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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.

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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

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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

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, pretransplantation 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-

sion, which often preclude OLT and ablation, respectively. Unlike OLT, there is also no obligatory waiting time. Liver resection and OLT allow complete pathologic evaluation of the specimen, which is precluded with ablative treatment. The efficacy of partial hepatectomy is critically dependent on the surgeon's ability to achieve a complete resection and maintain a liver remnant with adequate volume, perfusion and biliary drainage. Outcome after resection or OLT is closely linked to disease extent and the best outcomes are achieved in patients with solitary, small HCC confined to the liver without major vascular invasion. Resection is preferred in patients with HCC and non-cirrhotic liver and is applicable for selected patients with Child-Pugh A cirrhosis. Unlike OLT, however, it does not address the precancerous cirrhotic liver remnant.

The perioperative risk of partial hepatectomy for HCC has been a critical historical issue because operative mortality rates often exceeded 10%. Cirrhosis and portal hypertension increase the risk of perioperative hemorrhage requiring transfusions, impair liver regeneration and increase the risk of liver failure. Even in relatively current series, operative mortality of 8% for extended hepatectomy in patients with HCC has been reported.[18] Importantly, however, overall morbidity and mortality after resection for HCC have significantly decreased, with most major centers now reporting mortality rates <5% with lower operative blood loss and transfusion rates.[19,20,21]

Post-operative morbidity has been significantly associated with degree of underlying liver dysfunction, small liver remnant volume, blood loss, transfusion, and co-morbidities. The most effective strategies to minimize post-operative morbidity after resection relate to careful patient selection particularly in patients with cirrhosis based on assessment of liver function and restriction of resection to patients with compensated Childs A cirrhosis without portal hypertension, the use of parenchymal sparing resections, and the use of intraoperative techniques to minimize blood loss, such as low central venous pressure anesthetic management and intermittent portal triad clamping.[22]

The overall 5-year survival of 25–50% after hepatic resection for patients with HCC supports its therapeutic role. Importantly, however, resection does not address the remnant liver. Consequently, long-term outcome for patients with cirrhosis is poor because of the progressive decompensation of the cirrhotic liver with liver failure and ongoing hepatocarcinogenesis. Survival after resection has been associated with many clinical and pathologic factors. Tumor factors associated with reduced survival include high serum alpha-fetoprotein levels (>1000), size and number of HCC, and vascular invasion. The risk of microscopic vascular invasion increases proportionally to HCC size. Overall 5-year survival rates >50% have been reported for patients with small, solitary HCC and preserved liver function.[20,23,24]

The type and extent of resection have been associated with outcome based on reports of clinical series. Anatomic hepatectomy which is defined as an uni- or multisegmental resection that includes the portal venous branches to the segment(s) harboring

the HCC has been associated with improved survival[24] but is unsupported by prospective study and other retrospective clinical series. Although wide margins (1–2 cm) of resection for HCC have been generally recommended, many retrospective series have reported similar overall survival and patterns of recurrence for close margins of resection.[25] A recent prospective randomized trial compared the outcomes of 1 cm versus wide 2 cm margins of resection in 169 patients with limited HCC. Survival was significantly improved for patients with wide margins which provides strong evidence supporting the importance of surgical margin status as an outcome predictor after resection of small HCC.[26] Multi-focal HCC and major vascular invasion have been associated with poor survival and have been considered major contraindications to resection. Nonetheless, prolonged overall survival has been reported in highly selected patients. These factors, however, are generally associated with >95% recurrence rates and 5-year overall survival rates of <25%.[20,27,28] Resection for single large HCC (>10 cm) has been associated with favorable long-term survival and suggests that size alone is not a contraindication for resection.[29,30]

Patients with compensated cirrhosis and preserved liver function who harbor HCC within the Milan criteria (1 HCC < 5 cm or 3 HCC ≤ 3 cm) are candidates for either resection or OLT, and which should be the treatment of choice remains controversial. Importantly, most reported resection series include many patients with disease that is well beyond the Milan criteria and therefore not amenable to OLT, making direct comparison of outcomes impossible. When analyses are restricted to patients with similar disease extent, however, the overall survival difference between resection and OLT narrows. Indeed, overall survival at 5 years for patients with Milan criteria HCC after resection has been reportedly similar to that of OLT when accounting for dropouts while awaiting OLT and prolonged duration of time on wait list, However, HCC recurrence is greater after resection.

