

# AASLD GUIDELINES FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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## AASLD APPROVAL

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## **GUIDING PRINCIPLES AND OBJECTIVES**

### *Guiding Principles*

This document presents official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the surveillance, diagnosis, and treatment of hepatocellular carcinoma (HCC) occurring in the setting of adults with cirrhosis. Unlike previous AASLD practice guidelines, the current guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach<sup>1</sup>. Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. An enhanced understanding of the guideline can be obtained by reading the applicable portions of the systematic reviews. In addition, more detailed information may be found in the associated guidance document related to clinically important aspects of HCC that lacked sufficient evidence to warrant a systematic review.

The guideline focuses on a broad spectrum of clinical practice, including surveillance of patients with cirrhosis for HCC, establishing the diagnosis of HCC, and various therapeutic options for the treatment of HCC. To address other issues on HCC such as epidemiology, staging, and additional aspects of diagnosis and treatment, the authors have created a new guidance document that will be published soon (reference when available), which is based upon the previous HCC AASLD guidelines by Bruix and Sherman<sup>2</sup>.

### *Key Questions*

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The guideline developers from the AASLD identified key questions that health care providers are faced with frequently in the evaluation and management of patients with HCC. These questions were:

- 1. Should adults with cirrhosis undergo surveillance for HCC? If, so which surveillance test is best?**
- 2. Should adults with cirrhosis and suspected HCC undergo diagnostic evaluation with multiphasic CT or multiphasic MRI?**
- 3. Should adults with cirrhosis and an indeterminate hepatic nodule undergo a biopsy, repeated imaging, or alternative imaging for the diagnostic evaluation?**
- 4. Should adults with Child's class A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or locoregional therapy?**
- 5. Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy or not?**
- 6. Should adults with cirrhosis awaiting liver transplantation and HCC (T1) be treated or undergo observation?**
- 7. Should adults with cirrhosis awaiting liver transplantation and HCC (Organ Procurement and Transplantation Network [OPTN] T2) undergo transplant alone or transplant with bridging therapy while waiting?**
- 8. Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) be transplanted following downstaging to within Milan criteria?**
- 9. Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?**

**10. Should adults with Child's A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease be treated with systemic or locoregional therapies or no therapy?**

*Target Audience*

This guideline is intended primarily for health care providers caring for patients with cirrhosis. Additionally, the guideline may inform policy decisions regarding patients with HCC.

**BACKGROUND**

*Burden of Disease*

According to the World Health Organization, HCC is the fifth most common tumor worldwide and the second most common cause of cancer-related death ( [globacan.iarc.fr](http://globacan.iarc.fr) ). Male to female predominance is greater than 2:1 with liver cancer, and approximately 83% of the estimated 782,000 new HCC cases in 2012 occurred in less developed regions of the world, with East and South Asia plus sub-Saharan Africa being the high-incidence regions, while Southern Europe and North America are the intermediate regions, and Northern Europe and South Central Asia are the low-incidence regions<sup>3</sup>.

The incidence of HCC has been rapidly rising in the United States over the last 20 years<sup>4</sup>.

According to estimates from the Surveillance Epidemiology End Result (SEER) program of the National Cancer Institute, the United States will witness an estimated 39,230 cases of HCC and 27,170 HCC deaths in 2016 ( [seer.cancer.gov](http://seer.cancer.gov) ). In addition, a recent study using the SEER registry projects that the incidence of HCC will continue to rise until 2030<sup>5</sup>, with the highest

increase in Hispanics, followed by African Americans, and then Caucasians, with a decrease noted among Asian Americans. The increase in incidence of HCC in the United States is attributed primarily to the hepatitis C (HCV) epidemic, prompting Petrick et al. to suggest that preventive efforts should target the birth cohort with the highest prevalence of HCV infection (1945-1965)<sup>4</sup>. Recent data have also shown that metabolic disorders—defined as nonalcoholic fatty liver disease (NAFLD) and the metabolic syndrome—contribute numerically more to the burden of HCC than any other risk factor including HCV infection<sup>6</sup>, which is due primarily to the high prevalence of NAFLD in the population overall.

### *High-Risk Group*

The presence of cirrhosis represents a key risk factor for the development of HCC. The prevalence of cirrhosis among patients with HCC has been estimated to be 85%-95%<sup>7, 8</sup>, and the HCC incidence rate among patients with cirrhosis has been shown to be 2%-4% per year<sup>9</sup>.

Therefore, patients with cirrhosis constitute a high-risk group for efforts at prevention and early detection. The fact that patients with HCC have underlying liver disease significantly impacts the management and therapeutic options.

The key questions posed above reflect common scenarios in this patient population and provide the framework for this practice guideline. We used the Child classification to define the underlying degree of liver dysfunction instead of the Model for End Stage Liver Disease (MELD) classification, mainly because it is more commonly used in this context.

## **METHODS OF GUIDELINE DEVELOPMENT**

An experienced methodologist moderated and facilitated the process of selecting the “key questions” (see above). A group of AASLD content experts worked collaboratively with an independent research group specializing in conducting systematic reviews to synthesize the available evidence. The research group provided curated evidence summaries following the GRADE approach (Table 1)<sup>1</sup>. In this approach, the quality of evidence in each systematic review is rated as high, moderate, low, or very low based on the domains of precision, directness, consistency, and risk of bias. Following a comprehensive analysis of each systematic review, the guideline-writing group based its recommendations on the quality of the evidence, balance of benefits and harms, patients’ values and preferences, and other clinical considerations. Based on this assessment, the guideline writing group generated AASLD recommendations that are graded as either strong (apply to most patients with minimal variation) or conditional (apply to a majority of patients). The strength of recommendation is not only determined by the quality of evidence. Other factors, such as the balance of benefits and harms, patients’ values and preferences, and feasibility of the recommended action, all play a role in determining the strength of recommendations. Technical remarks are added to recommendations to help reconcile the level of the recommendation with the quality of the evidence and in order to facilitate implementation. Evidence profiles for the corresponding systematic review for each of the key questions are presented as an appendix to this article. For the key questions with sparse, indirect evidence, relevant studies are summarized after each recommendation.

## **1. SHOULD ADULTS WITH CIRRHOSIS UNDERGO SURVEILLANCE FOR HCC, AND IF SO, WHICH SURVEILLANCE TEST IS BEST?**

### *Recommendations*

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**1A. The AASLD recommends surveillance of adults with cirrhosis because it improves overall survival.**

Quality/Certainty of Evidence: Moderate

Strength of Recommendation: Strong

**1B. The AASLD suggests surveillance using ultrasound (US), with or without alpha-fetoprotein (AFP), every 6 months.**

Quality/Certainty of Evidence: Low

Strength of Recommendation: Conditional

**1C. The AASLD suggests not performing surveillance of patients with cirrhosis with Child's class C unless they are on the transplant waiting list, given the low anticipated survival for patients with Child's C cirrhosis.**

Quality/Certainty of the Evidence: Low

Strength of Recommendation: Conditional

*Technical Remarks*

1. It is not possible to determine which type of surveillance test, US alone or the combination of US plus AFP, leads to a greater improvement in survival.
2. The optimal interval of surveillance ranges from 4-8 months.
3. Modification in surveillance strategy based on etiology of liver diseases or risk stratification models cannot be recommended at this time.

## *Background*

The goal of surveillance and screening is to reduce mortality<sup>10</sup>. HCC meets the criteria for the development of a surveillance program<sup>11</sup> given that patients with cirrhosis are a high-risk group<sup>7</sup> and they can be readily identified. The previous AASLD guidelines on HCC<sup>2</sup> summarize the populations at the highest risk to have chronic viral hepatitis B and cirrhosis due to hepatitis C. A randomized surveillance study performed in another high-risk group, hepatitis B (HBV) carriers, showed a 37% reduction in mortality for those who underwent surveillance<sup>12</sup>. However, there are no randomized trials in Western populations with cirrhosis secondary to chronic hepatitis C or fatty liver disease, and thus there is some controversy surrounding whether surveillance truly leads to a reduction in mortality in this population of patients with cirrhosis. Another source of controversy is which surveillance test(s) should be utilized. While it is well established that US should be part of surveillance, it is unknown whether the addition of biomarkers, such as AFP, allows for improved survival. The previous AASLD guidelines recommends that US was the primary modality to be used<sup>2</sup>. Because of these uncertainties, the aim of this question was to determine whether current data are in support of HCC surveillance in adults with cirrhosis, and if so, what type of surveillance is best.

## *Evidence and Rationale*

The evidence profile of surveillance for HCC is included in Supporting Table 1, which utilizes the data from a recent systematic review on surveillance<sup>13</sup>. There were no randomized controlled trials (RCTs) of surveillance in patients with cirrhosis. There were 38 observational cohort studies that evaluated surveillance in patients with cirrhosis, making the overall quality of the evidence moderate (Supporting Table 1). The majority of the data was reported with 3-year survival. The pooled 3-year survival rate was 50.8% among the 4735 patients who underwent

HCC surveillance, compared to only 27.9% among the 6115 patients without prior surveillance, with an odds ratio of 1.90 (95% CI: 1.67-2.17;  $P < 0.001$ ). There were 6 studies that controlled for lead-time bias, and the improvement in survival persisted (3-year survival rates of 39.7% for surveillance vs 29.1% without surveillance,  $P < 0.001$ ). Of the 23 studies evaluated, 10 were considered high-quality studies in which the 3-year survival with surveillance was greater than no surveillance (45.6% vs 28.8%,  $P < 0.001$ .)

In addition to improved survival, surveillance also led to an increase in the detection of early-stage HCC, with an odds ratio of 2.11 (95% CI: 1.88 to 2.33) compared to no surveillance. In terms of anticipated absolute effects, surveillance led to 163 per 1,000 more patients detected at early stages compared to no surveillance. In addition, surveillance led to more curative treatments compared to no surveillance (61.8% vs 38.2%,  $P < 0.001$ ). Thus, improvement in survival seen with surveillance appears to be due to higher early-stage detection and higher curative treatment rates.

The surveillance tests most commonly used were US and AFP. Of the studies identified, only 4 studies used US alone, while the rest of the studies relied on US and AFP at 6-month intervals. The use of US plus AFP improves detection of early-stage HCC compared with no surveillance, with an odds ratio of 2.16 (95% CI: 1.80 to 2.60), while US alone had an odds ratio of 2.04 (95% CI: 1.55 to 2.68). Both US alone and US plus AFP led to similar rates of curative treatment (odds ratio 2.23 for US [95% CI: 1.83-2.71) and 2.19 for US plus AFP [95% CI: 1.89 to 2.53]). There were no studies that directly compared US alone versus US plus AFP to determine which was superior in terms of early-stage detection or curative therapy.

