Chapter 9

Assessment and Optimization of the Future Liver Remnant

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Additional information is available at the end of the chapter

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Abstract

Safe liver resection is a vital element in the management of primary and secondary hepatic malignancies. The indications for resection have evolved Over time, and this has in part been due to the ability to improve the future liver remnant (FLR). This chapter reviews the current and future methods used for assessing the future liver remnant volume and function in order to minimize the risk of post-hepatectomy liver failure (PHLF). Current and evolving methods used in augmenting the future liver remnant are also considered. Since its introduction in the 1990s, portal venous embolization (PVE) has become the most widely used method of augmenting the FLR. The factors that affect hypertrophy following embolization as well as techniques used in portal venous embolization will be reviewed. Other methods of augmentation discussed include portal vein ligation (PVL) and the emerging method of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). The chapter also considers the various methods in the context of limiting tumour progression in the future liver remnant and attempts to integrate newer techniques such as ALPPS into current treatment algorithms.

Keywords: future liver remnant, volume, portal venous embolization, hypertrophy, liver function measurement, resectability

1. Introduction

Safe liver resection is a vital element in the curative management of primary and secondary hepatic malignancies. The ability to perform major liver resections relies on the capacity of the future liver remnant (FLR) to maintain normal liver function. The quality of the FLR may also be influenced by pre-existing liver disease and/or prior chemotherapy, thereby limiting the size of resection possible. Various methods have been utilized to assess the size and functionality of the

Characteristics	Historical indications	Current indications
Tumour number	<4 lesions	Any
Lobes involved	Unilobar	Bilobar or unilobar
Size of tumour	<5 cm	Any
Extrahepatic disease	None	Treatable extrahepatic disease
Functional Liver Remnant	Adequate	Adequate or amenable to augmentation
Lymph node involvement	No hepatic pedicle nodes	No coeliac node involvement
Synchronicity	Metachronous	Metachronous or synchronous
Venous involvement	No vena caval or hepatic venous involvement	Venous resection or reconstruction

Adapted from Sherman and Mahvi [2].

Table 1. Indications for surgical resection of liver metastases.

future liver remnant to avoid post-hepatectomy liver failure and, when major liver resections are being considered, techniques are available to increase the volume of the FLR.

The commonest indication worldwide for hepatic resection is to treat colorectal cancer metastatic to the liver, and overtime the criteria for surgical resectability of colorectal liver metastases has evolved (**Table 1**). Initially, surgically resectable colorectal liver metastases included low volume, unilobar disease of 1–3 metastases which could be resected with a 1 cm macroscopic margin and no evidence of extrahepatic disease [1]. More recently, the number or bilaterality of metastases is not in itself a contraindication provided they can be resected with a macroscopic margin with an adequate FLR [2], and increasingly the presence of localized extrahepatic disease [2] is not an absolute contraindication to resection. However, the response of metastases to chemotherapy has emerged as an important prognostic factor for disease-free survival [3], and consequently, most patients now receive neoadjuvant treatment prior to resection. These factors and a globally more aggressive policy of resection have increased the numbers of patients eligible for potentially curative therapy but placed new emphasis on the importance of accurate assessment of the volume and function of the FLR.

The aim of this chapter is to review currently available methods to assess the quality and volume of the FLR pre-operatively as well as summarizing the methods used to improve the FLR including pre-operative portal venous embolization (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).

2. Pre-operative assessment of liver function

Whether the indication for liver resection is a primary or secondary liver malignancy in order for surgery to be successful, the patient must be able to tolerate the physical and psychological challenges of surgery and the FLR must be able to sustain liver function. A thorough history and examination should identify presence and extent of comorbidities [4]. The assessment

should also include assessment of liver function tests, coagulation status, full blood count and platelet count, relevant tumour markers and cross-sectional radiology [4]. All radiology and clinical information should be reviewed in a multidisciplinary meeting and early input obtained from specialist services such as hepatology, interventional radiology and medical oncology.

2.1. Assessing liver function

2.1.1. Liver function tests

The assessment of liver function is complex and largely reliant on surrogate markers. Initial clinical assessment involves assessment for signs of overt liver disease such as jaundice, spider naevi and palmar erythema. An initial set of liver function tests including measurement of plasma bilirubin, transaminases, γ-glutamyl transferase and alkaline phosphatase as well as albumin and prothrombin time should be performed [5]. Two commonly used scoring systems have been developed using these parameters to assess liver function and associated surgical risk.

2.1.2. Scoring systems

The Child-Pugh (CP) and Model for End-Stage Liver Disease (MELD) scores are the most widely used stratification scores used in making decisions regarding surgery in cirrhotic patient (**Tables 2** and **3**).

Factor	1 point	2 points	3 points
Bilirubin (μmol/L)	<34	34–50	>50
Albumin (g/L)	>35	28–35	<28
INR	<1.7	1.7–2.2	>2.2
Ascites	None	Diuretic controlled	Refractory
Encephalopathy	None	Grade I-II (medication controlled)	Grade III-IV (refractory)

Class A = 5–6 points, Class B = 7–9 points, Class C = 10–15 points.
INR; international normalized ratio.
Modified from Hanje and Patel [10].

