New frontiers in liver resection for hepatocellular carcinoma

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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.

Keywords: Liver resection; HCC; Laparoscopy; Surgery

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Introduction

Liver cancer is the fifth most common cancer globally and the fourth most common cause of cancer-related death.[1] 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.[2–4] 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.[2] 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%.[5–8] 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.[9,10] As about one-third of cases of non-alcoholic fatty liver disease (NAFLD)-related HCC will develop in the absence of cirrhosis,[11,12] 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.[10,13,14] 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.[15,16] 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.[17] 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

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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) (Fig. 1).[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]

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.

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

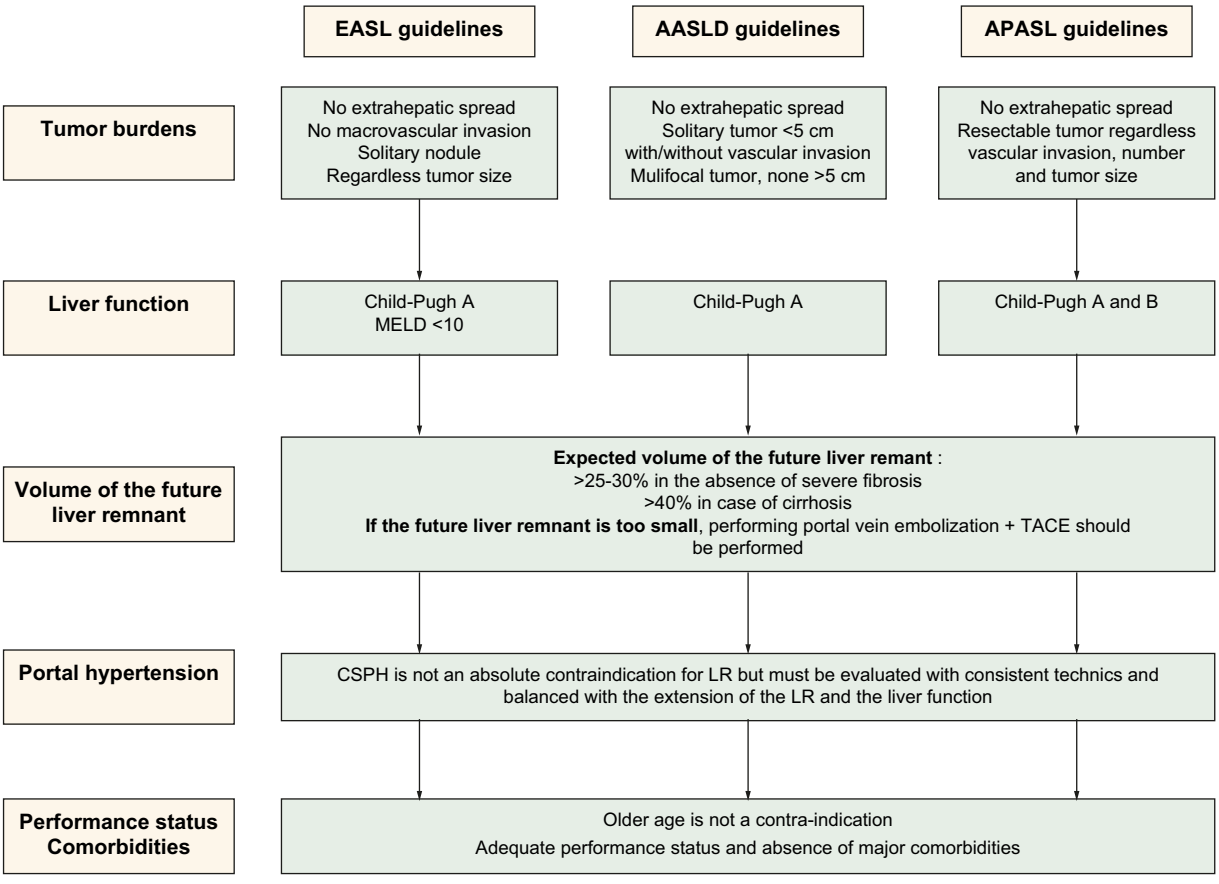

Fig. 1. Current indications for liver surgery according to EASL, AASLD and APASL guidelines. Indications of treatment by liver surgery for hepatocellular carcinoma differ according to the guidelines. EASL guidelines recommend surgery in case of solitary lesion without vascular invasion, in well compensated 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.

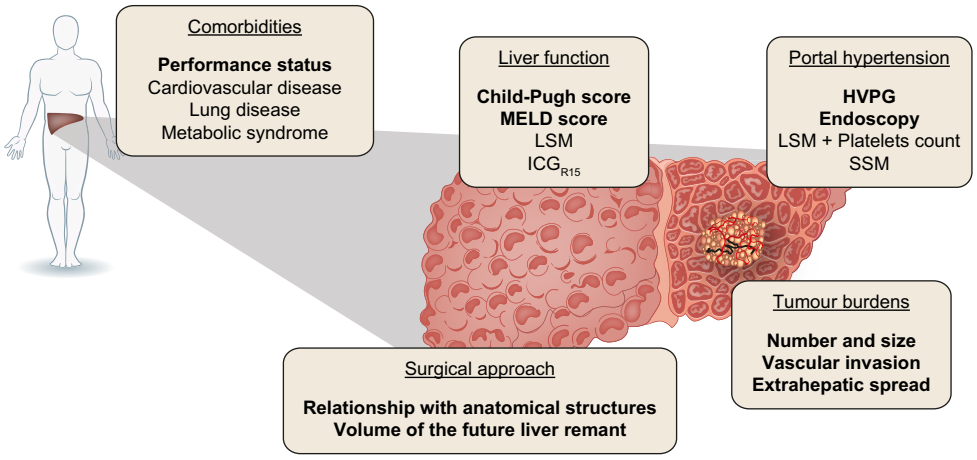

Fig. 2. Standard assessment to determine if HCC is suitable for liver resection. To determine if liver resection is appropriate, it is necessary to consider tumour burdens but also liver function, extent of hepatectomy and the expected volume of the future liver remnant, as well as the presence of portal hypertension and the comorbidities of the patients. HVGP, hepatic venous gradient pressure; ICG_{15}, hepatic clearance of indocyanine green 15 minutes after its intravenous administration; LSM, liver stiffness measurement; MELD, model for end-stage liver disease score; SSM, spleen stiffness measurement.

