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REVIEW

Hepatocellular carcinoma: natural history, current management, and emerging tools

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Christopher L Tinkle
Daphne Haas-Kogan

Department of Radiation Oncology, University of California, San Francisco, CA, USA

Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver tumor and represents the third-leading cause of cancer-related death in the world. The incidence of HCC continues to increase worldwide, with a unique geographic, age, and sex distribution. The most important risk factor associated with HCC is liver cirrhosis, with the majority of cases caused by chronic infection with hepatitis B (HBV) and C (HCV) viruses and alcohol abuse, although nonalcoholic fatty liver disease is emerging as an increasingly important cause. Primary prevention in the form of HBV vaccination has led to a significant decrease in HBV-related HCC, and initiation of antiviral therapy appears to reduce the incidence of HCC in patients with chronic HBV or HCV infection. Additionally, the use of ultrasonography enables the early detection of small liver tumors and forms the backbone of recommended surveillance programs for patients at high risk for the development of HCC. Cross-sectional imaging studies, including computed tomography and magnetic resonance imaging, represent further noninvasive techniques that are increasingly employed to diagnose HCC in patients with cirrhosis. The mainstay of potentially curative therapy includes surgery – either resection or liver transplantation. However, most patients are ineligible for surgery, because of either advanced disease or underlying liver dysfunction, and are managed with locoregional and/or systemic therapies. Randomized controlled trials have demonstrated a survival benefit with both local therapies, either ablation or embolization, and systemic therapy in the form of the multikinase inhibitor sorafenib. Despite this, median survival remains poor and recurrence rates significant. Further advances in our understanding of the molecular pathogenesis of HCC hold promise in improving the diagnosis and treatment of this highly lethal cancer.

Keywords: hepatocellular carcinoma, viral hepatitis, liver transplantation, ablation, embolization, sorafenib

Natural history

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and the leading cause of death in patients with cirrhosis.[1,2] Symptoms attributable to HCC are usually absent. Rather, patients typically manifest symptoms related to underlying cirrhosis, a condition present in 80%–90% of patients with HCC.[3] Consequently, the majority of patients are diagnosed with advanced disease, often precluding potentially curative therapies. This has resulted, in part, in a 5-year overall survival rate of 12% and a median survival following diagnosis ranging from 6 to 20 months.[3,4]

When symptomatic, HCC is often associated with nonspecific complaints, including right upper abdominal or epigastric pain, early satiety, weight loss, and malaise.

Correspondence: Daphne Haas-Kogan
Department of Radiation Oncology, University of California, San Francisco, 1600 Divisadero Street, Suite H1031, San Francisco, CA 94115-1708, USA
Phone +1 415 353 7187
Fax +1 415 353 9883
Email dhaaskogan@radonc.ucsf.edu

The onset of ascites, encephalopathy, jaundice, or variceal bleeding in patients with previously compensated cirrhosis should raise clinical suspicion for HCC.[5] Rarely, patients may present with acute onset of severe abdominal pain and distension, hypotension, and a sudden drop in hematocrit resulting from tumor rupture and intraperitoneal bleeding. Emergent embolization of the bleeding blood vessel and/or surgery may be required for this complication.[6]

HCC is associated with a number of paraneoplastic syndromes resulting in hypoglycemia, erythrocytosis, hypercholesterolemia, hypercalcemia, severe watery diarrhea, and cutaneous manifestations.[7] Extrahepatic spread at presentation is relatively uncommon, ranging between 10% and 30%.[8–10] The most common sites of metastasis include lung, adrenal gland, regional lymph node regions (including the portahepatic and celiac lymph node chains), and bone.[11] Importantly, extrahepatic nodal involvement is often difficult to assess based on cross-sectional imaging, as perihepatic lymphadenopathy is frequently present in patients with cirrhosis.[12]

Risk factors and epidemiology

The vast majority of cases of HCC occur in the setting of liver cirrhosis, and thus the etiology of HCC mirrors that of chronic liver disease and cirrhosis. Broadly, risk factors for HCC include viral infections, environmental toxins, comorbid conditions, inherited errors of metabolism, and autoimmune disorders.[13] The unique geographic, sex, and age distributions of HCC are largely a result of the specific patterns of these risk factors, with the majority of cases the sequelae of hepatitis B and C viral infection and alcoholic liver disease.[14]

