Two-Stage Liver Surgery with Portal Vein Occlusion

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Abbreviations

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

The Evolution of Staged Liver Surgery

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

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for liver tumors, revealing insufficient regeneration of the remnant liver in some cases. The challenge of the small FLR evoked innovative surgical strategies, all relying on the liver's regenerative potential as initially described in the myth of Prometheus. This chapter addresses the concepts and variants of two-stage liver surgery with portal vein occlusion as an elementary tool enabling staged surgery.

Interestingly, the effect of portal vein occlusion had already been known for many years before the first anatomic liver resections [4], and the first reports on liver regeneration after major hepatectomy in humans appeared in the 1950s [5]. In 1920, Rous and Larimore [6] from Rockefeller Institute in New York recognized the importance of portal blood flow for liver volume maintenance in a rabbit model of portal vein occlusion. They performed ligation of the left portal vein (PVL) and observed atrophy of the ipsilateral liver and a corresponding hypertrophy of the contralateral liver. Within a few weeks, the grown portalized liver took over full liver function, and the deportalized liver steadily shrank to a fibrous tag [6].

Despite the early experimental discoveries, it took more than 70 years until the effect of unilateral disruption of portal flow entered into the clinical practice of liver surgery. Makuuchi et al. [7] pioneered the use of portal vein occlusion in liver surgery. He first described a series of 14 patients with hilar cholangiocarcinoma undergoing pre-operative portal vein embolization (PVE) to induce atrophy in the tumor-bearing lobe and parenchymal hypertrophy in the contralateral lobe (Figs. 14.1, and 14.2). This report was pioneering for all subsequent surgical strategies manipulating liver volume to increase resectability of hepatic tumors (Fig. 14.3).

Fig. 14.1 Masatoshi Makuuchi from the National Cancer Center in Tokyo

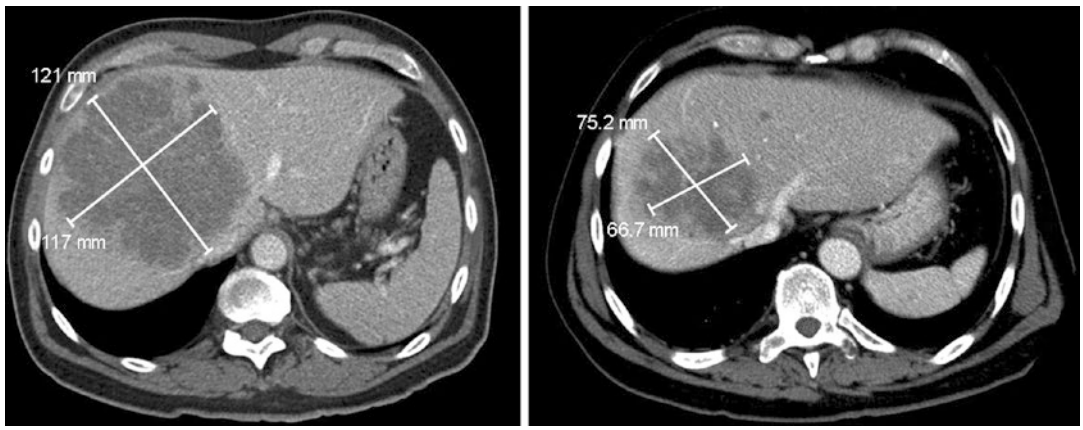

Fig. 14.2 Portal vein embolization: hypertrophy of the future liver remnant, atrophy of the tumor bearing lobe (colorectal liver metastases)

