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Aasld practice guidelines

AASLD develops evidence-based practice guidelines and practice guidances which are updated regularly by a multi-disciplinary panel of experts, including hepatologists, and include recommendations of preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. Alcohol-associated liver disease (ALD) represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcoholic hepatitis (AH), alcohol-associated cirrhosis (AC), and acute AH presenting as acute-on-chronic liver failure. ALD is a major cause of liver disease worldwide, both on its own and as a co-factor in the progression of chronic viral hepatitis, nonalcoholic fatty liver disease (NAFLD), iron overload, and other liver diseases. ALD develops through several stages, beginning with hepatic steatosis, and, in some individuals, gradually progressing through AH (the histological correlate of which is alcoholic steatohepatitis), culminating in cirrhosis. Progression through these various stages is dependent on continued heavy alcohol use and other risk factors, including female sex, genetic susceptibility, diet, and comorbid liver disease. ALD carries a significant stigma in society. It is increasingly recognized by providers that patients and their families seek to reduce the stigma of ALD, and a change from the term “alcoholic” to “alcohol-associated” will help; thus, alcohol-associated liver disease, alcohol-associated steatohepatitis, and alcohol-associated cirrhosis are suggested, retaining the familiar abbreviations (ALD, ASH, and AC, respectively). Due to longstanding usage, the term “alcoholic hepatitis” will likely persist. Diagnosis and Treatment of Alcohol-Associated Liver Disease Patient Guideline As a library, NLM provides access to scientific literature. Inclusion in an NLM database does not imply endorsement of, or agreement with, the contents by NLM or the National Institutes of Health. Learn more: PMC Disclaimer | PMC Copyright Notice . Author manuscript; available in PMC: 2024 Dec 1. This guidance document provides an updated approach to the prevention, diagnosis, and treatment of hepatocellular carcinoma (HCC). The prior American Association for the Study of Liver Diseases (AASLD) HCC guidance document was updated at this time to reflect clinically significant changes to approaches in several of these areas. Notable examples of these updates include recommendations for use of ultrasound and alpha fetoprotein (AFP) for HCC surveillance, expanded indications for surgical therapies, incorporation of immune checkpoint inhibitor (ICI) therapy for first-line systemic therapy, and explicit recommendations for multidisciplinary care and advance care planning (ACP). This guidance on HCC was developed with the support and oversight of the AASLD Practice Guidelines Committee. AASLD guidelines are supported by systematic reviews of the literature, formal ratings of evidence quality and strength of recommendations, and, if appropriate, meta-analysis of results using the Grading of Recommendations Assessment Development and Evaluation system. In contrast, this document was developed by consensus of a multidisciplinary expert panel and provides guidance statements based on formal review and analysis of the literature on the topics and questions related to the prevention, diagnosis, and treatment of HCC. Although the literature review for this document is comprehensive and unbiased, the lack of mandatory systematic reviews facilitated more rapid publication. The expert panel rated the level of evidence for each recommendation based on the Oxford Center for Evidence-Based Medicine.[1] Additionally, the panel categorized the strength of recommendations based on the level of evidence, risk–benefit ratio, and patient preferences. Primary liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths—both worldwide and in the United States as of 2020.[2] HCC is the most common type of primary liver cancer, accounting for 75% – 86% of cases.[3] Men are affected approximately two to three times more than women, with higher incidence and mortality across most countries.[4] There are also notable racial and ethnic disparities in HCC, with a disproportionate burden of disease affecting American Indian, Hispanic, and Black persons more than non-Hispanic White persons.[5] In the United States, HCC incidence and mortality rates increased from 1970 to 2010, but incidence began to decrease in 2011, and mortality plateaued in 2013, with one study showing a subsequent ~3% decrease per year.[6] This improvement is likely related to changing demographics and risk factors for HCC as well as advances in prevention, early detection, and treatment. The strongest risk factor for developing HCC is cirrhosis from any liver disease etiology, which is present in over 80% of patients with HCC.[7] Patients with cirrhosis from any etiology typically have a ~2% annual risk of developing HCC.[8] Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain the predominant etiologic risk factors in many parts of the world, although the proportion of patients with HCC with HBV or HCV infection is declining in areas with dedicated viral hepatitis elimination programs (Figure 1).[10] For example, universal newborn HBV vaccination programs in Asia are associated with significant decreases in HCC incidence.[11] Areas without robust viral hepatitis elimination programs continue to have a disproportionately high burden of HBV-associated HCC. For example, HCC develops at substantially younger ages (median age 46 y) in Sub-Saharan Africa because of vertical transmission, and projections suggest HCC incidence will double by 2040.[12,13] This age disparity persists in people who are HBV-infected and emigrate elsewhere, such that more than one third of persons from Africa who develop HCC are diagnosed before age 40 years.[14] Antiviral therapy for HBV and HCV also significantly reduces HCC risk, although patients with cirrhosis (and possibly those with advanced fibrosis) continue to have persistent risk of developing HCC. Accordingly, viral hepatitis-related HCC has plateaued in most of the developed world, including the United States. Worldwide incidence of HCC and most common risk factors. ASR, age standardized incidence rate; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; Reprinted with permission from Llovet et al. [9] and the International Agency for Research on Cancer/World Health Organization.In parallel, alcohol and NAFLD-related HCC have increased in both incidence and mortality,[6] highlighting a need for public policies targeting these emerging risk factors to promote continued declines in HCC incidence. Alcohol-associated cirrhosis is a known risk factor for HCC development, and alcohol use as a cofactor with other etiologies increases HCC risk as much as 5-fold.[15] NAFLD has become a significant public health concern, related to significant increases in the prevalence of obesity and metabolic syndrome,[16] and is currently the fastest growing cause of HCC in liver transplant (LT) candidates.[17] NAFLD has also become the leading cause of HCC in the absence of cirrhosis, with approximately one-fourth to one-third of NAFLD-related HCC occurring in the absence of cirrhosis; however, further data are still needed to identify which patients with noncirrhotic NAFLD have sufficient risk to warrant HCC surveillance.[18–21] A long list of other cofactors can increase or decrease individual HCC risk in at-risk patients with chronic liver disease, and combinations of risk factors are often synergistic rather than additive. Lifestyle factors, such as alcohol and tobacco use, increase risk of many cancers, including HCC.[15] Smoking is associated with a 20%–86% increased risk of HCC, which can return nearly to baseline after 30 years of smoking cessation.[22] Obesity is associated with a 1.5–4.5 times higher risk of HCC and contributes to nearly 10% of HCC worldwide.[23–25] Similarly, metabolic syndrome components, including diabetes, nearly double HCC risk in the absence of overweight/obesity.[26–28] In the United States, state-level HCC incidence has a moderate correlation with regional obesity and lack of physical activity, suggesting a possible benefit of public policy interventions.[29] Although no studies have demonstrated that weight loss significantly reduces HCC risk, this intervention has known beneficial effects on NAFLD activity and fibrosis, so it should be recommended in patients with overweight or obesity and chronic liver disease.[30] Physical activity also likely has beneficial effects in primary HCC prevention, as well as after cancer diagnosis, beyond the confounding effect of weight loss.[23] Dietary exposure to aflatoxin B1 and aristolochic acid are known cofactors for HCC in patients with HBV infection.[31,32] Ideally, risk assessment would move beyond broad population-based estimates and instead assess individual-level risk based on specific patient characteristics. This is particularly important in populations with unclear benefits of HCC surveillance but large within-group variation in HCC risk, such as post–sustained virological response (SVR) patients with advanced fibrosis or those with noncirrhotic NAFLD. Multiple risk scores have been developed in patients with cirrhosis, using clinical features and/or laboratory data to risk stratify patients; however, most require validation in large populations and further refinement.[33–35] There are also several risk stratification models in patients with HBV, although fewer have been validated in Western populations in the setting of antiviral therapy. One model that has been more widely validated is the PAGE-B score, composed of sex, age, and platelets, with scores ≤ 9, 10–17, and ≥ 18 equating to low, intermediate, and high risk of HCC, respectively.[36] Thus far, it is unclear which risk scores, if any, are adequately accurate, and none are currently recommended for regular use in routine practice. Antiviral treatment significantly decreases HCC risk in patients with and without cirrhosis from HBV or HCV infection and remains one of the most effective methods of primary prevention for HCC (Figure 2).[37] HBV vaccination has also been shown to significantly reduce HCC risk, so this should be performed in all newborns as well as high-risk adults who failed to undergo vaccination at birth. Efforts to develop an HCV vaccine are ongoing, but one does not exist at this time. Proven and emerging primary prevention strategies for hepatocellular carcinoma. Abbreviations: AFP, alpha fetoprotein; GALAD, Gender, Age, AFP-L3%, AFP, and DCP model; HBV, hepatitis B virus; HCV, hepatitis C virus. 1Included in guidance statements given more favorable risk-benefit ratio compared with other potential strategies.Other chemoprevention measures in at-risk patients, particularly those with nonviral etiologies of liver disease, remain an area of significant need. A meta-analysis of case-control and cohort studies demonstrated that at least one cup of coffee consumption is dose-dependently associated with a significant reduction in HCC risk.[38] Decaffeinated coffee appears to have similar benefits, although to a lesser magnitude.[39] Given the relatively low risks associated with coffee intake, and multiple studies suggesting possible benefits, coffee consumption may be recommended in patients with chronic liver disease. However, it remains unclear what preparation and quantity of coffee is most beneficial, and patients should be cautioned against additives such as cream and sugar. Medications, including aspirin and statins, also have potential chemoprevention effects (Figure 2). Studies from Sweden and the United States demonstrated a 43%–60% reduction in HCC risk with aspirin use exceeding 5 years.[40,41] Similarly, meta-analyses found statin use may be associated with reduced HCC risk, with a relative risk of 0.54, regardless of underlying disease.[42,43] The type of statin may be important, with one study showing a potential benefit from lipophilic but not hydrophilic statins.[44] Lastly, antidiabetic medications, including metformin, have been explored as HCC chemoprevention agents; however, data have been conflicting.[45,46] Although supporting data for aspirin, statins, and metformin are similar to that of coffee—that is, observational data with risk of confounding—these medications have higher potential risks of toxicity and adverse events (AEs). Therefore, these medications are not currently recommended for HCC chemoprevention alone but can be considered in patients with relevant indications for their use. Notably, statins need not be avoided by patients with chronic liver disease, including those with cirrhosis. Ongoing prospective trials are anticipated to provide further insights into their roles in patients with cirrhosis, including for potential chemoprevention. HCC surveillance should be performed in at-risk individuals, including subsets with chronic HBV infection or those with cirrhosis from any etiology (Table 1). Among these broader populations, surveillance should be targeted to those who would be potentially eligible for curative treatment that can improve survival. Two of the most important factors to consider are the severity of the underlying liver disease and presence of comorbid conditions (Figure 4). In contrast, there are few data showing a difference in surveillance benefit by patient demographics, including age, sex, race, or ethnicity. Surveillance is associated with improved survival in patients with Child-Turcotte-Pugh A or B cirrhosis but has no benefit in most patients with Child-Turcotte-Pugh C cirrhosis—outside of liver transplantation—given the high competing risk of liver-related mortality.