, 29]. Both intraoperative and percutaneous ablation are routinely utilized [30–32]. Although intraoperative ablation is traditionally used as the combined approach for patients undergoing liver resection, patients who receive hemihepatectomy with intraoperative ablation were reported to have higher rates of local tumour progression (LTP), postoperative liver failure, and postoperative mortality. In addition, technical limitations such as intraoperative adhesions and the inability to identify the target tumour with intraoperative ultrasound (US) are known to be factors that hinder the use of intraoperative US-guided ablation. In contrast, image-guided ablation with cross-sectional imaging (CT) has the potential to overcome these limitations. In recent studies, the

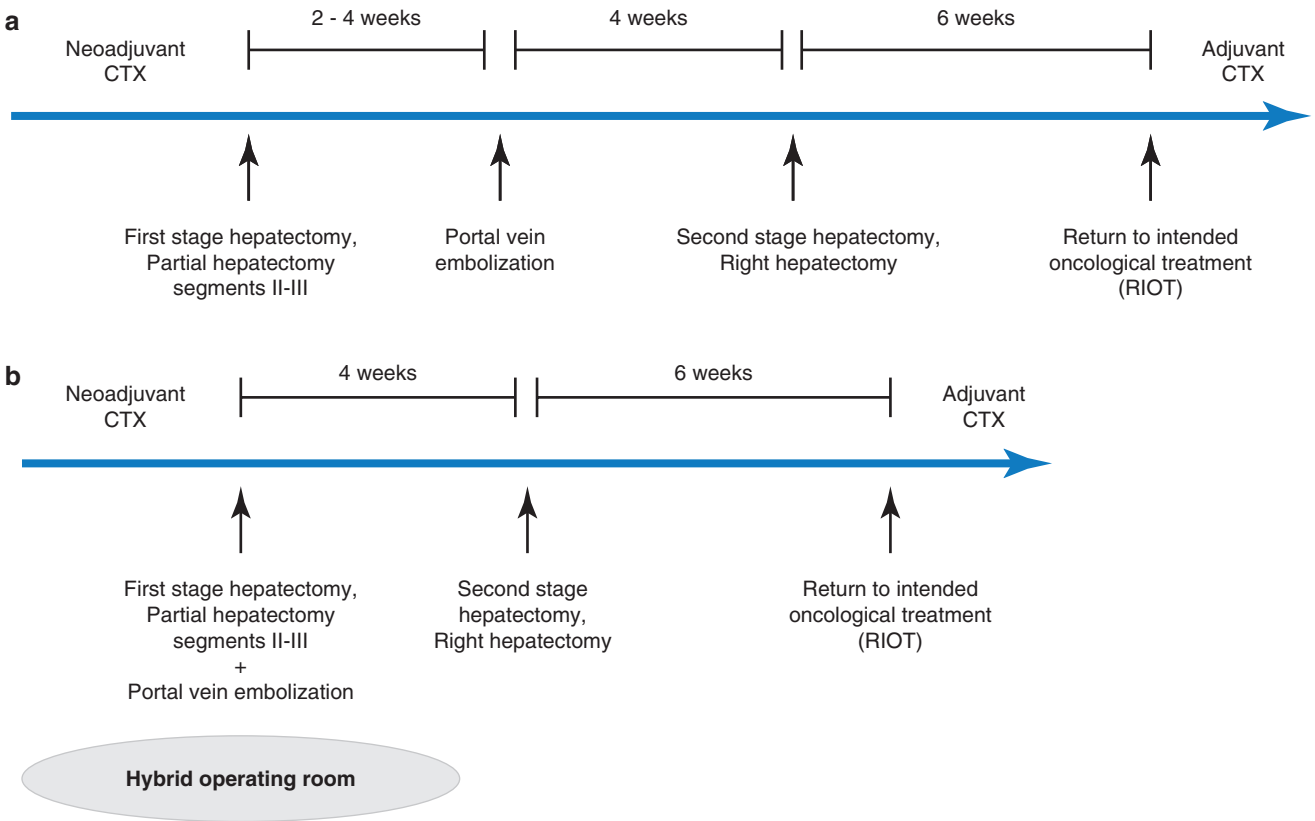

Fig. 53.2 Workflow illustration of (**a**) traditional and (**b**) fast-track two-stage hepatectomies approach. Legend CTX: chemotherapy. With permission from Odisio BC et al. (https://www.sciencedirect.com/science/article/pii/S1072751518303260?via%3Dihub#fig2)

use of image-guided percutaneous ablation reduced the associated rate of LTP to a rate comparable to surgical resection [33–35]. Furthermore, in a recent study, postoperative image-guided percutaneous ablation under CT or MR of intentionally untreated CLM demonstrated lower rates of complications and local tumour progression when compared to intraoperative US-guided ablation [35]. The use of a hybrid room equipped with cross-sectional imaging for intraoperative ablation has several theoretical advantages over intraoperative US-guided ablation because the use of cross-sectional contrast-enhanced imaging allows clear depiction of the target lesion and prompt assessment of ablation margins on a three-dimensional plane [36–38].

53.4.5 Management of Complications

Intra-abdominal hemorrhage is a severe complication of hepatectomy, with an incidence of 4.2–10% [39, 40]. The three most common causes are injury to a hepatic vein in 33% of cases, superficial bleeding in 25%, and arterial injury in 16% [41, 42] [43]. The most severe complication is a recurrent bleeding requiring specific surgical treatment or embolization and has a mortality rate of about 50%. It is worth noting that for the second surgical intervention, the estimated mortality rate is about 9% if the surgery is performed within 6 h of the onset of bleeding, while the estimated mortality rate is 25% after 6 h [44]. Therefore, rapid treatment of intra-abdominal bleeding is considered a relevant factor for improving patient outcomes. In this setting, hybrid operating rooms have the potential to improve treatment efficacy and patient safety because patients can be evaluated with cross-sectional CT/CBCT or angiography imaging to identify bleeding sources, and treated with embolization and/or surgery. This approach has been utilized in several trauma centers and showed significant improvement in patient outcomes [45, 46].

53.5 Conclusions

Compared to conventional operating rooms, hybrid operating rooms reduced the burdens that patients are subjected to during pre-, peri-, and postoperative care. Specifically, improvements in patient workflow, oncological outcomes, and complications have been demonstrated. Further efforts are needed to improve cost-effectiveness, ergonomics, and seamless integration of intraoperative workflow. Multiprofessional collaboration is a key component because the inherent multidisciplinary nature of hybrid rooms and contemporary cancer care are needed.

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Part VIII

Role of Multidisciplinary Team and Recovery and Surveillance Strategy

Multidisciplinary Liver Tumour Board

54

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Learning Objectives

- To give readers an insight on how to initiate and organize a multidisciplinary liver tumour board for colorectal liver metastases.
- The multidisciplinary liver tumour board maximizes clinical effectiveness in the management of patients with colorectal liver metastases.
- To understand how team dynamics positively impact patient care.

54.1 Introduction

With 1.4 million new cases per year, colorectal cancer (CRC) is the third leading cause of cancer death globally, as reported in 2018 by Globocan. Its incidence is steadily rising in developing nations [1–3].

The liver is the most common site of metastases from colon and rectal cancer (mCRC). It is estimated that 15–20% of colorectal cancer patients harbor synchronous liver metastases on diagnosis, and 50–60% will develop liver metastases in their lifetime [4, 5].

Surgical liver resection remains to be the only treatment modality that offers better overall survival with a chance of cure. However, only 10–15% are resectable upon diagnosis. However, the major challenge comes from the fact that approximately 80% of patients with metastatic disease are unresectable at presentation. In initially unresectable or borderline resectable cases, achieving resectability is the goal [6, 7].

Arriving at today's 50% of the 5-year overall survival is not purely due to surgical strategy. Much development took place and modalities such as chemotherapy, local ablative, and regional treatments have all contributed to the current milestone of converting liver metastases from incurable to a chronic disease achieving 10 year survival in at least 25–30% of patients who underwent multimodal treatments and even repeated surgical resections in specialized high volume centers [8–10].

Advances in diagnostic imaging, 3D reconstructions and volumetric liver studies, functional testing, and augmented reality and simulations in a more sophisticated setting provide better patient selection, and meticulous surgical planning, expanding indications allowing safe surgery with better outcomes [11, 12].

Current advances in chemotherapy, biologicals and immunotherapy, radiation, and other locoregional approaches to down-size or control liver metastases form the complete range of armamentarium in managing liver metastases. Improvement in systemic treatment has developed alongside with better understanding of tumour biology and next-generation sequencing [13–15]. Simultaneously, progress in surgical, and anesthetic techniques synergistically increases resectability, where the value of liver resection is made even more profound in specialized multidisciplinary team approach increasing resectability rate and consequently improving 5-year overall survival to as high as 60% in some centers from a dismal 2% in the 70s [16].

The LiverMetSurvey holds real-world data of 28,081 patients in 366 centers from 63 countries globally in June 2020, showing 5- and 10-year overall survival of 43% and 26% in those who underwent liver resection versus 5- and 10-year overall survival of 10% and 2% in those who did not undergo liver resection for colorectal liver metastases [17]. The AsianLiverMetSurvey comprising of 843 patients mCRC across eight countries in Asia correlates well with the global data with an overall resection rate of 25.7% and 5-year overall survival more significant than 70% for patients with 1–3 metastases and those treated with a curative intent on the get-go. The 5-year overall survival significantly dropped to less than 25% for those with the following factors: more than three metastases in number and 50 mm in size, bilateral, syn-

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chronous lesions, and concomitant extrahepatic disease. Even with the available data, surgery remains to be underutilized globally [18–20].

Surgical resectability is dependent on the remnant liver volume rather than the amount or number of lesions to be taken out. Ideally, R0 resection must be achieved. Whether an R0 or R1 resection is achievable remains to be a subject of debate as well. The majority will be truly unresectable, where multiple bilobar disease and extrahepatic metastases are widespread. They will perhaps resort to palliative options. A highly selected population of patients who have a significant response to conversion systemic therapy may eventually be surgical candidates. With various existing consensus guidelines [4, 6, 21–29] and clinical risk scoring systems [30–32], still several issues will need to be addressed within a multidisciplinary liver tumour board (MDLTB) setting because what should be done (which is strategic in principle) versus what can be done (which varies based on surgeons, teams, and institutions).

Jones et al. clearly described the denial of potentially curative surgical options in patients who were not reviewed and managed by the MDLTB. This data underpins the value of specialized MDLTB [33, 34]. Huiskens et al. analyzed prospective resectability evaluation of patients with CRLM by a panel of radiologists and liver surgeons and showed a high rate of disagreement among experienced liver surgeons. This reflects the complexity of defining treatment strategies for colorectal liver metastases and supports the use of a panel of liver surgeons rather than a single-surgeon decision which highlights the importance of teamwork [35].

Quality radiologic assessment [4, 6, 36–38], meticulous functional hepatic reserve evaluation, tumour burden scores, and treatment response appraisal are crucial steps to help surgeons achieve the goal of resectability to determine whether hepatic resection is contraindicated or not, technically and oncologically (Table 54.1). These will guide the multidisciplinary team and the patient in arriving at shared decision-making best suitable for the patient [6, 12]. This highlights that the best treatment approach is multimodal. Thus, multidisciplinary approach, [39–41] discussed within the liver tumour board, will serve the patient best, keeping in mind the evolving evidence and recommendations, available expertise, and what matters to the patients most [42]. Complex surgical procedures are best referred to high-volume centers for optimal outcomes even achieving 60% of 5-years overall survival in the recent Finnish systematic approach by performing nationwide centralized and specialized multidisciplinary tumour board resulting in impressive patient outcomes [15].

Table 54.1 Considerations for resectability depend on different factors

Technical resectability	Oncologic resectability
Remnant liver volume	Extrahepatic disease
Preservation of adequate vascular inflow and outflow, and biliary drainage	Treatment response
R0 vs. R1	Tumour burden
Surgical team expertise	Tumour progression

54.2 The Multidisciplinary Tumour Board, Its Beginnings and Evolution

Multidisciplinary team conferences in the form of tumour boards have existed in the United States for the past 50 years [43]. In the last two decades, there has been a transition of tumour boards' primary goal from education to care delivery. This has since then evolved in various disciplines, primarily evident in cancer care. The multidisciplinary treatment approach can now be described as a harmonized approach within a regularly conducted hospital. Tumour Boards bring together different cancer specialists as well as other clinicians and allied health professionals in planning the appropriate treatment and other integral services for a cancer patient before initiating complex, multimodality therapies.

This was initially driven by striking differences in the treatment process for cancer patients in the United Kingdom in the 90s [44] In 2003, "Plan Cancer" [45] was implemented in France, as a political mandate in the management of cancer patients, describing a set of requirements that include membership, schedules, regularity, documentation, and quality indicators defining the multidisciplinary team (MDT). Further, it implies presenting and reviewing each cancer patient at least once in the MDT meetings for a treatment recommendation following a consensus gathered at the meeting where the attending physician takes the responsibility to prepare and present the medical information and represent the patient as his or her advocate. Patients are then advised based on conclusions derived from the meeting.

This format serves as a central decision-making process based on evidence or institutional practice approach. MDT meetings since then have developed in different centers predominantly in Europe, Canada, and Australia, while another approach in the United States advocates personalized treatment plans in centers of excellence where patients are seen and managed like a "one-stop-shop" after a discussion with members of the multidisciplinary tumour board [46].

Diffusion to the Asian region is identified in Taiwan where MDT is required for healthcare reimbursements [47, 48] and in the Philippines where the establishment of multidisciplinary approach team management was stipulated in the National Integrated Cancer Control Act [49]. A nationwide virtual multidisciplinary tumour board under the Philippine College of Surgeons Cancer Commission has commenced to address the lack of expertise in the rural areas of the archipelago [50].

Several key issues merit pretreatment review and discussion of patients in a multidisciplinary setting offer profound benefits to patients, providers, and institutions alike. These initiatives empower cancer patients with a right to best management care plans, [51–53] physicians to understand the pathophysiology, to have the opportunity of life-long learning and interprofessional exchange of current advances. In turn, institutions gain reputation, optimize resources, and establish better patient referral pathways.

Goals of the MDLTB: To Maximize Clinical Effectiveness

1. Patient-centered approach
2. To ensure designated specialists work efficiently and effectively together as a team
3. To ensure that the team is committed to a common purpose and approach in the management for which they hold themselves mutually accountable
4. To determine resectability by liver surgeons and commence optimal approach, timing, and sequence of treatment in a timely fashion
5. To ensure that care is based on agreed local and international evidenced-based clinical guidelines and/or best practices
6. Attention to survivorship issues, quality of life, patient preferences, and economic sustainability
7. To ensure that mechanisms are in place to support the entry of eligible patients into clinical trial
8. To improve communication, enhance collegiality and professional skills and knowledge between MDTB members leading to maximal clinical effectiveness in cancer care
9. To identify service gaps or breakdowns in coordination so that they can be rectified or improved
10. To manage resources to avoid duplication of effort and diagnostic tests

Key Issues Especially When Patients Present with Synchronous Liver Metastases:

- Symptomatic or asymptomatic primary tumour?
- Is the primary tumour easily resectable?
- Is the metastatic disease resectable with curative intent at the time of detection?
- If so, simultaneous versus staged resection?
- If the metastases are unresectable, is it feasible to convert to resectability?
- If converted, simultaneous or staged resection?
- Is liver-first approach a valid option?
- What are the options when there is concurrent lung or peritoneal metastases or both?
- What can be offered if there is no hope of conversion (multi-site metastatic disease)?
- What is the role of systemic chemotherapy? Conversion? Neoadjuvant? Adjuvant? Palliative?
- Is there a role for targeted therapy?
- Is there a role for immunotherapy?
- Is there a role for radiotherapy in rectal primary?
- What is the role of local ablative therapy for liver metastases?
- Is there any chance of cure?
- Is the patient fit for the treatment strategy?
- Does the patient want the treatment strategy?
- Can the patient afford the treatment?
- What are the risks and benefits of the treatment?

54.3 Decision-Making Members of the Multidisciplinary Liver Tumour Board (MDLTB)

The MDLTB brings more than two groups of professionals caring for patients with liver metastases together, focusing on complementary procedures and perspectives that provide opportunities to learn about each other. They are motivated by a desire to focus on assessing resectability, improving survival and quality of life of stage IV colorectal cancer patients with liver metastases, and develop a professional understanding of their separate.

The MDLTB will not be complete without a proficient team consisting of the necessary key players to identify patients who will benefit from liver resection, systemic therapy, whether neoadjuvant or adjuvant setting, conversion therapy in the case of borderline or unresectable liver metastases, or even multimodal locoregional treatment options such as ablation and intra-arterial chemotherapy or radiation therapy. Likewise, there must be an advocate for patients who clearly will not benefit from any aggressive treatment that will be futile and costly, or even causing more harm, compromising the quality of life. No single physician can adequately provide all the needs of patients with colorectal liver metastases.

With an opportunity to maximize communication and facilitate patient-centered treatment planning among its members within the MDLTB, the approach to liver metastases in the MDLTB will provide a goal-directed, risk-adjusted, biomarker targeted and biologically driven personalized management of colorectal liver metastases [21] which may also include inclusion into clinical trials (Fig. 54.1).

An ideal multidisciplinary liver tumour board includes core members composed of experts in hepatobiliary cancer surgery, colorectal surgeons, thoracic surgeons, medical and radiation oncologists, diagnostic and interventional radiologists, anatomic and molecular pathologists who are all dedicated to colorectal cancer, hepatologists, and the tumour board coordinator. Other surgical oncologists with expertise in peritoneal disease, nuclear physicians, palliative care physicians, primary care physicians, oncology nurses, nutritionists, social workers, and patient navigators are a valuable addition to the team seeing the patient through the entire continuum of cancer care [55–59].

The role of the surgeon proficient in hepatobiliary cancer cannot be overemphasized. Her or his judgment and decision-

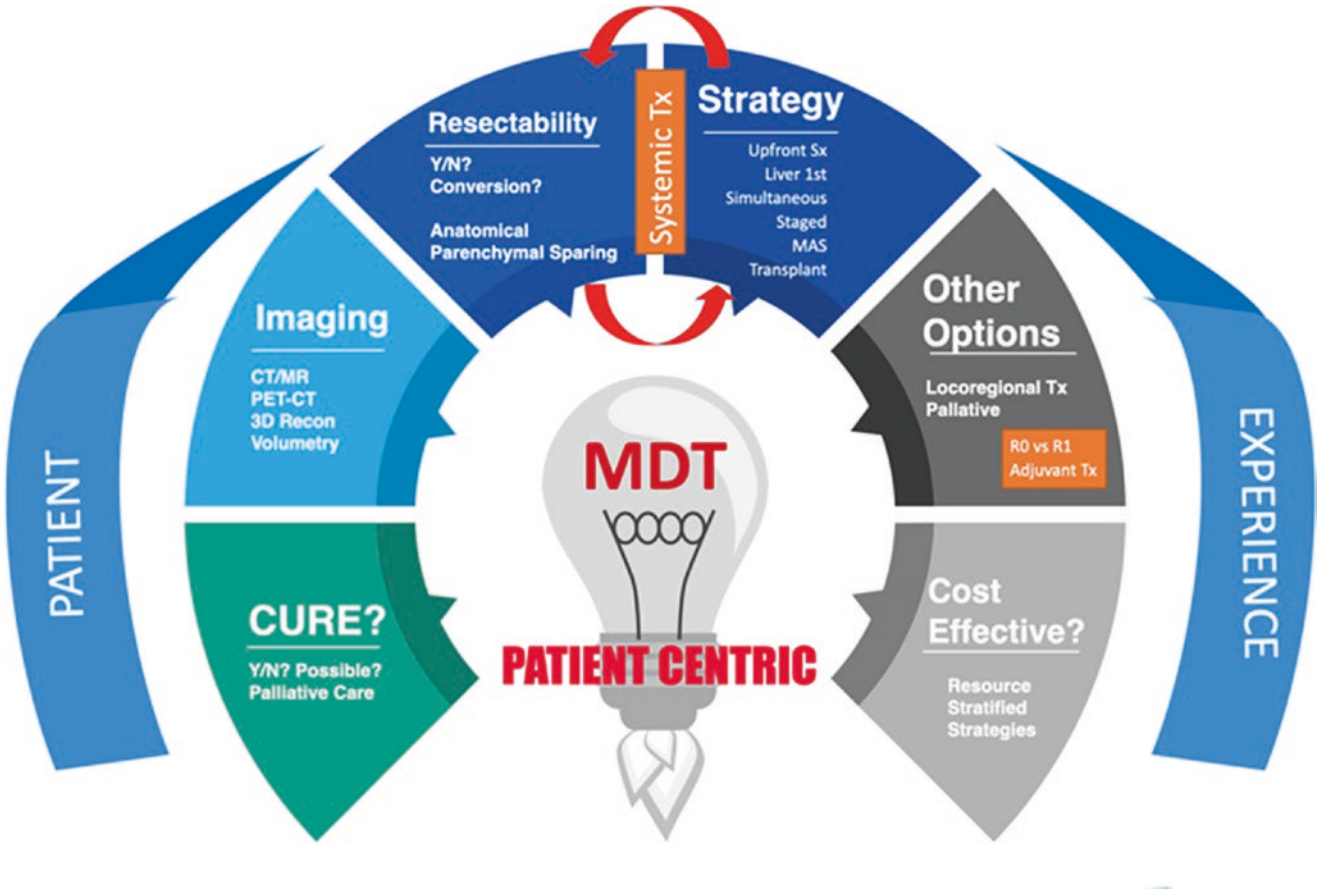

Fig. 54.1 Patient-centric multidisciplinary liver tumour board

making will be critical in selecting patients who will benefit from a surgical approach. Resectability is assessed on a per-patient basis considering technical and oncologic criteria. Likewise, disseminated disease or widespread bilobar liver metastases with unfavorable biology may be more suitable for palliative or best supportive care. Most patients with borderline or initially unresectable liver metastases and bulky liver metastases will require specific attention focusing on conversion or neoadjuvant therapy and ideal timing of surgery, including those pertaining to the primary colorectal tumour in the context of synchronous liver metastases [14, 60, 61].

