



Review article

Controversies and evidence of hepatic resection for hepatocellular carcinoma[☆]



Jian-Hong Zhong^{a,1}, Guido Torzilli^{b,1}, Hao Xing^{c,1}, Chao Li^{c,1}, Jun Han^{c,1}, Lei Liang^c, Han Zhang^c, Shu-Yang Dai^c, Le-Qun Li^a, Feng Shen^{c,*}, Tian Yang^{c,*}

^a Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China

^b Department of Surgery, Division of Hepatobiliary and General Surgery, Humanitas University, Humanitas Research Hospital-IRCCS, Rozzano, Milan, Italy

^c Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China

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ABSTRACT

Symptoms of early hepatocellular carcinoma (HCC) often go unnoticed, so more than half of patients with primary HCC are diagnosed after their disease has already reached an intermediate or advanced stage, or after portal hypertension has appeared. While hepatic resection is widely recognized as a first-line therapy to treat very early or early HCC, its use in treating intermediate or advanced HCC or HCC involving portal hypertension remains controversial. Here we review PubMed-indexed literature covering the use of hepatic resection for such patients. The available evidence strongly suggests that, as a result of improvements in surgical techniques and perioperative care, hepatic resection can benefit many patients with intermediate or advanced HCC or with HCC associated with portal hypertension.

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1. Introduction

Prevalence of hepatocellular carcinoma (HCC) is increasing in some countries [1]. Although past decades have seen great progress in

diagnosis of HCC, treatment options remain limited, particularly for those whose disease is diagnosed in intermediate or advanced stages. For example, official guidelines [2–5] recommend the oral multikinase inhibitor sorafenib for patients with advanced HCC and Child-Pugh A liver function for whom locoregional therapy is unsuitable. However, sorafenib prolongs median overall survival (OS) by only 2–3 months and is associated with higher rates of adverse events and higher cost than the best supportive care [6–7]. The more aggressive approach of hepatic resection is a safe and effective option for many patients with intermediate, advanced or complicated HCC, and indeed many liver care centers, make use of this treatment [8–12]. This reflects remarkable advances in radiological technology [13–14], surgical techniques, and perioperative care. However, some liver care centers and official

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* Corresponding authors at: Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China.

E-mail addresses: shenfenghebh@sina.com (F. Shen), yangtian6666@hotmail.com (T. Yang).

¹ These authors contribute equally to this work.

guidelines in the West do not recommend hepatic resection for such patients [15–29].

Hepatic resection is a well-established, popular curative treatment for patients with good liver function and HCC satisfying the Milan criteria, which involves up to 3 lesions <3 cm or a single lesion <5 cm and no extrahepatic manifestations or vascular invasion [30]. The 5-year OS of such patients exceeds 50% after hepatic resection [31–33]. Unfortunately, since the symptoms of early HCC often go unnoticed, more than half of patients with primary HCC are diagnosed after their disease has already reached an intermediate or advanced stage [34–35]. Most of these patients have developed multinodular tumors or macrovascular invasion; in addition, a substantial proportion has portal hypertension because HCC often co-occurs with liver cirrhosis. Based on Western official guidelines, none of these patients should be offered hepatic resection as first-line therapy. Instead, they should be offered largely palliative treatments, such as sorafenib or radioembolization [2–3].

Substantial evidence exists that a substantial number of such patients can, in fact, benefit from hepatic resection, as reflected in expert consensus statements [36–37] and official guidelines from Asian liver health organizations [4–5]. However, this contrasts strongly with the official guidelines from the US³ and Europe [2], particularly the authoritative Barcelona Clinic Liver Cancer (BCLC) staging and treatment system [38]. In this review, we examine the evidence for the safety and efficacy of hepatic resection for patients with large multinodular HCC or HCC involving macrovascular invasion or portal hypertension.

