Update on the Diagnosis and Treatment of Hepatocellular Carcinoma

Nicole D. Ferrante, MD,[1,2] Anjana Pillai, MD,[3] and Amit G. Singal, MD, MS[4]

[1]Division of Gastroenterology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Department of Biostatistics, Epidemiology, and Informatics; Center for Clinical Epidemiology and Biostatistics; Center for Pharmacoepidemiology Research and Training; Perelman School of Medicine; University of Pennsylvania; Philadelphia; Pennsylvania

[3]Division of Gastroenterology and Hepatology, University of Chicago Medicine, Chicago, Illinois

[4]Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, Texas

Corresponding author:
Dr Amit G. Singal
Division of Digestive and Liver Diseases
UT Southwestern Medical Center
5959 Harry Hines Blvd
PO Box 1, Suite 420
Dallas, TX 75390-8887
Tel: (214) 645-4018
E-mail: amit.singal@utsouthwestern.edu

Abstract: Hepatocellular carcinoma (HCC) is the fourth-leading cause of cancer-related mortality worldwide and the fastest-rising cause of cancer-related death in the United States. Given the strong association between tumor stage and prognosis, HCC surveillance is recommended in high-risk patients, including patients with cirrhosis from any etiology. The diagnosis can be made based on characteristic imaging findings, with histologic confirmation primarily reserved for patients with atypical imaging findings. Over the last 2 decades, the treatment landscape for HCC has experienced significant advances. Curative therapies, including liver transplantation and surgical resection, are available to patients with early-stage HCC; however, recent data have expanded the potentially eligible patient population. Locoregional therapies, including transarterial chemoembolization and transarterial radioembolization, continue to be standard therapies for patients with intermediate-stage disease. The greatest advances have been observed for patients with advanced HCC, where there are now multiple first- and second-line options that can prolong survival by up to 2 years when used sequentially. The increasing complexity of HCC treatment options underlies the necessity for multidisciplinary care, which has been associated with increased survival. This article reviews data on best practices for early detection and diagnosis of HCC and the current status of treatment options.

Keywords
Hepatocellular carcinoma, screening, diagnosis, LI-RADS, treatment, immunotherapy

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fourth-leading cause of cancer-related mortality worldwide.[1,2] HCC has been increasing in incidence since the 1980s,[3] and is now the fastest-rising cause of cancer-related death in the United States, with an estimated 1,284,252

Table. LI-RADS Major and Minor Imaging Features on Contrast-Enhanced CT/MRI That Favor Hepatocellular Carcinoma[a]

Major Features	Minor Features
Nonrim-like arterial phase hyperenhancement	Nodule-in-nodule architecture
Enhancing capsule	Nonenhancing capsule
Nonperipheral washout	Mosaic architecture
Threshold growth (≥50% increase in size of a lesion in ≤6 months)	Blood products in the lesion
Size ≥20 mm	Fat in the lesion (more than adjacent liver)

CT, computed tomography; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging.

[a]Based on LI-RADS version 2018.

deaths predicted between 2018 and 2040 worldwide.[1,4] The majority of HCC occurs in the setting of chronic liver disease, with the most common risk factors being chronic hepatitis B virus (HBV) worldwide and hepatitis C virus–related cirrhosis and nonalcoholic steatohepatitis in the Western world. The estimated 5-year survival rate for HCC is only 18%,[5] which is driven by a large proportion of patients being diagnosed at advanced stages when curative options are not feasible, as well as underuse of curative therapies among patients detected at early stages.[6,7] This article reviews best practices for early detection and diagnosis of HCC and the current status of treatment options that can afford improved survival when applied in clinical practice.

Hepatocellular Carcinoma Surveillance

Given the connection between tumor stage and prognosis, the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver recommend surveillance in patients with cirrhosis and in subsets of patients with chronic HBV infection.[8-10] Two large randomized, controlled trials (RCTs) found that semiannual screening reduced HCC-related mortality among patients with HBV infection.[11,12] Although no RCTs have evaluated HCC surveillance in patients with cirrhosis, several cohort studies have reported earlier detection and improved survival in patients with cirrhosis who undergo surveillance.[6,13] Major guidelines recommend surveillance testing with semiannual abdominal ultrasound, and many experts also recommend serologic testing for alpha-fetoprotein (AFP), a serum biomarker.[8,9] At best, semiannual ultrasound with AFP achieves a sensitivity of 63% for early-stage HCC, missing over one-third of tumors at that stage, and is associated with screening-related harms from false-positive results in 10% to 20% of patients.[14,15] Ongoing studies are evaluating novel blood-based biomarker panels and imaging techniques to optimize surveillance outcomes, although none has sufficient data to be implemented into routine practice at this time.[16,17] Despite improved utilization over time, surveillance is implemented in less than 50% of patients with cirrhosis, with few receiving consistent semiannual surveillance.[18] These data highlight the need for interventions to improve surveillance effectiveness.[19]