Medical oncologists play an active role in determining the most appropriate and optimal first-line systemic therapy for borderline or initially unresectable liver metastases based on the molecular profiles. For resectable lesions, the debate over surgery first or chemotherapy first, surgery for disappearing lesions after neoadjuvant treatment, merit discussions. In contrast, experience with hepatic arterial infusion for unresectable liver-only metastases non-responsive to systemic chemotherapy and the need for adjuvant treatment regimens after R0 resections are included in a comprehensive treatment plan. Medical oncologists and surgeons should collaborate from the start to give the patients a clear vision of the treatment plan.

Clinical radiology is indispensable in dealing with stage IV disease, especially in liver metastases [62, 63]. The radiologists provide valuable inputs in tumour characterization, their relations to vasculobiliary anatomy and 3D reconstruction, extrahepatic disease, lymph node involvement, and anatomic variation. At the same time, liver volumetry is acquired together with the hepatobiliary surgeons' surgical plan to assess resectability. The presence or absence of extrahepatic metastases is of paramount importance, which is also contributed by advances in nuclear imaging through PET-CT. Treatment response evaluations based on changes in size, early tumour shrinkage, morphology, depth of response, and metabolic activity are within the radiologic assessment realm, which aid in prognostication and patient selection. Radiologists put in a significant amount of work before the MDLTB, requiring time to organize and prepare before the liver tumour board meeting, allowing fruitful discussions and a sound decision-making process. When a diagnostic or treatment dilemma arises, the radiologist may recommend the best suitable diagnostic imaging for evaluation [63–65].

The interventional radiologists provide locoregional treatment options for patients who are not surgical candidates. Options include thermal ablation, arterial embolization using

chemotherapy or radio nuclear particles such as Yttrium 90, portal vein embolization, and other nonsurgical techniques that complement the entire range of treatment options for colorectal liver metastases from curative to palliative [66–68].

Pathologists provide the histopathologic characteristics such as grading and differentiation, tumour size, resection margins, and tumour necrosis score for those who received neoadjuvant or conversion therapy, including chemotherapeutic effects on the adjacent normal liver parenchymal. With parenchymal sparing hepatectomies, tumour resection margins can be challenging to define. Residual tumours or resurgence were detected by Brandt in the periphery of tumours, especially those who underwent neoadjuvant therapy [69]. When disappearing lesions (radiologically) are resected, information on residual tumour or complete pathologic response must be reported. In the era of personalized medicine in cancer, molecular pathologists give insights on the molecular markers and genetic mutation profiles essential to guide the oncologist's choice of systemic treatment as well as prognostication. In general, RAS and BRAF mutation predict poor prognosis.

Hepatologists support the team's decision according to the liver reserve of the patients. With increasing chemotherapy cycles, injury to the liver is inevitable. Pretreatment optimization of liver function and support to the liver during treatment are essential.

Inputs from the colorectal surgeons regarding the necessity of primary tumour resection or diversion in synchronous lesions and neoadjuvant treatment for rectal primaries deserve attention to define ideal timing and surgical approach, whether simultaneous or staged. The thoracic surgeons are also called upon whenever there are pulmonary metastases to assess the respectability and feasibility of R0 resection [4, 16, 48, 70].

54.4 Process and Workflow

All stage IV colorectal cancer with liver metastases should be listed and reviewed in the MDLTB conducted regularly [16, 29] preferably at least once a week, to assess resectability and provide timely management [71, 72] (Fig. 54.2). Radiologic imaging must be made available for the radiologist's preparations prior to the MDLTB to arrive at a consensus regarding resectability and treatment options. Patients are reviewed frequently for interval assessments, completion of preoperative treatments, resectability, readiness for surgery, postsurgical adjuvant management, and surveillance. Nurses who are an essential staff of the MDLTB guide and provide psychosocial support and efficient care may also serve as patient navigators facilitating referrals, healthcare insurance access, and institutional and social service processes following the consensus generated from the discussions [73–75].

The coordinator (who may be a nurse or a nonclinical manager) of the liver tumour board sees to the day to day administrative functions, enlists patients and retrieves all necessary information from referring physicians, ensures meeting adhere to schedules, providing lists of patients,

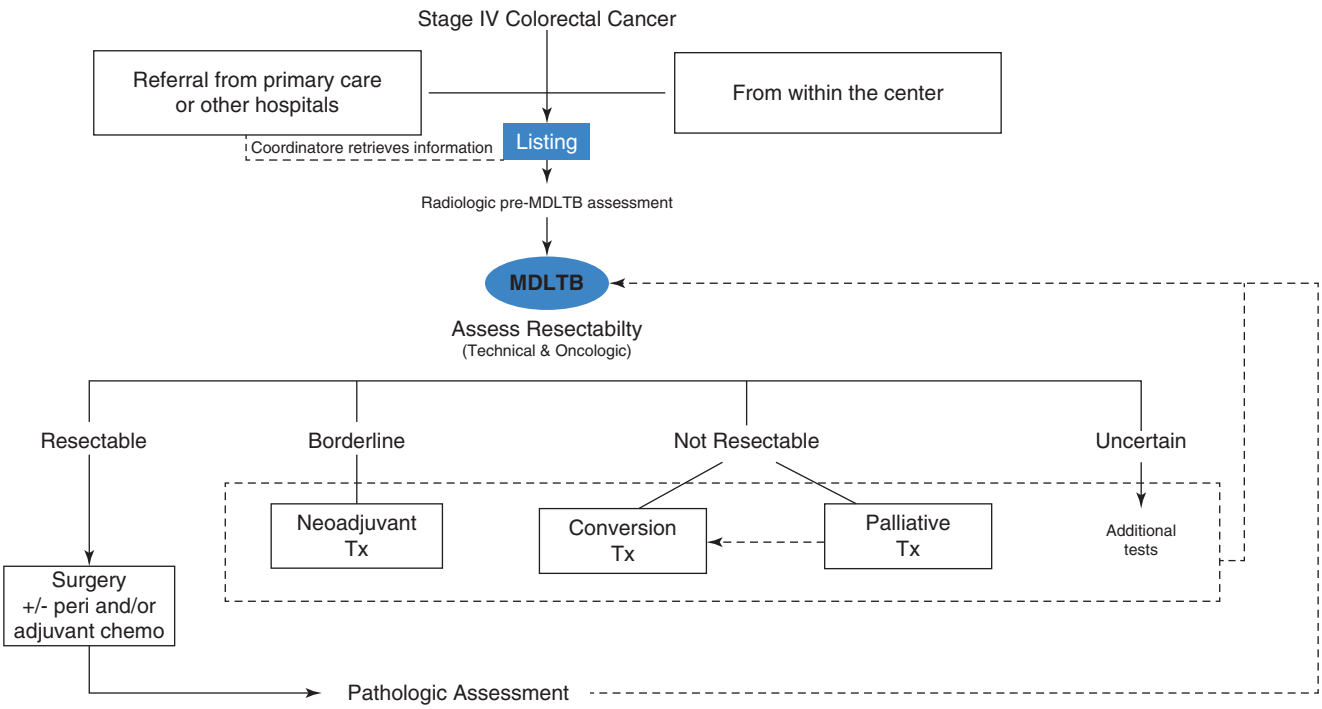

Fig. 54.2 Workflow for Stage IV Colorectal Cancer

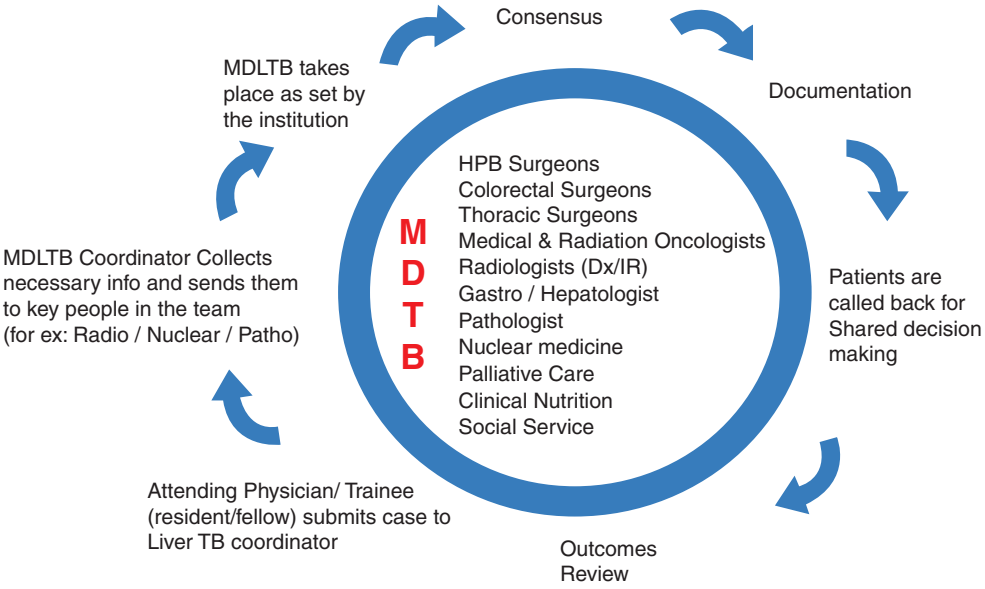

Fig. 54.3 The multidisciplinary Liver tumour board model

coordinating the attendance of necessary specialists, keeping communication with patients open, ensuring patient confidentiality and data privacy is maintained during meeting discussions, record keeping, documentation, and data processes [57, 58, 76, 77]. Outcomes must be reviewed periodically to measure the success of the MDLTB (Fig. 54.3). Data generated are valuable contributions to further research and improvement of the MDLTB.

Information Necessary to Achieve Consensus

1. Patient factors
   (a) Age
   (b) ECOG status
   (c) Relevant medical history and co-morbids
   (d) Fitness of patient if surgery is an option
   (e) Patient preference
2. Disease Factors
   (a) Radiologic Imaging (+/− series of)
   (b) Liver function tests and other relevant laboratory exams
   (c) Previous or ongoing systemic treatment
   (d) Molecular or genetic mutation profiles
   (e) Histopathology findings if available

54.5 Leadership and Team Dynamics

Administrative support, leadership, and commitment of doctors managing liver metastases are needed to sustain the MDLTB [78]. Several barriers exist, albeit widespread understanding of its need in achieving better outcomes. Most challenges pertain to (1) time constraints and workload, (2) lack of resources such as including expertise, (3) lack of administrative support, (4) weak leadership, and (5) poor team dynamics [76].

While administrative support is a crucial component, exceptional leadership is necessary to establish the direction, build the capacity and bring about the effectiveness of the MDLTB. The chair of the MDLTB, who is usually the surgeon competent in hepatobiliary cancers, leads by example, serving as a role model, implementing good time management, case prioritization, communication skills, and conflict resolution. Communication and interpersonal relations are the main challenges to effective collaboration within the team—diverse personalities and lack of trust between colleagues, especially when quality information is lacking.

Under strained circumstances, an effective leader, chairperson, or moderator maintains a respectful ambiance within the board, empowering members to contribute willingly and interactively to the focused discussion. A debate culture is central to effective team consensus decision-making utilizing an evidence-based approach, and innovative processes foster better patient outcomes and improved professional development and collegiality [79–81].

Leadership and chairing skills are necessary, albeit the paucity of evidence on structured training and assessment. A recent study utilizes an observational tool rating leadership skill in 12 domains that effectively captures MDLTB leadership and team dynamics' key attributes [82].

54.6 Impact of the MDLTB

Multidisciplinary conferences can positively impact clinical decision-making and directly influence patient care in various clinical settings [83–85]. Oxenbery described that "despite 84% clinicians being certain of their original plan before discussion in the multidisciplinary conferences, a change was recommended in 36% of cases where 72% of which are major." [86] A specialized multidisciplinary liver

tumour board dedicated to colorectal stage IV cancer has proven to be more effective than a general tumour board [60, 87, 88]. Technical and oncologic resectability is the subject of debates and discussions when disease burden, tumour biology, and molecular profiling are increasingly considered in prognostication and selection of patients who will benefit from aggressive surgical management as indications continue to expand with current advances [71, 72, 90].

Although there seems to be no direct evidence between the presence of MDLTB and better overall survival in patients with colorectal liver metastases, many studies have shown increased resectability rates up to 41% [16, 47] translated to improved overall survival, adherence to clinical practice guidelines and development of treatment algorithms have contributed to a better systems approach that contributes to patient safety and better patient experience [83–96]. There is also an increase in recruitment into clinical trials [97]. Additionally, Wein reported cost-effectiveness and better outcomes, [98] while others identified better outcomes for colorectal cancer associated with better clinical diagnostic and decision-making, timely delivery of treatment, reduced overall unnecessary referrals, optimal patient support, and better patient care in a setting of MDT [9, 46, 54, 84, 85, 92, 99].

54.7 Summary

Considerable progress in both surgical treatments of liver metastases combined with systemic therapies makes decision-making more complex. Referral and review of advanced colorectal cancer in the multidisciplinary liver tumour board is integral in managing colorectal liver metastases. Proper evaluation and assessment of resectability are pivotal in optimizing the management of CRLM in the hope of achieving long-term overall survival, a better quality of life, and promoting a better patient experience. This can be best achieved in a robust, collaborative, multidisciplinary liver tumour board setting where planning, communication, and learning are crucial to achieving a unified goal of improving survival in mCRC. Achieving resectability as a goal in managing CRLM is a product of collaboration, availability of resources, and expertise from within a multidisciplinary setting. However, this does not come without challenges. Leadership in the MDLTB is central to a performing MDLTB, and every member of the multidisciplinary team plays a vital role in contributing to the patient journey.

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Role of Advanced Practice Providers in Enhancing Perioperative and Intraoperative Patient Care

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Steven H. Wei, Elsa M. Arvide, and Jenilette Cristo

Learning Objectives

- Describe the role of advanced practice providers (APPs) within collaborative practice teams, including their scope of practice in the field of hepato-pancreato-biliary (HPB) surgical oncology.
- Discuss how APPs are utilized in the perioperative management of patients with colorectal liver metastasis, including the ambulatory, inpatient, and surgical assist practice settings.
- Describe how the utilization of APPs helps to optimize care for patients with colorectal liver metastasis.

55.1 Introduction

In today's ever-changing and increasingly complex health care delivery system, there has been a growing emphasis to provide high-quality, team-based care. With the national shortage of physicians, and the shift to value-based reimbursement models, the role of nonphysician providers, such as physician assistants (PA) and nurse practitioners (NP), continues to expand. PAs and NPs, collectively known as advanced practice providers (APPs), have become fundamental contributors to the care of cancer patients [1, 2], including those diagnosed with complex gastrointestinal malignancies. Additionally, the population of patients with hepato-pancreato-biliary (HPB) diseases is among the most complex. The surgical management of these patients can be associated with significant morbidity and mortality [3]. The successful integration of APPs into all facets of patient care, including outpatient, inpatient, surgical assist, research, and survivorship long-term care, has been associated with overall improvements in healthcare team productivity, quality, and patient satisfaction [4–6]. Within the US healthcare system challenged by high cost, poor quality, lack of access, APPs fill an important gap in team-based practice for the care of HPB surgery patients.

55.2 The Role of APPs in Perioperative Care

APPs are highly skilled medical providers who evaluate, manage, and treat patients under supervision and/or in collaboration with a licensed physician in most health care disciplines and practice settings. In the HPB surgery clinical setting, APPs function in similar roles. The key difference between PAs and NPs is in the training and education they receive to prepare for their careers (Table 55.1). In general, like physician counterparts, PAs are trained under a "medical model" which places an emphasis on disease pathology, disease process, and how it affects patients. NPs are trained under a "nursing model" which takes a more patient-centered, holistic approach with an emphasis on promoting health and addressing outcomes of care. In general, both PAs and NPs offer a diverse skill set to assist, facilitate, and complement the work of physicians and other health care professionals.

In the care of HPB surgery patients, APPs may practice clinically in the outpatient/clinic setting, inpatient/hospital setting, in the operating room as a surgical assistant, or a combination of all three main roles. APPs may also be involved in clinical research and hold administrative and management positions. Moreover, APPs often participate in the education and clinical training of students, residents, and fellows. Other expanded roles of APPs include a variety of non-direct patient care roles, such as the navigation of patient access to care, the coordination of care across disciplines and services, prior authorization of care, and patient education. As the expansion of clinical services continues to grow,

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Table 55.1 Comparison of physician assistants and nurse practitioners: overview of education, licensure, certification, and scope of practice

Advanced practice role	Education/degree/length of training	Licensure/certification	Prescriptive authority	Surgery assist
Physician assistant (PA)	Master's degree; ~1000 didactic hours 2000+ clinical hours	State Medical Board; NCCPA	Yes, require supervising or collaborating physician agreement	Yes
Nurse practitioner (NP)	Master's degree or Doctorate (DNP) (preferred by AACN) ~500 didactic hours ~500–700 clinical hours (1000 for DNPs) beyond RN training	State Board of Nursing; AANP NP specialization: adult, pediatric, geriatrics, acute care, Women's health, mental health	Yes, scope regulated by state board of nursing	Require RNFA certification

Note: *DNP* Doctor of Nursing Practice; *AANP* American Association of Nurse Practitioners; *NCCPA* National Commission on Certification of Physician Assistants; *RNFA* Registered Nurse First Assistant

APPs have been utilized in other independent clinical settings, such as in providing care in long-term surveillance and survivorship clinics, as well as telemedicine. The following sections highlight the more common roles of APPs within the HPB surgery perioperative care, and specifically among patients with colorectal liver metastases (CLM).

55.3 Preoperative Care

55.3.1 New Patient Access

In the preoperative setting, APPs remain at the forefront of direct patient care. APPs help expedite the screening of new patients for surgical consultation thereby improving patient access to immediate care. APPs become experts within their own specialty and can decipher if each patient may benefit from a surgical consultation or not. If they do, APPs are aware of the diagnostic tests, such as imaging, laboratory studies, and procedures, that need to be completed to help optimize the visit with the surgeon. In practices where surgeons have both high-volume and complex operative obligations, precluding them from being able to conduct clinical consultations daily, their APP partners are available to evaluate patients and arrange appropriate diagnostic and staging tests that can expedite care. This allows the surgeons to utilize their time more effectively by focusing more on other clinical, administrative, or research duties. In a study by Bohm et al. [7], APPs were able to save their supervising physician about 204 h per year in both direct and non-direct patient care duties.

In a complex disease process such as CLM, initial patient review, and planning prior to the first clinic appointment requires an extensive amount of time and attention to detail. Furthermore, the diversity of each patient within this disease population adds an additional level of complexity. In addition to being familiar with the patient's comprehensive medical and surgical history, APPs must consider the location of the primary colorectal tumour, distribution, and extent of liver metastases, as well as the coordination of care of multiple disciplines and ancillary services. APPs should be familiar with the variety of standard of care approaches in the management of CLM, including investigative and clinical trials, to help explain and educate patients of their disease process and treatment options. Each patient may present with different oncologic treatment history, ranging from extensive treatment to lack of treatment. Additionally, APPs must be mindful of the patient's overall health for surgical candidacy by optimizing care of any underlying comorbidities. APPs dedicate a significant amount of time and effort to review each patient in detail prior to determining surgical candidacy as well as the need for multifaceted patient care.

55.3.2 Coordination of Care and Patient Education

In the era of increasing number of patients with complex metachronous presentation of CLM, coordination of care with multidisciplinary facets is becoming more common. Surgical APPs play a significant role in coordinating patient care with other providers from medical oncology, interventional radiology, radiation oncology and even other surgeons, including transplant teams. APPs utilize their expertise to help patients navigate through the complexities of their disease process and multidisciplinary care. Patient education in this setting can include pamphlets that explain the CLM disease process, including the various perioperative procedures and therapies that can take place prior to surgery. Patient education material can also include a list of expectations for before and 6–8 weeks after surgery. APPs work closely with other clinical team members (e.g., nursing, medical assistants, social work, or nutrition) to improve patient communication and correspondence across disciplines and other health care teams. Moreover, in preparation for a patient's

perioperative period, APPs may assist nursing staff with the completion of necessary patient forms that include disability and leave absences from work.

55.4 Intraoperative Care

55.4.1 APP Surgical Assist Role

The increasing APP workforce within surgical teams in academic institutions has resulted in an expansion of roles beyond basic patient care. While the majority of APPs work primarily in the outpatient and inpatient settings, others work in the operating room (OR) in a surgical assist role. Although both NPs and PAs have similar roles in the OR, their training is different. PAs experience observation and hands-on surgical assist experience during their surgical rotations in PA training programs. Furthermore, there are several postgraduate PA training programs in surgical subspecialties that integrate first-assist training into their curriculum [8]. For most hospitals, the surgery assist role is considered a core privilege for staff PAs. On the other hand, in addition to completing their NP training program, NPs are required to complete the Registered Nurse First Assistant (RNFA) training program before providing surgical assist role in the OR. Subsequently, both PAs and NPs receive on-the-job training from their supervising physicians and from other experienced APPs already employed in the practice. In comparison to using a second surgeon in the operating room, there is now an increasing trend of utilizing APPs in the operating room, such as in the setting of minimally invasive procedures [9]. According to a study by Hepp et al. [10], having a consistent APP available for OR preparation (positioning and room-set up) and intraoperative postoperative care (closing incision, room cleaning, and patient transitions) helps to decrease overall surgical time.

For patients with CLM, the R0 surgical resection of liver metastases can be quite challenging with a broad range of technical complexities and potential complications. Oftentimes, a single surgical case may occupy a surgeon's full daily schedule. Having an APP to offload certain routine OR duties and assist with these complex procedures can provide a surgeon with focused and purposeful attention during surgeries [10]. APPs can be utilized to assist at the beginning of the case to lyse adhesions, optimize field exposure, mobilize the liver, complete a cholecystectomy, and possibly complete minor liver wedge resections. APPs can also assist with surgical closures and the transitioning of a patient to the postanesthesia recovery room. This allows the surgeon to either start another surgical case or conduct other patient care duties in the hospital thereby improving their overall productivity and efficiency while maintaining quality care. APPs who consistently work with an HPB surgeon can also assist in directing the surgical technicians and circulating nurses to prepare specific surgical instruments for each case. By the time the supervising surgeon is called in the operating room, he/she can focus on the most integral part of the surgical procedure, and in academic settings, devote teaching time to the surgical trainees/fellows.