Chronic HBV infection (ie, hepatitis B surface antigen seropositivity) is the leading cause of HCC in Asia and Africa, where the virus is endemic and vertical transmission common.[1,3] While HBV-induced HCC typically develops in cirrhotic livers, select populations of hepatitis B carriers remain at risk for HCC even in the absence of liver cirrhosis (Table 1).[15] While the incidence of HCC in hepatitis B carriers depends on several factors, results from a prospective controlled study have revealed the annual incidence of HCC in hepatitis B carriers to be 0.5% in those without known cirrhosis and 2.5% in those with cirrhosis.[16]

HCV infection represents a major risk factor for HCC, accounting for around one-third of cases in the United States and is thought, at least in part, to be responsible for the increasing incidence of HCC in the US.[17,18] HCV infection confers the highest risk of HCC in patients with cirrhosis, with an annual incidence ranging between 2% and 8%.[15] A prospective population-based study has revealed a 20-fold increased risk of HCC in those with HCV infection compared to those without infection.[19] While the incidence of HBV-related HCC has decreased after the initiation of a universal vaccination program, the incidence of HCV-induced HCC, where an effective vaccine is currently unavailable, is expected to continue to increase over the next several decades.[3,20]

Table 1 At-risk groups for which surveillance for HCC is recommended

Patients at increased risk for HCC	
Cirrhosis	**Without cirrhosis**
• Hepatitis B	**Hepatitis B carrier**
• Hepatitis C	• Family history of HCC
• Alcoholic cirrhosis	• Africans >20 years
• Nonalcoholic steatosis	• Asian males ≥40 years
• Genetic hemachromatosis	• Asian females ≥50 years
• Primary biliary cirrhosis	
• α-1 antitrypsin deficiency	

Abbreviation: HCC, hepatocellular carcinoma.

Excess alcohol consumption is a well-recognized risk factor for HCC, although the threshold dose and duration are less clear. Furthermore, viral hepatitis is a frequent comorbid condition in many patients suffering from alcoholism, and infection with either HBV or HCV further increases the risk of alcohol-induced HCC.[21,22] Cigarette smoking has also been shown to be a risk factor for HCC, and a recent European-population-based case-control study revealed that smoking contributed to nearly 50% of all HCCs.[23] However, given the high prevalence of smoking in this population and the frequent comorbid conditions of alcohol and viral hepatitis, smoking likely represents a cofactor in the development of HCC, rather than an independent etiologic agent.[24]

Epidemiologic studies have suggested a close correlation with obesity and diabetes and an increased risk of development of HCC.[25–27] Both of these conditions are also strongly associated with the development of nonalcoholic steatohepatitis (NASH), an increasingly recognized cause of cirrhosis.[28] A recent observational study of patients with cirrhosis due to either NASH or HCV infection revealed annual incidence rates of HCC of 2.6% and 4%, respectively, suggesting that HCC surveillance may be indicated in NASH-induced cirrhotic patients.[29] The most commonly associated environmental factor associated with HCC development is aflatoxin, a product of the *Aspergillus* fungus. High rates of dietary aflatoxin exposure, which commonly contaminates peanuts, soybeans, and corn, are frequent in developing countries and are associated with HCC.[30,31]

Several inherited metabolic disorders of the liver have been implicated in the development of HCC, including alpha-1 antitrypsin deficiency, certain porphyrias, Wilson's disease, and hereditary hemachromatosis, each typically in the setting of cirrhosis.[32–34] Additionally, a number of automimmune disorders have been implicated in HCC pathogenesis, including autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis.[13,33] Among these disease entities, available data suggesting that the incidence rate of HCC in patients with cirrhosis resulting from both hereditary hemochromatosis and advanced primary biliary cirrhosis appear significant enough to justify active surveillance.[35–38]

Surveillance

Surveillance is generally recommended in patients considered high risk for the development of HCC (Table 1).[3,37,38] Evidence for the ability of surveillance to impact overall survival comes from a large randomized controlled trial conducted in China comparing no surveillance to semiannual evaluation of serum α-fetoprotein (AFP) and abdominal ultrasonography (US) in HBV-infected patients or those with chronic hepatitis.[39] Despite the fact that less than 60% of the patients in the surveillance arm were screened appropriately, a 37% reduction in HCC-related mortality was found. Additionally, several nonrandomized trials and observational studies have reported a survival benefit in patients ultimately diagnosed with early stage disease, the target population in which early treatment interventions would most likely provide meaningful improvement in survival duration.[40]