Resection in selected patients with cirrhosis continues to be recommended because of its broader applicability and reported survival (35–50% at 5 years). However, accurate identification of such potential long-term disease-free survivors for resection with Milan criteria HCC based on current clinicopathological risk factors remains limited. OLT may be avoided in some patients because resection has been associated with prolonged recurrence-free survival. , Although OLT is associated with greater disease-free survival, nearly 10% of patients recur systemically after OLT, which similarly indicates refinement of selection criteria for OLT are needed. Although salvage OLT has been proven safe and effective in selected patients,[31–33] wide application of this approach as support for standard resection remains highly controversial.

Laparoscopic liver resection

Recently laparoscopic resection for HCC has been reported in limited clinical series. The majority of laparoscopic resections have been performed for single, small tumors in accessible parts of

the liver in highly selected patients. Nonetheless, the reported series suggest feasibility and no obvious compromise in oncologic surgical principles.[34,35]

Consensus statement

1. Resection with wide margins is the treatment of choice for HCC in patients without cirrhosis and applicable for selected patients with cirrhosis (Childs-Turcotte-Pugh A without portal hypertension) with single HCC, regardless of size.
2. Minimizing blood loss and the amount of non-tumoral liver resected optimizes perioperative outcome.
3. Highly selected patients with multifocal HCC or major vascular invasion may be candidates for resection but the efficacy of resection in these patients remains controversial and requires further clarification.
4. Laparoscopic resection is feasible but unproven.

Liver transplantation for Milan and extended criteria for HCC

OLT is recognized as the optimal treatment for selected patients with cirrhosis and HCC, because recurrence and de novo HCC in the remnant liver are eliminated and hepatic replacement reestablishes normal hepatic synthetic function. Currently only patients with cirrhosis and early stage HCC are recognized as standard candidates for OLT[36] according to the criteria from the United Network for Organ Sharing (UNOS). Candidacy for OLT in patients with cirrhosis and HCC is currently based on estimates of HCC stage by cross-sectional imaging, usually magnetic resonance (MR) or computed tomography (CT). Although other prognostic criteria for HCC such as the presence of microvascular invasion or genotyping have been proposed for selection of patients for OLT[37,38] the availability and accuracy of such data has not been widely confirmed regardless of preoperative biopsy. Thus, most patients with chronic liver disease are considered candidates for OLT and undergo evaluation for OLT listing if imaging depicts a contrast enhanced mass consistent with HCC with the support of laboratory and clinical features but without tumor biopsy. Patients with early stage HCC, that is, meeting Milan criteria (see below), are usually listed based on the UNOS point system for the stage of the underlying liver disease and the added exception points for HCC. Patients with more advanced stage of HCC usually undergo therapeutic attempts at downstaging before transplant listing, although the benefits of such an approach remain to be firmly established.

Milan criteria

In their landmark report from 1996, Mazzaferro *et al.* showed that survival after OLT in patients with cirrhosis and early-stage HCC was equivalent to that after OLT in patients with similar causes and stages of chronic liver disease without malignancy.[36] The 'Milan criteria' of early stage HCC, that is, a single tumor <5 cm or 1- 3 tumors each <3 cm, were subsequently adopted by UNOS in

