Hepatocellular Carcinoma
New Developments

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KEYWORDS

• Hepatocellular carcinoma • Cirrhosis • Chemoembolization • Radioembolization
• Liver cancer • Immunotherapy

KEY POINTS

- The epidemiology of hepatocellular carcinoma (HCC) is rapidly evolving, with nonalcoholic fatty liver disease becoming an increasing cause of fibrosis, cirrhosis, and HCC.
- The diagnosis and surveillance of HCC are evolving with the advent of novel biomarkers and development of personalized screening recommendations based on cause of HCC.
- The traditional Barcelona Clinic Liver Cancer staging system has been modified to better represent severity of liver dysfunction and delineate treatment options, especially with the formal introduction of the concept of treatment stage migration.
- There are now advances in curative, noncurative, and combinations of the 2 treatment options. There is increasing research evaluating combinations of therapeutic approaches, including the use of locoregional treatments to "down stage" individuals to reach transplant eligibility.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide and a leading cause of death in cirrhosis. The prognosis in HCC is poor, with mortalities approximating incidence rates worldwide.[1,2] The epidemiology of HCC has changed considerably in the past decade. A decrease of viral hepatitis-related cases in certain parts of the world has been offset by an increase in cases related to alcohol and nonalcoholic fatty liver disease (NAFLD) in Western countries. Advancements in the management of HCC, particularly in the advanced stage, have been groundbreaking. Immunotherapy is now being studied in earlier stages of HCC in combination with surgery and locoregional therapy (LRT). This review article provides a summary of recent updates in the epidemiology, diagnosis, staging, and management of HCC.

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Epidemiology

In the United States, the median age of diagnosis is in the sixth decade of life (60–65 among men; 65–69 among women). Generally, HCC is more prevalent among men. There are also numerous observed socioeconomic disparities in HCC incidence, mortality, and survival. HCC incidence and mortality significantly vary by race and ethnicity in the United States, with increased incidence in African American and Hispanic populations. Ongoing research is revealing disparities in HCC by many socioeconomic measures, including neighborhood resources/neighborhood socioeconomic status, insurance type, and geographic location (rural vs urban settings).

HCC occurs in the setting of cirrhosis in approximately 90% of cases. The cause of cirrhosis varies considerably by country. In the United States, the most common causes of cirrhosis leading to HCC are alcohol-related liver disease (ALD), NAFLD or nonalcoholic steatohepatitis (NASH), and viral hepatitis (hepatitis B [HBV] and hepatitis C [HCV]). The most common cause of HCC in the absence of cirrhosis is related to HBV, although there has been an increase in noncirrhotic NAFLD-related HCC.[2] An understanding of risk factors contributing to HCC is essential for prevention efforts, risk stratification, and screening strategies.

DETECTION AND DIAGNOSIS

Surveillance

Surveillance recommendations regarding target population, frequency, and modality of surveillance are complex and dependent on the cost-effectiveness within a targeted population. Early diagnosis with surveillance has consistently demonstrated superior outcomes than symptom-based diagnosis, with respective pooled 3-year survival rates of 50.8% and 27.9%.[3] The American Association for the Study of Liver Diseases (AASLD) will endorse ultrasound (US) + alpha-fetoprotein (AFP) every 6 months in individuals with cirrhosis or certain individuals with HBV (**Box 1**). A meta-analysis reported a higher sensitivity for the detection of early HCC with US + AFP (63%; 95% CI: 48–75%) compared with US alone (53%; 95% CI: 35–70%). Surveillance is not recommended in patients with Child-Pugh C (CP C) or those with comorbid conditions who are not otherwise candidates for liver transplant.[4] Changes in the epidemiology of HCC (ie, increasing incidence of NAFLD), advances in serologic biomarkers, and improvement in imaging modalities may lead to changes in surveillance recommendations in the future.

Moving away from a "one-size-fits-all" approach for HCC surveillance and toward an individualized calculated HCC risk is needed. A personalized approach in patients

Box 1
Surveillance tools

AASLD
Annual US + serum AFP in:
- All individuals with cirrhosis
- The following groups with chronic HBV:
  - Asian men ≥40 years old
  - Asian women ≥50 years old
  - Family history of HCC
  - Individuals born in Africa ≥20 years old

If unable to adequately assess on US, can pursue multiphase MRI or CT liver.

AASLD guidelines for HCC surveillance in individuals with cirrhosis and/or chronic HBV.

with HCV with sustained virologicresponse (SVR) has been proposed in several risk scores, which may become endorsed if validated in larger cohorts.[5] In addition, such tools may better define the HCC risk in the populations that are not clearly defined (eg, cured HCV with stage 3 fibrosis). Risk scores are also being investigated in other causes of chronic liver disease. A serum protein-based prognostic liver secretome signature (PLSec) comprising 8 proteins has been reported to predict risk of HCC development.[6] This signature combined with AFP (PLSec-AFP) had a superior predictive value than AFP alone. Such an approach could be used to individualize the risk of future HCC to improve cost-effectiveness and focus novel biomarkers (discussed later) on those at the highest risk to detect early HCC.