The studies were also evaluated to determine whether US alone or US plus AFP improved survival. US plus AFP had a pooled risk ratio of 1.86 (95% CI: 1.76-1.97) for improving survival, while US alone had a slightly lower pooled risk ratio of 1.75 (95% CI: 1.56-1.98) for improving survival. There was no statistical difference between the 2 strategies. However, there are serious issues when comparing these surveillance tests for their impact on survival, which include: (1) no description of the trigger to perform a diagnostic test, (2) some studies appear to evaluate AFP or US rather than the combination, (3) no mention of the performance characteristics of these tests, and (4) most importantly, the studies were not powered to determine an improvement in survival.

#### *Future Research*

Given the current burden of HCC and the projected continued increase in incidence of this tumor, better studies including appropriate study design comparing US to US plus AFP as surveillance strategies are needed. Such studies should evaluate the characteristics of US, including its operator dependency and reliability as a surveillance test in specific patient populations. In addition, it would be important to determine whether other serum biomarkers in addition to AFP complement US, such as des-gamma carboxy prothrombin, AFP L3, and other novel serum tests<sup>14</sup>.

## **2. SHOULD ADULTS WITH CIRRHOSIS AND SUSPECTED HCC UNDERGO DIAGNOSTIC EVALUATION WITH MULTIPHASIC CT OR MULTIPHASIC MRI?**

### *Recommendations*

**2. The AASLD recommends diagnostic evaluation for HCC with either multiphasic CT or multiphasic MRI because of similar diagnostic performance characteristics.**

Quality/Certainty of Evidence: Low for CT versus MRI

Strength of Recommendation: Strong

### *Technical Remarks*

1. The selection of the optimal modality and contrast agent for a particular patient depends on multiple factors beyond diagnostic accuracy. These include modality availability, scan time, throughput, scheduling backlog, institutional technical capability, exam costs and charges, radiologist expertise, patient preference, and safety considerations.
2. All studies were performed at academic centers. Because of the greater technical complexity of multiphasic MRI compared to multiphasic CT, generalizability to practices without liver MRI expertise is not yet established.

### *Background*

In patients with cirrhosis and suspected HCC, diagnostic imaging is used to noninvasively verify the presence of HCC (diagnosis) and determine its extent (radiological staging). The goals are to measure tumor burden, guide management, and help prioritize patients for possible liver transplantation. Unlike most other malignancies, the diagnosis of HCC can be established noninvasively, and treatment may be initiated based on imaging alone, without confirmatory

biopsy. The rationale is that in patients with cirrhosis, the pretest probability of HCC is sufficiently high, and the pretest probability of lesions that may mimic HCC at imaging is sufficiently low such that a lesion meeting HCC imaging criteria can be assumed reliably and confidently to be HCC. Although there is strong consensus that the imaging diagnosis of HCC requires multiphase imaging, there is not agreement about which diagnostic imaging test to use. Commonly used methods in clinical practice include multiphase CT with extracellular agents, multiphase MRI with extracellular agents (gadolinium-based compounds that stay in the extracellular space and permit characterization of blood flow), and multiphase MRI with gadoxetate disodium (a specific gadolinium-based compound that accumulates in hepatocytes and permits characterization of hepatocellular “function” in addition to blood flow).

### *Evidence and Rationale*

The evidence profile of diagnostic accuracy for HCC is included in Supporting Table 2, which utilizes the data from a de novo systematic review on imaging in HCC performed to address this question (reference when available). There were no randomized comparative studies of CT vs MRI, no studies identified that compared multiphase MRI with an extracellular agent vs multiphase MRI with gadoxetate disodium, and no data on patient preference. There were 19 observational studies in patients with cirrhosis and suspected HCC that compared the per-lesion diagnostic accuracy of CT and MRI, reporting true positive, false positive, false negative, and true negative values. An additional 14 studies reported only detection rate (sensitivity), but these are not further discussed, as sensitivity cannot be interpreted in the absence of data on specificity and/or positive predictive value. Quality of evidence was low and was downgraded because of

the methodological limitations of the included studies, inconsistency across studies, and possible publication bias. The performance characteristics of these imaging modalities overall and for lesions of different sizes are reviewed below.

With regard to overall accuracy, 8 studies compared multiphasic MRI using an extracellular agent vs multiphasic CT. MRI with an extracellular agent provided higher pooled sensitivity than CT (0.76 [0.72, 0.81] vs 0.63 [0.57, 0.69],  $P < 0.001$ ) with similar specificity (0.78 [0.63, 0.88] vs 0.82 [0.71, 0.89],  $P = 0.62$ ). Eight studies compared multiphasic MRI with gadoxetate disodium vs multiphasic CT. MRI with gadoxetate disodium provided higher pooled sensitivity than CT (0.87 [0.79, 0.93] vs 0.73 [0.64, 0.81],  $P < 0.02$ ) with similar specificity (0.94 [0.90, 0.97] vs 0.96 [0.90, 0.98],  $P = 0.47$ ).

When looking specifically at lesions larger than 2 cm, 3 studies compared multiphasic MRI with an extracellular agent vs multiphasic CT and showed a similar pooled sensitivity, with a higher pooled specificity of 0.87 versus 0.7,  $P = 0.02$ . Examining accuracy in HCC between 1-2 cm, there were 6 studies that compared multiphasic MRI vs CT, and this also showed similar sensitivity and specificity. For HCC < 1 cm, 2 studies compared multiphasic CT vs multiphasic MRI with an extracellular agent. The sensitivity of MRI for <1 cm was significantly higher compared to CT (0.69 vs 0.49,  $P = 0.049$ ), while the specificity was, at a trend level, lower (0.46 vs 0.69,  $P = 0.08$ ).

While multiphasic MRI may be marginally more sensitive than CT in a pooled analysis of comparative studies, the differences in pooled diagnostic performance are insufficient to

recommend MRI over CT. Mitigating factors include the low quality of the evidence, concerns about generalizability to nonacademic settings, and recognition that multiple factors beyond diagnostic accuracy inform the selection of optimal imaging modalities in individual patients. Compared to multiphase CT, multiphase MRI has important advantages and disadvantages. Advantages include greater soft tissue contrast, more comprehensive assessment of nodule and background liver tissue properties, and absence of ionizing radiation. Disadvantages include greater technical complexity, longer scan times, lower throughput, increased susceptibility to artifact, less consistent image quality (largely because of patient factors such as breath holding, difficulty holding still, or high-volume ascites), larger number of potential contraindications, higher charges, and—especially outside the United States—lower availability and longer scheduling backlogs. From a patient perspective, CT is faster, more spacious, and provokes less claustrophobia, but it exposes patients to radiation. Both modalities require IV access and contrast agents, the use of which may be problematic in patients with acute kidney injury or chronic renal failure<sup>15,16</sup>.

### *Future Research*

Although not used widely in North America, multiphase contrast-enhanced ultrasound (CEUS) also can be used to diagnose HCC noninvasively, and further studies are needed<sup>17-24</sup>. Prospective studies should include multiphase CT, multiphase MRI with an extracellular agent, and multiphase MRI with gadoxetate disodium 8, and data on costs and patient preference should be collected. Of note, a multicenter trial of US transplant patients with HCC underwent both MRI and CT at multiple fixed time points while awaiting transplantation has recently completed

enrollment and may further elucidate which technique is optimal in this particular patient population (NCT01082224.)

### **3. SHOULD ADULTS WITH CIRRHOSIS AND AN INDETERMINATE HEPATIC NODULE UNDERGO A BIOPSY, REPEATED IMAGING, OR ALTERNATIVE IMAGING FOR THE DIAGNOSTIC EVALUATION?**

#### *Recommendation*

**3A. AASLD suggests several options in patients with cirrhosis and an indeterminate nodule, including follow-up imaging, imaging with an alternative modality or alternative contrast agent, or biopsy, but cannot recommend one option over the other.**

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

**3B. AASLD suggests against routine biopsy of every indeterminate nodule**

Quality/Certainty of Evidence: very low

Strength of Recommendation: conditional

#### *Technical Remarks*

1. Biopsy may be required in selected cases, but its routine use is not suggested. Biopsy has the potential to establish a timely diagnosis in cases in which a diagnosis is required to affect therapeutic decision making; however, biopsy has a risk of bleeding, tumor seeding, and the

possibility that a negative biopsy is due to the failure to obtain tissue representative of the nodule rather than a truly benign nodule.

2. Stringent imaging criteria with high specificity for  $\geq 10$  mm HCC have been developed by the American College of Radiology (ACR) through its Liver Imaging Reporting And Data System (LI-RADS)<sup>25</sup>, by the OPTN<sup>26</sup>, and by prior AASLD guidelines<sup>2</sup>, and include arterial phase hyperenhancement in combination with washout appearance and/or capsule appearance. Lesions which do not meet these guidelines or are smaller than 1 cm are considered indeterminate.

### *Background*

In its prior HCC clinical practice guidelines<sup>2</sup>, the AASLD recommended biopsy for all indeterminate lesions initially detected by surveillance ultrasound, with the presumed rationale being that biopsy can establish a definitive diagnosis, thereby permitting earlier intervention. Because of its many limitations, however, biopsy may not be an optimal strategy in all cases. Biopsy is expensive, may cause anxiety or pain, and has a risk of complications, including tumor track seeding and bleeding<sup>27</sup>. Sampling error, especially for very small lesions, is an additional drawback. A negative biopsy may not exclude malignancy, and repeated biopsies may be necessary to establish a diagnosis. Follow-up imaging may be especially relevant in patients awaiting liver transplantation with a single small, indeterminate nodule, given that biopsy confirmation of  $< 20$  mm HCC would not change management or contribute to liver transplantation priority. Because there is controversy regarding optimal workup for an indeterminate nodule, the aim of this question was to determine whether current data are able to elucidate an optimal strategy.

## *Evidence and Rationale*

The evidence profile is included in Supporting Table 2, which utilizes the data from a de novo systematic review on imaging in HCC performed to address this question (reference when available). Based on an extensive search strategy detailed in the systematic review, there were no comparative studies identified that directly address this question, although 2 single-center, noncomparative studies were identified that examined the role of biopsy.

