New frontiers in liver resection for hepatocellular carcinoma

Manon Allaire, Claire Goumard, Chetana Lim, Aline Le Cleach, Mathilde Wagner, Olivier Scatton

Summary
Liver resection is one of the main curative options for early hepatocellular carcinoma (HCC) in patients with cirrhosis and is the treatment of choice in non-cirrhotic patients. However, careful patient selection is required to balance the risk of postoperative liver failure and the potential benefit on long-term outcomes. In the last decades, improved surgical techniques and perioperative management, as well as better patient selection, have enabled the indications for liver resection to be expanded. In this review, we aim to describe the main indications for liver resection in the management of HCC, its role compared to percutaneous ablation and liver transplantation in the therapeutic algorithm, as well as the recent advances in liver surgery that could be used to improve the prognosis of patients with HCC.

Introduction
Liver cancer is the fifth most common cancer globally and the fourth most common cause of cancer-related death. Hepatocellular carcinoma (HCC) accounts for about 90% of liver cancers and is associated with a 5-year overall survival (OS) of 10–15%, mostly due to late diagnosis. However, 5-year OS reaches 50–70% when patients are diagnosed at an early stage and can access curative treatments such as liver resection (LR), liver transplantation (LT) and ablation. Recent studies have shown encouraging results when LR is extended to more advanced stages, which supports the need to redefine the frontiers of surgical resection and its place in the therapeutic algorithm.

In this review, we will first summarise the current indications for LR in HCC management and then describe the innovations in LR that could overcome the current challenges.

Current indications for liver resection
HCC in non-cirrhotic liver
LR is currently the treatment of choice for non-cirrhotic patients. The absence of cirrhosis allows for larger and more complex resections, and is associated with acceptable postoperative mortality and morbidity rates of less than 4% and 33%, respectively, after major hepatic resection, with a 5-year OS reaching 50%. However, these results may vary according to the presence of comorbidities and the existence of an underlying liver disease. Therefore, an accurate evaluation of the underlying liver parenchyma remains crucial at diagnosis and a preoperative liver biopsy enables the pathological assessment of inflammatory activity, the degree of liver fibrosis and the presence of steatosis. Indeed, the risk of perioperative complications increases with the presence of active hepatitis in patients with viral related chronic liver disease and with steatosis. As about one-third of cases of non-alcoholic fatty liver disease (NAFLD)-related HCC will develop in the absence of cirrhosis, and because these patients are at higher risk of postoperative complications, LR in this setting is a challenging issue. Steatosis, one of the major features of NAFLD, is associated with impaired liver regeneration, explaining in part the higher incidence of liver failure after LR in this population of patients. Moreover, the presence of metabolic syndrome is associated with a twofold higher rate of postoperative mortality and complications (sepsis, cardiovascular and pulmonary complications) after LR. Thus, the absence of extensive fibrosis does not put the patient at lower operative risk, as the association between steatosis and chronic inflammation also influences the tolerance for resection. Therefore, as the rate of patients with NAFLD and metabolic syndrome increases, it seems important to identify patients without cirrhosis who are at a higher risk of postoperative complications in order to refine the perioperative management of these patients.

HCC in cirrhotic liver
Initially, among patients with cirrhosis in Western countries, the best candidates were defined as those with a single tumour, bilirubin <1 mg/dl and without portal hypertension (defined by hepatic venous pressure gradient [HVPG] <10 mmHg or platelet count >100,000/µl). In this situation, OS
following LR was close to that observed after LT (5-year OS of 74% for LR and 69% for LT).18

The last decades saw an extension of tumour burden-related indications for LR. Currently, the EASL guidelines recommend LR in cases of a resectable solitary nodule without macrovascular invasion and extrahepatic spread regardless of its size, while the AASLD guidelines advocate LR in patients with Child-Pugh A cirrhosis and resectable T1 or T2 HCC (solitary tumour of less than 5 cm with or without vascular invasion or multifocal tumour of less than 5 cm). Meanwhile, according to APASL, all tumours without extrahepatic metastases are potentially resectable regardless of vascular invasion status, number and size of lesion(s).2–4 However, determining whether a patient is eligible for LR must consider not only tumour burden but also liver function, the extent of hepatectomy and the expected volume of the future liver remnant, as well as the presence of portal hypertension and comorbidities (Fig. 2).

Liver function is usually estimated by the Child-Pugh score and patients with Child-Pugh B or C are at a high risk of liver failure even after a minor hepatectomy. Recently, a preoperative model for end-stage liver disease (MELD) score higher than 9 was associated with a low OS after LR, leading to the incorporation of the MELD score into the EASL guidelines for treatment allocation.19

The extent of surgery and the volume of the future liver remnant can be estimated by calculating the volumes of the removed part, as well as the remnant part as a fraction of the total liver volume. These volumes are calculated using routine CT and MRI with semi-automatic software. It has been demonstrated that a remnant liver volume of approximately 25–30% of the total liver volume is required to achieve a successful outcome after LR. The presence of portal hypertension is not an absolute contraindication but must be balanced with liver function and the extent of the hepatectomy. MELD, model for end-stage liver disease.