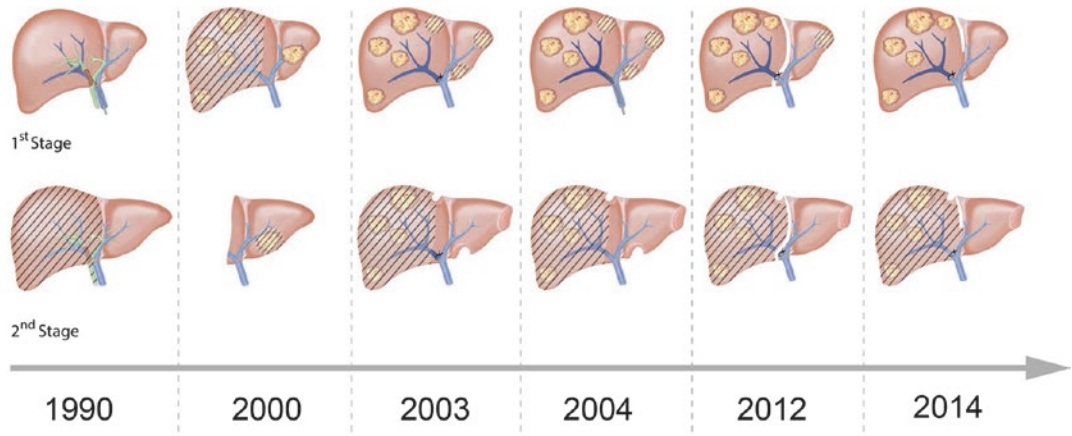

Fig. 14.3 Evolution of staged hepatectomies

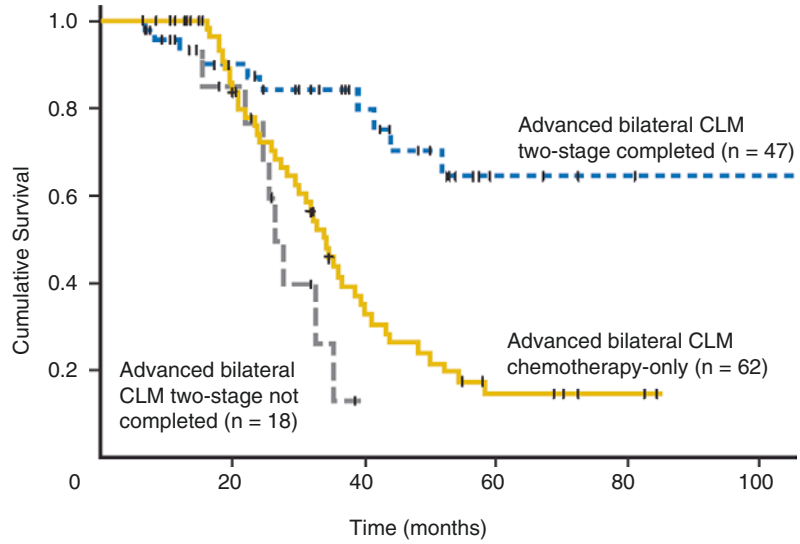

Fig. 14.4 Overall survival of patients undergoing a two stage hepatectomy (completed or not completed) and chemotherapy alone

Resection of hepatic metastases, especially colorectal liver metastases (CLM), was controversially discussed for a long time after its first description in 1940 by Cattell [8], due to a high peri-operative mortality and low 5-year survival rates. These figures have dramatically changed today. The currently largest series of two-stage hepatectomies for advanced bilateral CLM ($n = 890$) has been reported by Brouquet et al. in 2011. In this series, patients undergoing staged hepatectomy had a 5-year survival rate of 51% compared to 15% for patients receiving chemotherapy only [9] (Fig. 14.4).

The concept of two-stage hepatectomy for CLM, not necessarily with portal vein occlusion, was introduced by the Paul Brousse group from Paris in 2000 [10]. In a first stage, a maximum of metastases were removed. After a postoperative waiting interval of 2–14 months, enabling the liver to regenerate, the remaining tumors were resected. During this period, chemotherapy was frequently applied to reduce tumor growth. The authors reported a feasibility rate of 81% for both stages, with a median survival of 31 months from the second hepatectomy [10]. The next advancement of staged hepatectomy to achieve curative resection of bilobar CLM was reported by Jaeck et al. in 2004. This group described the non-anatomic removal of metastases of the left lobe (subsequently called "cleaning"), followed by PVE and later by right or extended right

hepatectomy after sufficient growth of the FLR [11]. In 76% of all patients enrolled, it was possible to achieve a second stage, resulting in a 3-year survival rate of 54%. Belghiti et al. [12] proposed portal vein ligation (PVL) as a surgical variant of portal vein occlusion (PVO), including simultaneous cleaning of the FLR in the same procedure (Figs. 14.5, 14.6, and 14.7), even in combination with resection of the primary tumor at the first stage. In this study, a total of 20 patients were included (12 patients with colorectal cancer and eight patients with neuroendocrine tumors). Finally, 15 of 20 patients (75%) were eligible for a definitive second-step operation due to absence of recurrent disease. This approach proved to be safe and feasible, as no major complications

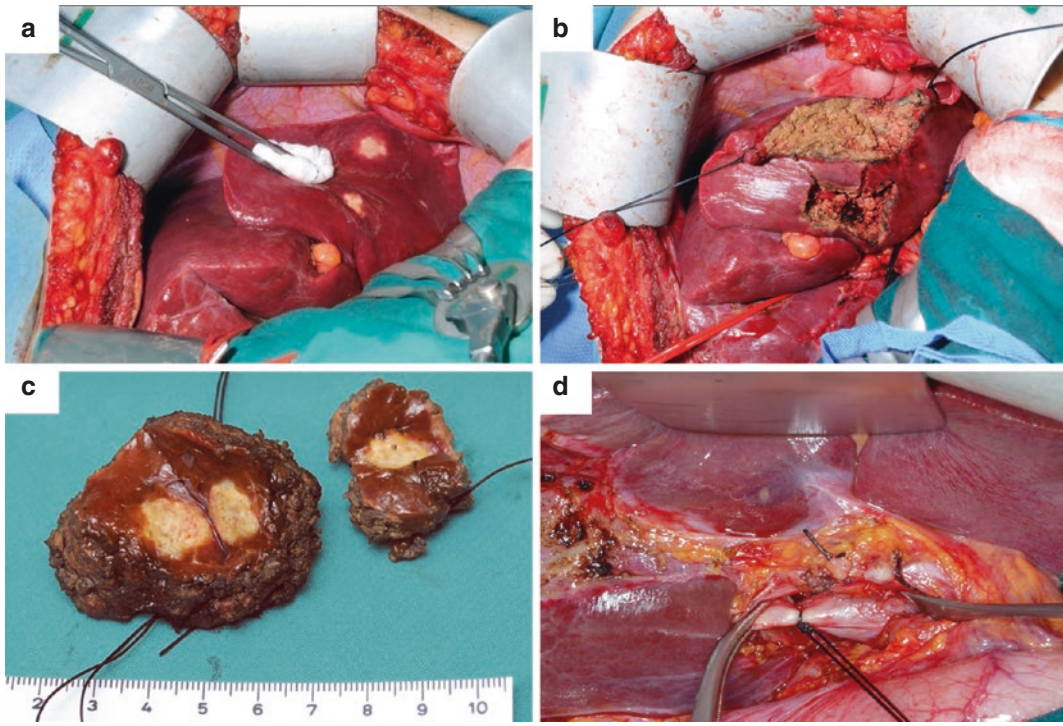

Fig. 14.5 First stage of a two-stage hepatectomy: "cleaning" of the future liver remnant (**a**–**c**) and portal vein ligation (**d**)