Forner et al. in 2008 reported outcomes for  $\leq 2$  cm hepatic nodules detected during surveillance ultrasound in patients with cirrhosis<sup>17</sup>. The authors performed percutaneous biopsy of  $\leq 2$  cm nodules in addition to MRI and CEUS. They found a sensitivity and specificity of MRI to be 61.7% and 96.6%, while CEUS was 51.7% and 93.1% compared to the standard, which was biopsy. When both tests were in concordance, the sensitivity was only 33%, with 100% specificity. Biopsy had a false negative rate of 30%, as patients with suspicious imaging findings or growth were rebiopsied up to 3 times. In 2011, Khalili et al. reported that in patients with cirrhosis, only 14%-23% of 1-2 cm indeterminate nodules initially detected at surveillance ultrasound are malignant<sup>28</sup>. Given the low likelihood of malignancy, they argued that biopsy for all indeterminate hepatic nodules may be impractical and suggested an alternative strategy of close follow-up imaging with sequential contrast imaging using an alternate technique for most indeterminate  $\leq 2$  cm nodules, with biopsy reserved for 1-2 cm nodules with arterial phase hyperenhancement or in the presence of a synchronous HCC. Numerous other studies also reported low likelihoods of malignancy among  $\leq 2$  cm indeterminate nodules, as characterized by CT or MRI<sup>19, 23, 29-37</sup>.

Since many if not most indeterminate small hepatic nodules are nonmalignant, strategies for risk stratification are needed. Tanabe et al. evaluated the natural history of indeterminate lesions detected at CT or MRI<sup>38</sup>. The indeterminate lesions were categorized as probably benign, intermediate probability of HCC, and probably HCC based only on imaging features<sup>25</sup>. No lesions initially categorized as probably benign progressed to definite HCC during follow-up, while 7% of lesions initially categorized as intermediate probability progressed to HCC, and 38% of lesions initially categorized as probably HCC progressed to definite HCC. Similarly, Darnell et al. in 2015 showed that the various LI-RADS categories are associated with different likelihood of HCC in patients with cirrhosis, using contemporaneous biopsy as the reference standard<sup>39</sup>.

Taken together, these studies suggest that a substantial proportion of 1-2 cm indeterminate nodules are nonmalignant histologically and unlikely to progress to HCC during imaging follow-up. Thus, a strategy of obtaining a biopsy of all indeterminate nodules would result in a considerable number of unnecessary biopsies. However, indeterminate nodules do require further evaluation. Other diagnostic options include follow-up imaging, imaging with an alternative modality or contrast agent, and referral to a specialty center. A study by Serste et al. performed CT, MRI, and biopsy for a series of 74 patients with nodules identified by surveillance ultrasound. The authors concluded that sensitivity and specificity of the combination of the two diagnostic tests was 98% and 81% respectively, and that biopsy could be reserved for those without definitive findings on either CT or MRI<sup>40</sup>. An individualized diagnostic workup based on clinical context and imaging findings such as nodule characteristics, feasibility of biopsy, and

institutional expertise may be the optimal approach. In selected circumstances, a multidisciplinary group may elect to treat a probable HCC without biopsy confirmation, though practitioners and patients need to be aware that such treatment may affect transplant priority.

#### *Future Research*

Future research is needed to standardize the definition of and independently verify the prognostic value of different nodule characteristics and to identify additional nonimaging features to more precisely predict lesion progression<sup>38,39</sup>, potentially including endpoints other than survival, such as patient preference or drop-off from the transplant waiting list.

#### **4. SHOULD ADULTS WITH CHILD'S CLASS A CIRRHOSIS AND EARLY-STAGE HCC (T1 OR T2) BE TREATED WITH RESECTION OR LOCOREGIONAL THERAPY?**

##### *Recommendation*

- 1. The AASLD suggests that adults with Child's A cirrhosis and resectable T1 or T2 HCC undergo resection over radiofrequency ablation.**

Quality/Certainty of Evidence: Moderate

Strength of Recommendation: Conditional

##### *Technical Remarks*

1. Direct comparative studies of resection versus other types of locoregional therapy (LRT)—such as TARE and TACE or other forms of ablative therapy, such as radiation and microwave—are not available, though indirect evidence favors resection.

2. The definition of resectability is not uniform across studies or in clinical practice, and variability is seen not only in what is defined as resectable from a purely technical standpoint but also in patient-related factors such as acceptable degree of portal hypertension and performance status. This variability leads to challenges in comparing study findings.
3. Stage T1 and T2 HCC include a wide range of tumor sizes from <1 cm to 5 cm, and the effectiveness of available therapies depend in large part on the size, number, and location of the tumors. Whereas smaller, single tumors (<2.5cm) that are favorably located may be equally well treated by either resection or ablation, tumors larger than 2.5-3 cm, multifocal, or near major vascular or biliary structures may have limited ablative options. Multiple tumors which are bilobar or centrally located may not be resectable.

4. Randomized trials performed to date comparing radiofrequency ablation (RFA) to resection have been performed primarily in East Asian patients, in whom there is a higher etiologic prevalence of HBV (including noncirrhotic HBV-associated HCC) and a lower prevalence of other liver diseases such as NAFLD or HCV compared to Western patients. The impact of these demographic differences on oncologic outcomes of different therapies is unknown.

### *Background*

Because cirrhosis is one of the primary risk factors for HCC, the selection of treatment modality depends as much on the underlying liver function and the degree of portal hypertension as on the oncologic stage of the tumor. Therefore, while therapeutic options are limited for patients who present with advanced liver disease and/or advanced tumor stages, multiple options exist for those presenting with well-compensated cirrhosis and smaller, potentially resectable tumors.

These include ablative strategies such as radiofrequency, microwave, chemical or cryoablation, as well as surgical resection. Most studies define patients with resectable HCC as those (i) with 1-3 unilobar lesions, with an upper size limit of 5 cm for single lesions and 3 cm for more than 1 lesion (some trials accept 2 lesions up to 4 cm); (ii) without radiographic evidence of extrahepatic disease or macrovascular invasion; and (iii) occurring in the setting of minimal or no portal hypertension and in the absence of synthetic dysfunction (BCLC 0 or A). However, a number of clinical and laboratory variables and circumstances, including the availability of alternative therapies, can influence the individual clinician's decision to proceed with resection. The absence of a standard definition of resectability constitutes a limitation of the interpretation of data from analyses of studies comparing resection to ablation of "resectable" tumors and may lead to biased analyses and conclusions.

In addressing this particular question, it should be noted that the existing evidence was reviewed in order to compare resection to ablative therapy (also comparing different ablative options) specifically to determine the optimal therapeutic option for patients with early-stage (T1-T2), potentially resectable HCC occurring in the setting of compensated cirrhosis (minimal or no portal hypertension and preserved synthetic function). Given that liver transplantation is reserved for patients with unresectable HCC, we did not include a review of studies comparing transplantation to either resection or ablative therapies.

#### *Evidence and Rationale*

The evidence profile is included in Supporting Table 3, which utilizes the data from a recent systematic review performed by Weis et al.<sup>41</sup> on treatment for early-stage HCC in patients with

Child's A or B cirrhosis. This systematic review did not cover the use of TACE or TARE, though it covered multiple other comparative groups—including RCTs comparing RFA to percutaneous ethanol or acetic acid ablation—and found moderate quality evidence that RFA prolonged survival. In both the RFA versus resection comparison and the RFA versus other techniques comparison, the authors of the systematic review concluded that the total number of included patients was too low to reach a firm conclusion.

Importantly, there were 3 RCTs which compared RFA to resection, including a total of 578 patients<sup>42-44</sup>. Two of these 3 trials had a low risk of bias and moderate evidence quality<sup>42,43</sup>, while one had a high risk of bias<sup>44</sup>. The results of the 2 low-risk-of-bias trials demonstrate that hepatic resection is more effective than RFA regarding overall survival (HR 0.56; 95% CI 0.40 to 0.78) as well as 2-year survival (HR 0.38; 95% CI 0.17 to 0.84). When a third trial with a high risk of bias is added to the analysis, the difference in survival between resection and RFA became insignificant (overall survival: HR 0.71; 95% CI 0.44 to 1.15). The reason for an increased risk of bias in the third study is related to an unusually high number of patients (N = 19) who switched from the RFA arm to the resection arm yet were still counted within the RFA group because of intention to treat, thus potentially overstating the benefit of RFA. The additional endpoints of 2-year event-free survival and local progression favored resection regardless of inclusion of the potentially biased trial. Not unexpectedly, the complication rate was higher for resection compared to RFA (O.R. = 8.3).

In addition to the trials included in the systematic review by Weis et al. comparing resection to RFA, there are two additional RCTs published more recently that confirm the

findings of improved survival for patients following resection<sup>45, 46</sup>. One single-center RCT (Lui et al. 2016) compared resection to RFA combined with TACE (TACE was performed first, followed by RFA within 4 weeks) and demonstrated improved survival at 1, 3, and 5 years for the resection group ( $P = 0.007$ )<sup>45</sup>. Another RCT trial by Yin et al. (2014) compared resection to TACE alone for lesions up to and exceeding Milan criteria (up to 5 tumors, with the largest being <5 cm) and found resection to be superior in 1 and 3 years of follow-up (HR 0.4,  $P < 0.001$ )<sup>46</sup>.

Size of the lesion was a risk factor for worse outcome in both arms of the systematic review.

This is not surprising given that it is known that RFA is more effective in lesions <3 cm.

However, the specific question of survival for patients with single HCC lesions <3 cm treated with resection versus RFA has not been addressed in a RCT. A recent multicenter retrospective report from Italy did examine this question<sup>47</sup>. This report included 544 Child's A patients from 15 centers, and the authors observed similar complication rates (4.5% for resection, 2.0% for RFA,  $P = 0.101$ ), recurrence rates (56% for resection, 57.1% for RFA,  $P = 0.765$ ), and 4-year survival rates (74.4% for resection, 66.2% for RFA,  $P = 0.353$ ). A subgroup analysis for outcomes of smaller single lesions was not performed by Weis et al., but examining the 3 individual RCT trials included in the systematic review, Huang et al. (2010)<sup>42</sup> demonstrated that survival following resection remained favorable compared to RFA ( $P = 0.03$ ) in patients with smaller tumors. This subgroup analysis was not performed in the other two RCTs.

### *Future Research*

The comparative effectiveness of ablative strategies other than RFA techniques, such as stereotactic body radiation and microwave ablation, remain unclear. In addition, the effectiveness

of embolization strategies such as transarterial approaches (TACE and TARE) have not been systematically compared to either resection or ablative strategies in Child's A patients with T1 or T2 HCC.

## **5. SHOULD ADULTS WITH CIRRHOSIS AND HCC THAT HAS BEEN RESECTED OR ABLATED SUCCESSFULLY UNDERGO ADJUVANT THERAPY?**

### *Recommendation*

**5. The AASLD suggest against the routine use of adjuvant therapy for patients with HCC following successful resection or ablation.**

Quality/Certainty of Evidence: Low

Strength of Recommendation: Conditional

### *Technical Remarks*

1. The modified Response Evaluation Criteria in Solid Tumors (mRECIST) may be the most common criteria used to evaluate radiological response in patients affected by HCC and treated with LRT, though other classification systems are also used<sup>48</sup>.
2. The risk of recurrence after surgical resection or ablation is related to characteristics of the tumor at the time of surgery, such as size, degree of differentiation, and the presence or absence of lymphovascular invasion.

