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REVIEW

Current concepts in hepatic resection for hepatocellular carcinoma in cirrhotic patients

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Abstract

Hepatocellular carcinoma (HCC) is one of the most frequent neoplasms worldwide and in most cases it is associated with liver cirrhosis. Liver resection is considered the most potentially curative therapy for HCC patients when liver transplantation is not an option or is not immediately accessible. This review is aimed at investigating the current concepts that drive the surgical choice in the treatment of HCC in cirrhotic patients; Eastern and Western perspectives are highlighted. An extensive literature review of the last two decades was performed, on topics covering various aspects of hepatic resection. Early post-operative and long-term outcome measures adopted were firstly analyzed in an attempt to define an optimal standardization useful for research comparison. The need to avoid the development of post-hepatectomy liver failure represents the "conditio sine qua non" of surgical choice and the role of the current tools available for the assessment of liver function reserve were investigated. Results of hepatic resection in relationship with tumor burden were compared with those of available competing strategies, namely, radiofrequency ablation for early stages, and trans-arterial chemoembolization for intermediate and advanced stages. Finally, the choice for anatomical versus non-anatomical, as well as the role of laparoscopic approach, was overviewed. The literature review suggests that partial hepatectomy for HCC should be considered in the context of multi-disciplinary evaluation of cirrhotic patients. Scientific research on HCC has moved, in recent years, from surgical therapy toward non-surgical approaches and most of the literature regarding topics debated in the present review is represented by observational studies, whereas very few well-designed randomized controlled trials are currently available; thus, no robust recommendations can be derived.

Key words: Hepatocellular carcinoma; Hepatic resection; Surgical therapy; Ablation techniques; Transplantation; Survival; Liver failure

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, represents the fifth most common cancer in men and the seventh in women[1].

The incidence of HCC varies widely in the different geographic areas according to the regional variations in exposure to risk factors for this tumor[1-14]. Overall, 75%-80% of HCCs are attributable to chronic hepatitis B virus (50%-55%) or hepatitis C virus (25%-30%) infections[3-7]. Chronic alcohol abuse, obesity, and diabetes have also been recognized as important risk factors, as well as hereditary hemochromatosis, primary biliary cirrhosis and several hereditary metabolic conditions[8-14]. In all etiologies there is a male gender predominance[1,8-14]. Most HCCs ensue in a cirrhotic liver, although the association rate between cirrhosis and HCC may range from 60% up to 90% in relation to the relative prevalences of the risk factors, that greatly differ worldwide[5].

Risk stratification has been proposed to identify patients who benefit from surveillance for HCC occurrence[5,13]. Indeed, surveillance can detect the tumor at early stages, amenable to curative treatments. The increasing use of surveillance in clinical practice and the advancements in diagnostic ability achieved in the last decades have greatly improved HCC management and patient survival[15,16]. Liver resection still remains a mainstay of HCC treatment, being a potentially curative approach not only for early stage HCCs but also for some lesions not amenable to liver transplantation. Thanks to the considerable improvements in surgical techniques and perioperative care, the rates of death and complications after liver resection have remarkably decreased over time, giving added value to this procedure[17,18]. In addition, the long-term survival after liver resection has been improved by the increased accuracy in detecting recurrences at early stages and the availability of potentially curative approaches even for patients no longer amenable to surgical re-treatment[19]. The present review examines concepts driving the therapeutic choice for HCC toward hepatic resection in cirrhotic patients, and its results in both the Western and Eastern world.

SELECTING ADEQUATE OUTCOME MEASURES

Early outcome measures

The most feared complication of hepatic resection is the development of post-hepatectomy liver failure (PHLF) which is the main cause of perioperative mortality. Currently, there is no standardized definition of PHLF that allows an unequivocal comparison of results from different studies[20]. This can explain, at least in part, the great variability of PHLF incidence, ranging from 1.2% to 32%, although differences in populations and surgical procedures may have contributed to this disparity[21-28]. The analysis of the postoperative course of liver tests demonstrates that serum bilirubin and INR ordinarily return within the normal range on postoperative day 5, including patients who have undergone major resections and those with cirrhosis[29,30]. A first attempt to standardize the definition of PHLF was made by Balzan *et al*[31]. In an unselected population including patients with primary and secondary liver tumors undergoing elective surgery (12% only with cirrhosis), the authors observed that the association of prothrombin time < 50% and serum total bilirubin > 50 μmL/L (2.9 mg/dL) on post-operative day 5 was a strong predictor of mortality ("50-50 criteria"). Namely, patients who met this criterion had a 59% early postoperative mortality rate, compared with 1.2% found in their counterparts. The usefulness of such a definition is boosted by the selection of simple and objective criteria, while its drawbacks are: (1) the lack of a grading system able to segregate several strata at increasing death risk; and (2) the late identification (only on post-operative day 5) of a category with a huge mortality rate. Thus, PHLF definition needs to be better graded and detected earlier to be of clinical utility.