55.4.2 Fellow/Resident Training

In the setting of surgical trainee duty hour restrictions, the integration of APPs has been a safe and cost-effective method to help manage arising challenges in the intraoperative setting [11]. One study from the perspective of residents commented on the favorable integration of APPs in the surgical practice, particularly in the operating room as well as on the hospital floor. Some institutions consistently use APPs in robotic cases as bedside first-assist in order to enhance trainees' experience on the robotic console [9]. In the report, Best Practice for Robotic Surgery Programs, Estes et al. [12] remarked as a future endeavor to integrate exposure to robotic surgery into their PA training program.

Some institutions use APPs in open hepatobiliary surgical cases in addition to surgical trainees in order to improve operative quality and efficiency. In a study by Velasco [13] at a single high-volume academic center, a designated APP served as a primary first surgical assist to surgical oncology fellows during their hepatobiliary rotation. A qualitative survey was sent to rotating surgical fellows that focused on the perceived benefit of having an APP in the operating room. The overall result was unanimously positive highlighting improvements in efficiency, educational benefits, and increased operative autonomy (Fig. 55.1). One surgical fellow commented that "having an APP in the OR during hepatectomy cases increased the level of operative autonomy, aided with an easier transition to practice and helped the preparation to instruct residents on how to assist with hepatectomy cases in my current practice" [13]. APPs can assist the fellows and residents with extensive lysis of adhesions, liver mobilizations, and closure of abdominal incisions. Subsequently, the surgical faculty can purposely dedicate more time in the OR to teach surgical trainees thereby improving educational experience and overall satisfaction.

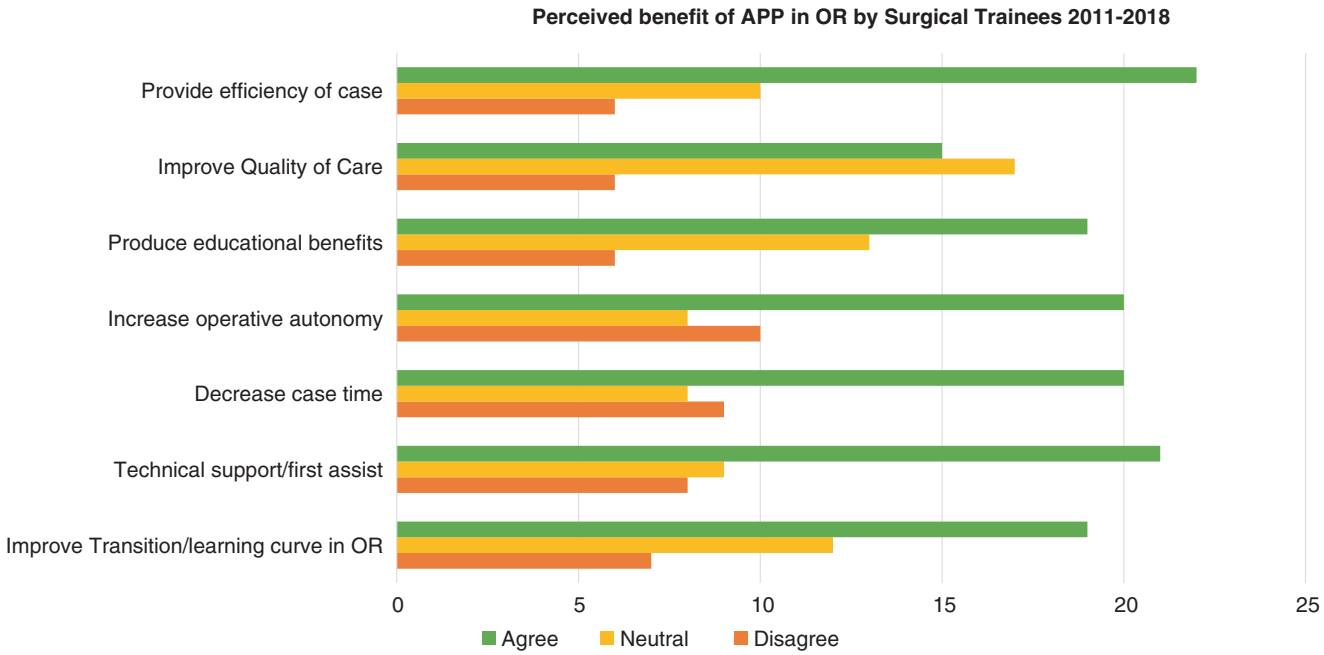

Fig. 55.1 Perceived benefit of APP in OR by surgical trainees, 2011–2018 [13]

55.5 Postoperative Management

55.5.1 Inpatient Care/Management

In response to the Accreditation Council for Graduate Medical Education (ACGME) workforce restrictions of surgical trainees, the successful integration of inpatient surgical APPs has resulted in the improvement of both overall patient care and satisfaction [11]. In providing care for post-hepatectomy CLM patients, APPs must possess fundamental knowledge of both medical and surgical oncology, while also being a proficient hospitalist. In addition to managing postoperative complications, the inpatient APPs should also understand the clinical indications, multiple treatments, and modalities in treating patients with CLM.

Like other APP roles, having an inpatient APP enables surgeons to trust their medical team so that they may focus on other clinical and academic duties (e.g., surgery, clinic, research). The inpatient APP is a constant staff to the surgical service that allows for effective communication and collaboration that may enhance a trainee's experience in clinical education [14, 15]. Additionally, inpatient APPs can provide quality postoperative inpatient care while allowing trainees to focus on augmenting their clinical and surgical skills. Having the ability to spend time with the patients daily as well as communicate with their families is essential for an enhanced patient experience and efficient coordination of care. Having a dedicated inpatient APP available for post-hepatectomy care ensures timely interventions when needed. The ability to assess patients within minutes of having acute changes in their vital signs, mental status, or other postoperative events have demonstrated an overall cost-savings to institutions [16]. Furthermore, a study by Hanna et al. [17] showed that a patient's perception of pain control affects patient satisfaction. The study showed that satisfaction was more strongly correlated with the perceptions that the caregivers were doing something to control their pain irrespective of how well their pain was actually controlled. The inpatient APP's ability to respond to their patient's pain control is paramount for an enhanced postsurgical experience.

55.5.2 Postoperative Pathways in Managing Complications

The standards of postoperative care for patients with CLM have continued to evolve over time. Having a dedicated APP competent in caring for post-hepatectomy patients facilitates opportunities for quality improvement initiatives. Postoperative care for CLM patients falls into two categories: liver only or synchronous liver/colon surgery. The latter is at a higher risk for complications due a more complex procedure, longer OR time, and usually a multi-surgeon approach. Nevertheless, liver surgery for CLM is complex and an understanding of the liver/biliary anatomy is required for post-hepatectomy care.

Enhanced Recovery After Surgery (ERAS) has been widely adopted and is becoming the standard of care at most institutions [18]. ERAS concepts, as it pertains to post-hepatectomy care, have demonstrated improvements in length of stay (LOS), pain-related measures, and morbidity [19]. These improvements have set the groundwork for stratifying patients into specific post-hepatectomy pathways. Recently, a new grading system for classifying hepatectomy complexity based on complication risk and postoperative morbidity was validated for open liver resection [20–22]. Using the Kawaguchi-Gayet Classification system (Table 55.2) allowed for the creation of post-hepatectomy pathways [23] (Fig. 55.2). Inpatient APPs help guide patients to complete their postoperative milestones prior to discharge. These milestones include tolerating a regular diet, pain well controlled with oral pain meds, voiding spontaneously, and return of bowel function [24]. The creation of these pathways allowed a streamlined and standardized approach to post-hepatectomy care among providers at a single institution that since its adoption has resulted in decreasing LOS [23]. Additionally, the post-hepatectomy pathways provide consistent measures for trainees that rotate through the inpatient service and help to ensure that all patients receive the same standard of care.

Table 55.2 Kawaguchi-Gayet classification system [20]

Grade 1	• Wedge resection, tumour size <3 cm for anterolateral (AL) and posterosuperior (PS) segments • Left lateral sectionectomy
Grade 2	• Mono-segmentectomy (AL)[a] • Left hepatectomy
Grade 3	• Mono-segmentectomy (PS)[a] • Posterior sectionectomy • Right hepatectomy • Central hepatectomy • Extended hepatectomy (left or right)

[a]Including wedge resection for tumour size ≥3 cm

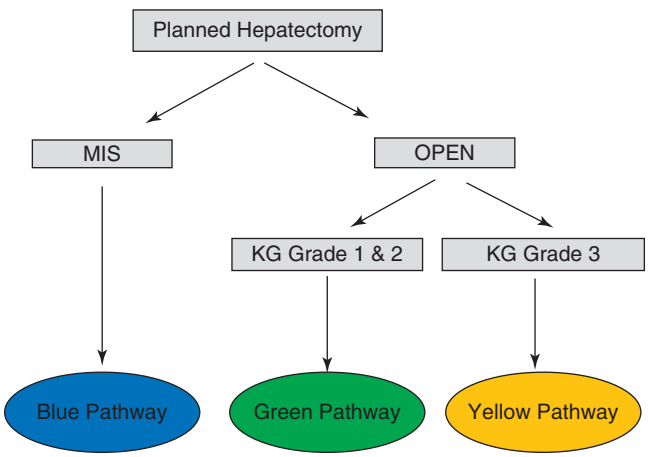

Fig. 55.2 Post-hepatectomy pathways using the Kawaguchi-Gayet classification system [23]

55.5.3 Immediate Postoperative Care and Clinic Follow-Up

Effective communication between the inpatient and outpatient APPs is essential for patient safety. Patients who had a more complex surgery or experienced postoperative complications require a closer detailed attention and follow-up care. Immediately following discharge, the inpatient APP can continue to provide "continuity of care" until the patient is seen in the clinic. Post-discharge communication with patients is crucial for troubleshooting common problems and/or intervening when necessary. Several studies have shown that the addition of an APP in their surgical practice has decreased the need for unnecessary ER visits and has also decreased the 30- and 90-day readmissions rate [5, 25]. Additionally, using the risk-stratified post-hepatectomy pathways (Fig. 55.2) can help identify a patient's propensity for complications, readmissions, or even IR interventions [26] (Figs. 55.3 and 55.4). Post-hepatectomy pathways may be used as a guide to recommend certain high-risk patients to stay in closer proximity to the hospital following discharge, which in turn can result in a decreased financial burden as well as traveling inconveniences to patients [26]. Additionally, because APPs are intimately involved in the patient's discharge planning, they are also uniquely positioned to make an impact on patient's opioid usage during their postoperative course. For example, a study conducted in collaboration with APPs showed that there was no significant difference between the amount of opioid refill rates between patients who received a predetermined "5x-multiplier dosing" of opioids when compared to patients who received a clinician-specific bias set number of opioid pills [27]. APPs routinely provide both consistency and continuation of care as patients transition from inpatient to outpatient care.

55.5.4 Surveillance and Survivorship Care of CLM Patients

Active treatment and management of patients with CLM continue even after the surgical resection of their liver metastases. In most cases, patients require adjuvant systemic chemotherapy and, in some settings, treatment of their primary colorectal tumour. APPs often help direct the transition of surgical care back to medical oncology or with providers involved in direct patient care in order to facilitate the continuation and completion of treatment.

After the perioperative period, in collaboration with their attending physicians, APPs play a dynamic role in long-term active surveillance of each patient for disease recurrence and symptom management. Often, APPs are experts in their field and participate in shared decision-making and communication, especially in the setting of disease recurrences. While

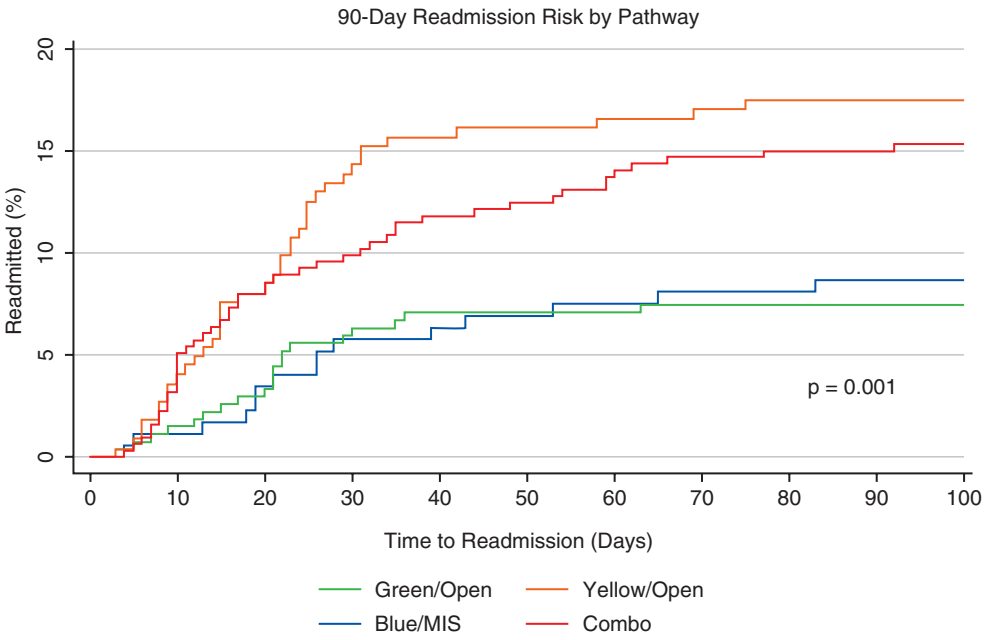

Fig. 55.3 90-day readmission risk by post-hepatectomy pathway [26]

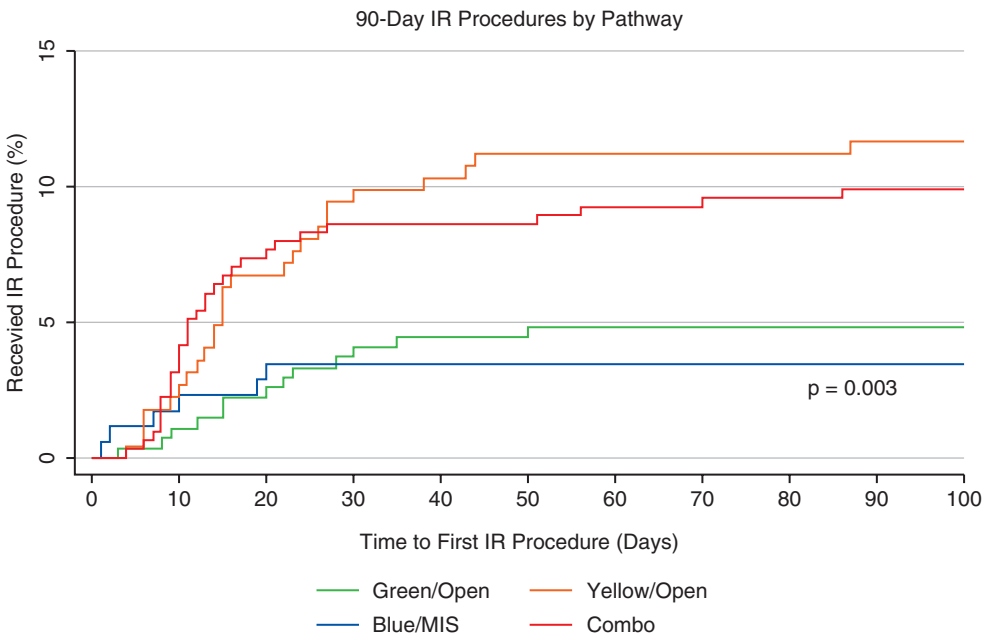

Fig. 55.4 90-day IR procedures by post-hepatectomy pathway [26]

APPs can identify and interpret disease recurrences and have the autonomy to help manage oncology patients, the plan for subsequent treatments requires the final authorization of the involved physician(s). According to the National Comprehensive Cancer Network (NCCN) guidelines for stage IV colorectal cancer, surveillance in patients after CLM resection includes history and physical examination, repeat axial imaging, and laboratory studies with carcinoembryonic antigen (CEA) measurement every 3–6 months for 2 years after resection and every 6 months, thereafter for 5 years. More recently, the frequency of surveillance has recently become more strategic when taking into consideration a patient's disease biology as demonstrated by biomarkers and molecular genetics. In a recent study by Kawaguchi et al. [28], aside from lymph node status, number of CLM, and largest liver metastasis diameter, RAS mutation alone was significantly associated with recurrence in patients free from recurrence 2 years after resection. In academic research institutions, APPs often collaborate with multiple physicians to integrate new and supported findings into their practice to help improve and personalize oncologic patient care. For example, understanding disease biology by identifying the somatic mutational status of a patient with CLM from a sample of their solid tumour can help personalize the

type and extent of systemic treatment they receive. Moreover, identifying the presence of circulating DNA (ctDNA), in addition to axial images, in a postoperative setting can help identify patients at high risk for disease recurrence [29].

With the increased rates of CLM cases and the limitation of oncology and HPB surgery providers, the utilization of APP-run outpatient clinics for patients needing long-term surveillance and survivorship care has continued to evolve. The off-loading of long-term CLM patients to an APP-run survivorship clinic helps to increase access for more newly diagnosed CLM patients to physicians. Additionally, patients who are at high-risk for recurrence or those receiving complex perioperative care receive more specialized care and attention in the physician-led HPB surgery clinic. Less complex patients who are considered low-risk for cancer recurrence still receive personalized care from APPs with a slightly more holistic approach to cancer care. Furthermore, APPs trained in HPB survivorship can address issues unique to cancer survivors which may help improve overall patient satisfaction [30]. In addition to the review of cross-sectional imaging and colonoscopy results, APPs can help with the coordination of care and early referrals to other specialties for benign or malignant conditions thereby improving access for these patients within the health care system.

55.6 APP Productivity and Value

APPs are versatile, health care providers that not only perform clinical and diagnostic functions but also are instrumental in providing education, research, mentorship, and advocacy for many different patient populations. Numerous reports have indicated that within their areas of competence, APPs deliver quality care equivalent to that of care provided by physicians [31, 32]. Also, patients generally report being satisfied with the quality of care provided by APPs, particularly related to the interpersonal aspects of care [4]. Furthermore, APPs provide quality care that is cost-effective and improves patient outcomes, such as fewer complications, reduced hospital readmission and emergency center visits, and shorter length of stay [4, 33]. With the increased number of cancer diagnoses, increased number of cancer survivors, along with the significant projected shortfall of fellowship-trained oncology physicians, APPs have helped to bridge the gap to meet the demand for patient oncology needs [1].

In the era of value-based health care, APPs are key members of care delivery teams that increase operational efficiency and improve outcomes while keeping costs relatively down. Several studies have demonstrated APP value that improves outcomes, including outcomes that matter to patients, such as their functional status, return to usual activities, symptom control, and minimizing wait times [34]. Additionally, APPs play a key role in taking care of patient services that would otherwise be done or provided by the physician in the absence of the APP. In a time and effort allocation study, Moote et al. [35] reported that APPs spent only approximately 36% of their time in direct, billable patient care. However, up to 49% of the APP time and effort included other non-billable activities that would otherwise require a physician to perform. This study illuminates the extensive amount of time spent by APPs in non-billable activities not reflected in work relative value units (RVUs), but that is still essential to quality patient care. Furthermore, APP clinical activity can also be hidden in "shared" visits with collaborating physicians which further obscures APP value metrics. Overall, understanding APP productivity and their impact on patient care, especially among the multiple HPB surgery roles, remains challenging and difficult to measure. Although their contributions may not be easily measured, APPs remain integral members of the patient's care team.

55.7 Conclusion

With the growing complexity of cancer care and impending workforce shortages, APPs remain key contributors to high-quality, team-based, patient-centered care. APPs practice in multiple roles within the HPB specialty setting, including outpatient, inpatient, and surgery assist. Additionally, APPs contribute to patient care in many other ways that are not always easily measure but remain central to the care of the patient. Studies have demonstrated that APPs improve outcomes and increase team productivity and efficiency. As HPB care continues to progress and evolve, effective collaborative practice teams will be needed to provide optimal, high-quality, and high-value care to patients.

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Enhanced Recovery in Liver Surgery

56

Bradford J. Kim and Thomas A. Aloia

Learning Objectives

- Define enhanced recovery in liver surgery (ERILS).
- Understand the foundation and pillars of a successful ERILS program.
- Review the value of a validated Patient Reported Outcome tool to measure recovery.

56.1 Introduction

Liver surgery safety and outcomes have improved due to improved patient selection [1–3], advanced surgical techniques [4], parenchyma sparing operations [5–7], clinical rescue strategies [8, 9], and Enhanced Recovery After Surgery (ERAS) protocols [10–14]. Enhanced Recovery in Liver Surgery (ERILS) represents the modern preoperative and postoperative care model for the hepatectomy patient. This standardized plan stands on the foundation of Patient Education/Engagement with four principle pillars of early feeding, goal-directed fluid therapy (GDFT), perioperative pain control, and early ambulation (Fig. 56.1) [10, 12]. The following will review these four pillars as well as additional supporting elements to design a successful enhanced recovery program for liver surgery.

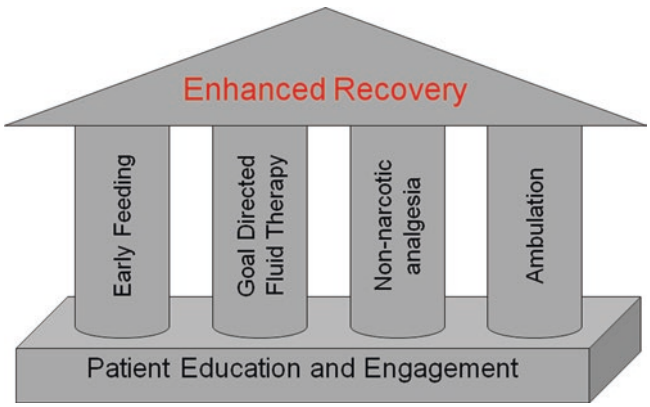

Fig. 56.1 The enhanced recovery foundation includes patient education and engagement. Pillars of successful enhanced recovery include perioperative fundamental strategies: early feeding, goal-directed fluid therapy, nonnarcotic analgesia, and ambulation. From Kim BJ, Aloia TA. What is "enhanced recovery," and how can I do it? *Journal of Gastrointestinal Surgery*. 2017;22(1):164–171; with permission

56.2 Preoperative Evaluation and Prehabilitation

The (new patient) surgical consultation should occur before any neoadjuvant therapy is initiated for proper evaluation of the patient's baseline medical condition, functional status, and symptom burden. Standard preoperative evaluation must include a complete history and physical examination for all comorbid conditions, uncontrolled medical conditions, and prior procedures. In the cancer patient, oncologic history of neoadjuvant cytotoxic/biologic chemotherapy, radiation therapy, and future intent for adjuvant therapy should be reviewed individually in the clinic and at a multidisciplinary conference. If operability is borderline due to patient condition status because of chronic medical conditions (i.e., uncontrolled hypertension, uncontrolled diabetes, or chronic kidney disease) [15], medical optimization should occur before hepatectomy. Further, if the risk-benefit of hepatectomy is appropriate for pursuing resection after medical optimization and prehabilitation, an extended discussion between

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the patient and surgeon needs to be conducted to review appropriate expectations in these complex situations.