Thus, serum AFP and US are the most commonly employed methods for screening for HCC, and while controversial,[41] they are frequently performed in combination. The use of US in the detection of HCC generally results in >60% sensitivity and >90% specificity.[42] However, US is highly operator-dependent, and the detection of tumors within a nodular cirrhotic liver is compromised and the sensitivity inferior.[43] The sensitivity of AFP, using the commonly employed 20 ng/mL cutoff point, ranges between 25% and 60%,[3] and is compromised by the fact that AFP is frequently not elevated in early stage disease. As a result, the sole use of AFP as a screening tool is not recommended. The time interval of surveillance is dependent on tumor doubling time, and based on estimates for HCC, is between 6 and 12 months.[15] However, shorter interval follow-up has been recommended for cirrhotic patients with documented small liver nodules.[44]

Diagnosis

The modalities employed in the diagnosis of HCC depend on both the size of the lesion and underlying liver function, and include cross-sectional imaging, biopsy, and serum AFP. The incidental finding of a liver nodule, the detection of a liver nodule during surveillance US, or a rising AFP in the absence of a liver nodule on US, is typically followed by cross-sectional imaging. HCC lesions possess a distinct blood supply from the surrounding normal liver parenchyma, relying primarily on arterial blood from the hepatic artery while the surrounding liver is supplied mainly via the portal vein.[45] Based on this, the use of four-phase (unenhanced, arterial, venous, delayed venous) helical computed tomography (CT) and dynamic contrast-enhanced magnetic resonance imaging (MRI) have established a classic imaging profile of HCC lesions characterized by arterial enhancement followed by hypointensity, or "washout," in the delayed venous phase.[46,47]

Lesions less than 1 cm are generally followed by serial imaging every 3–6 months to assess changes in growth or vasculature that are suggestive of malignancy. Stability over a period of 1–2 years suggests the lesion is unlikely to be HCC.[15] In cirrhotic patients or those with chronic liver disease, lesions greater than 1 cm in size that display both arterial enhancement and venous washout on either CT or MRI are considered diagnostic, and biopsy is typically not necessary.[37,38] If, however, either of these classic imaging findings is not observed, complementary imaging is recommended, where again both imaging findings would be considered diagnostic of HCC. Discordant imaging on subsequent evaluation is frequently followed by biopsy. It should be pointed out that characterization of these-sized lesions is often difficult, and some experts recommend confirmation of enhancement and washout with both CT and MRI.[3,48]

In patients without underlying liver dysfunction, biopsy is generally recommended for lesions larger than 1 cm to confirm the diagnosis of HCC. Biopsy, either via fine-needle aspiration or core biopsy, unfortunately has several limitations, including sampling error, the inherent difficulty in discerning between high-grade dysplastic nodules and HCC, and the remote possibility of seeding tumor cells along the needle track.[49–51] Thus, in patients with a nondiagnostic biopsy, repeat biopsy and/or imaging are recommended.

The role of AFP in the diagnosis of HCC is controversial. While elevated levels of AFP in combination with a known hepatic mass have been shown to have a high positive predictive value in retrospective studies, AFP can be elevated in other primary liver malignancies as well as metastasis

and is within normal limits in a large proportion of patients with known HCC.[37,52–54] As a result, both the National Comprehensive Cancer Network (NCCN) and the American Association for the Study of Liver Diseases (AASLD) no longer recommend its use in the diagnosis of HCC. Additionally, while other serum biomarkers, including des-gamma-carboxyprothrombin and lectin-bound α-fetoprotein, have been investigated in both surveillance and diagnosis of HCC, they are not currently recommended.[55,56]

Introduction to the management of HCC

Surgical resection

Surgical resection (ie, partial hepatectomy) is the optimal treatment for HCC. Preoperative assessment aims to address both resectability and operability. Resectability focuses on two issues: anatomical constraints of the primary tumor(s) and the probability of extrahepatic spread, and is typically ascertained via four-phase dynamic CT or MRI of the liver.[46,57] Given the most common metastatic sites of HCC, a chest CT and bone scan are most commonly employed to evaluate distant spread.