[47] Therefore, patients with Child-Turcotte-Pugh C cirrhosis on the LT list should undergo regular surveillance because early-stage HCC can lead to higher priority on the transplant waitlist and larger tumor burden may preclude liver transplantation; however, surveillance should not be performed in those with Child-Turcotte-Pugh C cirrhosis who are not eligible for transplantation. Similarly, AASLD recommends against surveillance in patients with life-limiting comorbid conditions (life expectancy less than 1–2 y) that cannot be remedied by liver transplantation or other directed therapies. At-risk population for surveillance Population group Incidence of HCC Sufficient risk to warrant surveillance Child-Pugh A-B cirrhosis, any etiology ≥ 1.0% per year   Hepatitis B   Hepatitis C (viremic or post-SVR)   Alcohol associated cirrhosis   Nonalcoholic steatohepatitis   Other etiologies Child-Pugh C cirrhosis, transplant candidate Non-cirrhotic chronic hepatitis B ≥ 0.2% per year   Man from endemic countrya   age > 40 y   Woman from endemic countrya   age > 50 y   Person from Africa at earlier ageb   Family history of HCC   PAGE-B score > 10c Insufficient risk and in need of risk stratification models/biomarkers   Hepatitis C and stage 3 fibrosis < 0.2% per year   Noncirrhotic NAFLD Overall value of hepatocellular carcinoma (HCC) surveillance is determined by balance of benefits and harms.Two of the most common etiologies of liver disease leading to HCC in contemporary cohorts from North America and Europe are eradicated HCV and NAFLD.[48,49] Although the target population has been unchanged for years, there are some populations with evolving data informing the value of HCC surveillance: (A) patients with HCV cirrhosis after SVR, (B) patients with noncirrhotic HCV after SVR, and (C) patients with noncirrhotic NAFLD. As a framework, recent modeling studies have questioned the annual HCC incidence required for surveillance to be cost-effective, with recent studies suggesting a threshold of approximately 1.0% for initiating surveillance in patients with cirrhosis—lower than the traditional threshold of 1.5% per year.[50,51] Available data demonstrate patients with HCV cirrhosis remain at an increased HCC risk for up to 10 years after SVR, so surveillance should be continued indefinitely unless future data demonstrate sufficiently reduced HCC incidence.[52] HCC incidence is significantly lower in post-SVR patients without cirrhosis, and surveillance is not cost-effective or recommended in this population.[53] Patients with noncirrhotic NAFLD have posed a dilemma for surveillance programs because nearly one fourth of NAFLD-related HCC occurs in the absence of cirrhosis; however, these patients have a very low annual HCC incidence of 0.008 per 100 person-years, so surveillance is not cost-effective in this population.[20,54] Patients with HCV and NAFLD without cirrhosis, particularly those with advanced fibrosis, would benefit from risk stratification tools to identify those at highest risk to whom surveillance could be targeted in the future. In the interim, surveillance may be considered in select patients with advanced fibrosis on a case-by-case basis, particularly for those in whom there is clinical suspicion for understaging of fibrosis by noninvasive markers or biopsy. The highest quality data for HCC surveillance come from a large randomized controlled trial (RCT) in patients with HBV infection, in which surveillance significantly improved clinical outcomes, including reduced HCC mortality (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.41–0.98) (Figure 3).[55] Prior attempts at an RCT comparing surveillance with no surveillance in patients with cirrhosis failed given poor enrollment, so there are no similar Level 1 data in patients with cirrhosis.[57] Meta-analyses of cohort studies demonstrate surveillance is associated with improved early detection, curative treatment, and improved survival (Figure 3).[56,58,59] These studies have several potential limitations, including lead time bias, length time bias, risk of overdiagnosis, and residual confounding, although the benefits of surveillance remained in studies that statistically accounted for these biases.[60,61] Data supporting benefits of hepatocellular carcinoma (HCC) surveillance. HCC surveillance has been shown to significantly reduce HCC-related mortality in a randomized controlled trial among patients with chronic HBV infection (left panel) and in several cohort studies among patients with cirrhosis from any etiology (right panel). Reprinted with permission from Zhang et al.[55] and Singal et al.[56]The overall value of HCC surveillance programs must balance surveillance benefits against potential physical, financial, and psychological harms (Figure 4). To date, few data exist on surveillance harms, including few data quantifying psychological or financial harms.[62,63] Available data suggest HCC surveillance harms that are due to false positives and indeterminate tests occur in ~10% of patients with cirrhosis and most harms are mild in severity.[56] Therefore, the benefit of HCC surveillance appears to outweigh potential harms. bdominal ultrasound has been the cornerstone of surveillance testing for over 20 years, although it is highly operator dependent and has worse performance in patients with obesity.[64–67] The incremental benefit of adding AFP has long been debated. A meta-analysis of available data showed the sensitivity and specificity of ultrasound alone for early-stage HCC detection is only 53% (95% CI, 35%–70%) and 91% (95% CI, 86%–94%), respectively,[68] whereas ultrasound plus AFP achieves a sensitivity of 63% for early-stage HCC (95% CI, 48%–75%). Although a small decrease in specificity offsets this increased sensitivity, the diagnostic odds ratio of the combination was higher than ultrasound alone. A cost-effective analysis comparing the strategies found ultra-sound plus AFP was the most cost-effective approach.[50] Therefore, AASLD recommends HCC surveillance using a combination of liver ultrasound and AFP. Several promising biomarkers are being evaluated for HCC surveillance, although most are in early phases of evaluation and still require validation in large Phase III and Phase IV biomarker cohort studies (Table 2).[69–74] Two well-studied biomarkers include the Lens culinaris lectin binding subfraction of the AFP, or AFP-L3%, which measures a subfraction of AFP,[75] and des gamma carboxy prothrombin (DCP), also called protein induced by vitamin K absence/antagonist-II (PIVKA-II), a variant of prothrombin that is also specifically produced at high levels by a proportion of HCCs.[76,77] These biomarkers are currently Food and Drug Administration (FDA) approved for risk stratification but not HCC surveillance in the United States. AFP-L3% and DCP have insufficient sensitivity to detect early-stage HCC when used alone; however, these biomarkers may be complimentary to AFP, underscoring the potential of biomarker panels to improve surveillance test performance. A biomarker panel incorporating patient gender, age, AFP-L3%, AFP, and DCP (GALAD) levels achieved sensitivities of 60%–80% for early HCC detection in a multinational case-control study.[78] GALAD was subsequently evaluated in a large Phase III biomarker study, the Hepatocellular carcinoma Early Detection Strategy (HEDS) study, in which it was found to have a sensitivity and specificity of 65% and 82% for HCC, respectively[79] There has also been interest in use of liquid biopsy (e.g., circulating tumor DNA [ctDNA]) for early HCC detection, with multicenter case-control studies demonstrating encouraging accuracy of methylated DNA marker panels, although available data are too premature to recommend routine use in clinical practice.[70,80] Status of surveillance tests for the early detection of hepatocellular carcinoma Test Early detection research network (EDRN) phase of validation Performance characteristics US plus AFP[55] 5 Sensitivity 61% Specificity 92% AFP-L3%[69] 3 Sensitivity 62% Specificity 90% dcp [69] 3 Sensitivity 40% Specificity 81% Multitarget algorithm[70] 2 Sensitivity 82% Specificity 87% galad [71] 2/3 Sensitivity 54–72% Specificity 90% Doylestown plus[72] 2/3 Sensitivity 90% Specificity 95% Although there are emerging data for computed tomography (CT)- and magnetic resonance imaging (MRI)–based surveillance, the AASLD does not recommend routine use of these modalities in at-risk patients. Cohort studies from South Korea demonstrated that both two-phase CT and hepatobiliary contrast-enhanced MRI have superior sensitivity for early-stage HCC detection compared with US-based surveillance (83% and 86% vs. 28%–29%, respectively).[81,82] However, neither have been validated in cohorts of Western patients without HBV. Further, CT-based surveillance is limited by concerns about radiation and contrast exposure, particularly if repeated semiannually. MRI is not hampered by these same concerns, but questions have been raised about radiology service capacity, patient acceptance, and cost-effectiveness. Although a decision analysis suggested MRI-based surveillance may be cost-effective in select populations, there were large variations in the incremental cost-effectiveness ratio based on HCC incidence, costs, and cirrhosis etiology.[83] To potentially reduce cost, abbreviated MRI examination protocols with shorter in-scanner time are being tested and have achieved encouraging sensitivities and specificities of 80%–90% and 91%–98%, respectively, in small cohort studies.[84,85] Early data suggest MRI-based surveillance may have poorer performance in patients with Child-Turcotte-Pugh B or C cirrhosis, so this may be a population in which blood-based biomarkers are particularly important.[86] Ongoing studies may clarify the most appropriate niche for cost-effective and safe use of CT- or MRI-based surveillance, perhaps in patients in whom ultrasound performs least reliably, such as those with truncal obesity or marked parenchymal heterogeneity. HCC surveillance should be performed at semiannual (approximately every 6 months) intervals. This recommendation was initially based on HCC tumor doubling time,[87,88] although subsequent analyses demonstrated semiannual surveillance is associated with earlier tumor stage and improved survival compared with annual surveillance after adjusting for lead time bias (40.3 vs. 30 mo, p = 0.03).[89] A subsequent multicenter RCT demonstrated quarterly surveillance did not improve early HCC detection or survival compared with semiannual surveillance.[90] Several studies have demonstrated underutilization of surveillance, even among patients followed by hepatology subspecialists, because of patient and provider barriers.[91–93] Several models of organized surveillance programs have been proposed to improve surveillance implementation. Outreach efforts using mailed surveillance invitations as well as “in-reach” efforts, such as electronic medical record reminders and provider education, have been shown to significantly improve surveillance utilization.[91,94,95] The AASLD recommends use of these evidence-based interventions to increase surveillance utilization in clinical practice. Recall procedures for subsequent surveillance or diagnostic testing in patients undergoing HCC surveillance are based on ultrasound visualization, presence of liver lesions, and AFP levels (Figure 5). Patients with adequate sonographic visualization (Liver Imaging Reporting and Data System [LI-RADS] visualization score A), no liver lesion (US LI-RADS 1, US-1), and normal AFP levels should continue to be observed with semi-annual surveillance using ultrasound and AFP.[96] Patients with a subcentimeter liver lesion on ultrasound (US-2) can be safely observed with repeat short-interval surveillance using ultrasound and AFP in 3–6 months given a low risk of HCC, suboptimal performance of CT or MRI to accurately diagnose HCC in lesions 90%[115] in patients with HBV infection and PAGE-B score ≥ 10 (i.e., intermediate to high risk of HCC).[116] Applicability of Liver Reporting and Data System (LI-RADS) in surveillance populations. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGE-B score, platelet, age, and gender-hepatitis B score.The probability of HCC and recommended management strategies differ by LI-RADS category (Figure 8). Multiple studies, including meta-analyses, demonstrate that LR-5 lesions have a 95%–99% probability of being HCC.[108,117–120] Conversely, HCC probability is ~75% for LR-4 lesions, so these patients are advised to undergo biopsy or close-interval follow-up imaging at 3 months, depending on the clinical scenario.[120,121] Given several factors that should be considered in these circumstances, AASLD advises multidisciplinary discussion to determine optimal follow-up for patients with LR-4 observations. LR-3 observations have a ~30% probability of HCC, so AASLD advises continued surveillance with repeat CT or MRI in 3–6 months.[122,123] LR-M observations have radiological features suggesting malignancy; 93%–100% of cases are malignant on tissue sampling, but only 29%–44% are HCC.[106,108,120,123–125] Among LR-M cases, rim APHE suggests non-HCC malignancy.[124] Therefore, biopsy should be performed for patients with LR-M observations. Similarly, the positive predictive value of LR-TIV for being HCC is lower, and biopsy is recommended in those patients. Risk of hepatocellular carcinoma (HCC) and recommended management strategy. Abbreviations: CT, computed tomography; LR, LI-RADS; MRI, magnetic resonance imaging. Pathological diagnosis of HCC should be obtained for liver nodules in patients without cirrhosis or without HBV infection because LI-RADS criteria are not applicable to this population. With the advent of molecular therapies and precision oncology, AASLD also advises performing biopsies in the setting of clinical trials for all LR-4–5 lesions, and this practice can be considered by multi-disciplinary teams even outside clinical trials to confirm diagnosis and enable molecular analyses, as endorsed by a recent AASLD consensus conference.