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# Epidemiology and Management of Hepatocellular Carcinoma

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**The major risk factors for hepatocellular carcinoma (HCC) in contemporary clinical practice are becoming increasingly related to sustained virological response after hepatitis C, suppressed hepatitis B virus during treatment, and alcoholic and nonalcoholic fatty liver disease. We review the emerging data on the risk and determinants of HCC in these conditions and the implications of HCC surveillance. However, from a public health perspective, active hepatitis C and B continue to drive most of the global burden of HCC. In United States, the age-adjusted incidence rates of HCC in Hispanics have surpassed those of HCC in Asians. Prognosis in HCC is complex because of the competing risk imposed by underlying cirrhosis and presence of malignancy. In addition to tumor burden, liver function and performance status; additional parameters including tumor biopsy, serum markers, and subclassification of current staging systems; and taking into account patterns of tumor progression may improve patient selection for therapy. Advancements in the treatment of HCC have included identification of patients who are most likely to derive a clinically significant benefit from the available therapeutic options. Additionally, the combination strategies of locoregional therapies and/or systemic therapy are being investigated.**

*Keywords:* Epidemiology; Hepatocellular Carcinoma; Hepatitis C.

The incidence and mortality of hepatocellular carcinoma (HCC) have been increasing in North America and several European regions and declining in traditionally high-risk regions, including Japan and parts of China. The main risk factors for HCC are chronic hepatitis C virus (HCV) or hepatitis B virus (HBV), heavy alcohol drinking, diabetes, and, possibly, nonalcoholic fatty liver disease (NAFLD).[1] HCC has been the fastest-rising cause of cancer-related deaths in the United States. In an analysis including all 50 US states, HCC age-adjusted incidence rates increased from 4.4/100,000 in 2000 to 6.7/100,000 in 2012, increasing by 4.5% annually between 2000 and 2009 (Figure 1)[2]. There has been a recent slowing of the increase in incidence and mortality rates for HCC in the United States, with an annual increase of only 0.7% from 2010 through 2012. However, HCC incidence is disproportionately increasing in men ages 55 to 64 years—especially those born in the peak era of HCV infection and in certain ethnic/racial groups, including Hispanics, African Americans, and whites. Asian men had the highest age-adjusted incidence rates attributed to chronic HBV, especially among immigrants from HBV-endemic areas. Subsequent generations of US-born Asians have much lower rates of HBV infection, and recent immigrants from HBV-endemic areas may be benefitting from reduced aflatoxin exposure and an increase in HBV vaccinations.

HCC age-adjusted incidence rates among Hispanics have surpassed those among Asians. The rates are higher in US-born Hispanics than in non–US-born Hispanics. The reasons are likely related to higher rates of HCV (particularly in Mexican Americans),[3] alcoholic liver disease, NAFLD,[4,5] and metabolic syndrome, including diabetes, which increases the risk of developing HCC either independently or through potentiating the effect of viral hepatitis and alcoholic liver disease. Hispanics with chronic HCV or NAFLD have a higher risk of progression to cirrhosis and HCC, which may be partly a genetic (eg, *PNPLA3*) predisposition.

The consistently high and increasing HCC incidence rates among individuals born in the peak-HCV cohort (1945–1965), irrespective of age or calendar year, support a

***Abbreviations used in this paper:*** **AASLD, American Association for the Study of Liver Disease; AFP, α-fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; CHB, chronic hepatitis B; CI, confidence interval; CP, Child-Pugh; CSPH, clinically significant portal hypertension; DAA, directly acting antiviral; DEB, drug eluting beads; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; LRT, locoregional therapy; MELD, Model for End Stage Liver Disease; MVI, macrovascular invasion; NA, nucleoside/nucleotide analogue; NAFLD, nonalcoholic fatty liver disease; NLR, neutrophil-lymphocyte ratio; OLT, orthotopic liver transplantation; PAF, population-attributable fraction; PVT, portal vein thrombosis; RCT, randomized controlled trial; RFA, radiofrequency ablation; RT, radiotherapy; SVR, sustained virologic response; TACE, transarterial chemoembolization; TTP, time to tumor organization; VHA, Veterans Health Administration; Y90, yttrium.**