Adjuncts to medical optimization within an ERILS program should include nutritional and physical optimization. Two out of three patients who undergo gastrointestinal surgery are malnourished and will have a threefold higher risk for complications and fivefold higher risk for death [16–18]. Despite these concerns and evidence for perioperative nutritional interventions that will reduce morbidity and mortality, only 20% of patients receive any preoperative nutrition intervention [17]. In particular, the ERAS society guidelines for liver surgery recommend delay in resection to allow for nutrition optimization if a patient has one of three criteria for malnourishment: serum albumin <3 g/dL, BMI <18.5 kg/m^2, or weight loss >10–15% within 6 months [19]. Additionally, sarcopenic obesity should be identified on staging computed tomography imaging because it is associated with poor liver hypertrophy following portal vein embolization and postoperative complications [20, 21]. Malnourished patients should meet with a dietician to improve weight gain through a high protein and nutrient-dense meal plan. Sarcopenic obesity should similarly be targeted with dietician consultation and meal plan that targets weight loss while maintaining high protein and nutrient intake. Consistent follow up (with surgeon and/or dietician) during preoperative prehabilitation is crucial to ensure compliance and appropriate progress with the prescribed meal plan.

For functional status, patients are first assessed with the Eastern Cooperative Oncology Group (ECOG) grade or other validated scoring systems. In the clinic, functional capacity can be quantified with validated tools such as the 6-min walk, timed up and go, or grip strength tests in conjunction with patient reported outcome tools [21–25]. Further, neurocognitive dysfunction should be tested with a Mini Cog or Mini Mental Status Examination [26–28]. All of these tools will identify higher risk patients to allow for targeted prehabilitation and a meaningful informed discussion of expectations postoperatively. Lastly, the diagnosis of frail or borderline patients does not preclude patients from being placed on an Enhanced Recovery pathway, rather it provides an opportunity for the treatment team to intervene medically, physically, and emotionally before hepatectomy (Fig. 56.2) [10].

Among patients undergoing major abdominal surgery, prehabilitation provides benefit to length of stay (mean difference, −2.2 days; 95% CI −3.5 to −0.9) metrics and improves function many weeks after a major abdominal operation. In liver surgery, one randomized clinical trial improved cardiopulmonary exercise testing and preoperative quality of life in low fitness patients with a 4-week supervised exercise program [29]. Identifying deficits from these objective metrics of functional status can identify patients who need physical prehabilitation to prevent morbidity or failure to rescue after hepatectomy (Fig. 56.2). Currently, there is mixed data from both feasibility studies and small-scale randomized controlled trials that studied prehabilitation interventions for long-term patient outcome benefits [30].

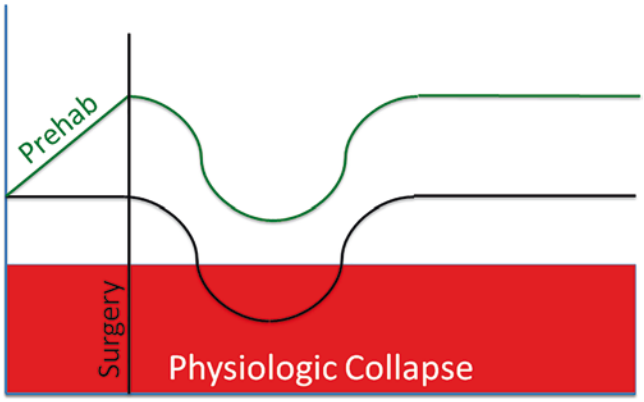

Fig. 56.2 Prehabilitation can be implemented before hepatectomy for neurocognitive, nutritional, and physical function deficits. Successful prehabilitation increases preoperative clinical reserve and can be applied to any Enhanced Recovery in Liver Surgery program. From Kim BJ, Aloia TA. What is "enhanced recovery," and how can I do it? *Journal of Gastrointestinal Surgery*. 2017;22(1):164–171; with permission

56.3 Patient Education and Engagement

The information conveyed to a patient before undergoing any hepatectomy is vast and complex. A successful enhanced recovery plan begins with proper patient education and counseling of appropriate expectations before and after liver surgery. This process should also include education materials detailing the operation itself, as well as enhanced recovery principles, goals, and expectations. Timely discharge from the hospital relies on patients being knowledgeable and properly prepared for early ambulation, feeding strategies, and nonopioid pain control strategies. During the initial preoperative consultation, follow ups during neoadjuvant therapy, and at the final preoperative visit, time should be dedicated to answering any questions from the patient and family, to allow for sufficient comprehension of all aspects of liver surgery preparation and subsequent recovery. Lastly, family members and caretakers should be equally well informed of the recovery expectations as they will be significantly involved with important care aspects such as ensuring ambulation and adequate nutrition/hydration outside of the hospital after discharge.

56.4 Perioperative Nutrition and Early Feeding

Perioperative fasting has many consequences: exacerbation of surgical stress response, increased insulin resistance, exaggerated protein loss, and impaired gastrointestinal function [31]. Additionally, patient-centered consequences include hunger, thirst, headaches, and anxiety. It is well known that overnight fasting is unnecessary and clear liquids can be taken up 2 h before a procedure in most situations without any increased risk for aspiration [32, 33]. In the advent of enhanced recovery protocols, the administration of oral carbohydrates has been suggested to reduce the degree of postoperative insulin resistance by replicating the normal metabolic responses of eating breakfast [34]. The use of carbohydrate loading preoperatively is associated with a statistically significant reduction of LOS for patients undergoing major abdominal surgery (mean difference, −1.66 days; 95% Confidence Interval [CI] −2.97 to −0.34) [35]. Common carbohydrate loading protocols suggest consumption of 50 grams of carbohydrate as a clear liquid 2–3 h preoperatively. This should be consumed within a 5–10-min interval to enhance insulin secretion and decrease the extent of peripheral insulin resistance thereby ameliorating the surgical stress response.

Multiple meta-analyses have reported the benefit of feeding within 24 h after gastrointestinal surgery with a reduction in both morbidity and mortality (relative risk [RR] 0.42, 95% Confidence Interval [CI] 0.18–0.96) [36–38]. Ideally, >60% of protein needs should be consumed over the first three postoperative days [31]. In particular for liver surgery, bowel mobilization, manipulation, and resection is limited. A diet of clear liquids or gastrointestinal-oriented (soft, bland) food options that are high in protein can be provided as early as postoperative day 1 without concern for increased risk of nausea or gastrointestinal dysfunction.

56.5 Goal-Directed Fluid Therapy

Precise intravascular volume management in liver surgery is paramount due to dramatic intravascular fluid shifts from low central venous pressures during parenchymal transection and aggressive resuscitation following resection of the specimen. The role of goal-directed fluid therapy (GDFT) is to provide a balanced and effective circulatory blood volume to allow for adequate organ perfusion. Hypo- or hypervolemia fluid imbalance will lead to prolonged hospital stays, increased morbidity, and cardiopulmonary and/or renal complications [39]. Intraoperatively, GDFT guides fluid administration with the use of stroke volume variation (SVV) and/or pulse pressure variation rather than traditional indices such as urine output, mean arterial pressure, and central venous pressure [40].

Following the operation, GDFT should be extended into the postoperative period to optimize traditional care parameters such as urine output and hemodynamic values to guide resuscitation. Additionally, serum brain natriuretic peptide (BNP) is an adjunct that can be utilized to provide a balanced and effective circulatory blood volume. BNP is a 32-amino acid protein produced by cardiac myocytes in response to dilation to reflect volume overloaded states. The addition of BNP to a GDFT plan has been more effective than BUN/creatinine ratios in assessing intravascular volume after pancreas surgery [41] and reduces both cardiopulmonary and renal complications following liver surgery [42].

56.6 Perioperative Pain Control

The opioid epidemic continues to be a major public health problem worldwide, with over 120,000 deaths worldwide [43] and an annual cost of over $50 billion per year for treating prescription opioid dependence and abuse [44]. Surgeons are responsible for 10% of all opioid prescriptions [45]; further, approximately 10–15% of opioid naïve cancer surgery patients will become persistent users [46, 47].

In the cancer patient, opioid exposure can also lead to negative consequences on tumour biology. Recent data show that opiates activate vascular endothelial growth factors, which are linked to stimulating both cancer growth and metastatic potential [48–50]. Similar in vivo findings were observed with worse overall survival in breast, esophageal, and lung cancer patients who had tumours expressing certain polymorphisms of the μ-opioid receptor (MOR) [51–53].

In addition to the detrimental impacts on both public health and cancer biology, opioid use has a negative effect on patient experience, function and recovery with common side effects that include nausea/vomiting, xerostomia, gut dysfunction, and respiratory depression. Optimal perioperative pain control stands as a pillar for Enhanced Recovery [10]; and with proper execution, these protocols have decreased rates of inpatient opioid use after hepatectomy [11]. Additionally, hepatectomy patients on Enhanced Recovery pathways have decreased postoperative discharge prescriptions opioids and outpatient opioids without detriment to pain control [44, 54].

Multimodal opioid-sparing analgesia is the strategy of choice for any enhanced recovery protocol. First, preoperative administration of nonnarcotic neuromodulators (i.e.,

Pregabalin) [55] in combination with anti-inflammatory nonsteroidal drugs (i.e., NSAIDS, COX-2-inhibitors) should be considered. The use of NSAIDS reduces postoperative nausea/vomiting, overall narcotic use, and hospital length of stay [56]. Regional analgesia via neuraxial or field block can be employed to cover incisional pain through, epidural analgesia (EA) or transversus abdominis plane (TAP) infiltration [57, 58]. The first 48 h following hepatectomy is the most critical time to limit opioid exposure from opioid boluses. Opioid exposure can be reduced with regional analgesic strategies such as EA or TAP. Historically, there were safety concerns utilizing EA due to increased episodes of hypotension, cardiopulmonary, and renal events. These fears were absolved when the University of Texas MD Anderson Cancer Center conducted a randomized controlled trial comparing EA to intravenous patient-controlled analgesia (IV PCA). The study demonstrated that patients receiving EA had superior pain control, equivalent safety profiles, and decreased opioid use compared to those using IV PCA. A randomized controlled trial comparing EA vs. TAP in liver surgery is ongoing (NCT 03214510) [59].

56.7 Ambulation: Early Removal of Tubes

Postoperative mobilization is critical to promoting an effective enhanced recovery program. Successful early ambulation results in decreased rates of ileus, postoperative thromboembolic events, and cardiopulmonary complications [19]. On postoperative day 0 after major liver resection, the vast majority of patients should be assisted to the bedside to prevent instability and dizziness. By postoperative day 1, most patients should be out of bed in a chair and ambulating in the halls with assistance. Physical therapy and occupational therapy should be considered early in more frail, deconditioned, and elderly patients that may need early evaluation and assistance to meet ERILS protocol ambulatory goals. To support early ambulation, the placement of surgical drains and nasogastric tubes should be limited. Urinary catheters may be removed when there is stable circulatory blood volume, GDFT interventions are not required, and when ambulation is achieved. Alpha blockade can be prescribed prophylactically to prevent urinary retention and subsequent urinary catheter replacement in older males.

56.8 Patient-Reported Outcomes and Return to Intended Oncologic Therapy

The goal of enhanced recovery is to return a patient to baseline after surgery. This cannot be measured through common surgical outcomes such as length of stay and complication rates. Validated patient-reported outcome (PRO) tools are instrumental to measuring patient recovery objectively following hepatectomy. In contrast to traditional comorbidities and complication rates, PRO data is more patient-centric and dynamic, allowing for a better opportunity to make improvements for individual patients. To be most effective, the same validated PRO tool should be utilized frequently preoperatively in the clinic, postoperatively in the hospital, and in the clinic weeks after hepatectomy.

In the cancer patient, return to baseline is imperative to allow for a timely and successful Return to Intended Oncologic Therapy (RIOT). This quality metric is quantified by the ability (yes/no) and time (from surgery) to RIOT [60]. For patients undergoing resection for biliary tract tumours and colorectal liver metastases, adjuvant therapy is proven to provide survival benefit [61–63]; and if the ability to RIOT due to general disability or complications is not possible, increased risk of recurrence and decreased overall survival are more likely.

Patients who present with severe preoperative symptom burden on the MD Anderson Symptom Inventory (MDASI)—Gastrointestinal Version (Fig. 56.3) [13], a validated PRO tool, have a 7-day delay to RIOT [64]. These findings are likely due to delayed postoperative recovery and may be targeted for further preoperative optimization before hepatectomy is pursued. Further, the use of minimally invasive approaches and enhanced recovery protocols have both been shown to decrease time to RIOT [13, 60].

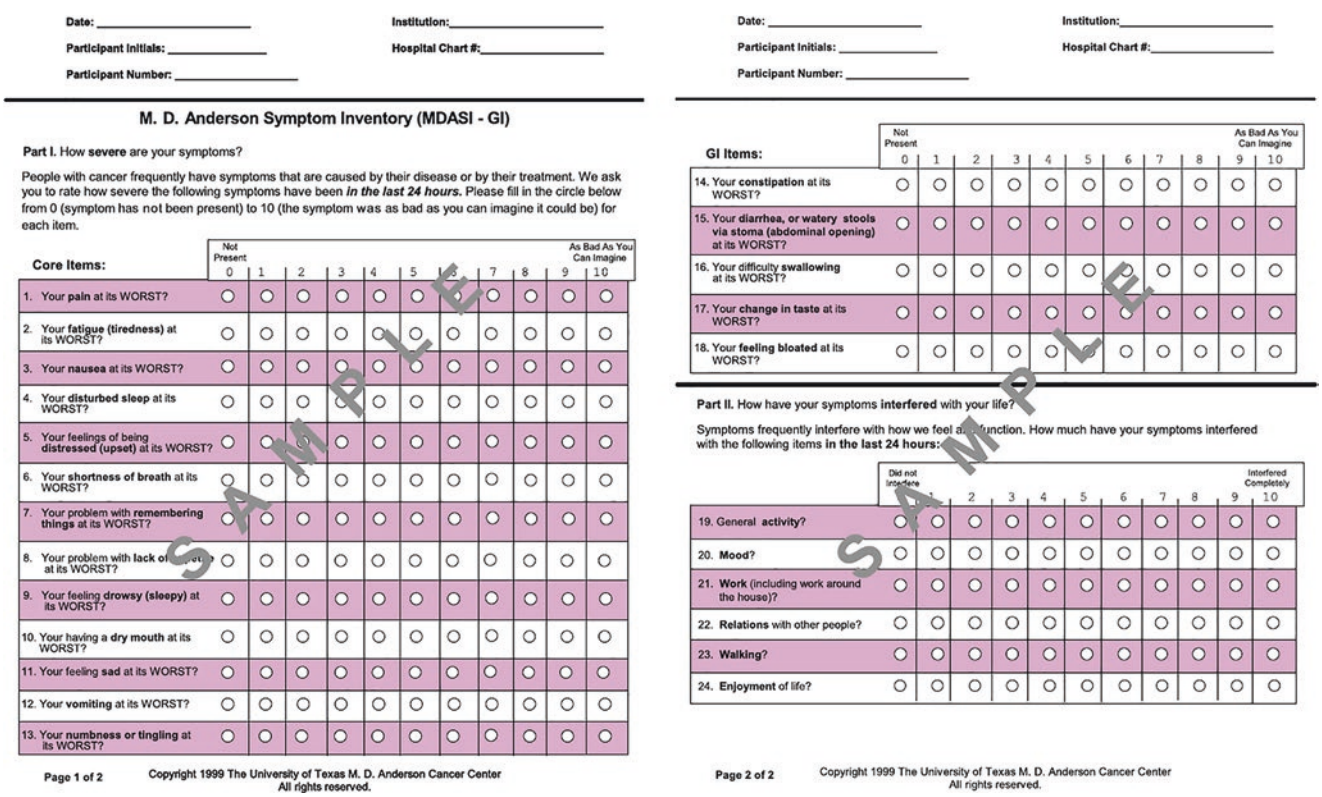

Fig. 56.3 The University of Texas MD Anderson Symptom Inventory—Gastrointestinal Version. A validated Patient Reported Outcome Tool. From Day RW, Cleeland CS, Wang XS, et al. Patient-reported outcomes accurately measures the value of an enhanced recovery program in liver surgery. *Journal of American College of Surgeons*. 2015;221(6):1030.e1–2, with permission

56.9 Summary

Enhanced recovery in liver surgery is a standardized care plan for the hepatectomy patient. In the current modern era of liver surgery, it should be utilized in the vast majority of cases. Proper execution of the Enhanced Recovery pillars will translate into a successful program benefiting both patient-centric and hospital-centric outcomes. Future high-quality clinical trials within each domain of the enhanced recovery pillars will enrich the field's knowledge to allow for further improvement of these pathways.

Acknowledgments *Financial Disclosures*: None.

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Improved Survival After CLM Resection over 20 Years

57

Yoshikuni Kawaguchi and Jean-Nicolas Vauthey

Learning Objectives

- The 5-year overall survival in patients undergoing resection of colorectal liver metastases was 30–35% before 2000, and improved to approximately 50–60% after 2000.
- Surgical managements and techniques are refined in 2000s to use portal vein embolization, staged hepatectomy, and parenchyma-sparing liver resection.
- A new three-level complexity classification of liver resection performed better than the traditional minor/major classification with respect to stratifying surgical complexity and postoperative complication.
- The 2000s had three breakthroughs in the management of colorectal liver metastases: irinotecan- and/or oxaliplatin-containing regimen, molecular-targeted therapy, and next-generation sequencing.

57.1 Introduction

Colorectal cancer is the third highest incidence of cancers (10.0%) for both sexes in 2020 following female breast cancer (11.7%) and lung cancer (11.4%) [1]. Liver is the most common organ of metastases from colorectal cancer. Liver resection was established as the most effective curative-intent treatment in patients with colorectal liver metastases (CLM) [2]. Studies reported that the 5-year overall survival (OS) after CLM resection was approximately 30% before 1990 [3–7]. This slightly improved to approximately 35% of the 5-year OS after CLM resection according to reports during 1990–2000 [8–10]. After 2000, clinical management of colorectal cancer have rapidly advanced and results in improving the 5-year OS after CLM resection to approximately 50% [11, 12]. A recent report from the group of MD Anderson Cancer Center showed 59% of OS in patients undergoing CLM resection during 2007–2017 [13]. This improvement in survival was likely owing to the following advancements in the management of colorectal cancer. First, the surgical management and technique of CLM resection were refined. Second, effective medical treatments including irinotecan, oxaliplatin, and anti-vascular endothelial growth factor (VEGF), and anti-epidermal growth factor receptor (EGFR) became available as a multidisciplinary treatment of CLM. Last, understanding of molecular biology (e.g., somatic gene alteration) was improved.

In this chapter, we summarize changes in surgical techniques/managements and advancements in the management of CLM in the group of MD Anderson Cancer Center over 20 years and evaluate prognosis after CLM resection in relation to the three landmark advancements: adoption of irinotecan and/or oxaliplatin-containing regimen, molecular-targeted therapy, and multigene alteration testing.

57.2 Refinements of Surgical Management and Technique

The success of surgical treatment of CLM relies on planning of liver resection, avoiding hepatic insufficiency, and minimizing postoperative complications.

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57.2.1 Planning of Liver Resection

For safe planning of liver resection, our group defined the minimal requirement of future liver remnant (FLR)/standardized liver volume (calculated as "−794 + 1267.28 × body surface area") [14]. For patients with normal liver, the minimal FLR requirement is 20–25% [15, 16], and for patients with hepatic injury, the minimal FLR requirement is 30% [17].

57.2.2 Avoiding Hepatic Insufficiency

For patients with insufficient FLR, portal vein embolization (PVE) is an established safe method to induce hypertrophy of FLR. To increase resectability of bilobular CLMs, a two-stage hepatectomy was established in 2000s [18]. This treatment approach typically includes the sequence of prehepatectomy medical therapy, first-stage hepatectomy, PVE (± medical therapy), and second-stage hepatectomy [19–22]. The rate of two-stage hepatectomy increased from 0% during 1998–2000, to 3% during 2001–2005, and to 7% during 2006–2014 in our group (Fig. 57.1a).

57.2.3 Minimizing Postoperative Complication

For patients with extensively distributed CLMs, concomitant use of intraoperative ablation was one of the choices during surgery to eradicate lesions while preserving sufficient functional FLR. In our group, intraoperative ablation was commonly used in early 2000s and gradually decreased from 36% during 1998–2000, to 28% during 2001–2005, and to 11% during 2006–2014 (Fig. 57.1b). This shift was made based on studies showing that the combined use of resection and intraoperative ablation was associated with a higher incidence of postoperative complication than resection alone [23, 24]. Our group recently reported a new sequential treatment strategy for patients with extensively distributed CLMs: a planned incomplete resection and postoperative percutaneous completion ablation for intentionally untreated lesions under computed tomography guidance [25, 26]. This new concept was detailed in another chapter of this book (Chap. 6).