### *Background*

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Given the unique biology of HCC in which risk includes both recurrence of the primary tumor and the development of de novo tumors, the ideal adjuvant therapy would have an antineoplastic component aimed at the original tumor and a chemopreventive effect aimed at the development of a de novo tumor. The distinction of these two scenarios is difficult and often based on the time of the recurrence (e.g., early vs late, with the latter believed to be related to the development of a de novo tumor)<sup>49</sup>. Early studies with the adjuvant use of acyclic retinoids were promising<sup>50</sup>, with a decrease in the development of secondary tumors, but larger studies did not confirm a benefit<sup>51</sup>. The lack of proven active agents in advanced disease has hampered the development of agents targeting early-stage disease. To date, most of the adjuvant agents studied did not have clinical evidence that they improve survival in any stage of HCC. Of the agents evaluated in the adjuvant setting, only sorafenib has been shown to improve survival in advanced disease<sup>52</sup>, yet it ultimately did not show any improvement in outcomes for the adjuvant treatment of HCC in randomized studies<sup>53</sup>. Resection of HCC with curative intent or ablation is associated with rates of recurrence at 5 years as high as 75%<sup>47</sup>. Therefore, there is a clear need for adjuvant systemic therapies.

#### *Evidence and Rationale*

The evidence profile is included in Supporting Table 5, which utilizes the data from a recent systematic review performed by Wang et al.<sup>54</sup> on adjuvant treatment for HCC after treatment. The systematic review by Wang et al.<sup>54</sup> identified that adjuvant IFN therapy can improve both recurrence-free and overall survival in patients with virus-associated liver disease; however, the side effects of interferon are significant, limiting its use in clinical practice<sup>55</sup>. RCTs of adjuvant chemotherapy, internal radiation, and heparanase inhibitor PI-88 therapy were included in the systematic review and failed to improve recurrence-free or overall survival. The efficacy of

several cytotoxic chemotherapy regimens has also been tested in RCTs and has never been shown to improve survival in advanced HCC<sup>56</sup>, which limits their use in the adjuvant setting.

#### *Future Research*

There is a clear need for the development of new, effective chemotherapy agents for treatment of HCC in both the advanced setting and in the adjuvant setting. In addition, the impact of HCV eradication by direct-acting antiviral therapies on the future risk of HCC is uncertain and requires further study<sup>57</sup>. Finally, the role of statin therapy in the adjuvant setting is unknown, though it may warrant investigation given the recent reports of an associated reduction in HCC risk for patients with HBV who are on statin therapy<sup>58</sup>.

### **6. SHOULD ADULTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION AND T1 HCC BE TREATED OR UNDERGO OBSERVATION?**

#### *Recommendation*

- 6. The AASLD suggests observation with follow-up imaging over treatment for patients with cirrhosis awaiting liver transplantation who develop T1 HCC.**

Quality/Certainty of Evidence: Very Low

Strength of Recommendation: Conditional

#### *Technical Remarks*

1. This recommendation is intended for patients who are already on the liver transplantation waitlist—and thus presumably with an indication for transplantation in addition to HCC—and is based on current organ allocation policies in the United States. Future allocation policy revisions may impact this recommendation.

2. The choice of observation with follow-up imaging versus treatment depends on several factors including patient preference, anticipated waiting time, rate of growth of the lesion, degree of liver decompensation, and AFP.

### *Background*

The decision to offer local-regional therapy (LRT) consisting of either local ablation or transarterial treatment to patients with cirrhosis who have a single HCC nodule between 1 and 2 cm (T1) and are listed for liver transplantation is dependent in large part on an assessment of the patient's underlying liver function and ability to safely undergo LRT, anticipated wait time, and organ allocation policy. In the US, current liver allocation policy prioritizes patients with OPTN T2 stage HCC (either a single lesion between 2-5 cm, or 2 or 3 lesions each between 1-3 cm) but not for those with OPTN stage T1 (<https://optn.transplant.hrsa.gov/governance/policies/>).

Therefore, if a T1 lesion is treated with LRT, it may not reach stage T2, denying the patient increased priority for transplantation. LRT of a T1 HCC may be of significant benefit to patients who are well compensated and have no other indication for transplantation, as they may be able to avoid transplantation. Importantly, the patient will remain at risk for HCC recurrence and will require continued monitoring. This is the outcome assessed by the study by Huo et al., discussed below<sup>59</sup>.

If the patient has other indications for transplant other than the presence of HCC, especially if these complications are not captured by the current MELD-Na score, such as encephalopathy or ascites, the decision to treat with LRT requires careful consideration. If observation is contemplated, a key consideration is the possibility that the tumor, if untreated, may grow to

beyond T2 criteria and/or metastasize during the observation period. This is the question addressed in the observational study by Mehta et al., discussed below<sup>60</sup>.

### *Evidence and Rationale*

The data are summarized in Supporting Table 6, including the findings of a de novo systematic review of all studies that enrolled adults with cirrhosis awaiting liver transplantation and treated with bridging or down-staging therapies before transplant. There were no RCTs. Eighty-seven noncomparative trials were identified, and only 2 of these address the question of waitlist outcomes for patients with T1 HCC who were or were not treated with LRT.

The study by Mehta et al.<sup>60</sup> is a retrospective observational study of 114 patients with T1 HCC listed for liver transplantation at a single US institution between 2004-2012 who were not treated with LRT. The median age was 60, with equal proportions in Child's A (48%) and Child's B/C (52%) Median follow-up was 2.4 years, and during the observation period, 100 patients (87%) progressed from T1 to T2 at a median of 6.9 months. Six patients (5.3%) remained within T1, 6 other patients (5.3%) progressed from T1 to beyond T2 at a median of 5.1 months from listing, and 2 additional patients died of non-HCC causes. The cumulative probability of waitlist dropout was 4.5% within 6 months, 7.1% within 1 year, and 15.6% within 2 years, and the rate of tumor growth was estimated to be 0.14 cm per month. Risks for wait list dropout included AFP >500 and rapid growth. The authors concluded that observation for patients with T1 HCC waiting for liver transplantation is an acceptable strategy, though based on their observations of the patients who dropped out, they recommended LRT rather than observation for patients with T1 HCC with high AFP >500 or with rapid growth. It is important to note that this study was performed in

an area with prolonged waiting time, and the findings may not be generalizable to areas with shorter wait times.

The study by Huo et al.<sup>59</sup> reported on outcomes for 390 patients in Taiwan with T1 (n = 94) and T2 (n = 296) HCC who were eligible for transplant but who were treated instead with LRT.

Patients were treated with a number of different methods including RFA, percutaneous ethanol or acetic acid injection (PEI, PAI), and TACE. Patients treated with RFA had the lowest rate of waitlist dropout. Overall, patients with T1 HCC had a 6-month waitlist dropout rate of 5.3% for tumor progression beyond T2 criteria, though this represented only 2% of patients treated with RFA. Notably, a majority of patients in the study had HBV and were of an age slightly older than the typical transplant patient, which may limit the generalizability of the findings. In addition, the primary aim of the study by Huo et al. was to validate a potential allocation score proposal called the HCC-MELD score rather than to observe the impact of LRT on waitlisted patients with T1 or T2 HCC.

#### *Future Research*

Additional longitudinal data from multicenter cohorts of patients with T1 HCC would be beneficial in order to gain a better understanding of its natural history. In addition, predictive markers of poor biologic behavior such as rapid progression would also better inform decisions about nontreatment of T1 HCC in regards to a risk/benefit analysis.

## **7. SHOULD ADULTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION AND HCC (OPTN T2) UNDERGO TRANSPLANT ALONE OR TRANSPLANT WITH BRIDGING THERAPY WHILE WAITING?**

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*Recommendation*

**7A. The AASLD suggests bridging to transplant in patients listed for liver transplantation within OPTN T2 (Milan) criteria to decrease progression of disease and subsequent dropout from the waiting list**

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

**7B. The AASLD does not recommend one form of liver-directed therapy over another for the purposes of bridging to liver transplantation for patients within OPTN T2 (Milan) criteria.**

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

*Technical Remarks*

1. Bridging is defined as the use of locoregional therapy (LRT)—such as TACE, Y90, ablative therapy, or a combination of different types of LRT such as TACE and ablation—to induce tumor death and deter tumor progression beyond the Milan criteria.
2. The risk of hepatic decompensation because of LRT must be considered when selecting patients for bridging therapy.
3. Patients in the United States with HCC within Milan criteria have been granted access to liver transplant via MELD exception point allocation since February 2002. While patients with T2 HCC have continued to have access to deceased donor liver transplantation, multiple changes to the policy to reduce access combined with ever-increasing waiting times have impacted the interpretation of studies before and in the early days following adoption of MELD allocation compared to current practice.
4. Given that organ availability is variable, the practices for liver transplant for HCC may differ based on geographic location and access to living and deceased donor organs.

5. The MELD allocation system with additional prioritization for HCC is not practiced worldwide.

### *Background*

The primary aim of bridging therapy is to minimize the risk of HCC progression while awaiting liver transplantation. Patients with T2 tumors, synonymous with the Milan criteria, have been granted additional HCC MELD exception points since 2002 because of an excellent overall survival with a low risk for HCC recurrence posttransplant (10%-15%)<sup>61</sup>. Progression beyond the Milan criteria while awaiting transplant eliminates access to exception points, and thus, maintaining tumor burden within or below T2 while waiting for transplant is the only way to continue earning exception points. Studies have demonstrated that without liver-directed therapy, the dropout rate is as high as 25% and 38% at 6 months and 12 months, respectively<sup>62-64</sup>. This question assesses the benefit of the addition of bridging therapy for patients with T2 HCC awaiting LT.