Patients with abnormal surveillance tests should undergo follow-up testing to confirm their HCC diagnosis. Patients with small ultrasound nodules (<10 mm) have a low risk of HCC and should undergo repeat ultrasound imaging in 3 to 6 months.[8,20] In contrast, patients with nodules 10 mm or larger or abnormal AFP should undergo diagnostic imaging with multiphase computed tomography (CT) or magnetic resonance imaging (MRI) to establish a diagnosis.[8,20]

Hepatocellular Carcinoma Diagnosis

Unlike most solid malignancies, HCC can be diagnosed with imaging alone in high-risk individuals.[9,20] The American College of Radiology has proposed a nomenclature called the Liver Imaging Reporting and Data System for the standardization of interpreting and reporting multiphase CT scan and MRI.[21] Lesions are classified into 5 main categories ranging from definite benign (LR-1) to definite HCC (LR-5) based on a combination of major criteria, including arterial hyperenhancement, delayed washout, and an enhancing capsule, as well as several minor criteria (Table).[21] The sensitivity of LR-3, LR-4, and LR-5 for HCC is 38%, 74%, and 94%, respectively.[22] Therefore, patients with characteristic imaging (ie, LR-5) can be treated for HCC without histologic confirmation.

Serum tumor markers play a minor role in the diagnosis of HCC. AFP has limited sensitivity and specificity for HCC, and therefore was removed from the diagnostic criteria for HCC. AFP can be elevated in a variety of other