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.[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.[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.[2] 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.[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.[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.[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.[3] 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.[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).[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.[2–4] 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 nor microvascular invasion.[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.[36,37]

Recently, adult living donor transplantation has emerged as a new option for patients with HCC not fulfilling criteria for deceased donor LT.[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

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[28]	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.) DFS at 3 years: 66.7% in LR *vs.* 44.1% in RFA (p = 0.071)	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[29]	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.) DFS at 3 years: 50.9% in LR *vs.* 46.6% 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[30]	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.) DFS at 3 years: 41.3% in LR *vs.* 55.4.1% in RFA (p = n.s.)	27.5% in LR *vs.* 5% in RFA (p <0.05) No deaths
Feng *et al.* *J Hepatol* 2012[31]	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.) Recurrence at 3 years: 37.7% in LR *vs.* 49.6% 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[32]	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: 34% in LR *vs.* 49% in RFA (p = 0.024)	28% in LR *vs.* 4% in RFA (p <0.05) No deaths
Cheng *et al.* *Ann Surg* 2006[33]	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.) DFS at 3 years: 52% in LR *vs.* 60% 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[34]	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.) DFS at 3 years: 82.4% in LR *vs.* 51.3% 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.

donor group, but these first observations could be due to more advanced HCC in this group.[39] 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.[40–43] 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.[44–49] 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.[50] The EASL guidelines consider there to be a significant risk of postoperative liver failure for LSM values above 12–14 kPa.[2] Other elastography methods (shear wave elastography (acoustic radiation force impulse), magnetic resonance elastography) have also shown promise for the prediction of liver failure after LR, but are not used routinely.[51,52]

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

10%,[53] but ICG clearance is usually delayed in cases of liver disease. In the *Makuuchi* 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. In 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]

99mTc-galactosyl serum albumin (Tc-GSA) bonds specifically to asialoglycoprotein receptors on hepatocytes. By calculating the maximal GSA removal rate in the predicted residual liver, some authors identified patients at higher risk of liver failure after hepatectomy.[59,60]

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 an hepato-specific 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.[61–65]

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.[2,3] 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 pedicules) 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 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 hemi-liver 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).[87]

- **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 precapillary level and emit lethal internal radiation.[95] 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 LRs, 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

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 oesophago-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 cm.[156] 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).[2,157] 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 PVTT 1 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.[161] 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 morbi/mortality			
			LR	TACE	*p* value		LR	TACE	*p* value
Fukami *et al.* *Ann Surg* 2019[156]	Japan 2000–2007; Observational retrospective Study; Propensity matching[1]	Patients	1,944	1,302		Global 5-year OS	52%	42%	<0.001
		HBV	22%	12%	<0.001	With propensity score[1]	60%	41.6%	<0.001
		Cirrhosis				Complications (Grade 3–4)	n.d.	n.d.	n.d.
		Portal hypertension				Hospital mortality	0.57%	0%	n.s.
		3 tumours HCC	26%	36%	<0.001				
		Tumour size ≥3 cm	67%	57%	<0.001				
		Vascular invasion	13%	7%	<0.001				
Yin *et al.* *J Hepatol* 2014[149]	China 2008–2010; Randomized controlled trial	Patients	88	85		Global 5-year OS	52%	18%	<0.001
		HBV	92%	93%	n.s.	Complications (Grade 3–4)	7%	0%	n.s.
		Cirrhosis	78%	87%	n.s.	Hospital mortality	1.1%	0%	n.s.
		Portal hypertension	n.d.	n.d.	n.d.				
		Multinodular HCC	100%	100%	n.s.				
		Tumour size	9.5 cm	10.4 cm	n.s.				
		Vascular invasion	0%	0%	n.s.				
Zhong *et al.* *Ann Surg* 2014[151]	China 2000–2007; Observational retrospective study; Propensity matching[2]	Patients	908	351		Global 5-year OS	39%	16%	<0.001
		HBV	93%	90%	0.018	With propensity score[2]	40%	18%	<0.001
		Cirrhosis	n.d.	n.d.	n.d.	5-year OS for large	34%	16%	<0.001
		Portal hypertension	19%	23%	n.s.	tumour (≥10 cm)			
		Multinodular HCC	n.d.	n.d.	n.d.	5-year OS for ≥3 lesions	33%	6%	<0.001
		Tumour size	8 cm	10 cm	<0.001	Complications			<0.05
		Vascular invasion	27%	24%	n.s.	Hospital mortality	27%	19%	n.s.
							3.1%	2.8%	
Zhong *et al.* *Plos One* 2013[150]	China 2000–2007; Observational retrospective Study; Propensity matching[3]	Patients	257	135		Global 5-year OS	37%	14%	<0.001
		HBV	94.6%	90.4%	n.s.	With propensity score[3]	62%	20%	<0.05
		Cirrhosis	n.d.	n.d.		5-year OS for large tumour	41%	18%	<0.001
		Portal hypertension	18%	22%	n.s.	5-year OS for multinodular form	24%	4%	<0.05
		Multinodular HCC	23%	23%	n.s.	Complications			<0.05
		Tumour size	8.9 cm	8.8 cm	n.s.	Hospital mortality	28%	18.5%	n.s.
		Vascular invasion	n.d.	n.d.	n.d.		3.1%	3.7%	
Hsu *et al.* *Ann Surg Oncol* 2012[152]	Taiwan 2002–2010; Observational retrospective study; Propensity matching[4]	Patients	268	455		Global 5-year OS	63%	15%	<0.001
		HBV	66%	50%	<0.001	With propensity score[4]	68%	22%	<0.001
		Child-Pugh A	93%	79%	<0.001	Complications	n.d.	n.d.	n.d.
		Portal hypertension	n.d.	n.d.	n.d.	Hospital mortality	2.7%	8.2%	n.s.
		Multinodular HCC	40%	60%	<0.001				
		Tumour size ≥7 cm	64%	50%	n.s.				
		Vascular invasion	67%	39%	<0.001				
Lin *et al.* *World J Surg* 2010[153]	Taiwan 2001–2007; Observational retrospective study	Patients	93	78		3-year OS	49%	2%	<0.001
		HBV	88%	99%	n.s.	Complications	n.d.	n.d.	n.d.
		Cirrhosis	n.d.	n.d.	n.d.	Hospital mortality	n.d.	n.d.	n.d.
		Multinodular HCC	47%	72%	<0.05				
		Tumour size	8 cm	7.7 cm	n.s.				
		Vascular invasion	n.d.	n.d.	n.d.				