In 2010, the International Study Group of Liver Surgery performed an extensive literature search and proposed to define post-hepatectomy liver failure as "the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after post-operative day 5"[20]. On the basis of this definition, the severity of PHLF should be graded based on its impact on clinical management (as the Dindo-Clavien classification[32]): grade A requires no change of the patient's clinical management; grade B needs the clinical management of patients to deviate from the regular course but not to require invasive therapy; grade C claims invasive treatment, for example liver transplantation[20]. Such a grading system overcomes the 50-50 criteria limits and well depicts the post-surgical course of patients; however, it is not liver specific, also being influenced by non-hepatic complications.

Long-term outcome measures

When selecting endpoints for studies, it should be considered that cirrhotic patients with HCC represent a peculiar oncologic category as their prognosis relies not only on the tumor burden but also on the severity of underlying liver disease. According to the guidelines released by the Panel of Experts in HCC-Design Clinical Trials, overall survival should be considered as the primary end-point for phase Ⅲ trials[33]. The document discourages the use of cancer-related mortality since it is a more subjective endpoint, particularly in HCC patients, in whom it can be difficult to ascertain the role played on mortality by the concurrent cirrhosis. Since the high rate of HCC recurrence is the main factor affecting survival after partial hepatectomy, many studies report composite endpoints including this adverse event, such as disease-free survival. However, such a composite endpoint can make the results unreliable because imbalance between groups in deaths, resulting from the natural history of cirrhosis, can mask the real benefit

provided by surgery (type Ⅱ error). Therefore, disease-free survival should be considered as a tertiary end-point (indirect surrogate), and its use as main endpoint necessarily implies a restrictive selection of patients with well-preserved liver function to minimize the impact of death unrelated to tumor progression[33]. As mentioned above, tumor recurrence represents the main obstacle in achieving better results from hepatic surgery and recent efforts were directed toward adjuvant therapies aimed at reducing such an event[34-36]. In these scenarios, *time-to-recurrence* or *recurrence-rate* can be used as primary and/or secondary end-points for phase Ⅱ and Ⅲ HCC studies assessing the outcome of hepatic resection and the utility of such therapies, such as sorafenib, capecitabine or interferon-based therapies[34-36]. Even if there is currently no high level evidence for efficacy of any adjuvant protocols proposed until now, the correct choice of clinical endpoints is essential to detect an actual treatment advantage[37].

ASSESSMENT OF LIVER FUNCTION RESERVE

HCC ensued in a cirrhotic liver represents an extremely heterogeneous clinical condition in which several treatments may potentially be considered, according to the tumor stage and liver function[38]. The assessment of the latter is therefore essential in selecting the optimal strategy to adopt. The estimation of hepatic functional reserve before liver surgery is aimed at achieving proper patient selection and predicting, on an individual basis, the safety limit of the parenchymal resection. This may be performed with different tools.

Child-Turcotte-Pugh classification

The Child-Turcotte-Pugh (CTP) score is a simple system for grading liver function based on five easily measurable variables and has been considered a gold standard for more than four decades for selecting candidates for surgical resection. Indeed, there is general agreement that, in cirrhotic patients belonging to CTP class A, surgical resection can be safely performed. However, even Child-Pugh class A patients may develop hepatic decompensation following surgery due to limited functional hepatic reserve[21,23,26]. Thus, the CTP score is not able to identify, among class A patients, those with an elevated risk of post-surgical liver failure, a drawback that can be defined as a "floor effect". Other tools for assessing the underlying liver disease of candidates for surgery are therefore proposed.