Another trend of changes in surgical management/technique is the use of parenchyma-sparing liver resection [27]. The concept of this approach is to remove lesions while preserving as much FLR as possible. Given our data that

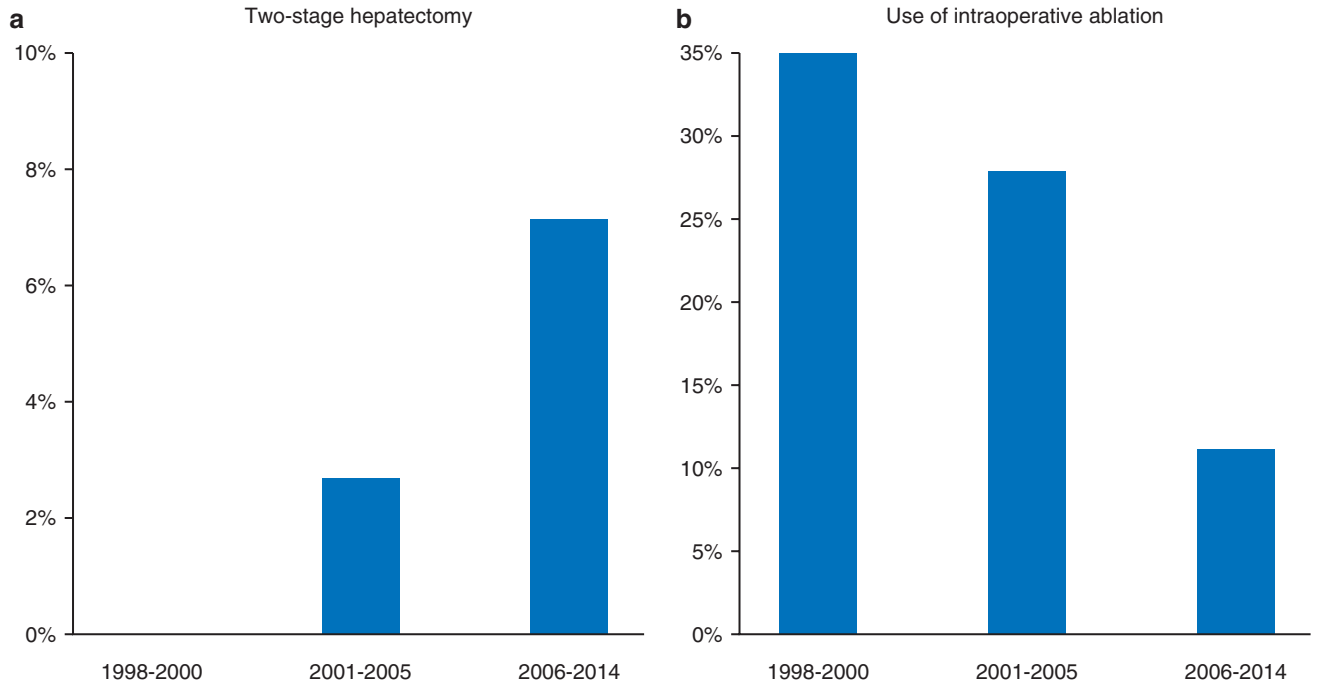


Fig. 57.1 Changes over time in (**a**) two-stage hepatectomy, (**b**) concomitant use of intraoperative ablation, (**c**) use of a parenchymal-sparing approach, and (**d**) complexity of liver resection. *Defined as frequency of multiple resections (≤ Couinaud 1 segment) for multiple CLM. †Grade I, low complexity; grade II, intermediate complexity; grade III, high complexity [29]. (Adapted from Kawaguchi [63] with permission)

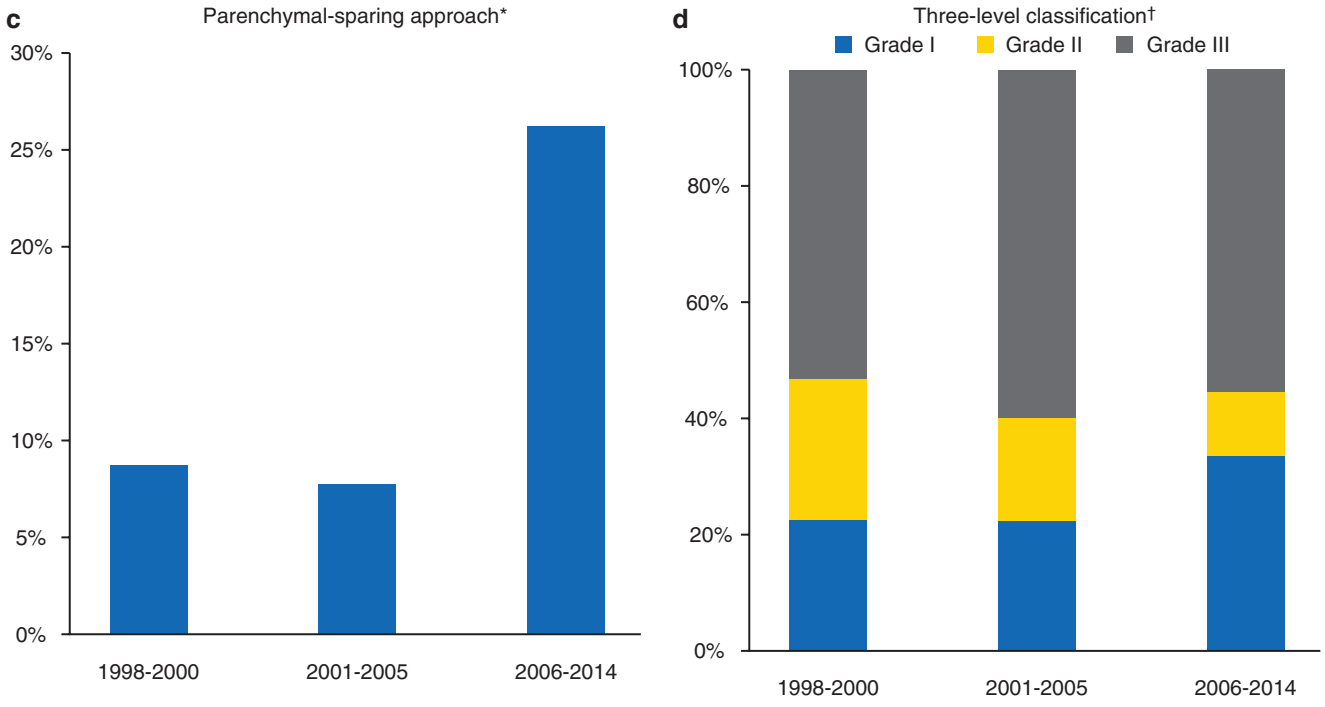


Fig. 57.1 (continued)

parenchyma-sparing approach was associated with improved survival [28], the rate of parenchyma-sparing approach rapidly increased after 2006: 9% during 1998–2000, 8% during 2001–2005, and 26% during 2006–2014 (Fig. 57.1c).

57.2.4 New Classification for Liver Resection: Three-Level Complexity Classification

The advancements in the surgical technique resulted in changing the proportion of surgical complexity (Fig. 57.1d) proposed by the three-level complexity classification (grade I, low complexity; grade II, intermediate complexity; grade III, high complexity) (Fig. 57.2) [29–32]. This new classification was originally developed for laparoscopic liver resection to stratify surgical complexity and postoperative outcomes because the classification based on the nomenclature, minor or major (i.e., the minor/major classification) do not always stratify procedures effectively in terms of surgical and postoperative outcomes [29, 33–35]. The original classification for laparoscopic liver resection was tested and validated for open liver resection [36–38]. Operative time, estimated blood loss, and postoperative complication were stratified well using the three-level complexity classification for laparoscopic liver resection (Fig. 57.3) and open liver resection (Fig. 57.4). These factors incrementally increased from grade I to grade III. The three-level complexity classification performed better than the minor/major classification for both open and laparoscopic approaches with respect to predicting surgical complexity and postoperative morbidity [30, 36]. As such, our three-level complexity classification may be useful for a training pathway (Fig. 57.5) [32], adjustment of intergroup imbalance of surgical complexity [39–41], and assessment of changes in complication risks over time [37].

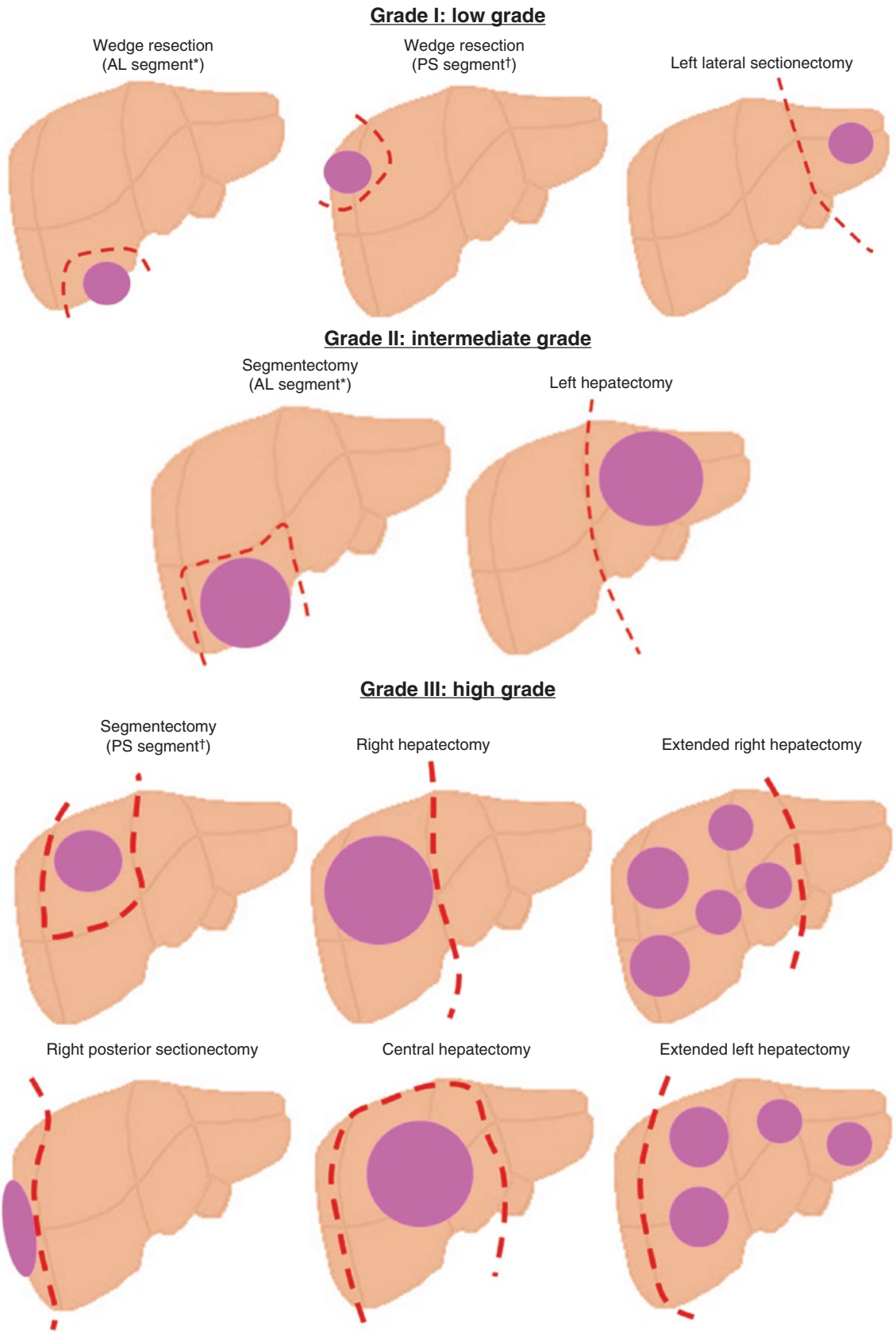


Fig. 57.2 New three-level complexity classification. *Anterolateral (AL) segments are defined as Couinaud segments 2, 3, 4b, 5, and 6. †PS segments are defined as Couinaud segments 1, 4a, 7, and 8. (Adapted from Kawaguchi, Y., et al. (2020). "Surgical Resection." Clin Liver Dis 24(4): 637–655, with permission [32])

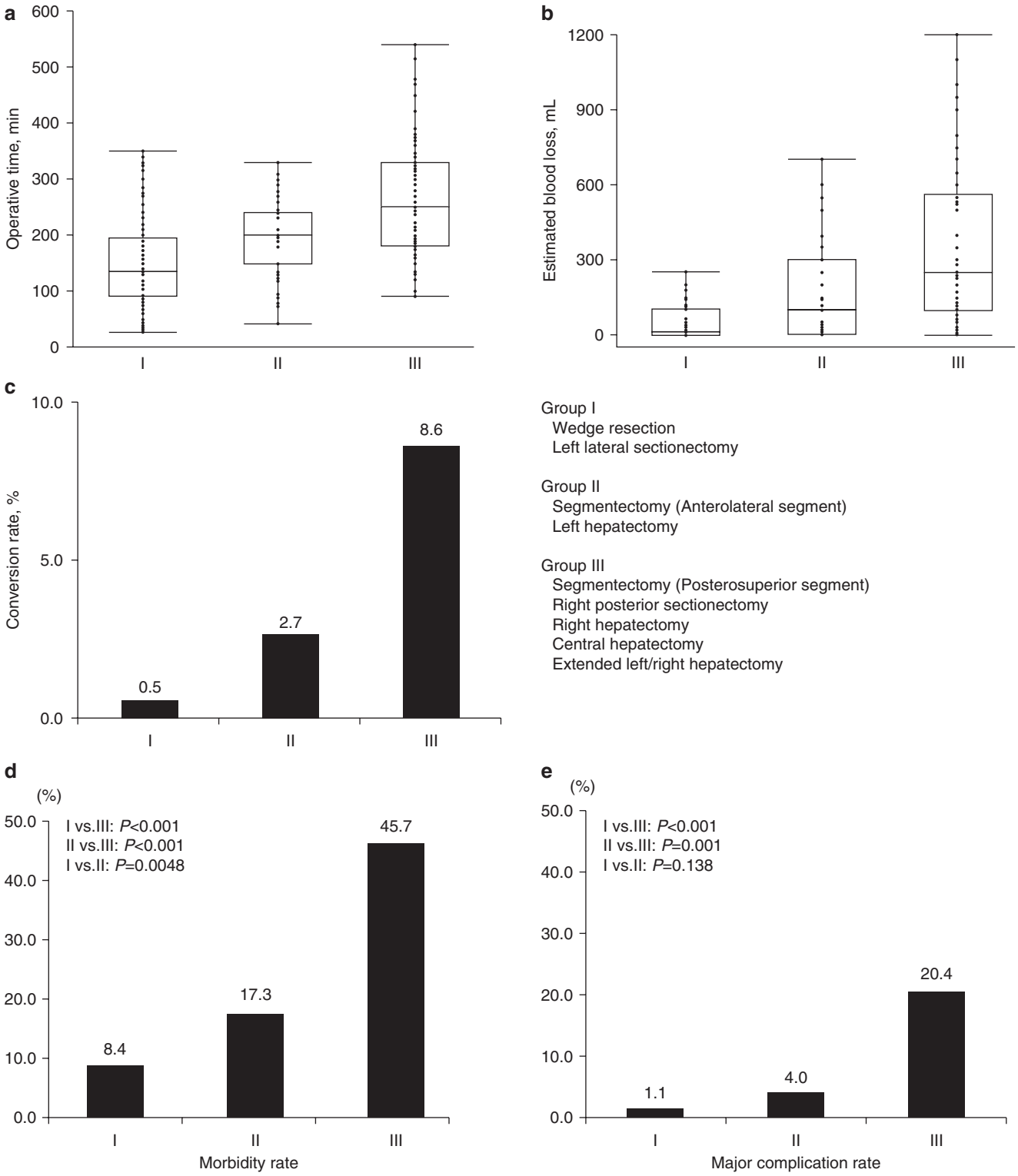


Fig. 57.3 Surgical and postoperative outcomes for three grades in our three-level classification. (**a**) Duration of operation, (**b**) estimated blood loss, (**c**) conversion rate, (**d**) morbidity rate, and (**e**) major complication rate. (Adapted from Kawaguchi, Y., et al. (2018). "Difficulty of Laparoscopic Liver Resection: Proposal for a New Classification." Ann Surg 267(1): 13–17, with permission [29])

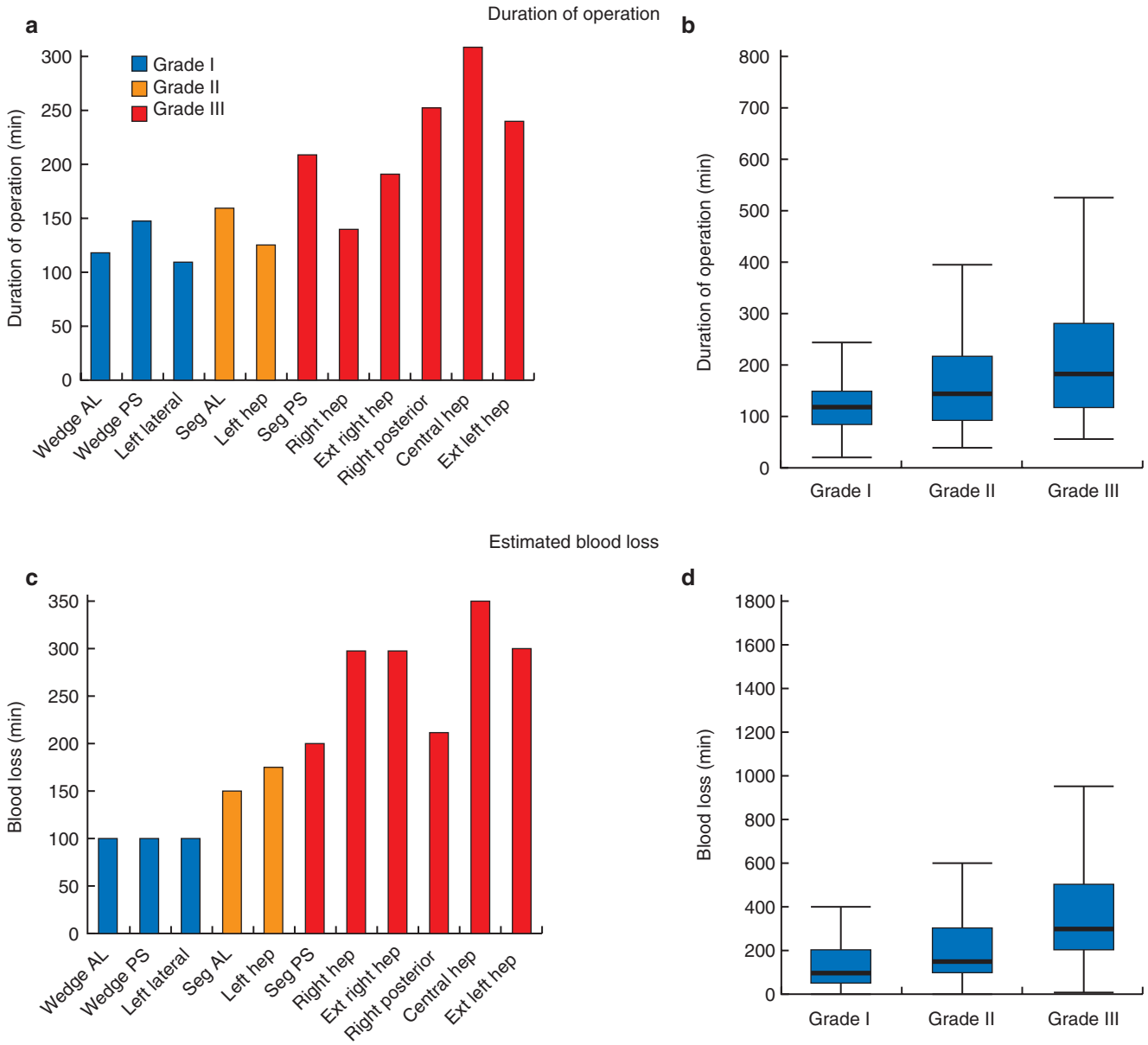


Fig. 57.4 Surgical and postoperative outcomes for 11 open liver resection procedures (**a**, **c**, **e**) and three grades (**b**, **d**, **f**) in our three-level classification. (**a**, **b**) Duration of operation, (**c**, **d**) estimated blood loss, and (**e**, **f**) comprehensive complication index (CCI) [64]. *Central hep* central hepatectomy; *Ext left hep* extended left hepatectomy; *Ext right hep* extended right hepatectomy; *Left hep* left hepatectomy; *Left lateral* left lateral sectionectomy; *Right hep* right hepatectomy; *Right posterior* right posterior sectionectomy; *Seg-AL* anterolateral segmentectomy; *Seg-PS* PS segmentectomy; *Wedge-AL* wedge resection of anterolateral segment; *Wedge-PS* wedge resection of PS segment. (Adapted from Kawaguchi, Y., et al. (2020). "Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity." Br J Surg 107(3): 258–267, with permission [31])

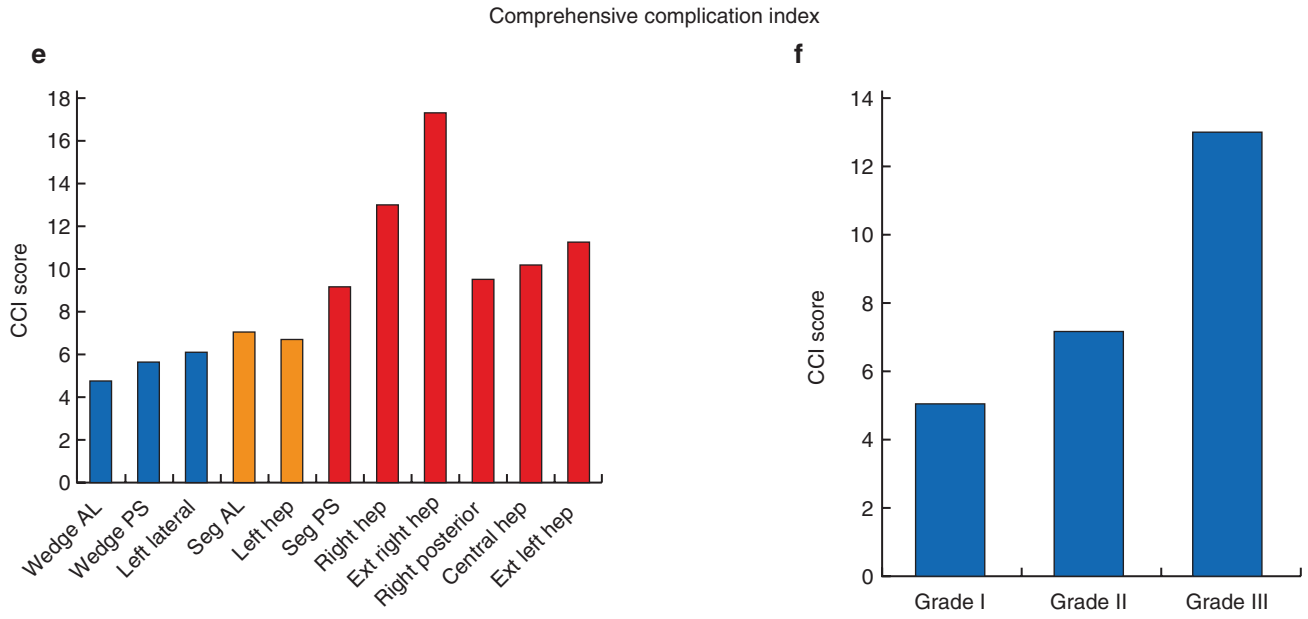


Fig. 57.4 (continued)