Table 2. Child-Pugh score.

MELD = 3.78 × ln[serum bilirubin (mg/dL)] + 11.2 × ln[INR] + 9.57 × ln[serum creatinine (mg/dL)] + 6.43
Predicts development post-operative liver failure post-hepatectomy for hepatocellular carcinoma where a score >11 is predictive of worse outcome. Maximum creatinine is 4.0 mg/dL. Patients dialysing twice within the last week are assigned the maximum creatinine.
Adapted from Hanje and Patel 2007 [10] and Cha 2012 [39].

Table 3. MELD score.

The CP score has been in clinical use for several decades and is based on the patient's albumin, bilirubin, coagulation studies, severity of ascites and encephalopathy [6]. Individuals are stratified to Child A, B and C, and these correspond to increasing risk of perioperative mortality as well as post-operative complications such as bleeding, infection, ascites, renal failure and hepatic failure [6] (**Figure 1**).

The MELD score originally used to predict mortality following transjugular intrahepatic portosystemic shunt (TIPS) has since been extrapolated to stratifying liver transplant patients as well predicting perioperative mortality [6] (**Figure 1**).

2.2. Dynamic tests of liver function

These tests are based on complete hepatic clearance or metabolism of a substrate following intravenous administration and include indocyanine green (ICG) clearance as well as nuclear medicine techniques.

2.2.1. Indocyanine green clearance

ICG is the most widely discussed pre-operative test to assess liver function. Historically, the test entails intravenous administration of ICG with multiple blood samples taken at 15-min intervals to determine plasma clearance but has become easier to perform with the availability of non-invasive bedside monitors [7]. ICG is a water soluble, inert tricarbocyanine with a hepatic extraction rate above 70%, and is almost completely excreted in its unchanged form by the liver [7].

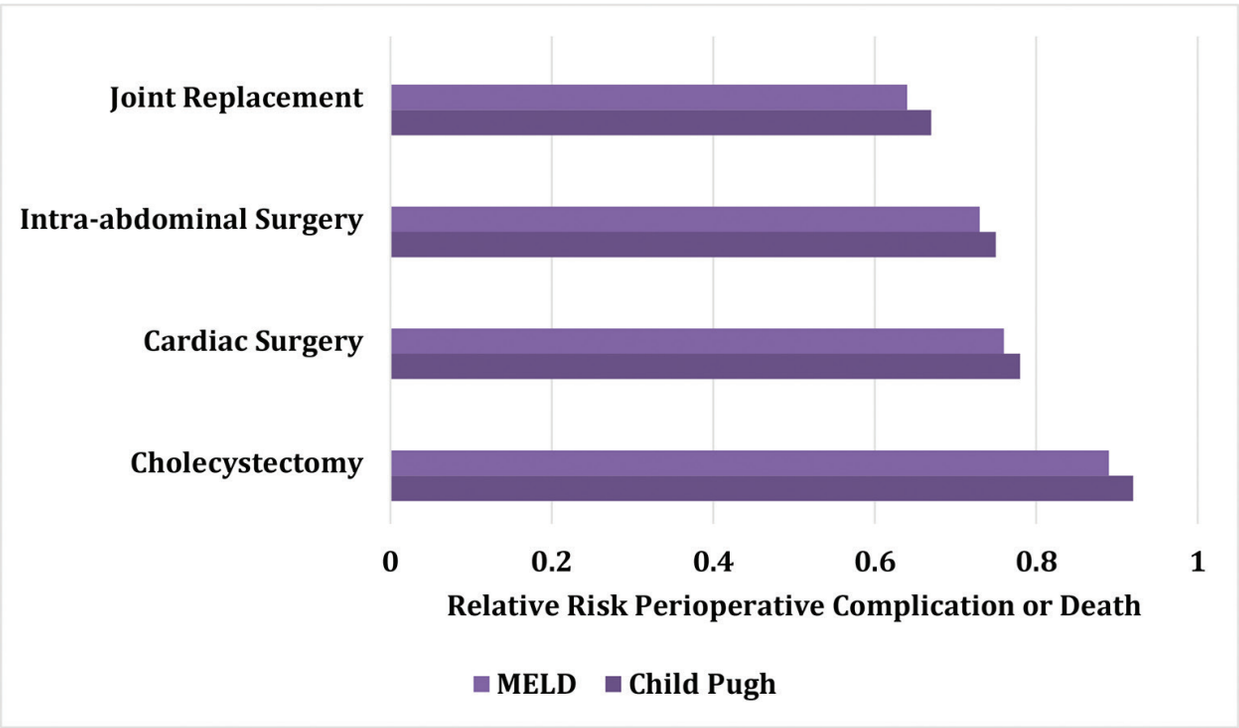

Figure 1. Relative risk of perioperative complication or death with increasing Child-Pugh and MELD scores. Adapted from Hanje and Patel [10].