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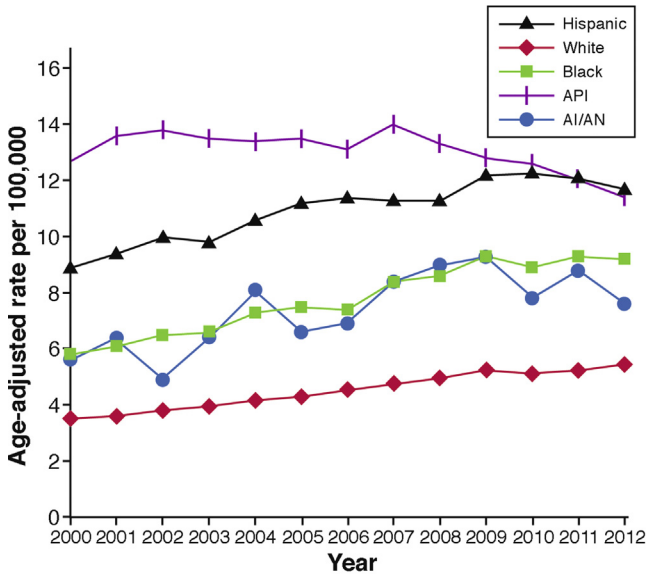


**Figure 1.** Yearly age-adjusted incidence rates of HCC in United States between 2000 and 2012 by race and ethnicity. Adapted from White et al.[2]

potential birth-cohort effect related to HCV that has not yet decreased but that is anticipated to do so by 2020. Directly acting antivirals (DAAs) may affect overall HCC incidence rates over the next 1–2 decades,[6] but the magnitude and timing of anticipated decreases in HCC incidence rates depend on the availability and penetration of HCV treatment, as well as increased detection, diagnosis, and linkage to care for individuals with chronic HCV infection.

## Changes in the Major HCC Risk Factors

### *Hepatitis C Virus*

Patients with HCV-induced cirrhosis are at particularly high risk for the development of HCC, with an annual incidence of HCC ranging from 0.5% to 10%. Sustained virologic response (SVR) with DAA has emerged as the most dominant modifier of HCC in patients with HCV. Other than cirrhosis, the residual role of most traditional risk factors among those with active untreated or uncured HCV is unclear; these factors include older age, male sex, Hispanic ethnicity,[7] diabetes, obesity, smoking, HCV genotype 3,[8] heavy alcohol use, and HIV or HBV coinfection.[9] Although DAA is likely to change the epidemiology of HCV-related HCC in those who are treated, most HCV-infected populations remain untreated.[10]

Although few studies report a possibly unexpected high incidence of de novo and recurrent HCC after DAA treatment,[11] growing data consistently illustrate a considerable (50%–80%) and steady HCC risk reduction over time of de novo HCC among those achieving DAA-related SVR. DAAs offer a chance of cure for patients with advanced cirrhosis, older patients, and those with alcohol use—all characteristics independently associated with risk of HCC in HCV.[12–14] These patients were not treated or had poor response to interferon (IFN)-based treatment. Despite these historical differences, in a systematic review of 26 studies on de novo HCC occurrence (IFN, n = 17; DAA, n = 9), there was no evidence for differential HCC occurrence or recurrence risk after SVR from DAA and IFN-based therapy.[15]

The implications of SVR-related change in HCC risk on HCC surveillance are evolving. Kanwal et al.[16] found that patients who achieved SVR with DAAs had a 76% reduction in risk of HCC compared with patients who did not achieve SVR.[16] The HCC-preventive effect of SVR was evident early on and increased over time. However, despite the relative reduction in risk of HCC, the absolute risk of HCC persisted in patients with DAA-induced SVR. HCC developed in 183 patients during approximately 20,415 patient-years of follow-up, at an annual incidence of 0.90%. Risk of HCC was the highest among those with cirrhosis, ranging from 1.0% to 2.2% per year, based on other demographic and clinical characteristics (Figure 2). These estimates reached or exceeded the cutoffs (0.8%–1.5% per year) beyond which HCC surveillance may become cost effective.[17,18] In contrast, the risk of HCC was low in almost all patients without cirrhosis, with the exception of patients with a high baseline Fibrosis-4, suggesting presence of advanced fibrosis. Based on these data, HCC surveillance is likely to continue to be needed for all patients with cirrhosis or advanced fibrosis at the time of SVR. The extent of reduction of HCV-related HCC is also dependent on screening and detection of HCV-infected cohorts and the dissemination of DAA treatments.