[126] Although no biomarker has yet been linked to treatment-related clinical benefit, except for AFP levels ≥ 400 ng/ml and ramucirumab in advanced HCC,[127] systematic collection of histological specimens can facilitate precision treatment initiatives. Aside from diagnostic purposes, HCC biopsies can be informative of molecular and immune classes of HCC,[9] oncogenic mutations associated with immune excluded phenotypes,[128] and gene signatures predictive of response to immunotherapy.[129] Even if in few circumstances, histology can capture mixed HCC-cholangiocarcinoma among LR-5 cases, a feature with significant clinical implications. Pathological diagnosis of HCC should be based on the definitions of the International Consensus Group for Hepatocellular Neoplasia.[130] This group proposed major histologic features of HCC, which include stromal invasion, increased cell density, intratumoral portal tracts, unpaired arteries, pseudoglandular pattern, and diffuse fatty changes. Biopsies should be assessed by an expert hepatopathologist, and use of special stains may help resolve diagnostic uncertainties. Positive staining in two of four markers (glypican 3 [GPC3], glutamine synthetase, heat shock protein 70 [HSP70], and clathrin heavy chain) is highly specific for HCC.[131,132] Additional staining can be considered to detect progenitor cell features (K19 and epithelial cellular adhesion molecule) or neovascularization (CD34).[133,134] Sensitivity of liver biopsy ranges between 70% and 93% for most tumors but has been reported as low as ~60% in tumors < 2 cm.[97,135–137] A negative biopsy does not eliminate the possibility of HCC, and a second biopsy is recommended when findings are inconclusive, particularly if tumor growth or change in enhancement pattern are identified during follow-up but the lesion is still not categorized as LR-5.[97] Risk of complications after liver biopsy, such as tumor seeding and bleeding, has been reported to be ~3%, although this has substantially decreased with coaxial needle technique.[138] AFP, at a threshold of 400 ng/ml, was previously recommended as a diagnostic criterion for HCC, although over 40% of HCC have normal AFP levels, and elevated AFP levels can be observed in other cancers, including intrahepatic cholangiocarcinoma, gastric cancer, and germ cell tumors.[139] Given insufficient accuracy, AFP is no longer recommended for HCC diagnosis.[135,140] Therefore, patients with non-characteristic imaging are advised to undergo biopsy, independent of AFP level. Liquid biopsy entails the analysis of tumor components released by cancer cells, including circulating tumor cells, ctDNA, and extracellular vesicles. Several ctDNA-based tests are currently approved by the FDA in oncology.[141] Alterations in ctDNA, ctDNA methylation profiles,[142] and extracellular RNA signatures from exosomes[143,144] have been explored in case-control studies for early detection and diagnosis. These findings still require validation in Phase III–IV biomarker cohort studies, and until then, AASLD advises against the diagnosis of HCC based on biomarkers or liquid biopsy. All patients with HCC should undergo high-quality multiphase CT or contrast-enhanced MRI for assessment of tumor extent. Patients, particularly those with tumors ≥ 2 cm, are also advised to have a noncontrast chest CT to assess for lung metastases as part of initial tumor staging. Fluorodeoxyglucose PET CT is not recommended as part of staging given the low sensitivity of only 50%–65%.[145] Similarly, routine staging with CT of the pelvis or technetium-99m methylene diphosphonate bone scans is not cost-effective but can be considered in patients with AFP > 1000 ng/ml, macrovascular invasion, or multifocal bilobar disease to assess for asymptomatic bone metastases.[146] AASLD advises review of staging imaging studies by a multidisciplinary tumor board with an expert diagnostic radiologist (see Multidisciplinary Care). Information for tumor staging, including the degree of tumor burden, degree of liver dysfunction, and performance status should be documented for all patients at the time of HCC diagnosis prior to making treatment recommendations. Despite its use in staging other solid tumors, the tumor-node-metastasis classification, based solely on tumor burden, is of less utility in HCC. There are multiple proposed staging systems for HCC including the Barcelona Liver Clinic Cancer (BCLC), Italian Liver Cancer, Hong Kong Liver Cancer (HKLC), and Chinese Liver Cancer systems, but none are universally accepted. The BCLC staging system is most commonly applied and remains the staging system recommended by the AASLD given its incorporation of liver dysfunction and Eastern Cooperative Oncology Group performance status (ECOG PS) into staging assessments, external validation in multiple cohorts, and ease of use in clinical practice.[147] The BCLC staging system, initially created in 1999, is a dynamic classification that stratifies patients according to prognostic stages and provides evidence-based actualized treatment allocation.[148] The BCLC system classifies tumors as very early stage (Stage 0) followed by Stages A–D, with Stage D referring to terminal stage. The BCLC was updated in 2022 (Figure 9) to refine prognostication by highlighting the benefit of using objective scores, such as Model for End-Stage Liver Disease (MELD) and albumin-bilirubin (ALBI) score to assess liver dysfunction as well as biomarkers, including AFP levels.[149] It also recognizes the heterogeneity among patients with BCLC Stage B and incorporates concepts of downstaging and stage migration over time. Additionally, the BCLC update underscores the importance of personalized decision-making on a case-by-case basis by an expert multidisciplinary group. Updated Barcelona Clinic Liver Cancer Staging System 2022. Abbreviations: AFP, alpha fetoprotein; ALBI, albumin-bilirubin; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; HCC, hepatocellular carcinoma; LT, liver transplant; MELD, Model for End-Stage Liver Disease; TACE, transarterial chemoembolization. Reprinted with permission from Reig et al.[147]Given heterogeneity within BCLC stages, other staging systems have been proposed for more accurate prognostication, although these have typically been more complex in nature and are not as widely validated. For example, the Italian Liver Cancer (ITA.LI.CA) system subclassifies patients with BCLC Stage B into Stages B1, B2, and B3 to account for heterogeneity within patients with BCLC Stage B.[150] The HKLC system initially had nine stages, which were condensed to five stages to allow more nuanced stratification in intermediate- and advanced-stage HCC.[151] Both of these staging systems have been externally validated in HBV-HCC populations but have few data in North American populations. Treatment options for patients with HCC include surgical, locoregional, and systemic therapies, depending on tumor burden, degree of liver dysfunction, and patient performance status. Although decisions for some patients are well delineated by guidelines, with widespread consensus among providers, other patients are eligible for multiple therapies, with decisions requiring input from different specialties. A growing number of trials evaluating combination therapies and transitions between types of therapies during follow-up—related to tumor progression or response—also highlight the importance of close collaboration and communication between disciplines. Accordingly, multidisciplinary care is critical for HCC management, with a goal to review clinical data to verify HCC diagnosis and staging, facilitate provider communication, determine optimal treatments, and thereby improve clinical outcomes. This process extends beyond initial HCC presentation and continues over time as treatment strategies evolve based on changes in HCC tumor burden and patient status. Multidisciplinary care most commonly occurs in the form of a tumor board, in which providers review imaging with radiology and discuss management among a broad base of consultants. Presentation at a multidisciplinary tumor board can change imaging and histological interpretation in 18.4% and 10.9% of patients, respectively, with management plans altered in 41.7% of all patients.[152] Core disciplines typically include but are not limited to hepatologists; radiologists; pathologists; interventional radiologists; transplant and hepatobiliary surgeons; and medical, radiation, and surgical oncologists. Essential to the discussion are nurses, nurse navigators, case managers/care coordinators, social workers, and palliative care providers. Some centers have transitioned to an interactive multidisciplinary team structure, such as a fluid referral system, in which patients are seen sequentially by specialists from different disciplines as needed, or co-located clinics, in which patients are seen concurrently by multiple specialties in a single visit.[153] Multidisciplinary care for patients with HCC significantly increases patient satisfaction, improves timely guideline concordant care, and increases overall survival (OS), highlighting this approach as a best practice that should be considered standard of care for the management of patients with HCC.[154] A single-center study showed a multidisciplinary co-located clinic paired with a multidisciplinary tumor board increased receipt of curative treatment, decreased time to treatment, and improved stage-by-stage survival.[155] Similarly, a multicenter study from the national Veterans Affairs health system found multi-specialty evaluation was associated with higher likelihood of receiving HCC therapy, and review by a multidisciplinary tumor board was associated with reduced mortality.[156] Based on these data, patients with HCC should be discussed and managed in a multidisciplinary care setting. Surgical resection is the curative treatment of choice for patients with localized HCC in the absence of cirrhosis. Noncirrhotic HCC has historically accounted for only ~10% of cases in the Western world, although up to 30% of NAFLD-related HCC develop in the absence of cirrhosis.[157,158] Patients without cirrhosis have lower postoperative liver-related morbidity, lower cumulative HCC recurrence rates, and higher disease-specific survival compared with those with underlying cirrhosis who undergo resection.[159] Although comorbidities associated with NASH may prevent potentially curative therapies in a higher proportion of patients compared with viral-related HCC, outcomes are similar among those who undergo resection.[160] Despite higher rates of perioperative complications (post-hepatectomy liver failure, prolonged length of hospitalization) and morbidity, a meta-analysis of nine studies comparing outcomes of curative therapy in NAFLD and non-NAFLD HCC reported improved disease-free and OS after liver resection in patients with NAFLD HCC.[161] Although there are significant limitations in these retrospective studies, including selection bias and heterogeneity in the populations, current evidence suggests that acceptable postresection outcomes can be achieved in well-selected patients with NAFLD HCC. In patients with HCC and underlying liver cirrhosis, recommendations for surgical resection must consider a multidimensional assessment of tumor characteristics and nontumor factors, such as degree of liver dysfunction. From an oncologic perspective, tumor number,[162,163] anatomic location, presence of vascular invasion, and planned extent of hepatectomy[164,165] are important determinants of feasibility for surgical resection. Of equal importance is an assessment of the anticipated future liver remnant (FLR) size,[166] underlying liver dysfunction, and presence of clinically significant portal hypertension (CSPH). Balancing oncologic outcomes and potential postoperative liver decompensation requires experienced, multidisciplinary team assessment to optimize outcomes (Figure 10). Although numerous algorithms incorporating tumor size, extent of resection, and measures of liver dysfunction have been proposed to predict postresection outcomes,[164,167] most data support surgical resection of a single lesion in a patient with compensated cirrhosis without CSPH and an adequate FLR (typically > 30% in the absence of cirrhosis and > 40% in patients with cirrhosis).[168] In these patients, surgical resection affords 5-year survival exceeding 70% and postoperative mortality of < 3%. Although larger tumor size has been associated with increased risk of recurrence, eligibility for resection is not restricted by tumor size, provided the FLR is sufficient. Algorithm for surgical treatment of early-stage hepatocellular carcinoma (HCC). Abbreviations: CTP, Child-Turcotte-Pugh; UNOS-DS, United Network for Organ Sharing Down-Staging. 1In non-liver transplant (LT) candidate, can consider surgical resection if >1 lesion in the same lobe. 2In non-LT candidate, can consider minor surgical resection if CTP score B7 and/or mild portal hyper-tension. 3E.g., varices, splenomegaly, platelets < 100 × 109/L, hepatic venous pressure gradient >10 mmHg. 4Living donor liver transplant can be considered on a case-by-case basis for patients beyond UNOS-DS criteria. 5Eligible for Model for End-Stage Liver Disease exception without 6-month wait period.The most widely utilized assessment of liver reserve remains the Child-Turcotte-Pugh score, with surgical resection reserved to those with Child-Turcotte-Pugh class A cirrhosis.[169] The presence of CSPH, defined as a hepatic venous pressure gradient ≥ 10 mmHg, is associated with post-hepatectomy liver failure[170] and can be directly measured by calculating the difference between the free and wedged hepatic venous pressures. Because this may not routinely be measured, lack of ascites, portosystemic varices, and platelet count > 100,000 per microliter are useful surrogates in clinical practice indicating the absence of CSPH. Other measures including the MELD score or MELD including sodium (MELD-Na), ALBI score,[171] indocyanine green kinetics,[172] and liver stiffness measurement by transient elastography[173] are associated with risk of postresection hepatic decompensation and may also be used to refine patient selection. An assessment of the FLR is easily made with contrast-enhanced CT or magnetic resonance volumetric imaging, allowing for precise measurements of the liver volume that is expected to remain behind. If there are concerns regarding the adequacy of the FLR, preoperative portal vein embolization can increase the size of the contralateral hepatic lobe to allow for safer resection.