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**Key points**

- Tumours developed on non-cirrhotic liver or small individual HCCs developed on a background of compensated cirrhosis (without portal hypertension) are the ideal targets for liver resection.
- Extending criteria for liver resection to include multifocal HCC, large HCC, presence of macrovascular invasion or portal hypertension should be balanced with morbidity, long-term outcomes and the availability of alternative treatments.
- The sequence of frontline liver resection followed by salvage liver transplantation after tumour recurrence could be proposed in some transplantable patients with HCC.
- Preoperative planning and management of a predicted insufficient liver remnant are essential to increase the rate of operability and decrease morbidity and mortality.
- Minimally invasive surgery is associated with lower morbidity and similar long-term oncological outcomes as open resection.

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**Fig. 1. Current indications for liver surgery according to EASL, AASLD and APASL guidelines.** Indications of treatment by liver surgery for hepatocellular carcinoma differ according to the guidelines. EASL guidelines recommend surgery in case of solitary lesion without vascular invasion, in well compensated patients with an MELD score <10. For AASLD guidelines, all potential resectable solitary tumours <5 cm, with or without vascular invasion, and multifocal <5 cm tumours should undergo surgery in the absence of impaired liver function. APASL guidelines enlarge the indication to all resectable tumours even those with vascular invasion and in patients with decompensated cirrhosis (Child-Pugh B). The presence of portal hypertension is not an absolute contraindication but must be balanced with liver function and the extent of the hepatectomy. MELD, model for end-stage liver disease.
the total liver volume in patients without cirrhosis, and 40% in case of cirrhosis, is required before a major hepatectomy to minimise the risk of postoperative liver failure.\textsuperscript{20,21}

Clinically significant portal hypertension (CSPH), defined as HVPG >10 mmHg, is a well-identified predictive factor for liver decompensation and death after LR.\textsuperscript{22–25} The risk of liver decompensation increases with the extent of the hepatectomy. In patients with CSPH, the rate of liver-related mortality could reach 25% after a major hepatectomy vs. 9% after minor hepatectomy.\textsuperscript{7} The latest EASL guidelines did not formally preclude surgery in cases of CSPH if minor hepatectomy could be performed in a patient with an MELD score <10.\textsuperscript{2}

Performance status and comorbidities also play a major role in the decision process and must be considered ahead of any intervention. Indeed, as introduced previously, the presence of metabolic syndrome, as well as cardiovascular and lung diseases, are associated with a higher rate of postoperative complications. Specific preoperative evaluation in association with close postoperative monitoring should be proposed in high-risk populations.\textsuperscript{2}

Currently, optimal surgical candidacy for LR in EASL guidelines is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10, to be matched with grade of portal hypertension, acceptable remaining parenchyma and the possibility of a laparoscopic/minimally invasive approach.\textsuperscript{2} According to AASLD guidelines, LR is the treatment of choice for resectable HCC occurring in the setting of cirrhosis, if liver function is intact and there is no CSPH.\textsuperscript{1} In addition, in APASL recommendations, LR is considered a first-line curative treatment for HCC among patients with Child-Pugh A cirrhosis when resectability is confirmed – in terms of tumour burden and liver functional reserve – by multidisciplinary evaluation.\textsuperscript{4}

### Position of resection in the HCC therapeutic algorithm

#### Resection vs. ablation

For HCC ≤2 cm (Barcelona Clinical liver cancer [BCLC]-0), recent randomised controlled studies comparing LR and radiofrequency ablation (RFA) showed similar results in terms of OS, while RFA was associated with a lower cost (Table 1).\textsuperscript{26–34} In this setting, EASL guidelines recommend the use of RFA if LT is not indicated, leaving LR for patients amenable to LT, those with tumours inaccessible to RFA, or following failure of RFA. In the APASL guidelines, ablation is recommended for first-line treatment, while, in the AASLD guidelines, LR remains the first choice for very early HCC.\textsuperscript{2,3} For a single HCC ≥2 cm (BCLC-A), all guidelines recommend LR as the first approach when feasible.

#### Resection vs. transplantation

LT is the best curative treatment in cirrhotic patients fulfilling transplantation criteria, as it can cure both the tumour and the underlying liver disease. However, due to organ shortages and the long waiting times associated with risk of dropout due to tumour progression, a new paradigm has emerged in the last decade for early HCC developed on compensated cirrhosis, regarding the choice between LT and LR as a first-line treatment. The concept of salvage transplantation was initially proposed in the case of HCC recurrence after upfront LR. Following series showed comparable survival results (OS and disease-free survival [DFS]) between patients who underwent upfront and salvage LT, especially in patients with well-differentiated, single and small HCC without satellite nodules or microvascular invasion.\textsuperscript{35} These latter “good prognosis factors” retrieved on pathological examination of resected tissue may guide the decision on whether to propose salvage or upfront (“de principe”) LT to patients after HCC resection. Selecting only patients at high risk of recurrence for LT is one modern way to manage HCC treatment with regards to organ shortages and tailored risk evaluation.

Consequently, LT should be saved for patients who are not candidates for LR or RFA due to the severity of the liver disease and for patients who present transplantable tumour recurrence or bad prognostic factors on pathological examination after curative treatment.\textsuperscript{36,37}

Recently, adult living donor transplantation has emerged as a new option for patients with HCC not fulfilling criteria for deceased donor LT.\textsuperscript{38} This option involves a major hepatectomy in the donor, carrying a significant operative risk. Preliminary results were in favour of higher and more rapid recurrence in the living
Advanced HCC in this group. Recent studies, using intent-to-treat analysis, showed a significant decrease in risk of death when measured from time of listing, due to shorter waiting periods and lower dropout rates in patients undergoing living donor LT instead of deceased donor LT. Liver donor transplantation could provide a new option for patients who do not have access to a deceased donor organ. Nevertheless, donor safety remains a risk to be balanced with the probability of tumour recurrence.