### *Hepatitis B Virus*

Chronic hepatitis B (CHB) is the leading etiology of HCC worldwide. The indications for antiviral therapy using nucleoside/nucleotide analogues (NAs) has been expanded in the past 1–2 decades to cover considerably more CHB patient groups. HBV can cause HCC in the absence of cirrhosis, although most cases of HBV-related HCC (70%–90%) occur in patients with cirrhosis.[19] Risk factors for HCC in CHB include demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral (higher levels of HBV replication; HBV genotype; longer duration of infection; coinfection with HCV, human immunodeficiency virus, or hepatitis delta virus), clinical (cirrhosis), and environmental (exposure to aflatoxin, heavy intake of alcohol or tobacco) factors.

However, like HCV treatment, NA viral suppression has emerged as the dominant modifier of HCC risk among patients with CHB. NA has been associated with risk reduction, but not elimination, of HCC in patients with CHB.[20–22] Several scoring systems, such as CU-HCC, GAG-HCC, and REACH-B, were set up to predict the risk of HCC.[23–25] Although these systems were externally validated and can attain high negative predictive values (above 95%) for HCC development over a 3- to 10-year period in untreated patients, they may not adequately predict HCC in patients receiving NAs.[26,27] Studies have shown that age, cirrhosis, male sex, platelet count, liver stiffness, and diabetes are risk factors for HCC in patients with CHB receiving NAs,[28–30] whereas pretreatment viral load, hepatitis B e antigen status, hepatitis B surface antigen quantity, and

