Liver functional reserve estimation: state of the art and relevance for local treatments

The Western perspective

Fotini Manizate · Spiros P. Hiotis · Daniel Labow · Sasan Roayaie · Myron Schwartz

Abstract More than 90% of cases of hepatocellular carcinoma (HCC) develop as a consequence of underlying liver disease (most commonly viral hepatitis), often resulting in impaired liver function. In such cases, transplantation is an appealing alternative as it can potentially cure both the malignancy and the underlying disease. When transplant is not readily available due to organ scarcity, borderline cases must be considered for resection. The function of the underlying liver can be assessed by the Child Pugh score or by quantitative tests such as indocyanine green (ICG) clearance, metabolism of lidocaine to the metabolite MEG-X, and the arterial body ketone ratio (AKBR); liver biopsy pathology scoring and the platelet count can serve as indicators of fibrosis and portal hypertension. Another important factor to be considered is the risk of tumor recurrence, either because of unrecognized metastasis or due to de-novo tumor formation. Both factors must be considered in weighing resection against nonsurgical alternatives. Preoperative portal vein embolization is a strategy that can evoke regeneration in anticipation of surgery, serving as a "stress test" of the liver's regenerative capacity.

Keywords Hepatic reserve · Liver resection · Liver function · Hepatocellular carcinoma

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Introduction

Surgery, including orthotopic liver transplantation (OLT), remains the most effective treatment in patients with hepatocellular carcinoma (HCC). However, fewer than 30% of patients are eligible for liver resection, either due to tumor multifocality or due to the severity of their underlying liver disease [1, 2]. In recent years, with advances in imaging, interventional radiology techniques such as portal embolization and transcatheter arterial chemoembolization (TACE) [3], and surgical techniques [4, 5], but most importantly, with the optimized selection of candidates for resection by accurate preoperative evaluation of hepatic reserve, the safety of liver resection has been markedly improved. Herein, we review available data for the selection of patients for hepatic resection, in the background of underlying liver disease.

Treatment of HCC in the United States

The mainstays of HCC treatment are local treatments that attack either the tumor directly or its blood supply. While resection is the optimal local treatment from a tumor standpoint, the fact that most often HCC develops in the background of cirrhosis and impaired liver function results in many patients not being candidates for resection. In the United States, the most common underlying etiology is hepatitis C (Fig. 1).

Liver transplantation offers an appealing alternative to resection as it cures both the tumor and the cirrhosis. In the United States, liver transplantation is widely available, with a well-organized organ procurement system facilitating deceased-donor transplantation; furthermore, patients with HCC meeting the Milan criteria are prioritized on the transplant waiting list. Partly as a result of the
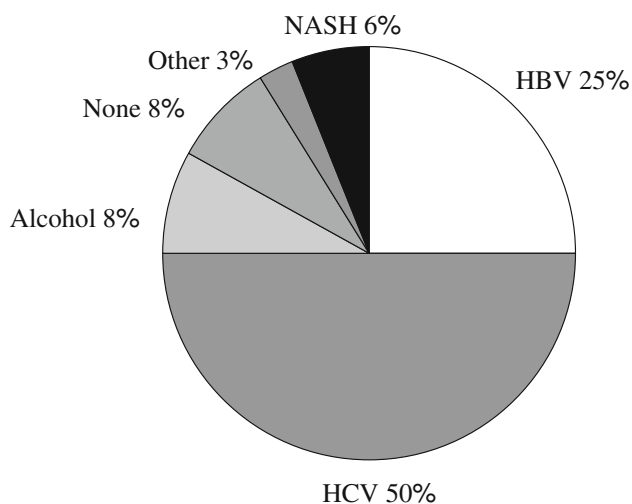
Fig. 1 Diagnosis of liver diseases underlying hepatocellular carcinoma (HCC); The Mount Sinai Medical Center overall experience ($n = 2,380$). *NASH* Non alcoholic steatohepatitis, *HBV* hepatitis B virus, *HCV* hepatitis C
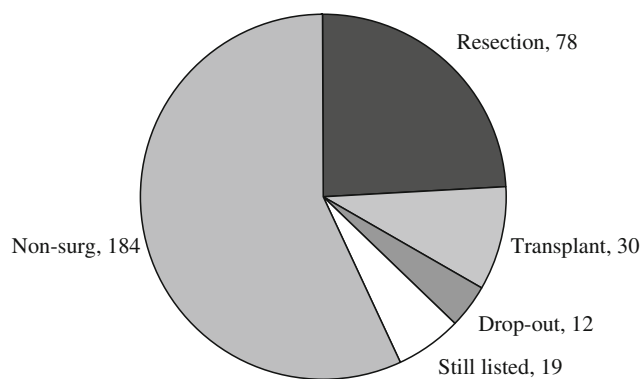

