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ORIGINAL ARTICLE

Surgical treatment of hepatocellular carcinoma: expert consensus statement

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Abstract

As the number of effective treatment options has increased, the management of patients with hepatocellular carcinoma has become complex. The most appropriate therapy depends largely on the functional status of the underlying liver. In patients with advanced cirrhosis and tumor extent within the Milan criteria, liver transplantation is clearly the best option, as this therapy treats the cancer along with the underlying hepatic parenchymal disease. As the results of transplantation has become established in patients with limited disease, investigation has increasingly focused on downstaging patients with disease outside of Milan criteria and defining the upper limits of transplantable tumors. In patients with well preserved hepatic function, liver resection is the most appropriate and effective treatment. Hepatic resection is not as constrained by tumor extent and location to the same degree as transplantation and ablative therapies. Some patients who recur after resection may still be eligible for transplantation. Ablative therapies, particularly percutaneous radiofrequency ablation and transarterial chemoembolization have been used primarily to treat patients with low volume irresectable tumors. Whether ablation of small tumors provides long term disease control that is comparable to resection remains unclear.

Keywords

consensus conference, hepatocellular cancer, hepatoma, surgery, laparoscopic, laparoscopy, chemotherapy, radiotherapy, chemoembolization, ablation, liver transplantation

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Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in the world and is the leading cause of cancer death in many areas. In the United States, HCC incidence is rising and is projected to further increase over the next two decades.[1–3] Cirrhosis and chronic hepatitis infection are important risk factors for developing HCC, and globally HCC incidence is closely linked to these conditions. Hepatitis C is an important underlying factor, particularly in the United States, where approximately 4 million people are afflicted with chronic hepatitis C infection, one third of which will go on to develop chronic liver disease and a large proportion will develop cancer.[4] In general, the incidences of cirrhosis and HCC are closely related, but there is some variability depending on geographic location, which reflects differences in etiology.[5] Areas with high rates of hepatitis C infection tend to have higher rates of HCC arising in the setting of cirrhosis, in contrast to areas where hepatitis B is more prevalent.

The presence of underlying hepatic parenchymal disease is critically important in determining both treatment options and outcome. The extent of the underlying hepatic dysfunction often

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dictates the therapeutic options may well be more important than cancer extent in determining survival. Patients with advanced cirrhosis, with or without cancer, have a very high risk of mortality related to liver failure and the sequelae of portal hypertension, which is as high as 55% at one year in patients in the Child-Pugh C category.[6] In such patients, aggressive treatment of the neoplastic disease may well offer little survival benefit, if the underlying liver disease is not addressed as part of the therapy (ie, transplantation); resection or even ablative therapies are usually contraindicated, given the risk of precipitating liver failure. On the other hand, patients with normal livers or with well compensated cirrhosis are typically limited more by the extent of the malignant disease. In this setting, resection, orthotopic liver transplantation (OLT) or ablative therapies are potentially available, depending on disease related factors.

Over the past several years, surveillance programs have been used with greater frequency in high risk patients,[7] resulting in earlier detection. Also, from a treatment standpoint, OLT and ablative techniques have emerged as potentially effective alternatives to resection, which had previously been considered the gold standard. As a result, the best treatment strategy for patients with early stage tumors has become increasingly controversial. Definitive prospective trials directly comparing these treatment modalities have not been performed, largely due to the heterogeneity in disease extent and underlying hepatic function that make it difficult to randomly assign patients to different treatment arms.

This section summarizes the results of a recent AHPBA consensus on the surgical treatment of HCC, including the use of ablative therapy and emerging technology, in addition to resection and OLT.

Thermal ablation and emerging technologies in the curative therapy of HCC

Ablative therapy

Non resectional ablative therapies have emerged as effective treatment options for patients with HCC. The most common of these approaches are radiofrequency ablation (RFA) and transarterial embolization / transarterial chemoembolization (TAE/TACE). These techniques are aimed at affecting tumor necrosis and can be reasonably effective for small tumors. However, both suffer from significant limitations. The role of TACE will not be discussed in detail in this section, as it is addressed in depth elsewhere in this review.

RFA is used percutaneously in the large majority of cases, but is greatly limited by tumor size and location. In a report from Mulier *et al.* that included over 5,000 treated tumors, recurrence at the treatment site was 14% when the tumor diameter was ≤3 cm but increased to 25% when the diameter was 3 to 5 cm and was 58% in tumors >5 cm in size. Vascular proximity (ie, tumors close to major vascular structures) had similarly high recurrence rates of 37%, compared to 3% for those that were not.[8] Despite these limitations however, up to 80% tumor necrosis has been reported for tumors that are <2.5 cm in diameter.[9] In 2008, Livraghi *et al.*, recorded results of a prospective multicenter analysis of percutaneous RFA with patients with solitary HCC ≤2 cm. Treatment was successful in nearly all patients, and 5-year overall survival was 55% but increased to 68% in patients with tumors considered operable.[10] Chen *et al.* recently reported equivalent overall and disease-free survival in a randomized controlled trial comparing resection with radiofrequency ablation for tumors up to 5 cm in size.[11] The results from these and other studies have led many to consider RFA as an effective alternative to resection in patients with small (≤3 cm) HCC.

Both percutaneous RFA and TAE/TACE are used as a primary treatment in patients with advanced, unresectable HCC. Additionally, these approaches are used frequently to treat patients with limited HCC while on the liver transplant waiting list. While these 'bridging' techniques are employed commonly, with the aim of controlling disease in patients while awaiting a new graft, pre-transplantation therapy has never been shown to improve overall disease free survival after OLT.[12,13] The role of bridging therapy for patients awaiting OLT will be discussed in more detail later in this review.

New and emerging treatment approaches

Microwave ablation is a new modality that is promising and may prove to be more effective than RFA for treating larger tumors and tumors in close proximity to major vascular structures.[14] However, with this greater potential comes the possibility of increased complications. The clinical experience with microwave ablation is still immature, and definitive conclusions regarding its role are therefore not possible. Other modalities, such as high intensity focused ultrasound (HIFU) and electroporation[15] remain experimental at this time.

Radiofrequency-based treatment with nanoparticles is an example of an emerging technology, currently in pre-clinical development, with potential therapeutic applications in HCC.[16,17]

Consensus statement

1. RFA may have long-term survival rates similar to resection or OLT in patients with small HCC but this must be assessed in prospective, randomized controlled clinical trials
2. RFA is not recommended for HCC >4 cm in diameter because of high incomplete tumor. destruction rates, and the highest probability for complete local tumor control of HCC with RFA occurs in tumors <2 cm in diameter.
3. Given the poor overall survival for most patients with HCC, novel treatment avenues should be aggressively explored in an effort to improve outcomes.

Laparoscopic And open liver resection for HCC

Open liver resection

Hepatic resection has been the primary treatment for HCC in selected patients with limited disease. Resection has several practical advantages. First, it is more widely applicable, because there are no restrictions on tumor size, number or macrovascular inva-