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REVIEW

# Surgical resection of localized hepatocellular carcinoma: patient selection and special consideration

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**Abstract:** Localized hepatocellular carcinoma (HCC) refers to a solitary or few tumors located within either the left or right hemiliver without evidence of bilobar or extrahepatic spread. This term encompasses a heterogeneous morphology with no regard to stage of prognosis of the disease. Surgical resection remains the mainstay of curative treatment for the localized HCC. Various biochemical and radiological tests constitute an indispensible part of preoperative assessment. Emergence of laparoscopic hepatectomy has brought liver resection into a new era. Improved understanding of the pathophysiology of HCC allows more aggressive surgical resection without compromising outcomes. New insights into the management of special situations, such as ruptured HCC, pyogenic transformation of HCC, and HCC with portal vein tumor thrombus, rekindle the hopes of curative resection in these terminal events. Amalgamating salvage liver transplantation into the surgical management of resectable HCC has revolutionized the treatment paradigm of this deadly disease.

**Keyword:** hepatocellular carcinoma, hepatectomy, future liver remnant, transarterial chemoembolization (TACE), transarterial radioembolization (TARE)

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy. It is the fifth most common cancer and is ranked the third most common cause of cancer-related mortality around the world, leading to over 1 million deaths every year.[1,2] Majority of the patients present with unresectable disease due to the presence of extrahepatic spread, insufficient future liver remnant (FLR), poor liver function, performance status, etc. Survival of this group of patients are counted in months despite the development of various forms of palliative treatment such as transarterial chemoembolization (TACE),[3–5] transarterial radioembolization,[6] and vascular endothelial growth factor receptor antagonist, also known as sorafenib.[7,8] Localized HCC does not necessarily infer straightforward management; huge tumor, strategic tumor location, major vasculobiliary invasion, rupture of HCC, and pyogenic transformation are situations that complicate the picture. For the minority of fortunate patients who have early disease, liver transplantation (LT) offers the "best chance of cure", with 5-year survival ranging from 70% to 90% depending on different selection criteria (Table 1).[9–15] However, due to a scarcity of liver graft and stringent selection criteria, only a small fraction of these patients can benefit from LT, with almost 90% of them having to undergo either ablative therapy or partial hepatectomy. Despite the fact that radiofrequency and microwave ablation have been proven to be as effective

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**Table 1** HCC survival after liver transplantation from different series

| Criteria | Tumor size | Tumor number | Additional restriction | Overall 5-year survival (%) |
|---|---|---|---|---|
| UCSF[10] | <6.5 cm | Solitary | – | 75.2 |
| | <4.5 cm | 3 or less | | |
| | Total <8 cm | | | |
| University of Tokyo[11] | ≤5 cm | 5 or less | – | 75 |
| Chang Guan University[12] | 6.5 cm | 1 | – | 90 |
| | 4.5 cm | 3 or less | | |
| Asan[13] | ≤5 cm | 6 or less | – | 82 |
| Up-to-7[14] | ≤7 | 7 or less | Numerical sum of tumor size and number must be <7 | 71.2 |
| Hangzhou[15] | Total size ≤8 cm | No limit | For total tumor size >8 cm, histological grade must be I or II and AFP must be ≤400 ng/L | 72 |

**Abbreviation:** AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; UCSF, University of California, San Francisco.

as resection for small-sized HCC,[16–19] their applicability is limited by a number of constraints, such as tumor size (too big would risk incomplete ablation), location (too subscapular or too deep-seated), and vicinity to vascular (fear of heat sink effect), biliary, and hollow organ structure (possible collateral damage). At present, liver resection remains the mainstay of curative measure due to its availability, flexibility, and inherent efficacy. The overall 5-year survival of HCC patients after resection is >50% in most series, and this number can be >70% for early disease.[20–22] In this article, we will go through the technical advances in surgical resection of HCC, stratification and selection of patients via different investigation modality, and how to deal with special circumstances in patients with localized HCC.