NAFLD/NASH-induced HCC is increasing owing to the obesity epidemic and is recognized to be the current second most common cause for HCC-related liver transplant. An area of debate is HCC surveillance in noncirrhotic NASH.[7] Although HCC is known to occur in noncirrhotic NASH (20% of NAFLD HCC), screening is not deemed cost-effective and therefore has not been supported by societal guidelines.[8] Recognizing the progression to compensated cirrhosis in NAFLD/NASH to initiate HCC surveillance can be challenging. The SAFE (Steatosis-Associated Fibrosis Estimator) score is a newly devised tool to aid in the detection of stage 2 fibrosis ($\geq$F2 associated with increased morbidity and mortality) among patients with NAFLD, which outperformed both Fibrosis-4 Index (FIB-4)- and NAFLD fibrosis score (NFS). This tool may aid streamlining the most appropriate referrals to liver specialists who have reported higher surveillance rates compared with primary care providers, 73.7% versus 29.5%, respectively.[9] The ability to accurately risk-stratify the plethora of patients with NAFLD (approximately 100 million in the United States) to specialized longitudinal care may lead to timely therapy to prevent development of advanced fibrosis as well as identify those who progress to cirrhosis.

The potential harms of surveillance related to false positive US or AFP levels should be considered when establishing surveillance recommendations. In HCC, the main potential harms are psychological distress, costs of surveillance, and physical harm. A Markov model that considered potential of harm related to additional imaging or biopsy found that US + AFP was the most cost-effective approach over US alone or no surveillance in patients with compensated cirrhosis. A threshold analysis showed that an annual risk of HCC > 0.4% and an adherence of greater than 19.5% were required for US + AFP to be more cost-effective relative to no surveillance.[10]

US may be of limited utility in certain scenarios, including advanced cirrhosis with excessive liver nodularity and/or morbid obesity. One study found that 20% of patients have suboptimal visualization of the liver on US surveillance. Factors significantly associated with US inadequacy include male sex, morbid obesity, fat-associated liver disease, such as ALD and NASH, and advanced liver disease.[11] Such individuals would benefit from cross-sectional imaging. When US is inconclusive, multiphase computed tomographic (CT) scan or MRI should be pursued for surveillance purposes. Although multiphase MRI (liver protocol) may be best for detection of HCC, it is impractical as a surveillance test for all patients. Two studies evaluating MRI demonstrated a pooled sensitivity and specificity of 83.1% (95% CI: 72%–90.5%) and 89.1% (95% CI: 86.5%–91.3%).[12] The PRIUS study reported MRI to be superior to US for early-stage detection of HCC.[13] More recent studies are evaluating abbreviated MRI protocols for screening, which may prove to be more practical as a surveillance method.

Although AFP is used for HCC surveillance, other potential biomarkers are being investigated. Two markers, lens culinaris agglutinin-reactive AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP), are currently approved for risk-stratification for

future development of HCC. GALAD, a composite score of gender, age, AFP, AFP-L3, and DCP, demonstrated sensitivity for any-stage and early-stage detection of greater than 70% and greater than 60% in a multinational cohort of more than 2400 individuals. The Hepatocellular carcinoma Early Detection Strategy study showed that GALAD performed the best for early detection of HCC.[14]

Biomarkers may also function as a prognostic tool. A single-center, prospective study comprising 203 patients (94% received LRT, 18.2% down-staged) with AFP, AFP-L3, and DCP before transplant, was analyzed for post-LT outcomes.[15] Those with an elevated AFP-L3 > 15% and DCP > 7.5% at the time of LT incurred an increased risk of HCC recurrence (HR = 28.4; CI: 6.76–119.9; p< 0.001) post-LT and a significantly lower 3-year overall survival (OS) of 41% compared with 98% in patients without an elevation of AFP-L3 and DCP. Among the 8 recurrences, 63% had elevations in both these biomarkers in contrast to 3.6% not meeting a dual increase in AFP-L3 and DCP. The prognostic role of biomarkers closest to LT was also reported in an earlier retrospective trial.[16] Of note, the cutoff levels for the biomarkers used in these studies were the defined levels to predict risk of developing HCC. Further refinement in the cutoff levels used for LT selection may be warranted.

Possible serum biomarkers that may be of clinical utility in the future include plasma microRNA (miRNA), methylated DNA, circulating tumor DNA (ctDNA) and tumor cells (CTCs), and gene expression profiles (GEPs). MiRNAs are endogenous, short RNA sequences that are involved in posttranscriptional regulation. Certain circulating miRNA levels have been shown to be associated with cirrhosis and HCC in various studies. MiRNA-16, when combined with serologic markers used in the GALAD model, effectively detected 92.4% of HCC cases with 78.5% specificity.[17] Methylated DNA marker (MDM) panels have shown promise in detection of HCC, with some studies demonstrating greater performance than AFP.[18] However, the use of MDM panels needs to be studied in larger cohorts across multiple centers before incorporation into routine surveillance practices. The use of ctDNA and CTCs for surveillance is complex. Because their circulating levels correlate with stage of disease, these tests may not be optimal for *early*-stage detection. One systematic review evaluating ctDNA and CTCs concluded that these tests will likely be more useful for prognostication and monitoring for recurrence as opposed to initial detection of HCC.[19] Finally, the use of GEPs at the tissue level has identified genetic signatures unique to HCC in smaller sample sizes.[20,21] However, this has yet to be translated to a practical serologic test and has not been evaluated as a screening modality.

