HEPATOLOGY

PRACTICE GUIDELINE | HEPATOLOGY, VOL. 67, NO. 1, 2018

AASLD Guidelines for the Treatment of Hepatocellular Carcinoma

Julie K. Heimbach,[1] Laura M. Kulik,[2] Richard S. Finn,[3] Claude B. Sirlin,[4] Michael M. Abecassis,[5] Lewis R. Roberts,[6] Andrew X. Zhu,[7] M. Hassan Murad,[8] and Jorge A. Marrero[9]

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.[1] 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 and is based upon the previous HCC AASLD guidelines by Bruix and Sherman.[2]

KEY QUESTIONS

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

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; CI, confidence interval; CT, computed tomography; DEB-TACE, drug-eluting beads TACE; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; LRT, local-regional therapy; MELD, Model for End-Stage Liver Disease; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; OS, overall survival; PEI, percutaneous ethanol injection; PVT, portal vein thrombosis; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; TACE, transarterial chemoembolization; TACI, transarterial chemoinfusion; TAE, transarterial embolization; TARE, transarterial radioembolization; US, ultrasound; Y90, yttrium-90.

The funding for the development of this Practice Guideline was provided by the American Association for the Study of Liver Diseases.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29086/suppinfo.

Received January 10, 2017; accepted January 10, 2017.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.29086

Potential conflict of interest: Laura M. Kulik is on the advisory board for Gilead, Bayer, Eisai, Salix, and Bristol-Myers Squibb. Richard Finn consults for Pfizer, Bayer, Novartis, Merck, and Bristol-Myers Squibb. Claude B. Sirlin consults for and has received grants from Virtualscopics. Lewis R. Roberts consults for Wako, Medscape, and Axis; advises Tavec and Bayer; is on the speakers' bureau for Onlive; and has received grants from Ariad, BTG, and Gilead. Andrew Zhu consults for Bristol-Myers Squibb, Eisai, Merck, Novartis, Sanofi, and Bayer.

computed tomography (CT) or multiphasic magnetic resonance imaging (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-Pugh class A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or local-regional (LRT) therapy?
5. Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy?
6. Should adults with cirrhosis awaiting liver transplantation and HCC (T1) be treated or undergo observation?
7. Should adults with cirrhosis and HCC (Organ Procurement and Transplantation Network [OPTN] T2) awaiting liver transplantation undergo transplantation alone or transplantation with bridging therapy while waiting?
8. Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) undergo transplantation after being down-staged 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-Pugh class 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 who care 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 (http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp). 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 regions of highest incidence, Southern Europe and North America being the regions of intermediate incidence, and Northern Europe and South Central Asia being the regions of lowest incidence.[3]

The incidence of HCC has been rising rapidly in the United States over the last 20 years.[4] According to estimates from the Surveillance Epidemiology End Results (SEER) program of the National Cancer Institute, the United States will have witnessed an estimated 39,230 cases of HCC and 27,170 HCC deaths in 2016 (https://seer.cancer.gov). In addition, a recent study using the SEER registry projects that the incidence of HCC will continue to rise until 2030,[5] with the highest increase in Hispanics, followed by African Americans and then Caucasians, with a decrease noted among Asian Americans.

ARTICLE INFORMATION:

From the [1]Division of Transplant Surgery, William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN; [2]Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University, Chicago, IL; [3]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica Geffen School of Medicine at UCLA, Los Angeles, California; [4]Liver Imaging Group, Department of Radiology, University of California, San Diego; [5]Northwestern University Feinberg School of Medicine, Chicago, IL; [6]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [8]Mayo Clinic Evidence-based Practice Center, Mayo Clinic, Rochester, MN; [9]Digestive and Liver Diseases Division, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Julie K. Heimbach, M.D.
Mayo Clinic
William J. von Liebig Transplant Center
Charlton 10
200 First Street SW
Rochester, MN 55905-0001
E-mail: heimbach.julie@mayo.edu
Tel.: 507-266-6640

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	High	Risk of bias	Large effect (e.g,. RR = 0.5)
	Moderate	Inconsistency	Very large effect (e.g., RR = 0.2)
		Imprecision	Dose response gradient
Observational	Low	Indirectness	All plausible confounding would increase the association
	Very low	Publication bias	

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.

For patients, a strong recommendation implies that most patients in this situation would want the recommended course of action and only a small proportion would not. For clinicians, this would imply that patients should receive the recommended course of action, with consistent benefits and few side effects. For policy makers, the recommendation could be adopted as a policy in most situations and potentially could be used as a quality measure. For strong recommendations, the recommendation is prefaced by "The AASLD recommends..." In contrast, a conditional recommendation (also sometimes termed a "weak" recommendation) for patients would imply that the majority of patients in this situation would want the recommended course of action, but many would not. For clinicians making a conditional recommendation, the balance of benefits, harms, and burdens is uncertain; and they should be prepared to help patients make a decision that is consistent with their own values using a shared decision-making approach. For policy makers, this recommendation type could imply a need for substantial debate and involvement of all stakeholders and is likely insufficient to be used as a quality measure. For conditional recommendations, the recommendation is prefaced by "The AASLD suggests..."

The increase in incidence of HCC in the United States is attributed primarily to the hepatitis C virus (HCV) epidemic, prompting Petrick et al.[4] to suggest that preventive efforts should target the birth cohort with the highest prevalence of HCV infection (1945-1965). 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,[6] 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%,[7,8] and the HCC incidence rate among patients with cirrhosis has been shown to be 2%-4% per year.[9] 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 impacts the management and therapeutic options substantially.