## Surgical resection for HCC

Liver resection was once considered as an ultra-high-risk procedure, and usually resulted in massive blood loss, high morbidity, and mortality.[23] Until the 1980s, the mortality rate of liver resection was still ~10% in many centers.[24,25] Over the last few decades, a multitude of perioperative and technical advances have emerged, changing the landscape in the field of liver resection. Liver resection can be classified into nonanatomical and anatomical resection. The former essentially means excision of HCC with a rim of normal

liver tissue regardless of the location of the tumor; anatomical resection refers to resection of a specific part of the liver according to corresponding pedicle supply and biliary drainage. Because most HCC recurrences are intrahepatic and it has been postulated that cancer cells spread by microscopic invasion and dissemination along portal pedicle,[26–28] liver resection following its corresponding portal pedicle should theoretically maximize oncological clearance.[29–32] However, this oncological benefit is not demonstrated in some other studies.[33–38] The reason behind the discrepancy was that, a majority of the nonanatomical resections were performed for patients with cirrhosis with the hope of conserving the more functional liver remnant, and a cirrhotic liver is more prone to tumor recurrence due to "field change" and has a worse prognosis when compared to the noncirrhotic one; hence, it is falsely perceived as the cause of inferior oncological outcome. Further well-designed randomized controlled trial is needed to properly address this issue.

Besides the controversy of anatomical and nonanatomical resection, the surgical approach of hepatectomy has been a topic for debate. Since the first laparoscopic hepatectomy (LH) performed by Gagner in 1992,[39] there has been growing enthusiasm to pursue this challenging operative approach from all around the world. Initial indication of LH was limited to benign diseases of the liver. Thanks to the accumulation of experience and reports of encouraging results, the indication of LH has been extended to various types of hepatic malignancies, chiefly colorectal liver metastasis and HCC.[40–43]

The main concerns about laparoscopic hepatectomy were oncological clearance and safety issues of this approach. However, apart from the inherent benefit of laparoscopic surgery, such as shorter hospital stay,[44–47] operation time,[46,48,49] less analgesic requirement,[45] and early resumption of oral intake,[45] it has been demonstrated that LH is associated with good safety profile, as evidenced by less blood loss,[46,48–50] and postoperative morbidities and mortality.[46,47,49,51] From the perspective of oncological efficacy, a meta-analysis comprising 244 patients with open hepatectomy and 165 patients with LH for liver cancers found that there were no significant differences in tumor-free resection margin, disease-free and overall survival.[52] Subsequent studies confirmed these advantages in the context of treating HCC.[53–55] Despite the fact that the laparoscopic approach has been recommended as the standard of care for minor wedge resection and left lateral sectionectomy,[56] its application in major liver resection was still considered as "in exploration phase" due to the complexity of the procedure and the steep learning curve.[56,57] With the constantly

emerging laparoscopic devices and effective hemostatic products,[58] hurdles in laparoscopic major hepatectomy would be overcome in the near future.

## Patient selection

As a rule of thumb, careful patient selection is always the key to treatment success regardless of the type and approach of liver resection used. Treatment options for HCC are largely inferred by patient, livers, and tumor factors at presentation and these factors form the backbone of a number of well-adopted treatment algorithms (Table 2).[59–63] The association between general health condition and prognosis of HCC had been well documented.[22,59,64–67] In general, patients with poor cardiopulmonary function, limited life expectancy, or poor quality of life (i.e., bedridden and noncommunicable) due to underlying medical comorbidities are not a surgical candidate. Liver factors are traditionally assessed by the Child–Pugh score.[68,69] This score was originally used to predict the survival of patients with portal hypertension after portosystemic shunt surgery and subsequently was applied to predict liver-related mortality of cirrhotic patients. Lack of discrimination within the same grade and involvement of subjective clinical parameters limit its role in preoperative assessment. Objective biochemical, radiological, and metabolic assessments have become the standard practice in many centers. Indocyanine green (ICG) is a metabolically inert dye. It does not get metabolized or degraded in blood, is solely and actively excreted by hepatocytes, and is not reabsorbed via the enterohepatic pathway; hence, it is an ideal marker for liver function assessment.[70–74] ICG is injected at a dosage 0.5 mg/kg intravenously; serum retention of ICG