[174] Transarterial radioembolization (TARE) with Yttrium-90 has recently been established as an acceptable treatment for solitary unresectable HCC,[175] and there are increasing data for its utilization to enhance FLR[176] and allow for surgical resection.[177] Other emerging methods to augment the FLR and allow surgical resection, such as associating liver partition and portal vein ligation for staged hepatectomy[178,179] and liver venous deprivation with portal vein and hepatic vein embolization,[180] are under investigation. Minimally invasive surgical (MIS) approaches, including laparoscopy and robotic assisted hepatectomy, may be appropriate in well-selected patients with HCC.[181] Although many centers commonly perform limited minor resections in anatomically favorable locations (Segments 2, 3, 5, and 6) using MIS techniques,[182] major hepatectomy via an MIS approach should only be performed in high-volume, experienced centers.[183] For HCC, MIS approaches may permit safer surgery because of decreased physiologic disruption, leading to lower risk of postoperative complications.[184] Thus, MIS approaches may extend resectability criteria, allowing patients with mild portal hypertension to safely undergo minor liver resection (Figure 10).[185,186] Although surgical resection for HCC is mainly limited to BCLC Stage 0/A HCC, data support the role of surgical resection in select patients with multifocal HCC beyond BCLC Stage A criteria (Figure 10). A meta-analysis of 18 studies comparing surgical resection with transarterial chemoembolization (TACE) reported a significant survival advantage for surgical resection in BCLC Stage B HCC (HR, 0.56; 95% CI, 0.35–0.90).[187] Similarly, a Western multicenter study also reported a 52.8% 5-year survival in multinodular HCC beyond Milan criteria.[188] Resection of patients with HCC with macrovascular portal vein tumor thrombus (PVTT) is more controversial because these patients have higher risk of metastatic disease and are typically recommended to undergo systemic therapy. Although most data for hepatic resection in PVTT comes from Asia,[189,190] limited available data from Western centers support the role of surgical resection in selected patients,[191,192] particularly in subsegmental (Vp1) and segmental (Vp2), in which meaningful long-term survival has been reported.[193] With significant improvement in systemic therapy for advanced-stage disease, future studies are necessary to best define which subpopulation of patients with multifocal disease or PVTT may benefit from surgical resection. While awaiting these data, extended indications for surgical resection should only be performed in high-volume centers after multidisciplinary discussion. The risk of recurrence following surgical resection remains high, approaching 50%–70% at 5 years, with the highest risk in the first year after resection.[162,194] Factors associated with recurrence include older age; male sex; degree of liver dysfunction; and tumor size, number, and grade/differentiation; microvascular and macrovascular invasion; presence of satellite lesions; and AFP level. Given the higher HCC risk than those without prior HCC, patients should undergo surveillance following surgical resection with cross-sectional imaging of the abdomen and chest plus serum AFP every 3–6 months. The optimal timing and duration of surveillance after surgical resection is unknown, although AASLD recommends indefinite surveillance. Although risk prediction models to stratify individualized risk of postsurgical resection have been proposed,[195,196] current evidence does not support a survival benefit of more frequent surveillance.[197] There is a need for effective (neo)adjuvant therapy to reduce risk of HCC recurrence after surgical resection. In HCV-associated HCC, two large multicenter studies from North America[198] and Italy[199] confirmed that eradication of HCV with direct-acting antiviral therapy does not increase risk of HCC recurrence and improves survival. Preoperative TACE in patients with large resectable HCC does not improve recurrence-free survival and may increase risk of interval tumor progression, precluding surgical resectability.[200] Current data do not support use of neoadjuvant systemic therapies in patients with HCC undergoing surgical resection outside of a clinical trial, although recent data have demonstrated benefit of adjuvant therapy in patients at high risk of recurrence. An RCT of adjuvant sorafenib in patients with HCC undergoing resection or thermal ablation did not improve recurrence-free survival in patients compared with placebo (HR, 0.94; 95% CI, 0.78–1.13).[201] The open-label phase III RCT comparing atezolizumab plus bevacizumab versus active surveillance (IMbrave 050) in the adjuvant setting for HCC patients at high-risk of recurrence after resection or local ablation was the first to demonstrate positive results.[202] High-risk features for resection patients included tumor size > 5 cm, more than 3 tumors, microvascular or macrovascular invasion, and poor tumor differentiation. Patients randomized to atezolizumab plus bevacizumab were started on therapy within 12 weeks of the surgery and treated for 12 months unless the patient experienced disease recurrence or dose-limiting toxicity. After a median follow-up of 17.4 months, the trial hit its primary endpoint for superiority of recurrence-free survival (RFS 0.72, 95%CI 0.56 – 0.93), with 12-month recurrence-free survival estimates of 78% versus 65% for the intervention and surveillance arms, respectively. The median duration of treatment for atezolizumab plus bevacizumab was 11 months, with 34.9% of patients experiencing grade 3–4 treatment related adverse events. Data evaluating overall survival (a secondary endpoint) were immature at the interim analysis and continued follow-up is ongoing. The optimal management of patients with recurrence during or after adjuvant therapy is currently unclear, so recommendations are based on extrapolation of prior data and expert opinion (Figure 11). Although salvage transplantation has been recommended for patients with post-surgical recurrence within Milan Criteria, it is possible that tumor biology and post-transplant outcomes may be worse in patients with recurrence after adjuvant therapy. Therefore, a period of observation on the transplant list may be beneficial to assess tumor biology despite eligibility for immediate MELD exception points. Patients with liver-localized recurrence beyond Milan Criteria can be treated with liver directed therapy, with consideration of liver transplantation in those who are successfully downstaged. Patients with vascular invasion, extrahepatic spread, or TACE unsuitable disease should be considered for systemic therapy, although choice of systemic therapy would likely depend on timing of recurrence. Patients who recur during or shortly after adjuvant therapy would be regarded as having a failure of atezolizumab plus bevacizumab and would be best treated with alternative systemic therapy options. Alternatively, in those with late recurrence, i.e., at least greater than 6 months after discontinuation of atezolizumab plus bevacizumab, reinitiating atezolizumab plus bevacizumab or starting alternative first-line systemic treatment options may be considered. Management of patients with recurrence during or after adjuvant therapy. 1High-risk features include tumor size > 5 cm, more than 3 tumors, microvascular or macrovascular invasion, and poor tumor differentiation.Recent proof-of-principle studies utilizing neoadjuvant systemic therapies prior to surgical resection have been reported, and there are several ongoing adjuvant and neoadjuvant phase II–III RCTs. In a single-arm phase Ib study, neoadjuvant cabozantinib plus nivolumab in 15 patients with borderline resectable HCC allowed for margin-negative resection in 80% of patients, with 42% having a major pathologic response.[203] In another single-center phase II study of neoadjuvant nivolumab with or without ipilimumab, 6 (30%) of 20 patients who underwent resection had a major pathologic response.[204] AASLD advises against the use of neoadjuvant systemic therapies in patients undergoing liver resection outside of a clinical trial setting. For patients with early-stage HCC who are ineligible for resection because of liver dysfunction or tumor multi-focality, LT is an optimal treatment strategy because it provides a cure for both HCC and the underlying liver disease. LT is also associated with a median survival of 10 years and a significantly lower risk of recurrent cancer compared with resection or ablation (5-year incidence: ~10% vs. 50%–60%).[205] The Milan criteria (one lesion between 1 and 5 cm or two to three lesions between 1 and 3 cm) has been well established as the standard for optimal patient selection.[206] Based on the excellent observed outcomes in patients with HCC within the Milan criteria, proposals for patients with larger tumor burden have been developed including the University of California, San Francisco (UCSF) criteria (81% 5-year survival), total tumor volume cutoff of 115 cm (75% 4-year survival), up to seven criteria (71% 5-year survival), extended Toronto criteria (68% 5-year survival), and Kyoto criteria (65% 5-year survival) (Table 3).[207–211] Proposed expanded criteria for liver transplantation and associated outcomes Examples of expanded criteriaa Post-transplant survival UCSF criteria[207] One tumor ≤ 6.5 cm or 2–3 tumors, each ≤ 4.5 cm, with total tumor volume ≤ 8 cm 81% 5-year survival Total tumor volume < 115 cm[208] Sum of volume for each tumor ≤ 115 cm3 75% 4-year survival Up-to-seven criteria[209] Diameter or largest tumor (cm) + number of tumors ≤ 7 71% 5-year survival Extended Toronto criteria[210] Biopsy demonstrating well-to-moderate differentiation for patients beyond Milan criteria and ECOG performance status 0–1 68% 5-year survival Kyoto criteria[211] Number or tumors ≤ 10, maximum diameter of each tumor ≤ 5 cm, and serum DCP ≤ 400 mAU/ml 65% 5-year survival The main barrier to LT is a shortage of available liver allografts compared with demand, prompting an allocation system that directs access to deceased donor organs for patients both with and without HCC. In the United States, the allocation system is based on the sickest-first principle and utilizes MELD-Na to rank candidates with decompensated cirrhosis according to risk of death on the waiting list. Access to LT for patients with HCC continues to evolve in terms of priority access (Figure 12). Currently, patients within Milan criteria or downstaged to within Milan criteria from United Network for Organ Sharing (UNOS) downstaging criteria (UNOSDS: one lesion 5.1–8 cm; two to three lesions < 5 cm; and four to five lesions 3 cm, each lesion ≤ 5 cm, and a total diameter of all lesions ≤ 8 cm; or four or five lesions each < 3 cm, and a total diameter of all lesions ≤ 8 cm; AFP levels ≥ 1000 ng/mL are required to show a reduction in AFP level to < 500 ng/mL before liver transplantation. (Boxes shaded in gray denote historical policies; boxes in white reflect current policy.).Since 2012, there have been stringent HCC imaging criteria to receive MELD exception points for LT. Arterial phase hyperenhancing lesions ≥ 2 cm were designated as Organ Procurement and Transplant Network (OPTN) class 5 (consistent with HCC) if they exhibited venous or delayed phase washout or peripheral rim enhancement on delayed phase, whereas arterial phase enhancing lesions between 1 and 2 cm required washout and peripheral rim enhancement or threshold growth. Changes adopted to LI-RADS in 2018 created alignment of LR-5 with OPTN class 5 for lesions ≥ 2 cm; however, lesions between 1 and 2 cm with APHE and venous or delayed phase washout now meet the definition of LR-5 but not OPTN-5, so a proposed OPTN revision is under consideration to allow for alignment of such lesions (i.e., OPTN class 5).[216] Notably, patients will still be required to have UNOS T2 HCC (e.g., unifocal lesion ≥ 2 cm or two synchronous lesions 500 ng/ml in patients who had prior AFP ≥ 1000 ng/ml Timing of liver transplant in relation to downstaging There should be a minimum observation period of 3 mo of disease stability from successful downstaging to liver transplant Per current UNOS policy, the patient must remain within Milan criteria for 6 mo after successful downstaging before receiving MELD exception points To allow a pathway for MELD exception in patients with unresectable Stage T1 HCC (single lesion 100 ng/ml) are more likely to have rapid tumor growth and progress to beyond Milan criteria during an observation period[88,244] and therefore immediate LRT may be considered. Patients with a T1 HCC who are not eligible for LT or would not otherwise need LT (e.g., compensated cirrhosis) should undergo immediate treatment given the lower risk of microvascular invasion and recurrence in tumors 0.3 cm per month increase in tumor diameter. Worldwide, nearly all LT