Diagnosis

Multiphase CT or MRI with contrast is used for definitive diagnosis of HCC; arterial phase enhancement (APHE); and washout on the portal venous phase. The Liver Reporting and Data System (LIRADS) allows for the classification of liver lesions in cirrhosis in a standardized manner. Multiphase MRI may have higher sensitivity but comparable specificity to CT. Imaging is often sufficient to definitively diagnose HCC (LIRADS-5), eliminating the need for a biopsy for diagnostic purposes. However, when imaging findings are nondiagnostic but highly suspicious for HCC (LIRADS-4), clinicians may repeat an imaging study in 3 months, attempt the alternative imaging modality, or consider pursuing a biopsy for definitive diagnosis. The advantages of CT include shorter duration of examination and lower cost. The disadvantages include exposure to radiation and iodinated contrast. This is especially relevant in individuals with advanced liver disease who can often have concurrent renal dysfunction. The disadvantages of MRI include greater cost, technical complexity, longer examination times, and higher risk of artifact with motion. Of note, the use of gadoxetate disodium,

a partially hepatocellular-specific contrast agent for MRI, has not been recommended over traditional extracellular MRI contrast agents. However, some studies suggest that the use of gadoxetate improves sensitivity in detection of small HCC lesions less than 2 cm. For T1 lesions (<2 cm), currently United Network for Organ Sharing (UNOS) requires APHE plus 2 criteria (venous washout, 50% growth over 6 months, or enhancing capsule), whereas LIRADS criteria are less stringent with a diagnosis of HCC made with APHE + venous washout or threshold growth or APHE and 2 criteria. It is anticipated that UNOS will adopt the LIRADS approach in the future for T1 lesions.

STAGING

Staging of HCC is dependent on performance status (PS), degree of liver dysfunction, and traditional TNM staging. The Barcelona Clinic Liver Cancer (BCLC) staging system is recommended by AASLD and European Association for the Study of the Liver (EASL). BCLC classification was recently updated in 2022 to better characterize prognosis and available treatment options. The most notable changes include the following: (1) replacement of CP classification of liver dysfunction with a simplified binary definition of compensated or decompensated liver disease; (2) the introduction of the concept of stage migration; and (3) clarification on decision making in the setting of "evolutionary events" or progression.[22]

Liver function is now characterized as "compensated" or "decompensated." Decompensated liver disease includes the presence of jaundice, ascites, or hepatic encephalopathy, regardless of Model for End-Stage Liver Disease (MELD) or CP classification. Importantly, history of variceal bleeding may represent clinically significant portal hypertension (CSPH) but is not necessarily incorporated into the classification of decompensated or compensated liver disease. Treatment stage migration is the notion that patients may need to be reclassified as more advanced stages because of a variety of factors, even if their overall PS, degree of liver function, and TNM classification remain unchanged. Determining stage migration includes specification of the pattern of progression, considering superior prognosis of enlarging or new intrahepatic lesions compared with new extrahepatic lesions (EHS) or new vascular invasion (VI).

BCLC stage 0 is characterized by a lesion $\leq$2 cm, without portal vein tumor thrombosis (PVTT) or EHS, compensated liver function, and Eastern Cooperative Oncology Group (ECOG) PS of 0. Expected median survival exceeds 5 years. BCLC stage A also prognosticates survival greater than 5 years. BCLC A consists of a solitary lesion of any size or up to 3 nodules, all $\leq$3 cm, without vascular or extrahepatic invasion, preserved liver function, and PS of 0. It is important to note that patients who meet criteria for liver transplantation based on tumor burden may be classified as BCLC D because of liver dysfunction or PS. BCLC B is classified as multifocal HCC that exceeds BCLC A, without VI or EHS, preserved liver function, and PS 0. Median survival is 2.5 years for individuals with BCLC stage B HCC. BCLC stage C is defined by VI or EHS, PS $\leq$ 2, and preserved liver function. Median survival of this stage is approximately 2 years. Finally, BCLC D is characterized by ECOG PS > 2 and impaired liver function. Median survival of individuals with BCLC stage D, if not eligible for orthotopic liver transplantation (OLT), is 3 months.

TREATMENT

Overview

Treatment options are broadly categorized as curative (liver transplantation, resection, or ablation/segmental transarterial radioembolization [TARE]) and noncurative

(transarterial chemoembolization [TACE], systemic therapies). When feasible, transplantation is the most definitive treatment option, but organ shortage limits this curative therapy. Systemic therapies are being studied in BCLC A and B to see if this addition to traditional therapy can further improve OS.

Transplantation

Individuals with cirrhosis, significant degree of liver dysfunction, or CSPH, without medical or psychosocial contraindications should pursue liver transplantation. The Milan criteria (MC) have been successfully used as the selection tool for appropriate candidates for OLT based on tumor size and number (**Box 2**). Although this approach has fulfilled an acceptable 5-year OS of greater than 50%,[23] many have thought that the MC are too restrictive and thereby deter OLT in some candidates who would derive long-term OS from transplantation. The field of transplant oncology is evolving because of many concomitant factors: the decrease in patients with HCV requiring OLT because of direct-acting antivirals, living donors, increased use of decreased cardiac death and HCV+ organs, and improvement in available systemic therapies for HCC.

Since the concept of downstaging (DS) to the MC was first published by the University of California, San Francisco (UCSF) group in 2008, additional data support DS as a viable approach to gain access to OLT with excellent post-LT results.[24] Traditionally, the premise of DS is to gain insight into the biological activity of tumors exceeding the MC based on the response to LRT. A key component of the UCSF-DS protocol has been an upper tumor burden: 1 lesion greater than 5 cm and $\leq$8 cm, 2 or 3 lesions each $\leq$5 cm and total diameter of all lesions $\leq$8 cm, 4 or 5 lesions each $\leq$3 cm and total diameter of all lesions $\leq$8 cm, and absence of VI/EHS. UCSF-DS criteria have been synonymous with UNOS-DS since acceptance of DS into UNOS guidelines.