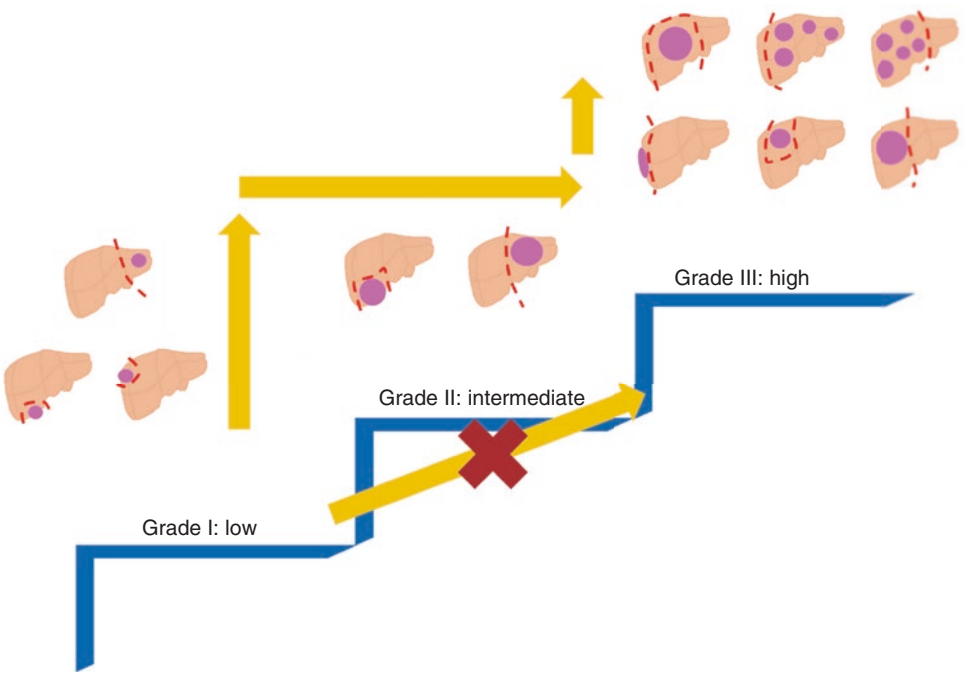


Fig. 57.5 Proposed training pathway based on three-level complexity classification. (Adapted from Kawaguchi, Y., et al. (2020). "Surgical Resection." Clin Liver Dis 24(4): 637–655, with permission [32])

57.3 Advancements in Medical Treatments

In 2000s, medical treatments for colorectal cancer have advanced. Irinotecan and oxaliplatin were found to be effective for patients with colorectal cancer and remain key drugs for patients with colorectal cancer [42]. Another breakthrough is that molecular target therapy including anti-vascular endothelial growth factor (VEGF) agent and anti-epidermal growth factor receptor (EGFR) agent proved to be effective for colorectal cancer. The clear evidences to support preoperative and postoperative use of these medical therapies for patients with resectable CLM are limited [43–47]. However, studies showed that the regimens including these drugs improved survival and response rate in patients with unresectable metastatic colorectal cancer and conversion rate in patients with unresectable CLM [48–52]. More information on advancements in medical therapy are detailed in other chapters of the book (Chap. 31). Figure 57.6 shows the trend of the preoperative use of chemotherapy regimen and molecular-targeted therapy for patients undergoing CLM in our group. The irinotecan/oxaliplatin-containing regimen was preoperatively used in more than 50% of patients undergoing CLM resection after 2001(Fig. 57.6a). The molecular-targeted therapy-containing regimen was preoperatively used in more than 50% of patients after 2006 (Fig. 57.5b).

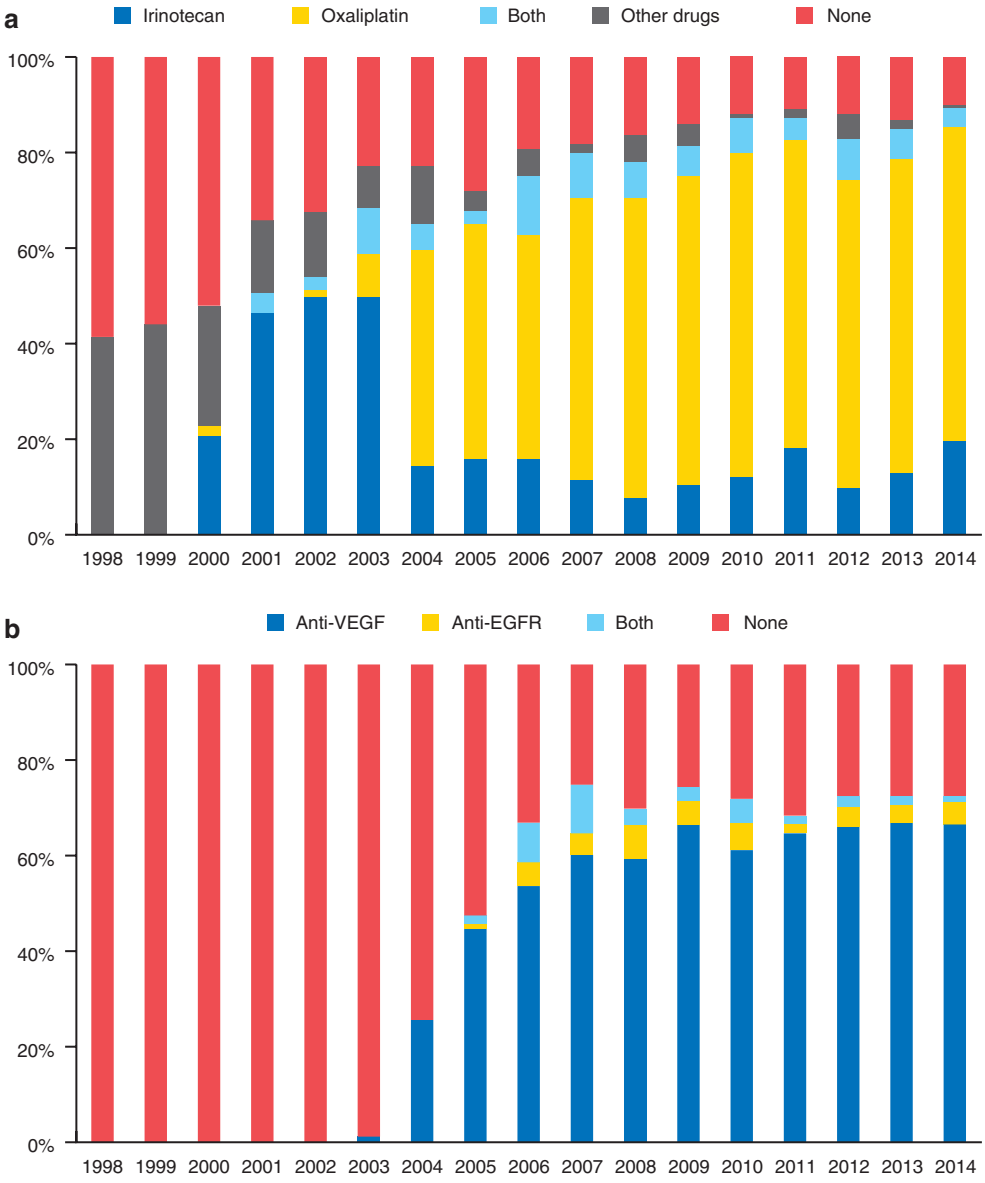


Fig. 57.6 Chronological trends in (**a**) prehepatectomy chemotherapy and (**b**) molecular-targeted therapy. Abbreviations: *anti-VEGF* anti-vascular endothelial growth factor; *anti-EGFR* anti-epidermal growth factor receptor. (Adapted from Kawaguchi [63] with permission)

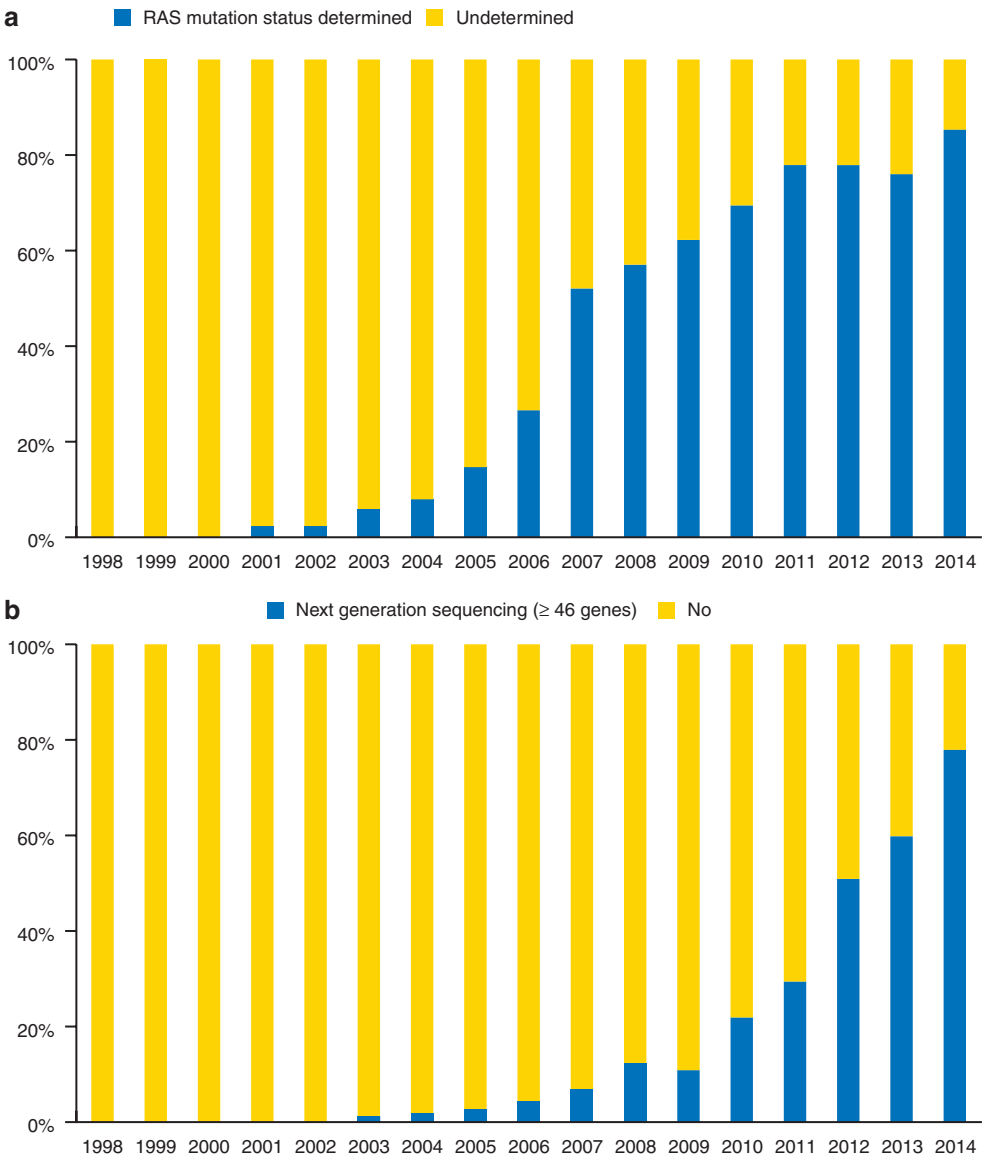


Fig. 57.7 Chronological trends in (**a**) *RAS* alteration testing and (**b**) next-generation sequencing. (Adapted from Kawaguchi, Y, et al. (in press) "Improved Survival Over Time after Resection of Colorectal Liver Metastases and Clinical Impact of Multigene Alteration Testing in Patients with Metastatic Colorectal Cancer." J Gastrointest Surg., with permission [63])

57.4 Clinical Implication of Molecular Biology

Molecular biology of colorectal cancer was characterized by the Cancer Genome Atlas project [53]. Because anti-EGFR agents show lack of response for patients with mutations in *RAS* gene family (*KRAS*, *NRAS*, and *HRAS*), the testing of somatic mutation status was noted in patients with colorectal cancer [54]. Accordingly, *RAS* mutation status was rapidly tested in our group after 2007 (Fig. 57.7a). Subsequent studies reported that patients with mutations of *RAS* and *BRAF* were associated with worse survival after CLM resection than patients with wild-type of *RAS* and *BRAF* [13, 55–58]. Our group showed that the multiple somatic gene mutation (*RAS*, *TP53*, *SMAD4*, and *FBXW7*) is important for better prognostication [59–62]. The testing of multiple gene mutation was increasingly performed in our group after 2012. This topic is detailed in other chapters of the book (Chaps. 50, 51).

57.5 Changes in Overall Survival After CLM Resection

Figure 57.8 summarizes the breakthroughs in the management of CLM by period in terms of medical therapy. The management of CLM in recent 20 years is characterized as follows. The first period during 1998–2000 is characterized as the limited availability of effective medical therapy. The second period during 2001–2005 is characterized as the use

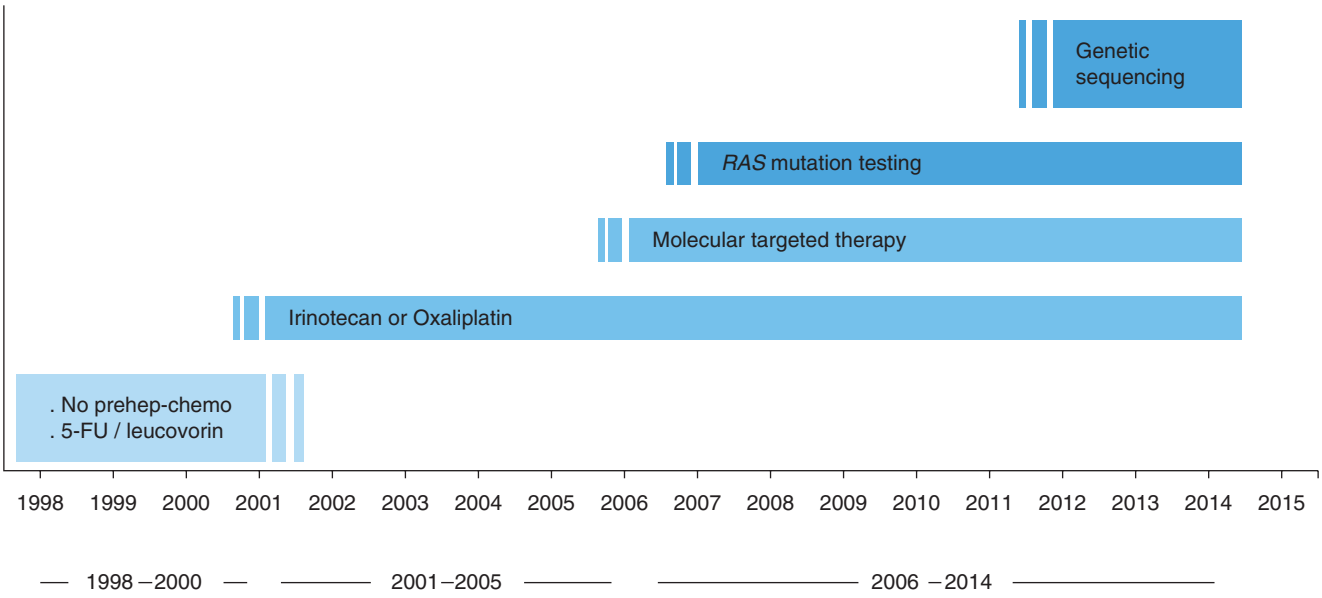
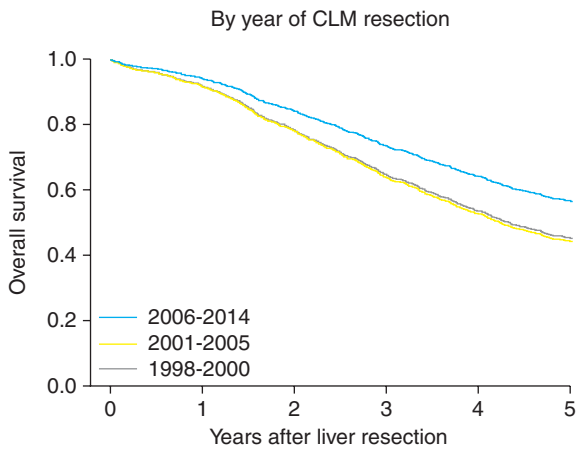


Fig. 57.8 A summary of trends in treatment from 1998 to 2014. Abbreviations: *Prehep-chemo* prehepatectomy chemotherapy; *5-FU* 5-fluorouracil. (Adapted from Kawaguchi [63] with permission)



Patients at risk

Period							5-year OS (95% CI)	HR (95% CI)	*P* value
2006–2014	979	908	802	669	552	409	56.5% (53.3%–59.6%)	0.97 (0.73–1.29)	.845
2001–2005	425	389	332	272	219	184	44.1% (39.5%–48.6%)	1 (reference)	-
1998–2000	141	128	104	83	75	69	45.1% (36.5%–53.2%)	0.68 (0.57–0.81)	< .001

Fig. 57.9 Overall survival by year of resection in patients with CLM resection during 2006–2014. Overall survival curves after adjustment for age, primary tumour location, T category, lymph node metastasis, prehepatectomy chemotherapy, extrahepatic disease, number of CLM, largest liver metastasis diameter, and surgical margin status. (Adapted from Kawaguchi [63] with permission)

of effective chemotherapy regimen including irinotecan and oxaliplatin. The third period during 2006–2014 is characterized as the combined use of molecular-targeted therapy. The covariates-adjusted 5-year OS was significantly higher during 2006–2014 (56.5%) than during 2001–2005 (44.1%) and during 1998–2000 (45.1%) in our group (Fig. 57.9).

57.6 Conclusions

We showed the changes in surgical and medical management of CLM in 2000s. This included the refinements of surgical management and techniques, the advancements in medical therapy, and the understanding of molecular biology of

colorectal cancer. These changes may have contributed to the improvement of the 5-year overall survival in patients undergoing CLM resection from approximately 30–35% before 2000 to approximately 50–60% after 2000. Multiple somatic gene testing may be increasingly used with the recent development of next-generation sequencing. We believe that information on multiple gene mutation is useful for finer prognostication, clinical decision-making, and risk stratification for future clinical trials and further improve the management of CLM in the next 20 years.

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The LiverMetSurvey Registry

58

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Learning Objectives

- Understanding the aims of the LiverMetSurvey registry.
- Knowing the main results provided by the registry.

58.1 Introduction

The treatment of colorectal liver metastases (CLM) has considerably changed over the last decades. The role of surgical resection is now clearly established and CLM is the first indication of hepatectomy in most western countries [1].

Although the literature about surgical management of CLM is abundant, there are still several unanswered questions about various aspects of CLM such as onco-surgical strategy, perioperative chemotherapy, prognostic factors of outcome, or surgical technique. Some of these questions cannot be addressed without a critical number of patients.

The *LiverMetSurvey* is an international registry designed to prospectively collect data of patients surgically operated on for CLM and to offer adequate materials for clinical research and epidemiology.

The aim of this chapter is to discuss the main aspects of the registry and to provide a brief overview of the main scientific results.

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58.2 Missions and Organization of the *LiverMetSurvey* Registry

58.2.1 Study Population and Aims of the Registry

This registry includes all patients who underwent an operation with intention to resect CLM, whether the liver resection was achieved or canceled during the operation.

The goals of the registry are:

- to prospectively collect all the critical information of patients undergoing surgery for colorectal liver metastases,
- to assess the short- and long-term outcome after surgery and to identify prognostic factors
- to analyze the survival of specific subgroups,
- to address several unanswered questions regarding indications, type of surgery, adjuvant treatment, and the role of chemotherapy.

58.2.2 Nomination of a Scientific Committee

A scientific committee involving 14 expert surgeons from different European countries built a questionnaire designed to collect all critical information needed to explore various aspects of liver resection for CLM. The questionnaire was made so that it could be filled in less than 20 min by young surgeons. There is now a new scientific committee involving surgeons and medical oncologists, experts in metastatic colorectal cancer (CRC). The new committee aims to update the questionnaire and to define LMS missions and vision as well as short- and long-term goals and strategies.

J.-N. Vauthey et al. (eds.), *Colorectal Liver Metastasis*, https://doi.org/10.1007/978-3-031-09323-4_58

58.2.3 Participating Centers

All centers managing patients with CLM are encouraged to participate, without any criteria of experience or volume, so that the registry might provide a "true-life" evaluation of CLM surgical treatment worldwide. An independent professional data manager is in charge of the registry administration. All centers taking part in the *LiverMetSurvey* registry have access to an individualized, auto-administered, confidential, and secured database that can be used for monocentric research. The principal investigator and coinvestigators can freely export data from their own centers but have no access to data from other registered centers.

58.2.4 Managing and Protecting the Data

The quality of data is controlled with regular feedback information in case of incompleteness or incoherence of the specific data for each patient. The registry is secured using SSL protection. Therefore, data are encrypted between the user's computer and the *LiverMetSurvey* server and are only deciphered when they reach the *LiverMetSurvey* server.