### *Evidence and Rationale*

The data are summarized in Supporting Table 6, including the findings of a de novo systematic review all studies that enrolled adults with cirrhosis awaiting liver transplantation and treated with bridging or down-staging therapies before transplant. There were 18 comparative studies which reported the outcome of interest, though there were no RCTs. The reported outcomes included dropout because of HCC progression and because of all causes, recurrence rate, and overall recurrence-free survival post-liver transplant. Among the comparative studies, 1 study enrolled only patients meeting Milan criteria, 6 enrolled patients both within and exceeding the Milan criteria, and 2 did not specifically define criteria. The quality of the evidence overall was very low because of studies with significant risk of bias and imprecision. The data were analyzed

using all included studies and among the subset of those performed in the United States to control for the MELD era effect. This stratification did not reveal any significant difference among the various outcomes. Importantly, there was a trend toward lower dropout because of progression and lower dropout from all causes in patients who received bridging LRT (RR 0.32 and 0.38, respectively), but the difference did not reach statistical significance. Posttransplant recurrence and survival rates were not significantly different between the two reported cohorts, despite the lack of randomization and potential for selection bias regarding which patients were selected to receive bridging. Outcomes were noted to be similar when examined by TACE, transarterial embolization (TAE), RFA, TACE + RFA, or multitherapies. The RR of recurrence was  $< 1$  in those treated with TACE + RFA and RFA alone with noted wide CI and was limited to single studies with relatively small numbers in each respective therapy. Despite this limited evidence, bridging therapy is conditionally recommended because of selection bias for the patients selected to receive LRT as well as shorter waiting time during the study period compared to the present time and the relatively low risk of harm for the intervention compared to the potential benefit. Noncomparative studies of LRT have been associated with lower rates of waitlist dropout of 8.7% at 6 months and 22.9% at and 12 months, respectively<sup>65</sup>. Furthermore, 3-year observed survival (OS) post-liver transplant has been reported to be significantly improved in patients with HCC who received LRT compared to those who did not using the SRTR data: 76% vs 71%, ( $P = 0.03$ )<sup>66</sup>. The decision to bridge patients with HCC to transplant is largely dependent upon their anticipated waiting time, with those exceeding 6 months being considered for LRT if deemed appropriate based on the degree of hepatic dysfunction<sup>67</sup>.

### *Future Research*

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A RCT comparing bridging LRT versus not receiving bridging LRT for waitlisted patients with HCC is unlikely to be performed due primarily to logistical reasons, including geographically variable wait time within the United States for deceased donor transplants in patients with HCC. Greater attention to stratifying outcomes based on pretransplant radiographic response using mRECIST may help to delineate the true potential benefit derived from LRT. The addition of biomarker data may also help stratify HCC with regard to its biologic behavior and response to LRT.

## **8. SHOULD ADULTS WITH CIRRHOSIS AND HCC BEYOND MILAN CRITERIA (T3) BE TRANSPLANTED FOLLOWING DOWN-STAGING TO WITHIN MILAN CRITERIA?**

### *Recommendation*

**8. The AASLD suggests that patients beyond the Milan criteria (T3) should be considered for LT after successful down-staging into the Milan criteria.**

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

### *Technical Remarks*

1. The optimal form of liver-directed therapy for the purposes of down-staging cannot be determined based on the available data.
2. Currently, in the US, MELD exception may be granted by appeal to the regional review board system for patients initially presenting with T3 HCC after successful down-staging to within T2/Milan criteria, or they may appeal with a T3 tumor, though this is not a practice which is

widely accepted. HCC organ allocation policy may be revised in the future to allow access to standardized MELD exception for down-staged patients rather than requiring appeal.

3. There is no standard, agreed-upon waiting period following down-staging to determine efficacy of down-staging and subsequent optimal timing for liver transplant.

4. Many studies define down-staging as a reduction in tumor burden to within Milan criteria based on radiographic findings, though some studies define down-staging as a complete absence of tumor by radiographic findings. Other studies use explant pathology to define successful down-staging, which is not useful in patient selection and makes direct comparison of results challenging.

### *Background*

Down-staging is defined as a reduction in tumor burden to predefined criteria, most commonly the Milan criteria, through the use of LRT. While some may consider the Milan criteria to be too restrictive, the severe organ shortage and concerns about futility support limiting access to organs to patients within these criteria. Within the US, patients who exceed these criteria who can be successfully down-staged to within the Milan criteria may become eligible for HCC MELD exception points after undergoing review by their respective regional review board. Reported success with down-staging is highly variable (24 to 90%)<sup>68</sup>. This variability is largely because of differences in tumor burden prior to LRT, type of LRT used, definition of successful down-staging, as well as differing methods to assess radiographic response (WHO, EASL, RECIST, mRECIST) and lack of a standardized time period at which response to therapy is gauged. Furthermore, some have proposed the incorporation of tumor markers in addition to tumor size and number to meet criteria for successful down-staging. This key question attempts

to determine whether patients with HCC burden beyond Milan criteria should undergo LT after successful down-staging to within Milan criteria.

### *Evidence and Rationale*

The data are summarized in Supporting Table 6, including the findings of a de novo systematic review of all studies that enrolled adults with cirrhosis awaiting liver transplantation and treated them with bridging or down-staging therapies before transplant. There were a total of 24 studies examined for outcomes associated with down-staging and transplantation. There were no RCTs. Only 3 of these compared down-staging of T3 tumors versus T2 tumors with no down-staging prior to liver transplant, while the remaining studies were noncomparative, as summarized in Supporting Table 6. There were no comparative studies for transplantation of T3 with and without down-staging. The outcomes reported in the 3 comparative studies were limited to post-liver transplant overall (1, 3, and 5 years) and recurrence-free survival (1 and 5 years). Down-staging of T3 patients compared to no therapy (in T2 patients) prior to liver transplant was associated with similar overall and recurrence-free survival. The 5-year observed survival with down-staging had a RR of 1.17 (CI 1.03-1.32), relative to no down-staging.

Heckman et al. provided the only comparative yet nonrandomized US study, which includes 123 patients transplanted from 2000-2006, spanning both pre- and post-MELD era patients<sup>69</sup>. In this series, patients had a very short wait list time: 28 days in the 50 patients receiving LRT (TACE, Y90, RFA, or resection) prior to transplant and 24 days in those without LRT pretransplant.

There were 12 of 50 patients who were successfully down-staged from T3 to within T2 at the time of transplantation. No significant difference in OS was noted between the 12 that were

down-staged compared to the remaining patients in the LRT group, of whom most were T2 at the time of transplantation.

Holowko et al. present outcomes for patients reported to be beyond T2 treated with LRT, compared to those within T2 who were not treated with LRT, noting no difference in 5-year OS<sup>70</sup>. The third comparative study was from Asia and consisted predominately of living donor liver transplants (LDLT), with down-staging consisting mostly of TACE<sup>71</sup>. A total of 51 T3 patients were successfully down-staged radiographically to the Milan criteria and were compared to 110 patients who presented within Milan criteria and thus underwent LT without LRT. A small number of T3 patients underwent resection for down-staging. There was a trend favoring LRT for both OS and RFS, despite the down-staged patients being at a more advanced stage, though these differences did not reach significance (OS 83.7% vs 78.9%; RFS 90% vs 86%).

The majority of the remaining studies that examined down-staging were noncomparative studies. Among the 21 noncomparative studies, 14 reported recurrence rates posttransplantation that averaged 20.4% (CI 0.15-27.7), with the lowest recurrence rate noted to be in studies that employed multitherapies. Overall, the 5-year post LT OS was 77.6%. These outcomes are comparable to what has been reported posttransplant among patients with HCC within Milan criteria. The number of studies that examined various individual modalities (including Y90, DEB-TACE, PEI, RFA, TACE, TACI, and TAE) were small, with a range 1-4 for each modality. The highest 5-year OS was reported in those treated with multitherapies (84.4%), and the lowest 5-year OS was seen in those that were treated with TACI (54.1%). A lack of a comparative group beyond historical controls severely limits interpretation. Noncomparative studies

examining the success of down-staging may include patients that are not deemed liver transplant candidates for other reasons (such as advanced age or significant co-morbidities), and thus the results of these studies may be affected by the inclusion of nontransplant candidates in whom LRT is palliative in intent.

#### *Future Research*

Determining the variables which predict outcomes after down-staging as well as the optimal waiting period between down-staging and transplantation are key targets for future studies.

Effectiveness of down-staging prior to transplant can only be determined if the many variables that can confound these analyses are standardized, and Parikh et al. have proposed criteria that should be included in all down-staging studies, including patient demographics, center characteristics such as volume and waiting time, tumor characteristics such as BCLC stage, treatment details, and posttransplant details such as recurrence and survival<sup>72</sup>.

### **9. SHOULD ADULTS WITH CIRRHOSIS AND HCC (T2 OR T3, NO VASCULAR INVOLVEMENT) WHO ARE NOT CANDIDATES FOR RESECTION OR TRANSPLANTATION BE TREATED WITH TRANSARTERIAL CHEMOEMBOLIZATION, TRANSARTERIAL RADIOEMBOLIZATION, OR EXTERNAL RADIATION?**

#### *Recommendation*

**9A. The AASLD recommends LRT over no treatment in adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation.**

Quality/Certainty of Evidence:

Transarterial chemoembolization (TACE): Moderate

Transarterial bland embolization (TABE): Very low

Transarterial radioembolization (TARE): Very low

External radiation (XRT): Very low

Strength of Recommendation: Strong

**9B. The AASLD does not recommend one form of LRT over another.**

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

*Technical Remarks*

1. The available evidence is for Child's A and highly selected Child's B. There are no data to support the use of LRT for patients with Child's C or poor performance status, and use of LRT should be weighed against the risk of harm.
2. The data for the use of TARE and external beam radiotherapy is emerging. As discussed below, the results to date are encouraging but inadequate to make a recommendation.
3. Radiofrequency ablation (RFA) is another treatment strategy that may be utilized for selected patients with unresectable T2 HCC, depending on the size, location, and number of lesions.

*Background*

TACE and bland TAE are widely used in patients with unresectable HCC, either as bridge to transplantation or as a recommended treatment to extend survival in the setting of patients with HCC not amenable to either resection or transplantation. More recently, with advances in technology to improve precision, external beam radiotherapy and TARE have also been utilized

as a treatment strategy for HCC. The intent of this question was to review the existing evidence in order to attempt to determine the optimal therapy for those patients with larger (>2.5 cm) or multinodular T2 or T3 tumors with no evidence of distant metastasis or macrovascular invasion who are not eligible for resection or liver transplantation.

### *Evidence and Rationale*

The data used for this question are based on recent existing systematic reviews. A meta-analysis performed by Llovet and Bruix in 2002 comparing TACE versus placebo identified 7 RCTs on TACE versus placebo with a total of 545 patients<sup>73</sup>, establishing TACE as an effective strategy for unresectable multinodular HCC occurring in patients with compensated cirrhosis.