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; ICG-R15, hepatic clearance of indocyanine green 15 minutes after its intravenous administration; LR, liver resection; OS, overall survival; n.d., not determined; n.s., not significant; TACE, transarterial chemoembolisation.
[1]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.
[2]Parameters included to generate propensity score: age, tumour size, hepatitis B, platelets count, alanine aminotransferase, and total bilirubin level.
[3]Parameters included to generate propensity score: age, gender, tumour size, tumour number, serum bilirubin, ALT, albumin, and AFP.
[4]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.[164–170] 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.[169] 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 extrahepatic 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-curative treatment, mainly TACE, to maximally curative options such as LT, re-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 extrahepatic 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 extrahepatic 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 extrahepatic disease. Overall, oligometastatic patients can undergo intra and/or extrahepatic resections. The most frequent extrahepatic 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 laparoscopic resection was associated with less blood loss (despite longer operating times) and better short-term outcomes. Long-term outcomes were similar in both groups.[177]

In conclusion, there are curative options for intrahepatic and/or extrahepatic 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 pression 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

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Authors' contributions

Study concept and design: Allaire and Scatton. Drafting of the manuscript: Allaire, Goumard and Scatton. Final approval of the version to be submitted: Allaire, Goumard, Lim, Wagner, Le Cleac'h and Scatton.

Supplementary data

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References

[1] GLOBOCAN [Internet]. Available at: http://globocan.iarc.fr/old/summary_table_site-html.asp?selection=14070&title=Liver&sex=0&type=0&window=1&africa=1&america=2&asia=3&europe=4&oceania=5&build=6&sort=0&submit=%C2%A0Execute%C2%A0.

[2] European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56(4):908–943.

[3] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018

practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68(2):723–750.
[4] Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11(4):317–370.
[5] Smoot RL, Nagorney DM, Chandan VS, Que FG, Schleck CD, Harmsen WS, et al. Resection of hepatocellular carcinoma in patients without cirrhosis. Br J Surg 2011;98(5):697–703.
[6] Thelen A, Benckert C, Tautenhahn HM, Hau HM, Bartels M, Linnemann J, et al. Liver resection for hepatocellular carcinoma in patients without cirrhosis. Br J Surg 2013;100(1):130–137.
[7] Lewis RH, Glazer ES, Bittenbinder DM, O'Brien T, Deneve JL, Shibata D, et al. Outcomes following resection of hepatocellular carcinoma in the absence of cirrhosis. J Gastrointest Cancer 2019;50(4):808–815.
[8] Lang H, Sotiropoulos GC, Dömland M, Frühauf NR, Paul A, Hüsing J, et al. Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. Br J Surg 2005;92(2):198–202.
[9] Noun R, Jagot P, Farges O, Sauvanet A, Belghiti J. High preoperative serum alanine transferase levels: effect on the risk of liver resection in child grade A cirrhotic patients. World J Surg 1997;21(4):390–394. discussion 395.
[10] De Meijer VE, Kalish BT, Puder M, Ijzermans JNM. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg 2010;97(9):1331–1339.
[11] Allaire M, Dupont B, Nahon P, Ganne-Carrié N, Nault JC. Hepatocellular carcinoma: the impact of NAFLD. Curr Hepatol Rep 2016;15(3):190–198.
[12] Pais R, Fartoux L, Goumard C, Scatton O, Wendum D, Rosmorduc O, et al. Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period. Aliment Pharmacol Ther 2017;46(9):856–863.
[13] Allaire M, Gilgenkrantz H. The impact of steatosis on liver regeneration. Horm Mol Biol Clin Investig 2018;41(1).
[14] Kele PG, van der Jagt EJ, Gouw ASH, Lisman T, Porte RJ, de Boer MT. The impact of hepatic steatosis on liver regeneration after partial hepatectomy. Liver Int 2013;33(3):469–475.
[15] Bhayani NH, Hyder O, Frederick W, Schulick RD, Wolgang CL, Hirose K, et al. Effect of metabolic syndrome on perioperative outcomes after liver surgery: a National Surgical Quality Improvement Program (NSQIP) analysis. Surgery 2012;152(2):218–226.
[16] Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, et al. Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. Br J Surg 2013;100(1):113–121.
[17] Reddy SK, Steel JL, Chen H-W, DeMateo DJ, Cardinal J, Behari J, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology 2012;55(6):1809–1819.
[18] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30(6):1434–1440.
[19] Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol 2015;62(3):617–624.
[20] Farges O, Belghiti J, Kianmanesh R, Marc Regimbeau J, Santoro R, Vilgrain V, et al. Portal vein embolization before right hepatectomy. Ann Surg 2003;237(2):208–217.
[21] Imamura H, Shimada R, Kubota M, Matsuyama Y, Nakayama A, Miyagawa S, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29(4):1099–1105.
[22] de Franchis R, Faculty BV. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53(4):762–768.
[23] Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134(7):1908–1916.
[24] Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Terzi E, Bolondi L, et al. Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. Clin Cancer Res 2012;18(16):4397–4405.
[25] Roayaie S, Jibara G, Tabrizian P, Park J-W, Yang J, Yan L, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62(2):440–451.
[26] Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, et al. Resection of hepatocellular cancer ≤2 cm: results from two Western centers. Hepatology 2013;57(4):1426–1435.
[27] Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology 2010;51(4):1284–1290.
[28] Lee HW, Lee JM, Yoon JH, Kim YJ, Park JW, Park SJ, et al. A prospective randomized study comparing radiofrequency ablation and hepatic resection for hepatocellular carcinoma. Ann Surg Treat Res 2018;94(2):74–82.
[29] Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg 2017;104(13):1775–1784.
[30] Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. J Gastroenterol Hepatol 2014;29(1):193–200.
[31] Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012;57(4):794–802.
[32] Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010;252(6):903–912.
[33] Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243(3):321–328.
[34] Lü M, Kuang M, Liang L, Xie X, Peng B, Liu G, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial. Zhonghua Yi Xue Za Zhi 2006;86(12):801–805.
[35] Pinna AD, Yang T, Mazzaferro V, De Carlis L, Zhou J, Roayaie S, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. Ann Surg 2018;268(5):868–875.
[36] Tribillon E, Barbier L, Goumard C, Irtan S, Perdigao-Cotta F, Durand F, et al. When should we propose liver transplant after resection of hepatocellular carcinoma? A comparison of salvage and de principe strategies. J Gastrointest Surg 2016;20(1):66–76. discussion 76.
[37] Ferrer-Fàbrega J, Forner A, Liccioni A, Miquel R, Molina V, Navasa M, et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology 2016;63(3):839–849.
[38] Abu-Gazala S, Olthoff KM. Current status of living donor liver transplantation in the United States. Annu Rev Med 2019;70:225–238.
[39] Kulik LM, Fisher RA, Rodrigo DR, Brown Jr RS, Freise CE, Shaked A, et al. Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: results of the A2ALL cohort†. Am J Transplant 2012;12(11):2997–3007.
[40] Goldaracena N, Gorgen A, Doyle A, Hansen BE, Tomiyama K, Zhang W, et al. Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival vs. deceased donation. J Hepatol 2019;70(4):666–673.
[41] Wong TCL, Ng KKC, Fung JYY, Chan AAC, Cheung TT, Chok KSH, et al. Long-term survival outcome between living donor and deceased donor liver transplant for hepatocellular carcinoma: intention-to-treat and propensity score matching analyses. Ann Surg Oncol 2019;26(5):1454–1462.
[42] Azoulay D, Audureau E, Bangi P, Belghiti J, Boillot O, Andreani P, et al. Living or brain-dead donor liver transplantation for hepatocellular carcinoma: a multicenter, western, intent-to-treat cohort study. Ann Surg 2017;266(6):1035–1044.
[43] Bhangui P, Vibert E, Majno P, Salloum C, Andreani P, Zocrato J, et al. Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus deceased donor transplantation. Heparology 2011;53(5):1570–1579.
[44] Rajakannu M, Cherqui D, Ciacio O, Golse N, Pittau G, Allard MA, et al. Liver stiffness measurement by transient elastography predicts late posthepatectomy outcomes in patients undergoing resection for hepatocellular carcinoma. Surgery 2017;162(4):766–774.
[45] Chong CCN, Wong GLH, Chan AWH, Wong VWS, Fong AKW, Cheung Y-S, et al. Liver stiffness measurement predicts high-grade post-hepatectomy liver failure: a prospective cohort study. J Gastroenterol Hepatol 2017;32(2):506–514.
[46] Li C, Zhang JY, Zhang XY, Wen TF, Yan LN. FibroScan predicts ascites after liver resection for hepatitis B virus-related hepatocellular carcinoma: a prospective cohort study. Int J Surg 2015;20:21–25.