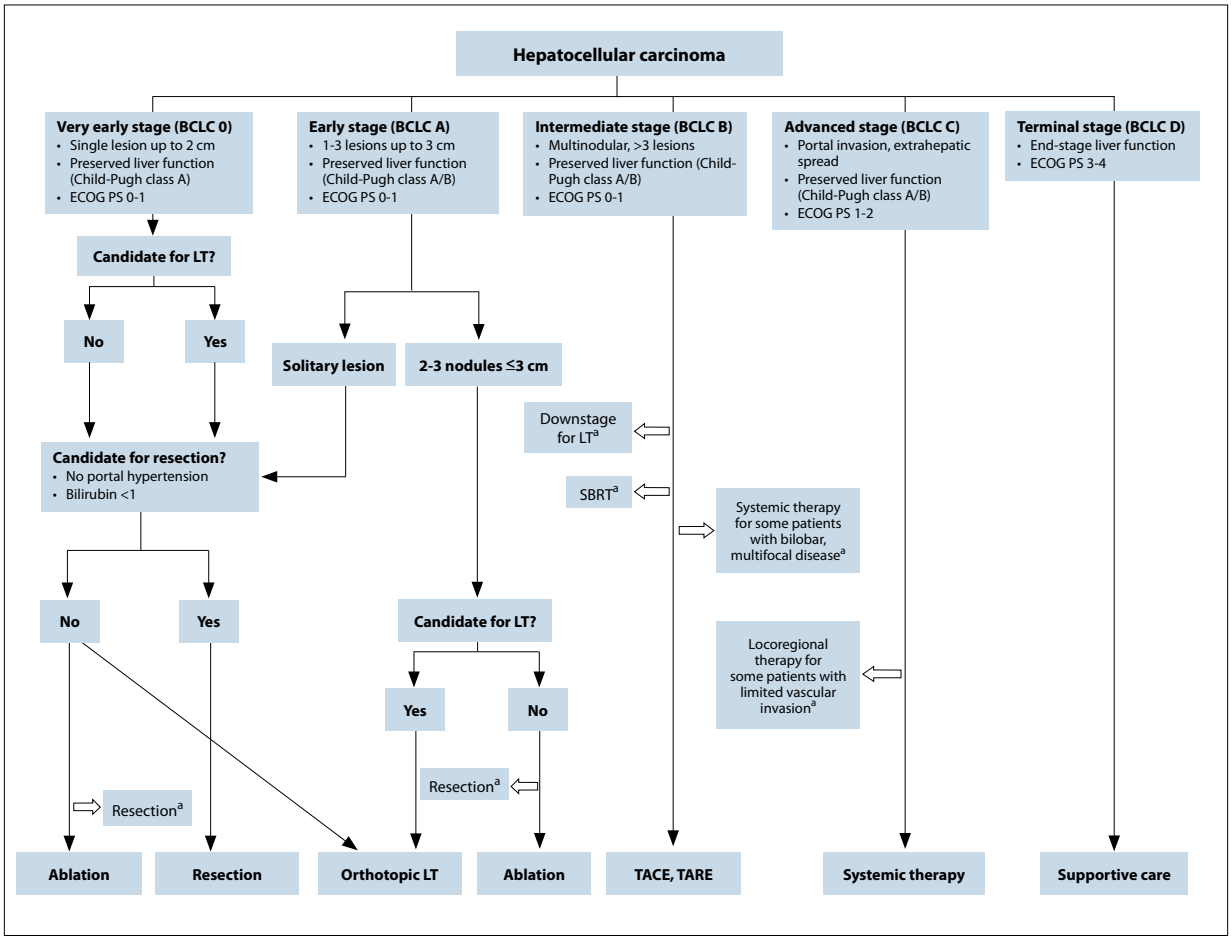

Figure 1. BCLC treatment recommendations according to BCLC stage, including additional evidence-based therapies.

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; LT, liver transplantation; PS, performance status; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

[a]These therapies have not yet been incorporated into guidelines but are evidence-based.

gastrointestinal malignancies, including cholangiocarcinoma, and is often normal in patients with early-stage HCC.[23-25]

Biopsy is primarily reserved for select patients with atypical imaging, which can be observed in 10% of HCC patients. Some HCC lesions can have enhancement without washout or washout with enhancement (often classified as LR-4), whereas other lesions have atypical features worrisome for malignancy but not definite for HCC (classified as LR-M), such as rim arterial phase enhancement or peripheral washout.[21] There are well-defined histopathologic criteria for classifying and grading HCC, with classic histologic features including wide trabeculae, prominent acinar pattern, cytologic atypia, vascular invasion, and vascularization.[26,27] Although most HCC diagnoses can be established using histology alone, stains such as glypican-3, glutamine synthetase, and heat shock protein 70 can be helpful in some cases.[26,27]

Tumor Staging

Staging is necessary for prognostication and selection of therapy, and should take into account the degree of underlying liver dysfunction. Multiple staging systems have been proposed for HCC, and there is no universally recommended system. The Barcelona Clinic Liver Cancer (BCLC) system classifies patients based on tumor burden (number of lesions, maximum tumor diameter, and presence of vascular invasion or metastasis), degree of liver dysfunction (Child-Pugh class), and cancer-related symptoms (Eastern Cooperative Oncology Group performance status).[28] A study comparing 7 staging systems

reported that the BCLC system had the best independent predictive power for estimating survival in a US cohort.[29] The BCLC system has also been validated in several cohorts from North America, Europe, and Asia, and is, therefore, recommended by both the AASLD and EASL for HCC staging.[20] The BCLC classification ranges from very-early–stage HCC (BCLC 0), with a 5-year survival rate exceeding 70%, to terminal-stage HCC (BCLC D), with a median survival below 6 months.

Hepatocellular Carcinoma Treatment

The BCLC system is linked to a treatment algorithm (Figure 1) that includes curative options for early-stage HCC and palliative options for intermediate- and advanced-stage HCC. Given an increasing number of treatment options, a multidisciplinary approach is recommended and has been shown to improve appropriate treatment receipt and overall survival (OS).

Surgical Resection

Surgical resection is the therapy of choice in HCC patients without cirrhosis and those with Child-Pugh class A cirrhosis without portal hypertension; however, careful patient selection is critical. Although resection is widely used in Asia because many patients have HBV-related HCC and compensated liver function, only a small proportion of patients in the United States and Europe are eligible for resection given underlying liver dysfunction. Patients with advanced liver dysfunction are at high risk of postoperative liver failure. The best outcomes are observed in patients with Child-Pugh class A cirrhosis, bilirubin 1 mg/dL or less, and no portal hypertension.[30,31] A Model for End-Stage Liver Disease (MELD) score greater than 9 has been associated with an increased risk of perioperative mortality and postoperative liver failure in retrospective studies.[32-34] In addition to the degree of underlying liver dysfunction, the risk of postoperative liver failure is driven by the quantity of future liver remnant (FLR).[35] In patients without cirrhosis, the risk of postoperative liver failure is low if the FLR exceeds 20%; however, an FLR of 40% is typically required in patients with cirrhosis.[36] In patients with insufficient FLR, portal vein embolization or neoadjuvant transarterial radioembolization (TARE) promotes hypertrophy of the contralateral lobe and allows for resection in select cases.[36-38]