The key questions posed above reflect common scenarios in this patient population and provide the framework for this practice guideline. We used the Child-Pugh 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 aforementioned key

TABLE 2. Clinical Questions Evaluated

Question	Population	Intervention	Comparison	Outcome
1	Adults with cirrhosis	Surveillance for HCC	No surveillance	Survival
2	Adults with cirrhosis and suspected HCC	Diagnostic evaluation with multiphasic CT	Diagnostic evaluation with multiphasic 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-Pugh 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	Down-staging 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-Pugh class A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease	Systemic therapy	Local-regional therapy or no therapy	Survival

questions. 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).[1] 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—including 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 to facilitate implementation. Evidence profiles for the corresponding systematic review for each of the key questions are presented in the Appendix. 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

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 Child-Pugh class C cirrhosis unless they are on the transplant waiting list, given the low anticipated survival for these patients.

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 to 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.[10] HCC meets the criteria for the development of a surveillance program[11] given that patients with cirrhosis are a high-risk group[7] and can be readily identified. The previous AASLD guidelines on HCC[2] summarize the populations at the highest risk to have chronic viral hepatitis B and cirrhosis due to HCV. A randomized surveillance study performed in another high-risk group, hepatitis B virus (HBV) carriers, showed a 37% reduction in mortality for those who underwent surveillance.[12] However, there are no randomized trials in Western populations with cirrhosis secondary to chronic HCV 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 tests should be used. Although 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 recommend US as the primary modality.[2] 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 uses the data from a recent systematic review on surveillance.[13] 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 with only 27.9% among the 6115 patients without previous surveillance, with an odds ratio (OR) of 1.90 (95% confidence interval [CI], 1.67-2.17; $P < 0.001$). There were six studies that controlled for lead-time bias, and the improvement in survival persisted (3-year survival rates of 39.7% for surveillance versus 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% versus 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 OR of 2.11 (95% CI, 1.88-2.33) compared with no surveillance. In terms of anticipated absolute effects, surveillance led to 163 per 1000 more patients detected at early stages compared with no surveillance. In addition, surveillance led to more curative treatments compared with no surveillance (61.8% versus 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 used most commonly were US and AFP. Of the studies identified, only four used US alone, whereas the rest 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 OR of 2.16 (95% CI, 1.80-2.60), whereas US alone had an OR of 2.04 (95% CI, 1.55-2.68). Both US alone and US plus AFP led to similar rates of curative treatment (OR, 2.23 for US [95% CI, 1.83-2.71] and 2.19 for US plus AFP [95% CI, 1.89-2.53]). 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, whereas 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 two 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 with 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.[14]

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

Recommendation

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, examination 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 with 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 multiphasic imaging, there is not agreement about which diagnostic imaging test to use. Commonly used methods in clinical practice include multiphasic CT with extracellular agents, multiphasic MRI with extracellular agents (gadolinium-based compounds that stay in the extracellular space and permit characterization of blood flow), and multiphasic 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 uses the data from a de novo systematic review on imaging in HCC performed to address this question. There were no randomized comparative studies of CT versus MRI, no studies identified that compared multiphasic MRI with an extracellular agent versus multiphasic 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, eight studies compared multiphasic MRI using an extracellular agent versus multiphasic CT. MRI with an extracellular agent provided higher pooled sensitivity than CT (0.76 [95% CI, 0.72-0.81] versus 0.63 [95% CI, 0.57-0.69]; $P < 0.001$) with similar specificity (0.78 [95% CI, 0.63-0.88] versus 0.82 [95% CI, 0.71-0.89]; $P = 0.62$). Eight studies compared multiphasic MRI with gadoxetate disodium versus multiphasic CT. MRI with gadoxetate disodium provided higher pooled sensitivity than CT (0.87 [95% CI, 0.79-0.93] versus 0.73 [95% CI, 0.64-0.81]; $P < 0.02$) with similar specificity (0.94 [95% CI, 0.90-0.97] versus 0.96 [95% CI, 0.90-0.98]; $P = 0.47$).

When looking specifically at lesions larger than 2 cm, three studies compared multiphasic MRI with an extracellular agent versus 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 and 2 cm, there were six studies that compared multiphasic MRI versus CT, and this also showed similar sensitivity and specificity. For HCC <1 cm, two studies compared multiphasic CT versus multiphasic MRI with an extracellular agent. The sensitivity of MRI for <1 cm was significantly higher compared with CT (0.69 versus 0.49; $P = 0.049$), whereas the specificity was, at a trend level, lower (0.46 versus 0.69; $P = 0.08$).

Although 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 with multiphasic CT, multiphasic 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.[15,16]

FUTURE RESEARCH

Although not used widely in North America, multiphasic contrast-enhanced US also can be used to diagnose HCC noninvasively, and further studies are needed.[17-24] Prospective studies should include multiphasic CT, multiphasic MRI with an extracellular agent, and multiphasic MRI with gadoxetate disodium 8, and data on costs and patient preference should be collected. Of note, a multicenter trial of US transplantation 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?

Recommendations

3A. The 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. The 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 ≥10 mm HCC have been developed by the American College of Radiology through its Liver Imaging Reporting and Data System (LI-RADS),[25] the OPTN,[26] and previous AASLD guidelines,[2] and include arterial phase hyperenhancement in combination with washout appearance and/or capsule appearance. Lesions that do not meet these guidelines or are smaller than 1 cm are considered indeterminate.