[47] Wong JSW, Wong GLH, Chan AWH, Wong VWS, Cheung YS, Chong CN, et al. Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. Ann Surg 2013;257(5):922–928.
[48] Cescon M, Colecchia A, Cucchetti A, Peri E, Montrone L, Ercolani G, et al. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. Ann Surg 2012;256(5):706–712. discussion 712–3.
[49] Kim SU, Ahn SH, Park JY, Kim DY, Chon CY, Choi JS, et al. Prediction of postoperative hepatic insufficiency by liver stiffness measurement (FibroScan) before curative resection of hepatocellular carcinoma: a pilot study. Hepatol Int 2008;2(4):471–477.
[50] Huang Z, Huang J, Zhou T, Cao H, Tan B. Prognostic value of liver stiffness measurement for the liver-related surgical outcomes of patients under hepatic resection: a meta-analysis. PLoS One 2018;13(1):e0190512.
[51] Rinaldi L, Guarino M, Perrella A, Pafundi PC, Valente G, Fontanella L, et al. Role of liver stiffness measurement in predicting HCC occurrence in direct-acting antivirals setting: a real-life experience. Dig Dis Sci 2019;64(10):3013–3019.
[52] Dh L, Jm L, Nj Y, Kw L, Ks S, Jh L, et al. Hepatic stiffness measurement by using MR elastography: prognostic values after hepatic resection for hepatocellular carcinoma. Eur Radiol 2016;27(4):1713–1721.
[53] De Gasperi A, Mazza E, Prosperi M. Indocyanine green kinetics to assess liver function: ready for a clinical dynamic assessment in major liver surgery? World J Hepatol 2016;8(7):355–367.
[54] Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 2005;12(1):16–22.
[55] Zhang ZQ, Xiong L, Zhou JJ, Miao XY, Li QL, Wen Y, et al. Ability of the ALBI grade to predict posthepatectomy liver failure and long-term survival after liver resection for different BCLC stages of HCC. World J Surg Oncol 2018;16:208.
[56] Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 2017;66(2):338–346.
[57] Wang YY, Zhong JH, Su ZY, Huang JF, Lu SD, Xiang BD, et al. Albumin-bilirubin versus Child-Pugh score as a predictor of outcome after liver resection for hepatocellular carcinoma. Br J Surg 2016;103(6):725–734.
[58] Ma XL, Zhou JY, Gao XH, Tian L, Wu J, Zhang CY, et al. Application of the albumin-bilirubin grade for predicting prognosis after curative resection of patients with early-stage hepatocellular carcinoma. Clin Chim Acta 2016;462:15–22.
[59] Kato A, Nakamoto Y, Ishimori T, Seo S, Uemoto S, Togashi K. Predictability of 99mTc-galactosyl human serum albumin scintigraphy for posthepatectomy liver failure. AJR Am J Roentgenol 2018;210(1):158–165.
[60] Mizutani Y, Hirai T, Nagamachi S, Nanashima A, Yano K, Kondo K, et al. Prediction of posthepatectomy liver failure proposed by the international study group of liver surgery: residual liver function estimation with 99mTc-galactosyl human serum albumin scintigraphy. Clin Nucl Med 2018;43(2):77–81.
[61] Haimerl M, Verloh N, Zeman F, Fellner C, Nickel D, Lang SA, et al. Gd-EOB-DTPA-enhanced MRI for evaluation of liver function: comparison between signal-intensity-based indices and T1 relaxometry. Sci Rep 2017;7:43347.
[62] Kubota K, Tamura T, Aoyama N, Nogami M, Hamada N, Nishioka A, et al. Correlation of liver parenchymal gadolinium-ethoxybenzyl diethylenetriaminepentaacetic acid enhancement and liver function in humans with hepatocellular carcinoma. Oncol Lett 2012;3(5):990–994.
[63] Lin CY, Chang WC, Chou CT, Chen RC. Dynamic-contrast-enhanced magnetic resonance imaging of cirrhotic liver parenchyma: a comparison between gadolinium–diethylenetriamine pentaacetic acid and gadolinium–ethoxybenzyl–diethylenetriamine pentaacetic acid. J Chin Med Assoc 2015;78(11):666–672.
[64] Ippolito D, Pecorelli A, Famularo S, Bernasconi D, Orsini EB, Giani A, et al. Assessing liver function: diagnostic efficacy of parenchymal enhancement and liver volume ratio of Gd-EOB-DTPA-enhanced MRI study during interstitial and hepatobiliary phase. Abdom Radiol N Y 2019;44(4):1340–1349.
[65] Geisel D, Raabe P, Lüdemann L, Malinowski M, Stockmann M, Seehofer D, et al. Gd-EOB-DTPA-enhanced MRI for monitoring future liver remnant function after portal vein embolization and extended hemihepatectomy: a prospective trial. Eur Radiol 2017;27(7):3080–3087.