The analysis demonstrated improvement in 2-year survival for patients treated with TACE versus placebo (41% versus 27%, OR 0.53,  $P = 0.017$ .) However, Oliveri et al. performed a more recent systematic review that questioned the beneficial effect of TACE<sup>74</sup>. In this report, TACE or TAE were compared to placebo for T2 or T3 HCC not amenable to resection or transplantation. The primary outcome was all-cause mortality, with secondary outcomes of tumor response, adverse events, and quality of life also included. In this analysis, there were 9 RCT identified on the use of TACE (6) or TAE (3), published from 1990-2005, reporting on a total of 645 patients<sup>75-84</sup>. Compared to the meta-analysis by Llovet and Bruix, there were 2 additional RCTs included<sup>77,75</sup>. Of the 9 included trials, 2 were noted to have a high risk of bias. Analysis of the HRs from seven trials with low risk of bias showed no significant effect of TACE or TAE compared to placebo on survival (overall HR 0.88; 95% CI 0.71 to 1.10;  $P = 0.27$ ), though the data from TACE were pooled with the data from TAE. The 2 trials with high risk of bias showed a significant effect (HR 0.53; 95% CI 0.34 to 0.83;  $P = 0.005$ ). When all 9

trial trials were analyzed together for overall mortality, no significant intervention effect (HR 0.81; 95% CI 0.64 to 1.02;  $P = 0.07$ ) was noted. Notably, a subgroup analysis of TACE only was performed, and this still failed to demonstrate a statistically significant benefit to TACE (HR 0.79; 95% CI 0.58 to 1.06;  $P = 0.11$ ). The authors calculated the number of subjects that was required to be included in a meta-analysis in order to accept or reject an intervention effect at  $N = 1028$ , and therefore only about two-thirds of the required number of study subjects were available to be included in the analysis. Looking at the overall outcomes for the more recent trials of TACE only versus TACE plus an ablative strategy without a placebo control arm, the overall survival for the TACE-only groups in these studies is superior to the TACE-only groups from the earlier studies, suggesting that refinements in techniques may have had an impact on outcomes following TACE alone.

A meta-analysis specifically comparing TACE using drug eluting beads (DEB-TACE) versus conventional TACE (cTACE) treatment performed by Facciorusso et al. (2015) identified 4 RCTs and 8 observational trials<sup>85</sup>. Nonsignificant trends were noted in 1-, 2-, and 3-year survival in favor of DEB-TACE compared to cTACE. Pooled analysis of objective response and of complications showed no difference between the two therapies.

In order to determine the potential benefit of TARE using yttrium-90 microsphere radioembolization, a systematic review was performed by Abdel-Rahmen and Elseyed (2016)<sup>86</sup>. In this analysis, two RCTs were identified with a total of 64 patients. One of the trials compared TARE to TACE for intermediate-stage HCC, while the other was a planned interim analysis of TARE plus sorafenib versus sorafenib alone for advanced stage cancer, which is not the

population addressed in this question. Neither trial reported on mortality or disease progression. Both trials were classified as having a high risk of bias and low quality. Both trials demonstrated a similar adverse event frequency in each arm. Looking specifically at the Kolligs et al. (2015) trial for TARE versus TACE, there were a total of 28 patients included, with 13 patients treated with TARE and 15 treated with TACE<sup>87</sup>. There were 2 patients in each arm successfully down-staged to either undergo LT (n = 3) or RFA (n = 1). Though the current data is simply too sparse to make an assessment of efficacy, the authors identified 5 ongoing trials, so additional data is anticipated in the near future. Importantly, a single-center RCT comparing TARE versus TACE performed at a US transplant center has just been reported and has demonstrated longer time to progression for waitlisted patients with HCC receiving TARE compared to TACE<sup>88</sup>. This trial was not adequately powered to detect a survival advantage.

An additional meta-analysis of trials performed primarily in China published in 2015 assessed the available data for the combination of TACE plus PEI compared to TACE alone for T2 and T3 unresectable tumors and identified 19 RCTs that met this inclusion criteria<sup>89</sup>. This analysis included 1,948 patients and found a benefit to the combination of TACE and PEI in both survival at 1 and 2 years as well as in local tumor response rates and decreased AFP values. The patients who benefited the most from the combination therapy were those with preserved liver function. There was heterogeneity in the included studies, and while the authors concluded that combination therapy appears to be beneficial compared to TACE alone, further multicenter RCTs are clearly needed. Another meta-analysis of trials of TACE alone versus TACE plus external beam radiotherapy has also been performed by Huo and Eslick that included 11 RCT and 25 trials overall<sup>90</sup>. This analysis demonstrated significant benefit to the combination therapy

for OS at 1, 2, 3 and 5 years posttreatment as well as for local tumor control. The RCTs analyzed in this trial were all from Asian centers, and the eligibility criteria were variable among the studies. It is unknown if RFA or PEI would be equivalent to external beam radiotherapy in combination to TACE.

#### *Future Research*

Additional data on the efficacy of TARE and external beam radiotherapy is anticipated in the near future. Efforts will likely need to focus on defining which patient characteristics (tumor number, location, size, underlying liver disease, and degree of liver dysfunction) are most important in determining efficacy of therapy. Patient factors may also determine which patients may benefit from combination therapy of TACE or TARE plus an ablative strategy and which ablative strategy should be used.

### **10. SHOULD ADULTS WITH CHILD–PUGH A/B CIRRHOSIS AND ADVANCED HCC WITH MACROVASCULAR INVASION AND/OR METASTATIC DISEASE BE TREATED WITH SYSTEMIC OR LOCOREGIONAL THERAPY (LRT) OR NO THERAPY?**

#### *Recommendation*

**10: The AASLD recommends the use of systemic therapy over no therapy for patients with Child–Pugh A cirrhosis or well-selected patients with Child’s B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease.**

Quality/Certainty of Evidence: Moderate

Strength of Recommendation: Strong

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### *Technical Remarks*

1. It was not possible to make a recommendation for systemic therapy over LRT as there was inadequate evidence to inform the balance of benefit versus harm.
2. Advanced HCC is a heterogeneous group. The selection of treatment type may vary depending on the extent of macrovascular invasion and/or metastatic disease, the degree of underlying cirrhosis, and patient's performance status, and when patients have very poor performance status and/or advanced cirrhosis, no therapy may be the best option.
3. It is not possible to identify a preferred type of LRT based on the available evidence.
4. Most patients involved in the studies had Child's A cirrhosis, although studies were mixed and included some patients with Child's B.

### *Background*

Patients with advanced HCC (macrovascular invasion and/or metastatic disease) represent a unique clinical challenge. The prognosis and treatment decision is generally dependent on the extent of the vascular invasion and/or metastatic disease, the severity of underlying cirrhosis, and the performance status of the patient. Even for patients with metastatic disease, particularly those with limited extrahepatic tumor burden, the presence of concurrent macrovascular invasion often leads to rapid tumor progression with disease-related symptoms. Therefore, many patients with limited extrahepatic metastatic disease burden and concurrent macrovascular vascular invasion have been treated with LRT. While various LRTs are provided in this setting, the evidence supporting the routine use of many of these approaches has not been established, and thus far, regardless of the treatment strategy utilized, the prognosis remains poor.

The intent of this question was to review the existing evidence in order to determine the optimal treatment recommendation for those patients with advanced HCC (macrovascular invasion and/or metastatic disease) in the setting of underlying Child–Pugh A/B cirrhosis.

### *Evidence and Rationale*

The evidence of a de novo systematic review including all studies that enrolled adults with advanced HCC is summarized in Supporting Table 7. Of the 15 studies identified, 4 were RCTs, while the additional 11 were observational studies. The 4 RCTs were not designed to compare the outcome of sorafenib versus local-regional therapy in advanced HCC. There were no comparative trials and only a few noncomparative studies that addressed the question of whether patients should be treated with either sorafenib or LRT. The only level-one evidence that exists in patients with advanced HCC (macrovascular invasion and/or metastatic disease) is the randomized Phase III trial with sorafenib in comparison with placebo. In the pivotal SHARP trial, of the total 602 patients enrolled, 231 patients had macrovascular invasion and 309 patients had extrahepatic metastasis. In the sorafenib arm, there were 108 patients (35%) with macrovascular invasion versus the placebo arm that had 123 patients (41%) with macrovascular invasion. Additionally, in the sorafenib arm, 159 patients (53%) had extrahepatic disease versus the placebo arm that had 150 patients (50%) with extrahepatic disease. Of note, the extent of macrovascular invasion was not detailed, and the extent of metastatic disease was only provided for lungs and lymph nodes. Sorafenib significantly improved the median overall survival in the entire population included in the study (sorafenib 10.7 months versus placebo arm 7.9 months, HR 0.69, 0.55-0.87) and demonstrated a trend for improvement both for patients with macrovascular invasion (sorafenib 8.1 months versus placebo arm 4.9 months, HR 0.68, 0.49-

0.93) and for patients with metastatic disease (sorafenib 8.9 months versus placebo arm 8.3 months, HR 0.85, 0.64-1.15)<sup>52, 91</sup>.

Similarly, in the Asia-Pacific phase III trial, of the 226 patients randomized, 80 (35%) patients had macrovascular invasion and 155 (69%) patients had extrahepatic disease. Sorafenib significantly improved the median OS in comparison with placebo in the whole study population (sorafenib 6.5 months versus placebo arm 4.2 months, HR 0.68, 0.50-0.93) and demonstrated a positive trend in both patients with macrovascular invasion (HR 0.63, 0.39-1.03) and with metastatic disease to either lungs or lymph nodes (HR 0.82, 0.57-1.18)<sup>92, 93</sup>.

The definitive benefits of sorafenib in advanced HCC with underlying Child's B cirrhosis has not been clearly established, though an ongoing randomized phase III trial conducted in Italy is evaluating sorafenib versus placebo in patients with advanced HCC and underlying Child-Pugh B cirrhosis (NCT01405573). There have been 4 published phase III randomized trials comparing sorafenib versus either other targeted agents (sunitinib, brivanib, linifanib) or the combination of sorafenib with erlotinib<sup>92, 94, 95</sup>. Collectively, there were an additional 2,001 patients enrolled in the sorafenib arm, with 688 patients with macrovascular invasion and 1,220 patients with metastatic disease, reinforcing the benefits of sorafenib in advanced HCC. No RCTs have been published to critically assess the relative benefits of sorafenib versus LRT in advanced HCC with either macrovascular invasion or metastatic disease.

Specific to patients with macrovascular disease, one single-center retrospective observational study (N = 557) has attempted to compare the relative benefits of TACE alone (n =

295) or TACE with radiation (RT) (n = 196) with sorafenib (n = 66) in patients with advanced HCC with portal vein thrombosis (PVTT)<sup>96</sup>. The TACE/RT group had longer median time to progression (TTP) and OS than the chemoembolization alone and sorafenib groups ( $P < 0.001$ ).

In an observational retrospective study, Nakazawa and colleagues compared the survival benefits of sorafenib versus RT in patients with advanced HCC with PVTT in the main trunk or its first branch<sup>97</sup>. Of the 97 patients included, 40 received sorafenib and 57 received RT. Median survival did not differ significantly between the sorafenib group (4.3 mo) and the RT group (5.9 mo;  $P = 0.115$ ). In another retrospective observational study, Song and colleagues attempted to compare the efficacy of hepatic arterial infusion chemotherapy (HAIC)—which involves an actual infusion catheter directly in the hepatic artery as opposed to embolized particles mixed with chemotherapy released in the artery—with sorafenib in advanced HCC with PVTT<sup>98</sup>. The median OS was significantly longer in the HAIC group than in the sorafenib group (7.1 vs 5.5 mo,  $P = 0.011$ ).