Assessment of operability relies on a variety of factors, including a patient's performance status, presence of comorbidities, severity of underlying liver disease, and estimates of the volume and function of the future liver remnant. The severity of underlying liver disease is most commonly determined through a combination of clinical and laboratory evaluation within the context of a scoring system, namely the Child–Pugh classification and the Model for End-Stage Liver Disease. However, additional information required to ensure adequate patient selection includes evaluation of portal hypertension, including clinical signs and symptoms, findings on CT or MRI, and/or measurement of the hepatic vein pressure gradient.[58,59] Estimates of predicted postoperative liver volume and function are obtained through CT-based volumetric imaging, and these estimates have been shown to predict hepatic dysfunction in patients undergoing major liver resections.[60,61] Finally, determination of the future liver remnant volume and function may be used to help determine if portal vein embolization, a technique employed to initiate hypertrophy in the anticipated liver remnant, is of value to extend the possibility of resection in otherwise suitable candidates.[62,63]

While thorough preoperative evaluation of the above parameters represents the standard of care, there are no fixed rules regarding tumor size, tumor number, presence of major vascular invasion, or extent of underlying liver disease. However, optimal patient and tumor characteristics include normal hepatic function or compensated (Child–Pugh A classification) cirrhosis, no evidence of portal hypertension, sufficient future liver remnant, and solitary, intrahepatic tumor without evidence of major vascular invasion.[37,38,64] While perioperative mortality ranges widely in modern retrospective series (1%–24%), with more rigorous patient selection partial hepatectomy mortality rates are generally less than 5%.[65–68] Overall 5-year survival rates following resection of early stage HCC are often greater than 50%, and in highly selected patients with solitary lesions without vascular invasion, survival rates greater than 70% have been reported.[59,66,69,70]

Despite impressive survival rates, surgical resection is limited by high rates of local recurrence, often exceeding numbers achieved with 5-year survival outcomes.[15,71] In the majority of cases, this is thought to be secondary to occult micrometastasis within the remaining liver parenchyma rather than inadequate surgical resection, and thus both neoadjuvant and adjuvant therapies have been explored. However, at least one controlled trial examining the role of neoadjuvant transarterial chemoembolization and a meta-analysis of three randomized trials of adjuvant systemic chemotherapy have demonstrated a worse outcome compared with resection alone.[72,73] Yet given the recent success of systemic targeted therapy in advanced HCC (see below), the role of the multikinase inhibitor sorafenib in the postresection setting is being explored.[74]

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT) represents an additional potentially curative therapy for early stage HCC. In a landmark paper, Mazzaferro et al reported an 85% 5-year survival and less than 10% recurrence rate of a highly selected group of patients with unresectable HCC who underwent liver transplantation.[75] The shared tumor characteristics: solitary lesion <5 cm or $<$ three lesions <3 cm each, became known as the Milan criteria and have since been adopted by the United Network for Organ Sharing as the requisite tumor characteristics for potential transplantation for the treatment of HCC. Additional United Network for Organ Sharing criteria include lack of radiographic evidence of macroscopic invasion or extrahepatic spread.[76] Importantly, subsequent studies in which the Milan criteria were employed have demonstrated similar outcomes.[77,78]

An area of active debate focuses on the possibility of expanding the Milan criteria in order to provide OLT to patients with higher-stage disease. Several centers using

expanded criteria have demonstrated 5-year survival rates within the range of those achieved using the Milan criteria.[79–81] Chief among these is the University of California, San Francisco, which has expanded criteria to include solitary tumors <6.5 cm and < three tumors <4.5 cm and cumulative tumor size <8 cm. While wide variation in survival exists in studies using these criteria, a recent study demonstrated a 5-year survival rate of 75%.[82] Despite this, given the correlation between tumor size and number and risk of dissemination and the critical shortage of liver donors, Milan criteria are considered the standard of care at most transplant centers.[83]

Given the importance of maintaining sufficient functional liver capacity following surgical resection for HCC, it is generally accepted that first-line treatment for early stage HCC in patients with moderate to severe cirrhosis (Child–Pugh classes B and C) is OLT. However, with recurrence rates generally ~10% with OTL versus up to ~70% with surgical resection, optimal treatment for patients with compensated cirrhosis (Child–Pugh class A) with early HCC who meet the Milan criteria is controversial.[84,85] There are currently no randomized controlled trials comparing these two modalities in this patient population, and current NCCN guidelines indicate initial treatment with either is acceptable.[38]

Ablation

The use of ablation for the treatment of HCC runs the gamut from agent used – toxic chemical agents (ethanol, acetic acid) or selective temperature gradients (radiofrequency, cryotherapy) – to method used – percutaneous, laproscopic, or open. The anticipated end result of each method is the same, that of selective tumor necrosis, commonly assessed by a lack of contrast uptake on dynamic CT or MR imaging following treatment and assessment of periprocedure serum AFP.[86,87]