BACKGROUND

In its previous HCC clinical practice guidelines,[2] 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.[27] 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 uses the data from a *de novo* systematic review on imaging in HCC performed to address this question. Based on an extensive search strategy detailed in the systematic review, there were no comparative studies identified that directly address this question, although two single-center, noncomparative studies were identified that examined the role of biopsy.

Forner et al.[17] in 2008 reported outcomes for ≤2 cm hepatic nodules detected during surveillance ultrasound in patients with cirrhosis. The authors performed percutaneous biopsy of ≤2 cm nodules in addition to MRI and contrast-enhanced US. They found a sensitivity and specificity of MRI to be 61.7% and 96.6%, whereas contrast-enhanced US was 51.7% and 93.1% compared with 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 three times. In 2011, Khalili et al.[28] reported that in patients with cirrhosis, only 14%-23% of 1- to 2-cm indeterminate nodules initially detected at surveillance ultrasound are malignant. 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 ≤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 ≤2 cm indeterminate nodules, as characterized by CT or MRI.[19,23,29-37]

Because many if not most indeterminate small hepatic nodules are nonmalignant, strategies for risk stratification are needed. Tanabe et al.[38] evaluated the natural history of indeterminate lesions detected at CT or MRI. The indeterminate lesions were categorized as probably benign, intermediate probability of HCC, and probably HCC based only on imaging features.[25] No lesions initially categorized as probably benign progressed to definite HCC during follow-up, whereas 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.[39] 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.

Taken together, these studies suggest that a substantial proportion of 1- to 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 Sersté et al.[40] 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. 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,[38,39] potentially including endpoints other than survival, such as patient preference or drop-off from the transplant waiting list.

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

Recommendation

4. The AASLD suggests that adults with Child-Pugh class 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 LRT—such as transarterial radioembolization (TARE) and transarterial chemoembolization (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 (<2.5 cm) 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 that 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 with 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, whereas 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, and cryoablation, as well as surgical resection. Most studies define patients with resectable HCC as those (1) with one to three unilobar lesions, with an upper size limit of 5 cm for single lesions and 3 cm for more than one lesion (some trials accept two lesions up to 4 cm); (2) without radiographic evidence of extrahepatic disease or macrovascular invasion; and (3) occurring in the setting of minimal or no portal hypertension and in the absence of synthetic dysfunction (Barcelona Clinic Liver Cancer stage 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 to compare resection with 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.[41] on treatment for early-stage HCC in patients with Child-Pugh class 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 with 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 three RCTs that compared RFA with resection, including a total of 578 patients.[42-44] Two of these three trials had a low risk of bias and moderate evidence quality,[42,43] and one trial had a high risk of bias.[44] The results of the two low-risk-of-bias trials demonstrate that hepatic resection is more effective than RFA regarding overall survival (hazard ratio [HR], 0.56; 95% CI, 0.40-0.78) as well as 2-year survival (HR, 0.38; 95% CI, 0.17-0.84). 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, 0.44-1.15). 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 with RFA (OR, 8.3).

In addition to the trials included in the systematic review by Weis et al.[41] comparing resection with RFA, two recently published RCTs confirm the findings of improved survival for patients after resection.[45,46] One single-center RCT compared resection with 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 ($P = 0.007$).[45] Another RCT trial compared resection with TACE alone for lesions up to and exceeding Milan criteria (up to five tumors, with the largest being <5 cm) and found resection to be superior in 1 and 3 years of follow-up (HR, 0.4; $P < 0.001$).[46]

Lesion size 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 an RCT. A recent multicenter retrospective report from Italy did examine this question.[47] This report included 544 Child-Pugh class 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.,[41] but examining the three individual RCT trials included in the systematic

review, Huang et al.[42] demonstrated that survival following resection remained favorable compared with 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 with either resection or ablative strategies in Child-Pugh class 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 suggests 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.[48]
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

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 versus late, with the latter believed to be related to the development of a de novo tumor).[49] Early studies with the adjuvant use of acyclic retinoids were promising,[50] with a decrease in the development of secondary tumors, but larger studies did not confirm a benefit.[51] 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,[52] yet it ultimately did not show any improvement in outcomes for the adjuvant treatment of HCC in randomized studies.[53] Resection of HCC with curative intent or ablation is associated with rates of recurrence at 5 years as high as 75%.[47] Therefore, there is a clear need for adjuvant systemic therapies.

EVIDENCE AND RATIONALE

The evidence profile is included in Supporting Table 5, which uses the data from a recent systematic review performed by Wang et al.[54] on adjuvant treatment for HCC after treatment. The systematic review by Wang et al. identified that adjuvant interferon 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.[55] 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,[56] 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.[57] 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.[58]

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 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, the anticipated wait time, and organ allocation policy. In the United States, 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.,[59] which is discussed below.

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.,[60] which is discussed below.

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 downstaging therapies before transplantation. There were no RCTs. Eighty-seven noncomparative trials were identified, and only two of these trials 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.[60] is a retrospective observational study of 114 patients with T1 HCC listed for liver transplantation at a single United States institution between 2004-2012 who were not treated with LRT. The median age was 60 years, with equal proportions in Child-Pugh class A (48%) and Child-Pugh class B/C (52%). The 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, six other patients (5.3%) progressed from T1 to beyond T2 at a median of 5.1 months from listing, and two 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.[59] reported on outcomes for 390 patients in Taiwan with T1 (n = 94) and T2 (n = 296) HCC who were eligible for transplantation but who were treated instead with LRT. Patients were treated with a number of different methods including RFA, percutaneous ethanol injection (PEI) or acetic acid injection, 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 slightly older age than the typical transplantation 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 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 with regard to a risk/benefit analysis.