Fig. 2 Treatment of HCC at The Mount Sinai Medical Center. Patients first seen in 2007 ($n = 323$); 43% were eligible for potentially curative treatment

predominance of transplantation, there are not many centers in the United States that have developed significant expertise in hepatic resection in the setting of cirrhosis; cases where the liver function is borderline tend to be directed towards transplantation. For this reason, the sophisticated tests used in Asian countries (where transplantation has been less readily available) in order to try and precisely determine the degree of hepatic dysfunction and ability to tolerate resection are not used to the same extent in the United States. To provide some perspective, among 323 patients with HCC first seen at The Mount Sinai Medical Center in 2007, 78 (24%) were treated with resection, 61 (19%) were listed for transplant, and 184 (57%) were treated nonsurgically. Among the 61 patients placed on the transplant waiting list, 30 were transplanted, 12 dropped out, and 19 remain listed. The median time to

transplant was 116 days, and the median waiting time for those patients still listed is 176 days (Fig. 2).

Nonsurgical treatments, primarily radiofrequency ablation (RFA) and chemoembolization, are used both as primary treatment in patients with inoperable disease, and in patients awaiting transplant in an effort to control the tumor and prevent drop out. Increasingly, RFA is being considered as an alternative to resection. In a study published by Ng et al. in 2007 [6], RFA achieved initial complete ablation in 192/209 patients (93%); 36 patients had no subsequent recurrence of disease. In analyzing patterns of recurrence, 94/209 patients presented with recurrence either locally at the ablation margin, or within the anatomic segment of the liver initially affected. These are the patients who, one might hypothesize, would be the true beneficiaries of anatomic liver resection [6]. The optimal application of RFA is in patients with HCC 2 cm or less, where a sustained complete response of 97% at 31 months has been reported [7]; in patients with HCC more than 3 cm in diameter, complete ablation, as confirmed by pathology, has been reported to be as low as 29% [8].

Liver resection for HCC

Apart from transplantation, resection is the most certain way to eliminate any particular nodule of HCC: with negative margins the incidence of local recurrence is near zero, and segmental resection also removes satellite lesions in the local vascular bed. The function of the underlying liver clearly has an important role in the early postoperative outcome; patients with more advanced liver disease also have a higher incidence, stage for stage, of HCC recurrence. While anatomic resection is preferable in HCC because of the tendency for vascular invasion into segmental portal/hepatic venous branches, impaired function and regeneration in cirrhotic livers provides a strong rationale to spare liver parenchyma; major resection in cirrhosis, even when well-compensated, is best avoided.

In the United States most resection programs base the assessment of hepatic reserve on the Child Pugh classification. Only patients with Child's A cirrhosis are candidates for resection. The results of resection in patients with Child's B cirrhosis are significantly worse, and in our view resection does not offer any significant benefit over nonsurgical therapies in this group; we thus prefer local ablation and transplant referral for these patients. Further stratification is possible among patients with Child's A cirrhosis. The bilirubin level has been shown both in our data and in data from Barcelona to correlate with survival, with a cutoff of 1 mg/dL. A second relevant factor is the presence of portal hypertension. We use the platelet count as a surrogate indicator of portal pressure, with a platelet

count of more than 100,000/µl indicating the absence of substantial portal hypertension. Imaging studies are also reviewed, and the presence of varices is taken as de-facto evidence of portal hypertension. Wedged hepatic venous pressure gradient measurement is employed only in questionable cases, with a gradient of more than 10 mmHg indicating portal hypertension. At Mount Sinai, as in most centers in the United States, true tests of liver function, such as indocyanine green (ICG) clearance, arterial ketone body ratio (AKBR), or the metabolism of lidocaine to the metabolite MEG-X are not used.