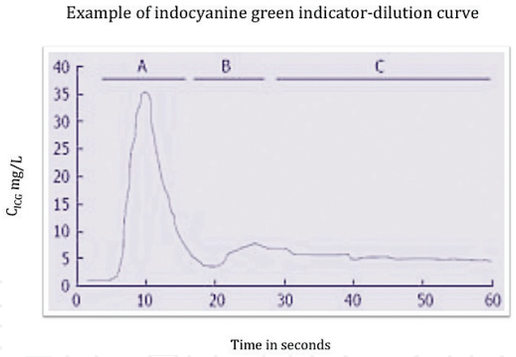

Figure 2. Indocyanine green plasma clearance curve obtained from serial blood sampling or optical pulse spectrophotometry. Retention at 15 min (arrow) is commonly used to assess liver function. Modified from Cha *et al*. [39].

Test results are most commonly expressed as percentage of ICG retained after 15 min (ICG-R15), and however, they can also be reported as the plasma disappearance rate (ICG PDR) or as the ICG elimination rate constant [8] (**Figure 2**). The safety limit when expressed as ICG-R15 varies from 14 to 20% [8].

The use of ICG is limited in the presence of hyperbilirubinaemia since uptake is by the same hepatic transporters [8] and will therefore artificially decrease ICG clearance. The test is also dependent on overall liver blood flow and is less reliable in those with non-flow-dependent liver diseases [8].

2.2.2. Nuclear Medicine

Scintigraphy has been used to provide quantitative information on total and regional liver function using a variety of radiolabelled probes.

2.2.2.1. ^{99m}Tc-Mebrofenin

Mebrofenin is the iminodiacetic acid (IDA) analogue with the highest specificity for hepatocytes [8, 9]. It is absorbed by hepatocytes and eliminated in the bile without biotransformation in a similar fashion to bilirubin [8, 9]. The rate of hepatocyte uptake of technicium-labelled mebrofenin can be quantitatively assessed using scintigraphy and rate of biliary excretion determined.

2.2.2.2. ^{99m}Tc-GSA

(99m)Tc-DTPA-galactosyl serum albumin (where DTPA is diethylenetriaminepentaacetic acid) binds to the asialoglycoprotein receptor found on the sinusoidal surface of the hepatocyte[8]. ^{99m}Tc-GSA is an asialoglycoprotein analogue that is taken up only in the liver [8]. The uptake of this agent is not affected by hyperbilirubinaemia and can therefore still be used for liver function assessment in the cholestatic patient [8]. Scintigraphy permits assessment of hepatic uptake as measure of function, and ^{99m}Tc-GSA remains trapped in the liver which permits further assessment of liver volume. However, this agent is not widely available outside of Japan.

2.2.3. ^{13}C-Methacetin Breath Test (LiMax)

The ^{13}C-methacetin breath test is based on activity of the cytochrome P450 1A2 (CYP1A2) enzyme system [8]. The system is distributed throughout the liver and is not affected by drugs or genetic variation [8]. ^{13}C-methacetin is exclusively metabolized by CYP1A2 into paracetamol and $^{13}CO_2$ [10]. The test is performed by measuring $^{13}CO_2/^{12}CO_2$ ratio in expired breath before and after administration of ^{13}C-methacetin. The result is expressed in μg/kg/h and gives total liver function. If combined with computed tomographic (CT) scan, it may be used to approximate the function of a section of liver, and however, this assumes uniform distribution of hepatic function, and it is known that this may vary between segments [8].

3. Radiological measurement of liver volume

Multiple cross-sectional imaging modalities are available for imaging the liver and include ultrasound, CT and magnetic resonance imaging (MRI). Data obtained with these investigations can be used to volumetrically assess the FLR as well as define the presence and position of hepatic tumours and the presence of chronic liver disease.

3.1. Ultrasound

Transabdominal ultrasound is widely available, non-invasive and low cost. However, it is operator independent, and its accuracy may be affected by body habitus, the presence of ileus or ascites as well as the presence of diffuse hepatic disease and steatosis which may be seen following chemotherapy [11].

In patients with colorectal liver metastases, the sensitivity of lesion-by-lesion analysis ranges from 60.9 to 64.9%. The specificity ranges from 50 to 60%, and the range increases from 76.7 to 83.3% with the use of contrast [11]. The increased sensitivity of contrast-enhanced US (80–90%) makes it useful in guiding the percutaneous biopsies of lesions [11].

Three-dimensional ultrasound probes are available, but the use of transabdominal ultrasound in hepatic volumetry assessment remains limited by the previously stated problems of body habitus and operator expertise [12]. Ultrasound is also routinely used intraoperatively where it may identify occult liver metastases denoting unresectable disease in up to 25% of patients [13] but currently has no role in assessing FLR volume.

3.2. Computed tomography (CT)

CT has become widely available and is relatively inexpensive. It offers the ability not only to detect lesions, but also to detect accurately localize lesions as well as their vascular and biliary relations [11]. It does involve exposure to ionizing radiation and the risk of allergic reactions to iodinated contrast [11]. The lesion-by-lesion sensitivity is up to 75% [11] although the rate of detection decreases with size of the lesion with a 16% detection rate for lesions smaller than 10mm in diameter [11]. The ability to construct three-dimensional (3D) models from the images allows for more accurate planning of surgical resection and appreciation of intrahepatic vascular anatomy prior to resection [14].