A subsequent study compared UCSF-DS with an AC-DS, which allowed any tumor size, number, or diameter without VI/EHS.[25] A difference between these 2 cohorts included a longer minimal observation period from successful DS to the MC to OLT in the AC-DS group (6 months) compared with the USCF-DS group, 3 months. In addition, the development of any new lesion in the AC-DS group was criteria for exclusion for OLT. Among the 74 patients that were treated in the AC-DS group, 48 (64.8%) achieved DS of which 10 (13.5%) underwent OLT and 3 developed recurrent HCC after a median of 21 months posttransplant. The only factor that was associated with successful DS in the AC-DS group was a decrease after LRT in the sum of the largest lesion + number of tumors. The AC-DS group was more likely to drop out at 1 and 3 years (53.5% and 80.0%) compared with the UCSF-DS group (25.0% and

Box 2
Milan criteria and eligibility for downstaging

Milan criteria
- 1 lesion $\geq$2 cm and $\leq$5 cm or
- Up to 3 lesions, each $\geq$1 cm and $\leq$3 cm and
- No vascular invasion or extrahepatic spread

UNOS/UCSF eligibility for downstaging:
- 1 lesion >5 cm $\leq$ 8 cm or
- 2–3 lesions >3 cm and $\leq$5 cm, total tumor diameter $\leq$8 cm
- 4–5 lesions each $\leq$3 cm, total tumor diameter $\leq$8 cm

Criteria for liver transplant eligibility in patients with HCC followed by criteria that is acceptable for attempting down-staging to reach transplant eligibility.

36.1%). In addition to sum of largest lesion and tumor number, CP class B/C was an independent predictor of dropout. Furthermore, the post 5-year OLT survival was lower in the AC-DS group (21.1%) compared with UCSF-DS (56.0%). The overall inferior rate of successful DS, OS post-OLT, and higher dropout rates led the authors to conclude that an upper limit of tumor burden is required for optimal outcomes (see **Box 2**).

A national study comprising 3819 transplants with an MELD upgrade that occurred between 2012 and 2015 explored the outcome of 3 groups: MC (N = 3276), UNOS-DS (N = 422), and AC-DS (N = 121).[26] Those who underwent OLT among AC-DC had significantly lower 3-year OS (71.4%) compared with the MC group (83.2%). From an HCC perspective, the AC-DS cohort had worse 3-year HCC recurrence rates (16.7% vs 12.8% vs 6.9%), higher rates of VI on explant (23.7% vs 16.9% vs 14.2%), and higher explant pathology (40.5% vs 32.5% vs 14.2%) compared with UNOS-DS and MC, respectively. Key findings of this study showed the importance of tumor biology in the selection of candidates for LT after DS to the MC. The first was that the median wait time defined as short (2.6 months) was a significant predictor of death post-LT in those who required DS relative to regions with mid (6.5 months) and long (12.8 months) waiting times (HR, 3.07; CI: 1.41–6.67). An AFP > 100 ng/mL versus less than 20 ng/mL closest to LT was also an independent predictor of mortality post-LT in the UNOS-DS and AC-DS groups, with a 3-year OS of 60% and recurrence rate of 25% in the DS groups when the AFP > 100 ng/mL. Specifically in the AC-DS group, the 3-year OS dropped to 50% if the AFP was greater than 20 ng/mL. The interplay of AFP and tumor burden noted in this study is in line with Metroticket 2.0, which considers AFP level, tumor size, and number to predict HCC-specific 5-year OS post-LT.[27]

Additional valuable data on DS to LT come from a prospective trial for the Multicenter Evaluation of the Reduction in Tumor Size before Liver Transplantation Consortium,[28] which recruited patients from 7 centers in the United States from 4 different regions from 2016 to 2019. All 209 enrolled patients fulfilled the UNOS-DS criteria. DS was successful in 83% of patients. Although patients were more likely to be treated with TACE, there was no significant difference in the success of DS between TACE (N = 132) and TARE (N = 62). DS was successful in 83% of patients. The dropout rate was 37%, including the 35 patients that were never downstaged and 40 patients that progressed after initial DS. The only factor that predicted dropout was a pretreatment AFP-L3 $\geq$ 10%. Although this supports the validity of DS with a 3-year OS of 72% from the receipt of initial LRT, it did have a cautionary finding of 43% of patients exceeding the MC on explant. The risk of understaging was associated with the number of tumors plus the largest tumor diameter on the last pre-LT scan. These results support using LRT for the goal of complete response (CR) to minimize the risk of understaging.

A randomized controlled trial (RCT) called the XXL trial from 4 centers in Italy randomized patients exceeding the MC (without PVTT/EHS) to LT versus continued LRT.[29] Patients who were BCLC B were recruited using the Metroticket 2.0 calculator and those with a predicted 5-year OS of at least 50% using baseline tumor size, number, and AFP level were eligible. A total of 74 patients were enrolled, of which 54 met criteria for successful DS using LRT, surgery, or systemic therapy (limited to sorafenib) per each center's multidisciplinary team (MDT). They were then randomized after a 3-month observation period to continued LRT and systemic therapy at the time of tumor progression versus listing for LT. A total of 45 patients were randomized in a 1:1 fashion to LT arm (n = 23) or to the control group (n = 22); 21 underwent LT (2 refused transplant). This study was intended to enroll 260 subjects; however, the trial was stopped prematurely reflecting the challenges of conducting an RCT that involves

LT. Nonetheless, transplantation resulted in superior 5-year OS of 77.5% (95% CI: 61.9–97.1) compared with the nontransplant group (31.2%; 95% CI: 16.6–58.5). Some of the limitations of the trial included a long time to reach DS criteria (18 months), which was not the traditional MC. The accompanying editorial to this trial suggested that the more ideal trial design would have been a centralized MDT, with successful DS defined as CR and a longer period of observation before randomization (6 months is required by UNOS post-DS to MC) and inclusion of explant pathology in the analysis.[30] To date, this is the only study that has included LT in a randomized trial. The results are encouraging and reinforce the role of DS to LT. It remains to be seen how the deprioritization of the HCC MELD to the median MELD score at transplant for a given transplant referral region minus 3 points will impact dropout in patients who have been successfully DS.