Model for end-stage liver disease score

The model for end-stage liver disease (MELD) score was developed for survival prediction of patients undergoing the transjugular intrahepatic portosystemic shunt procedure[39] and has been principally adopted for selecting patients for liver transplantation[40]. The use of MELD for predicting surgical risk in the non-transplant setting has provided good results, and it may thus ultimately supplant the CTP classification as the method for determining surgical risk. Evidence has been provided that good candidates for partial hepatectomy should have a MELD score $\leqslant 10$[23,41-43]. These patients will not experience mortality or post-hepatectomy liver failure and will have very low morbidity. Above this threshold, the morbidity rate is very high (up to 50%), with an unacceptable probability of developing irreversible hepatic failure (up to 15%) and dying (up to 29%)[23,41-43]. Thus, patients with a MELD score > 10 should be considered for hepatic resection only in the setting of salvage transplantation[23]. The pros of adopting the MELD score are represented by the fact that it does not require any extra-routine evaluation; the cons are represented by the fact that this score, being developed on a population quite different from surgical series[39], requires further validation before being universally adopted in this setting.

Indocyanine green clearance test

The indocyanine green (ICG) clearance test is a popular liver function test in Asia. The cut-off of ICG retention rate at 15 min (ICGR-15) after intravenous injection of the dye that allows safe major hepatectomy is 14%[44]. Indeed, the safe cut-off value for major hepatectomy can be pushed to 17% and to 22% for minor hepatectomy; limited resection may be allowed for ICGR-15 values up to 40%[45-47]. However, these suggested thresholds derive from populations including cirrhotic and non-cirrhotic patients[45-47] and to what extent these cut-offs are applicable to cirrhotic patients remains unsettled. The ICG test may overcome the above mentioned drawbacks of the CTP score system. Indeed, about 65% of CTP class B patients have been shown to have an ICGR-15 < 22%[48]; thus, the evaluation on the basis of the Child-Pugh classification only would lead to the exclusion of a large proportion of CTP B patients from surgery[47]. The ICG R15 was recommended (grade B strength) for assessing liver function before surgery in the recent Japanese evidence-based clinical guidelines for the treatment of hepatocellular carcinoma[49]. Indeed, ICGR-15 is easily applicable to all patients, and represents a routine exam in Eastern countries. Nevertheless, this test is unpopular in Western countries, and this drawback limits the reliability of its results in a clinical scenario where higher proportions of hepatitis C infected and cirrhotic patients can be expected as compared with Eastern countries.

In the setting of hepatic resection, there is no study that compared the utility of MELD score and ICGR-15, or challenged their combination against each single test. A recent report, comparing MELD score and ICGR-15 in the prognosis of a cohort of 395 cirrhotic patients not undergoing surgery, suggested that ICG half-life was the most accurate in predicting survival[48]. This result was at variance with a smaller study conducted on 90

patients with decompensated cirrhosis reporting a better prognostic accuracy of the MELD score[50]. Comparative data on MELD and ICGR-15 in the field of hepatic resection are warranted.

Hepatic vein portal gradient

The presence of clinical signs of portal hypertension implies a more advanced liver disease and, consequently, a poorer long-term outcome after hepatic resection. The Barcelona Clinic Liver Cancer (BCLC) group recommends hepatic resection only in patients without clinically significant portal hypertension, i.e. with a hepatic vein portal gradient (HVPG) < 10 mmHg[13]. This is supported by data obtained in a small cohort (77 patients) studied in the 1990s[51] and without external validation until recently[52]. Data from 39 patients, 46% of whom with cirrhosis, undergoing hepatic resection after HVPG measurement showed a higher incidence of post-operative liver dysfunction and ascites in patients with HVPG > 5 mmHg[52]. However, the small sample size and the proposed HVPG cut-off, that is roughly equivalent to the lowest value observed in cirrhotic patients of 6 mmHg[53], do not help in clarifying the true usefulness of HVPG in the selection of candidates for hepatic resection. It can be said that the HVPG measurement can probably select surgical candidates, belonging to CTP class A, with a very low probability of post-operative hepatic decompensation; however, the drawback is represented by the exclusion of patients that can still benefit from surgery. In fact, there is growing evidence, coming from large Western[54,55] and Eastern series[56], that the presence of clinical signs of portal hypertension does not affect early postoperative and long-term survival in selected patients.

The BCLC group defines clinical signs of portal hypertension as the presence of esophageal varices at endoscopy or splenomegaly (major diameter > 12 cm) with a platelet count < 100 000/mm^3 and, for these authors, the detection of these signs should contraindicate hepatic resection[57]. In keeping with modern Western and Eastern perspectives, the presence of portal hypertension should not be considered an absolute contraindication for hepatic resection in patients with well compensated cirrhosis, belonging to Child-Pugh A or with a MELD score < 10[54,55]. In fact, complications associated with portal hypertension, such as bleeding from variceal rupture and hemostatic disorders caused by thrombocytopenia, can be safely managed by applying appropriate pre- and peri-operative treatments[28,58].