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

Recommendations

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 LRT—such as TACE, yttrium-90 (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 due to 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 transplantation by way of MELD exception point allocation since February 2002. Although 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 with current practice.
4. Given that organ availability is variable, the practices for liver transplantation 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 posttransplantation (10%-15%).[61] Progression beyond the Milan criteria while awaiting transplantation eliminates

access to exception points, and thus, maintaining tumor burden within or below T2 while waiting for transplantation 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.[62-64] 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 of all studies that enrolled adults with cirrhosis awaiting liver transplantation and treated with bridging or downstaging therapies before transplantation. There were 18 comparative studies that 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 after liver transplantation. Among the comparative studies, one study enrolled only patients meeting Milan criteria, six enrolled patients both within and exceeding the Milan criteria, and two 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 (relative risk [RR], 0.32 and 0.38, respectively), but the difference did not reach statistical significance. Posttransplantation 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 patients treated with TACE + RFA and RFA alone with a markedly 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 with the present time and the relatively low risk of harm for the intervention compared with 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.[65] Furthermore, 3-year overall survival (OS) after liver transplantation has been reported to be significantly improved in patients with HCC who received LRT compared with those who did not using the Scientific Registry Transplant Recipients data: 76% versus 71% ($P = 0.03$).[66] The decision to bridge patients with HCC to transplantation 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.[67]

FUTURE RESEARCH

An 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 pretransplantation 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 DOWNSTAGING TO WITHIN MILAN CRITERIA?

Recommendation

8. The AASLD suggests that patients beyond the Milan criteria (T3) should be considered for liver transplantation after successful downstaging 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 downstaging cannot be determined based on the available data.
2. Currently, in the United States, 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 that 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 transplantation.
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. Although 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 United States, 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%-90%).[68] This variability is largely because of differences in tumor burden before 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 liver transplantation 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 transplantation. There were a total of 24 studies examined for outcomes associated with down-staging and transplantation; there were no RCTs. Only three of these studies compared down-staging of T3 tumors versus T2 tumors with no down-staging before liver transplantation, whereas 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 three comparative studies were limited to post–liver transplantation overall (1, 3, and 5 years) and recurrence-free survival (1 and 5 years). Down-staging of T3 patients compared with no therapy (in T2 patients) before liver transplantation was associated with similar overall and recurrence-free survival. The 5-year observed survival with down-staging had an RR of 1.17 (95% CI, 1.03-1.32), relative to no down-staging.

Heckman et al.[69] provided the only comparative yet nonrandomized United States study, which includes 123 patients undergoing transplantation between 2000 and 2006, spanning both pre- and post-MELD era patients. In this series, patients had a very short wait list time: 28 days in the 50 patients receiving LRT (TACE, Y90, RFA, or resection) before transplantation and 24 days in those without LRT before transplantation. 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 with the remaining patients in the LRT group, most of whom were stage T2 at the time of transplantation.

Hołówko et al.[70] present outcomes for patients reported to be beyond T2 treated with LRT, compared with those within T2 who were not treated with LRT, noting no difference in 5-year OS. The third comparative study was from Asia and consisted predominately of living donor liver transplantations, with down-staging

consisting mostly of TACE.[71] A total of 51 T3 patients were successfully down-staged radiographically to the Milan criteria and were compared with 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% versus 78.9%; RFS 90% versus 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 posttransplantataion among patients with HCC within Milan criteria. The number of studies that examined various individual modalities (including Y90, drug-eluting beads TACE [DEB-TACE], PEI, RFA, TACE, transarterial chemoinfusion [TACI], and TAE) were small, with a range of 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 who are not deemed liver transplant candidates for other reasons (e.g., advanced age or significant comorbidities), and thus the results of these studies may be affected by the inclusion of nontransplant candidates in whom LRT is palliative in its 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 before transplantation can only be determined if the many variables that can confound these analyses are standardized, and Parikh et al.[72] 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 Barcelona Clinic Liver Cancer stage, treatment details, and posttransplant details such as recurrence and survival.

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

Recommendations

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:
TACE: Moderate
Transarterial Bland Embolization: Very Low
TARE: Very Low
External Radiation: 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-Pugh class A and highly selected Child-Pugh class B. There are no data to support the use of LRT for patients with Child-Pugh class 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. RFA is another treatment strategy that may be used 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 used as a treatment strategy for HCC. The intent of this question was to review the existing evidence 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[73] comparing TACE with placebo identified seven RCTs on TACE versus placebo with a total of 545 patients, 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.[74] performed a more recent systematic review that questioned the beneficial effect of TACE. In this report, TACE or TAE were compared with 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 nine RCTs identified on the use of TACE (six RCTs) or TAE (three RCTs), published between 1990 and 2005, reporting on a total of 645 patients.[75-84] Compared with the meta-analysis by Llovet and Bruix, there were two additional RCTs included.[75,77] Of the nine 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 with placebo on survival (overall HR, 0.88; 95% CI, 0.71-1.10; $P = 0.27$), though the data from TACE were pooled with the data from TAE. The two trials with high risk of bias showed a significant effect (HR, 0.53; 95% CI, 0.34-0.83; $P = 0.005$). When all nine trials were analyzed together for overall mortality, no significant intervention effect (HR, 0.81; 95% CI, 0.64-1.02; $P = 0.07$) 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, 0.58-1.06; $P = 0.11$). The authors calculated the number of subjects required to be included in a meta-analysis to accept or reject an intervention effect at 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 DEB-TACE with conventional TACE treatment performed by Facciorusso et al.[85] identified four RCTs and eight observational trials. Nonsignificant trends were noted in 1-, 2-, and 3-year survival in favor of DEB-TACE compared with conventional TACE. Pooled analysis of objective response and of complications showed no difference between the two therapies.