2. Staging systems

Several systems have been proposed for staging HCC, including Cancer of the Liver Italian Program (CLIP) [39], French Score [40], BCLC staging [38], Chinese University Prognostic Index [41], Japan Integrated Staging (JIS) Score [42], Hong Kong Liver Cancer (HKLC) system [43], Italian Liver Cancer (IT.ALI.CA) system [44], and the Model to Estimate Survival for HCC patients (MESH score) [45]. Only the BCLC [38] and HKLC [43] staging systems also recommend stage-appropriate treatment modalities. Studies suggest that the BCLC system can predict prognosis more accurately for Caucasian HCC patients than Asian ones, while the converse is true of the HKLC staging system [46–50]. However, even these widely used staging systems leave large treatment gaps: indeed, many patients with HCC do not fall neatly into their pre-specified treatment pathways [49], and even patients within the same BCLC or HKLC stage can differ substantially. For example, the BCLC classifies intermediate HCC as disease involving 2–3 tumors with a maximum diameter >3 cm or >3 tumors of any diameter [51–54]. The present review focuses on the BCLC system, since it is the only one endorsed by the European Association for the Study of the Liver [2] and the American Association for the Study of Liver Disease [3].

3. Intermediate HCC

HCC involving 2–3 tumors with a maximum diameter >3 cm or >3 tumors of any diameter is classified as intermediate disease [52–55]. Recommended treatments for such patients include transarterial chemoembolization (TACE), radioembolization, or sorafenib, but not hepatic resection. Although the initial version of the BCLC system classified HCC involving a single large tumor (>5 cm) as intermediate stage [38], and still guidelines are unclear and somehow contradictory in this sense as recently pointed out [10,11], although recent reviews written by BCLC proponents seems trying to recalibrate their position stating that a single-HCC, regardless of tumor size, should be considered as an early stage disease [52–55]. Anyhow for patients with single HCC, hepatic resection is first-line therapy.

This approach of stratifying patients by tumor size goes against a substantial body of evidence from studies in Western and Asian countries that hepatic resection can be safe and effective in patients

with single and multinodular HCC, regardless of tumor size, so long as resection is feasible based on tumor location and preserved liver function [10,56–89]. This highlights the need to expand official indications for hepatic resection [20–22].

Official guidelines also fail to reflect available evidence by continuing to recommend TACE when its efficacy is far from clear, particularly in comparison with hepatic resection. Median OS for patients with intermediate HCC following TACE is approximately 14 months [52–54]. In contrast, a systematic review of 50 studies involving 14,808 patients with large or multinodular HCC found median OS after hepatic resection to be 81% at 1 year, 56% at 3 years, and 42% at 5 years [90]. The corresponding OS for 4945 patients with multinodular HCC was 75%, 48%, and 30%, while disease-free survival (DFS) was 60%, 32%, and 25% [91]. Large meta-analyses have suggested that hepatic resection is associated with better overall survival than TACE [92–93], and this was also demonstrated in a parallel comparison in a randomized controlled trial of 173 patients with multinodular HCC outside Milan criteria [94].

Substantial evidence, then, exists that hepatic resection is associated with better survival than TACE or sorafenib, raising the possibility that official guidelines are restricting many patients with intermediate HCC to palliative therapy when they could benefit from more aggressive resection. It is true that some situations may limit the safety or efficacy of resection. For example, liver cirrhosis may increase the risk of perioperative morbidity and mortality [95]. In addition, resection may be less effective in patients with larger or multiple tumors because of the possibility of vascular invasion and organ metastasis [96]. Indeed, the size and number of tumors are associated with OS and DFS [88]. Nevertheless, continuous improvements in surgical technique and perioperative care support expanding official indications of hepatic resection.