The presence of PVVT has been considered an absolute contraindication for LT because of the high rate of HCC recurrence post-LT. UNOS recently has clarified that careful selection of some patients with branch PVVT who have had achieved prolonged (minimum of 12 months) treatment response may be considered for LT.

A multicenter, international retrospective trial reported the outcomes of 30 patients with PVTT,[31] excluding main PVTT (pV4) who underwent LT after LRT. The 5-year OS was 60%. The investigators identified that the pre-LT AFP was an independent predictor of HCC recurrence post-LT with the ideal AFP cutoff being less than 10 ng/mL. An AFP < 10 ng/mL was associated with a recurrence rate of 11% compared with 50% in those with an AFP > 10 ng/mL ($P = .019$). Explant findings that significantly increased the chance of HCC recurrence included the presence of viable HCC, number of viable tumors, satellite nodules, and greater than MC.

A pilot study from Italy enrolled 17 patients with PVTT (Vp1, n = 3; Vp2, n = 5; Vp3, n = 9) attempted to DS with TARE and listed 6 patients for OLT post-Y90 after meeting the following criteria: tumor burden fulfilled MC, a sustained response greater than 6 months of no enhancement in the PVTT, and AFP < 100 ng/mL.[32] Five patients underwent OLT, of which 3 developed HCC recurrence. Although there was no significant difference in characteristics between the nontransplanted and transplanted patients, there was a higher portion of patients in the nontransplant group with an AFP > 100 ng/mL (41.7% vs 0%). The 1 patient who died of progressive HCC post-LT had an AFP > 10 ng/mL (19 ng/mL) before transplant, which emphasizes the role of tumor biology in DS. The other 2 patients with HCC recurrence occurred in the lung treated with resection, highlighting the important role of resection when feasible for HCC recurrence post-LT to attain long-term OS.

The field of transplant oncology is rapidly evolving as the treatment options, particularly immunotherapy, have expanded. The use of immune checkpoint inhibitors (ICIs) before LT had been considered a contraindication because of fear of graft dysfunction/loss. A case report of a patient who had received Nivolumab for 2 years before LT (8 days after the last dose) died 6 days post-LT owing to hepatic necrosis despite aggressive therapy for acute cellular rejection that supported this theoretical concern. However, subsequent small retrospective series have not seen graft loss.[33–35] UNOS has put forth that, although data on the use of immunotherapy to bridge or DS to LT are preliminary, receipt of ICI alone is not a contraindication to receive an HCC MELD upgrade. Ongoing trials in China, PLENTY202001 and DULECT2020-1, are exploring the role of combination therapy with ICI plus TKI (**Table 1**). It is hoped that such trials will address several critical questions, such as: (1) Does response to combination therapy allow decrease post-LT HCC recurrence in those exceeding the MC? (2) Do ICIs increase risk of graft dysfunction? (3) What is the appropriate time period to stop ICIs

Table 1
Current trials evaluating immune checkpoint inhibitors in combination with tyrosine kinase inhibitors

	PLENTY202001 NCT04425226 (N = 192)	Dulect2020-1 NCT04443322 (N = 20)
Study design	RCT: Lenvatinib + pembrolizumab vs no intervention	Prospective open label: Durvalumab + lenvatinib
Population	HCC > MC before LT	Locally advanced HCC before LT
Primary endpoint	Recurrence-free survival up to 4 years	Recurrence-free survival up to 4 y
Duration of therapy	• Pembrolizumab until 42 days before LT or unacceptable toxicity • LEN until 7 days before LT	• Durva until 42 d before LT or unacceptable toxicity • LEN until 7 days before LT

before LT and observe for PD off ICI as well as minimize risk of ACR? (4) Are there biomarkers to determine the tumor response and immune system degree of activation?

Resection

Resection is recommended for early-stage HCC without VI. In select patient groups, outcomes with resection are comparable to those with transplant. Resection is equivalent to ablation for tumors $\leq$2 cm, so radiofrequency (RFA) or microwave ablation (MWA) should be pursued for smaller tumors. There is also mounting evidence that MWA may be appropriate for tumors up to 4 cm. For larger tumors, resection is preferred. Although not performed frequently in the United States, resection in the setting of low-grade VI or portal vein tumor thrombus (PVTT) is used in certain countries with successful outcomes.[36]

Multiple studies are evaluating the use of neoadjuvant therapies before resection. Notable neoadjuvant modalities include TACE, TARE, and systemic therapies. TACE before resection has been associated with worse survival, increased morbidity, and greater utilization of medical resources in multiple earlier studies because of delay to resection and progressive disease.[37,38] TARE is safe and effective in bridging patients with initially unresectable HCC to resection or transplant.[39] However, there have been no randomized trials evaluating its role as standard neoadjuvant therapy. The safety and tolerability of neoadjuvant immunotherapy are being investigated across multiple phase 2 trials. Kaseb, Pinato, and colleagues[40–42] report a 25% complete pathologic response in a small cohort of patients who were randomized to nivolumab or combination ipilimumab/nivolumab perioperatively. A recent phase 3 multicenter RCT in China showed significantly improved OS and progression-free survival (PFS) with neoadjuvant transarterial FOLFOX chemotherapy compared with standard resection (3-year OS 63.5% vs 46.3%; $P = .016$).[43] The risk of recurrence after resection depends on tumor differentiation, presence of microvascular invasion, and tumor size or burden. Annual recurrence rate after resection is estimated to be $\geq$10%, with 5-year recurrence risk approaching 70% to 80%.[44] Approximately 66% of recurrence events will occur within the first 2 years following resection, and it remains to be seen if immunotherapy can decrease, delay, or impact the pattern of recurrence.