The two most frequently used methods include percutaneous radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI). Percutaneous ablation is a well-tolerated procedure, with major complications generally less than 10% for RFA and less than 3% for PEI, and morbidity rates less than 1% for RFA and extremely rare for PEI.[88–90] With regards to the optimal type of ablation, multiple prospective randomized controlled trials have demonstrated superior local tumor control with RFA, and three meta-analyses have demonstrated superior overall survival.[91–96] That said, the efficacy of complete control rates between RFA and PEI appears to be fairly similar for tumors less than 2 cm.[91,92,97] While both of these methods have distinct advantages and disadvantages, it is important to note that they are limited by tumor size and location.[98–100]

There is wide variation in reported overall survival rates, yet long-term studies of both RFA and PEI have achieved 5-year overall survival of over 50%.[101,102] Like survival outcomes, local recurrence rates range widely among studies. Results from a recent randomized controlled trial demonstrate local recurrence rates with both RFA and PEI to be between 13% and 34%,[103] while estimated 4-year recurrence rates of 70% and 85% with RFA and PEI, respectively, were obtained in a separate randomized controlled trial.[93] On the other hand, a recent cohort study found a less-than-3% recurrence rate at 31 months in select patients with tumors less than 2 cm treated with RFA.[104]

Given the generally comparable survival and recurrence rates of ablation to surgical resection for early HCC, three randomized controlled trials have compared ablation with surgical resection. Two studies failed to show a significant benefit to surgery, with similar 3-year overall and disease-free survival.[105,106] However, a recent larger study of patients with HCC meeting the Milan criteria demonstrated superior 5-year overall survival (76% vs 55%) and recurrence-free survival (51% vs 29%), as well as significantly lower overall recurrence rates (42% vs 63%) for those who underwent surgical resection compared to RFA.[23] Taken together, most physicians favor surgical resection for patients with early HCC who are deemed both resectable and operable, even with small tumors. For nonsurgical patients with tumors less than 2 cm, either ablative technique can be used and case-specific characteristics often guide ultimate treatment decisions, while RFA is generally preferred for larger tumors.

Transarterial embolization

The principle of embolization relies on the same biologic feature of HCC exploited by hepatic imaging used for diagnosis: selective hepatic artery blood supply to tumors.[45] In the case of embolization, selective tumor hypoxia and resultant necrosis is achieved via significant reduction in arterial blood flow through the use of image-guided catheter-based infusion of particles.[107] Much like ablation, there is wide variation in the types of particles used, types of antitumor adjuvants employed, types of emulsifying agents used with adjuvant treatments, and number of treatment sessions given, all of which complicate the interpretation of the many studies examining its clinical utility.

Broadly speaking, embolization can be categorized as transarterial embolization (TAE) (ie, bland embolization), transarterial chemoembolization (TACE), and transarterial

radioembolization (TARE). In the case of TACE, transarterial infusion of a chemotherapeutic agent (frequently doxorubicin or cisplatin) with or without an emulsifying agent (commonly Lipiodol, an oily substance with selective tumor retention) precedes infusion of embolic particles.[108] Newer methods of TACE have employed drug-eluting beads as a way to concomitantly reduce blood flow and deliver sustained and controlled adjuvant therapy and reduce systemic side effects.[109]

Conversely, radionuclide conjugation of Lipiodol (iodine-131 Lipiodol) is generally done in the absence of specific embolization and is thought to exert sufficient antitumor effect through selective high-dose radiation.[110] Additionally, while radionuclide-conjugated microspheres (commonly yttrium-90) do exhibit microvascular occlusive properties based on sizing of microspheres, embolization is less dramatic and resulting tumor necrosis is thought to be mediated predominantly via radiation rather than ischemia.[107,111]

Two landmark randomized controlled trials involving patients with unresectable HCC with preserved liver function have demonstrated a significant survival advantage with TACE compared to best supportive care. In the study by Llovet et al, 112 patients were randomized to either TAE, TACE, or best supportive care, and survival probabilities at 1 year and 2 years were 75% and 50% for TAE, 82% and 63% for TACE, and 63% and 27%, respectively, for supportive care. The study was stopped early after interim analysis revealed statistically significant survival advantage for TACE versus supportive care ($P = 0.009$); unfortunately, the study was underpowered to detect a difference between TACE and TAE.[112] In the study by Lo et al, 80 patients were randomized to TACE vs best supportive care, and actuarial survival was significantly better in the TACE arm than in the supportive-care arm (1 year, 57% vs 32%; 2 years, 31% vs 11%; 3 years, 26% vs 3%; $P = 0.002$).[113]