Observational studies suggest that surgical resection can be expanded to select patients with portal hypertension, multifocal tumors, and vascular invasion.[39,40] Retrospective studies have reported acceptable 5-year survival rates in patients with Child-Pugh class A cirrhosis with portal hypertension.[41-44] The BRIDGE study, a large multicenter, retrospective study, demonstrated no significant differences in survival among patients with or without portal hypertension undergoing liver resection.[45] The use of surgical resection in patients with portal hypertension may be further facilitated by adoption of laparoscopic resection. Although multifocality may be a risk factor for HCC recurrence, retrospective studies have reported improved survival with surgical resection compared to ablation, transarterial chemoembolization (TACE), and supportive care for select patients with multifocal HCC.[46,47] These findings were confirmed in an RCT in which 230 patients with HCC within the Milan criteria (unifocal lesion ≤5 cm or 2-3 lesions each ≤3 cm, without large-vessel invasion or metastases) were randomized to surgical resection or radiofrequency ablation (RFA); the study reported 5-year survival rates of 76% and 55%, respectively.[48] In patients with limited vascular invasion, a case-control study of 603 patients with resectable HCC and portal vein tumor thrombus found that resection improved survival compared to TACE.[49] Taken together, these data suggest that survival may be increased with surgical resection compared to palliative treatment in select patients in high-volume, expert centers.

Although resection is considered curative, with a 5-year survival rate greater than 60%,[50] it is associated with a high rate of tumor recurrence; thus, close surveillance is critical.[51] The risk of recurrence increases with tumor size, number of lesions, and presence of microvascular invasion with up to a 50% risk of tumor recurrence within 5 years for larger or multinodular HCC.[51] The STORM trial failed to find any benefit of adjuvant sorafenib (Nexavar, Bayer) in improving time to recurrence or survival.[52] There are several ongoing studies evaluating the role of neoadjuvant and adjuvant checkpoint inhibitors to reduce the risk of recurrence.[53-56]

Liver Transplantation

Liver transplantation (LT) provides the best chance for long-term survival, as it offers a cure for both HCC and the underlying cirrhosis. When LT was initially offered to all patients with HCC in the late 1980s and early 1990s, it was associated with a 5-year survival rate of only 30% to 40% and, thus, a moratorium was placed for this indication.[57] In a landmark study published in 1996, Mazzaferro and colleagues identified the Milan criteria, which were associated with excellent posttransplant outcomes.[58] Subsequently, the Milan criteria defined the standard eligibility of HCC patients for LT, resulting in improved 5-year survival rates of more than 70% and recurrence rates of approximately 10%.[58,59]

In 2002, the Milan criteria were adopted for the MELD exception pathway in the United States, providing additional points for HCC patients. Initially, HCC patients within the Milan criteria were provided a MELD

score of 24 to 29 based on tumor size and a 10% increase every 3 months until LT or removal from the waiting list.[60] However, this over-advantaged patients with HCC, raising concern for disparities in LT access compared to non-HCC patients.[61] Over time, changes have been made to the allocation system, involving decreases in allocated MELD exception points. As of May 2019, HCC patients are required to wait 6 months from listing before being granted MELD exception points, at which time they receive a score of the median MELD score for the region minus 3 points.[62]

Given the success of LT for HCC, there is substantial interest in expanding LT to additional populations. In 2001, the University of California San Francisco (UCSF) derived the UCSF criteria (single tumor ≤6.5 cm or 2-3 tumors with largest lesion ≤4.5 cm and total tumor volume ≤8 cm, without vascular invasion or metastases) from explant pathology, and reported similar 1- and 5-year posttransplant survival rates compared to patients who underwent LT within the Milan criteria.[63] Subsequent single-center observational studies reported similar posttransplant survival rates among patients undergoing LT within the Milan criteria and UCSF criteria.[64-66] The up-to-7 criteria is an additional proposal to expand HCC size limits, which has been associated with a 5-year posttransplant survival rate of 71%.[67]