**Improvements in patient selection**

**Evaluation of liver function**

As mentioned, liver function is traditionally assessed using Child-Pugh score and MELD score. However, alternative parameters for evaluating liver functional reserve have been developed to identify patients at higher risk of post hepatectomy liver failure.

In numerous studies, liver stiffness measurement (LSM) – measured by transient elastography – has been independently associated with postoperative morbidity and mortality. However, the optimal LSM cut-off to predict a higher risk of complications after LR varied among studies, probably due to the different definitions of postoperative complications used, and the heterogeneous causes of underlying liver disease. Moreover, it is not clear if LSM is independently associated with postoperative complications, or if the LSM value could be influenced by the location or size of HCC. In a recent meta-analysis, the cut-off values proposed to predict postoperative complications in Asian and European populations were >14.3 kPa and >11.3 kPa, respectively. The EASL guidelines consider there to be a significant risk of postoperative liver failure for LSM values above 12–14 kPa. Other elastography methods (shear wave elastography (acoustic radiation force impulse), magnetic resonance elastography) have also shown promise for the prediction of liver failure after LT, but are not used routinely.

The measurement of indocyanine green (ICG) clearance is widely used in Asia. It is a dynamic method for studying liver functional reserve that consists of evaluating the hepatic clearance of indocyanine green 15 minutes after its intravenous administration (ICG-R15); normal values of ICG-R15 are around

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**Table 1. Randomised controlled trial comparing liver resection with radiofrequency ablation.**

| Study                  | Characteristics of the study | Characteristics of the patients | Endpoints                                                       | Morbidity/mortality                                      |
|------------------------|------------------------------|---------------------------------|----------------------------------------------------------------|----------------------------------------------------------|
| Lee et al. Ann Surg Treat Res 2018<sup>10</sup> | Korea 2005–2008 RCT | 29 LR vs. 34 RFA % cirrhosis n.d. % viral hepatitis n.d. 100% solitary tumour 24% HCC between 3–4 cm | OS at 3 years: 96.6% in LR vs. 97.1% in RFA (p = n.s.) | 37.9% in LR vs. 26.5% in RFA (p = n.s.)Deaths 3.4% in LR vs. 0% in RFA |
| Ng et al. BJS 2017<sup>23</sup> | China 2002–2007 RCT | 109 LR vs. 109 RFA % cirrhosis n.d. 90% viral hepatitis 91% solitary tumour 100% In Milan criteria | OS at 3 years: 80.6% in LR vs. 82.3% in RFA (p = n.s.) | 16.5% in LR vs. 9.2% in RFA (p = n.s.)Deaths 0.9% in LR vs. 0% in RFA |
| Fang et al. JGHF 2014<sup>10</sup> | China 2000–2012 | 60 LR vs. 60 RFA 80% cirrhosis 90% viral hepatitis 80% solitary tumour 100% HCC ≤ 3 cm | OS at 3 years: 77.5% in LR vs. 82.5% in RFA (p = n.s.) | 27.5% in LR vs. 5% in RFA (p < 0.05) No deaths |
| Feng et al. J Hepatol 2012<sup>21</sup> | China 2005–2008 RCT | 84 LR vs. 84 RFA 60% cirrhosis 84% viral hepatitis 60% solitary tumour 64% HCC between 2–4 cm | OS at 3 years: 74.8% in LR vs. 67.2% in RFA (p = n.s.) | 21.4% in LR vs. 9.5% in RFA (p < 0.05) No deaths |
| Huang et al. Ann Surg 2010<sup>12</sup> | China 2003–2005 RCT | 115 LR vs. 115 RFA 70% cirrhosis 93% viral hepatitis 55% solitary tumour 50% HCC between 3–5 cm More solitary tumour in LR Larger HCC in RFA group | OS at 3 years: 92% in LR vs. 76% in RFA (p = 0.001) Recurrence at 3 years: 37.7% in LR vs. 49.6% in RFA (p = n.s.) | 28% in LR vs. 4% in RFA (p < 0.05) No deaths |
| Cheng et al. Ann Surg 2006<sup>13</sup> | China 1999–2004 RCT | 90 LR vs. 90 RFA % cirrhosis n.d. % viral hepatitis n.d. 100% solitary tumour 50% HCC between 3–5 cm | OS at 3 years: 73% in LR vs. 69% in RFA (p = n.s.) | 55% in LR vs. 4% in RFA (p < 0.05)Deaths 1.1% in LR vs. 0% in RFA |
| Lu et al. Zhonghua Yi Xue Za Zhi 2006<sup>14</sup> | China RCT Written in Chinese | 54 LR vs. 51 RFA % cirrhosis n.d. % viral hepatitis n.d. % solitary tumour n.d. 100% In Milan criteria | OS at 3 years: 86.4% in LR vs. 87.1% in RFA (p = n.s.) | 11.1% in LR vs. 7.8% in RFA (p = n.s.)% n.s. Deaths |

DFS, disease-free survival; HCC, hepatocellular carcinoma; LR, liver resection; OS, overall survival; n.d., not determined, n.s., not significant; RFA, radiofrequency ablation; RCT, randomised controlled trial.
10%, but ICG clearance is usually delayed in cases of liver disease. In the Makucchi decisional algorithm, in cases of total bilirubin level <1 mg/dl without ascites, major resections should only be performed in patients with ICG-R15 lower than 10–20%, and limited resections when ICG-R15 is lower than 40%.54