Abdel-Rahman and Elsayed[86] performed a systematic review to determine the potential benefit of TARE using Y90 microsphere radioembolization. In this analysis, two RCTs were identified with a total of 64 patients. One of the trials compared TARE with TACE for intermediate-stage HCC, whereas 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.[87] trial for TARE versus TACE, there were a total of 28 patients included, with 13 patients treated with TARE and 15 treated with TACE. There were two patients in each arm who were successfully down-staged to either undergo liver transplantation (n = 3) or RFA (n = 1). Though the current data are too sparse to make an assessment of efficacy, the authors identified five ongoing trials, so additional data is anticipated in the near future. Importantly, a single-center RCT comparing TARE with TACE performed at a United States transplantation center has just been reported and has demonstrated longer time to progression for waitlisted patients with HCC receiving TARE compared with TACE.[88] 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 with TACE alone for T2 and T3 unresectable tumors and identified 19 RCTs that met this inclusion criterion.[89] This analysis included 1948 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 although the authors concluded that combination therapy appears to be beneficial compared with 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.[90] 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 whether RFA or PEI would be equivalent to external beam radiotherapy in combination with 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 CLASS A/B CIRRHOSIS AND ADVANCED HCC WITH MACROVASCULAR INVASION AND/OR METASTATIC DISEASE BE TREATED WITH SYSTEMIC THERAPY OR LRT OR NO THERAPY?

Recommendation

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

Quality/Certainty of Evidence: Moderate

Strength of Recommendation: Strong

Technical Remarks

1. It was not possible to make a recommendation for systemic therapy over LRT, because 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-Pugh class A cirrhosis, although studies were mixed and included some patients with Child-Pugh class B cirrhosis.

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 used, the prognosis remains poor.

The intent of this question was to review the existing evidence 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 class 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, four were RCTs, and the other 11 were observational studies. The four RCTs were not designed to compare the outcome of sorafenib with LRT 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 a randomized phase 3 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, which had 123 patients (41%) with macrovascular invasion. Additionally, in the sorafenib arm, 159 patients (53%) had extrahepatic disease versus the placebo arm, which 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 OS in the entire population included in the study (sorafenib, 10.7 months versus placebo, 7.9 months; HR, 0.69; 95% CI, 0.55-0.87) and demonstrated a trend for improvement both for patients with macrovascular invasion (sorafenib, 8.1 months versus placebo, 4.9 months; HR, 0.68; 95% CI, 0.49-0.93) and for patients with metastatic disease (sorafenib, 8.9 months versus placebo, 8.3 months; HR, 0.85; 95% CI, 0.64-1.15).[52,91]

Similarly, in the Asia-Pacific phase 3 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, 4.2 months; HR, 0.68; 95% CI, 0.50-0.93) and demonstrated a positive trend in both patients with macrovascular invasion (HR, 0.63; 95% CI, 0.39-1.03) and with metastatic disease to either lungs or lymph nodes (HR, 0.82; 95% CI, 0.57-1.18).[92,93]

The definitive benefits of sorafenib in advanced HCC with underlying Child-Pugh class B cirrhosis has not been clearly established, though an ongoing randomized phase 3 trial conducted in Italy is evaluating sorafenib versus placebo in patients with advanced HCC and underlying Child-Pugh B cirrhosis (NCT01405573). There have been four published phase 3 randomized trials comparing sorafenib versus either other targeted agents (sunitinib, brivanib, linifanib) or the combination of sorafenib with erlotinib.[92,94,95] Collectively, there were an additional 2001 patients enrolled in the sorafenib arm, with 688 patients with macrovascular invasion and 1220 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 (n = 196) with sorafenib (n = 66) in patients with advanced HCC with portal vein thrombosis (PVT).[96] The TACE/radiation group had longer median time to progression and OS than the chemoembolization alone and sorafenib groups ($P < 0.001$). In an observational retrospective study, Nakazawa et al.[97] compared the survival benefits of sorafenib versus radiation in patients with advanced HCC with PVT in the main trunk or its first branch. Of the 97 patients included, 40 received sorafenib and 57 received radiation. Median survival did not differ significantly between the sorafenib group (4.3 months) and the radiation group (5.9 months; $P = 0.115$). In another retrospective observational study, Song et al.[98] compared 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 PVT. The median OS was significantly longer in the HAIC group than in the sorafenib group (7.1 versus 5.5 months; $P = 0.011$).

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 3 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 3 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 to sorafenib (RTOG 1112) through a randomized phase 3 trial comparing sorafenib with or without stereotactic body radiation in patients with advanced HCC (NCT01730937). Phase 3 trials comparing lenvatinib or nivolumab with sorafenib are ongoing in an attempt to improve survival in patients who have advanced HCC with metastatic disease (NCT01761266 and NCT02576509).