[66] Hobeika C, Cauchy F, Sartoris R, Beaufrère A, Yoh T, Vilgrain V, et al. Relevance of liver surface nodularity for preoperative risk assessment in patients with resectable hepatocellular carcinoma. Br J Surg 2020;107(7):878–888.
[67] Peng W, Li JW, Zhang XY, Li C, Wen TF, Yan LN, et al. A novel model for predicting posthepatectomy liver failure in patients with hepatocellular carcinoma. PLoS One 2019;14(7):e0219219.
[68] Peng W, Zhang XY, Li C, Wen TF, Yan LN, Yang JY. Spleen stiffness and volume help to predict posthepatectomy liver failure in patients with hepatocellular carcinoma. Medicine (Baltimore) 2019;98(18):e15458.
[69] Marasco G, Colecchia A, Colli A, Ravaioli F, Casazza G, Bacchi Reggiani ML, et al. Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection. J Hepatol 2019;70(3):440–448.
[70] Stefanescu H, Rusu C, Lupsor-Platon M, Nicoara Farcau O, Fischer P, Grigoras C, et al. Liver stiffness assessed by ultrasound shear wave elastography from general electric accurately predicts clinically significant portal hypertension in patients with advanced chronic liver disease. Ultraschall Med 2019. https://doi.org/10.1055/a-0965-0745.
[71] Thiele M, Hugger MB, Kim Y, Rautou PE, Elkrief L, Jansen C, et al. 2D shear wave liver elastography by Aixplorer to detect portal hypertension in cirrhosis: an individual patient data meta-analysis. Liver Int 2020;40(6):1435–1446.
[72] Jansen C, Bogs C, Verlinden W, Thiele M, Möller P, Görtzen J, et al. Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension: a prospective multicentre study. Liver Int 2017;37(3):396–405.
[73] Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015;275(2):589–598.
[74] Ronot M, Lambert S, Elkrief L, Doblas S, Rautou P-E, Castera L, et al. Assessment of portal hypertension and high-risk oesophageal varices with liver and spleen three-dimensional multifrequency MR elastography in liver cirrhosis. Eur Radiol 2014;24(6):1394–1402.
[75] Nedredal GI, Yin M, McKenzie T, Lillegard J, Luebke-Wheeler J, Talwalkar J, et al. Portal hypertension correlates with splenic stiffness as measured with MR elastography. J Magn Reson Imaging 2011;34(1):79–87.
[76] Sartoris R, Rautou PE, Elkrief L, Pollorsi G, Durand F, Valla D, et al. Quantification of liver surface nodularity at CT: utility for detection of portal hypertension. Radiology 2018;289(3):698–707.
[77] Berardi G, Morise Z, Sposito C, Igarashi K, Panetta V, Simonelli I, et al. Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in Child-Pugh B cirrhosis. J Hepatol 2020;72(1):75–84.
[78] Chan MY, She WH, Dai WC, Tsang SHY, Chok KSH, Chan ACY, et al. Prognostic value of preoperative alpha-fetoprotein (AFP) level in patients receiving curative hepatectomy- an analysis of 1,182 patients in Hong Kong. Transl Gastroenterol Hepatol 2019;4:52.
[79] Kamiyama T, Nakagawa T, Nakanishi K, Kamachi H, Onodera Y, Matsushita M, et al. Preoperative evaluation of hepatic vasculature by three-dimensional computed tomography in patients undergoing hepatectomy. World J Surg 2006;30(3):400–409.
[80] Mise Y, Hasegawa K, Satou S, Shindoh J, Miki K, Akamatsu N, et al. How has virtual hepatectomy changed the practice of liver surgery?: experience of 1194 virtual hepatectomy before liver resection and living donor liver transplantation. Ann Surg 2018;268(1):127–133.
[81] Yang T, Lin S, Xie Q, Ouyang W, Tan T, Li J, et al. Impact of 3D printing technology on the comprehension of surgical liver anatomy. Surg Endosc 2019;33(2):411–417.
[82] Truant S, Bouras AF, Petrovai G, Buob D, Ernst O, Boleslawski E, et al. Volumetric gain of the liver after major hepatectomy in obese patients: a case-matched study in 84 patients. Ann Surg 2013;258(5):696–702. discussion 702–704.
[83] Terasawa M, Allard MA, Golse N, Sa Cunha A, Cherqui D, Adam R, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization alone before major hepatectomy for patients with large hepatocellular carcinoma: an intent-to-treat analysis. Surgery 2020;167(2):425–431.
[84] Aoki T, Imamura H, Hasegawa K, Matsukura A, Sano K, Sugawara Y, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. Arch Surg 2004;139(7):766–774.