Future remnant liver volume and extension of hepatectomy

There is general agreement that, for patients without chronic liver disease, the minimal residual liver volume able to prevent severe postoperative hepatic dysfunction ranges from 20% to 30%[59]. Conversely, the safe limit for liver resection in chronic liver disease and cirrhosis is not well established. Very few studies, all published in the 1990s, investigated the prognostic role of future remnant liver (FRL) volume in cirrhotic patients. Shirabe *et al*[60] analyzed 80 patients with chronic liver disease (50% cirrhotics) who underwent major liver resection and showed that all liver failure-related deaths occurred in patients with a FRL volume < 250 mL/m^2. The authors therefore concluded that this FRL volume may be considered the safe limit for major liver resections.

More recently, most studies and treatment algorithms have been focused on the extension of hepatectomy as a surrogate of the FRL volume. A decision tree for hepatectomy procedure, very popular in Japan, has been proposed by Makuuchi *et al*[61]. This surgical algorithm has indeed improved the operative mortality and morbidity in HCC patients. The decision tree in based on 3 variables: absence/presence of ascites, serum bilirubin level and ICGR-15. Patients with ascites or high bilirubin level are considered not candidates for hepatic resection. In the remaining cases, the maximal extent of hepatectomy is calculated according to the ICGR-15 value as previously reported. Using this decision tree, a post-operative mortality close to zero has been reported[61-63]. Thus, the ICGR-15 test might be useful for discriminating good and poor risk CTP A patients. There is also some evidence that the MELD score could be used to guide the extent of hepatectomy[43]. In particular, data from a Western dual-center study suggest that patients with MELD score < 9 could be safely submitted to major hepatectomy with a risk of PHLF below 1%, and that serum sodium can add some information for cases with borderline MELD values (9 and 10): in the presence of a value < 140 mmol/L, resection should be limited to segmentectomy or wedge resection[43].

Other liver function tests

Several other quantitative estimations of liver function, based on the hepatic clearance of substrates, have been proposed to predict the outcome of resection. Substrates include lidocaine, galactose, aminopyrine, amino acid and methacetin. Such tests have not been shown to be superior to the ICG clearance test in predicting liver failure or complications after surgery, and have never been compared to HVPG or MELD score[47].

There is an interesting seminal experience, conducted on 72 patients, regarding the predictive role of transient elastography[64]. The stiffness cut-off selected by receiver operating characteristics (ROC) curve analysis was 25.6 kPa, which gave the best statistical accuracy (sensitivity 71.4%; specificity 88.6%; positive predictive value 55.6%; negative predictive value 93.9%). It should be noted that the positive predictive value was quite low, whereas the negative predictive value was very high. Thus, liver stiffness would adequately identify patients who will not develop post-operative hepatic insufficiency while it has a suboptimal ability in identifying patients that should be excluded from surgical option because of a high risk of

post-hepatectomy failure. In this series, the area under the ROC curve of liver stiffness measurement was not statistically higher than that of ICGR-15, probably as a consequence of large confidence intervals. Given the increasing interest in elastography in relationship with different outcomes of cirrhotic patients, a possible role in pre-operative evaluation of surgical candidates seems reasonable[65].

TUMOR STAGE

Cancer staging should serve to estimate the prognosis, select the most appropriate primary and adjuvant therapy for each stage, and assist in comparing results of different treatments or coming from different patient series. Ultimately, an accurate cancer stage can help physicians in managing oncologic patients and scientists in exchanging unambiguous information. According to the European Association for Study of the Liver (EASL) recommendations, a staging system for HCC should take into account four issues: tumour burden, degree of liver function impairment, general condition, and treatment efficacy[13,15]. Indeed, staging of HCC is complex and, currently, there is no universally accepted staging system[66]. The consensus conference of the American Hepato-Pancreato-Biliary Association (updated in 2010) reproposed the use in clinical practice of different systems for different patients[67]: as survival of early stage patients is greatly modified by treatment, prognostic prediction must include treatment-related variables; conversely, as treatment may not be a key predictor in advanced stages, it may not be a crucial variable of a prognostic index for patients with these tumors. Nowadays, clinicians can choose among several staging systems, although it should be underlined that only the BCLC staging system provides a treatment algorithm linked to the HCC stage.