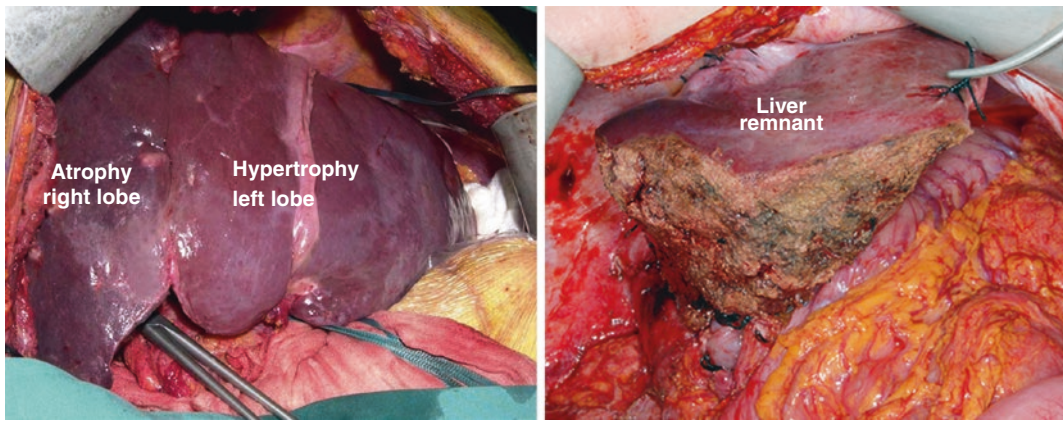

Fig. 14.6 Second stage of a two-stage hepatectomy: volume increase of the left lobe, atrophy of the right lobe

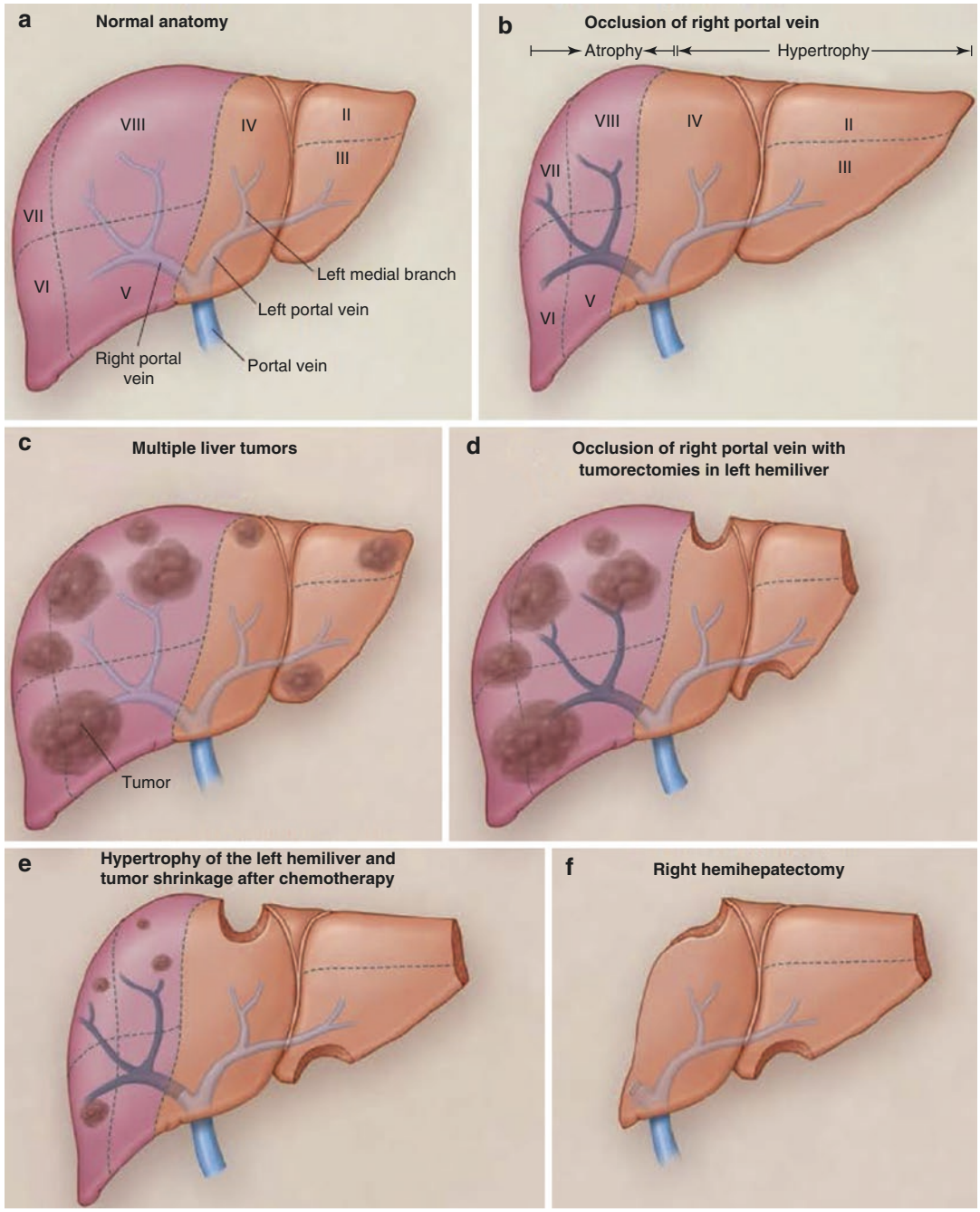

Fig. 14.7 Liver hypertophy induced by portal vein occlusion (**a**, **b**) and the concept of two-stage procedures (**c**–**f**)

were reported [12]. In another study of the Belghiti group, PVE and PVL were compared to assess liver hypertrophy in the setting of two-stage hepatectomies [13]. The degree of hypertrophy before second stage operation was measured by CT-based volumetry, revealing a comparative volume increase of 35% after PVE versus 38% after PVL.