[85] Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg 2006;93(9):1091–1098.
[86] Esposito F, Lim C, Lahat E, Shwaartz C, Eshkenazy R, Salloum C, et al. Combined hepatic and portal vein embolization as preparation for major hepatectomy: a systematic review. HPB 2019;21(9):1099–1106.
[87] Guiu B, Quenet F, Escal L, Bibeau F, Piron L, Rouanet P, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. Eur Radiol 2017;27(8):3343–3352.
[88] Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255(3):405–414.
[89] Croome KP, Hernandez-Alejandro R, Parker M, Heimbach J, Rosen C, Nagorney DM. Is the liver kinetic growth rate in ALPPS unprecedented when compared with PVE and living donor liver transplant? A multicentre analysis. HPB 2015;17(6):477–484.
[90] Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260(5):829–836. discussion 836–838.
[91] Wang Z, Peng Y, Hu J, Wang X, Sun H, Sun J, et al. Associating liver partition and portal vein ligation for staged hepatectomy for unresectable hepatitis B virus-related hepatocellular carcinoma: a single center study of 45 patients. Ann Surg 2020;271(3):534–541.
[92] Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg 2012;256(3):e9. author reply e16–19.
[93] D'Haese JG, Neumann J, Weniger M, Pratschke S, Björnsson B, Ardiles V, et al. Should ALPPS be used for liver resection in intermediate-stage HCC? Ann Surg Oncol 2016;23(4):1335–1343.
[94] Chan ACY, Chok K, Dai JWC, Lo CM. Impact of split completeness on future liver remnant hypertrophy in associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) in hepatocellular carcinoma: complete-ALPPS versus partial-ALPPS. Surgery 2017;161(2):357–364.
[95] Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138(1):52–64.
[96] Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36(19):1913–1921.
[97] Chauhan N, Bukovcan J, Boucher E, Cosgrove D, Edeline J, Hamilton B, et al. Intra-Arterial TheraSphere yttrium-90 glass microspheres in the treatment of patients with unresectable hepatocellular carcinoma: protocol for the STOP-HCC phase 3 randomized controlled trial. JMIR Res Protoc 2018;7(8):e11234.
[98] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18(12):1624–1636.
[99] Gabr A, Abouchaleh N, Ali R, Baker T, Caicedo J, Katariya N, et al. Outcomes of surgical resection after radioembolization for hepatocellular carcinoma. J Vasc Interv Radiol 2018;29(11):1502–1510.e1.
[100] Edeline J, Lenoir L, Boudjema K, Rolland Y, Boulic A, Le Du F, et al. Volumetric changes after (90)y radioembolization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? Ann Surg Oncol 2013;20(8):2518–2525.
[101] Theysohn JM, Ertle J, Müller S, Schlaak JF, Nensa F, Sipilae S, et al. Hepatic volume changes after lobar selective internal radiation therapy (SIRT) of hepatocellular carcinoma. Clin Radiol 2014;69(2):172–178.
[102] Garlipp B, de Baere T, Damm R, Irmscher R, van Buskirk M, Stübs P, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatology 2014;59(5):1864–1873.
[103] Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, Lemoine A, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg 2000;232(5):665–672.
[104] Alvarez FA, Castaing D, Figueroa R, Allard MA, Golse N, Pittau G, et al. Natural history of portal vein embolization before liver resection: a 23-year analysis of intention-to-treat results. Surgery 2018;163(6):1257–1263.
[105] Goumard C, Farges O, Laurent A, Cherqui D, Soubrane O, Gayet B, et al. An update on laparoscopic liver resection: the French Hepato-Bilio-Pancreatic Surgery Association statement. J Visc Surg 2015;152(2):107–112.
[106] Cherqui D, Laurent A, Tayar C, Chang S, Van Nhieu JT, Loriau J, et al. Laparoscopic liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: midterm results and perspectives. Ann Surg 2006;243(4):499–506.
[107] Sarpel U, Hefti MM, Wisnievsky JP, Roayaie S, Schwartz ME, Labow DM. Outcome for patients treated with laparoscopic versus open resection of hepatocellular carcinoma: case-matched analysis. Ann Surg Oncol 2009;16(6):1572–1577.
[108] Nguyen KT, Marsh JW, Tsung A, Steel JJL, Gamblin TC, Geller DA. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg 2011;146(3):348–356.
[109] Kasai M, Cipriani F, Gayet B, Aldrighetti L, Ratti F, Sarmiento JM, et al. Laparoscopic versus open major hepatectomy: a systematic review and meta-analysis of individual patient data. Surgery 2018;163(5):985–995.
[110] Di Sandro S, Danieli M, Ferla F, Lauterio A, De Carlis R, Benuzzi L, et al. The current role of laparoscopic resection for HCC: a systematic review of past ten years. Transl Gastroenterol Hepatol 2018;3:68.
[111] Morise Z, Sugioka A, Kawabe N, Umemoto S, Nagata H, Ohshima H, et al. Pure laparoscopic hepatectomy for hepatocellular carcinoma patients with severe liver cirrhosis. Asian J Endosc Surg 2011;4(3):143–146.
[112] Xiangfei M, Yinzhe X, Yingwei P, Shichun L, Weidong D. Open versus laparoscopic hepatic resection for hepatocellular carcinoma: a systematic review and meta-analysis. Surg Endosc 2019;33(8):2396–2418.
[113] Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, et al. The Southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation. Ann Surg 2018;268(1):11–18.
[114] Kawaguchi Y, Fuks D, Kokudo N, Gayet B. Difficulty of laparoscopic liver resection: proposal for a new classification. Ann Surg 2018;267(1):13–17.
[115] Goumard C, Komatsu S, Brustia R, Fartoux L, Soubrane O, Scatton O. Technical feasibility and safety of laparoscopic right hepatectomy for hepatocellular carcinoma following sequential TACE-PVE: a comparative study. Surg Endosc 2017;31(5):2340–2349.
[116] Levi Sandri GB, Lai Q, Ravaioli M, Di Sandro S, Balzano E, Pagano D, et al. The role of salvage transplantation in patients initially treated with open vs minimally invasive liver surgery: an intention-to-treat analysis. Liver Transpl 2020;26(5):878–887.
[117] Takasaki K. Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. J Hepatobiliary Pancreat Surg 1998;5(3):286–291.
[118] Figueroa R, Laurenzi A, Laurent A, Cherqui D. Perihilar Glissonian approach for anatomical parenchymal sparing liver resections: technical aspects: the Taping Game. Ann Surg 2018;267(3):537–543.
[119] Miyata A, Ishizawa T, Tani K, Shimizu A, Kaneko J, Aoki T, et al. Reappraisal of a dye-staining technique for anatomic hepatectomy by the concomitant use of indocyanine green fluorescence imaging. J Am Coll Surg 2015;221(2):e27–e36.
[120] Majlesara A, Golriz M, Hafezi M, Saffari A, Stenau E, Maier-Hein L, et al. Indocyanine green fluorescence imaging in hepatobiliary surgery. Photodiagnosis Photodyn Ther 2017;17:208–215.
[121] Aoki T, Yasuda D, Shimizu Y, Odaira M, Niiya T, Kusano T, et al. Image-guided liver mapping using fluorescence navigation system with indocyanine green for anatomical hepatic resection. World J Surg 2008;32(8):1763–1767.
[122] Aoki T, Murakami M, Yasuda D, Shimizu Y, Kusano T, Matsuda K, et al. Intraoperative fluorescent imaging using indocyanine green for liver mapping and cholangiography. J Hepatobiliary Pancreat Sci 2010;17(5):590–594.
[123] Kobayashi Y, Kawaguchi Y, Kobayashi K, Mori K, Arita J, Sakamoto Y, et al. Portal vein territory identification using indocyanine green fluorescence imaging: technical details and short-term outcomes. J Surg Oncol 2017;116(7):921–931.
[124] Inoue Y, Arita J, Sakamoto T, Ono Y, Takahashi M, Takahashi Y, et al. Anatomical liver resections guided by 3-dimensional parenchymal staining using fusion indocyanine green fluorescence imaging. Ann Surg 2015;262(1):105–111.
[125] Ishizawa T, Saiura A, Kokudo N. Clinical application of indocyanine green-fluorescence imaging during hepatectomy. Hepatobiliary Surg Nutr 2016;5(4):322–328.