Early stage tumors

According to the BCLC definition, a very early HCC is represented by single nodule < 2 cm, and an early HCC is a tumor fulfilling the Milan criteria at imaging techniques (one nodule ⩽ 5 cm or 3 nodules each ⩽ 3 cm, without vascular or lymph nodal invasion)[57]. In CTP class A patients, survival after hepatic resection for early HCC reaches 70% at 5 years, and up to 90% for very early HCC[68]; however, whether to prefer, in these patients, hepatic resection over liver transplantation, or percutaneous treatments such as radiofrequency ablation (RFA), still remains a matter of debate[69,70]. Thus, the actual role of hepatic resection should be viewed in the light of such competing strategies.

The literature comparing the results of hepatic resection versus RFA for early HCC encompasses a number of retrospective studies, some case-control studies and only two randomized controlled trials (RCT), both coming from the Eastern world[71,72]. The first one, conducted on 161 CTP class A patients with a solitary tumor ⩽ 5 cm, reports similar survival rates after surgery (90 patients) and percutaneous treatments (71 patients), with 4-year survival rates of 68% and 64%, respectively (5-year survival rates were not reported)[71]. Also, DFS was not affected by the treatment adopted either in the whole population or in the subgroups of patients with tumors < 3 cm and between 3.1 cm and 5 cm[71]. The second RCT was conducted on 230 patients with HCC meeting the Milan criteria, 6.1% of whom belonging to CTP class B[72]. The authors found that resection (115 patients) was significantly superior to RFA (115 patients) in terms of both 5-year survival (75.7% *vs* 54.8%, respectively) and 5-year recurrence-free survival (51.3% *vs* 28.7%), and this was confirmed in post-hoc analyzes focused on individuals with solitary HCCs ⩽ 3 cm, those between 3.1 and 5 cm, as well as with multifocal tumors[72]. Thus, the two RCTs provide conflicting results making it impossible to propose robust recommendations. Nevertheless, when observational studies are also considered, a trend seems to emerge toward better overall and disease-free survivals after resection. In fact, the 5-year survival rate of surgical patients with early HCC can be estimated to be around 70% while the rate of those submitted to RFA is around 60%; the difference is much more striking for the 5-year DFS, the figures being around 60% and 20%, respectively[69,70]. However, the considerable heterogeneity among studies regarding both patient selection and results does not make it possible to reach definite conclusions on this topic. Pertinently, it should be noted that a recent multicenter prospective cohort study, in patients with a single tumor ⩽ 2 cm and potentially amenable to hepatic resection, reported a complete response (without local recurrence) in 97% of cases after RFA, and a 5-year survival rate up to 75%[73]. In another study considering 104 of these patients, the 5-year survival rate achieved with resection and RFA was excellent (> 80%) and equivalent after correction to the one-to-one propensity analysis model for the confounding factors[74].

Therefore, it can be said that in patients with early HCC, RFA provides a worse DFS as compared with hepatic resection, so that the need for retreatment is greater. Instead, hepatic resection and RFA would achieve similar results in very early HCCs. However, the drawback of RFA in terms of radicality is somehow counterbalanced by lower mortality, morbidity and costs (shorter hospital stay) and the easy repeatability of ablation. On the other hand, Markov models indicate that in HCC early stages, hepatic resection should be considered in the case of RFA local failure[75] and that surgery provides better quality of life-adjusted survival, due to the lower risk of local recurrent disease requiring retreatment[76]. Taken together, these observations suggest that hepatic resection and RFA should be considered as complementary rather than competitive treatments. In cases of deep tumor location, that require a removal of a large volume of parenchyma if resected (i.e., major hepatectomy), it is reasonable to consider RFA as the preferred strategy to adopt; conversely, superficial tumor location or tumors adjacent to main vessels or biliary structures, are

much better managed with hepatic resection. Nonetheless, for many experts, recommending RFA as first-line therapy for resectable small HCCs still requires a higher level of evidence[77]. Such uncertainty is highlighted by the conclusions of the conference of the Japan Society of Hepatology held in 2009[78]: to the question "Which treatment would you perform for 2-cm sized HCC nodules in patients with Child-Pugh A liver function?" 80% of surgeons responded "resection", while 68% of non-surgeons responded "RFA"[78]. Greater agreement was observed when asking about the optimal treatment of 3-cm sized nodules in patients with Child-Pugh A: 95% of surgeons and 79% of non-surgeons responded "resection"[78].