#### *Future Research*

Given the recognized poor prognosis for patients with advanced HCC with macrovascular invasion, clinical trials with combined strategies using sorafenib and LRT are ongoing. Two phase III trials are comparing the survival benefits of sorafenib versus radioembolization in advanced HCC with macrovascular invasion (NCT01135056, NCT01482442). In addition, the added benefits of LRT (radiation, TACE, and HAIC) combined with sorafenib versus sorafenib alone is being studied in ongoing phase III clinical trials (NCT01730937, NCT01829035, NCT02774187, and NCT01214343). For patients with metastatic disease, there is an attempt to assess the added benefits of stereotactic body radiation (SBRT) to sorafenib (RTOG 1112)

through a randomized phase III trial comparing sorafenib with or without SBRT in patients with advanced HCC (NCT01730937). Phase III trials comparing lenvatinib or nivolumab with sorafenib are ongoing in an attempt to improve the survival in patients with advanced HCC with metastatic disease (NCT01761266 and NCT02576509).

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**Table 1. The GRADE Approach**

**1. Rating the Quality of Evidence**

Study design	Initial rating of quality of evidence	Rate down when:	Rate up when:
RCT (e.g. RR: 0.5)	High	Risk of bias	Large effect
effect (e.g. RR: 0.2) gradient	Moderate	Inconsistency Imprecision	Very large Dose response
Observational	Low confounding would increase the association Very low	Indirectness Publication bias	All plausible

**2. Determinants of the Strength of a Recommendation**

- Quality of evidence
- Balance of benefit and harms
- Patient values and preferences
- Resources and costs

**3. Implication of the Strength of a Recommendation**

**Strong**

- Population: Most people in this situation would want the recommended course of action and only a small proportion would not.
- Health care workers: Most people should receive the recommended course of action.
- Policy makers: The recommendation can be adapted as policy in most situations.

**Conditional**

- Population: The majority of people in this situation would want the recommended course of action, but many would not.
- Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making.
- Policy makers: There is a need for substantial debate and involvement of stakeholders.

**Table 2. Clinical Questions Evaluated**

<b>Question</b>	<b>Population</b>	<b>Intervention</b>	<b>Comparison</b>	<b>Outcome</b>
1	Adults with cirrhosis	Surveillance for HCC	No surveillance	Survival
2	Adults with cirrhosis and suspected HCC	Diagnostic evaluation with multiphase CT	Diagnostic evaluation with multiphase MRI	Sensitivity and specificity
3	Adults with cirrhosis and an indeterminate hepatic nodule	Biopsy	Repeated or alternative imaging	Sensitivity and specificity
4	Adults with Child's class A cirrhosis and stage T1 or T2 HCC	Resection	Local-regional therapy	Survival, recurrence, morbidity
5	Adults with cirrhosis and HCC successfully resected or ablated	Adjuvant therapy	No adjuvant therapy	Survival
6	Adults with cirrhosis awaiting liver transplantation and T1 HCC	Local-regional therapy	Observation	Survival, progression to T3/waitlist dropout
7	Adults with cirrhosis awaiting liver transplantation and T2 HCC	Bridging therapy	Observation	Survival, progression to T3/waitlist dropout
8	Adults with cirrhosis awaiting liver transplantation and T3 HCC	Downstaging and transplant	No transplant	Posttransplant survival, recurrence
9	Adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation	Transarterial chemoembolization	Transarterial radioembolization or external radiation	Survival
10	Adults with Child's A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease	Systemic therapy	Local-regional therapy or no therapy	Survival

## Appendix. Evidence Profiles

Table 1. Evidence profile for Q 1: Should adults with cirrhosis undergo surveillance for HCC, and if so, which surveillance test is best?

Outcomes	No. of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Early tumor detection rate	10 904 (38 observational studies)	⊕⊕○○ LOW	OR 2.11 (1.88 to 2.33)
Early tumor detection rate (defined early stage using BCLC or Milan criteria)	6348 (23 observational studies)	⊕⊕○○ LOW	OR 2.08 (1.80 to 2.37)
Early tumor detection rate (using BCLC to define early stage)	6573 (6 observational studies)	⊕⊕○○ LOW	OR 1.96 (1.41 to 2.73)
Curative treatment rate	24.374 (34 observational studies)	⊕⊕⊕○* MODERATE	OR 2.24 (1.99 to 2.52)
3-year survival rate*	10 850 (23 observational studies)	⊕⊕⊕○* MODERATE	OR 1.90 (1.67 to 2.17)
Early detection (ultrasound only)	(5 observational studies)	⊕⊕○○ LOW	OR 2.04 (1.55 to 2.68)
Early detection (ultrasound +/- AFP)	(14 observational studies)	⊕⊕○○ LOW	OR 2.16 (1.80 to 2.60)
Receipt of curative treatment (ultrasound only)	(8 observational studies)	⊕⊕○○ LOW	OR 2.23 (1.83 to 2.71)
Receipt of curative treatment (ultrasound +/- AFP)	(24 observational studies)	⊕⊕○○ LOW	OR 2.19 (1.89 to 2.53)

\*Upgraded because of large effect size

Table 2. Evidence profile for Q 2: Should adults with cirrhosis and suspected HCC undergo diagnostic evaluation with multiphasic CT or multiphasic MRI?

Modality	Studies (n)	Sensitivity (95% CI) I <sup>2</sup> (%)	P value	Specificity (95% CI) I <sup>2</sup> (%)	P value	+ likelihood Ratio (95% CI)	P value	- likelihood Ratio (95% CI)	P value	Diagnostic Odds Ratio (95% CI)	P value	Quality of Evidence
Contrast-enhanced CT	19	0.66 (0.60, 0.72) I <sup>2</sup> = 72.53	0.0003	0.92 (0.84, 0.96) I <sup>2</sup> = 86.74	0.83	8.1 (4.1, 16.2)	0.86	0.37 (0.30-0.44)	0.001	22 (10, 50)	0.24	⊕⊕⊕○* MODERATE
MRI with and without contrast	19	0.82 (0.75, 0.87) I <sup>2</sup> = 72.90		0.91 (0.82, 0.95) I <sup>2</sup> = 89.81		8.8 (4.6, 16.9)		0.20 (0.15-0.28)		43 (20, 92)		⊕⊕⊕○* MODERATE

\*serious risk of bias and possible publication bias

Table 3. Evidence profile for Q 4: Should adults with Child's A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or locoregional therapy?

Outcomes	No. of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Overall survival (low-risk-of-bias studies)	230 (2 RCTs)	⊕⊕⊕○ <sup>3</sup> MODERATE	RR 0.60 (0.44 to 0.82)
Event-free survival	578 (3 RCTs)	⊕⊕⊕○ <sup>1</sup> MODERATE	HR 0.70 (0.54 to 0.91)
2-year survival (low risk of bias studies)	398 (2 RCTs)	⊕⊕⊕○ <sup>3</sup> MODERATE	HR 0.38 (0.17 to 0.84)
Local progression	168 (1 RCT)	⊕⊕⊕○ <sup>3</sup> MODERATE	HR 0.48 (0.28 to 0.82)
Rate of complications (low risk of bias studies)	398 (2 RCTs)	⊕⊕○○ <sup>2</sup> LOW	OR 4.6 (1.4 to 14.7)
Length of hospital stay (days)	559 (3 RCTs)	⊕⊕⊕○ <sup>1</sup> MODERATE	Standardized Mean Difference 2.18 (1.97 to 2.39)

<sup>1</sup>High risk of bias <sup>2</sup>High heterogeneity <sup>3</sup>Small number of events

Table 4. Evidence profile for Q5: Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy?

Outcomes	No. of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Recurrence-free survival (Chemotherapy)	(8 RCTs)	⊕○○○ <sup>1,2,3</sup> VERY LOW	<b>HR 0.94</b> (0.80 to 1.10)
Recurrence-free survival (internal radiation therapy)	(1 RCT)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.6</b> (0.3 to 1.3)
Recurrence-free survival (radioimmunotherapy)	(1 RCT)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.3</b> (0.1 to 0.7)
Recurrence-free survival (heparanase inhibitor PI-88 therapy)	(1 RCT)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.6</b> (0.3 to 1.2)
Recurrence-free survival (transhepatic arterial chemotherapy)	(3 RCTs)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.7</b> (0.4 to 1.2)
Recurrence-free survival (systematic and transhepatic chemotherapy)	(2 RCTs)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 1.5</b> (0.9 to 2.4)
Overall survival (chemotherapy)	(7 RCTs)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 1.01</b> (0.80 to 1.40)
Overall survival (internal radiation therapy)	(1 RCT)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.7</b> (0.3 to 1.5)
Overall survival (radioimmunotherapy)	(1 RCT)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 0.3</b> (0.1 to 0.8)
Overall survival (oral chemotherapy)	(3 RCTs)	⊕○○○ <sup>1,2,3</sup> VERY LOW	<b>HR 1.01</b> (0.70 to 1.50)
Overall survival (transhepatic arterial chemotherapy)	(2 RCTs)	⊕○○○ <sup>1,2,3</sup> VERY LOW	<b>HR 0.6</b> (0.3 to 1.1)
Overall survival (systematic and transhepatic chemotherapy)	(2 RCTs)	⊕⊕○○ <sup>1,3</sup> LOW	<b>HR 1.7</b> (0.9 to 3.2)

<sup>1</sup>High risk of bias <sup>2</sup>High heterogeneity (>50%) <sup>3</sup>Small number of events

Table 5. Evidence profile for Q 6: Should adults with cirrhosis awaiting liver transplantation and T1 HCC be treated or undergo observation?

Outcomes	Nº of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Dropout from all causes (at 6 months)	1 noncomparative study	⊕○○○ <sup>1,2</sup> VERY LOW	0.05 (0.01-0.1)
Dropout from all causes	1 noncomparative study	⊕○○○ <sup>1,2</sup> VERY LOW	0.30 (0.20-0.32)
Progression to T2	1 noncomparative study	⊕○○○ <sup>1,2</sup> VERY LOW	0.88(0.82-0.94)

<sup>1</sup>High risk of bias <sup>2</sup>Small number of events

Table 6. Evidence profile for Q 7: Should adults with cirrhosis awaiting liver transplantation and HCC (OPTN T2) undergo transplant alone or transplant with bridging therapy while waiting?