[126] Ishizawa T, Masuda K, Urano Y, Kawaguchi Y, Satou S, Kaneko J, et al. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol 2014;21(2):440–448.
[127] Morita Y, Sakaguchi T, Unno N, Shibasaki Y, Suzuki A, Fukumoto K, et al. Detection of hepatocellular carcinomas with near-infrared fluorescence imaging using indocyanine green: its usefulness and limitation. Int J Clin Oncol 2013;18(2):232–241.
[128] Rhaiem R, Piardi T, Chetboun M, Pessaux P, Lestra T, Memeo R, et al. Portal inflow modulation by somatostatin after major liver resection: a pilot study. Ann Surg 2018;267(6):e101–e103.
[129] Amato B, Aprea G, De Rosa D, Milone M, di Domenico L, Amato M, et al. Laparoscopic hepatectomy for HCC in elderly patients: risks and feasibility. Aging Clin Exp Res 2017;29(Suppl 1):179–183.
[130] Nomi T, Hirokawa F, Kaibori M, Ueno M, Tanaka S, Hokuto D, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a multi-centre propensity score-based analysis. Surg Endosc 2020;34(2):658–666.
[131] Yu X, Yan YC, Chen G, Yu H. The efficacy and safety of totally laparoscopic hepatectomy for non-cirrhotic hepatocellular carcinoma in the elderly. BMC Surg 2018;18(1):118.
[132] Andert A, Lodewick T, Ulmer TF, Schmeding M, Schöning W, Neumann U, et al. Liver resection in the elderly: a retrospective cohort study of 460 patients - feasible and safe. Int J Surg 2016;28:126–130.
[133] Cauchy F, Fuks D, Nomi T, Dokmak S, Scatton O, Schwarz L, et al. Benefits of laparoscopy in elderly patients requiring major liver resection. J Am Coll Surg 2016;222(2):174–184.e10.
[134] Lim C, Osseis M, Lahat E, Doussot A, Sotirov D, Hemery F, et al. Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study. Surg Endosc 2019;33(3):811–820.
[135] Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: the Louisville Statement, 2008. Ann Surg 2009;250(5):825–830.
[136] Magistri P, Tarantino G, Assirati G, Olivieri T, Catellani B, Guerrini GP, et al. Robotic liver resection for hepatocellular carcinoma: a systematic review. Int J Med Robot 2019;15(4):e2004.
[137] Kawai T, Goumard C, Jeune F, Savier E, Vaillant J-C, Scatton O. Laparoscopic liver resection for colorectal liver metastasis patients allows patients to start adjuvant chemotherapy without delay: a propensity score analysis. Surg Endosc 2018;32(7):3273–3281.
[138] Giulianotti PC, Coratti A, Sbrana F, Addeo P, Bianco FM, Buchs NC, et al. Robotic liver surgery: results for 70 resections. Surgery 2011;149(1):29–39.
[139] Lai ECH, Yang GPC, Tang CN. Robot-assisted laparoscopic liver resection for hepatocellular carcinoma: short-term outcome. Am J Surg 2013;205(6):697–702.
[140] Chen P-D, Wu C-Y, Hu R-H, Chou W-H, Lai H-S, Liang J-T, et al. Robotic versus open hepatectomy for hepatocellular carcinoma: a matched comparison. Ann Surg Oncol 2017;24(4):1021–1028.
[141] Magistri P, Tarantino G, Guidetti C, Assirati G, Olivieri T, Ballarin R, et al. Laparoscopic versus robotic surgery for hepatocellular carcinoma: the first 46 consecutive cases. J Surg Res 2017;217:92–99.
[142] Imura S, Shimada M, Utsunomiya T, Morine Y, Ikemoto T, Mori H, et al. Impact of splenectomy in patients with liver cirrhosis: results from 18 patients in a single center experience. Hepatol Res 2010;40(9):894–900.
[143] Ikegami T, Shimada M, Imura S. Recent role of splenectomy in chronic hepatic disorders. Hepatol Res 2008;38(12):1159–1171.
[144] Tomikawa M, Hashizume M, Akahoshi T, Shimabukuro R, Gotoh N, Ohta M, et al. Effects of splenectomy on liver volume and prognosis of cirrhosis in patients with esophageal varices. J Gastroenterol Hepatol 2002;17(1):77–80.
[145] Sugawara Y, Yamamoto J, Shimada K, Yamasaki S, Kosuge T, Takayama T, et al. Splenectomy in patients with hepatocellular carcinoma and hypersplenism. J Am Coll Surg 2000;190(4):446–450.
[146] Zhang X-Y, Li C, Wen T-F, Yan L-N, Li B, Yang J-Y, et al. Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: a case-control study. World J Gastroenterol 2015;21(8):2358–2366.
[147] Miyoshi A, Ide T, Kitahara K, Noshiro H. Appraisal of simultaneous laparoscopic splenectomy and hepatic resection in the treatment of hepatocellular carcinoma with hypersplenic thrombocytopenia. Hepatogastroenterology 2013;60(127):1689–1692.
[148] Kong J, Shen S, Wang W. Synchronous hepatectomy and splenectomy vs hepatectomy for selected patients with hepatocellular carcinoma and clinically significant portal hypertension: a systematic review and meta-analysis. J Surg Oncol 2019;119(7):964–973.
[149] Yin L, Li H, Li A-J, Lau WY, Pan Z-Y, Lai ECH, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: a RCT. J Hepatol 2014;61(1):82–88.
[150] Zhong JH, Xiang BD, Gong WF, Ke Y, Mo QG, Ma L, et al. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. PLoS One 2013;8(7):e68193.
[151] Zhong J, Ke Y, Gong W, Xiang B, Ma L, Ye X, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014;260(2):329–340.
[152] Hsu CY, Hsia CY, Huang YH, Su CW, Lin HC, Pai JT, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. Ann Surg Oncol 2012;19(3):842–849.
[153] Lin CT, Hsu KF, Chen TW, Yu JC, Chan DC, Yu CY, et al. Comparing hepatic resection and transarterial chemoembolization for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? World J Surg 2010;34(9):2155–2161.
[154] Koh YX, Tan HL, Lye WK, Kam JH, Chiow AKH, Tan SS, et al. Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic Liver Cancer stage hepatocellular carcinoma: a critical appraisal of the evidence. World J Hepatol 2018;10(6):433–447.
[155] Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind J-FH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016;64(1):106–116.
[156] Fukami Y, Kaneoka Y, Maeda A, Kumada T, Tanaka J, Akita T, et al. Liver resection for multiple hepatocellular carcinomas: a Japanese nationwide survey. Ann Surg 2019;272(1):145–154.
[157] Ikai I, Kudo M, Arii S, Omata M, Kojiro M, Sakamoto M, et al. Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatol Res 2010;40(11):1043–1059.
[158] Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57(4):821–829.
[159] Shi J, Lai ECH, Li N, Guo WX, Xue J, Lau WY, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2010;17(8):2073–2080.
[160] Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. Hepatology 2017;66(2):510–517.
[161] Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65(5):938–943.
[162] Ban D, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y, et al. Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. J Gastrointest Surg 2009;13(11):1921–1928.
[163] Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. J Clin Oncol 2019;37(24):2141–2151.
[164] Ho MC, Hasegawa K, Chen XP, Nagano H, Lee YJ, Chau GY, et al. Surgery for intermediate and advanced hepatocellular carcinoma: a consensus report from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014). Liver Cancer 2016;5(4):245–256.
[165] Nakamura A, Esaki M, Nakagawa K, Asakura K, Kishi Y, Nara S, et al. Three risk factors for pulmonary metastasectomy in patients with hepatocellular carcinoma. Gen Thorac Cardiovasc Surg 2019;67(9):782–787.
[166] Kuo TM, Chang KM, Cheng TI, Kao KJ. Clinical factors predicting better survival outcome for pulmonary metastasectomy of hepatocellular carcinoma. Liver Cancer 2017;6(4):297–306.
[167] Hu Z, Li W, Huang P, Zhou Z, Xu J, Xu K, et al. Therapeutic significance and indications of pulmonary metastasectomy for hepatocellular carcinoma following liver resection. Int J Surg Lond Engl 2017;48:23–31.
[168] Takahashi Y, Ikeda N, Nakajima J, Sawabata N, Chida M, Horio H, et al. Prognostic analysis of surgical resection for pulmonary metastasis from hepatocellular carcinoma. World J Surg 2016;40(9):2178–2185.
[169] Berger Y, Spivack JH, Heskel M, Aycart SN, Labow DM, Sarpel U. Extrahepatic metastasectomy for hepatocellular carcinoma: predictors of long-term survival. J Surg Oncol 2017;115(4):505–506.