Locoregional Therapies

Uses

LRTs encompass a wide variety of techniques, some of which are used with curative intent. Broadly, ablative techniques are curative therapies used for smaller tumors.

Embolization techniques are used for relatively advanced stages (BCLC B) to prolong survival. Embolization can also be used as a "bridge" to transplant (prevent progression of HCC beyond MC) or to downstage HCC to within MC. There are multiple ongoing RCTs evaluating combinations of LRTs and systemic therapies, in either the neoadjuvant or the adjuvant setting.

Ablation

Ablation is an appropriate therapeutic approach for smaller tumors, ideally less than 3 to 4 cm. Thermal ablation includes the use of microwaves, radiofrequency, cryotherapy, and laser interstitial thermal therapy (LITT). Other ablative techniques incorporate the use of alcohol or electroporation. At this time, MWA and RFA are most common. Multiple studies have shown comparable efficacy between MWA and RFA, but more recent studies suggest improved tumor control with MWA.[45,46] Important considerations aside from tumor size include location of the tumor, risk of tumor seeding, and the inability to obtain tumor samples to be evaluated by a pathologist. Tumors should be more centrally located with a sufficient margin of normal liver tissue to ensure successful ablation. Generally, the use of ablative techniques should achieve a 10-mm margin surrounding the tumor. This is to maximize removal of any microsatellite lesions, which have been shown to predominantly occur within 10 mm of HCC lesions. RFA and MWA have been shown to be comparable to resection for smaller tumors (<2 cm) and should be the first-line approach, consistent with AASLD, EASL, and APASL.[47] Median OS with RFA is 60 months, with a 5-year relative risk of 50% to 70%.[48] A recent meta-analysis that compared local ablative techniques to surgical resection showed similar OS but improved RFS and local recurrence rates with resection (HR, 0.75; 95% CI: 0.65–0.96). Resection led to improved OS and RFS compared with MWA and RFA + TACE.[49] The major complications of ablative techniques include infection or abscess formation, excessive bleeding, liver failure, and tumor seeding. Predictors of increased risk of complication include advanced liver disease, increased tumor size, and increased ablation zone size.[50]

Cryoablation, electroporation, and LITT are less frequently used. Alcohol ablation should no longer be used, as RFA and MWA are known to be superior in terms of tumor response and survival. Cryoablation has been shown to be similarly efficacious to and possibly safer than RFA and MWA in certain settings.[51,52] However, limited studies evaluating this technique prevent its widespread adoption in the United States. Electroporation may be of use when tumors are in unfavorable locations (ie, near vasculature or biliary ducts). The nature of electroporation, which involves delivery of a high-voltage current to target tissue, allows more precise targeting of tumor and less off-target effects to healthy tissues.[50]

Some studies have suggested increased benefit when RFA is combined with chemoembolization, intratumoral iodine, or intravenous liposomal doxorubicin. One study reported superior OS with the combination of TACE and RFA compared with RFA alone in HCC tumors less than 7 cm.[53] Another study demonstrated improved survival with combination RFA and intratumoral iodine-125 seed implantation compared with RFA alone.[54] There may be a role for combination immunotherapy, tyrosine kinase inhibitors (TKIs), and anti-VEGF therapies with ablative techniques. Ablation has been shown to increase recruitment of cytotoxic T cells to the tumor microenvironment. Increased cytotoxic T-cell activity by immune checkpoint inhibition may prove to be complementary to increased T-cell recruitment observed with ablation. Although multiple studies have demonstrated improved survival with adjuvant or neoadjuvant therapies, no multimodal approach has accumulated enough evidence to be incorporated into AASLD recommendations at this time.

A novel ablative technique in development is phototherapy. Photodynamic and photothermal therapies use certain light wavelengths to induce physical and chemical changes that result in tumor death. Challenges to this potential technique include limited delivery of certain light wavelengths percutaneously. Hence, various technologies to aid in local delivery of phototherapy are being developed. Multiple groups have reported effective nanoparticle-based phototherapeutics to ablate orthotopic HCC in mouse models.[55,56]

Embolization

There are multiple embolization techniques, including transarterial bland embolization (TAE), TACE, drug-eluting bead TACE (DEB-TACE), and TARE. TAE consists of bland embolization of arteries supplying a tumor without concurrent administration of any antitumoral agents. This is not commonly performed since the advent of more advanced techniques (eg, TACE, TARE).

Transarterial chemoembolization

TACE involves the administration of lipiodol-based chemotherapeutics before embolization of arterial vessels feeding a tumor. DEB-TACE replaces the lipiodol-based antitumoral agent with DEB carrying an antitumoral agent. This has been shown to increase local delivery of antitumoral agents and decrease systemic exposure. TACE, which is regarded as equivalent to DEB-TACE, is the current standard of care for intermediate stage HCC (BCLC B).[50] TACE can be used to promote survival, as a bridge to transplant, or for DS. Expected survival with TACE in appropriately selected patients is 20 to 37 months, with a median survival of 30 months. A notable challenge with TACE and other LRTs is the identification of patients who would be able to safely tolerate and derive significant benefit from TACE. BCLC B within the new staging system should better identify individuals who will benefit from TACE.