Acknowledgment: This practice guideline was produced in tandem with three *de novo* systematic reviews that were written by the same writing group, including M. Hassan Murad, M.D., M.P.H., who participated in the selection of the clinical questions and provided expertise regarding the GRADE approach. The AASLD Practice Guidelines Committee approved the scope and directed the development of the practice guideline and provided the peer review. Members of the committee included Raphael B. Merriman, M.D., F.A.C.P., F.R.C.P.I. (Chair); Tram T. Tran, M.D. (Vice-Chair); Michael W. Fried, M.D., F.A.A.S.L.D. (Board Liaison); Jawad Ahmad, M.D., F.A.A.S.L.D.; Joseph Ahn, M.D.; Fredric Gordon, M.D., F.A.A.S.L.D.; Julie Heimbach, M.D.; Simon P. Horslen, M.D.; Christine Hsu, M.D.; Whitney E. Jackson, M.D.; Fasiha Kanwal, M.D., M.S.H.S.; Michael D. Leise, M.D.; Jacqueline G. O'Leary, M.D.; Michael L. Schilsky, M.D., F.A.A.S.L.D.; Amit Singal, M.D. (Committee Liaison); James R. Spivey, M.D.; R. Todd Stravitz, M.D., F.A.A.S.L.D.; Jayant A. Talwalkar, M.D., M.P.H., F.A.A.S.L.D.; Helen S. Te, M.D., F.A.A.S.L.D.; and Michael Volk, M.D.

REFERENCES

1) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
2) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. HEPATOLOGY 2011;53:1020-1022.
3) Choo SP, Tan WL, Goh BK, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer 2016;122:3430-3436.
4) Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. Int J Cancer 2016; 139:1534-1545.
5) Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 2016;34:1787-1794.
6) Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer 2016;122:1757-1765.
7) Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl. 1):S35-S50.
8) Kanwal F, Hoang T, Kramer JR, Asch SM, Goetz MB, Zeringue A, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology 2011;140:1182-1188.e1.
9) El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365:1118-1127.
10) Smith R. Screening fundamentals. J Natl Cancer Inst Monogr 2015;1997:15-19.
11) Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980;64:1263-1272.
12) Zhang B-H, Yang B-H, Tang Z-Y. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-422.
13) Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014;11: e1001624.
14) Chaiteerakij R, Addissie BD, Roberts LR. Update on biomarkers of hepatocellular carcinoma. Clin Gastroenterol Hepatol 2015;13: 237-245.
15) Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. Radiol Clin North Am 2009;47:827-831.
16) Tao SM, Wichmann JL, Schoepf UJ, Fuller SR, Lu GM, Zhang LJ. Contrast-induced nephropathy in CT: incidence, risk factors and strategies for prevention. Eur Radiol 2016;26:3310-3318.
17) Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. HEPATOLOGY 2008;47:97-104.
18) Jang H-J, Kim TK, Wilson SR. Small nodules (1–2ccm) in liver cirrhosis: characterization with contrast-enhanced ultrasound. Eur J Radiol 2009;72:418-424.
19) Leoni S, Piscaglia F, Golfieri R, Camaggi V, Vidili G, Pini P, et al. The impact of vascular and nonvascular findings on the noninvasive diagnosis of small hepatocellular carcinoma based on the EASL and AASLD criteria. Am J Gastroenterol 2010;105: 599-609.
20) Leoni S, Piscaglia F, Granito A, Borghi A, Galassi M, Marinelli S, et al. Characterization of primary and recurrent nodules in liver cirrhosis using contrast-enhanced ultrasound: which vascular criteria should be adopted? Ultraschall Med 2013;34:280-287.
21) Manini MA, Sangiovanni A, Fornari F, Piscaglia F, Biolato M, Fanigliulo L, et al. Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of hepatocellular carcinoma. J Hepatol 2014;60:995-1001.
22) Pompili M, Riccardi L, Semeraro S, Orefice R, Elia F, Barbaro B, et al. Contrast-enhanced ultrasound assessment of arterial vascularization of small nodules arising in the cirrhotic liver. Dig Liver Dis 2008;40:206-215.
23) Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 2010;59:638-644.
24) Shin SK, Kim YS, Choi SJ, Shim YS, Jung DH, Kwon OS, et al. Contrast-enhanced ultrasound for the differentiation of small atypical hepatocellular carcinomas from dysplastic nodules in cirrhosis. Dig Liver Dis 2015;47:775-782.