2002 as the optimal criteria to guide OLT for HCC.[36] Organ allocation is based on the Model for End Stage Liver Disease (MELD), and currently only patients meeting the American Liver Tumor Study Group (ALTSG) modified TNM stage II[39] routinely receive allocation priority, now receiving a MELD score of 22. The current allocation priority usually allows for OLT within 6–12 months in most regions of the U.S.[40] Survival after OLT for patients with the Milan criteria have been excellent and have led to a significant increase in the number of OLT performed annually in the U.S. for HCC from about 8.8% prior to 2002 to approximately 22% in 2006.[41,42] Numerous reports have shown that overall 5-year and 10-year survival after OLT for patients with cirrhosis and early stage HCC have ranged from 60 to 80% and 50 to 60%, respectively.[43–45] Importantly, however, disease-specific survival after OLT for patients with cirrhosis and early stage HCC are excellent in such patients, since recurrence of HCC is uncommon after OLT.[43,44,46] Despite the limitations of the current level of evidence for clinical studies, the disease-free survival after OLT clearly exceeds that for partial hepatic resection , which is only in the range of 20 to 25% by 10 years, even in patients meeting Milan criteria at the time of hepatic resection.[31,32] Although these data clearly support the primary role of OLT for patients with cirrhosis and early stage HCC, the disease incidence, the economic and psychosocial impact of OLT and the fact that some will have equivalent outcomes after partial hepatic resection dictate further evaluation of selection criteria and treatment options.

Extended criteria HCC

OLT for patients with chronic liver disease and HCC beyond early stage disease remains controversial. In the original Milan multicenter trial,[36] 13 of the 48 patients with clinical stage II HCC actually exceeded stage II HCC pathologically in the liver explant. Survival for these patients was only 45% at 4 years and was significantly less than for those patients with early stage HCC.[36] This adverse outcome likely influenced the decision by UNOS not to allot routine MELD exception points to patients with HCC beyond stage II. Patients with cirrhosis and HCC beyond Milan criteria challenge current management approaches, because unlike patients with stage II HCC, patients with stage III or greater HCC do not routinely receive MELD priority points despite otherwise meeting criteria for OLT and most of these patients are not candidates for standard liver resection. Moreover even when resection is performed, both overall and disease-free survival is limited.[31] Transplant centers may selectively petition regional review boards for MELD exception points in patients with HCC exceeding the Milan criteria. Although patients with such HCC can be listed for OLT based on their actual MELD point score, timely OLT before HCC progression is unlikely without additional exception points. Alternatively OLT in this clinical setting can be undertaken by using livers from living donors or from very 'marginal' donors from whom organs would not otherwise be utilized.

Although limited availability of donor organs has prompted criticism of existing exception points for listing patients with

HCC for OLT, others believe that the current criteria for granting of exception points are too restrictive and that redefinition of selection criteria by expanding the maximum tumor size could allow OLT in more patients without compromising the results. Investigators at the University of San Francisco have proposed expanded size criteria for HCC in transplant candidates, 'UCSF criteria',[47,48] which includes a single HCC < 6.5 cm in diameter, or 1- 3 HCC with the largest 4.5 cm in diameter and a total HCC diameter of <8 cm.[48] Overall 1- and 5-year survival rates were 90% and 75% respectively for patients meeting UCSF criteria and without pre-transplant treatment to downstage HCC. These findings have been corroborated in a case-controlled series[44] which demonstrated equivalent survival after OLT for patients with cirrhosis and stage I, II, and III HCC compared to patients with similar causes and stages of liver disease without HCC during a similar time period. Thus, the expansion of UNOS criteria to include patients with stage III HCC as routine candidates for transplant listing is supported by the disease-specific survival of nearly 90% and limited recurrence after long-term follow-up.