4. Advanced HCC

In China, nearly half of patients with primary HCC are diagnosed in an advanced stage [35]. Most of these patients present with portal vein tumor thrombus (PVTT). One study compared Chinese patients with advanced HCC who received either initial hepatic resection (n = 339) or TACE (n = 105) [97]. Most of those patients (83%) had a tumor thrombus, 12% suffered preoperative tumor rupture, 14% had distant metastases, and 5% had lymph node invasion. Patients receiving either treatment showed similar postoperative morbidity as well as mortality at 30 and 90 days. However, patients in the resection group showed significantly longer median survival than those in the TACE group (16.4 vs. 11.8 months, *P* = 0.012). Other studies support these findings, even after using propensity score matching to reduce potential confounding due to patient differences at baseline [98–100].

Hepatic resection may be uniquely effective for patients who experience preoperative tumor rupture [101–103]. When a resectable tumor ruptures, emergency or staged resection can save the patient's life. In fact, hepatic resection is often the only option in the event of spontaneous tumor rupture. If a patient recovers hemostasis, staged resection may lead to better long-term OS than emergency resection [101]. Further work is needed to improve resection techniques or explore (neo)adjuvant therapies that can be administered in combination, in order to improve the relatively low long-term OS of patients who undergo resection following spontaneous tumor rupture. Certainly if surgery remains a suitable treatment for these complicated patients it is surprising not considering this treatment suitable for the advanced HCC once approached not in emergency.

Numerous studies, mostly from Asian countries, indicate that hepatic resection can be safe and effective in patients with HCC involving PVTT. For example, a large retrospective study from Japan compared OS of 2093 HCC patients with PVTT who underwent hepatic resection and 4381 patients who received other treatments [104]. Median OS was significantly longer in the resection group (2.87 yr) than in the

group that received other treatments (1.10 yr), corresponding to a survival benefit of 1.77 years for hepatic resection. Notably, hepatic resection showed no OS benefit among patients in whom PVTT affected the main trunk or contralateral branch (Vp3 or 4). A large multicentric study recruiting patients from Asia and Western countries showed long-term survival approaching 40% at 5 years when surgery was offered to these patients [10]. Our systematic review of 24 studies involving 4389 patients with HCC involving macrovascular invasion showed that hepatic resection was associated with median OS from 18% at 5 years to 50% at 1 year [90]. Conversely, median OS for such patients once treated with sorafenib ranged from 6.5–10.7 months [6–7] and from 5.4–10 months in presence of PVTT [105–106]. Radioembolization using yttrium-90 microspheres is associated with median OS of 8.8–13.8 months in patients with HCC and PVTT [105–106]. These median OS rates are not much higher than the rates of 4.2–7.9 months associated to the best supportive care [6–7]. Therefore, the survival benefit of sorafenib or radioembolization therapy is not obvious, also considering that these treatments come with risk of adverse events and high costs that can be prohibitive for medical centers or patients.

These considerations argue for expanding official guidelines to recognize hepatic resection as a therapeutic option for selected patients with advanced HCC and preserved liver function. Surgeons should not shy away from this option when it is feasible, though they should be prepared for the fact that the procedure is technically demanding. On the other hand, for patients whose PVTT has invaded the main trunk or contralateral branch, then radioembolization and sorafenib, alone or in combination, may be appropriate.

5. HCC involving portal hypertension

Portal hypertension may affect treatment outcomes of patients with decompensated cirrhosis, in whom such hypertension manifests as ascites and esophageal varices. Portal hypertension is typically diagnosed indirectly from the presence of at least one of the following: gastric and/or esophageal varices detectable by endoscopy and/or computed tomography, splenomegaly with a platelet count below 100,000/mm³, or hypertensive gastropathy. These surrogate signs can be inaccurate, since some patients diagnosed indirectly with portal hypertension turn out not to meet the pressure cut-off of ≥ 10 mmHg [107]. A promising non-invasive indirect marker of portal hypertension may be liver stiffness estimated by transient elastography [108–110]. Ideally, the pressure gradient in the hepatic vein should be measured directly before surgery in patients with clinically significant portal hypertension.