Based in part on these results, TACE has become the most commonly employed embolization technique. Several recent studies have subsequently compared "conventional" TACE with TACE using drug-eluting beads (DEB-TACE). While a retrospective study has suggested a survival advantage with drug-eluting beads,[114] a recent phase II prospective randomized trial revealed comparable effectiveness with the two modalities, albeit with significantly less systemic toxicity with DEB-TACE.[115] Additionally, results from this randomized trial as well as an additional randomized trial that compared DEB-TACE to TAE revealed nonsignificantly higher rates of complete tumor response and disease control with DEB-TACE.[115,116] There are currently no published randomized controlled trials comparing TACE (conventional or with drug-eluting beads) with TARE employing yttrium-90 microspheres. However, a recent comparative effective analysis of patients with unresectable HCC treated with either TACE or TARE with yttrium-90 revealed similar median survival outcomes (20.5 months vs 17.4 months, respectively, $P = 0.232$), while radioembolization resulted in significantly longer time to progression and reduced toxicity.[117]

While morbidity with embolization is relatively low, (generally $< 5\%$), complications are common and include a transient postembolization syndrome consisting of abdominal pain, nausea, ileus, and fever.[112,118,119] Overall survival rates vary widely, yet studies with TACE and TAE reported 2-year overall survival ranging from 20% to 60%.[112,113,120] However, durable long-term survival is rare with embolization, as initial complete response rates are low and revascularization within the tumor bed frequently occurs.[15] Thus, it is generally not employed with curative intent.

Systemic therapy

Despite the fact that most patients with HCC present with advanced disease, prior to 2008 no systemic therapy had demonstrated sustained improved survival, including single-agent or combined cytotoxic chemotherapy,[121,122] immunotherapy alone or in combination with cytotoxic chemotherapy,[123,124] tamoxifen or antiandrogens,[125–127] or somatostatin analogs.[128,129] However, with the publication of two randomized placebo-controlled phase III trials, the oral multikinase inhibitor sorafenib has become the new reference standard for treatment of advanced HCC.[130,131] Sorafenib inhibits both the rapidly accelerated fibrosarcoma (Raf) kinase and the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathways, resulting in suppression of tumor cell proliferation and angiogenesis.[132,133]

In the multicenter European Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, 602 patients with advanced HCC who were systemic therapy–naive received either sorafenib or placebo until radiological or symptomatic progression.[130] The study was stopped at the second planned interim analysis because of advantages in median overall survival (10.7 vs 7.9 months; hazard ratio, 0.69; 95% CI, 0.55–0.87; $P < 0.001$) and time to radiological progression (5.5 vs 2.8 months; $P < 0.001$) in the sorafenib arm. However, objective response rates to sorafenib were low according to radiographic criteria, and sorafenib did not increase the time to symptomatic progression. The underlying etiologies of HCC were

primarily HCV (28%), alcohol (26%), and HBV (18%). The vast majority of patients had compensated liver disease and good performance status.

In the Asia–Pacific trial, the efficacy of sorafenib in the Asian population was evaluated in 226 patients in a similar design and dosing to the SHARP trial.[131] Patients who received sorafenib again demonstrated significant benefits in median overall survival (6.5 vs 4.2 months; hazard ratio, 0.68; 95% CI, 0.50–0.93; $P = 0.014$) and time to radiological progression (2.8 vs 1.4 months) compared to placebo. While most patients again had preserved liver function, patients in the study tended to be younger, have more advanced-stage disease, and generally worse performance status. Additionally, the underlying etiology was different, with more than 70% of patients infected with HBV. These differences in patient and disease characteristics may account for the markedly reduced magnitude of benefit between the two trials (10.7 vs 6.5 months median overall survival).[134] That said, the hazard ratio for survival was nearly identical between the two trials, suggesting comparable efficacy of sorafenib. Sorafenib was well tolerated with manageable side effects in both trials. Despite the fact that the original Food and Drug Administration approval of sorafenib in the US did not specify its use in underlying liver disease, current NCCN guidelines recommend sorafenib with Child–Pugh classes A and B only with unresectable, inoperable, or metastatic disease.[38]