At the forefront of LT is tumor downstaging, which involves the application of locoregional therapy to reduce tumor burden to meet LT eligibility criteria and is associated with encouraging results.[68,69] An intention-to-treat analysis from UCSF reported similar 5-year posttransplant survival rates among patients transplanted after successful downstaging and patients who initially fulfilled the Milan criteria (77.8% vs 81.0%; *P*=.69).[70] The first multicenter study using the UCSF downstaging protocol evaluated outcomes of 187 HCC patients who underwent downstaging over a 10-year period and reported a 5-year posttransplant survival rate of 80% in patients transplanted after successful downstaging to within the Milan criteria.[71] In an effort to standardize downstaging criteria, the United Network for Organ Sharing (UNOS) adopted the UCSF criteria for downstaging in 2017 and allows patients to receive MELD exception points if the tumor is successfully downstaged.[70] A validation study used the UNOS database to compare outcomes among patients transplanted with HCC always within the Milan criteria, patients successfully downstaged to within the Milan criteria using the UCSF protocol, and patients successfully downstaged using other downstaging protocols nationwide.[72] The study reported similar 3-year posttransplant survival rates among patients always within the Milan criteria (83%) and patients successfully downstaged using the UCSF protocol (79%), but lower survival rates were reported in patients downstaged for HCC exceeding UCSF criteria (71%).[72]

The risk of HCC recurrence post-LT is estimated to be 12% to 19%.[73-75] AFP is predictive of post-LT survival and HCC recurrence, and has been incorporated into several models for predicting post-LT recurrence. The Risk Estimation of Tumor Recurrence After Transplant score is an externally validated model that uses the AFP at transplant and explant pathology to predict 5-year recurrence.[76] Similarly, the Model of Recurrence After Liver Transplant score incorporates preoperative factors to predict 5-year recurrence-free survival.[77] Currently, UNOS restricts patients with AFP levels higher than 1000 ng/mL from receiving MELD exception points regardless of tumor size unless successfully downstaged to AFP levels lower than 500 ng/mL.

Local Ablative Therapy

Ablative therapy is a potentially curative treatment for early-stage HCC. It destroys tumor cells via chemical injection or thermal destruction,[78] either percutaneously or surgically, and is recommended for patients with very-early–stage or early-stage HCC (BCLC 0-A) who are ineligible for surgical resection.[8] RFA generates heat via the application of high-frequency electric current and is most effective in lesions 2 cm or smaller, achieving a complete response of 97.2% over a median follow-up of 31 months.[79] Its efficacy is limited by large tumor size and proximity to large vessels and bile ducts, which results in the dissipation of heat (called the heat-sink effect).[80] Multiple RCTs have compared resection to RFA and have suggested that resection is likely associated with improved survival at 1, 3, and 5 years.[48,81,82] However, differences in outcomes between resection and ablation are mitigated in lesions 2 cm or smaller, as demonstrated by a retrospective study from Italy reporting similar rates of 4-year survival (74.4% for resection vs 66.2% for RFA), recurrence, and complications.[83-85] In a cost-effectiveness analysis, RFA offered similar quality-adjusted life-years at a lower cost than resection for very-early–stage HCC (≤2 cm).[86] In lesions that were 3 to 5 cm, resection offered better life expectancy and was more cost-effective compared to RFA.[86] Microwave ablation (MWA) is a newer technique that generates heat by creating an electromagnetic field, resulting in higher temperatures, larger ablation volumes over fewer sessions, and less heat-sink effect than RFA. A 2017 RCT reported similar rates of 1-, 3-, and 5-year local tumor progression, OS, and disease-free survival between RFA and MWA.[87] However, a meta-analysis reported no difference in tumor response, recurrence, 3-year survival rate, or major complications between the 2 modalities.[88] When only studies evaluating patients with larger tumor size were analyzed, MWA was