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CT scan is also commonly used to estimate the volume of the FLR by directly quantifying the volume from scan acquired data. The FLR volume is measured by CT and then standardized to the total estimated liver volume (TELV) [15].

$$\text{TELV}\ (\text{cm}^3) = -794.41 + 1267.28 \times \text{BSA}(\text{m}^2)$$

The ratio of the CT measured FLR volume to the TELV is known as the standardized FLR (sFLR) that allows a uniform comparison of FLR volume before and after PVE [15]. More commonly, total liver volume can be measured using data acquired in the CT scan, and comparison is made with the directly measured volume of the FLR (**Figure 3**).

3.3. Magnetic resonance imaging (MRI)

MRI is the most accurate of the available modalities in detecting colorectal metastases as well as many other malignancies. It does not make use of ionizing radiation and gadolinium-based extracellular agents or hepatocyte-specific contrast agents such as gadoxetic acid may be used as contrast [11]. Overall, the sensitivity of contrast-enhanced MRI is 94% for colorectal metastases[11] and is superior to CT scan in the detection of small lesions as well as lesions in steatotic livers [11]. MRI is not routinely used clinically to assess hepatic volumetry.

3.4. PET CT

Fluorodeoxyglucose positron emission tomography (^{18}FDG PET) provides metabolic information which when combined with CT provides a metabolic map of glucose uptake [16] that is highly specific for cancer. PET CT is less sensitive in the detection of hepatic lesions than CT or MRI but is more specific and is able to accurately define the presence of extrahepatic disease [16]. PET CT is not currently used to assess hepatic volumetry.

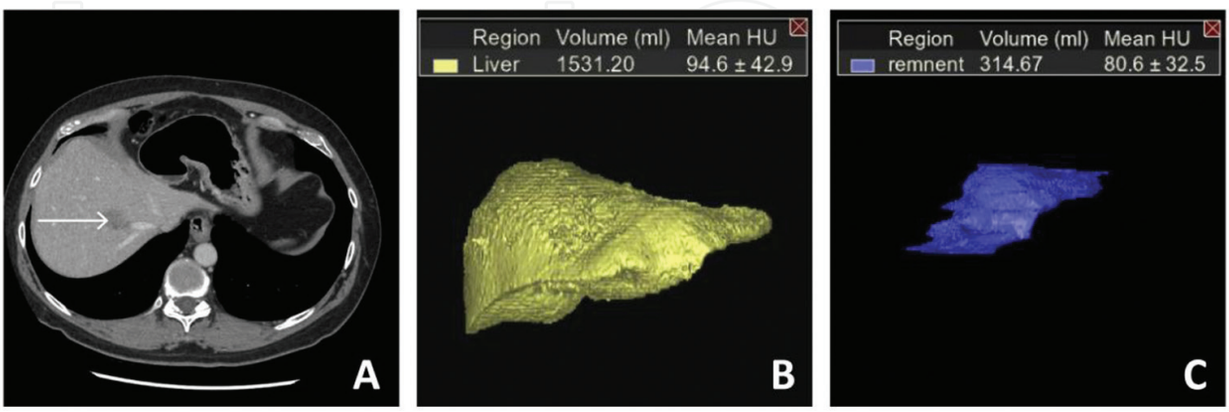

Figure 3. A: Axial CT scan showing solitary colorectal metastasis in segment 8 (arrow) with a congenitally small left lobe. B: Three-dimensional reconstruction and total liver volume (1531.20 ml) measured 6 weeks following right portal vein embolization. C: Three-dimensional reconstruction and total remnant volume (314.67 ml) measured 6 weeks following right portal vein embolization. The left-sided remnant now constitutes 20.5% of the total liver volume and the patient proceeded to right hepatic lobectomy.

4. Combined imaging and dynamic tests

As previously described, available imaging and liver function tests have a number of shortcomings with regard to estimation of function of the future liver remnant. This is important since hepatic volume and hepatic function do not have a linear correlation. A number of groups have attempted to improve predictability of FLR volume and function by combining modalities (**Table 4**).

Group	Modalities	Outcome
Chapelle *et al*. [25]	^{99m}Tc-mebrofenin/FLRV	Predicts future liver function after resection (eFLRF). Cut-off of 2.3%/min/m^2 for eFLRF would have prevented all mortalities related to PHLF
Hwang *et al*. [40]	FRL-kICG (derived ICG and CT volumetry)	Appeared to predict PHLF risk quantitatively
De Graaf *et al*. [41]	^{99m}Tc-mebrofenin/SPECT	No difference between actual FLR and predicted FLR

PHLF, post-hepatectomy liver failure. FRL-kICG is the ICG clearance rate constant (ICG-K) fraction of future remnant liver to total liver volume.

Table 4. Examples of combined modalities in FLR estimation.