Recently, the albumin-bilirubin (ALBI score) grade was also proposed to assess liver function in patients with HCC. Various studies, the ALBI score was better able to predict liver failure after LR, mostly in BCLC 0/A stages, than Child-Pugh score. Outcome was significantly better in patients with ALBI grade I compared to grade II-III.55–58

Liver parenchymal enhancement after injection of gadolinium-EOB-DTPA using MRI was also proposed for the evaluation of liver function. Gd-EOB-DTPA (Primovist/Eovist, Bayer Healthcare, Germany) is a hepatospecific magnetic resonance contrast agent. This contrast agent is taken up by hepatocytes and excreted in the biliary duct through the OATP1B1/B3-MRP2 pathway, like ICG. Several studies have shown that patients with impaired liver function presented with decreased liver parenchymal enhancement at the hepatobiliary phase (assessed using relative enhancement ratio or more advanced quantitative parameters) after Gd-EOB-DTPA injection. This could, in combination with liver volume, become a novel tool to assess liver function.59,60

Very recently, liver surface nodularity, quantitatively assessed on CT using dedicated software, was found to be an independent predictor of post-hepatectomy liver failure after LR for HCC.66 This promising method needs to be validated in further studies.

**Evaluation of portal hypertension**

As requested by the EASL/AASLD guidelines, preoperative portal hypertension should be assessed using the gold standard technique, i.e., HVPG measurement.53 Nevertheless, because of logistical and technical complexities, and the lack of reproducibility due to inter-operator variability, HVPG is not routinely measured in clinical practice. To overcome this reality, alternative methods to evaluate CSPH are available. In patients with advanced chronic liver disease, an LMS <20 kPa and a platelet count >150,000/µl are associated with a very low risk of having CSPH, according to Baveno consensus. Moreover, upper gastrointestinal endoscopy can also be easily performed to complete CSPH assessment.22–24

Spleen stiffness, obtained by transient elastography, has recently been suggested as a non-invasive tool to predict CSPH and post-surgical morbidity and mortality.67,68 Interestingly, spleen stiffness was also an independent predictor of HCC recurrence after LR.69 However, further prospective studies are needed before non-invasive methods can be integrated into the treatment algorithm in place of HVPG measurement. Other elastography methods, measuring liver and spleen stiffnesses, have shown promising results for CSPH assessment but require further investigation in larger cohorts.70–75 More recently, liver surface nodularity was found to be an accurate tool for CSPH assessment, with a high positive predictive value.76 Even if its accuracy needs to be confirmed, it could be an attractive, non-invasive, and easily accessible method for CSPH assessment.

**Expanding indications to more severe patients**

Recently, a nomogram to predict postoperative OS after LR in patients with Child-Pugh B cirrhosis was also proposed. This nomogram considered the presence of comorbidities and CSPH, the Child-Pugh score, the preoperative alpha-fetoprotein (AFP) level, the numbers and size(s) of lesions and previous HCC treatment. An accurate estimation of the surgical risk for these challenging patients could improve postoperative morbidity and global outcome.77

**Role of AFP level in patient selection**

AFP level could also influence the choice of LR. Indeed, high AFP levels >400 ng/ml were associated with a median DFS of 8.4 months and median OS of 38.4 months compared to 55.6 months and 133 months, respectively, for 1,182 patients with AFP <20 ng/ml who underwent LR.78

**Perioperative management**

**Preoperative planning**

**Tumour anatomical modelling and surgical planning**

Precisely locating the tumour and its relationship to inflow structures (glissonean pedicles) and outflow (hepatic veins) is essential prior to considering the surgical approach. In HCC surgery especially, anatomical resection, which implies the removal of the entire portal territory nourishing the tumour, has been associated with better oncological results. Therefore, 3D reconstructions have been developed to provide an accurate estimation of the anatomic relationships between the tumours and vessels in the liver, allowing for a more precise evaluation of the future liver remnant.79,80 Moreover, the use of a virtual 3D reconstruction model created by multidetector CT and prototyped using a 3D printer was proposed for a better preoperative understanding of the surgical liver anatomy and surgical resection planning.81 A prospective trial assessing the impact of 3D reconstruction on surgical planning is actually ongoing (3D HAPPI Trial IRCAD).

**Management of a predicted insufficient liver remnant**

The volume of the future remnant liver is one of the major parameters which determines the surgical decision. If the future liver remnant is too small, it can limit access to curative treatment when a major hepatectomy is required. Therefore, strategies to increase functional resectability have been developed and are still a key topic in the field of surgical research.

- **Portal vein embolisation (PVE)** involves occluding the portal vein branch supplying the hiliar-vascular to be removed, which induces compensating hypertrophy of the future liver remnant. Iterative volumetric measurement is usually performed 1 month after the procedure to ensure a sufficient volume increase of the future liver remnant.82 To prevent tumour growth between PVE and LR, the addition of sequential preoperative transarterial chemoembolisation (TACE) has been proposed, owing to its cytotoxic effect and the embolisation of the arterio-portal shunts in the tumour. Sequential preoperative TACE and PVE before LR were associated with greater hypertrophy and longer DFS compared to PVE alone in retrospective studies.83–85
- **Combined hepatic and PVE** have been proposed in patients who remain unsuitable for resection after PVE because of insufficient hypertrophy. After this procedure, the degree of hypertrophy of the future remnant ranged from 33% to 63% and liver surgery was finally performed in 85% of patients.86
Simultaneous PVE and right and middle hepatic vein embolisation have also been proposed for patients with cirrhosis or liver metastases; this approach was associated with rapid liver regeneration (+53.4% at 7 days). Intraoperative management of local complications which preclude LR.103,104 To date, no factor pertrophy of the remnant liver, disease progression or occurrence do not proceed with surgery due to the absence of sufficient liver remnant. However, approximately 20 to 30% of patients that predicts insufficiency of the remnant liver, disease progression or occurrence do not proceed with surgery due to the absence of sufficient liver remnant. However, approximately 20 to 30% of patients that predicts insufficiency of the remnant liver.103,104 To date, no factor pertrophy of the remnant liver, disease progression or occurrence do not proceed with surgery due to the absence of sufficient liver remnant.