As already stated, the role of hepatic resection in early stage HCC should be viewed in the light of competing strategies, and liver transplantation (LT) represents the most attractive alternative option because it removes both detectable and undetectable tumor nodules together with the pre-neoplastic cirrhotic background. However, LT use should be viewed in the context of shortage of available grafts, and decisions must consider, together with the benefit for the individual patient, the collective benefit of all potential liver recipients[79]. Liver transplantation achieves excellent results in patients with limited tumor burden. Patients with HCC fulfilling Milan criteria have a 5-year survival of about 70%, with recurrence in less than 10%. This survival well matches post-transplant survival of most other indications for LT[80,81]. This is a critical point, recalled by Recommendation No. 7 of the International Consensus Conference on Liver Transplantation for HCC, held in Zurich in 2010, which states that LT should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients[79]. When compared to LT, partial hepatectomy would seem to be inferior in terms of long-term survival, but most surgical series rely on patients who underwent resection of a wide spectrum of tumor extent, frequently beyond the Milan criteria. Notably, factors precluding LT, such as large or multifocal tumors and vascular invasion, are often included in series analyzing resection results, and are associated with early recurrence and shorter survival[82]. There is evidence that hepatic resection and LT can indeed achieve similar post-operative and intention-to-treat survivals in patients respecting Milan criteria[82]. Thus, when patients with more limited disease are selected, the results of hepatic resection are much more favorable, approaching the 5-year survival rate of 70% reported after LT[19,83-85]. It should be considered that this figure is the end-result currently achievable thanks to both improved diagnostic imaging and therapies for recurrences, including salvage LT, that have been shown to significantly prolong survival after partial hepatectomy[19]. Thus, the combination of resection and salvage LT seems to be a reasonable strategy to adopt for resectable HCC within Milan criteria[86]. This strategy could also increase the proportion of grafts offered to non-HCC candidates on the waiting list[87].

Beyond the early stages of the tumor

Beyond the early stages, there is debate on the ability of the current staging systems in segregating patients into homogeneous prognostic strata able to assist clinicians in selecting the optimal treatment strategy. The BCLC intermediate stage (BCLC-B) includes patients in Child-Pugh class A or B, with multi-nodular or large HCC, and preserved performance status[57]. This definition includes a very heterogeneous patient population, according to either tumor extent (from bifocal HCC to subtotal tumor replacement of liver parenchyma) or liver function (from perfectly compensated to decompensated cases with ascites and hyperbilirubinemia). The recommended treatment modality for this HCC stage by both EASL and American Association for the Study of Liver Diseases guidelines is trans-catheter arterial chemoembolization (TACE). Instead, due to the heterogeneity of this stage, patients are best served when the treatment decision is individualized and taken within a multidisciplinary team[88,89]. Indeed, retrospective analyses have shown that, in BCLC stage B patients, hepatic resection yielded better survival rates than TACE[90-92]. Stage B, but even stage C, patients can tolerate hepatic resection showing low mortality, acceptable morbidity, and survival benefits[90]. The reported 3-year survival rate ranges from 56% to 74% for stage B and from 28.6% to 67% for stage C patients[90-92]. Especially in stage B, resection is superior to the TACE in terms of survival[57,91]. A very recent case-control study, conducted on a population of 603 patients (1:2 ratio), has shown that in patients with a portal vein tumor thrombus (PVTT) within segmental branches (type Ⅰ) or the right or left portal vein (type Ⅱ), resection provides a significant survival benefit in comparison to TACE[93]. In particular, in the presence of type Ⅰ PVTT, the 5-year survival rate was 37.9% after resection and only 3.6% after TACE; in the presence of type Ⅱ PVTT, the corresponding figures were 17.2% and 0%, respectively. These results suggest a revision of the BCLC recommendations[89]. Although the BCLC staging classification has been claimed as standard HCC classification in Western regions, its validation across Eastern and Western regions is required and some refinements are probably needed before it can accepted for universal application. Indeed, most Asian experts state that the BCLC staging system does not satisfy the needs of surgeons and physicians in real clinical practice[94]: when participants of the Japan Society of Hepatology were asked if they usually follow the BCLC treatment algorithm, 70% responded "no"[78]. It should also be noted that resection is not excluded as an option for HCCs beyond the early stages in the Asian treatment algorithms[94] and in real clinical practice about half the physicians include resection as a treatment choice, albeit in cases of advanced HCC[79,95].