5. Definition of an adequate future liver remnant

With regard to the future liver remnant, an FLR ≤20% of total hepatic volume is the strongest predictor of hepatic insufficiency and is thus set as the minimum FLR volume for a healthy non-cirrhotic liver [17]. It has generally been regarded that those who have received chemotherapy for longer than 12 weeks should have an FLR >30% of total hepatic volume and those with fibrosis or cirrhosis an FLR >40–50% of total hepatic volume [17]. However, it must be emphasized that patients with cirrhotic livers, even where FLR is adequate, remain at increased risk of wound breakdown, infection, ascites and fluid retention, as they would be for any major surgery.

The increased FLR requirement for patients who have received chemotherapy is based on the premise that pre-operative chemotherapy may cause liver damage or increase the risk of post-operative complications [18]. Treatment with irinotecan is associated with rates of steatohepatitis as high as 20.2% compared to 4.4% in those not on chemotherapy [19]. Treatment with oxaliplatin is associated with hepatic sinusoidal injury that can result in venoocclusive disease and nodular regenerative hyperplasia [19]. There is greater morbidity following hepatectomy in those with evidence of sinusoidal obstruction syndrome and a greater risk of perioperative blood transfusion [19].

However, the majority of investigations have shown (**Table 5**) that liver injury in the setting of neoadjuvant therapy does not appear to have significant clinical consequences if chemotherapy is maintained until a response is observed and disease is then resected as early as is feasible [20].

Author	Intervention	No.	Comparison	FLR effect
Goéré *et al*. [42]	PVE	20	≥1 -month interval vs no interval	None
Ribero *et al*. [43]	PVE	112	Chemo vs no chemo	None
Gruenberger *et al*. [44]	Hepatectomy	52		None
Covey *et al*. [45]	PVE	100	Chemo vs no chemo	None
Aussilhou *et al*. [46]	PVE	40	Chemo+bevacizumab/chemo without bevacizumab	Impaired FLR/none
Tanaka *et al*. [47]	PVE/Hepatectomy	60	Chemo vs no chemo	None
Sturesson *et al*. [48]	PVE	26	Chemo vs no chemo	Impaired FLR
Sturesson *et al*. [49]	Hepatectomy	74	Chemo vs no chemo	Impaired FLR
Beal *et al*. [50]	Hepatectomy	72	Chemo vs no chemo >6 cycles vs ≤6 cycles	None
Dello *et al*. [51]	Hepatectomy	72	Chemo vs no chemo >6 cycles vs ≤6 cycles	None
Fischer *et al*. [52]	PVE	64	Chemo vs no chemo	None

PVE, portal vein embolization; FLR, future liver remnant.
Adapted from Simoneau *et al*. [27].

Table 5. Effect of chemotherapy on liver hypertrophy.

6. Augmentation of the future liver remnant

With advances in surgical technique and radiological imaging, more extensive liver resections have become feasible and the challenge remains the ability to maintain liver function post-operatively. Methods have been developed aiming to increase the size of the future liver remnant. These include portal venous embolization, portal vein ligation (PVL) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Augmentation is recommended where FLR is anticipated to be ≤20% for normal, ≤30% for those with chemotherapy associated steatohepatitis and ≤40–50% in those with cirrhosis [21].

6.1. Portal venous embolization

Portal venous embolization was developed to improve the size and function of the FLR in tumour bearing liver by occluding the ipsilateral portal vein, the non-tumour bearing contralateral side, which is to be the FLR, increases in volume by a combination of hypertrophy and hyperplasia [22]. The capacity for regeneration in the otherwise healthy liver is significant, and PVE results in increased FLR volume in roughly 60% of patients with the average increase in volume being 12% [17]. The response is variable, and the size of the FLR prior to PVE may predict the degree of hypertrophy [23]. There is evidence to suggest that the degree of hypertrophy is inversely proportional to the FLR ratio before PVE such that a smaller FLR will have a larger hypertrophy [24]. PVE is contraindicated in the presence of ipsilateral portal vein tumour thrombus or occlusion and in patients with severe portal hypertension [22].

PVE may be performed under general anaesthesia or local anaesthesia with sedation, and the approach may be contralateral or ipsilateral [24]. The procedure is commonly used to occlude the right portal vein and induce left lobe hypertrophy. In the contralateral approach, the left portal vein is punctured to give access for embolization of the right portal vein [24]. The contralateral approach is less technically demanding, and however, it does risk potential injury to the FLR [24]. Where extended right hepatectomy is considered, embolization of portal vein branches to segment IVa and IVb can be undertaken. A short segment (1 cm) of unembolized right portal vein may be left to allow for surgical ligation during resection [25].

Various agents have been used for embolization, and most are associated with adequate hypertrophy rates and acceptable complication profiles (**Table 6**).

The degree of FLR hypertrophy is also influenced by the health of the underlying liver. Non-cirrhotic liver hypertrophies at a rate of about 12–21 cm^3/day at 2 weeks compared to just 9 cm^3/day for a cirrhotic liver [22] and the growth rate can be used to predict the probability of liver failure and major complications [23] (**Figure 4**).