Both types of portal vein occlusion (PVL and PVE) proved to be safe and efficient in a

multimodal setting, and were therefore implemented in multi-stage procedures as proposed by Clavien et al. [14, 15] (Fig. 14.7). However, a major drawback of this staged strategy is the waiting interval of liver hypertrophy between the two stages. Initially, non-selective PVE required a 2–14-month waiting time after stage 1 until resection could be completed [10]. This exposed the patients to a high risk of tumor progression. Both experimental and clinical data suggest increased tumor progression in the FLR after PVO [16, 17]. Today, the waiting period after PVE or PVL could be reduced to 4–6 weeks. Despite the significant reduction of the inter-stage interval time, a period of 1 month or longer might be too long to control tumor disease in patients with extensive bilobar tumor load who are planned to undergo curative resection in the second step. Therefore, efforts were undertaken to accelerate liver growth and shorten the time interval between the two stages. In 2012, Schnitzbauer and Schlitt [18] from Regensburg in Germany reported a preliminary series of patients with extensive hepatic tumor burden from primary and secondary liver tumors who underwent parenchymal in situ splitting and PVL. The initially used term "in-situ splitting" was derived from liver transplantation but was later replaced by the term "associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)", as proposed by de Santibañes and Clavien [15]. Intriguingly, the combination of PVL with parenchymal transection was able to reduce the median inter-stage waiting time to 9 days, with a median FLR increase of 74% [18]. Further developments of this procedure include the use of PVE in combination with parenchymal transection [19], ALPPS procedures with partial transection [20, 21], and laparoscopic [22] variants. In 2014, Robles et al. from the University of Murcia in Spain presented the first series replacing parenchymal transection by the application of a tourniquet [23]. They were able to show a median FLR increase of 61% within 7 days, which is in line with the classical ALPPS procedure.

When comparing two-stage hepatectomies with PVO with or without parenchymal partition, it becomes obvious that the regenerative boost in ALPPS is much stronger. However, the molecular mechanisms responsible for this phenomenon still remain unclear. A recently published experimental study using a mouse model for ALPPS suggests circulating factors in combination with PVL could mediate this unprecedented regeneration [24].

The development of various types of two-stage hepatectomies with PVO probably represents the most successful advances in hepatobiliary surgery during the past two decades. The clinical practice of these procedures has led to an expansion of resectability in patients who are otherwise not amenable for curative liver surgery.

Indications and Limitations

Despite the enormous advances in chemotherapy, complete surgical removal of CLM remains currently the best chance for long-term survival [9]. Most patients who are evaluated for a two-stage hepatectomy have already undergone systemic chemotherapy for colorectal cancer (CRC). Brouquet et al. [9] compared patients with objective response to first-line chemotherapy undergoing two-stage hepatectomy versus patients with chemotherapy alone. The results of this case-matched analysis were clearly in favor of the two-stage hepatectomy group, with a superior 5-year survival rate (51 vs. 15%). This observation emphazises that the removal of liver tumor mass appears crucial for long-term survival [9]. In the same line are data from a study demonstrating the beneficial impact of negative resection margins on both local recurrence and long-term survival [25]. Interestingly, the width of a negative surgical margin does affects neither risk nor site of recurrence nor survival. Even estimated margins <1 mm should not be used as exclusion criteria not to undertake curative resection in CLM [25]. Finally, the availability of a more effective chemotherapy regimen has increasingly led to scenarios where initially unresectable CLM can be converted into resectable disease. Therefore, downsizing chemotherapy is becoming an important strategy to achieve disease eradication. Adam et al. reported in their series that 16% of a total of 184 patients with initially unresectable CLM were successfully converted by chemotherapy to resectable disease [26].

Any oncologic surgery strongly relies on the selection of candidates for surgery. Traditionally, local resectability and the presence of extrahepatic disease have been considered as contraindications for liver surgery. This paradigm has changed in the last few years. Patients with extensive hepatic tumors and limited, curable extrahepatic disease, such as resectable lung metastases, may be eligible for two-stage hepatectomy. The pre-operative workup for two-stage hepatectomy essentially does not differ from the routine workup for other major hepatectomies, with a particular focus on *the extent of the systemic disease* and an exact picture of local liver and tumor anatomy (*extent of the tumor, involvement of major anatomic structures, and size of the FLR*). Based on these principles, the ability to achieve curative resections can be estimated quite accurately. Computed tomography (CT) scan is the standard imaging modality for the diagnosis of CLM in most institutions. Particularly when combined with fluorodeoxyglucose positron electron tomography (FDG-PET), this imaging modality has shown a high diagnostic accuracy [27] and should be used to rule out extrahepatic metastases. A mandatory element of the diagnostic workup for patients considered for two-stage hepatectomy is the determination of the tumor extent and the volume of the FLR. This is ideally done by three-dimensional CT or MR volumetry, allowing the measurement of segmental liver volumes. However, the measurement of the total liver volume (TLV) by this method is usually more inaccurate, since the subtraction of multiple tumors might lead to over- or underestimation. To exclude this problem, various formulas have been developed to estimate the TLV based on weight, height, and body surface area (BSA). One of the most frequently used formulas for Western adults is relying on the linear correlation between BSA and TLV: TLV (cm^3) = −794.41 + 1267.28 * BSA (m^2) [28]. The ratio between volumetrically measured FLR and calculated TLV is called standardized future liver remnant (sFLR). How much FLR volume is enough to maintain liver function is not clearly defined, and strongly depends on factors like parenchymal quality of the FLR. A survey among 133 international hepatobiliary centers [29] has revealed that the widely accepted minimal FLR for resection was 25% (range 15–40%) in case of normal liver parenchyma (Fig. 14.8). For patients with underlying liver disease, a more conservative FLR volume was suggested, which was up to 50% in cirrhotic patients (range 25–90%) [29] (Fig. 14.9). Underlying liver conditions including fibrosis, cirrhosis, steatosis, old liver, and