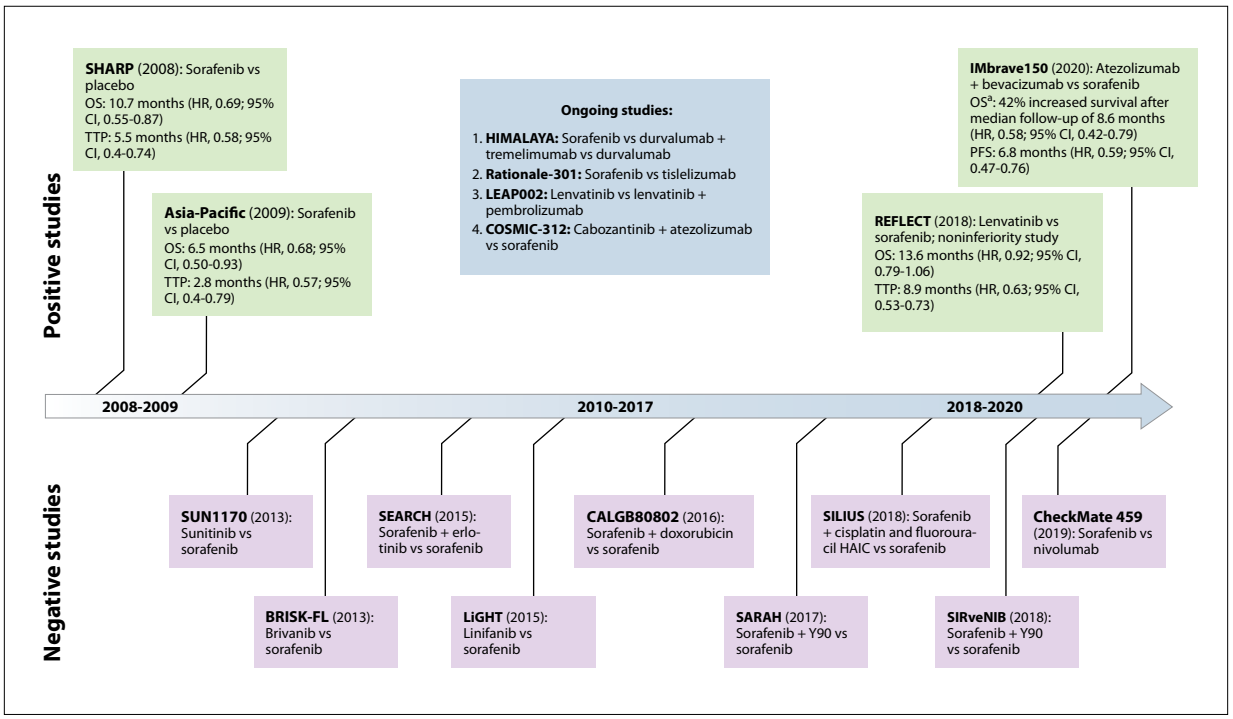

Figure 2. Timeline of major phase 3 clinical trials of first-line treatments for advanced hepatocellular carcinoma by year of publication or presentation at a national meeting.

HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

[a]Median survival not yet reached. Results reported are after a median follow-up of 8.6 months.

superior to RFA in terms of tumor response and recurrence rate.[88]

Transarterial Chemoembolization

TACE involves the intra-arterial administration of chemotherapy followed by embolization, and it has been the traditional standard-of-care therapy for patients with intermediate-stage HCC (BCLC B) per AASLD and EASL guidelines. Although the procedure is noncurative in most cases, robust data show TACE can produce objective responses in 16% to 70% of patients and significantly prolong survival compared to supportive management, providing a median survival of approximately 26 months.[89,90] Substantial center-to-center variation exists in terms of the number of treatments and chemotherapeutic agents used for conventional TACE. Adoption of drug-eluting beads with TACE (DEB-TACE), in which beads slowly release chemotherapy over time,[91] may help reduce some of the heterogeneity between centers, although there still remain differences in the degree of selectiveness when treating tumors. There have been no demonstrated differences in tumor response or OS between TACE and DEB-TACE; however, DEB-TACE is believed to be better tolerated with a lower incidence of postembolization syndrome.[92-94]

Transarterial Radioembolization

TARE, which is the intra-arterial administration of radioactive microemboli, has emerged as an alternative to TACE. Unlike TACE, TARE maintains patency of the hepatic artery and can, therefore, be used in patients with portal vein thrombosis. A prospective cohort study including 1000 patients with HCC stage BCLC A, B, or C reported an OS of 47.3, 25.0, and 15.0 months, respectively, in patients with Child-Pugh class A cirrhosis and of 27.0, 15.0, and 8.0 months in Child-Pugh class B cirrhosis patients.[95] Other nonrandomized studies have reported OS rates of approximately 17 months in patients with intermediate-stage HCC.[96,97] A small phase 2 RCT comparing TARE and conventional TACE demonstrated a significant improvement in time to progression (>26.0 months vs 6.8 months; P=.0012) with fewer adverse effects, but no significant difference in OS (18.6 months vs 17.7 months; P=.99).[98] A meta-analysis that included 2 RCTs and 8 retrospective studies found no significant difference in 1-year survival rates but significant

improvements in 2- and 3-year survival rates with TARE.[99] Lastly, observational studies have reported that TARE is better tolerated and associated with shorter hospital stays.[100] Although there are growing data supporting TARE and increased adoption in clinical practice, the lack of large phase 3 data have precluded its inclusion in clinical practice guidelines.

