



Controversies and evidence of hepatic resection for hepatocellular carcinoma☆



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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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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 (ITA.LI.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

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