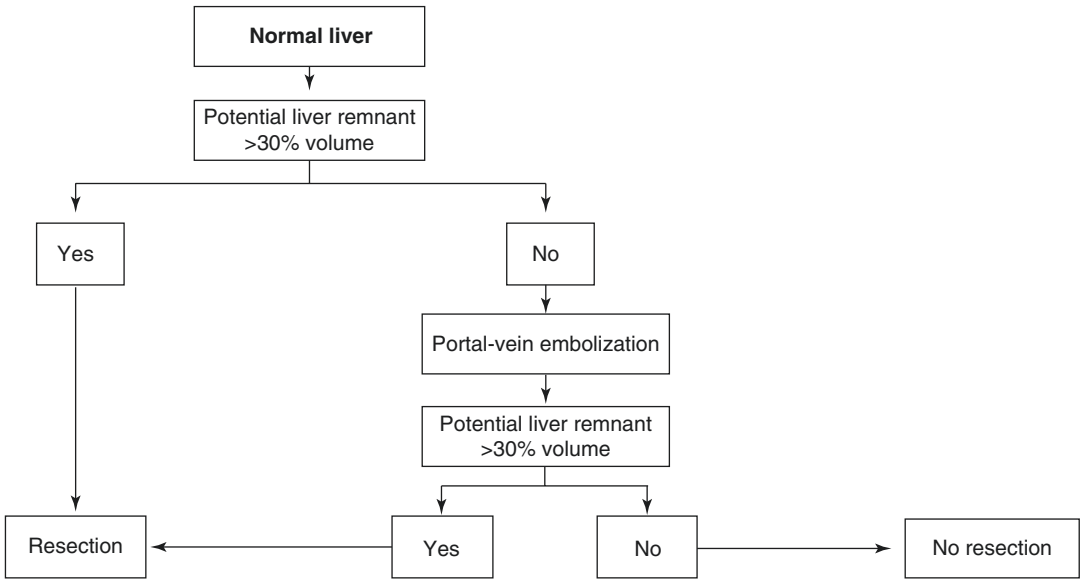

Fig. 14.8 Proposed algorithm for patients with normal liver parenchyma to undergo resection +/− portal-vein embolization

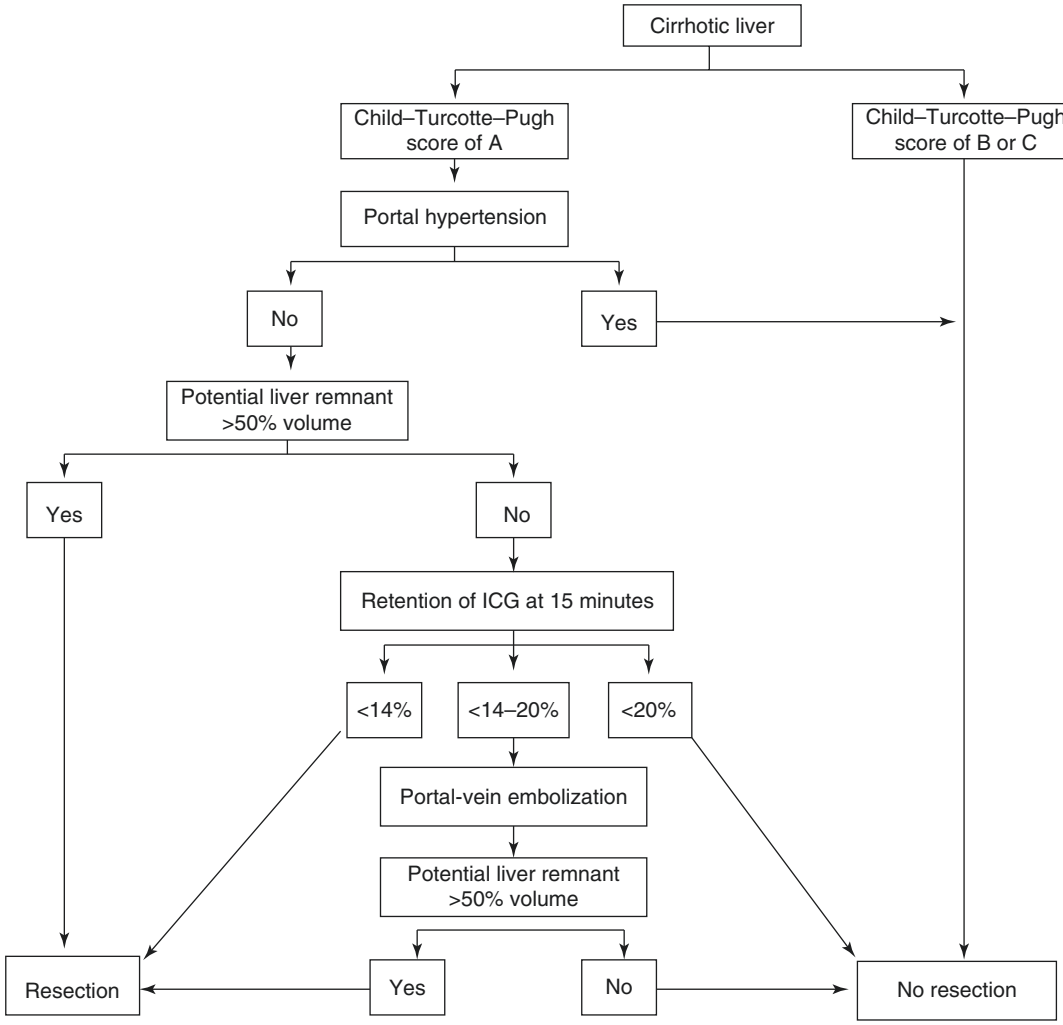

Fig. 14.9 Proposed algorithm for patients with diseased liver parenchyma to undergo resection +/− Portal-vein embolization