Intervention	Outcomes	No. of participants (studies) Follow-up	Overall quality of evidence	OR (95% CI)
<b>Any bridging therapy</b>	Dropout due to progression	2	⊕○○○ VERY LOW*†	0.321 (0.056-1.851)
	Dropout from all causes	3	⊕○○○ VERY LOW*†‡	0.378 (0.060-2.370)
	All-cause mortality (post-LT)	5	⊕○○○ VERY LOW*†	1.028 (0.752-1.404)
	Recurrence (post-LT)	10	⊕○○○ VERY LOW *	1.445 (0.0911-2.29)
	3-year survival (post-LT)	5	⊕○○○ VERY LOW*†	1.010 (0.890-1.147)
	5-year survival (post-LT)	5	⊕○○○ VERY LOW*†	0.879 (0.762-1.014)
	1-year survival (post-LT)	3	⊕○○○ VERY LOW *†	1.008 (0.945-1.076)
	5-year recurrence-free survival (post-LT)	3	⊕○○○ VERY LOW*† ‡	0.920 (0.75-1.127)
	1-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	1.007 (0.944-1.075)
	3-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	1.072 (0.965-1.190)
<b>TACE</b>	Dropout because of progression	1	⊕○○○ VERY LOW *†	0.371 (0.043-3.185)
	Dropout from all causes	1	⊕○○○ VERY LOW *†	0.212 (0.027-1.650)
	All-cause mortality (post-LT)	1	⊕○○○ VERY LOW *†	1.000 (0.270-3.705)
	Recurrence (post-LT)	3	⊕○○○ VERY LOW *†	1.74 (0.49-6.15)
	3-year survival (post-LT)	2	⊕○○○ VERY LOW *†	0.929 (0.717-1.203)
	5-year survival (post-LT)	3	⊕○○○ VERY LOW *†‡	0.888 (0.534-1.475)
	1-year survival (post LT)	2	⊕○○○ VERY LOW *†	1.036 (0.871-1.231)
	5-year recurrence-free survival (post-LT)	1	⊕○○○ VERY LOW *†	0.799 (0.667-0.956)
<b>TACE and RFA</b>	Recurrence (post-LT)	1	⊕○○○ VERY LOW *†	0.72 (0.0.18-2.91)
<b>TAE</b>	All-cause mortality (post-LT)	1	⊕○○○ VERY LOW *†	1.124 (0.675-1.873)
	Recurrence (post-LT)	1	⊕○○○ VERY LOW *†	2.374 (0.609-9.252)
<b>Multitherapies</b>	Dropout from all causes	1	⊕○○○ VERY LOW *†	0.131 (0.038-0.449)

	All-cause mortality (post-LT)	2	⊕○○○ VERY LOW *†	1.145 (0.688-1.907)
	Recurrence (post-LT)	4	⊕○○○ VERY LOW *†	1.49 (0.826-2.7)
	3-year survival (post-LT)	3	⊕○○○ VERY LOW *†	1.049 (0.868-1.268)
	5-year survival (post-LT)	2	⊕○○○ VERY LOW *†	0.880 (0.784-0.988)
	1-year survival (post-LT)	1	⊕○○○ VERY LOW *†	1.004 (0.936-1.077)
	1-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	1.007 (0.944-1.075)
	3-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	1.072 (0.965 - 1.190)
	5-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	0.986 (0.758-1.282)
<b>RFA</b>	Dropout because of progression	1	⊕○○○ VERY LOW *†	0.241 (0.012-4.946)
	Dropout from all causes	1	⊕○○○ VERY LOW *†	1.434 (0.793-2.594)
	All-cause mortality (post-LT)	1	⊕○○○ VERY LOW *†	0.706 (0.347-1.435)
	Recurrence (post-LT)	1	⊕○○○ VERY LOW *†	0.745 (0.069-8.003)

\*Serious risk of bias. †Imprecision ‡ Inconsistency

Table 7. Evidence profile for Q 8: Should adults with cirrhosis and HCC beyond Milan criteria (T3) be transplanted following down-staging to within Milan criteria?

Intervention	Outcomes	No. of participants (studies) Follow-up	Overall quality of evidence	Relative effect (95% CI)
All bridging therapies	1-year survival (post-LT)	2	⊕○○○ VERY LOW *†	1.11 (1.01-1.23)
	5-year survival (post-LT)	1	⊕○○○ VERY LOW *†	1.17 (1.03-1.32)
	3-year survival (post-LT)	1	⊕○○○ VERY LOW *†	1.02 (0.77-1.34)
	1-year recurrence-free survival (post-LT)	1	⊕○○○ VERY LOW *†	0.99 (0.91-1.07)
	5-year recurrence-free survival (post-LT)	2	⊕○○○ VERY LOW *†	1.04 (0.93-1.16)

\*Serious risk of bias. †Imprecision

Table 8. Evidence profile for Q 9: Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?

Intervention	Outcomes	No. of participants (studies) Follow-up	Overall quality of evidence	Relative effect (95% CI)
<b>TACE or TAE</b>	Overall survival	7/RCTs	⊕⊕⊕○ MODERATE*	HR 0.88 (0.71-1.10)
<b>TACE</b>	Overall survival	5/RCTs	⊕⊕⊕○ MODERATE*	HR 0.87 (0.67-1.14)
<b>Drug-eluting beads TACE vs conventional TACE</b>	Overall survival	2/ RCTs	⊕⊕○○ LOW *†	HR 1.07 (0.7-1.67)
<b>TACE and PEI vs monotherapy (TACE or PEA)</b>	1-year survival rate	17/ RCTs	⊕⊕⊕○ MODERATE†	RR 1.24 (1.17-1.31)
	3-year survival rate	10/ RCTs	⊕⊕⊕○ MODERATE†	RR 2.27(1.93-2.67)
<b>TACE + RT vs TACE Huo, 2015<sup>4</sup></b>	1-year survival	12/RCTs	⊕⊕⊕○ MODERATE†	OR 1.36 (1.12-1.66)
	3-year survival	9/ RCTs	⊕⊕⊕○ MODERATE†	OR 2.32 (1.64-3.28)
	5-year survival rate	2/RCTs	⊕⊕⊕○ MODERATE†	OR 6.32 (1.58-25.30)
<b>RFA vs PEI</b>	Overall survival	5/RCTs	⊕⊕⊕○ MODERATE†	HR 0.67 (0.51-0.87)

\*Serious risk of bias. †Imprecision

Table 9. Evidence profile for Q10: Should adults with Child–Pugh A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease be treated with systemic or locoregional therapy (LRT) or no therapy?

Intervention vs comparison	Design	Studies (n)	Child–Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
Macrovascular invasion:							
Sorafenib vs placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	311	HR 0.66 (0.51-0.87), I <sup>2</sup> =0%	⊕⊕⊕○ MODERATE †
**Sorafenib-cryoRx vs sorafenib	RCT	1	Class A (80.9%) Class B (0.19%)	1-year survival rate	104	RR 1.7 (0.99-2.78)	⊕⊕⊕○ MODERATE †
**Percutaneous RFA vs control	Observational study	1	Class A (78.9%) Class B (21.1%)	Mortality	57	RR 0.81 (0.67-0.97)	⊕○○○ VERY LOW *†
**TACE vs Y 90	Observational study	1	NR	Median Survival	323	OR 2.1 (1.04-4.2)	⊕○○○ VERY LOW *†
**131 I-lipiodol vs TACE/TAE	Observational study	1	Class A (59.7%) Class B (33.9%) Class C (6.4%)	1-year survival rate	20	RR 2.6 (0.39-16.9)	⊕○○○ VERY LOW *†
Cytotoxic chemotherapy vs sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	49	HR 0.5 (0.1-1.7)	⊕○○○ VERY LOW *†
**Transhepatic arterial chemotherapy vs control	Observational study	1	Intervention (7.0 ± 2.10) Control (8.5 ± 2.20)	6-month survival rate	23	RR 11.5 (0.69 – 190.8)	⊕○○○ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall survival	262	HR 0.28 (0.20-0.40)	⊕○○○ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (100%)	Overall survival	413	HR 0.34 (0.24-0.48)	⊕○○○ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class B (100%)	Overall survival	144	HR 0.26 (0.16-0.43)	⊕○○○ VERY LOW *†
**Chemoembolization vs sorafenib	Observational study	1	Class A (79.8%) Class B	Overall survival	361	HR 0.67(0.47–0.95)	⊕○○○ VERY LOW *†

			(20.2%)				
**Chemoembolization and RT vs chemoembolization	Observational study	1	Class A (75.4%) Class B (24.6%)	Overall survival	491	HR 0.56 (0.45–0.71)	⊕○○○ VERY LOW *†
**TACE + portal vein embolization vs TACE	Observational study	1	Class A (50%) Class B (50%)	1-year survival	116	RR 1.3 (1.05-1.7)	⊕○○○ VERY LOW *†
				3-year survival rate	116	RR 1.5 (0.84-2.54)	⊕○○○ VERY LOW *†
				5-year survival rate	116	RR 15.9 (0.92-276.6)	⊕○○○ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class A (43.6%) Class B (56.4%)	1-year survival	38	RR 1.33 (0.5-3.6)	⊕○○○ VERY LOW *†
				3-year survival rate	38	RR 3.3 (0.38-29.25)	⊕○○○ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class A (100%)	1-year survival	17	RR 1.1 (0.28-4.32)	⊕○○○ VERY LOW *†
				3-year survival rate	17	RR 2.92 (0.16-52.47)	⊕○○○ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class B (100%)	1-year survival	21	RR 1.33 (0.29-6.23)	⊕○○○ VERY LOW *†
				3-year survival rate	21	RR 2 (0.15-27.45)	⊕○○○ VERY LOW *†
**Sorafenib vs sorafenib-TACE	Observational study	1	Class 5(49.4%), 6 (26.9%) and 7 (23.6%)	Overall survival	89	HR 1.17 (0.52 - 1.8)	⊕○○○ VERY LOW *†
**RT vs sorafenib	Observational study	1	Class A (100%)	1-year survival	56	RR 1.3 (0.67-2.7)	⊕○○○ VERY LOW *†
**HAIC vs sorafenib	Observational study	1	Class A (83.6%) Class B (16.4%)	Mortality	110	RR 0.94 (0.79-1.21)	⊕○○○ VERY LOW *†
Metastatic disease:							
Sorafenib vs placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	311	HR 0.84 (0.67-1.1), I <sup>2</sup> = 0%	⊕⊕⊕○ MODERATE †
Cytotoxic	Observational	1	Class A	Overall	66	HR 0.7	⊕○○○

chemotherapy vs sorafenib	1 study		(76.1%) Class B (23.9%)	Survival		(0.2-1.9)	VERY LOW *†
Chemoembolization with or without RT vs sorafenib	Observational 1 study	1	Class A (64.4%) Class B (35.6%)	Overall Survival	101	HR 0.66 (0.43- 1.02)	⊕○○○ VERY LOW *†

\*Serious risk of bias. †Imprecision

\*\* Studies included only portal vein tumor thrombosis

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