>15% at 15 minutes is generally considered inadequate[75] although it has been reported that the safety cutoff can be as high as 20% for a Child-Pugh A patient.[76] The ICG clearance test has become a routine preoperative liver function assessment in many centers around the world, and its serum level can be checked with pulse spectrophotometry, which is faster and not influenced by potential human error during serial venous blood sampling.[77,78] In addition, the ICG disappearance rate and intraoperative ICG measurement for the FLR were found to have prognostic implication in liver resection and will continue to be a topic of research in the future.[71,79,80]

Apart from biochemical assessment with ICG, volumetric assessment of the FLR constitutes an indispensible part of the preoperative work-up. With the development of helical, multi-detector, thin-slicing CT technology, high-quality images can be obtained in just one breath holding time, and subsequent FLR volume calculation can be done by either an automated or a manual process with good accuracy.[81,82] The resultant volume is then divided by total liver volume (TLV), which is obtained either by CT volumetry (after subtraction of tumor volume) or deduced from various formulas.[83–85] The ratio of FLR volume to TLV of 25%–30% for noncirrhotic patients[86–88] and up to 40% for cirrhotic patients[89] are considered safe for hepatectomy. In case of situations like the presence of steatosis, fibrosis, and cirrhosis, where the liver function might not correlate well with the liver volume,[90] Technitium-99 mebrofenin or galactosyl human serum albumin scintigraphy can be used for metabolic assessment of the whole or partial liver function.[91–93]

**Table 2** Commonly referred treatment guidelines for HCC

| Guidelines | Parameters | Concept of vascular invasion | Tumor staging | Resectability |
|---|---|---|---|---|
| BCLC[59] | Performance status Liver function Tumor status | Invasion of PV branches signifies advance disease | Classified as very early, early, intermediate, advance and terminal | Solitary HCC or <3 tumor <3 cm |
| HKLC[60] | Performance status Liver function Tumor status | Main PV or IVC invasion | Early, intermediate or late | Early tumor in Child A/B cirrhosis Intermediate in Child A cirrhosis |
| JSH[61] | Liver function Presence of vascular invasion Prensece of metastasis | PV invasion classified into Vp1–4 | According to TNM stage of LCSGJ | Any resectable HCC |
| APASAL[62] | Liver function Presence of vascular invasion Prensece of metastasis | Involvement of main PV or IVC branches | 3 categories: Resectable, within Milan/unresectable within Milan and unresectable outside Milan criteria | HCC with invasion to sectorial branches of PV still be considered resectable |

**Notes:** PV tumor invasion was classified into: Vp0, no PV invasion; Vp1, thrombus beyond 2nd order PV branch; Vp2, thrombus at 2nd order branch; Vp3, thrombus at 1st order branch; Vp4, thrombus at main PV or involved contralateral PV.
**Abbreviations:** APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic for Liver Cancer; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer; JSH, Japan Society of Hepatology; LCSGJ, Liver Cancer Study Group of Japan; PV, portal vein; IVC, inferior vena cava.

The indication and patient selection principle should hold true for both open and LH; nonetheless, the decision of whether a particular HCC is suitable for laparoscopic resection involves a number of considerations. A 10-level difficulty index introduced by the Keio University group[94] provides a comprehensive stratification of HCC for pure LH. This score takes tumor size, tumor location, extent of resection, degree of cirrhosis, and proximity to the major vessel into account and serves as a useful guide for both patient selection and surgeon selection, i.e., operation with high difficulty index should only be performed by experienced laparoscopic surgeon while those with low difficulty index are suitable cases for beginners in LH. For patients with large posteriorly situated lesion with high difficulty score, use of a hand-assisted or hybrid laparoscopic approach had been suggested to reduce the patient risk and need for conversion.[49,95–97] In case the operating surgeon perceives that the laparoscopic approach would compromise patient safety or oncological outcome, conversion to open hepatectomy is indicated.