chemotherapy-associated liver disease are associated with impaired liver regeneration, and are risk factors for the development of the "small-for-size syndrome" (SFSS). In particular, intense chemotherapy in CLM influences postoperative morbidity and mortality. Irinotecan and 5-fluorouracil are known to cause chemotherapy-associated steatohepatits (CASH), whereas oxaliplatin may cause sinusoidal obstruction syndrome [30]. However, in most of the cases, patients are treated with different combinations, resulting in a mixture of these distinct syndromes. To address the functional quality, dynamic tests such as the indocyanine green (ICG) or Limax tests are important tools to provide information on the functional capacity of the liver. Ideally, a test can visualize the hepatic function of different topographic areas, which is very helpful to determine whether a staged approach is appropriate or when to proceed to the second stage. Recently, ^{99m}Tc-mebrofenin hepatobiliary iminodiacetic acid (HIDA) scan was shown to be a useful tool in visualizing regional functional differences in bile excretion as a measure of hepatic functional capacity [31].

The Three Elements of Two-Stage Hepatectomy

The rapid evolution of staged hepatectomies could be only achieved due to the concurrent development of an effective chemotherapeutic regimen and the advances in interventional radiological

procedures. In this setting of a multidisciplinary approach, the input of surgeons, hepatologists, oncologists, and interventional radiologists is absolutely essential. The concept of two-stage hepatectomy for CLM relies on three elements: portal vein occlusion, chemotherapy, and surgery, which are discussed in this section.

Portal Vein Occlusion (PVO)

The use of PVO, either PVE or PVL, to trigger hypertrophy of the contralateral liver is probably the most successful used concept in manipulating the liver volume. PVE is indicated in cases when the potential FLR is below the threshold of the minimal acceptable volume. Nowadays, PVE is mostly done by the percutaneous route using embolic materials including particles, coils, fibrin glue, gelatin sponge, or cyanoacrylate with ethiodized oil. Most surgeons consider a pre-operative waiting time of 4–6 weeks as enough to achieve adequate liver hypertrophy. After right PVE, a FLR volume increase of 30–80% can be expected within 4 weeks [32] (Fig. 14.10). Repeat imaging by CT or MR is usually performed at that time to assess the actual volume gain, and might be repeated if hypertrophy is not enough. In addition, PVE can be considered as a pre-operative stress test that assesses the capacity to regenerate [33]. Therefore, patients with failure of hypertrophy might not be eligible for a second stage. This becomes particularly important when the quality of liver parenchyma is impaired. Almost all candidates scheduled for two-stage hepatectomy have already received chemotherapy, which has potentially harming effects on liver parenchyma. The choice whether PVE or PVL is used depends on the presence of metastases in the FLR. In the scenario of bilobar CLM, PVL with simultaneous metastasectomies of the FLR is the preferred strategy of the first stage [14] (Fig. 14.3). The removal of all visible lesions in the FLR is necessary before exposing the liver to the desired

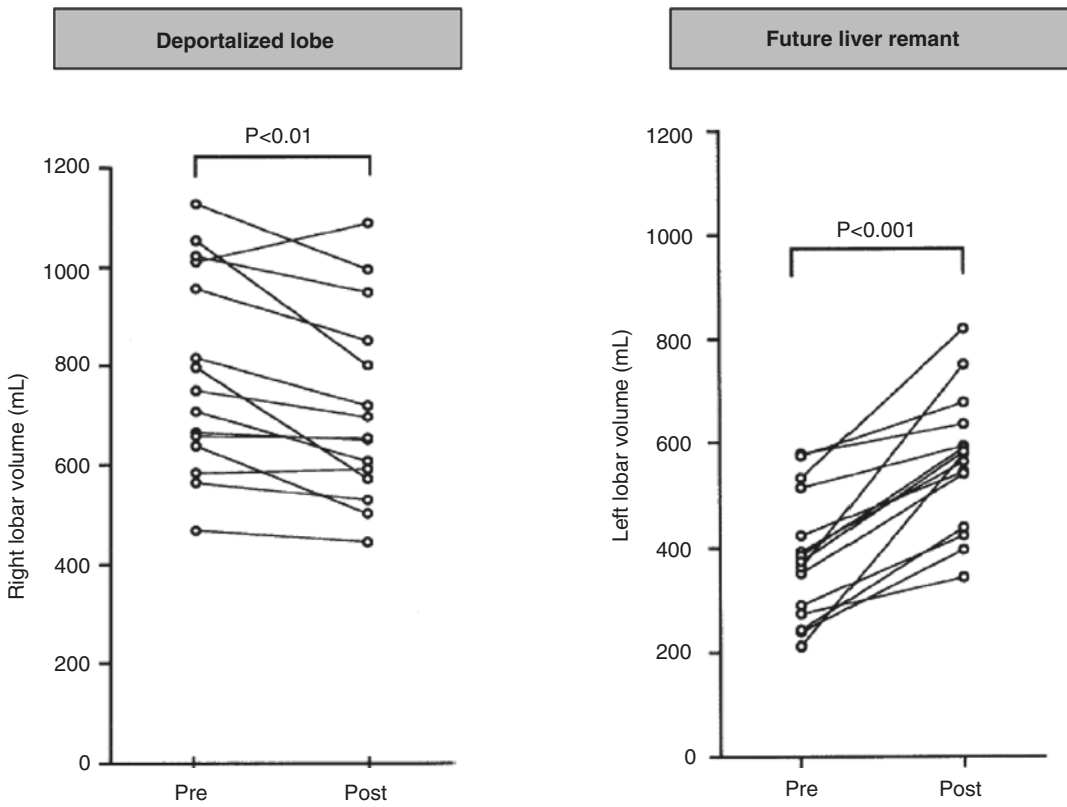

Fig. 14.10 Right Portal vein embolization: volumetric changes in 15 patients within 2–3 weeks before undergoing right trisectionectomy