Official guidelines from the West [2–3], while not regarding portal hypertension as an absolute contraindication of hepatic resection, do not recommend resection as first-line therapy. This is because resection in the presence of portal hypertension is associated with higher mortality at 30 and 90 days and greater risk of postoperative decompensation, as well as higher mortality at 3 and 5 years [111–119]. This reflects the higher frequency of comorbidities and cirrhosis among HCC patients with portal hypertension. Other evidence, much of it from these same studies, suggests that at least for certain patients with portal hypertension, hepatic resection may be safe and effective. Propensity score matching based on baseline characteristics showed similar mortality at 30 and 90 days for patients with or without portal hypertension [113,119]. In addition, short- and long-term OS as well as recurrence rates were similar between patients with or without portal hypertension when only patients with early HCC or patients who underwent minor hepatectomy were included in the analysis [119]. A systematic review concluded that although median perioperative mortality was 6.7% among patients with portal hypertension, median OS/DFS was 82/70% at 1 year, 71/50% at 3 years, and 37/38% at 5 years [120].

On balance, then, the available evidence suggests that hepatic resection can be appropriate for at least a subset of patients with HCC

involving portal hypertension. To clarify the indications for this treatment approach, it would be helpful to know how resection compares with other treatments for patients with portal hypertension, such as radiofrequency ablation, TACE, and liver transplantation. Few studies have addressed this question. In a retrospective study of patients with very early or early HCC (BCLC staging) and portal hypertension who underwent resection ($n = 81$) or radiofrequency ablation ($n = 40$), 5-year OS for the two groups was similar, although resection was associated with better 5-year DFS. Inverse probability weighting of the data led to similar results [121]. In a large retrospective study of patients with portal hypertension who underwent resection ($n = 173$) or TACE ($n = 80$), resection was associated with significantly higher OS at 1 year (76% vs. 73%), 3 years (38% vs. 17%), and 5 years (16% vs. 7%) ($P < 0.001$) [88]. This evidence, while scant, supports the safety and efficacy of resection for selected patients with portal hypertension.

This small evidence base has yet to identify prognostic factors that may predict post-resection outcomes for HCC patients with portal hypertension. Such factors may help clinicians exclude certain patients because of unacceptably high risk of perioperative death. Until more detailed analyses can be performed, clinicians should screen candidates for hepatic resection based on general health status, tumor size and number, vascular invasion, extrahepatic metastasis, preserved liver function, comorbidities, extent of hepatectomy, and residual hepatic volume. In general, major hepatectomy is not recommended in patients with cirrhosis. The relatively high 90-day mortality rate and complicated resection procedure in patients with portal hypertension mean that clinicians should carefully consider which treatment approach is likely to give the patient the best long-term OS.

6. Perspectives

Official guidelines have proven extremely useful for guiding research and treatment of HCC. However, despite the sometimes substantial evidence indicating the safety and efficacy of hepatic resection for patients with intermediate or advanced HCC or with HCC involving portal hypertension, official guidelines of US and European associations do not recommend it as a treatment option.

On the other hand, there is enough room of data to suggest nomogram based criteria for addressing patients to surgery based on their peculiar clinical profile [122–123]. This suggests that expanding the criteria for selecting patients for hepatic resection can increase access to potentially greater clinical benefits without significantly increasing in-hospital mortality or other adverse outcomes. The efficacy of resection may, in many patients, be higher when combined with other treatment modalities, which has only begun to be investigated [124–126].

7. Conclusions

Hepatic resection to treat HCC is associated with the best outcomes when the patient has only one tumor and no macrovascular invasion or portal hypertension. Various and worldwide spread reports suggest that surgery could be a proper treatment also for many patients with intermediate or advanced disease or with disease involving portal hypertension, as long as preserved liver function is adequate. There is now room, rather than debating whether or not surgery should have a room for these patients, for focusing better on selection criteria to further enhance the prognostic benefits of resection.

Potential competing interests

None.

Authors' contributions

J.-H.Z and T.Y conceived the study. All authors wrote and reviewed the manuscript.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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