Downstaging

Screening of patients with liver disease at risk for HCC should ideally detect early stage disease, for which patients would be 'transplant eligible'. Unfortunately, many screening programs remain inconsistently employed, are limited in efficacy and often detect advanced stage HCC at the initial presentation of previously unrecognized liver disease. Consequently, HCC is detected at an advanced disease stage in many patients with chronic liver disease. Unless listing criteria for OLT in patients with HCC are revised, candidacy for OLT in patients with more advanced-stage HCC can only be achieved by downstaging by the use of a neoadjuvant therapy. Downstaging of HCC by neoadjuvant therapy has not been widely investigated. Transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) of HCC have been effectively used to prevent progression of early stage HCC in patients awaiting OLT,[49,50] however, the efficacy of such therapy for downstaging advanced HCC to Milan criteria is unclear. Recently neoadjuvant TACE[51] was successfully used to downstage 18 of 76 (23.6 %) otherwise unselected patients with stage III/IV HCC to Milan criteria and, subsequently permitting OLT in 17 of these 18 patients. Both disease-specific and overall-survival after OLT in these highly selected patients were 94% with only 1 HCC recurrence after a median follow-up of 19.6 months. In that report,[51] the average time from initial TACE to OLT was 5.8 months during which time patients had regular follow-up imaging to assess disease status. This strategy addresses control of the primary tumor with a loco-regional strategy and avoids systemic therapy during observation, which potentially would allow detection of occult metastatic disease, if present, and thereby avoiding an OLT. Whether confirmation of HCC downstaging by neoadjuvant therapy to meet Milan criteria is too restrictive is unknown. The outcome of OLT for patients with stable HCC beyond the Milan criteria after neoadjuvant therapy is unknown.

The role of hepatic resection as neoadjuvant treatment for HCC is unknown. Broadly neoadjuvant treatment for HCC implies that OLT will be undertaken provided that criteria for OLT otherwise are present and extrahepatic HCC has been excluded by imaging. In this regard, neoadjuvant hepatic resection has not been evaluated. Patients with cirrhosis and HCC who are candidates for OLT and undergo hepatic resection are not eligible for exception points under current UNOS guidelines and consequently OLT is generally precluded by their underlying MELD score. Hepatic resection for HCC has been employed in patients with compensated cirrhosis (MELD < 9) and followed by OLT as 'salvage therapy' for patients with intrahepatic recurrence. This approach has been evaluated in patients with HCC eligible for OLT and reports have differed with outcomes showing equivalent survival after salvage OLT for recurrent HCC compared to primary OLT[33] and significantly worse survival after salvage OLT compared to primary OLT.[52] Hepatic resection has not been used to downstage HCC to meet criteria for OLT.

These data support a downstaging strategy of loco-regional therapy for any patient with HCC confined to the liver, but beyond Milan criteria, who is otherwise a transplant candidate. Patients who have confirmed downstaging to Milan criteria for a minimum of 3–6 months after initial TACE should be granted equivalent MELD exception points as for patients who initially present with stage II HCC. Patients undergoing loco-regional therapy with stable intrahepatic disease and no evidence of extrahepatic progression for 3–6 months should be considered for OLT on a case by case basis.

Consensus statement

1. OLT is established as the preferred approach for patients with cirrhosis and HCC meeting Milan criteria
2. OLT should be considered on a highly selective basis for patients beyond Milan criteria without pre-transplant downstaging (e.g. those meeting UCSF criteria)
3. Pre-transplant therapy (TACE and other) with an interval of observation (3 – 6 months minimum) to assess the biologic aggressiveness should be considered for patients beyond Milan criteria. Patients who downstage to meet Milan criteria with no evidence of extrahepatic disease on re-staging should be considered for MELD exception points to allow for OLT

Bridge to transplantation therapy for HCC

Bridge to transplantation therapies are used to prevent HCC progression while patients await OLT. The specific aims of such therapies are to 1) avoid HCC progression and drop-out on the waiting list; 2) increase tumor-free survival after OLT; 3) downstage advanced HCC to enable OLT; and 4) avoid or delay the need of OLT for selected patients that respond favorably to bridge treatment.

Three strategies have been used as bridge therapy to OLT: TACE or TAE, ablation therapy with either percutaneous ethanol

injection (PEI) or RFA, and surgical resection. The efficacy of these therapies remains controversial. In fact, clinical practices are highly variable, and some centers prefer no therapy at all. Published clinical experiences and trials of the different bridge therapies including those without treatment, were reviewed and the following standard metrics were assessed: 1) tumor response to therapy; 2) drop-out on the waiting list; 3) survival after OLT; 4) avoidance or delay of OLT for patients responding to therapy; and 5) treatment related morbidity and mortality. Reports comparing differences in bridge therapies were examined to determine relative efficacy, but such analysis is confounded by reports which include resection, OLT and non-transplantation candidates and patients treated by multiple bridge therapies. Finally, no randomized controlled trial has been designed to demonstrate efficacy of any bridge therapy for patients awaiting OLT.