## Special circumstances
### Insufficient FLR
Since the development of portal vein embolization (PVE) by Makuuchi,[98] insufficient FLR is no longer regarded as an absolute contraindication for major hepatectomy. This technique was originally described for the use in treating hilar cholangiocarcinoma,[99] and this application had been extended to many other primary and secondary hepatic malignancies. In the context of HCC, this technique is even more relevant as HCC often develops in the background of shrunken cirrhotic liver. Studies showed that the 5-year survival after resection for patients who had PVE before ranged from 50% to 70%, and this is comparable to HCC resection without prior PVE.[100–103] Besides promoting hypertrophy of FLR, this technique also acts as a selection tool to screen out patients who are unlikely to survive a major hepatectomy due to poor regenerative potential of the liver parenchyma and intolerance to portal hypertension after the procedure. However, PVE had been criticized of not being able to introduce sufficient FLR hypertrophy and possibility of disease progression during the 4-week hypertrophy time. It has been reported that due to increased arterial supply to the tumor-bearing liver during the post-PVE period, the tumor growth rate accelerates due to the hypervascularized nature of HCC,[104] and the patient dropout rate can be up to 20%–25%. With the introduction of the new technique of associating liver partition and portal vein ligation for staged

hepatectomy (ALPPS), problems of PVE seem to have been well addressed with faster and more FLR hypertrophy. The first report of ALPPS from Schnitzbauer found that this procedure induced liver hypertrophy of 75% in only 9 days.[105] However, in return for the improved resectability, ALPPS was noted to be associated with higher morbidity, mortality, and higher early recurrence rate.[106–108] Though early results of ALPPS were promising, these issues need to be clarified before this technique can gain further acceptance to become a standard of practice.

## Ruptured HCC
Ruptured HCC is associated with poor prognosis and its incidence varies geographically, from 10% in some Asian countries[109,110] to <5% in the Western world.[110] According to the tumor-node-metastasis staging, seventh edition,[111] ruptured HCC was classified as $T_4$ disease. While, some people considered it as a contraindication for curative surgery, the others reported that resectability of patients with ruptured HCC could be up to 12%–33%.[110,112–114] We have recently analyzed the surgical outcomes of patients with ruptured HCC undergoing liver resection and found that the 1-, 3-, and 5-year overall survivals were 66%, 37%, and 22.3%, respectively, which is statistically worse than nonruptured HCC (83.3%, 64.8%, and 53.4% respectively, $P<0.001$), but superior to those who received TACE or systemic therapy.[61] Therefore, resection should be contemplated for patients who have ruptured HCC without overt evidence of dissemination.

## Portal vein tumor thrombus
HCC has the tendency of invading the portal vein, which explains the high incidence of portal vein tumor thrombus (PVTT) of ~40%.[114] The presence of PVTT in HCC patients signifies poor prognosis with median survival of only 2.7 months if left untreated.[115] This tumor thrombus can propagate and lead to complete PV obstruction, causing torrential variceal hemorrhage. Treatment for PVTT remained limited, and its presence was usually considered a contraindication for resection and TACE. Resection is the only possible cure and is associated with an operative mortality of 0%–5.9% and the median survival ranged from 8.9 to 33 months.[116–119] Surgical management of PVTT depends on the level of involvement. For peripherally located PVTT confined to the ipsilateral first-generation portal vein, hepatectomy is recommended. Treatment options for PVTT extending to or beyond portal vein bifurcation include en-bloc resection and thrombectomy. Although portal vein en-bloc resection seems to give a sense

of better oncological clearance, majority of the literatures did not find a significant difference in survival benefit between the two.[118,120–122] Preoperative TACE had been proposed and was able to achieve 5-year survival in 45% of selected patients.[123] However, these encouraging results could not be repeated by others.[121,123] Efficacy of some newer adjuvant therapies such as sorafenib[7] and infusion of platinum-based chemotherapy via hepatic artery[124] are areas for further exploration.