Embolic agent	Authors	No. of patients	Increase FRL %
Gelatin sponge	Fuji *et al*. [53]	30	17.8
	Kusaka *et al*. [54]	18	21.2
	Kazikawa *et al*. [55]	14	23.8
	Nanashima *et al*. [56]	30	29.4
Polyvinyl alcohol + coils or plugs	Covey *et al*. [44]	100	24.3
	Van den Esschert *et al*. [57]	10	26.1
	Libicher *et al*. [58]	10	26.4
N-butyl cyanoacrylate	De Baere *et al*. [59]	107	57.8
	Giraudo *et al*. [60]	146	41.7
	Elias *et al*. [61]	68	59.1
	Broering *et al*. [62]	17	69.4
Fibrin glue	Nagino *et al*. [63]	105	27.4
	Liem *et al*. [64]	15	31.4

Modified from Loffroy *et al*. [24].

Table 6. Hypertrophic response to embolic agents.

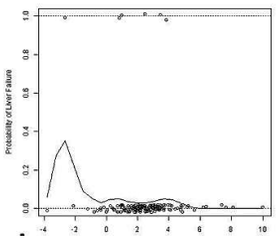

Figure 4. Nonparametric regression of measured future liver remnant growth rate to predict probability of liver failure. Minimal or negative remnant growth rate following portal vein embolization was associated with higher rates of post-resection liver failure. Reproduced from Leung *et al*. [23] with permission.

While PVE is used for its effect on the contralateral lobe of liver, it has also been associated with tumour progression. Liver growth is regulated by a number of growth factors and cytokines the up-regulation of which is known to be involved in multiple tumour pathways [26]. Other factors thought to contribute to tumour progression are the compensatory increased inflow via the hepatic artery and the cellular host response [26]. There are currently no specific therapies available aimed at limiting the effects of these growth factors and cytokines on tumour progression. However, two-stage hepatectomy or ablation can be used where disease in the FLR is resected or ablated prior to PVE or PVL [14].

The timing of definitive resectional surgery following PVE is not formally prescribed, and however, most investigations report repeating imaging (usually CT scan) at 4–6 weeks following PVE and, if sufficient FLR volume has been achieved, undertaking resection soon afterward. Simoneau *et al*. demonstrated an increase of 1-day post-PVE increased the risk of tumour progression by 1% [27]. It has been suggested that earlier surgery such as 2 weeks after PVE may reduce the risk of tumour progression [26].

6.2. Portal vein ligation

PVL is undertaken operatively and often in the setting of staged hepatectomies where small tumours in the FLR are removed or ablated and open ligation of the right portal vein is performed. Pandanaboyana *et al*. in their meta-analysis found that PVE and PVL had a mean percentage increase in FLR volume of 39% and 27%, respectively; however, this did not reach statistical significance [28]. They proposed that this may be explained the observation that the later formation of portoportal collaterals does not impact on liver hypertrophy as this is induced early after portal occlusion [28].

6.3. Associated liver partition and portal vein ligation

ALPPS was first performed in 2007 and was noted to result in significant hepatic hypertrophy with increased resectability in those with large tumours [29]. The procedure was performed during an exploration for hilar cholangiocarcinoma. A left hepaticojejunostomy was performed to reduce cholestasis to the FLR, the liver was divided along the falciform ligament, and the right portal vein was ligated [29]. A CT scan performed 8 days later demonstrated a 94% increase in FLR, and the resection was successfully completed the following day [29].

The classical ALPPS procedure for a large right-sided tumours involves right portal vein ligation, ligation and division of the segment IV portal branches as well as transection of the liver parenchyma along the falciform ligament [29]. Any tumour deposits within the future liver remnant can also be resected or ablated at this time.

Associating liver tourniquet and portal ligation for staged hepatectomy (ALTPS) is a variation in which rather than dividing the liver parenchyma and ligating the portal vein, the effect of occluding portal flow and transection is achieved by use of tourniquet [29] and radiofrequency or microwave ablation may also be combined with portal vein ligation [29]. In an attempt to reduce surgical complications following the initial surgical procedure, a partial ALPPS in which parenchymal transection is not complete has also been described [29].

The advantage ALPPS over two-stage hepatectomy is that it may improve the feasibility of resecting previously unresectable tumours owing to the very high FLR gains seen. The short time between the procedures makes tumour progression unlikely [30].

In 2012, the International ALPPS registry was formed to systematically collect data from multiple centres performing the procedure, and the first analysis was published in 2014 [31]. This analysis which included 202 patients, 70% of whom had an underlying diagnosis colorectal liver metastases, and reported a 90-day mortality of 9% [31] (**Table 7**). Independent risk factors for in hospital severe complications included patient age >60 years, tumours other than colorectal liver metastases as well as 2 markers of complex liver resection (stage 1 ALPPS procedure >5 h and/or the need for intraoperative blood transfusions) [31].

The data in **Table 7** confirm that ALPPS is a physiologically demanding procedure, and there is a paucity of data concerning long-term outcomes. Buac *et al*. [32] recently conducted a survey of 66% of the surgeons contributing to the International ALPPS registry and noted that there was significant variability in the indications for surgery as well as how it is performed. Currently, PVE is widely used while ALPPS is still under investigation. Schadde *et al*. [31] published a head to head comparison of the two procedures (**Table 8**).