58.2.5 Services to Participating Centers

LiverMetSurvey offers different services to encourage centers to collaborate and to reward participating centers. The registry can be used as an individual web database, with a user-friendly solution for exporting data in an adequate format for statistical analysis. Advanced statistical analysis is provided every 6 months to each center (e.g., overall survival, prognostic factors), enabling comparisons of its own practice with overall results of LiverMetSurvey. Finally, every contributing center may submit a research project to the scientific committee, using the data from the whole patient cohort. Once the project is approved, access to the whole database and assistance for statistical analysis are offered.

58.2.6 Sponsorship

Sponsorship is essential to maintain the quality of data and ensure the protection of data. After being sponsored by Sanofi, *LiverMetSurvey* is now financed since September 2017 by the ARCAD (*Aide et Recherche en Cancérologie Digestive*) foundation, created to promote research in digestive oncology and provide adequate information to patient and families [2].

58.3 Key Learnings from LiverMetSurvey

58.3.1 Unpublished Data

58.3.1.1 Study Population and Overall Survival

In June 2020, the registry included 29,622 patients treated in 366 centers from an overall number of 63 countries (Fig. 58.1).

58.3.2 Early and Long-Term Outcomes After Surgery

Overall, the 90-day mortality after surgery was 3%, and more than half of postoperative deaths occurred within the first month.

The 5-year overall survival (OS) rates after the first hepatectomy were 43% versus 10% for patients who underwent surgery but were not resected (Fig. 58.2).

58.3.3 The Prognostic Impact of Number and Maximal Tumour Size

The prognostic value of traditional cutoffs for number of lesions and the maximal tumour size, used in previous scoring systems, have been confirmed in the registry. The number of lesions correlates with 5-year OS, as shown in Fig. 58.3. Five-year OS rates of patients with 1–3 lesions, 4–6 lesions, and 7 lesions and more were 47%, 34%, and 27%, respectively. Similarly, survival was lower in patients with larger tumours. Patients operated on for the largest tumour size ≥50 mm had lower OS compared to patients operated on for smaller lesions (46% vs. 36% at 5 years, $P < 0.0001$).

58.3.4 CLM with Concomitant Extrahepatic Disease (EHD)

Concomitant EHD is frequently found in patients undergoing surgery for CLM. Traditionally, these patients were not considered for surgery, but some groups performed liver resection when EHD was deemed resectable using local treatments. Figure 58.4 shows the Kaplan-Meier OS curves after the first hepatectomy according to EHD in the *LiverMetSurvey* population. As expected, the prognosis of patients with EHD (1594, 6.8%) was poorer compared to patients without EHD. However, the OS rate after liver surgery in patients with EHD was 24% at 5 years. This validates the surgical indication in this subgroup of patients.

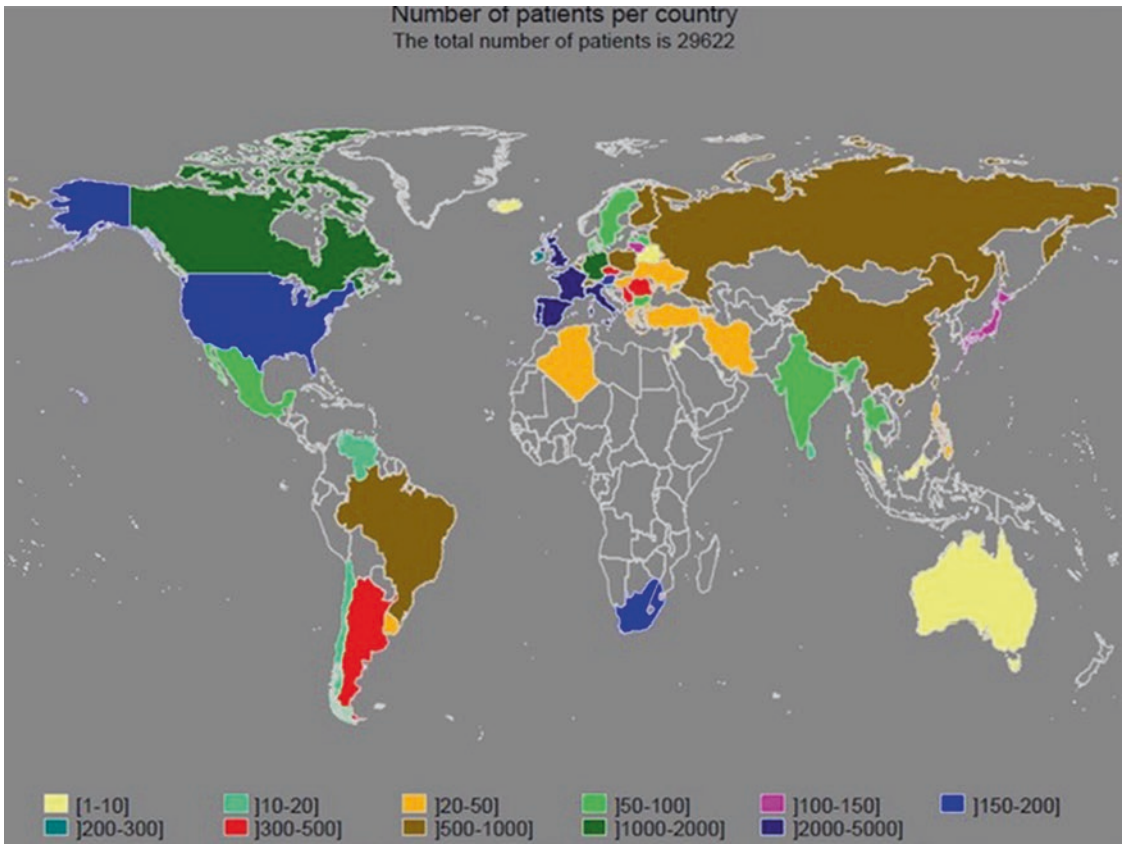
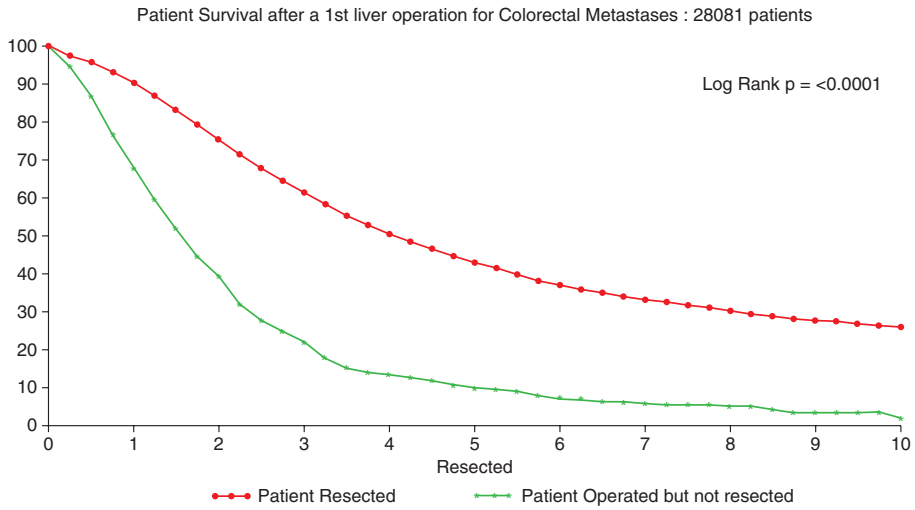


Fig. 58.1 Number of patients per country participating in the registry



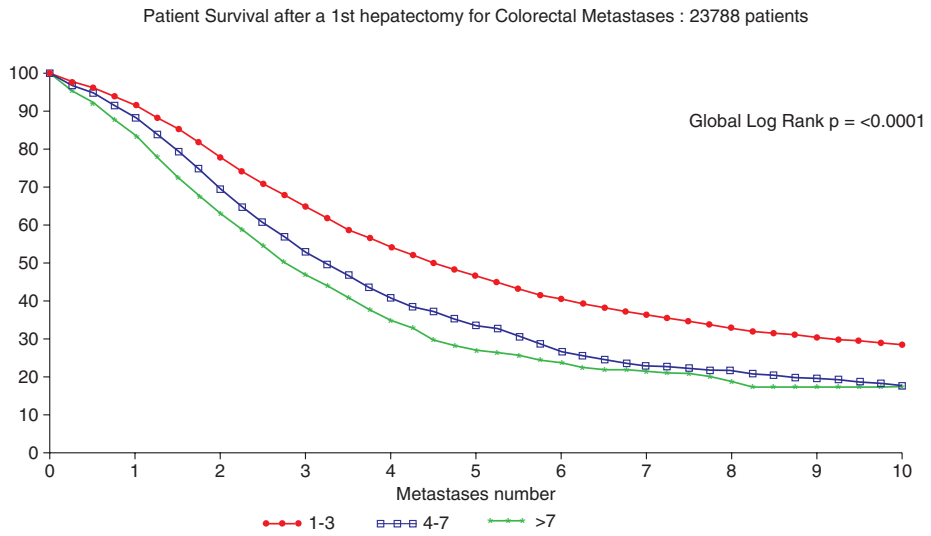
Survival %

Resected	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Not Resected	68%	39%	21%	13%	10%	7%	5%	5%	3%	2%
Resected	90%	76%	62%	50%	43%	37%	33%	30%	27%	26%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Not Resected	1410	688	330	154	75	48	28	15	9	4	1
Resected	26671	18170	12760	8730	5879	4059	2799	2045	1479	1055	767

Fig. 58.2 Kaplan-Meier overall survival cures of operated patients according to the possibility of resection



Details: Log rank p

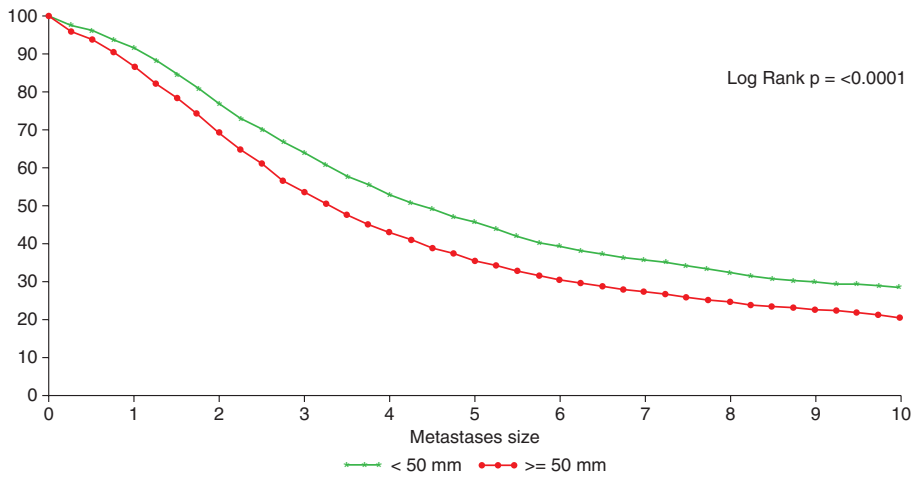
		proba
1-3	4-7	<0.0001
1-3	>7	<0.0001
4-7	>7	<0.0001

Survival %

Metastases number	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1-3	92%	78%	65%	54%	47%	40%	36%	33%	30%	28%
4-7	88%	70%	53%	41%	34%	27%	23%	21%	20%	18%
>7	84%	63%	47%	35%	27%	24%	21%	19%	17%	17%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
1-3	18411	12718	9141	6455	4478	3162	2215	1633	1183	854	622
4-7	3910	2673	1744	1063	649	434	273	185	133	90	64
>7	1467	909	552	329	200	109	75	48	28	21	14



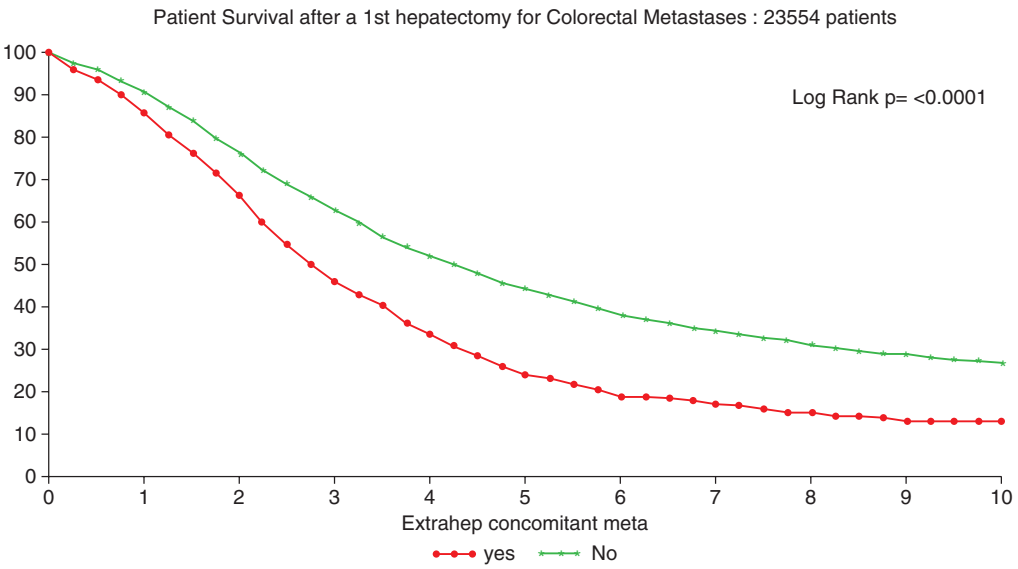
Survival %

Metastases size	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
<50 mm	92%	77%	64%	53%	46%	39%	36%	32%	30%	28%
>=50 mm	87%	70%	54%	43%	36%	30%	27%	25%	23%	20%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
<50 mm	16401	11408	8026	5564	3776	2648	1815	1323	942	662	491
>=50 mm	5644	3829	2660	1754	1188	814	578	417	307	226	151

Fig. 58.3 Kaplan-Meier overall survival cures of resected patients according to the number and maximal size of tumour



Survival %

Extrahep concomitant meta	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
0	91%	76%	63%	52%	45%	38%	34%	31%	29%	27%
1	86%	66%	46%	34%	24%	19%	17%	15%	13%	13%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
0	21960	15106	10650	7376	5048	3529	2444	1782	1284	920	669
1	1594	1006	648	375	215	123	80	52	46	33	25

Fig. 58.4 Kaplan-Meier overall survival cures of resected patients according to the presence of concomitant extrahepatic disease

58.3.5 Preoperative Chemotherapy

Another unpublished analysis addressed the question of preoperative chemotherapy in upfront resectable CLM. It was observed that survival probabilities following liver resection with or without preoperative chemotherapy were similar in patients with a single and small metastasis (<50 mm), whereas preoperative chemotherapy was associated with improved survival in patients with more advanced disease (>5 metastases with at least one tumour ≥50 mm; Fig. 58.5). Although more thorough analysis is required to identify the cutoff which ensures the benefit of preoperative chemotherapy for patients with resectable CLM, this result is in line with that the concept that more intensive preoperative chemotherapy is needed preoperatively in the setting of more advanced disease.

58.3.6 Published Studies

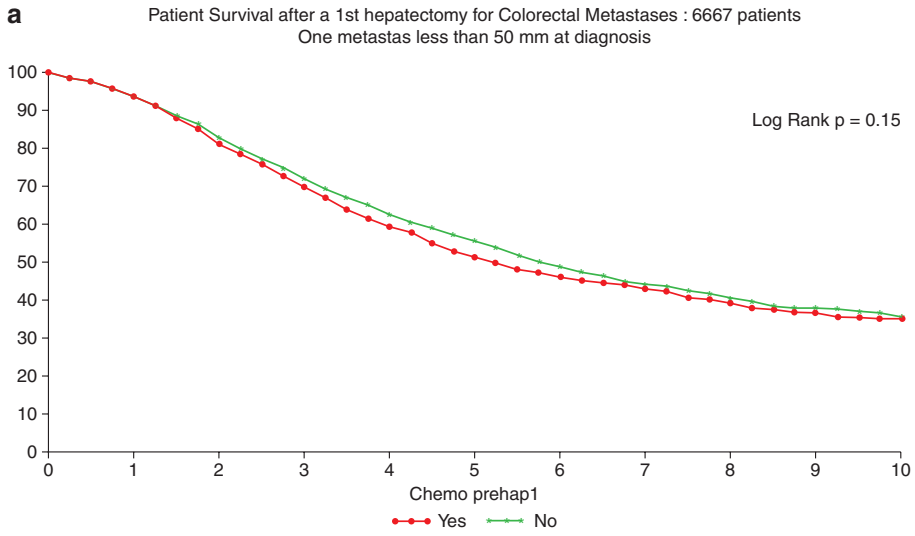
58.3.6.1 Patient and Tumour-Related Prognostic Factors

The registry large population was used to identify prognostic factors after CLM resection.

The question of surgery in elderly patients was explored. The results showed similar survival after hepatectomy in patients older than 70 years compared to younger patients [3]. Beyond 80 years, liver resection still yielded acceptable survival rates, indicating that age *per se* should not be considered an absolute contraindication for resection.

Patients with synchronous disease experienced lower survival compared to patients with metachronous CLM (5-year OS rates of 45% vs. 40%). The management of synchronous CLM raises several questions addressed during a multidisciplinary, international consensus by using expert opinions and data from the registry [4]. This meeting led to clarify the definition of synchronous CLM and primary colorectal cancer. Namely, synchronous CLM and primary colorectal cancer should refer to CLM diagnosed before or at the time of the primary tumour diagnosis. In contrast, "early" metachronous should be used for CLM diagnosed within 12 months following the diagnosis of the primary tumour, whereas late metachronous refer to lesions diagnosed beyond 12 months from the diagnosis of the primary tumour.

The impact of primary tumour location was confirmed in the surgical population of the registry. Left-sided tumours were associated with better long-term outcomes compared to

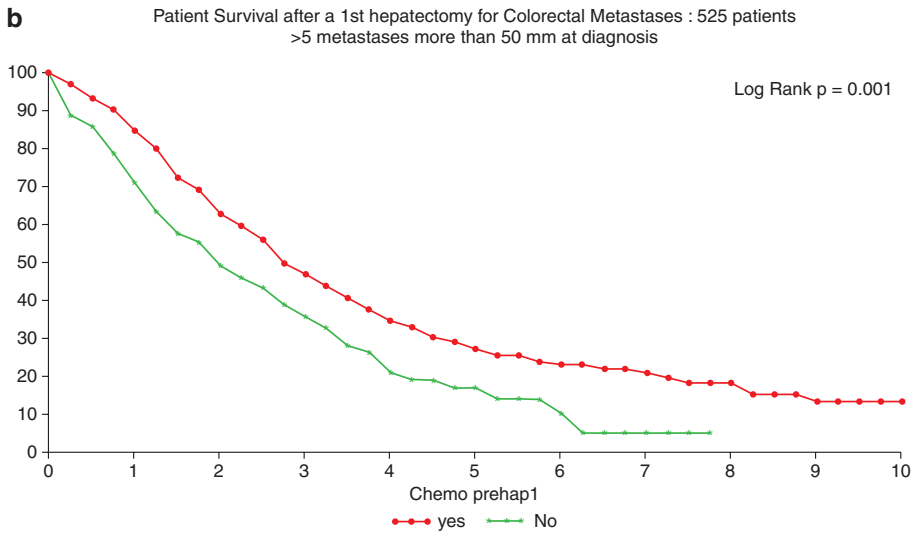


Survival %

Chemo prehep1	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	94%	83%	72%	63%	55%	49%	44%	40%	38%	36%
Yes	94%	81%	70%	59%	51%	46%	43%	39%	35%	35%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	4462	3156	2335	1722	1250	907	646	480	341	238	179
Yes	2205	1543	1103	786	555	397	271	200	145	102	74



Survival %

Chemo prehep1	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	72%	49%	36%	21%	17%	10%	5%			
Yes	85%	63%	47%	35%	27%	23%	21%	18%	13%	13%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	109	66	37	23	11	6	2	1	0	0	0
Yes	416	266	156	96	57	38	25	17	12	7	5

Fig. 58.5 Kaplan-Meier overall survival cures according to preoperative chemotherapy. (**a**) Subgroup of patients with a single lesion <50 mm. (**b**) Subgroup of patients with >5 metastases and at least one lesion >50 mm

patients with right-sided tumours consistent with previous studies in non-resectable mCRC patients [5].

58.3.6.2 Onco-surgical Strategies

Response to chemotherapy is an important determinant of outcome after resection. Long-term outcomes after CLM resection were worse in patients with progressive disease prior to resection of CLM. This suggested that resection should be avoided and even contraindicated in the context of progression [6]. The subgroup of resected patients despite disease progression while on chemotherapy was analyzed in *LiverMetSurvey*. Vigano et al. identified three predictive factors associated with worse survival in these patients: tumours >3, maximum size ≥50 mm, carcinoembryonic antigen (CEA) ≥ 200 ng/mL. Resection appeared to be still beneficial in patients with no more than one adverse factor [7].

The outcome of surgery after second-line chemotherapy was investigated using *LiverMetSurvey* [8]. Patients operated after second-line of chemotherapy experienced similar survival rates compared to those operated after a first-line, and some patients achieved prolonged survival. This result indicates that rescue liver surgery should not be contraindicated after the failure of first-line chemotherapy when a response is obtained with a second-line regimen.

58.3.7 Impact of Preoperative Bevacizumab

In 501 patients selected from the *LiverMetSurvey,* patients who received perioperative FOLFOX (n = 384) were compared with those who received perioperative FOLFOX and bevacizumab (n = 117). No difference was observed regarding primary tumour stage, synchronicity, and the number or size of metastases. Perioperative use of bevacizumab was not associated with improved 3-year OS (76.4% vs. 79.8%, P = 0.3), and 3-year disease-free survival (7.4% vs. 7.9%, P = 0.08) [9].

Therefore, the addition of bevacizumab to standard perioperative chemotherapy does not appear to improve OS or DFS in patients undergoing resection of resectable CLM.

58.3.7.1 Extended Indications

The benefit of surgery for patients with extensive disease was analyzed with *LiverMetSurvey*. One of the *LiverMetSurvey*-based studies showed that in 529 patients with 10 CLM or more, 5-year OS was 30% after R0/R1 resection [10]. Adjuvant chemotherapy and preoperative staging with MRI were associated with better outcomes in this patient subset.