Natural history (no treatment)

The natural history of untreated HCC presenting within transplant criteria is well known.[53] At least 70% of patients will have tumor growth, 20% will develop vascular invasion, and 9% will develop metastases within one year of diagnosis. The risk of drop-out (disease progression beyond transplant criteria) is approximately 20% during the first six months while awaiting OLT.

TACE and TAE

There are no randomized controlled trials demonstrating efficacy with either a decrease in drop-out on the waiting list or improved survival after OLT. Efficacy is supported by observations of tumor response to treatment and comparison of drop-out rates with historical controls. Several randomized controlled trials have demonstrated tumor responses and improved survival in nonsurgical patients treated with TACE or TAE compared to untreated controls.[54,55] Uncontrolled series have shown low drop-out rates achieved in patients treated with TACE, 0–15% at 6 months and 0–25% at 12 months.[56,57] TACE associated morbidity has been less than 5%.[55,58] Although TACE is more widely used than TAE, the efficacy and safety of TACE and TAE are similar.[59,60] A single randomized prospective trial has demonstrated greater rates of HCC response with TACE and thymalfasin.[61]

RFA and PEI

No randomized controlled trial has demonstrated less drop-out or increased survival due to RFA or PEI in patients awaiting OLT. Several studies have demonstrated HCC response to therapy, less than expected HCC progression, and lower than expected drop-out rates for patients awaiting OLT.[11,62–66]

Liver resection

Liver resection as a bridge to OLT is controversial. Although OLT is clearly feasible after resection, there are conflicting reports regarding the increased operative risk of OLT in patients previously submitted to a partial hepatectomy.[33,52] Approximately 70% of patients develop recurrent HCC after resection, but many are not candidates for OLT.[52] Liver decompensation soon after resection is salvageable by OLT. An advantage of liver resection as bridge therapy is that accurate pathological staging and identification of poor prognostic factors for HCC are available prior to OLT. Unlike other bridge therapies, resection may avoid or delay OLT. Selected patients with small HCC and low MELD scores achieve reasonable survival with resection alone.[67,68] Finally, liver resection as a bridge to OLT is problematic in the United States because resection precludes MELD score exception points for patients on the waiting list.

Combined experience and comparative data

Despite demonstrable HCC responses to TACE and RFA, overall efficacy remains controversial.[13,69] Survival after OLT for patients that have and have not undergone bridge therapy is similar.[13] Nevertheless, intention-to-treat analyses suggest that bridge therapy is effective for patients with anticipated waiting times longer than 6 months.[69]

Comparison studies of bridge therapies have been conducted in both non-surgical patients and those awaiting OLT. These studies show that small central HCC may be better treated with RFA than TACE,[63] combined TACE and RFA and RFA alone have equal efficacy for the treatment of small (≤3 cm) HCC (12); results with RFA exceed those with PEI;[65,66] and results with RFA are comparable to resection.[11,65]

Downstaging

Treatment with RFA, TACE, or resection has achieved downstaging of HCC exceeding Milan criteria and enabled 21 of 30 highly selected patients to undergo OLT.[70] Although median follow-up was only 16 months, no patient developed recurrent HCC. Successful downstaging from TACE was achieved in 18 of 76 (24%) patients with stage III and IV disease.[51] Seventeen underwent OLT and overall and disease-free survival was 96% at a median follow-up of 19.6 months with only one recurrent HCC. These findings clearly demonstrate the potential of bridge therapies to achieve significant tumor responses in patients with HCC beyond standard transplant criteria. A survival advantage is evident for these patients because none would have survived without OLT or otherwise been a candidate for OLT without bridge therapy.

Consensus statement

1. Bridge to transplantation therapy with TACE and RFA have low morbidity, are associated with favorable HCC responses, and probably reduce drop-out due to HCC progression for patients waiting at least 6 months to undergo OLT.
2. Liver resection may be a bridge to OLT or delay and possibly avoid the need of OLT for highly selected patients with small tumors and low MELD scores.

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