Transarterial radioembolization

TARE was granted approval for the treatment of HCC based on the Local radioEmbolization using Glass Microspheres for the Assessment of Tumor Control with Y-90 (LEGACY) study.[57] This was a multicenter, single-arm retrospective study in the United States of 162 patients with a single lesion greater than 2 cm and $\leq$8 cm, CP A, BCLC A or C (based on PS of 1) who were treated with TARE using an ablative dose of radiation (>190 Gy delivered to the targeted lesion). The primary outcomes were objective response rate (ORR) and duration of response (DoR) based on local mRECIST using blinded, independent central review. ORR was seen in 72.6% and DoR $\geq$ 6 months was seen in 76.1% of patients. The 3-year OS for the entire cohort was 86.6%, which increased to 93.1% among the 45 patients that subsequently had adjuvant therapy with hepatic resection (N = 11) or transplantation (N = 34) after Y90. Of note, the updated BCLC staging system now lists TARE as a potential therapy in early HCC not eligible for or failure after ablation, resection, or transplantation.

The DOSIPHERE trial was an RCT in France comparing the response rate in personalized dosimetry (PD; >205 Gy to the targeted tumor) with standard dosimetry (SD; 120 $\pm$ 20 Gy) in patients treated with glass microspheres.[58] In contrast to the LEGACY study, which excluded PV involvement, the majority of patients in this RCT had PVTT, and the median size of the treated lesion was up 10 to 11 cm compared with 2.7 cm in the LEGACY study. There was a significant improvement in response rate in those treated with PD (76.6%) compared with SD (22.2%), which led to significant improvement in the median OS between the 2 groups: 26.6 months (PD) versus 10.7 months (SD) (HR = 0.421; 95% CI: 0.215–0.826). In addition, the use of boosted radiation in the PD translated to a higher rate of secondary surgery (resection or OLT) 35%

compared with 3.5% in SD ($P = .0024$). Among the patients that had explant data, there was complete pathologic necrosis when segmental dose exceeded 400 Gy. These results challenge the validity of the negative RCTs that compared Y90 with sorafenib; none of these trials employed PD and had median OS in the Y90-treated group, similar to the SD arm in DOSIPHERE.

The TRACE trial, a multicenter RCT comparing glass microspheres to DEB-TACE, reported improved TTP,[59] the primary endpoint (17.1 vs. 9.5 months; $P = .002$) and OS (30.2 vs 15.6 months; $P = .06$) in the TARE group at the interim analysis, leading to early termination of this trial. The safety profile between the 2 forms of intra-arterial therapy was equivalent. PREMEIRE, an earlier RCT comparing Y90 to TACE, demonstrated similar results. Of note, boosted radiation using personalized dosimetry was not used in these RCTs and therefore may have underestimated the benefit seen with TARE. One form of intra-arterial therapy over the other is often driven by center experience and not endorsed by guidelines.

Stereotactic body radiation therapy

The role of stereotactic body radiation therapy (SBRT) in the management of HCC has not been established. SBRT is a form of external beam radiation therapy that allows high doses of radiation to be precisely delivered to tumors in a small number of fractions. RFA was reported to improve survival compared with SBRT in a meta-analysis.[60] Other retrospective analyses have shown similar rates of tumor control with SBRT compared with RFA or TACE. For certain tumor sizes, SBRT may be comparable to TACE in establishing tumor control and OS. The use of SBRT in more advanced HCC may improve survival when compared with sorafenib alone.[50,61] A pivotal prospective study established the role of SBRT in conjunction with embolization techniques to downstage patients with HCC and PVTT as a bridge to successful living donor transplantation.[62] Their findings suggest effective DS as evidenced by elimination of PVTT fluorodeoxyglucose avidity after SBRT and/or radioembolization.

Embolization + systemics

Several RCTs combining systemic therapy with intra-arterial techniques have not shown a benefit to support this practice. Specifically, the use of TACE + TKIs has failed to improve outcomes compared with TACE alone. Challenges in trial design and variability of embolization techniques have been posed as explanations for negative results. TACTICS, a trial in Japan, took a unique approach in its trial design and did not consider new hepatic lesions as progressive disease. Patients were continued in their respective treatment arm until development of untreatable, unTACEable progression, CP C, or VI/EHS. PFS, one of the primary endpoints, was significantly improved with TACE + sorafenib compared with TACE (22.8 vs 13.5 months; HR = 0.661; $P = .02$); however, OS did not meet its endpoint (36.2 vs. 30.8 months; $P = .40$).[63]

Based on data to support that LRT can provide a synergistic effect with immunotherapies, several trials are currently examining the safety and efficacy of TACE plus a single-agent ICI as well as TACE with combination systemic therapy including doublets of ICIs, ICI + TKI, and ICI + bevacizumab. One study is looking at TACE + cabozantinib with ipilimumab/nivolumab in a single-center, single-arm phase 2 study (NCT04472767). CheckMate 74W is a global phase 3 trial in patients with HCC that exceeds the MC but within up to 7 criteria randomized to 3 arms in a 1:1:1 fashion: NIVO + IPI + TACE (arm A), NIVO + IPI placebo + TACE (arm B), or NIVO placebo + IPI placebo + TACE (arm C) (NCT04340193). Similar studies are also being conducted using TARE + ICIs compared with TARE alone (NCT05063565). If positive, the management of intermediate HCC could become transformed. The more agents

used in combination must be balanced with the risk of increased adverse events and reduced tolerability even in well compensated cirrhosis.