6.4. Assessment of liver remnant volume using ICG clearance intraoperatively during vascular exclusion (ALIIVE)

This is a newly reported intraoperative procedure, which may have the advantage of some planned ALPPS procedures occurring as a single-step hepatectomy as well as identifying the need for an ALPPS procedure where one had not been planned [33]. The technique involves non-invasive measurement of ICG PDR at 5 points during resectional surgery. Measurement occurs before anaesthetic induction (ICG 1), following mobilization of FLR (ICG 2), during inflow occlusion of the resection lobe (ICG 3), following parenchymal transection with inflow occlusion (ICG 4) and finally during inflow as well as outflow occlusion following parenchymal transection (ICG 5/ALIIVE) [33].

The aim of this test is to replicate the post-resection state intraoperatively. Lau *et al*. published their initial experience and while their series was too small to deduce an ICG PDR cut-off level, they suggested that as the post-hepatectomy state was replicated, it was likely that previously demonstrated cut-off levels could be applied to the procedure [33]. Previous studies have suggested a PDR >9%/min would likely be safe, while a PDR <7%/min would confer a high risk of insufficiency [33]. Interestingly, the only mortality of the 10 patients had an ALIIVE ICG of 7.1%/min [33].

This procedure will require further validation studies, but could certainly spare some patients a second procedure or allow others the opportunity of an ALPPS procedure if not already planned pre-operatively.

6.5. Transarterial embolization (TAE)

Transarterial chemoembolization (TACE) is based on the concept that blood supply to tumour is generally derived from the hepatic artery [34]. Following portal venous embolization, the

Author	Number of patients	Simultaneous colorectal resection	FLR hypertrophy %	Mean LOS	Morbidity%	Mortality %	Follow-up days	DFS %	OS%
Schnitzbauer *et al*. [65]	25	0	74	nr	68	12	60-776	80	86
Alvarez *et al*. [66]	15	3	78.4	19	53	0	18–410	73	100
Li *et al*. [67]	9	nr	87.2	nr	100	22	nr	nr	nr
Dokmak and Belghiti [68]	8	nr	70	42	90	nr	nr	nr	nr
Machado *et al*. [69]	8	nr	88	nr	nr	0	nr	nr	nr
Donati *et al*. [70]	8	nr	66–200	nr	nr	nr	nr	nr	nr
Adriani *et al*. [71]	2	nr	nr	nr	nr	0	912–1460	0	100
Govil [72]	1	nr	nr	nr	nr	nr	nr	nr	nr
Oldhafer *et al*. [73]	1	0	nr	nr	nr	0	nr	nr	nr
Conrad *et al*. [74]	1	nr	45	nr	0	0	nr	nr	nr
Cavaness *et al*. [75]	1	0	100	13	nr	0	nr	nr	nr

Adapted from Alvarez *et al*. [76].
Nr, not reported; DFS, disease-free survival; OS, overall survival.

Table 7. Overview of hypertrophy, mortality and morbidity following ALPPS for various studies.

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Reason for failure	PVE/PVL (n = 83)	ALPPS (n = 48)
Perioperative death (90 days) %	6%	15%
No stage 2 due to tumour progression %	16%	0%
No stage 2 due to failure to grow%	7%	0%
R1 resection %	5%	2%
Failure to reach primary endpoint %	34%	17%

Table 8. Mortality and outcomes of ALPPS v PVE/PVL. Modified from Schadde *et al*. 2014 [31].

hepatic arterial flow is increased and this is thought to preserve viability of the embolized lobe [35]. However, there may still not be adequate hypertrophy of the FLR, and it has been suggested that further interruption of the vascular inflow (arterial occlusion) may result in further hypertrophy [35]. However, the near complete occlusion that occurs with PVE followed by TAE may induce parenchymal infarction, and this sequence currently has few applications [35].

Conversely, TAE followed by PVE has demonstrated safety in case of hepatocellular carcinoma with inadequate FLR [35]. Unfortunately, this has not been useful in management of colorectal metastases as these tumours are generally not fed by an artery [35].

6.6. Radioembolization

Selective internal radiation therapy (SIRT) with Y-90 has generally been used as treatment for locally advanced liver tumours. A transarterial catheter is introduced, and Y-90 microspheres are infused to lodge at the tumour arteriolar level. The radioactive microspheres result in reduced blood flow to the tumour but also deliver Y-90 brachytherapy [36]. The reported rates of response are 42–70% for colorectal liver metastases [36] and, in addition to the local control of tumour, unilateral treatment has been noted to result in hypertrophy of the contralateral liver lobe [37]. The theoretical advantage of SIRT over PVE would then be that tumour progression might not continue unabated while awaiting hypertrophy of the FLR if SIRT were selectively administered. Teo *et al*. [36] in a systematic review found that, while the degree of hypertrophy from SIRT was comparable to that of PVE (26–47% vs 10–46%), the time interval over which growth occurred was much slower than that of PVE (44 days to 9 months vs 2–8 weeks) making it less likely to be clinically useful.