## HCC with bile duct tumor thrombus

Bile duct tumor thrombus (BDTT) is an uncommon occurrence in the context of HCC. It happens in 0.53%–13% of the HCC patients.[125–127] Prognosis of HCC with BDTT is worse than HCC without BDTT.[128–130] This difference was thought to be related to a more aggressive tumor biology evidenced by higher proportion of coexisiting lymphovascular invasion in patients with BDTT.[131] Preoperative drainage is occasionally required in case of severe cholestasis or cholangitis, and can be done by endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage. Tumor thrombus is easily retrievable with balloon used for stone extraction due to its necrotic and friable nature. Although Ueda classification[132] could be used as a guide for calculating the extent of hepatectomy, our previous analysis[131] suggested that radical hepatectomy with extrahepatic bile duct resection was associated with better outcome. A 5-year overall survival of 38.5% with zero bile duct recurrence was achieved using this approach.

## HCC with abscess formation

The reported incidence of de novo pyogenic transformation of HCC is ~1%.[133] The manifestations of HCC complicated by liver abscess include pyrexia, right upper abdominal pain, right pleural effusion, and leukocytosis. Portal pyemia, ascending cholangitic sepsis, and hemotological inoculation of bacteria in a necrotic tumor are some postulated etiology.[134,135] There has been no standardized management for this rare entity; upfront hepatectomy for HCC with abscess formation was not recommended due to the reported higher morbidity, mortality, and worse oncological outcomes.[133] Early involvement of microbiologist and interventional radiologist is advisable; hepatectomy should be performed in a patient with sepsis under control and general conditions optimized so as to minimize the above-mentioned adverse outcomes.

## Surgical resection as a bridging therapy to LT

LT has been the best curative treatment for HCC within certain criteria. The 5-year survival of HCC patients after LT can be up to 90% in certain series.[12] However, due to graft shortage and disease progression, a 43% dropout rate for HCC patients on a waiting list had been reported.[136] The concept of salvage transplantation was introduced in 2000 by Majno et al[137] in which they advocated that HCC patients should proceed with resection first whenever possible and embark on LT only when recurrence developed. This strategy would relieve tension in donor pool by postponing the time of LT and even reducing the number of LT, as some of the patients might not develop HCC recurrence after resection. While salvage LT had been recognized as an incorporated part of HCC management,[138] opponents of the policy of salvage transplant worried that liver transplantation following previous hepatectomy might impair transplantability and increase the operative risk due to the presence of adhesion and distorted anatomy; compromised long-term survival of salvage transplant patients was also a concern.[139] We had previously reported that there was no significant difference in long-term survival between HCC patients treated by upfront resection or primary LT, provided that the factor of microvascular invasion is adjusted,[140] and when there is HCC recurrence, salvage LT gives the best 5-year model for end-stage liver disease-adjusted survival in comparison to repeat resection and ablation.[141] Therefore, localized HCC should be resected whenever possible, especially in the region of low organ donation rate. Salvage LT should be reserved for any unresectable HCC recurrence.

## Conclusion

With the advances in various preoperative biochemical and radiological assessments, the safety profile of hepatectomy for HCC has drastically improved. Situations such as insufficient FLR and PVTT that were once considered not amendable to surgical resection have now become resectable. Increased understanding of special conditions like HCC rupture, abscess transformation, and the role of salvage LT allows better choice of treatment and improves long-term outcomes for HCC patients.

## Disclosure

The authors report no conflicts of interest in this work.

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