selection criteria now include markers of tumor biology in addition to tumor size and number. Elevated AFP levels, as low as >20 ng/ml, have been consistently associated with increased post-LT recurrence.[245,246] Both the Metroticket 2.0[247] and French AFP models[248] demonstrated that a combination of AFP and tumor burden predicts post-LT outcome better than tumor burden alone. Additionally, patients with an elevated AFP who have a biochemical response to LRT have significantly improved post-LT outcomes compared with AFP nonresponders.[249,250] As noted above, candidates with an AFP ≥ 1000 ng/ml in the United States are not eligible for MELD exception points until AFP decreases to below 500 ng/ml with LRT. Additional serum biomarker cutoffs associated with high-risk explant pathology and worse post-LT outcome include AFP-L3 ≥15%, des-γ carboxyprothrombin (DCP) ≥ 7.5 ng/ml, and neutrophil-to-lymphocyte ratio (NLR) ≥ 5,[48–51] although these thresholds have not yet been validated. Even with adherence to the Milan criteria, HCC recurs post-LT in 10%–15%[246,251,252] and is the most common cause of death in this population. HCC recurrence after LT typically carries a poor prognosis with 3 cm compared with smaller tumors,[270,271] although some studies suggest efficacy may be improved by combining ablation with TACE in these cases.[272–274] Use of CEUS after ablation to assess for any viable disease and enable retreatment as needed can optimize complete response.[275] Adverse effects after thermal ablation are rare but can include pain, fever, bleeding, abscess, and pleural effusion.[276] As detailed above, the IMbrave 050 phase III RCT recently demonstrated superior recurrence-free survival using atezolizumab plus bevacizumab in the adjuvant setting for HCC patients at high-risk of recurrence after surgical resection or local ablation. High-risk features for patients undergoing ablation in this trial included tumor size > 2 cm but ≤ 5 cm and multifocal HCC.[202] Selective TARE or radiation segmentectomy is defined as the administration of an ablative dose of Y90 microspheres to a single angiographic hepatic segment or two adjacent angiographic segments. Radiation segmentectomy can be performed for subcapsular tumors in anatomic locations that may be challenging for ablation, such as subdiaphragmatic and peri-cardiac tumors and is also effective at treating microsatellites. Radiation segmentectomy can provide durable local tumor control, significantly prolong time to progression (TTP), and serve as an effective bridging therapy to liver transplantation (see TARE). In patients who are not amenable to thermal ablation, EBRT, including proton beam therapy (PBT) and stereotactic body radiation therapy (SBRT) delivered in five or fewer sessions, is another method of achieving durable local control. In contrast to ablation, EBRT can be used for central tumors and for tumors adjacent to vascular structures, with no age or absolute size limits (although most data are for HCC < 8 cm). EBRT should be avoided in patients with significant liver dysfunction (e.g., Child-Turcotte-Pugh score ≥ 8, uncontrolled ascites, or uncontrolled hepatic encephalopathy) given the risk of radiation-induced liver injury. HCC adjacent to stomach or bowel is also not well suited for EBRT given risk of ulceration.[277] EBRT has mostly been studied in single-arm studies. Propensity-matched analyses show similar if not higher local tumor control compared with thermal ablation, particularly for lesions >2 cm in maximum diameter; however, studies comparing survival have been discordant.[278] A phase III noninferiority RCT comparing PBT and radiofrequency ablation among patients with recurrent/residual HCC demonstrated noninferior 2-year local progression-free survival (PFS: 92.8% vs. 83.2%, respectively) and a lower proportion of patients with increased Child-Turcotte-Pugh score following PBT versus ablation (7.5% vs. 19.6%, respectively).[279] EBRT has also been used as a bridge to liver transplantation, with high observed response rates and comparable dropout rates with thermal ablation or TACE.[280] The RTOG1112 Trial reported higher survival with SBRT followed by sorafenib compared to sorafenib alone in patients with locally advanced HCC, although this difference did not reach statistical significance (15.8 vs. 12.3 mo; 1-sided p = 0.055).[281] The trial was prematurely terminated given changes in preferred first-line systemic therapy and may have been underpowered. TACE is the primary treatment option for patients with BCLC Stage B HCC.[282,283] TACE leverages the arterial blood supply of HCC, compared with portal venous blood flow to the background liver, and can be performed with lipiodol (conventional TACE) or drug-eluting beads (DEB-TACE). Meta-analyses of RCTs comparing TACE and best supportive care demonstrate significant improvements in OS among patients with BCLC Stage B HCC,[284] leading to adoption of TACE in management guidelines. A systematic review of 101 articles evaluating outcomes of conventional TACE reported ORRs of 52.5% (95% CI, 43.6%–61.5%) and median survival of 19.4 (95% CI, 16.2–22.6) months.[285] Patients who achieve objective response by modified response evaluation criteria in solid tumors (mRECIST) have prolonged survival compared with those without response (HR, 0.39; 95% CI, 0.26–0.619).[286] The most common AEs were liver enzyme abnormalities (18.1%), fever (17.2%), bone marrow toxicity (13.5%), pain (11%), and vomiting (6%), although mortality was low at 0.6%. RCTs comparing conventional and DEB-TACE methods show similar responses and safety profiles and have not consistently identified one approach as superior.[287–289] Patient selection and vascular selectivity are critical factors to optimize TACE outcomes. TACE should be performed using selective catheterization of segmental or distal branches, with c-arm CT when possible to ensure localization. This approach maximizes delivery of therapy to the tumor(s) to maximize chance of response and minimizes ischemic injury to noncancerous background liver. Patient selection for TACE eligibility must carefully consider degree of liver dysfunction and tumor burden to minimize risk of toxicity. Patients with significant liver dysfunction, PVTT, or large intrahepatic tumor burden have a lower chance of achieving objective responses and have a higher risk of hepatic decompensation after TACE, so these patients may be considered TACE unsuitable (Table 5); however, established cutoffs for liver dysfunction or tumor burden have not been well defined.[147] Several prognostic scoring systems have been proposed (e.g., beyond UNOS-DS, 6-and-12 model, or beyond up-to-7 criteria) based on factors including tumor number, tumor size, ALBI score, and AFP levels; however, further validation is needed to identify the subset of patients who are TACE unsuitable.[290–292] Patients considered unsuitable for TACE may be better treated with systemic therapy, particularly considering improved responses and survival reported in the advanced-stage setting.[293] Baseline factors that contribute to unsuitability for TACE Proposed factors for TACE unsuitability Tumor size Beyond UNOS-DS criteria Tumor appearance Multinodular, bilobar, with > 50% liver involvement Infiltrative or nodular with poorly defined margins Tumor marker Marked AFP elevationsa PVTT Large vessel vascular invasion, e.g., main PVTT or hepatic vein tumor thrombus Liver function ALBI 2–3, especially if tumor exceeds segmental treatment zone Deteriorating liver function over time Proposed factors for Y90 unsuitability Lung shunt >25 Gray in a single treatment>30 Gray cumulative in multiple treatments Nontarget treatment Infusion zone includes gastric/duodenal branches unable to correct with embolization PVTT Large vessel vascular invasion, e.g., main PVTT/Vp4 or hepatic vein tumor thrombusInability to deliver boosted dose and/or lack of uptake in the PVTT on 99mTc macroaggregated albumin scan Liver function ALBI 2–3, especially if tumor exceeds segmental treatment zone Deteriorating liver function over time Several trials comparing TACE alone versus TACE with multikinase inhibitors (mTKIs) failed to show significant improvements in PFS or OS.[294–298] Based on current data, the AASLD advises against combination therapy outside of clinical trials. However, several ongoing phase II and phase III RCTs are examining the potential benefit of immunotherapy with intra-arterial therapy, and if positive, these findings would alter clinical practice. TARE can be used an accepted alternative intra-arterial therapy for intermediate-stage HCC.[299,300] In a small single-center RCT, Y90 glass microspheres produced significantly prolonged TTP, but similar OS, compared with TACE.[299] TARE using Y90 was granted FDA approval in 2021 based on results of the LEGACY Trial,[175] a single-arm retrospective analysis of 162 patients with Child-Turcotte-Pugh A cirrhosis and solitary HCC up to 8 cm (median size 2.7 cm). TARE produced an ORR of 88.3% (mRECIST, best response) and duration of response (DoR) ≥ 6 months in 76.1% (localized mRECIST) using a radiation segmentectomy approach. Another single-center study in solitary lesions not amenable to radiofrequency ablation showed an ORR of 100%; 90% of patients had a sustained complete response after a single treatment.[301] The choice of intra-arterial therapy has largely been driven by center expertise and availability. An interim analysis of the TRACE trial, a phase II RCT comparing Y90 glass microspheres and DEB-TACE among 72 patients with BCLC A-B reported improved TTP (17.1 vs. 9.5 months, respectively; HR, 0.36; 95% CI, 0.18–0.70; mRECIST) and OS (median 30.2 vs. 15.6 months, respectively; HR, 0.48; 95% CI, 0.28–0.82) with TARE and comparable safety profiles between the two therapies.[302] This trial was terminated early after the interim analysis demonstrated the primary endpoint of TTP was met. The TRACE trial and earlier RCTs comparing Y90 and TACE employed standard dosimetry to calculate the radiation dose delivered to the targeted tumor, which results in inferior results compared with personalized dosimetry with the goal of > 205 Gy to the targeted area.[303] In the DOSISPHERE-01 trial, patients with unresectable HCC randomized to the personalized dosimetry arm had significantly improved objective responses (76.6% vs. 22.2%), downstaging to surgical treatments (35% vs. 3.5%) and survival (median 26.6 vs. 10.7 mo) compared with standard dosimetry.[304] Therefore, future trials evaluating Y90 and comparing with other treatment modalities should incorporate personalized dosimetry. Downstaging to Milan criteria is a viable option in intermediate HCC for patients who are otherwise transplant eligible.[240] Attempts to downstage with a goal of transplantation must be weighted with the probability of success using locoregional therapy. Considerations include tumor burden, liver function, AFP level, and ability to treat selectively. In the case of Y90, an additional consideration is the goal of a boosted dose to the tumor (>205 Gy) without excessive radiation delivery to surrounding nontumorous tissue, in doing so minimizing the chances of inducing liver dysfunction.[304] Such decisions should be made in the context of a multidisciplinary tumor board.[155] Patients treated with TACE should undergo multiphase CT or contrast-enhanced MRI approximately 6 weeks after treatment, whereas those treated with TARE or EBRT should undergo imaging to assess response approximately 12 weeks after treatment (Figure 14). Repeat treatment is provided on demand in those with continued viable disease, whereas repeat imaging every 3–6 months is recommended in those without definite viable disease. Patients who achieve objective responses to TACE for at least 6 months but then have local progression are likely to respond to additional locoregional therapy.[305] In contrast, patients who fail to have initial treatment response or have observed progression after one to two TACE/TARE sessions should be considered TACE/TARE refractory (Table 6) and alternative treatments, including systemic therapy, should be considered.[306–308] Radiologic assessment of treatment response and recall strategy. Abbreviations: AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; PS, performance status; TACE, transarterial chemoembolization. Factors suggesting TACE or TARE-refractory HCC TACE or TARE refractoriness Lack of objective response: > 50% definite viable disease after 2 TACE treatments or 1 TARE treatment Development of new HCC within treatment zone after 2 consecutive TACE Lack of improvement for tumor markers (e.g., AFP) after 2 consecutive TACE or 1 TARE Stage migration to advanced HCC, including new vascular invasion or extrahepatic metastases Response evaluation criteria in solid tumors (RECIST) v1.1 is the standard tool to measure response and progression in oncology.[309] mRECIST criteria has been proposed to adapt RECIST criteria to particularities of HCC, enabling capture of antitumoral response without observed shrinkage after local and systemic therapies.[310,311] mRECIST has become the standard tool to assess radiological response after locoregional therapy for patients with early and intermediate stages of HCC, whereas both RECIST 1.1 and mRECIST are recommended for patients with advanced-stage HCC undergoing systemic therapy.