regenerative stimulus induced by PVL. If cleaning of the FLR is not performed, it is very likely that tumor progression in the FLR will occur, as was shown in experimental models [17].

Chemotherapy (Systemic, Intra-arterial)

During the last decade, substantial progress has been made in shifting chemotherapy for CLM from a palliative to a potential curative setting in combination with staged liver surgery. Perioperative *systemic chemotherapy* is a crucial component of major [34] and staged liver surgery [9] which significantly improves disease-free and overall survival. Even patients with initially unresectable disease are now able to undergo effective downsizing chemotherapy with subsequent rescue surgery, offering them a chance of cure. Systemic chemotherapy has made significant advances during the past decades, starting with a purely 5-fluoruracil (5-FU) regimen to much more effective combinations such as FOLFOX (folinic acid, fluorouracil and oxaliplatin), FOLFIRI (folinic acid, fluorouracil and irinotecan) and FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin and irinotecan). In addition, specific "biological" therapy targeting vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptor (cetuximab and panitumumab) have been successfully introduced into clinical practice. In the past, chemotherapy has been discontinued before PVO to avoid any compromise of liver hypertrophy. However, it seems to become increasingly important to maintain systemic chemotherapy as "bridging chemotherapy" before the second stage to better control systemic disease. Clinical data suggest that chemotherapy neither impairs hypertrophy of the FLR after PVO nor increases postoperative morbidity [35].

Apart from systemic chemotherapy, *intra-arterial chemotherapy* (hepatic arterial infusion—HAI) was introduced to downsize extensive hepatic tumor load [36]. The rationale for the use of local chemotherapy via the hepatic artery is based on the fact that hepatic tumors are almost exclusively supplied by arterial branches [37]. Fluorouracil and floxuridine (FUDR) (the active metabolite of 5-FU) are continuously infused via implantable infusion pumps, resulting in a high drug concentration in liver metastases [38]. FUDR displays a high first-pass effect of around 95% resulting in low systemic toxicity. This pharmacokinetic profile makes the drug very useful for local tumor treatment. It has been demonstrated that the use of HAI increases the response rates of CLM [39] and leads to a higher resection rate of initially unresectable CLM compared to systemic chemotherapy [40]. Despite the improved hepatic progression-free survival after HAI treatment, extrahepatic progression-free survival is not improved in patients with unresectable CLM [41]. Therefore, HAI is a valuable therapy of downsizing CLM in unresectable situations, but needs to be supplemented with systemic chemotherapy to control systemic disease.

Surgery

Staged, margin-negative resection of extensive, bilobar CLM is the goal which can only be safely achieved in combination with strategically well-planned PVO and chemotherapy [14]. Typically, the first stage consists of PVO along with concomitant non-anatomic wedge resections of the FLR. The goal of this "cleaning" is the removal of small, isolated peripheral tumors in the FLR to prevent a potential accelerated tumor progression induced by PVO. For this reason, cleaning of the FLR is performed along with PVL in the majority of cases; however, PVE following a few days after FLR cleaning provides another option. After a waiting interval of 4–6 weeks, FLR size should have grown sufficiently to enable extended resection in a second stage with negative margins. Ideal candidates for this approach are patients with extensive tumor load in the right liver and segment 4, and single lesions in the left-lateral liver (segments II and III). In this situation, cleaning of segments II and III is performed with PVO of the right lobe (Fig. 14.5). After hypertrophy of the left lobe a right trisectionectomy can be performed with sufficient FLR size (Fig. 14.6).

How Far Can We Go? Failing Liver Regeneration and Small-for-Size Syndrome

The success of extended hepatic surgery primarily relies on an effective regeneration process of the FLR. The FLR size is important in predicting proper liver regeneration after major hepatectomy and is, therefore, the limiting factor of resectability in most cases. As mentioned before, there is a critical threshold where the FLR is unlikely to regenerate. Accepted figures are 25% for normal liver parenchyma and 40–50% for diseased liver. Quantifying functional capacity, a retention of ICG at 15 min (R15) should be less than 14% for safe resection [14]. Between 14 and 20%, a PVL should be attempted and patients with an R15 >20% should not undergo resection [14] (Fig. 14.9). In HIDA scan, a cutoff FLR uptake value of 2.69%/min/m^2 (^{99m}Tc-mebrofenin) has been proposed to identify patients with a significant risk for developing postoperative liver failure [31] (Fig. 14.11).