Emerging tools for early diagnosis and management

Significant advances in diagnostic and therapeutic interventions are required to help transform HCC from a disease often diagnosed late and restricted largely to palliative therapies to one diagnosed early where curative intent is the goal. Core to this is the elucidation of the molecular pathways operative in HCC pathogenesis. Histopathologic analysis and epidemiologic studies of HCC arising in the setting of cirrhosis have suggested multistep hepatocarcinogenesis through the identification of morphologically distinct precancerous lesions, including dysplastic foci and dysplastic nodules, and early small HCC (<2 cm).[135,136] Yet the pathologic distinction between these types of lesions is often difficult and biopsies of small tumors carry a false-negative rate of 30%–50%.[137]

Recent expression profiles of human samples have suggested particular mRNA expression subsets, or signatures, associated with both improved diagnostic accuracy and lesion discrimination.[138–141] For example, a 13-gene signature identified through high-throughput quantitative real-time polymerase chain reaction in 128 patient samples provided high diagnostic accuracy for HCC.[138] Additionally, the expression of three genes (*glypican 3*, *lymphatic vessel endothelial hyaluronan receptor 1* and *survivin*), has been reported to provide ~90% accuracy in distinguishing dysplastic nodules from early HCC.[139] Results of many of these genomic studies have been applied to more conventional immunohistochemical analysis, and a recent prospective analysis of the protein expression of glypican 3, heat shock protein 70, and glutamine synthetase revealed 72% sensitivity and 100% specificity in detecting well-differentiated HCC in biopsy samples.[142] These markers have been validated in a larger number of patients and have recently been suggested as part of the diagnostic algorithm for the American Association for the Study of Liver Diseases.[37,143]

Serum levels of several of these biomarkers have also been evaluated in diagnosis and surveillance, including glypican 3, des-gamma-carboxyl prothrombin (DCP), and *Lens culinaris* agglutinin-reactive AFP, an isoform of AFP.[144–147] While a recent study in a large population of patients with HCV-associated HCC suggested an improved sensitivity with a combination of AFP and DCP compared with either alone, to date additional serum biomarkers beyond AFP have not been incorporated in major HCC management guidelines.[55]

Radiographic imaging also plays a key role in the early diagnosis of HCC, and is critical for accurate staging and treatment-response assessment. The major difficulty in diagnostic imaging of the cirrhotic patient remains the accurate characterization of lesions less than 2 cm, and the incorporation of functional hepatic imaging and development of new contrast agents will likely improve the detection and characterization of these small tumors. Diffusion-weighted MRI has been shown to improve detection of HCC smaller than 2 cm, with sensitivities higher than multiphasic MRI alone, and represents a promising technique given its ease of implementation into current clinical practice.[148,149]

The use of two new hepatocyte-specific gadolinium chelate contrast agents, gadobenate dimeglumine (Multihance; Bracco, Milan, Italy) and gadoxetic acid (Primovist; Schering, Berlin, Germany), with multiphasic contrast-enhanced MRI has been shown to improve in the diagnosis of HCC over MRI or CT alone.[150,151] These agents have also been shown to enhance the differentiation of small HCCs (≤2 cm) from arterial-enhancing pseudolesions, common benign hepatic vascular lesions that mimic early HCC.[152,153]

[18F]fluorodeoxyglucose positron emission tomography (FDG-PET) is limited by the varying degrees of FDG

Table 2 Select phase III trials evaluating sorafenib

ID	Acronym	Active arm	Control arm	Primary outcome	Indications
NCT01009593	BRISK-FL	Brivanib	Sorafenib	Overall survival	First line tx for advanced HCC
NCT01135056	SIRveNIB	Yttrium-90 microspheres	Sorafenib	Overall survival	First line tx for advanced HCC
NCT00901901	SEARCH	Sorafenib + erlotinib	Sorafenib	Overall survival	First line tx for advanced HCC
NCT01015833	–	Sorafenib + doxirubicin	Sorafenib	Overall survival	First line tx for advanced HCC
NCT01004978	–	TACE + sorafenib	TACE + placebo	Progression-free survival	First line tx for intermediate HCC
ISRCTN24081794	HeiLivCa	TACE + sorafenib	TACE + placebo	Time to progression	Bridge therapy for liver transplantation
NCT00494299	–	Sorafenib	Placebo	Time to progression	Prevention of recurrence after embolization
NCT00692770	STORM	Sorafenib	Placebo	Recurrence-free survival	Prevention of recurrence after resection or ablation