[311] Systemic therapy is currently reserved for patients with unresectable HCC who are not suitable for locoregional therapy, including patients with advanced-stage HCC (BCLC Stage C), some patients with intermediate-stage HCC (BCLC Stage B), and those who have disease progression despite locoregional therapy. In clinical practice, systemic therapy can be administered by hepatologists or oncologists depending on available expertise locally; however, treatment decisions and administration are best performed in a multidisciplinary manner given the interplay between liver and tumor factors. Approved systemic therapies broadly fall into two groups: (1) antiangiogenic targeted therapies and (2) ICIs. Antiangiogenic targeted therapies include the mTKIs (sorafenib, lenvatinib, cabozantinib, regorafenib) and monoclonal antiangiogenic antibodies (ramucirumab and bevacizumab). ICIs currently include inhibitors of programmed death 1 (PD1) (pembrolizumab and nivolumab) or its ligand (PD-L1) (durvalumab and atezolizumab), and cytotoxic T lymphocyte–associated protein 4 (CTLA4) inhibitors (tremelimumab and ipilimumab) (Figure 15). As discussed below, the efficacy of these therapies has primarily been evaluated in select populations including those with preserved liver function (Child-Turcotte-Pugh A) and good performance status. Although each of these agents has a distinct AE profile (Tables 7 and 8), the mTKIs have an AE profile most commonly characterized by hand-foot skin reaction, diarrhea, fatigue, and weight loss. Hemorrhage, proteinuria, hypertension, thromboembolism, and gastrointestinal (GI) perforation are possible side effects of both antiangiogenic mTKIs and antiangiogenic antibodies. ICIs are often well tolerated but can be associated with immune-related AEs (irAEs) that can involve any organ system. The risks of irAEs are higher when two ICIs are used together, as with the combination of ipilimumab plus nivolumab. Given this risk, ICIs are not recommended in patients with moderate to severe autoimmune disease, and AASLD advises against use of ICIs in posttransplant patients given high risk of graft loss and mortality. Timeline of systemic therapies for hepatocellular carcinoma (HCC) and resultant survival. (First line therapies are above the timeline; second line therapies are below the timeline.) 1KEYNOTE 224 was a non-randomized phase 2 trial. Phase 3 studies of pembrolizumab versus sorafenib have had conflicting results, with improved median OS noted in an Asian population. Summary efficacy data for selected first line phase III randomized controlled trials compared with sorafenib Aspect IMbrave150[312] himalaya[323] reflect[313] Study drugs Atezolizumab + bevacizumab Sorafenib Durvalumab + tremelimumab Durvalumab Sorafenib Lenvatinib Sorafenib Median OS, months (95% CI) 19.2 (17.0–23.7) 13.4 (11.4–16.9) 16.4 (14.2–19.6) 16.6 (14.1–19.1) 13.8 (12.3–16.1) 13.6 (12.1–14.9) 12.3 (10.4–13.9) HR for death (95% CI) 0.66 (0.52–0.85) Durvalumab + tremelimumab vs. sorafenib: 0.78 (0.65–0.92) Durvalumab vs. sorafenib: 0.86 (0.73–1.03) 0.92 (0.79–1.06) Median PFS, months (95% CI) 6.8 (5.7–8.3) 4.3 (4.0–5.6) 3.8 (3.7–5.3) 3.7 (3.2–3.8) 4.1 (3.8–5.5) 7.3 (5.6–7.5) 3.6 (3.6–3.9) ORR by RECIST 1.1 29.8 11.3 20.1 17.0 5.1 18.8 6.5 Common AEsa Hypertension (30%), fatigue (20%), proteinuria (20%), AST increase (20%), pruritis (20%), diarrhea (19%) Diarrhea (49%), PPE (48%), hypertension (24%), decreased appetite (24%), fatigue (19%), AST increase (17%) Diarrhea (27%), pruritis (23%), rash (22%), decreased appetite (17%), fatigue (17%) Diarrhea (15%), pruritis (14%), constipation (11%), AST increased (14%), decreased appetite (14%) PPE (47%), diarrhea (45%), fatigue (19%), hypertension (18%), decreased appetite (18%) Hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), fatigue (30%), PPE (27%), proteinuria (25%), hypothyroidism (16%) PPE (52%), diarrhea (46%), hypertension (30%), decreased appetite (27%), fatigue (25%), decreased weight (22%) Summary efficacy data for selected second line studies after prior sorafenib therapy Aspect celestial[314] resorce[315] REACH-2[127] KEYNOTE-240[316] KEYNOTE-394[317] CheckMate 040[318] Study design Phase III: cabozantinib vs. placebo Phase III: regorafenib vs. placebo Phase III: ramucirumab vs. placebo Phase III: pembrolizumab vs. placebo Phase III: pembrolizumab vs. placebo Phase II: ipilimumab + nivolumab Population Prior sorafenib, second or third line Tolerated and progressed on sorafenib, second line Prior sorafenib, second line, AFP > 400 only Prior sorafenib, second line Prior sorafenib, second line, Asia only Prior sorafenib, multiple prior lines allowed Median OS 10.2 vs. 8.0 m 10.6 vs. 7.8 m 8.5 vs. 7.3 m 13.9 vs. 10.6 m 14.6 vs. 13.0 m 22.8 m OS HR 0.76 (0.63 to 0.92) 0.63 (0.50 to 0.79) 0.71 (0.53 to 0.95) 0.78 (0.61 to 0.998) 0.79 (0.63 to 0.99) N/A PFS 5.2 vs. 1.9 m 3.1 vs. 1.5 m 2.8 vs. 1.6 m 3.0 vs. 2.8 m 2.6 vs. 2.3 m Not reported ORR 4% vs. 1% 10% vs. 4% 5% vs. 1% 18.3% vs. 4.4% 12.7% vs. 1.3% 32% Common AEsa Diarrhea (54%), decreased appetite (48%), PPE (46%), fatigue (45%), nausea (31%), hypertension (29%), vomiting (26%) PPE (53%), diarrhea (41%), fatigue (40%), hypertension (31%), anorexia (31%), increased blood bilirubin (29%), abdominal pain (28%), increased AST (25%) Fatigue (24%), peripheral edema (24%), decreased appetite (22%), liver injury or failure (21%), nausea (19%), bleeding (19%), proteinuria (18%), hypertension (12%) AST increased (23%), blood bilirubin increased (19%), fatigue (19%), pruritis (18%), ALT increased (18%), decreased appetite (17%), diarrhea (17%) Immune-related AEs (18.1%), severe grade 3–5 immune-related AEs (3%) Pruritis (45%), rash (29%), diarrhea (24%), AST increased (20%), hypothyroidism (20%), fatigue (18%), ALT increase (16%), lipase increased (14%), adrenal insufficiency (14%), rash maculopapular (14%) Sorafenib was the first systemic therapy to demonstrate a survival advantage versus placebo for patients with advanced-stage HCC, and it has served as the control arm of multiple subsequent first-line clinical trials (Table 7). Sorafenib is an mTKI targeting the vascular endothelial growth factor receptor intracellular kinase pathway and other kinases. The modest absolute survival benefit of sorafenib of approximately 3 months (10.7 vs. 7.9 mo) was demonstrated in the phase III, double-blind, multicenter placebo-controlled SHARP trial,[319] and later confirmed in the Asia-Pacific study.[320] In 2018, lenvatinib (an oral mTKI targeting vascular endothelial growth factor [VEGF]2 and other kinases) met its primary endpoint of noninferiority versus sorafenib in a global phase III randomized study, REFLECT.[313] Although there was no significant difference in OS between the groups, lenvatinib improved secondary endpoints versus sorafenib such as TTP, PFS, quality of life, and ORR. Hypertension, proteinuria, dysphonia, and hypothyroidism were more common with lenvatinib, whereas hand-foot skin reaction, alopecia, and diarrhea were more common with sorafenib. Both sorafenib and lenvatinib remain first-line treatment options for patients with advanced HCC who are not candidates for newer first-line combination therapies. Nivolumab was well tolerated and showed clinical activity as single-agent PD1 inhibitor therapy as first-line therapy, but it failed to improve OS compared with sorafenib.[321] Subsequently, the open-label, randomized phase III IMbrave150 trial established the combination of atezolizumab, an immunotherapy targeting PD-L1, plus bevacizumab, a monoclonal antibody targeting VEGF, as the preferred first-line treatment option for patients with advanced HCC.[312] The median OS of 19.2 months with atezolizumab plus bevacizumab is the longest median OS of any first-line treatment for advanced-stage HCC to date. Additionally, improved PFS, ORR, and time to deterioration of quality of life all favored atezolizumab plus bevacizumab over sorafenib. Given bevacizumab increases the risk of GI bleeding, likely related to VEGF-mediated endothelial disruption, patients were required to have endoscopic evaluation within 6 months before enrollment, and patients who had incompletely treated varices or who were at high risk for bleeding were excluded. Although infrequent in the clinical trial, bleeding of any grade and fatal bleeding were more common with atezolizumab plus bevacizumab than sorafenib, underscoring the importance of appropriate endoscopic evaluation before atezolizumab plus bevacizumab is initiated. In clinical practice, patients with large varices should likely undergo at least one session of band ligation prior to atezolizumab plus bevacizumab initiation, although carvedilol may also be effective.[322] The optimal time to wait between band ligation and initiation of atezolizumab plus bevacizumab to minimize risk of bleeding from banding ulcers is unknown, although 2 weeks is likely reasonable given risk of post-banding ulcers. Data from the open-label, randomized phase III HIMALAYA trial demonstrated improved OS with the immunotherapy combination of durvalumab (a PD-L1 inhibitor) plus tremelimumab (a CTLA4 inhibitor) versus sorafenib (median OS 16.4 vs. 13.7 months, respectively) and noninferior OS with durvalumab monotherapy versus sorafenib.[323] Durvalumab plus tremelimumab produced a 36-month survival of 30.7%, compared to 20.2% for sorafenib. Serious irAEs occurred in 12.6% of patients with durvalumab plus tremelimumab and 6.4% of patients with durvalumab alone. Durvalumab plus tremelimumab is another preferred option for patients in the first-line setting, particularly for patients who are not candidates for anti-VEGF therapy. The HIMALAYA trial was not powered to compare durvalumab plus tremelimumab with durvalumab monotherapy, but absolute differences in efficacy endpoints appear to be modest, and durvalumab alone may be a treatment option for select patients in the first-line setting who are not candidates for combination therapies. In the global LEAP-002 study, the combination of pembrolizumab plus lenvatinib failed to demonstrate superior OS or PFS over lenvatinib monotherapy.[324] Interestingly, the median survival for the lenvatinib arm was longer than anticipated at 19.0 months, compared with 21.2 months for the combination of pembrolizumab plus lenvatinib, supporting the role of lenvatinib as a standard of care for patients with advanced HCC who are not candidates for immunotherapy-based combinations. The combination of cabozantinib plus atezolizumab met its PFS endpoint versus sorafenib in the COSMIC-312 study, but OS superiority was not demonstrated.[325] AASLD does not recommend lenvatinib plus pembrolizumab or cabozantinib plus atezolizumab as first-line therapies. Results from the anti-PD1/anti-CTLA4 combination of nivolumab plus ipilimumab in the first-line setting are anticipated soon. Three RCTs from Asia demonstrated superior survival with the combination of camrelizumab and rivoceranib versus sorafenib,[326] TACE plus lenvatinib versus lenvatinib[327] and noninferior survival of tislelizumab versus sorafenib[328]; however, it is unclear if these therapies apply to patients in the Western world or will obtain regulatory approval outside of Asia given fewer than 20% of patients in each trial were recruited outside the region. In addition, the combination of TACE and mTKI therapy failed to improve OS in prior studies of advanced-stage HCC.[329] Therefore, AASLD does not currently recommend the routine addition of TACE to systemic therapy for patients with advanced-stage HCC. Several multicenter randomized trials addressed systemic therapy options in the second-line setting following progression with sorafenib, including trials of cabozantinib, regorafenib, ramucirumab, and pembrolizumab—all randomized against a placebo control (Table 8). The Phase III trial of cabozantinib (CELESTIAL) included ~25% of patients who received up to two previous systemic regimens for HCC and is the only phase III data evaluating third-line treatment at this time.[314] OS was significantly improved versus placebo (10.2 vs. 8.0 mo), as were PFS and ORR. Because of the highly similar AE profiles of sorafenib and regorafenib, the phase III trial of regorafenib, RESORCE, selected patients who had tolerated but progressed on sorafenib.[315] OS, PFS, and ORR all significantly favored regorafenib over placebo. Ramucirumab was initially evaluated in the phase III REACH study, which found no significant difference in OS among patients with advanced HCC who were randomly assigned to either ramucirumab or placebo.[330] In subgroup analysis, a benefit of ramucirumab for patients with AFP ≥ 400 ng/ml was noted, which was confirmed in the subsequent REACH-2 study evaluating ramucirumab in the subgroup of patients with AFP ≥ 400, although the absolute OS benefit was modest.[127] Two randomized phase III studies of pembrolizumab versus placebo were conducted (KEYNOTE 240,[316] which enrolled globally, and KEYNOTE-394,[317] which exclusively enrolled patients in Asia). In both studies, survival trended in favor of pembrolizumab (HR, 0.78 and HR, 0.79). Whereas KEYNOTE-394 hit its primary OS endpoint, KEYNOTE 240 did not reach statistical significance per the prespecified statistical plan, which accounted for hypothesis testing at multiple time points and coprimary PFS and OS endpoints. Pembrolizumab in second line or beyond may be an option in patients who have not received prior anti-PD1 or anti-PDL1 therapy. The combination of ipilimumab plus nivolumab was evaluated in a phase II study that compared multiple different doses and schedules of these agents.[318] ORR (32%) was significantly higher than with anti-PD1 alone (14%–17%). The rate of serious irAEs was high; 53% of patients experienced serious treatment-related AEs. This regimen is now under Phase III investigation in the first-line setting for advanced-stage HCC. Systemic therapies with atezolizumab plus bevacizumab or durvalumab plus tremelimumab are considered as preferred first-line therapy options (Figure 16).[331] Noninvasive criteria for the presence of varices (e.g., Baveno VI criteria) have not been validated in patients with HCC. Therefore, all patients considered for atezolizumab plus bevacizumab should undergo an esophagogastroduodenoscopy (EGD) because those with high-risk stigmata for GI bleeding may instead be considered for durvalumab plus tremelimumab. Patients with recent GI bleeding or other contraindications to VEGF therapy (e.g., severe proteinuria) should also be considered for alternative first-line therapy, such as durvalumab plus tremelimumab. Patients with Child-Turcotte-Pugh A cirrhosis in whom immune-based regimes are contraindicated (e.g., severe autoimmune disorders or liver transplantation) should be offered sorafenib or lenvatinib. Posttransplant patients who are started on sorafenib or lenvatinib should be assessed and monitored for drug-drug interactions with their immunosuppression regimen. Treatment strategy for HCC with systemic therapies. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma. Solid arrows indicate treatments for which there is clear evidence; gray dotted arrows indicate treatments in the second/third line for which further studies are required. 1Treatments that got FDA accelerated approval based on phase II studies. Reprinted with permission from Llovet et al.[331]All second-line clinical trials were conducted after sorafenib in the first-line setting because this was the standard of care when these trials were initiated. Therefore, no high-quality data have been published on second-line therapy after atezolizumab plus bevacizumab or durvalumab plus tremelimumab. Treatment with an mTKI in the second-line setting may confer clinical benefit for patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0–1, who develop HCC progression or intolerance with first-line atezolizumab plus bevacizumab or durvalumab plus tremelimumab (Figure 16). Following first-line treatment with atezolizumab plus bevacizumab, AASLD advises treatment with a first-line mTKI (sorafenib or lenvatinib) as preferred agents, although second-line mTKIs (cabozantinib or regorafenib) or ramucirumab (if AFP ≥ 400 ng/ml) may also be considered. Ipilimumab plus nivolumab may be considered after progression on atezolizumab plus bevacizumab if patients are not eligible for an mTKI or if mTKI-related AEs might be detrimental. Patients who progress on first-line durvalumab plus tremelimumab are naïve to antiangiogenic therapy, so a first-line mTKI (sorafenib or lenvatinib) is likely most appropriate in this setting. The aforementioned prospective clinical trials were restricted to patients with a good performance status (ECOG 0–1), Child-Turcotte-Pugh A liver disease, and otherwise adequate organ function. There are limited clinical trials to guide systemic treatment for patients with Child-Turcotte-Pugh B liver disease.[332–334] Real-world data suggest well-selected patients with Child-Turcotte-Pugh B liver disease, particularly those with Child-Turcotte-Pugh B7 liver disease from cancer-related hyperbilirubinemia and hypoalbuminemia, can sometimes tolerate systemic therapies traditionally reserved for patients with Child-Turcotte-Pugh A liver disease. For the larger group of patients with Child-Turcotte-Pugh B liver disease, careful patient selection is necessary to identify patients likely to benefit from systemic therapy. The safety of sorafenib in this setting is supported by real-world, prospective registry data, although the median survival of patients with Child-Turcotte-Pugh B treated with sorafenib was only 5.2 months.[335] There are emerging data for safety of other mTKI agents, such as lenvatinib, in patients with Child-Turcotte-Pugh B liver disease as well. Single-agent anti-PD1 (e.g., nivolumab, pembrolizumab) or anti-PD-L1 (durvalumab) therapy may also be considered in patients with Child-Turcotte-Pugh B liver disease based on retrospective data and a small prospective, single-arm clinical trial. In the Checkmate 040 phase I/II trial, 49 patients with Child-Turcotte-Pugh B7-B8 HCC were treated with nivolumab.[336] Objective response was achieved in 12% of patients, median OS was 7.6 months, and grade 3/4 treatment-related AEs were observed in 24% of patients, similar to tolerability observed in patients with Child-Turcotte-Pugh A cirrhosis. In this setting, shared decision-making is particularly important to weigh this safety profile with likely modest observed clinical benefits. A new diagnosis of HCC represents a significant change in clinical status for most patients and presents an opportunity for education, counseling, and ACP. Although ACP may not be necessary for patients with early-stage HCC and compensated cirrhosis, it should be offered to patients with larger tumor burden and those receiving palliative-intent therapy or best supportive care for HCC, regardless of transplant eligibility.[337] Defining goals of care should be done early for these patients to facilitate shared decision-making and incorporate patients' personal values into treatment choices. ACP allows for the provider and patient to set expectations, discuss uncertainties, and reinforce the importance of timely care and follow-up.[338] Further, the treatment cascade for HCC is unpredictable and is governed by many things, including tumor biology and comorbidity, not to mention access and expertise. In cases when the clinical situation changes, initial ACP discussions serve as a foundation to reorient the patient to their goals in this new context. Both the patient and the healthcare system benefit from ACP because the patient remains informed of potential outcomes and the provider can help the patient make informed decisions about potential treatments. Delivering care according to patients' goals and engaging in ongoing ACP may avoid unnecessary or futile treatment and patient and caregiver stress and reduce strains and costs to health care systems.[339] 1Public health policies and interventions should be implemented to address the significant mortality of HCC in the United States (Level 5, Strong Recommendation). 2Vaccination for HBV infection should be given in all newborns as well as high-risk adults who failed to receive vaccination at birth to reduce the risk of HCC (Level 2, Strong Recommendation). 3Antivirals should be given in all patients who meet criteria for treatment according to AASLD Guidance documents for HBV and HCV infection. In patients with chronic viral hepatitis, suppression of HBV and eradication of HCV infection decreases the risk of HCC development (Level 2, Strong Recommendation). 4Patients with chronic liver disease should be counseled to maintain a healthy weight, have a balanced diet, avoid tobacco and alcohol, and achieve adequate control of comorbid conditions including components of the metabolic syndrome. A healthy lifestyle has multiple benefits and may decrease HCC risk (Level 3, Strong Recommendation). 5Coffee consumption may be recommended for patients with chronic liver disease, as it has associated with decreased risk of HCC development (Level 5, Weak Recommendation, 12 of 15 agree). There are insufficient data to recommend a specific dose, although studies suggest a dose–response curve. 6AASLD does not advise use of other chemoprevention therapies such as statins, aspirin, and metformin solely to reduce HCC risk, despite some evidence of risk reduction (Level 5, Weak Recommendation). In patients with other indications, these agents may be used in the setting of chronic liver disease (Level 3, Weak Recommendation). 7Patients at high risk of developing HCC (see Table 1) should be entered into HCC surveillance programs, provided they would be candidates for HCC treatment (Level 2, Strong Recommendation). Patients with Child-Turcotte-Pugh class C cirrhosis should not be enrolled in surveillance programs unless they are eligible for liver transplantation (Level 3, Strong Recommendation). All patients listed for liver transplantation should undergo semiannual HCC surveillance because identification of early-stage HCC changes priority for transplantation (Level 3, Strong Recommendation). AASLD recommends against HCC surveillance in patients with life-limiting comorbid conditions that cannot be remedied by liver transplantation or other directed therapies (Level 5, Strong Recommendation). 8AASLD recommends against routine use of HCC surveillance in patients with HCV infection post-SVR with advanced fibrosis but without cirrhosis (Level 3, Weak Recommendation). 9AASLD recommends against routine use of HCC surveillance in patients with NAFLD who have advanced fibrosis but without cirrhosis (Level 3, Weak Recommendation). 10HCC surveillance should be performed using ultrasound and AFP at semiannual (approximately every 6 months) intervals (Level 2, Strong Recommendation). AASLD recommends use of interventions such as best practice alerts or outreach programs to increase HCC surveillance adherence given the underuse of surveillance in clinical practice (Level 2, Strong Recommendation). 11AASLD does not recommend routine use of CT- or MRI-based imaging and tumor bio-markers, outside of AFP, for HCC surveillance in at-risk patients with cirrhosis or chronic HBV (Level 5, Weak Recommendation). Alternative imaging modalities, such as contrast-enhanced MRI, may be considered for HCC surveillance in select patients in whom US-based surveillance is suboptimal (Level 3, Weak Recommendation). 12US visualization should be assessed and reported for surveillance exams given its impact on recommended recall procedures (Level 5, Strong Recommendation). Patients with limited ultrasound visualization may undergo surveillance contrast-enhanced MRI or multiphase CT (Level 5, Weak Recommendation). 13AASLD advises repeat short-interval ultra-sound and AFP in approximately 3–6 months for patients with a 1000 ng/ml must be downstaged to AFP < 500 ng/ml to be considered downstaged (Level 2, Strong Recommendation). 37AASLD advises surveillance for detection of post-transplant HCC recurrence using multi-phasic contrast-enhanced abdominal CT or MRI and chest CT scan (Level 2, Strong Recommendation). The optimal timing and duration of post-transplant surveillance is uncertain; however, risk scores may be considered to guide decisions. 38Patients with solitary tumors ≤5 cm should be treated with curative intent using local ablative therapies if they are ineligible for or decline surgical therapy (Level 1, Strong Recommendation). 39Thermal ablation (radiofrequency or microwave ablation) should be considered the treatment of choice for patients with early-stage HCC ≤ 3 cm who are ineligible for or decline surgery (Level 1, Strong Recommendation). AASLD does not advise one thermal ablative modality over another. 40Targeted radioembolization (radiation segmentectomy) or EBRT may be used as alternative therapies to thermal ablation for patients with BCLC stage A HCC who are not candidates for surgical resection, including those with tumors >3 cm in size (Level 3, Strong Recommendation). 41Patients with BCLC Stage B HCC should be treated with transarterial chemoembolization (Level 1, Strong Recommendation). 42AASLD advises radioembolization as an alternative therapy to chemoembolization in patients with BCLC Stage B HCC (Level 3, Strong Recommendation). 43Transarterial therapies should be performed in a selective/segmental fashion (over lobar treatment) whenever possible given a lower risk of hepatic dysfunction (Level 5, Strong Recommendation). 44AASLD advises against the combination of systemic therapy with transarterial therapies for BCLC Stage B HCC outside of a clinical trial setting (Level 2, Strong Recommendation). 45AASLD advises systemic therapy in patients with intermediate HCC who are unsuitable for or refractory to locoregional therapies due to contraindications, worsening hepatic dysfunction, progression of HCC, or lack of objective response (Level 3, Strong Recommendation). 46Systemic therapy should be offered to patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0–1, who have BCLC Stage C HCC, or BCLC Stage B HCC not amenable to or progressing after locoregional therapy (Level 1, Strong Recommendation). Patients with advanced HCC who have Child-Turcotte-Pugh A cirrhosis should be offered atezolizumab plus bevacizumab or durvalumab plus tremelimumab as preferred first-line therapy options (Level 2, Strong Recommendation). Patients considered for atezolizumab plus bevacizumab should undergo an EGD to assess for high-risk stigmata of variceal or other GI bleeding (Level 5, Strong Recommendation). The optimal treatment of large varices prior to atezolizumab plus bevacizumab initiation is unknown, although AASLD recommends at least one session of banding. Carvedilol may be considered as an alternative management of varices prior to atezolizumab plus bevacizumab (Level 5, Weak Recommendation). Patients with recent GI bleeding within 6 months and those with high-risk stigmata for bleeding on EGD should have varices adequately treated prior to atezolizumab plus bevacizumab initiation, or these patients may be considered for durvalumab plus tremelimumab (Level 5, Strong Recommendation). Patients with Child-Turcotte-Pugh A cirrhosis in whom atezolizumab plus bevacizumab and durvalumab plus tremelimumab are contraindicated should be offered first-line sorafenib or lenvatinib (Level 1, Strong Recommendation). 47Well-selected patients with Child-Turcotte-Pugh B cirrhosis may be offered sorafenib, lenvatinib, or single-agent anti-PD1 or anti-PDL1 ICI therapy (Level 3, Weak Recommendation). 48AASLD advises second-line therapy in patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0–1, who develop HCC progression or intolerance with first-line systemic therapy (Level 1, Strong Recommendation). AASLD advises sorafenib or lenvatinib as preferred agents after first-line atezolizumab plus bevacizumab if patients are not eligible for clinical trials (Level 5, Weak Recommendation). Cabozantinib, regorafenib, or ipilimumab plus nivolumab may be used in these patients (Level 5, Weak Recommendation). AASLD advises sorafenib or lenvatinib as preferred agents after first-line durvalumab plus tremelimumab if patients are not eligible for clinical trials (Level 5, Weak Recommendation). AASLD advises cabozantinib or regorafenib (or ramucirumab in patients with AFP ≥ 400 ng/ml) as preferred agents after sorafenib or lenvatinib if patients are not eligible for clinical trials (Level 1, Strong Recommendation). Pembrolizumab (in patients without prior immunotherapy exposure) or ipilimumab plus nivolumab may be used in these 49AASLD advises against the use of ICIs in patients with recurrent HCC after liver transplantation given increased risk of graft loss and death (Level 4, Strong Recommendation). AASLD advises sorafenib or lenvatinib as first-line therapy for these patients 50Advance care planning should be offered to all patients receiving palliative-intent therapy or best supportive care for HCC, regardless of transplant eligibility (Level 5, Weak Recommendation).