Intra-arterial therapies combined with systemic therapy are also being explored in BCLC C. The LAUNCH study conducted in China with predominately HBV-induced HCC reached its primary endpoint of improved OS associated with lenvatinib + TACE compared with lenvatinib alone (17.8 vs 11.5 months; HR, 0.45; $P \leq .001$) in CP A patients with advanced HCC.[64] PFS was also superior, being 10.6 months with combination therapy compared with 6.4 months in lenvatinib monotherapy (HR, 0.43; $P < .001$). Although this study strengthens the potential role of LRT combined with systemic therapy, it is not clear that these results are translatable to a US population that has less HBV.

Systemic Therapies

After the approval of sorafenib in 2007 for advanced HCC, another systemic agent was not approved for over a decade. Over the last few years, the landscape for BCLC C has rapidly expanded. Although there has been approval of several single agents in first (lenvatinib) and second line (regorefenib, cabozantinib, ramucirumab, pembrolizumab), the era of combination therapy has demonstrated the most promising results. In 2019, the IMBRAVE 150 showed that the combination of atezolizumab/bevacizumab met its dual primary endpoint of significant improvement in OS and PFS compared with sorafenib (OS: 19.2 vs 13.2; PFS: 6.9 vs 4.2). This has led to this combination becoming the preferred primary therapy in advanced HCC. The HIMALAYA trial was presented at the American Society of Clinical Oncology Gastroenterology meeting in 2022. The combination of tremelimumab 300 mg, a CTLA 4 inhibitor $\times$ 1 + durvalumab 1500 mg $\times$ every 4 weeks, a PDL-1 inhibitor, outperformed sorafenib when it met the primary endpoint (OS: 16.4 vs 13.4 months; HR = 0.78; 95% CI: 0.65–0.92). However, PFS, the secondary endpoint, was comparable between the 2 groups (3.75 vs 4.07 months; HR = 0.86; 95% CI: 0.73–1.03). This is the first RCT in HCC to show significantly improved OS without improved PFS. Of note, an EGD before enrollment was not mandated. It is anticipated that tremelimumab plus durvalumab will become the next Food and Drug Adminstration–approved therapy in unresectable HCC. COSMIC 312, a phase 3 trial that looked at combination therapy with cabozantinib plus atezolizumab compared with sorafenib, failed to show a significant difference in OS despite a significant improved PFS in the combination group. Another phase 3 trial, CheckMate 9DW, is awaiting readout in first-line therapy comparing nivolumab plus ipilimumab (currently approved in the second line) to monotherapy LEN or sorafenib in BCLC C (NCT04039607).

TKIs have been postulated to decrease tumor resistance to immunotherapy and are being studied in combination with immunotherapy agents. A phase 1b trial reported a promising median OS of 22.0 months in patients with unresectable HCC treated with lenvatinib plus pembrolizumab.[65] A real world retrospective study examined 123 patients treated with LEN + pembrolizumab compared with LEN monotherapy and showed improved ORR, disease control rate, and PFS with combination therapy.[66] The results of LEAP-002, a phase 3 RCT of lenvatinib plus pembrolizumab, compared with lenvatinib monotherapy are anxiously awaited (NCT03713593). Overall, the role of TKIs as monotherapy may begin to decline; they remain an important therapeutic option for those who are ineligible for immunotherapy and may prove to be an efficacious adjunct to immunotherapy.

An unmet need in the systemic space is among those with decompensated cirrhosis, as the registration trials leading to approval of these agents were limited to CP A patients. Real world data sets in CP B patients treated with atezolizumab/

bevacizumab have been reported. D'Alessio and colleagues[67] conducted a retrospective study from 11 centers in UK/Europe/Asia January 2019 to January 2021 of 202 patients treated with atezolizumab/bevacizumab of which 48 patients were CP B (7–9) at the initiation of therapy. There was no significant difference in safety between CP A and B. EGD data were available in 53% of patients. Interestingly, there was no association with the initial size of esophageal varices or CP classification with risk of EV bleed, which occurred in 14% of patients.

SUMMARY

In this review, the authors summarize the current state of epidemiology, detection, diagnosis, and treatment of HCC. The epidemiology and management of HCC have undergone a significant transformation in the past decade. The cause of HCC is increasingly attributable to metabolic disorders and less to viral hepatitis as HBV and HCV treatment becomes more effective and available. The surveillance and diagnosis of HCC are evolving with the advent of novel biomarkers and repurposing existing surveillance tools. However, equally important is tailored risk-stratification of patients and understanding subgroups who would benefit from particular surveillance and treatment strategies. The new BCLC staging system, which has been updated with consideration of novel treatment strategies, should help clarify optimal treatment plans. The therapeutic landscape for HCC is vast and exponentially growing. There have been tremendous advancements in expanding transplant eligibility with the acceptance of the concept of "downstaging." More studies involving LRTs have allowed for improved identification of eligible candidates and an understanding of the risk/benefit profiles of these interventions. Immunotherapy has transformed the treatment of every stage of HCC and has potential to complement nearly every other therapeutic approach. These therapeutic innovations are accompanied by the challenge of rigorous head-to-head comparisons of various treatment strategies. Continued international collaboration will be key to understanding how to best manage HCC.

CLINICS CARE POINTS

- The adoption of the novel Barcelona Clinic Liver Cancer staging system is essential to navigating the numerous treatment options for hepatocellular carcinoma.
- Certain patients, as outlined by the United Network for Organ Sharing/UCSF down-staging criteria, may initially be beyond the Milan criteria but able to be down staged to transplant eligibility with locoregional therapy.
- Treatment stage migration is distinct from down-staging and represents the escalation to a later stage based on multiple characteristics.
- There are increasing indications for immunotherapy in hepatocellular carcinoma, with atezolizumab and bevacizumab becoming the preferred first-line therapy in eligible patients. Ongoing research is evaluating the use of immunotherapy in conjunction with definitive and locoregional therapies.

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