Adapted from Gastroenterology, 140:5, Villanueva A and Llovet JM, Targeted therapies for hepatocellular carcinoma, p. 17, © 2011, with permission from Elsevier Ltd.[163]
Abbreviations: tx, treatment; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

accumulation in primary HCC, and is not currently recommended in the diagnosis of HCC.[37,38] While several studies have demonstrated a greater sensitivity for detection of distant metastasis with FDG-PET compared to CT, MRI, or radionuclide bone scan, its use is limited by high false-positive rates and it is currently not recommended by the AASLD or NCCN.[8,37,38,154,155] The use of new radiotracers, including [11C]acetate may, however, improve the sensitivity and specificity of PET scanning in the diagnosis and evaluation of HCC.[156]

Assessment of tumor response to nonsurgical treatments has traditionally been based on changes in tumor size and number, delineated by the World Health Organization and the Response Evaluation Criteria in Solid Tumors criteria.[157,158] However, these criteria are often inadequate for the evaluation of HCC, particularly as it relates to novel molecular therapies, which often result in tumor necrosis.[159] Preliminary studies of both diffusion-weighted MRI and perfusion CT show promise in the evaluation of tumor response to both local ablative and systemic therapies.[160–162]

Elucidation of signal transduction pathways implicated in tumorigenesis and development of targeted molecular therapies have fueled a revolution in oncology, and this has impacted the management of HCC directly with the demonstration of a significant survival advantage with the use of sorafenib. Given this success, the role of sorafenib alone and in combination with traditional locoregional therapies, systemic chemotherapy and novel molecularly targeted therapies is currently being investigated in various stages of disease (Table 2).[163] Additionally, alterations in several signal transduction pathways have been detected in HCC, including Wnt signaling, p53, insulin-like growth factor, Ras, epidermal growth factor receptor (EGFR), Akt/target of rapamycin (TOR), c-MET, VEGFR, and fibroblast growth factor (FGF).[164] This has resulted in the application of a myriad of new targeted therapies in both the preclinical and clinical setting, including the monoclonal antibodies bevacizumab (anti-VEGF) and cetuximab (anti-EGFR), and the small molecule inhibitors erlotinib (EGFR inhibitor), brivanib (FGF and VEGFR inhibitor), everolimus (mammalian TOR inhibitor) and linifanib (VEGFR and PDGFR inhibitor).[133]

Many of these therapies target well-established proteins that regulate critical aspects of tumorigenesis, including angiogenesis, proliferation, and survival. However, recent work has implicated microRNA dysregulation in many of these processes during hepatocarcinogenesis, and early studies of human HCC microRNA expression profiling have suggested expression signatures predictive of metastasis and survival.[165,166] Epigenetic alterations, including DNA methylation and histone modification, have also been implicated in the pathogenesis of HCC.[164] Importantly, therapeutic interventions targeting some of these aberrant processes in the form of histone deacetylase inhibitors are currently being investigated in clinical trials of HCC.[163]

Conclusion

Hepatocellular carcinoma is an aggressive cancer that frequently occurs in the setting of chronic liver disease and cirrhosis. It is typically diagnosed late in the disease course, often precluding curative surgical therapies. Furthermore, concomitant liver dysfunction often further hampers both curative and palliative therapies. However, HCC is unique among many neoplasms in that effective preventative measures, including HBV vaccination, universal screening of blood products, use of safe injection practices, education and treatment of alcoholism and intravenous

drug abuse, reduction in aflatoxin through control of fungal contamination, and initiation of antiviral therapy are in place and have been shown to be effective.[13,167]

Advances in locoregional therapies, including the use of drug-eluting beads and radionuclide-conjugated microspheres, represent strategies that may further improve survival among patients with intermediate-stage HCC and preserved liver function. Moreover, the demonstration of the safety and efficacy of sorafenib as a frontline treatment for advanced HCC in patients with preserved liver function represents a significant advancement in what was an otherwise bleak set of treatment options for this group of patients. Effective molecularly targeted therapies may also hold promise as adjuvants to primary surgical therapies, currently limited by high rates of disease recurrence. Finally, it is hoped that, much as has been shown for breast and colorectal carcinoma, active research aimed at the elucidation of the molecular pathogenesis of HCC and the identification of new biomarkers will result in further advances in the prevention, diagnosis, and treatment of HCC.

Disclosure

The authors disclose no conflict of interest.

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