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AASLD American Association for the Study of Liver Diseases ACP advance care planning AE adverse event AFP alpha fetoprotein ALBI albumin-bilirubin APHE arterial phase hyperenhancement BCLC Barcelona Liver Clinic Cancer CEUS contrast-enhanced ultrasound CI confidence interval CSPH clinically significant portal hypertensio CT computed tomography ctDNA circulating tumor DNA DCP des gamma carboxy prothrombin EBRT external beam radiation therapy ECOG PS Eastern Cooperative Oncology Group Performance Status EGD esophagogastroduodenoscopy FDA Food and Drug Administration FLR future liver remnant GI gastrointestinal HBV hepatitis B virus HCC hepatocellular carcinoma HCV hepatitis C virus HR hazard ratio ICI immune checkpoint inhibitor irAE immune-related adverse event LDLT living donor liver transplantation LI-RADS Liver Imaging Reporting and Data System LT liver transplant MELD Model for End-Stage Liver Disease MIS minimally invasive surgery mRECIST modified response evaluation criteria in solid tumors; MRI, magnetic resonance imaging mTKI multikinase inhibitor OPTN Organ Procurement and Transplant Network ORR objective response rate OS overall survival PBT proton beam therapy PD1 programmed death 1 PD-L1 programmed death ligand 1 PET positron emission tomography PFS progression-free survival PVTT portal vein tumor thrombus RCT randomized controlled trial RECIST response evaluation criteria in solid tumors RETREAT Risk Estimation of Tumor Recurrence After Transplant SVR sustained virological response TACE transarterial chemoembolization TARE transarterial radioembolization TTP time to progression UNOS United Network for Organ Sharing UNOS-DS UNOS downstaging VEGF vascular endothelial growth factor 1.OCEBM Levels of Evidence Working Group: Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. 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CONFLICTS OF INTEREST Brent A. Neuschwander-Tetri consults/advises Akero, Arrowhead, BMS, Clinical Care Options, GSK, Glympse, Hepion, High Tide, HistoIndex, Labcorp, LG Chem, Madrigal, Merck, Sagimet, Senseion, Target RWE, 89Bio, has stock options with HepGene, HeptaBio and receives research grants paid to his institution from BMS, HighTide, Intercept, Inventiva, Madrigal. Mohammad S. Siddiqui consults/advises Sagimet and AMRA. Manal F. Abdelmalek consults/advises 89 Bio, Bristol-Myers Squibb, Hanmi, Intercept, Inventiva, Madrigal, Merck, NGM Bio, Novo Nordisk, SonicIncytes, Theratechnologies, Fishawack Inc., Terra Firma Inc. and receives research grants paid to her institution from Allergan, Boeringher- Ingelheim, Bristol Myers Squibb, Celgene, Durect, Enanta, Enyo, Galmed, Genentech, Gilead, Hanmi, Intercept, Inventiva, Madrigal, Novo Nordisk, Poxel, Target NASH, Viking. Stephen Caldwell receives research support from Gilead, Galectin, Madrigal, Prometheus, Exact, GenFit, Inventiva, Zydus, Durect, Royalty, Avanos. David E. Kleiner is an unpaid consultant/collaborator with HistoIndex and HighTide. Rohit Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, AstraZeneca, Eli Lilly, Inipharma, Intercept, Ionis, Madrigal, Novo Nordisk, Pfizer, Sagimet, Theratechnologies, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. Co-founder of LipoNexus Inc. The remaining authors have no conflicts to report.

FIGURE 1 Pathogenic drivers of NAFLD as... FIGURE 1 Pathogenic drivers of NAFLD as therapeutic targets. Overview of the major mechanisms that... FIGURE 1 Pathogenic drivers of NAFLD as therapeutic targets. Overview of the major mechanisms that lead to the phenotype of NASH and its consequences, many of which can be leveraged therapeutically. Not shown are the many areas where genetic polymorphisms may play a role and where important modifying factors such as cholesterol, types of dietary fats consumed [saturated vs. polyunsaturated fatty acid (PUFA)], the gut microbiome, uric acid, and periodic hypoxia (sleep apnea) may also influence these pathways. A primary disease driver may be an oversupply of fat to adipocytes such that their ability to store triglyceride without inducing cell stress is exceeded, which activates inflammatory pathways and causes insulin resistance. Understanding the major drivers of NASH facilitates the rational development of therapies for patients with NASH. Specific sites of intervention that might prevent or resolve NASH include interventions that modulate food intake (eg, portion sizes, bariatric surgery, satiety regulators), increase energy disposal (eg, exercise, thermogenesis), improve adipocyte insulin sensitivity [eg, peroxisome proliferator-activated receptor (PPAR)γ ligands], impair de novo lipogenesis (eg, acetyl-coenzyme A carboxylase and fatty acid synthase inhibitors), increase hepatic oxidative metabolism (PPARα ligands and thyroid hormone receptor beta agonists), and attenuate inflammation, cell death, and fibrogenesis. Therapeutic agents affecting multiple metabolic pathways throughout the body with potential beneficial effects on the liver include peptide hormone analogs (eg, analogs of fibroblast growth factor-19, fibroblast growth factor-21, glucagon-like peptide-1, gastric inhibitory peptide, glucagon) and nuclear receptor ligands such as drugs that target PPARα, PPARδ, PPARγ, thyroid hormone receptor β, and farnesoid X receptor. Abbreviations: ER, endoplasmic reticulum; CVD, cardiovascular disease. FIGURE 2 Algorithm for the evaluation of... FIGURE 2 Algorithm for the evaluation of patients at risk for or with established NAFLD... FIGURE 2 Algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings. Patients with steatosis noted on imaging or for whom there is a clinical suspicion of NAFLD, such as those with metabolic risk factors or unexplained elevation in liver chemistries, should undergo further evaluation. In settings with a low prevalence of advanced fibrosis, such as in the primary care setting, the emphasis is on excluding advanced fibrosis using a test with a high negative predictive value. When the fibrosis-4 index (FIB-4) is 2.0 should be used. FIB-4 has low accuracy in those under age 35; thus, secondary assessment should be considered in those 6 mo) above normal to exclude other causes of liver disease or when FIB4 > 2.67 due to the increased risk of clinically significant fibrosis. In higher prevalence settings, such as gastroenterology/hepatology clinics, additional risk assessment with magnetic resonance elastography (MRE) may be appropriate when noninvasive tests (NITs) are indeterminate or there is clinical suspicion of more advanced disease. Identification of cirrhosis should prompt screening for HCC and esophageal varices. In addition, MRE or corrected T1 (cT1) may help identify patients with "at-risk" NASH (NASH with NAFLD activity score ≥ 4 and fibrosis stage ≥ 2) who may benefit from a therapeutic intervention as they become available. If cirrhosis is suspected based on NITs, clinical data, or imaging findings, then cirrhosis-based management may be initiated without a liver biopsy. Liver biopsy should be considered when NITs suggest significant fibrosis (≥ F2), especially if additional evaluation suggests the presence of "at-risk" NASH (eg, using FAST, MEFIB, MAST, or cT1), NIT assessment is indeterminate, aminotransferases are persistently elevated (> 6 mo), or additional/alternate diagnoses are suspected. Note that in patients with confirmed or suspected advanced fibrosis, an ELF ≥ 11.3 is a predictor of future liver-related events and is approved for this purpose; use of other ELF cutoffs in secondary risk assessment is based on expert option. Patients at all stages of disease should be counseled on lifestyle modifications, and those with ≥ F2 fibrosis targeted for pharmacological interventions as they become available. Specific threshold values of NITs are approximations supported by current evidence and are meant to guide clinical management through primary care to gastroenterology/hepatology practices rather than be interpreted in isolation. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PCP, primary care provider. FIGURE 3 Histology of NAFLD. Liver biopsy... FIGURE 3 Histology of NAFLD. Liver biopsy shows characteristic features of the spectrum of NAFLD.... FIGURE 3 Histology of NAFLD. Liver biopsy shows characteristic features of the spectrum of NAFLD. (A) Hepatic steatosis (typically zone 3) without ballooned hepatocytes or fibrosis [hematoxylin and eosin (H&E), ×200]. (B) Multiple ballooned hepatocytes with Mallory-Denk bodies (arrows) and mild lobular inflammation (circles) (H&E, ×400). (C) Ballooned hepatocytes (arrows) with moderate lobular inflammation (circle) (H&E, ×200). (D) Some cases of steatohepatitis may show significant portal inflammation and interface hepatitis (arrows) (H&E, ×200). (E) Dense perisinusoidal and periportal fibrosis (blue stain), with a thin connecting fibrotic bridge (Masson trichrome, ×200). (F) Cirrhosis (nodule formation) due to steatohepatitis (Masson trichrome, ×100). FIGURE 4 A multidisciplinary approach to the... FIGURE 4 A multidisciplinary approach to the management of NAFLD. Optimal care of the patient... FIGURE 4 A multidisciplinary approach to the management of NAFLD. Optimal care of the patient with NAFLD requires a multidisciplinary approach. The majority of patients are in the primary care/endocrine setting, in which management of medical comorbidities should be optimized, with preference given to treatments for type 2 diabetes mellitus, hypertension, or obesity that likely also have beneficial effects on NAFLD. In this setting, at-risk patients should be identified and initial risk stratification performed [ie, fibrosis-4 index (FIB-4) ± vibration controlled elastography or Enhanced Liver Fibrosis]. The role of the gastroenterologist/hepatologist includes more comprehensive liver risk stratification, exclusion of other liver diseases, and a focus on liver-directed therapy. Close communication between gastroenterology/hepatology and primary care or endocrinology facilitates multidisciplinary management of metabolic comorbidities as well as the prioritization of medications or interventions that may also offer liver benefits (see the Treatment section). All patients should undergo dietary/nutritional assessment and a plan established for regular follow-up independent of gastroenterology/hepatology visits. The need for more specialized obesity management, including bariatric surgery referral, health psychology, and additional cardiology or lipid metabolic support, should be assessed on an individual basis (dotted arrows).

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