- **Portal vein ligation for staged hepatectomy (ALPPS)** consists of right portal ligation and *in situ* splitting of the liver parenchyma (Stage 1), followed by completion of the hepatectomy 1 week later (Stage 2). The surgery is possible thanks to a rapid liver hypertrophy related to a maximal disconnection of the hemi-liver to be removed, without risking dropout due to tumour progression while waiting for hypertrophy.88,89 However, ALPPS has been associated with a very high initial perioperative risk in patients with HCC (90-day mortality rate between 11–31%). Concerns have also been raised about leaving the tumour several days in an environment enriched with inflammatory mediators and growth factors after early recurrence for many patients.90–93 The high mortality rate can be explained by wide inclusion criteria regardless of portal hypertension and the severity of cirrhosis. Ongoing studies are focusing on the identification of good candidates for ALPPS and improving the classical ALPPS technique to reduce stage 1 morbidity (partial ALPPS with preservation of the middle hepatic vein, combination of ALPPS and PVE or partial ALPPS and PVE). When considering patients with Child-Pugh A or no cirrhosis, the 90-day mortality rate was reduced to 7%.94 In a recent series comparing ALPPS to PVE for patients with HCC (92% with hepatitis B infection), ALPPS conferred a higher resection rate with comparable short- and long-term outcomes. However, in the group of patients who underwent PVE, there were more cirrhotic patients (64% vs. 46%; p = 0.055) and more right hepatectomies were performed (64% vs. 50%; p = 0.069). Total blood loss was significantly higher in the ALPPS group. Therefore, the application of ALPPS, especially in case of underlying cirrhosis, is debatable, and hepatic and PVE should be discussed before performing an ALPPS procedure.

- **Radioembolisation** with yttrium-90 microspheres consists of injecting radiolabelled particles through the hepatic artery, which become trapped at the capillary level and emit lethal internal radiation.95–96 No improvement in survival was observed with radioembolisation compared to sorafenib (standard of care) in phase III randomised studies in advanced HCC.96–98 However, in addition to treating HCC, radioembolisation was associated with induction of contralateral hypertrophy in patients with cirrhosis.99–101 Although PVE has been associated with a greater degree of hypertrophy than radioembolisation in the non-cirrhotic liver,102 Moreover, the induction of contralateral hypertrophy by radioembolisation is not predictable and takes several months to be fully effective, limiting its use for upfront LR, though it could be useful as a downstaging strategy.

To date, PVE remains the first-line option for patients with small liver remnant. However, approximately 20 to 30% of patients do not proceed with surgery due to the absence of sufficient hypertrophy of the remnant liver, disease progression or occurrence of local complications which preclude LR.103,104 To date, no factor that predicts insufficient hypertrophy has been identified.

**Intraoperative management**

- **A laparoscopic approach** for LR has gained widespread acceptance despite the absence of a randomised controlled trial, and is associated with similar oncological results and better short-term outcomes compared to open surgery.105 This minimal invasive surgery allows the preservation of the abdominal wall, minimises peritoneal trauma, and is associated with decreased complication rates compared to open surgery, including overall complications and liver complications such as ascites and liver failure, but also reduced blood loss, decreased pedicle clamping time and shorter postoperative hospital stay compared to open LR, as confirmed in a recent meta-analysis including 6,812 patients.106–112 The laparoscopic approach has therefore been introduced in the recent EASL guidelines as a recommended technique for HCC resection in expert centres, and comprehensive recommendations on laparoscopic LR have been published from 3 consecutive consensus expert conferences.113 To standardise the safe implementation of laparoscopic liver surgery, a difficulty score correlated to surrogates of intraoperative complexity has been developed, and this difficulty score has been associated with postoperative morbidity.114 Moreover, the safety and feasibility of laparoscopic major hepatectomy has been reported after sequential TACE and PVE, which is usually associated with increased surgical difficulty.115 The laparoscopic approach was also shown to be beneficial prior to LT for HCC, with significantly reduced de-listing and death after LT when prior LR was performed laparoscopically.116

- **Fluorescence-guided surgery** can help identify the segmental anatomy in order to achieve proper anatomical resections. Likewise, injection of indigo-carmine into the segmental portal vein or selective Glissonian clamping for ischemic demarcation were used to identify segmental anatomy before LR.117–119 However, these techniques did not always provide clear identifications of the segment boundaries. Recently, ICG fluorescence imaging enabled identification of stained segments in 90% of patients, with similar results between patients with and without cirrhosis. It was especially effective in patients who underwent repeated LR for HCC recurrence. The quality of the data were enhanced by using fusion ICG fluorescence.120–124 Moreover, ICG tends to concentrate in HCC and near-infrared cameras can be used to detect HCC intraoperatively. Preoperative injection of ICG can help to identify lesions not detected on imaging with high sensitivity but poor specificity, as dysplastic nodules can retain ICG.125–127

- **Somatostatin use** in the intra-and postoperative period was found to have a positive effect on portal inflow during major hepatectomy in a recent but small series.128 These results must be confirmed and somatostatin’s impact on postoperative complications still needs to be determined in further randomised trials.