TYPE OF SURGICAL RESECTION

Anatomical vs non-anatomical resection

It remains unclear whether hepatectomy for HCC should be performed as anatomical resection (AR) or non-anatomical resection (NAR). The great majority of recurrences occur in the liver as a result of subclinical metastases, originating from the primary tumor through microscopic vascular invasion and peripheral spread along their intrasegmental branches, which are the most important factors associated with poor prognosis[19,96,97]. On this basis, the systematic removal of the hepatic segment fed by tumor-bearing portal tributaries, namely the entire functional unit through an AR, was suggested as theoretically more effective for tumor and metastases eradication[98]. Conversely, most surgeons prefer, in cirrhotic patients, to leave a portion of parenchyma greater than the functional unit, using the NAR, to reduce the risk of postoperative liver failure. Clear evidence of the superiority of one technique over the other is not available, since some studies report a survival benefit of AR[99-101] that was not manifest in others[102-104]. Two recent meta-analyses, conducted on observational studies, also reported conflicting results[105,106]. Importantly, underlying cirrhosis was significantly more common in the NAR patients who also showed more advanced hepatic dysfunction compared with those in the AR group: these features were recently shown by a meta-regression approach to significantly affect results from meta-analyses, that is, patient survival and DFS after AR seem to be superior to NAR because the worse liver function reserve in the NAR group significantly affects prognosis[107]. Thus, large randomized controlled trials are needed to define the best resective approach to patients with an HCC ensuing in a cirrhotic liver[107].

Laparoscopic resection

In contrast to other fields of surgery where laparoscopic procedures are routinely performed, laparoscopic hepatectomy is only being performed in a few institutions worldwide; nonetheless, since the first laparoscopic liver resection was described in 1992, there has been an exponential growth of reported laparoscopic liver resections, with almost 3000 cases reported in the English literature so far[108]. About 50% of them were performed for malignant tumors and, in this group, about half were HCCs. Since 2000, about 500 cases of laparoscopic resection for HCC can be collected from the literature[109]. Most patients were cirrhotics, but a considerable proportion (about 40%) had pre-cirrhotic chronic hepatitis. Laparoscopic surgery consisted of minor resections (< 3 segments removed) in 90% of cases[109]. Complications were more frequent after resection for HCC (50%) than for colorectal metastasis (11%), likely due to underlying liver disease[108]. The 5-year overall survival ranges from 50% to 60%[108]. These results are comparable to those achieved with open hepatic resection for HCC but the large proportion of patients without cirrhosis suggests that studies enrolling only cirrhotic patients are still required to adequately compare outcomes in this specific cohort of patients[109]. Advantages of laparoscopic liver resections are the less aggressive approach, less peritoneal dissection, less bleeding, minimal ascites and decreased post-hepatectomy liver failure[110,111], extending the indication to liver resection to selected Child B patients[110]. Moreover, fewer postoperative adhesions after laparoscopic liver resection compared to open liver resection facilitate subsequent salvage LT with decreased morbidity[112]. On the other hand, the longer learning curve, the greater difficulty in achieving wide resection margins and performing anatomical resections, the difficulties in mobilization and parenchymal transaction, with risk of massive bleeding, are the major obstacles to the widespread diffusion of laparoscopic liver resection. Lastly, lesions located in posterior segments are not good indications for pure laparoscopic approach but suitable for hand-assisted laparoscopic resection[113,114].

CONCLUSION

Despite improving results of non-surgical approaches, partial hepatectomy still represents a cornerstone for potentially curative treatment of HCC, able to offer long-term survival rates. However, like all the available treatments for HCC, hepatic resection should be considered in the context of multi-disciplinary evaluation of these patients, which increases the chances to cure the tumor and its recurrences, resulting in higher overall survival rates. As tumor recurrence remains the main obstacle in achieving better results in long-term survival after hepatic resection, clinical trials aimed at identifying effective adjuvant therapies are warranted. Regarding types of surgical approaches to HCC, the literature is rich in observational studies but very few well-designed RCTs are currently available; thus, no definitive suggestions can be derived regarding superiority of anatomic versus non-anatomic resection or laparoscopic approach.

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