25) American College of Radiology. Liver imaging reporting and data system. 2016. doi: http://www.acr.org/quality-safety/resources/LIRADS. Accessed on December 1, 2016.
26) Organ Procurement and Transplantation Network 2016. http://optn.transplant.hrsa.gov/governance/policies.
27) Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007;33:437-447.
28) Khalili K, Kyoung Kim T, Jang H-J, Kochak Yazdi L, Guindi M, Sherman M. Indeterminate 1-2-cm nodules found on hepatocellular carcinoma surveillance: biopsy for all, some, or none? Hepatology 2011;54:2048-2054.
29) Holland AE, Hecht EM, Hahn WY, Kim DC, Babb JS, Lee VS, et al. Importance of small (≤20-mm) enhancing lesions seen only during the hepatic arterial phase at MR imaging of the cirrhotic liver: evaluation and comparison with whole explanted liver. Radiology 2005;237:938-944.
30) O'Malley ME, Takayama Y, Sherman M. Outcome of small (10-20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol 2005;100:1523-1528.
31) Byrnes V, Shi H, Kiryu S, Rofsky NM, Afdhal NH. The clinical outcome of small (<20 mm) arterially enhancing nodules on MRI in the cirrhotic liver. Am J Gastroenterol 2007;102:1654-1659.
32) Hwang SH, Yu J-S, Kim KW, Kim JH, Chung J-J. Small hypervascular enhancing lesions on arterial phase images of multiphase dynamic computed tomography in cirrhotic liver. J Comput AssistTomogr 2008;32:39-45.
33) Yu JS, Lee JH, Chung JJ, Kim JH, Kim KW. Small hypervascular hepatocellular carcinoma: limited value of portal and delayed phases on dynamic magnetic resonance imaging. Acta Radiologica 2008;49:735-743.
34) Kim YK, Lee YH, Kwak HS, Kim CS, Han YM. Clinical implication of small (<20 mm) enhancing hepatic nodules observed only during three-dimensional gadobenate dimeglumine-enhanced hepatic arterial-phase MRI of the hepatitis B virus-induced mild cirrhosis. Clin Imaging 2008;32:453-459.
35) Khan AS, Hussain HK, Johnson TD, Weadock WJ, Pelletier SJ, Marrero JA. Value of delayed hypointensity and delayed enhancing rim in magnetic resonance imaging diagnosis of small hepatocellular carcinoma in the cirrhotic liver. J Magn Reson Imaging 2010;32:360-366.
36) Kim TK, Lee KH, Jang HJ, Haider MA, Jacks LM, Menezes RJ, et al. Analysis of gadobenate dimeglumine–enhanced MR findings for characterizing small (1–2-cm) hepatic nodules in patients at high risk for hepatocellular carcinoma. Radiology 2011;259:730-738.
37) Rimola J, Forner A, Tremosini S, Reig M, Vilana R, Bianchi L, et al. Non-invasive diagnosis of hepatocellular carcinoma ≤2 cm in cirrhosis. Diagnostic accuracy assessing fat, capsule and signal intensity at dynamic MRI. J Hepatol 2012;56:1317-1323.
38) Tanabe M, Kanki A, Wolfson T, Costa EAC, Mamidipalli A, Ferreira MPFD, et al. Imaging outcomes of Liver Imaging Reporting and Data System version 2014 category 2, 3, and 4 observations detected at CT and MR imaging. Radiology 2016; 281:152173.
39) Darnell A, Forner A, Rimola J, Reig M, García-Criado Á, Ayuso C, et al. Liver Imaging Reporting and Data System with MR imaging: evaluation in nodules 20 mm or smaller detected in cirrhosis at screening US. Radiology 2015;275:698-707.
40) Sersté T, Barrau V, Ozenne V, Vullierme M-P, Bedossa P, Farges O, et al. Accuracy and disagreement of computed tomography and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy. Hepatology 2012;55:800-806.
41) Weis S, Franke A, Mössner J, Jakobsen JC, Schoppmeyer K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. Cochrane Database Syst Rev 2013:1-73.
42) Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252:903-912.
43) Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012;57:794-802.
44) Chen M-S, Li J-Q, Zheng Y, Guo R-P, Liang H-H, Zhang Y-Q, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321-328.
45) Liu H, Wang ZG, Fu SY, Li AJ, Pan ZY, Zhou WP, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg 2016;103:348-356.
46) Yin L, Li H, Li A-J, Lau WY, Pan Z-y, Lai ECH, et al. Partial hepatectomy vs transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: a RCT. J Hepatol 2014;61:82-88.
47) Pompili M, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. J Hepatol 2013;59:89-97.
48) Vincenzi B, Di Maio M, Silletta M, D'Onofrio L, Spoto C, Piccirillo MC, et al. Prognostic relevance of objective response according to EASL criteria and mRECIST criteria in hepatocellular carcinoma patients treated with loco-regional therapies: a literature-based meta-analysis. PLoS One 2015;10:e0133488.
49) Poon RT-P, Fan S-T, Ng IO-L, Lo C-M, Liu C-L, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-507.
50) Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. N Engl J Med 1996;334:1561-1567.
51) Okita K, Izumi N, Matsui O, Tanaka K, Kaneko S, Moriwaki H, et al. Peretinoin after curative therapy of hepatitis C-related hepatocellular carcinoma: a randomized double-blind placebo-controlled study. J Gastroenterol 2015;50:191-202.
52) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
53) Bruix J, Takayama T, Mazzaferro V, Chau G-Y, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344-1354.
54) Wang J, He XD, Yao N, Liang WJ, Zhang YC. A meta-analysis of adjuvant therapy after potentially curative treatment for hepatocellular carcinoma. Can J Gastroenterol 2013;27:351-363.
55) Zhuang L, Zeng X, Yang Z, Meng Z. Effect and safety of interferon for hepatocellular carcinoma: a systematic review and meta-analysis. PLoS One 2013;8:e61361.