**Overcoming old barriers**

**Technical advances**

New surgical approaches are being developed to overcome barriers to LR, such as difficult locations, portal hypertension, comorbidities and/or impaired liver function.

A laparoscopic approach is increasingly used as a means of pushing the limits for LR. One study reported that patients with Child-Pugh A and Child-Pugh B/C cirrhosis who underwent laparoscopic LR had a similar perioperative course.111 Nevertheless, LT remains the treatment of choice in cases of liver cirrhosis or liver metastases; this approach was associated with rapid liver regeneration (+53.4% at 7 days). Intraoperative management of local complications which preclude LR.103,104 To date, no factor pertrophy of the remnant liver, disease progression or occurrence do not proceed with surgery due to the absence of sufficient liver remnant. However, approximately 20 to 30% of patients
dysfunction and further data about laparoscopic LR in patients not eligible for LT with altered liver function are needed. Interestingly, the use of a laparoscopic approach in the elderly was safe and associated with better outcomes and less complications, even for major hepatectomy, and should be applied when feasible.129–133 Laparoscopic LR also appears to be an interesting strategy in patients with CSPH. A recent study showed that expanding laparoscopic LR to patients with CSPH (evaluated by the HVPG measurement) increased the rate of resected patients by 40% at the cost of increases in morbidity and hospital stay compared to those without CSPH.134

Therefore, laparoscopic LR may be a preferred approach for patients with HCC, especially those with impaired liver function and comorbidities, but must be performed in specialised centres by trained surgeons.135

The robotic approach is also quickly gaining traction as an alternative minimally invasive surgical technique. Robotic surgery appears to be safe in terms of operative complications and postoperative morbidity and may allow for easier access to liver segments that were not resectable with a laparoscopic approach.136 However, the technical advantages of a robotic approach may be comparable to 3D modern laparoscopic techniques.137 and few data on long-term outcomes are currently available; rates of DFS and OS at 2 years have been reported to range from 72–84% and 94–98%, respectively, in well-selected patients. Considering the cost of the robotic surgical devices compared to laparoscopic equipment, robot-assisted procedures need to be better described before generalising this technique for the treatment of HCC.138–141

Combining splenectomy and hepatectomy in patients with cirrhotic hypersplenism has been proposed to counteract the consequence of portal hypertension in the surgical process and to improve liver function and nutritional metabolism.142–144 In an initial study, this 2-stage surgery (first splenectomy followed by hepatectomy) was shown to increase complications and the risk of HCC progression due to the delay between the 2 surgical steps.145 Recently, synchronous hepatectomy and splenectomy was reported to confer satisfactory outcomes and was associated with a decrease in the incidence of postoperative bleeding.146,147 In a recent meta-analysis which included 8 articles, synchronous hepatectomy and splenectomy was associated with better 5-year OS compared to hepatectomy alone, with no difference in terms of complications.148 However, no randomised controlled trial is available and these studies show some heterogeneity regarding the surgical approach and tumour burden. Moreover, data on liver function and portal hypertension are sparse (no mentions of HVPG and oesophageo-gastroduodenoscopy results for example), so it remains difficult to comment on the true degree of portal hypertension in these patients. Robust data are required to conclude on a potential benefit of this technique in patients with CSPH.

**Treating advanced HCC with resection**

LR for early HCC (BCLC 0 and A) is widely accepted as a standard of care, however surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial.2–4 LR for multifocal lesions and lesions with macrovascular invasion is nevertheless performed in international centres, especially in Asia, and is associated with competitive results in terms of OS compared to the standard of care (TACE or sorafenib).

For patients with intermediate stage (BCLC-B), several studies and 1 randomised controlled trial have shown a survival benefit of LR compared to TACE (Table 2).149–153 However, some observational studies did not provide data regarding the presence of cirrhosis and portal hypertension, which can impact the outcome of the patient and some series also included patients with solitary tumours that should currently undergo LR as a first treatment. Moreover, some patients received non-standardised neo-adjuvant and adjuvant treatment as well as non-standardised TACE treatment which may impact outcome. Nevertheless, a recent meta-analysis, including 74 articles, reported a 5-year OS of 54% following LR for HCC outside Milan criteria. In contrast, 5-year OS was 32.4% in a systematic review of conventional TACE, including 101 articles, leading to controversy about the use of TACE in some patients who could have received surgery.154,155 In addition, a large observational study focusing only on multinodular tumours (up to 3 lesions) confirmed better 5-year OS after LR compared to TACE (60% vs. 41.6%, p <0.001) and even for tumours >3 cm156 LR may yield better long-term survival than TACE for patients with BCLC-B HCC, but the identification of good candidates is crucial in order to avoid high rates of perioperative morbidity.