Underlying liver disease

It is our experience that there are significant differences among patients with varying etiologies of underlying liver disease as to the likelihood of resectability (see Fig. 3). Roughly 20% of patients with HCC in the setting of hepatitis B are not cirrhotic; even among the remaining 80% liver function is commonly preserved, with the majority in Child's class A. This is in contradistinction to patients with hepatitis C, who virtually all have cirrhosis, commonly Child's B or worse. Furthermore, hepatitis B is readily treatable with antiviral agents that, while they do not clear the infection, stop replication and thereby both slow the progression of cirrhosis and lower the incidence of de-novo tumorigenesis [9]; treatment of hepatitis C, on the other hand, is extremely difficult in cirrhotic patients, with complete response rates well under 50% [10].

Among patients with hepatitis C, the likelihood of developing new HCC correlates with the degree of hepatic fibrosis: new HCC develops at a rate of 0.5% per year in patients with platelet counts of more than 150,000/µl versus a rate of 2.6% per year in patients with platelet counts of less than 100,000/µl [11, 12]. The assessment of the underlying liver is taking on new significance with the use
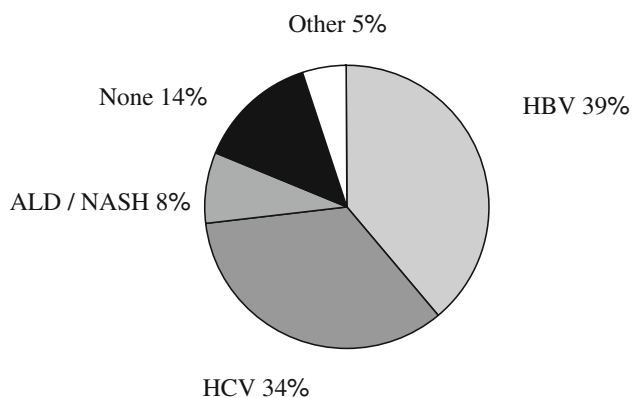
of molecular studies to identify gene signatures that can predict the likelihood of de-novo tumor development after hepatic resection [13].

Neoadjuvant treatment of HCC

In cases where hepatic reserve is borderline, particularly when a substantial amount of functioning parenchyma must be resected, preoperative portal vein embolization, in order to induce regeneration of the planned liver remnant in anticipation of surgery, is a commonly employed strategy. In our practice, we routinely use portal embolization in patients with HCC and cirrhosis who require right lobe lobectomy, unless the right portal vein is already occluded by tumor or the right lobe is largely replaced by tumor. Cirrhotic livers regenerate more slowly than normal; we thus wait a minimum of six weeks and often as long as three months after embolization before proceeding with resection. In order to prevent tumor progression during this waiting period, preliminary chemoembolization is typically employed. Patients who fail to develop hypertrophy of the contralateral liver in response to portal embolization are, in general, not good candidates for resection; portal embolization in this context serves as a "stress test" of hepatic reserve.

Conclusion

Preoperative assessment is critical when considering surgery for patients with HCC. The selection of patients must be based on both the patient's liver function and the risk of HCC recurrence. RFA is increasingly recommended in patients with early HCC, and is currently preferred in patients with tumor size less than 2 cm. Liver resection is recommended in noncirrhotic patients, as well as in patients with Child's A cirrhosis and no portal hypertension. In borderline cases, neoadjuvant treatment can beneficially modify surgical risk.

Other 5%
None 14%
HBV 39%
ALD / NASH 8%
HCV 34%

Fig. 3 Diagnosis of liver diseases underlying hepatocellular carcinoma (HCC); The Mount Sinai Medical Center resection experience (n = 579). *ALD* Alcoholic liver disease

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