56) Chen K, Ou TM, Hsu CW, Horng CT, Lee CC, Tsai YY, et al. Current systemic treatment of hepatocellular carcinoma: a review of the literature. World J Hepatol 2015;7:1412-1420.
57) Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-733.
58) Hsiang JC, Wong GL-H, Tse Y-K, Wong VW-S, Yip TC-F, Chan HL-Y. Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: a propensity score landmark analysis. J Hepatol 2015;63:1190-1197.
59) Huo T-I, Huang Y-H, Su C-W, Lin H-C, Chiang J-H, Chiou Y-Y, et al. Validation of the HCC-MELD for dropout probability in patients with small hepatocellular carcinoma undergoing locoregional therapy. Clin Transplant 2008;22:469-475.
60) Mehta N, Sarkar M, Dodge JL, Fidelman N, Roberts JP, Yao FY. Intention to treat outcome of T1 hepatocellular carcinoma with the "wait and not ablate" approach until meeting T2 criteria for liver transplant listing. Liver Transpl 2016;22:178-187.
61) Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-700.
62) Llovet JM, Bruix J, Fuster J, Castells A, Garcia-Valdecasas JC, Grande L, et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. HEPATOLOGY 1998;27:1572-1577.
63) Bismuth H, Majno P, Adam R. Liver transplantation for hepatocellular carcinoma. Semin Liver Dis 1999;19:311-322.
64) Yao F, Bass NM, Nikolai B, Merriman R, Davern TJ, Kerlan R, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. Liver Transplant 2003;9:684-692.
65) Park S-J, Freise CE, Hirose R, Kerlan RK, Yao FY, Roberts JP, et al. Risk factors for liver transplant waitlist dropout in patients with hepatocellular carcinoma. Clin Transplant 2012;26:E359-E364.
66) Freeman RB Jr, Steffick DE, Guidinger MK, Farmer DG, Berg CL, Merion RM. Liver and intestine transplantation in the United States, 1997-2006. Am J Transplant 2008;8:958-976.
67) Clavien P-A, Lesurtel M, Bossuyt PMM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11-e22.
68) Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. J Hepatol 2010:52: 930-936.
69) Heckman JT, deVera MB, Marsh JW, Fontes P, Amesur NB, Holloway SE, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol 2008;15:3169-3177.
70) Hołówko W, Wróblewski T, Wojtaszek M, Grąt M, Kobryń K, Ziarkiewicz-Wróblewska B, et al. Transarterial chemoembolization prior to liver transplantation in patients with hepatocellular carcinoma. Ann Transplant 2015;20:764-768.
71) Kim PTW, Onaca N, Chinnakotla S, Davis GL, Jennings LW, McKenna GJ, et al. Tumor biology and pre-transplant locoregional treatments determine outcomes in patients with T3 hepatocellular carcinoma undergoing liver transplantation. Clin Transplant 2013;27:311-318.
72) Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transplant 2015;21:1142-1152.
73) Llovet J, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. HEPATOLOGY 2003;37:429-442.
74) Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev 2011:1-60.
75) Akamatsu M, Yoshida H, Obi S, Sato S, Koike Y, Fujishima T, et al. Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial. Liver Int 2004;24:625-629.
76) Bruix J, Llovet JM, Castells A, Montañá X, Brú C, Ayuso MDC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. HEPATOLOGY 1998;27:1578-1583.
77) Doffoël M, Bonnetain F, Bouché O, Vetter D, Abergel A, Fratté S, et al. Multicentre randomised phase III trial comparing Tamoxifen alone or with transarterial lipiodol chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402). Eur J Cancer 2008;44:528-538.
78) Groupe Francophone d'Etude et de Traitement du Carcinome Hepatocellulaire. Treatment of unresectable hepatocellular carcinoma (HCC) by lipiodol-targeted transcatheter arterial chemoembolization (TACE). A multicenter randomized trial. HEPATOLOGY 1993;18:A58.
79) Li Q, Wang J, Sun Y, Cui YL, Juzi JT, Qian BY, et al. Postoperative transhepatic arterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma: a randomized study with 131 cases. Dig Surg 2006;23:235-240.
80) Lo C, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. HEPATOLOGY 2002;35:1164-1171.
81) Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990;11:181-184.
82) Pelletier G, Ducreux M, Gay F, Luboinski M, Hagège H, Thong D, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol 1998;29:129-134.
83) Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-1739.
84) Llovet J, Real MI, Vilana R, Planas R, Coll S, Aponte J, et al. Chemoembolization improves survival in patients with unresectable hepatocellular carcinoma (HCC). J Hepatol 2001;34:11.
85) Facciorusso A, Licinio R, Muscatiello N, Di Leo A, Barone M. Transarterial chemoembolization: evidences from the literature and applications in hepatocellular carcinoma patients. World J Hepatol 2015;7:2009-2019.
86) Abdel-Rahman OM, Elsayed Z. Yttrium-90 microsphere radioembolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev 2016:1-31.
87) Kolligs FT, Bilbao JI, Jakobs T, Iñarrairaegui M, Nagel JM, Rodriguez M, et al. Pilot randomized trial of selective internal radiation therapy vs chemoembolization in unresectable hepatocellular carcinoma. Liver Int 2015;35:1715-1721.
88) Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151:1155-1163.e2.

89) Fu Y, Zhao X, Yun Q, Zhu X, Zhu Y, Li Q, et al. Transarterial chemoembolization (TACE) plus percutaneous ethanol injection (PEI) for the treatment of unresectable hepatocellular carcinoma: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015;8:10388-10400.
90) Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma. JAMA Oncol 2015;1:756.
91) Bruix J, Raoul J-L, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-829.
92) Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
93) Cheng A-L, Guan Z, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia–Pacific trial. Eur J Cancer 2012;48:1452-1465.
94) Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2014;33:172-179.
95) Zhu AX, Rosmorduc O, Evans TRJ, Ross PJ, Santoro A, Carrilho FJ, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2014;33:559-566.
96) Kim G-A, Shim JH, Yoon SM, Jung J, Kim JH, Ryu M-H, et al. Comparison of chemoembolization with and without radiation therapy and sorafenib for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. J Vasc Interv Radiol 2015;26:320-329.e6.
97) Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J, et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol 2014;14:84.
98) Song DS, Song MJ, Bae SH, Chung WJ, Jang JY, Kim YS, et al. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol 2015;50:445-454.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29086/suppinfo.