Patients with HCC and macrovascular invasion (BCLC-C) are considered to have an advanced disease whose prognosis depends on the extension of the tumour-related portal vein thrombosis (PVTT), the AFP level and tumour size. PVTT can be graded as PVTT1 (segmentary), PVTT2 (secondary order branch), PVTT3 (first order branch) and PVTT4 (main truck/contralateral branch).145,146 Systemic therapy is currently the first-line treatment for patients with PVTT. Sorafenib prolongs OS by approximately 3 months in this population, with a median OS of 8.1 months vs. 4.0 months with placebo.158 However, OS under systemic therapy remains limited and associated with significant adverse events. Recently, some interesting results have been observed after LR for HCC with localised vascular invasion, combined or not with an additional thrombectomy when the thrombus was beyond the resection line.159–162 After matching Child-Pugh A patients using a propensity score (including tumour burden, liver function and portal hypertension), LR was associated with an increase of median OS by about 1 year in patients with PVTT1 to 3, and of about 1.6 years in patients with hepatic vein tumour thrombus, compared to patients who received others treatments (TACE, systemic therapy).160,161 However, no increase in OS was observed for PVTT-4, which was associated with a high R2 resection rate.162 In addition, in a recent randomised multicentre controlled trial, survival was improved by neoadjuvant 3D radiotherapy in patients with resectable HCC and portal vein invasion.163 This important trial highlights the need to develop preoperative treatments in the setting of HCC with PVTT and also confirms the potential benefit of surgical resection in this setting.

Patients with HCC and extrahepatic spread (BCLC-C) have a poor prognosis, with a median OS of 9 months under sorafenib.158 However, interesting results were observed for OS in patients who underwent synchronous or metachronous extrahepatic metastasectomy. However, most of these studies considered extrahepatic metastasectomy for patients with previous and treated liver HCC. Few data regarding liver treatment and extrahepatic metastasectomy at the same time are available.164–170 Factors associated with good outcome after extrahepatic metastasectomy were remission status in the liver before extrahepatic metastasectomy and distant metastasis-free interval between the last treatment of HCC and the occurrence of metastasis. On the contrary, a number of metastases resected
Table 2. Studies comparing liver resection with transarterial chemoembolisation for intermediate and advanced HCC.

| Study            | Characteristics of the study | Characteristics of the patients and surgical procedures | Outcomes and morbimortality |
|------------------|-----------------------------|--------------------------------------------------------|----------------------------|
| study            |                             | LR | TACE | p value | LR | TACE | p value |
| Patients         |                             |    |      |         |    |      |         |
| Patients         |                             |    |      |         |    |      |         |
| Fukami et al.    | Japan 2000–2007; Observational retrospective study; Propensity matching | 908 | 351 | 0.018 | 908 | 351 | 0.018 |
| Ann Surg 2019    |                             |    |      |         |    |      |         |
| Yin et al.       | China 2008–2010; Randomized controlled trial | 88  | 85   | n.s.   | 88  | 85   | n.s.   |
| Zhong et al.     | China 2000–2007; Observational retrospective study; Propensity matching | 93% | 90%  | 0.001 | 93% | 90%  | 0.001 |
| Ann Surg 2014    |                             |    |      |         |    |      |         |
| Zhong et al.     | China 2000–2007; Observational retrospective study; Propensity matching | 94.6% | 90.4% | n.s. | 94.6% | 90.4% | n.s. |
| Plos One 2013    |                             |    |      |         |    |      |         |
| Hsu et al.       | Taiwan 2002–2010; Observational retrospective study; Propensity matching | 66% | 50% | <0.001 | 66% | 50% | <0.001 |
| Ann Surg Oncol   |                             |    |      |         |    |      |         |
| Lin et al.       | Taiwan 2001–2007; Observational retrospective study | 88% | 99% | n.s. | 88% | 99% | n.s. |

Parameters included to generate propensity score: age, sex, hepatitis B and C, albumin, total bilirubin, ICG-R15, platelets count, prothrombin activity, alpha-fetoprotein, macrovascular invasion, number and tumour size.

Parameters included to generate propensity score: age, sex, hepatitis B and C, albumin, total bilirubin, ICG-R15, platelets count, prothrombin activity, alpha-fetoprotein, macrovascular invasion, number and tumour size.

Parameters included to generate propensity score: age, tumour size, hepatitis B, platelets count, alpha-fetoprotein, and total bilirubin level.

Parameters included to generate propensity score: sex, hepatitis B, hepatitis C, alcoholism, tumour burden, severity of cirrhosis, performance status, diabetes mellitus, BCLC classification, and Cancer of the Liver Italian Program score.

higher than 2 and a high AFP level correlated with poor outcome.14-179 Metachronous extrahepatic metastasectomy following primary LR or LT was associated with a 20 month increase in median OS compared to metastatic HCC treated with sorafenib alone.14-179 Thus, it could be a potential therapeutic option in patients with extrahepatic lesion(s) and controlled liver HCC.

Encouraging long-term outcomes have been achieved when using TACE or radioembolisation to downstage patients with BCLC-B/C. One of the goals of the downstaging is to give patients access to LT. However, due to the organ shortage, age and/or associated comorbidities, some patients will not be able to access LT; LR should be proposed in such cases. Indeed, LR after TACE conferred a survival benefit of up to 20 months in patients with macrovascular invasion and a partial response to TACE, similar to patients with a complete response to TACE.171-172

LR after radioembolisation for initially unresectable HCC also showed interesting survival results, without increasing perioperative complication rates, in patients at various BCLC stages.173,174 Moreover, radioembolisation was also associated with atrophy of the treated lobe and hypertrophy of the future liver remnant, thus facilitating LR. Some authors even suggest a higher rate of patients successfully downstaged compared to TACE, with longer time to disease progression.175
Treating intra and/or extrahaepatic recurrence of HCC