6.7. Associating portal embolization and artery ligation (APEAL)

This procedure combines portal vein embolization and arterial ligation [38]. At the first stage of the procedure, the FLR is surgically mobilized as in the ALPPS procedure. The right portal vein is embolized before being ligated and divided [38]. A right sectoral hepatic artery ligation is performed (either the artery for segments V/VIII or segments VI/VII), and the segment IVb inflow is also interrupted [38]. There is no parenchymal transection. The second, resection stage of the procedure is undertaken 1–2 months later.

Dupre *et al*. [38] published their series of 10 patients who had required two-stage extended right hemihepatectomy for bilobar colorectal metastases. All the patients included had a low FLR volume and/or prolonged pre-operative chemotherapy and the procedure resulted in

FLR hypertrophy of over 100% at day 7 [38]. There were no complications related to hepatic necrosis, and the authors suggest that the avoidance of parenchymal dissection reduces the risk of bile leak and infection. The interval of 1–2 months between stages was chosen to allow for post-operative recovery and to identify those with rapidly progressive disease. Initial results suggest morbidity and mortality rates comparable to ALPPS and PVE, and however, more long-term results and further validation studies are required [38].

7. Conclusion

The indications for liver resection continue to evolve as do the improvements in radiological ability to assess disease extent and accurately measure FLR volume. This information enables surgical teams to precisely calculate perioperative risk and determine resectability—almost to the millimetre. There is an evolving use biochemical markers which, when combined with imaging, may improve the safety of surgery further by allowing not only for estimating the volume but also the function of the future liver remnant.

The development of surgical techniques such as ALPPS, ALIIVE as well as adjuncts to surgery such as PVE/PVL and perhaps SIRT are increasing the number of patients who can be considered to have resectable disease. This would not be possible in the absence of oncological advancements as well as improvement in perioperative care. As our imaging and functional assessment technology improves, current management algorithms will also evolve (**Figure 5**).

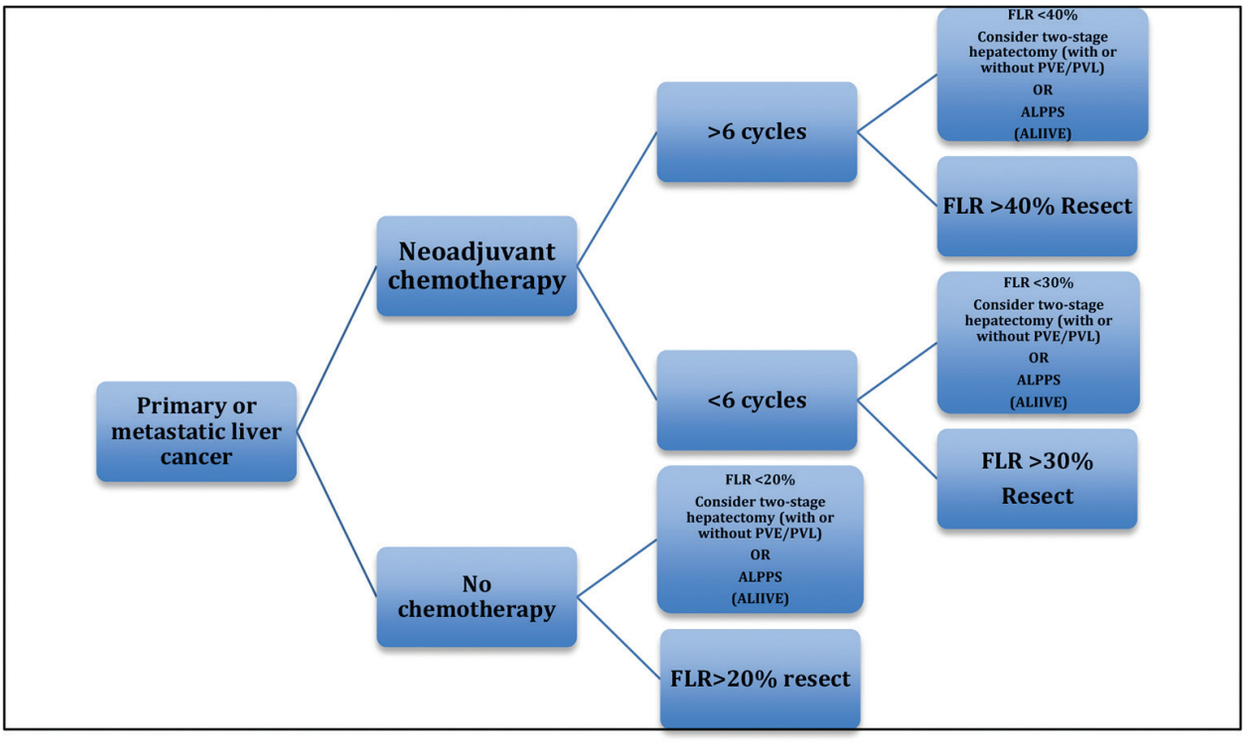

Figure 5. Example of future algorithm. ALIIVE technique could be utilized at the time of first stage hepatectomy or ALPPS to determine whether resection can be completed at first stage.

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