Stereotactic Body Radiation Therapy

HCC was historically thought to be radioresistant because sufficient doses of external beam radiation were limited by high rates of radiation-induced liver injury. Stereotactic body radiation therapy (SBRT) is an emerging therapy that uses overlapping beams of radiation to safely deliver sufficient radiation doses to HCC lesions while limiting radiation exposure to the background liver. There are increasing single-arm data demonstrating promising outcomes, as well as retrospective analyses comparing outcomes following SBRT to other therapies. In a retrospective analysis of 224 patients who underwent RFA vs SBRT, the latter was associated with improved 1- and 2-year local control rates (83.6% and 80.2%, respectively, with RFA vs 97.4% and 83.8%, respectively, with SBRT) and similar 1- and 2-year survival rates.[101] Similarly, analyses comparing SBRT vs TACE and RFA demonstrate similar OS rates, although these studies continue to be limited by risk of selection bias and residual confounding.[102,103]

Systemic Therapy

Systemic therapy is recommended for advanced HCC (BCLC C), that is, patients with vascular invasion, extrahepatic metastasis, or tumor-related symptoms (Eastern Cooperative Oncology Group 1-2), as well as patients who progress after locoregional therapy.[8,9] Over the last 10 years, the landscape of systemic therapy has rapidly expanded. Despite the introduction of sorafenib, the prognosis of advanced HCC remained poor over time.[104] New first- and second-line therapies have recently become available and are expected to improve survival.

First-line systemic options for advanced HCC include sorafenib, lenvatinib (Lenvima, Eisai), and combination atezolizumab (Tecentriq, Genentech) plus bevacizumab (Avastin, Genentech). The first agent approved was sorafenib, which is a multitargeted tyrosine kinase inhibitor with antiangiogenic effects through inhibition of vascular endothelial growth factor (VEGF) receptors.[105] Sorafenib was approved based on 2 large phase 3 RCTs, the SHARP trial[106] and the Asia-Pacific trial (Figure 2).[107] The SHARP trial randomized 602 patients to receive sorafenib or placebo, and was stopped early when the second interim analysis reported improved median OS of 10.7 vs 7.9 months (hazard ratio [HR], 0.69; 95% CI, 0.55-0.87).[106] The Asia-Pacific trial similarly reported improved OS of 6.5 vs 4.2 months with sorafenib (HR, 0.68; 95% CI, 0.50-0.93).[107] Notably, both studies predominantly included patients with Child-Pugh class A cirrhosis. No RCTs have evaluated sorafenib in patients with Child-Pugh class B cirrhosis, who represent a significant proportion of advanced HCC patients. The GIDEON study, a prospective observational database evaluating treatment practices, found that sorafenib in patients with Child-Pugh class B cirrhosis had acceptable tolerability with a median survival of 5.2 months.[108]

Lenvatinib was the second agent approved for first-line therapy. Like sorafenib, it is a multitargeted tyrosine kinase inhibitor with antiangiogenic effects through the inhibition of VEGF receptors as well as increased activity against other growth factor receptors, such as fibroblast growth factor receptors.[109] Lenvatinib was approved in 2018 based on the results of the REFLECT study, a phase 3 noninferiority trial that compared lenvatinib to sorafenib.[109] The trial included 954 patients with Child-Pugh class A cirrhosis and advanced HCC without significant (>50%) liver involvement or main portal vein invasion, and reported noninferiority of lenvatinib to sorafenib with an OS of 13.6 vs 12.3 months (HR, 0.92; 95% CI, 0.79-1.06). Lenvatinib also demonstrated superiority for several secondary outcomes, including increased objective response rate (24.1% vs 9.2%) and prolonged progression-free survival (7.4 vs 3.7 months).[109]

The combination of immune checkpoint inhibitor atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab, a VEGF inhibitor, was the most recent treatment approved for first-line therapy of advanced HCC and is the first treatment in more than 10 years to be associated with improved OS and progression-free survival compared to sorafenib. The combination therapy was first evaluated in a phase 1b study of patients with advanced HCC, which reported an objective response rate of 34% and a 6-month progression-free survival rate of 71%.[110] The treatment received breakthrough therapy designation by the US Food and Drug Administration (FDA) in April 2020 based on results of the IMbrave150 study, a multicenter phase 3 study that randomized 501 patients with Child-Pugh class A cirrhosis and advanced HCC in a 2:1 ratio to atezolizumab plus bevacizumab vs sorafenib.[111] Atezolizumab plus bevacizumab was associated with a 42% reduction in mortality (HR, 0.58; 95% CI, 0.42-0.79) after a median follow-up of 8.6 months and improved progression-free survival (HR, 0.59; 95% CI, 0.47-0.76) compared to sorafenib. At the interim analysis, median OS had not yet been reached for the atezolizumab plus bevacizumab arm but was 13.2 months for the sorafenib arm. The combination therapy was associated with an increased response rate (33.2% vs 13.2% per modified Response