As tumour recurrence is expected in 70% of patients who had a previous curative surgical treatment, the question of redo surgery or LT as a salvage strategy is crucial. Indeed, it is well known that recurrence is also the major determinant of OS. The options to treat intrahepatic recurrences vary from non-curate treatment, mainly TACE, to maximally curative options such as LT, resection or ablation. The value of salvage LT has been widely demonstrated, especially in well controlled patients with HBV, and salvage LT provides excellent long-term survival with limited short-term morbidity, especially when the first resection is performed laparoscopically. Obviously, the recurrence pattern should respect the Milan criteria or AFP score at the time of recurrence to ensure optimal long-term results. However, little is known about the role of surgery in the treatment of extrahaepatic recurrence. In a recent study from Yoh et al.,176 the authors investigated the long-term results of repeat surgery in various conditions of recurrence, including intra and/or extrahaepatic disease in more than 600 patients. Interestingly, in selected patients with the best hepatic functional reserve and longer time to recurrence, surgical treatment of recurrence was beneficial not only for intrahepatic recurrence but also in cases of extrahaepatic disease. Overall, oligometastatic patients can undergo intra and/or extrahaepatic resections. The most frequent extrahaepatic sites of surgically treated recurrence were lung and adrenal glands. The mortality of simultaneous resection was very low.

Moreover, since laparoscopic LR has emerged as a valuable approach in HCC, a laparoscopic approach for recurrence emerged as a logical option owing to technical improvements and increasing experience in expert centres. A recent study comparing open to laparoscopic resection revealed that repeat and increasing experience in expert centres. A recent study comparing open to laparoscopic resection revealed that repeat laparoscopic resection was associated with less blood loss (despite longer operating times) and better short-term overlaparoscopic resection was associated with less blood loss and short-term morbidity, especially when the first resection is performed laparoscopically. Obviously, the recurrence pattern should respect the Milan criteria or AFP score at the time of recurrence to ensure optimal long-term results. However, little is known about the role of surgery in the treatment of extrahaepatic recurrence. In a recent study from Yoh et al.,176 the authors investigated the long-term results of repeat surgery in various conditions of recurrence, including intra and/or extrahaepatic disease in more than 600 patients. Interestingly, in selected patients with the best hepatic functional reserve and longer time to recurrence, surgical treatment of recurrence was beneficial not only for intrahepatic recurrence but also in cases of extrahaepatic disease. Overall, oligometastatic patients can undergo intra and/or extrahaepatic resections. The most frequent extrahaepatic sites of surgically treated recurrence were lung and adrenal glands. The mortality of simultaneous resection was very low.

In conclusion, there are curative options for intrahepatic and/or extrahaepatic recurrences, mainly redo surgery, while laparoscopic approaches can be used safely in experts centres to treat intrahepatic recurrence, especially when HCC has been removed laparoscopically at the first stage.

Immunotherapy and resection, the future?

One of the major issues for patients who undergo LR is preventing the risk of recurrence, which occurs in about 70% of cases at 5 years. Patients are exposed to 2 types of recurrence: early recurrence occurring within the first 2 years after LR and late recurrence.178 Late recurrence corresponds mostly to de novo tumours and thus to the severity of the underlying disease. To prevent long-term recurrence, it is therefore necessary to control the underlying liver disease and propose an adapted treatment of the aetiology. Early recurrence is mostly related to the characteristics of the initial tumour and some predictive factors have been identified such as tumour size, vascular invasion, satellite nodules and poor differentiation of the tumour; in this high-risk population of patients, adjuvant therapy could be an interesting option. Nevertheless, to date, no adjuvant therapy has been associated with any benefit in terms of relapse (systemic treatment, TACE, internal radiation, retinoids) and adjuvant therapy is currently not recommended.179,180 In the last decades, immunotherapy was developed with the goal of boosting immunity after LR in order to prolong DFS, and some interesting preliminary results were observed. Indeed, the transfer (over 6 months) of autologous lymphocytes activated in vitro was associated with longer DFS (38% in the immunotherapy group vs. 22% in the control group at 5 years, p = 0.008).181 Currently, phase III trials, testing immune checkpoint inhibitors as adjuvant therapy, are ongoing and the future results may change the clinical practice and enlarge LR indications.

Conclusion

In the last decades, improved surgical techniques and perioperative management, as well as better patient selection, have expanded indications for LR in patients with HCC arising on a background of chronic liver disease. Currently, surgical resection is still considered a curative option and reserved for early stages. However, current advances in the surgical field will probably redefine the actual frontiers of LR, by including patients with more advanced disease.

Abbreviations

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; BCLC, Barcelona Clinic liver cancer; CSPH, clinically significant portal hypertension; DFS, disease-free survival; GSA, galactosyl serum albumin; HCC, hepatocellular carcinoma; HVGP, hepatic venous pressure gradient; ICG, indocyanine green; ICG-R15, hepatic clearance of ICG 15 minutes after its intravenous administration; IL-6, interleukin 6; LR, liver resection; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PVL, portal vein ligation; PVTT, tumour-related portal vein thrombosis; RFA, radiofrequency ablation; SSM, spleen stiffness measurement; TACE, transarterial chemoembolisation.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions

Study concept and design: Allaire and Scotton. Drafting of the manuscript: Allaire, Goumard and Scotton. Final approval of the version to be submitted: Allaire, Goumard, Lim, Wagner, Le Cleach and Scotton.

Supplementary data

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