[170] Jung SM, Jang JW, You CR, Yoo SH, Kwon JH, Bae SH, et al. Role of intrahepatic tumor control in the prognosis of patients with hepatocellular carcinoma and extrahepatic metastases. J Gastroenterol Hepatol 2012;27(4):684–689.
[171] Zhang Y, Huang G, Wang Y, Liang L, Peng B, Fan W, et al. Is salvage liver resection necessary for initially unresectable hepatocellular carcinoma patients downstaged by transarterial chemoembolization? Ten years of experience. Oncologist 2016;21(12):1442–1449.
[172] Kang WH, Hwang S, Song GW, Lee YJ, Kim KH, Ahn CS, et al. Prognostic effect of transarterial chemoembolization-induced complete pathological response in patients undergoing liver resection and transplantation for hepatocellular carcinoma. Liver Transpl 2017;23(6):781–790.
[173] Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol 2006;94(7):572–586.
[174] Labgaa I, Tabrizian P, Titano J, Kim E, Thung SN, Florman S, et al. Feasibility and safety of liver transplantation or resection after transarterial radioembolization with Yttrium-90 for unresectable hepatocellular carcinoma. HPB 2019;21(11):1497–1504.
[175] Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9(8):1920–1928.
[176] Yoh T, Seo S, Taura K, Iguchi K, Ogiso S, Fukumitsu K, et al. Surgery for recurrent hepatocellular carcinoma: achieving long-term survival. Ann Surg 2020. https://doi.org/10.1097/SLA.0000000000003358.
[177] Morise Z, Aldrighetti L, Belli G, Ratti F, Belli A, Cherqui D, et al. Laparoscopic repeat liver resection for hepatocellular carcinoma: a multicentre propensity score-based study. Br J Surg 2020;107(7):889–895.
[178] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100(10):698–711.
[179] Samuel M, Chow PK-H, Chan Shih-Yen E, Machin D, Soo K-C. Neoadjuvant and adjuvant therapy for surgical resection of hepatocellular carcinoma. Cochrane Database Syst Rev 2009;1:CD001199.
[180] Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16(13):1344–1354.
[181] Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet 2000;356(9232):802–807.