Proceeding with resection below these volumetric and functional thresholds can cause encephalopathy, coagulopathy, prolonged hyperbilirubinemia, and finally early postoperative death. This syndrome, mostly referred as "small-for-size syndrome" (SFSS) was adopted from liver transplantation. In liver transplantation,

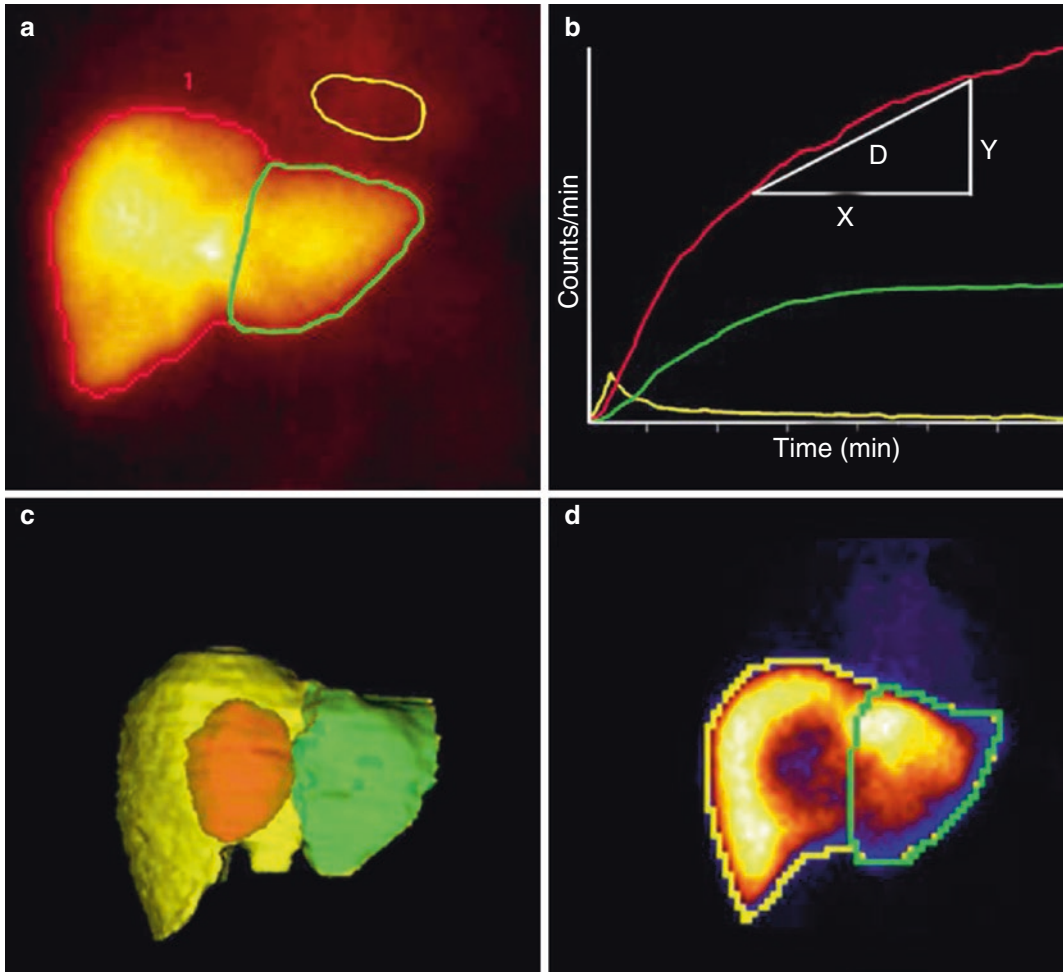

Fig. 14.11 HIDA scan 150-300 seconds after i.v. injection of ^{99m}Tc-mebrofenin (**a**) reveiling a blood pool corrected liver-uptake time-activity curve (**b**) of the whole liver and the FLR (*green*). Three-dimensional reconstructed CT images (**c**) are used to guide identification of the FLR on HIDA scan (**d**)

SFSS has been proposed to be defined as total serum bilirubin >100 µmol/l, INR > 2, and encephalopathy grade 3 or 4 with two of these features met on 3 consecutive days in the first postoperative week excluding technical, immunological, or infectious causes [42]. A simple approach to defining liver failure after extensive resection, named the "50–50 criteria" was proposed by Balzan et al. [43]. In this study, a prothrombin time <50% and serum bilirubin >50 µmol/l on postoperative day 5 (the "50-50 criteria") were an accurate predictor of more than 50% mortality rate after hepatectomy. In 2011, the International Study Group of Liver Surgery (ISGLS) has proposed a similar, easily applicable definition of post-hepatectomy liver failure, suggesting serum INR and bilirubin levels above the normal cut-off on or after postoperative day 5 [44]. In addition, Grade A requires no change of the clinical management, Grade B deviates from routine management without requiring invasive treatment and Grade C requires invasive treatment.

Therapeutic approaches to overcome the SFSS focus on the one hand on mitigating liver damage, and on the other hand on improving proliferation. However, such approaches are the focus of ongoing basic research. Therefore, prevention of SFSS by accurately choosing the appropriate two-stage strategy is absolutely essential. Assessment of liver volume by three-dimensional CT or MR along with dynamic liver function tests (ICG, Limax, HIDA, etc.) are helpful tools in decreasing the risk of SFSS.

Outlook

Major advances have been achieved for patients with unresectable liver tumors since the introduction of PVE by Makuuchi. Over the last decade, the criteria for resectability of CLM have undergone a paradigm shift from what is removed (number of metastases, size of metastases, extrahepatic disease) to what remains (adequate FLR, potential R0 resection). The two-stage hepatectomy has become an established part of a multidisciplinary approach including PVO and chemotherapy to achieve complete tumor removal, which is the most important factor to improve long-term survival.

Only fundamental mechanistic understanding of liver regeneration can help to further extend hepatic resections. Clinically applicable strategies overriding hepatic regenerative defects are highly wanted. In future, an ex-vivo growth of a fully functional partial liver might further push the limits of resectability. A major step in this direction was already performed by Takebe creating fully functional human three-dimensional liver buds from induced pluripotent stem cells (iPSCs) in vitro, which successfully rescued drug-induced liver failure in a mouse model [45].

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