Evaluation Criteria in Solid Tumors; $P<.0001$) and was well tolerated, with minimal adverse events.[111] Of specific note, incident gastrointestinal bleeding was low in the atezolizumab plus bevacizumab arm, likely due to patient selection (Child-Pugh class A cirrhosis without significant portal hypertension) and patients being required to have an upper endoscopy with control of varices prior to entering the trial.

Second-line options have become available since 2017 and include 2 tyrosine kinase inhibitors (regorafenib [Stivarga, Bayer] and cabozantinib [Cabometyx, Exelixis]), a monoclonal VEGF inhibitor (ramucirumab [Cyramza, Eli Lilly]), 2 programmed cell death protein 1 (PD-1) checkpoint inhibitors (nivolumab [Opdivo, Bristol Myers Squibb] and pembrolizumab [Keytruda, Merck]), and a combination regimen targeting PD-1 and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) (nivolumab and ipilimumab [Yervoy, Bristol Myers Squibb]). Regorafenib was the first agent approved based on the results of the phase 3 RESORCE study.[112] Patients who tolerated sorafenib but had radiologic progression were randomized to receive regorafenib vs placebo, and regorafenib provided a survival benefit of 10.7 vs 7.8 months (HR, 0.63; 95% CI, 0.50-0.79).[112] In a post hoc analysis, median survival from the start of sorafenib was 26.0 vs 19.2 months in the regorafenib vs placebo groups, highlighting the potential for second-line therapy to provide meaningful survival of approximately 2 years in select patients.[113] Cabozantinib was evaluated in the phase 3 CELESTIAL trial, which included patients who failed sorafenib due to intolerance or radiologic progression, and which reported improved median survival of 10.2 vs 8.0 months (HR, 0.76; 95% CI, 0.63-0.92).[114] Ramucirumab was initially evaluated in the REACH trial, which failed to show a survival benefit, but a post hoc analysis suggested it may be beneficial in patients with AFP levels higher than 400 ng/dL. In the subsequent REACH-II trial, among patients who failed sorafenib and had an AFP higher than 400 ng/dL, ramucirumab demonstrated a modest improvement in median survival of 8.5 vs 7.3 months compared to placebo (HR, 0.71; 95% CI, 0.50-0.95).[115,116]

Immune checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 are being evaluated for advanced HCC. Nivolumab and pembrolizumab are anti–PD-1 monoclonal antibodies that received accelerated approval based on phase 2 studies demonstrating long-lasting response rates in approximately 15% to 20% of patients, but failed to improve OS in subsequent phase 3 studies. Nivolumab was evaluated in the phase 3 CheckMate 459 trial, which did not significantly improve OS compared to sorafenib (Figure 2).[117] Pembrolizumab was evaluated in the phase 3 KEYNOTE-240 trial, which did not improve OS compared to supportive care.[118] Recently, the FDA granted accelerated approval for the combination of nivolumab and ipilimumab based on phase 2 single-arm data showing durable responses in 33% of patients.[116] Preclinical studies suggest a potential synergistic effect between checkpoint inhibitors and VEGF inhibitors, as well as with dual immune checkpoint blockade. Excitement for combination therapies has been further bolstered by results observed in the phase 3 IMbrave150 trial.[111] As a result, several ongoing trials are evaluating combination therapy with checkpoint inhibitors, tyrosine kinase inhibitors, and VEGF inhibitors.[119-122]

Conclusion

HCC surveillance is associated with earlier diagnosis of HCC and the best long-term survival given potentially curative treatment options such as surgical resection, local ablation, and LT. There are several new treatment options for patients with larger tumor burden, particularly for patients requiring systemic therapy. The availability of combination therapies, such as atezolizumab plus bevacizumab, and options for sequential therapy herald an opportunity to achieve survival approaching 2 years in patients with advanced HCC. With evidence-based application of surveillance, recall, and treatment principles, notable improvements in HCC survival may be seen.

Disclosures

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