The management of patients with simultaneous liver and lung metastases was studied [11]. Patients with CLM and simultaneous resectable lung metastases had similar survival compared to those with the liver-only disease (adjusted 5-year OS: 44.5% vs. 51.5% respectively). In contrast, unresectable or unresected lung lesions were associated with lower survival (14.3% at 5 years), suggesting that lung lesions removal or local treatment should be considered whenever feasible. However, resecting the liver metastases even in the presence of unresectable lung metastases seems to provide a better survival compared to the poor outcome of unresected liver and lung synchronous metastases.

58.3.7.2 Impact of Underlying Liver Steatosis

In a first study based on *LiverMetSurvey* based on 5853 patients who underwent first-time liver resection without preoperative chemotherapy, 1793 (30.6%) had background steatosis.

The existence of steatosis was associated with improved 5-year OS (47.4% versus 43.0%; log-rank, P = 0.0017) and cancer-specific survival (CSS) (56.1% vs. 50.3%; P = 0.002) compared with normal background liver [12]. After adjustments, the survival advantage associated with steatosis remained. Therefore, the presence of steatosis did not adversely influence survival in patients undergoing resection for colorectal liver metastases (CLM) without preoperative chemotherapy.

This hypothesis was also tested in patients undergoing resection for CLM following preoperative chemotherapy. The 90-day mortalities were 2.1% in patients with normal liver, 2.3% in patients with liver steatosis, and 3.5% in patients with other histopathology (P = 0.103). The 5-year OS rates were 39%, 42%, and 36%, respectively (P log-rank = 0.4), and the 5-year CSS rates were 43%, 45%, and 41% (P log-rank = 0.5), respectively [13].

The findings of similar perioperative outcomes and survivals challenge the common perception that steatosis in CLM patients with or without preoperative chemotherapy is associated with increased perioperative mortality and worse long-term survival.

58.3.7.3 Technical Issues

The value of the liver-first approach (reverse approach) in patients with synchronous has been compared to the classical approach (primary resection first) [14]. There was no difference between the two strategies provided both primary tumour and CLM could be treated. This result serves as a basis to treat the most advanced or the most complex tumour location first.

Studies showed that repeat hepatectomy was associated with improved survival [15–18]. This is the rationale to avoid an unnecessary sacrifice of parenchyma thus maintaining a high chance of iterative surgery. The benefit of parenchyma-sparing policy at first hepatectomy was then evaluated and confirmed using the registry [19]. The feasibility of repeat hepatectomy was much higher in patients after parenchyma-

sparing first hepatectomy and translated to an improved survival from the time of recurrence.

The *LiverMetsurvey* network has been used to perform a survey on the use of pharmacological agents to modify liver ischaemia reperfusion (IR) injury in patients undergoing hepatectomy for colorectal liver metastases. The results show that pharmacological modulation is used by only a minority of teams [20].

58.4 Conclusion

Fifteen years after launching the project, *LiverMetSurvey* has proved to meet its objective. The main achievement is likely to provide the largest number of patients resected for CLM worldwide thus confirming the crucial role of surgery for these patients. Besides, the registry allows us to explore numerous questions related to prognosis, onco-surgical strategy, and specific subgroup of patients with CLM. These results highlight the importance of a registry to explore real time questions that can hardly be addressed with monocentric retrospective series and even randomized trials. *LiverMetSurvey* provides a snapshot of the outcome of patients resected from CLM and serves as a robust basis to explore numerous unanswered questions concerning the optimal management of this patient group.

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59 Circulating Tumour DNA and Risk-Stratified Surveillance Strategies for Patients with Colorectal Liver Metastases

Timothy E. Newhook and Yoshikuni Kawaguchi

Learning Objectives

- More precise and dynamic biomarkers are required to accurately predict outcomes for patients with CLM who undergo surgical resection.
- Detection of circulating tumour DNA (ctDNA) after completion of definitive therapy for colorectal cancer and CLM is defined as minimal residual disease (MRD) and associated with a high risk of recurrence.
- Recommended surveillance strategies following resection for patients with CLM are not personalized or based upon individual risks for early or late recurrence.
- Patients with a somatic *RAS* mutation should undergo longer periods of higher intensity surveillance compared to *RAS* wild-type due to increased risk of early recurrence.

59.1 Introduction

Surgical resection remains the only potentially curative treatment option for patients with colorectal liver metastases (CLM), and oncologic outcomes following hepatectomy have greatly improved with reported 5-year overall survival (OS) rates between 48% and 58% [1, 2]. Most of these patients will experience a recurrence, with the risk being the highest within 2 years of initial hepatectomy [3]. Fortunately, many are able to again undergo surgical resection with 5-year OS rates of 41–73% following repeated hepatectomy or 39–54% if they undergo resection of a pulmonary recurrence [4–9]. Unfortunately, stratification of patients for appropriate treatment sequences and devising postoperative surveillance strategies to detect these treatable recurrences has remained generalized.

Common strategies to predict recurrence and survival following hepatectomy are largely based upon clinical factors, such as size and distribution of metastases and presence of nodal metastases in the primary tumour, and these have been used to formulate survival prediction scores [10–12]. However, these methods lack the sensitivity to adequately stratify patients by risk of recurrence in a precise fashion. More recently, tumour somatic mutations, such as in *RAS*, have provided a window into individual patient's tumour biology [13]. The substitution of *RAS* mutation status for vague clinical variables allowed for the creation of the modified clinical score (m-CS), which more accurately predicts survival after CLM metastasectomy [14]. Indeed, mutations in *RAS* are associated with worse recurrence-free survival (RFS) and OS after resection of CLM is prognostic for response to chemotherapy, and is used to stratify patients for targeted therapies [13, 15–17]. Further, the presence of additional and/or multiple somatic alterations in CLM refine prognostication, including *RAS* + *TP53* co-mutations, *RAS* + *TP53* + *SMAD4* triple mutations, or the presence of *FBXW7* or *BRAF* mutations [18–22]. Even more recently, the emergence of the detection of circulating tumour DNA (ctDNA) has shown promise as a sensitive biomarker for disease recurrence, response to therapy, and tumour burden for patients with colorectal cancer (CRC). The integration of clinical factors with these markers of tumour biology allows for much more sensitive prognostication that may influence clinical decision-making and strategies for postoperative surveillance.

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59.2 ctDNA: An Emerging Biomarker for Patients with CLM

59.2.1 The Case for ctDNA in Metastatic Colorectal Cancer

Early detection of the onset, recurrence, and progression of both primary and metastatic CRC is imperative to improving patient survival. In the case of primary CRC, risk stratification for recurrence and survival has included clinical and pathologic features, mismatch-repair status, and tissue-based signatures to guide therapy [23–27]. However, these data along with the commonly used biomarker, carcinoembryonic antigen (CEA), have unsatisfactory sensitivity and specificity [28]. This, along with the identification of multiple somatic genes frequently mutated in CRC tumours has led to efforts to detect the presence of these mutations circulating in the blood in order to predict recurrence and guide therapy [29, 30]. In fact, tumour-specific mutations can be found in the cell-free component of peripheral blood, termed circulating tumour DNA (ctDNA), and this ctDNA biomarker is detectable in a large proportion of patients with metastatic CRC and is a dynamic marker of tumour burden and treatment response [31–33].

In patients with localized CRC, ctDNA has become an attractive dynamic biomarker applicable throughout phases of care. For example, in a study by Tie and colleagues almost 80% of patients with detectable ctDNA following resection of AJCC stage II colon cancer experienced recurrent disease if they did not receive adjuvant chemotherapy, and detection of minimal residual disease (MRD) by ctDNA after completion of adjuvant chemotherapy was associated with worse RFS [34]. The same group also reported an almost sevenfold high risk of recurrence within 3 years of resection of AJCC stage III colon cancer if ctDNA was detected following adjuvant chemotherapy [35]. Moreover, Reinert and colleagues found that using longitudinal ctDNA analyses identified 88% of disease recurrences and that ctDNA-positivity 30 days after resection of AJCC stage I–III colon cancer conferred a sevenfold increased risk of disease relapse [36]. Lastly, early changes in ctDNA during chemotherapy for metastatic CRC predict progression-free survival and precede radiographic evidence of progression [33, 37, 38]. As sensitivity for recurrent disease improves with innovative detection platforms, ctDNA-based care strategies are poised to revolutionize the care of patients with CRC.

59.2.2 ctDNA and Surgical Management of CLM

Circulating cell-free DNA signals have been implicated as biomarkers for disease burden, response to chemotherapy, and resectability for patients who are being considered for CLM resection [39]. Moreover, ctDNA elements have been shown to have a stronger correlation with tumour burden than other imprecise biomarkers, such as CEA and CA19-9 [39]. Methylated ctDNA markers and their dynamics during neoadjuvant therapy have been associated with successful CLM resection, and specific circulating mutations have been associated with divergent outcomes if detected [39]. Moreover, high concordance between collected ctDNA and tumoural tissue has been demonstrated and may be superior to tissue genotyping in some circumstances due to shorter screening times, lower rates of sample unavailability, and higher trial enrollment rates for patients with metastatic CRC [40–43].

Preoperatively, ctDNA sampling can be prognostic for outcomes and is associated with survival following hepatectomy for CLM [44, 45]. Kobayashi and colleagues demonstrated that patients with solitary resectable CLM who do not have detectable ctDNA preoperatively are a group at low risk for postoperative recurrence and perhaps, those with an improved chance for cure [44]. However, 80% of their cohort were ctDNA-positive preoperatively, and these patients had a significantly lower RFS compared to those who were ctDNA-negative [44]. Narayan and colleagues also demonstrated that detection of circulating *TP53* mutations immediately pre-hepatectomy were associated with worse postoperative disease-specific survival [46]. Thus, preoperative ctDNA detection may help guide decision-making in a personalized fashion, such as recommending neoadjuvant chemotherapy if detected.

Postoperative ctDNA detection indicates likely residual disease and is associated with worse outcomes following resection of CLM. As reported by Scholer, detection of ctDNA within 3 months of CLM resection is associated with recurrence and significantly shorter RFS [47]. We have demonstrated that both having a node-positive primary CRC or having more than 2 CLM are associated with having detectable ctDNA after hepatectomy, and that postoperative ctDNA-positivity is associated with significantly worse RFS and OS [48]. In fact, perioperative dynamics in ctDNA status reveal patients with MRD, but also patients with preoperatively detected ctDNA that may be rendered negative by surgery [49]. Moreover, perioperative ctDNA dynamics predict postoperative survival better than somatic tumour mutations commonly referenced for prognostication (Fig. 59.1).

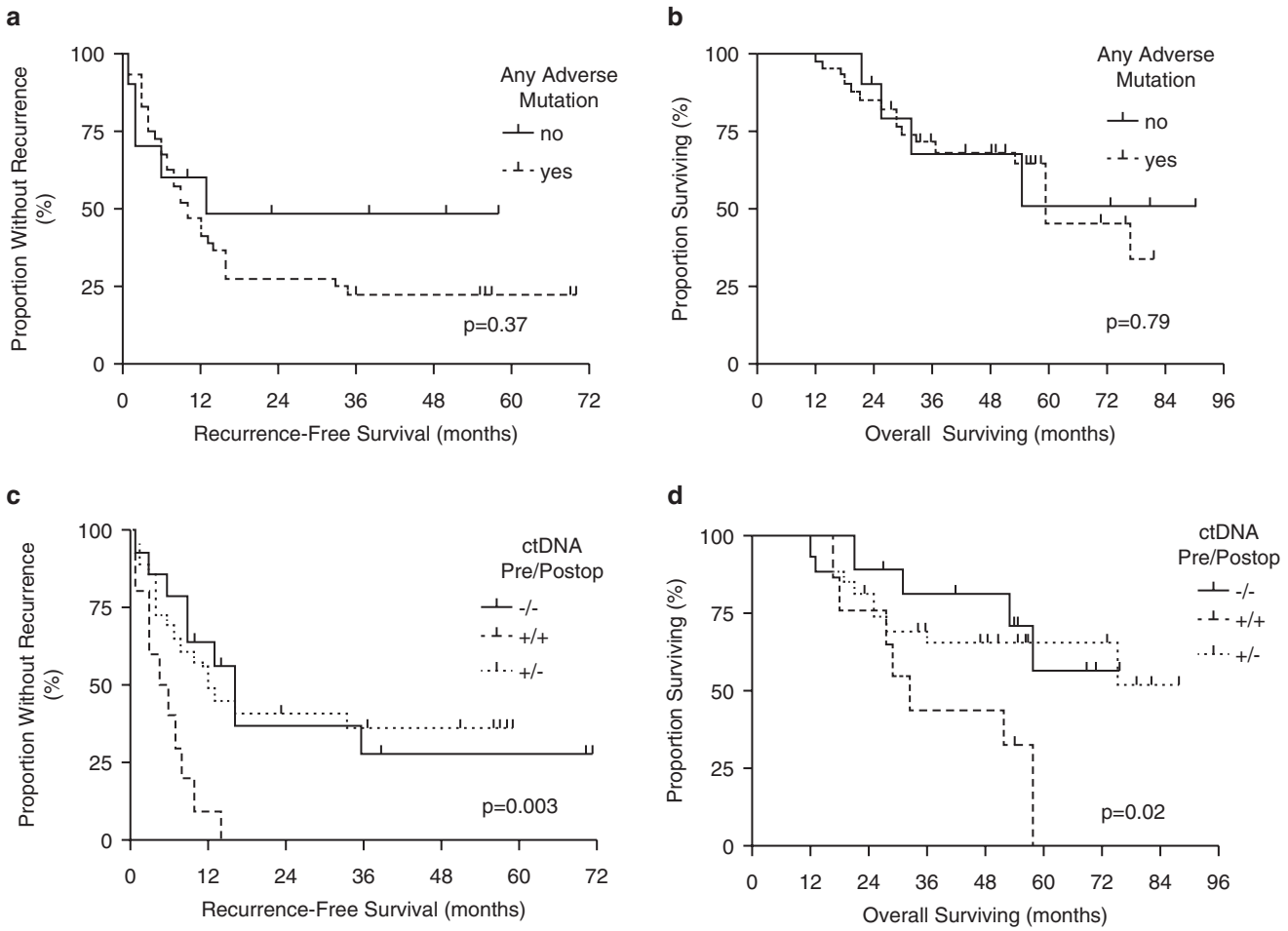

Fig. 59.1 Kaplan-Meier survival analysis for patients who underwent curative-intent resection of CLM. (**a**) Recurrence-free; and (**b**) overall survival based in *Any Adverse Mutation* in the tumour; and (**c**) recurrence-free survival; and (**d**) overall survival based upon dynamic *perioperative* ctDNA detection

59.3 Future Directions

In the future, ctDNA dynamics will likely be standard for the perioperative management of patients with CLM. Detection of certain preoperative ctDNA signatures may identify patients who will benefit from neoadjuvant therapy strategies, whereas those that are ctDNA-negative preoperatively may be optimal upfront surgery candidates. Those who have MRD following CLM resection may be referred for more intensive or targeted adjuvant therapies by postoperative ctDNA status, and the dynamic changes in ctDNA longitudinally may allow for evaluation of disease responses. Lastly, ctDNA detection and dynamics will inform treatment allocation and evaluation in prospective clinical trials for patients with CLM.

59.4 Risk-Stratified Surveillance for Recurrent Disease After Hepatectomy for CLM

59.4.1 Current Recommendations and Changing Risk of Recurrence

More than half of patients will experience recurrence after resection of CLM, and post-hepatectomy surveillance is oriented towards early detection of these recurrences [1, 2, 50]. Patients who undergo resection of both liver and/or lung recurrences may achieve favorable outcomes following initial CLM resection [4–9, 51]. Current NCCN recommendations for surveillance following CLM resection include evaluation and imaging every 3–6 months for 2 years, fol-

lowed by every 6 months for a total of 5 years for patients with Stage IV CRC [52, 53]. However, there is a paucity of objective surveillance strategies following CLM resection, particularly those with Stage IV disease who undergo surgery with curative intent. Current society guidelines do not individualize surveillance strategies based upon risk for recurrence that takes into account tumour biology (Table 59.1).

Studies have supported differential risks for recurrence following CLM resection based upon individual patient and tumour characteristics and molecular biomarkers. For example, previous studies have revealed that somatic mutations in *BRAF, RAS, TP53, APC, SMAD4,* and *FBXW7* are associated with oncologic outcomes after resection of CLM [13, 54–58]. Moreover, we have reported that co-mutations result in worse outcomes compared to individual mutations, such as *RAS* + *TP53* and *RAS* + *TP53* + *SMAD4* [18, 19]. Prior reports have shown that the risk for death after resection of CLM is not constant over time, and is the highest within the first year after surgery and decreases over time [59, 60]. However, conditional RFS and risk factors for recurrence over time are more relevant for surveillance intensity decisions and may result in personalized postoperative care [61]. In fact, we have reported that a *RAS* + *TP53* co-mutation has a continued deleterious association with recurrence over time following CLM resection [61]. Other factors at the time of surgery that are associated with increased risk for recurrence include primary lymph node metastases, multiple CLM, largest CLM >5 cm, and harboring a *RAS* mutation. However, in patients without recurrence at 2 years following CLM resection the only factor associated with an increased risk of recurrence is a *RAS* mutation [3]. Current NCCN guidelines for post-resection surveillance timing are similar for Stages II–IV disease, but there are clearly opportunities to tailor surveillance based on these biomarkers.

Table 59.1 Current recommendations for surveillance after resection of colorectal cancer [3]

Parameter		NCCN (2020) [62, 63] Stage IV[a]	ASCRS (2015) [64] Stage I–III and IV[b]	ASCO (2013) [65] Stage II and III
History and physical examination	0–2 years	Every 3–6 months	Every 3–6 months	Every 3–6 months
	2–5 years	Every 6 months	Every 6 months	Every 3–6 months
CEA measurement	0–2 years	Every 3–6 months	Every 3–6 months	Every 3–6 months
	2–5 years	Every 6 months	Every 6 months	Every 3–6 months
Axial imaging	0–2 years	Every 3–6 months	Every 12 months	Every 12 months[c]
	2–5 years	Every 6–12 months	Every 12 months	Every 12 months[c,d]

Abbreviations: *NCCN* National Comprehensive Cancer Network; *ASCRS* American Society of Colon and Rectal Surgeons; *ASCO* American Society of Clinical Oncology; *NS* not stated; *CEA* carcinoembryonic antigen; *CLM* colorectal liver metastases

[a]After curative-intent surgery for synchronous liver and/or lung metastases only

[b]After curative-intent surgery

[c]For high risk patients, every 6–12 months during 0–3 years

[d]For 3 years after surgery

59.4.2 Proposed Surveillance Algorithm After Resection of CLM

Patients may undergo repeated liver or lung metastasectomy for recurrent disease after CLM resection, and thus it is imperative to develop a surveillance strategy tailored to detect these recurrences while they remain amenable to surgical management. This requires evaluation at intervals that are optimized to postoperative periods based upon individual recurrence risk. Based on the increased risk of recurrence after CLM resection extending past 2 years for patients with *RAS*-mutant tumours, we have proposed a novel surveillance strategy that is tailored to patients based upon *RAS* status (Fig. 59.2) [3]. As the risk for recurrent disease is similar up

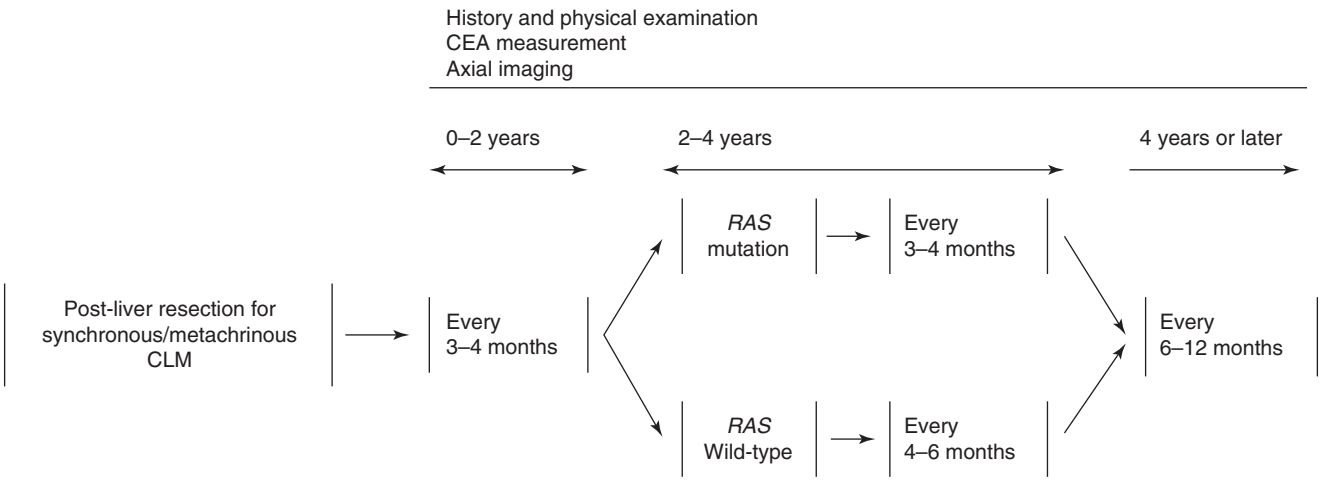

Fig. 59.2 Proposed risk-stratified surveillance algorithm for patients following resection of CLM based upon RAS mutation status

until 2 years post-resection, we suggest surveillance every 3–4 months during years 0–2 following CLM resection. As *RAS* status is associated with increased risk of recurrence during years 2–4 if recurrence-free at 2 years following CLM resection, we recommend surveillance every 3–4 months from years 2–4 if *RAS*-mutant, whereas if *RAS*-wild type every 4–6 months from years 2–4 postoperatively. Finally, every 6–12 months thereafter if recurrence-free at 4 years. This individualized surveillance strategy leverages individual tumour biology to target surveillance to discover recurrent disease to allow repeated surgical intervention.

59.5 Conclusion

In conclusion, the management of patients with CLM is becoming increasingly individualized and underpinned by patient's genomic profiles. Moreover, more precise and dynamic biomarkers are affording patients and caregivers the opportunity to detect recurrent disease much sooner than ever before, which will allow for early medical and surgical intervention and re-intervention. As our understanding of how individual tumour genomic profiles and ctDNA dynamics impact outcomes and are interrelated, the result will likely be treatment sequencing, intervention, and surveillance strategies that are unique and personalized for every patient with CLM.

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