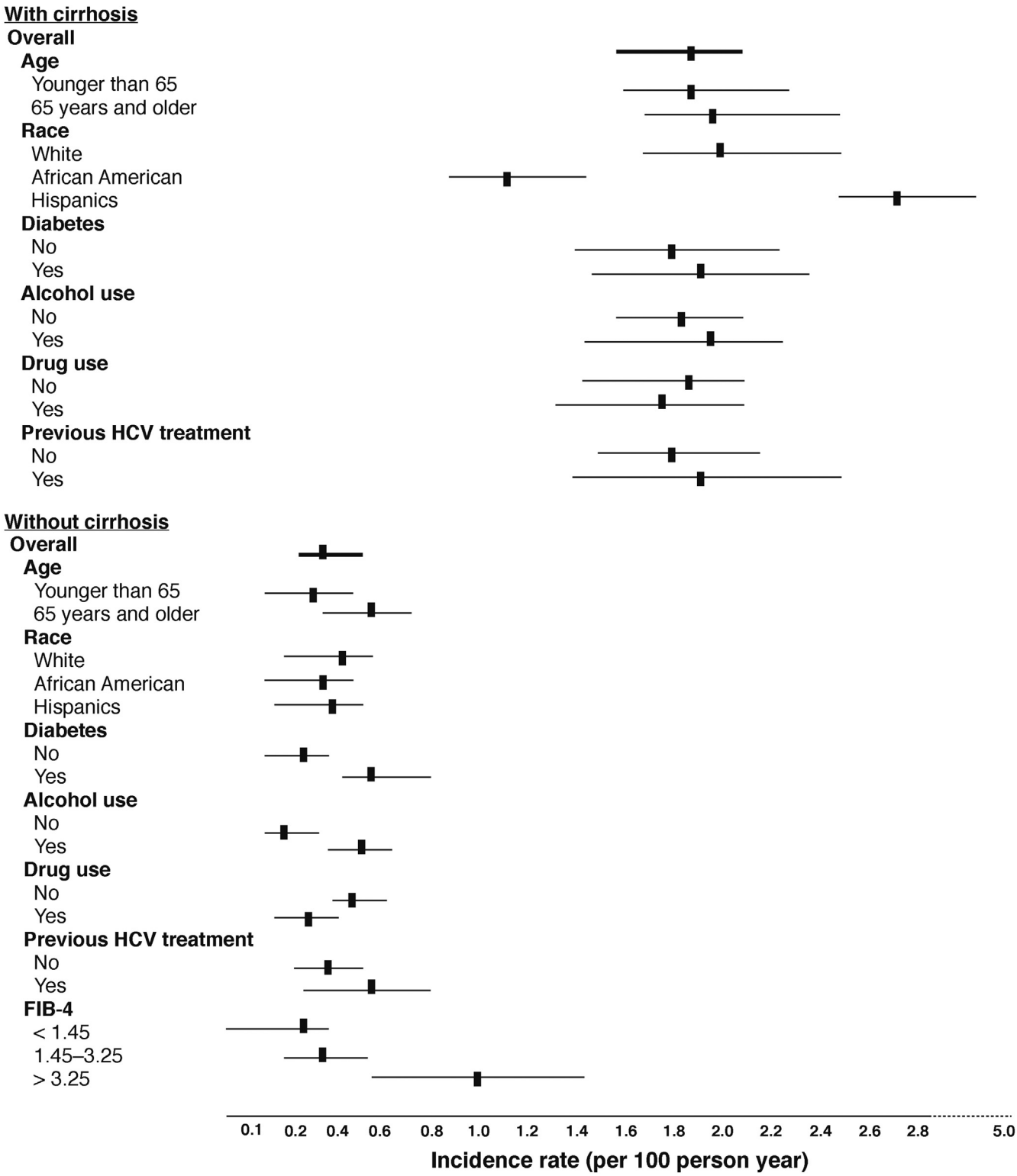


**Figure 2.** The cumulative incidence and determinants of HCC after DAA-related SVR among VHA patients with HCV. The incidence rates are shown according to several demographic and clinical features for patients with and without cirrhosis at baseline. Adapted from Kanwal et al.[15]

aminotransferase level are not predictive for treated patients.[31–33] The Cirrhosis, Age, Male sex, Diabetes (ie, CAMD) score was developed to predict HCC risk during the first few years of NA treatment, using data from patients continuously receiving entecavir or tenofovir for CHB in the national health care database in Taiwan[34] and was externally validated using population-wide data extracted from the state-run health care database in Hong Kong

(Figure 3).[34] This score appeared to be similarly accurate to the well-established PAGE-B score that was validated in white and Asian populations.[35] Although HCC incidence seems to decrease with cumulative NA treatment, it is unclear whether prolonged therapy can eventually eliminate the risk. Papatheodoridis et al[36] reported that a substantial risk of HCC remains after the first 5 years of entecavir or tenofovir treatment in patients with cirrhosis or older than 50 years. It is also unclear how the risk of HCC may change after NA cessation.

Most knowledge about the risk of HCC in HBV is based on studies conducted in Southeast Asia and sub-Saharan Africa, where HBV infection is endemic and acquired at birth or early childhood.[37] However, a multicenter study from the United States reported an annual incidence of 0.42%, although more than 50% of the cohort was Asian Pacific Islander in origin.[38] In addition, a recent cohort of 8329, mostly male, patients was identified in the national Veterans Health Administration (VHA) database with CHB infection from 2001 through 2013. The annual HCC incidence was highest in American Pacific Islanders (0.65%), followed by whites (0.57%) and African Americans (0.40%). There was no difference in HCC risk between African Americans and whites. HCC risk increased with age: adjusted hazard ratios (HRs) were 1.97 (95% confidence interval [CI], 0.99–3.87) for 40–49 years, 3.00 (95% CI, 1.55–5.81) for 50–59 years, and 4.02 (95% CI, 2.03–7.94) for >60 years vs <40 years. Patients with cirrhosis had higher risk of HCC than patients without cirrhosis (adjusted HR, 3.69; 95% CI, 2.82–4.83).[39] Even among patients without cirrhosis, the annual incidence of HCC was more than 0.2% for all patients older than 40 years with high levels of alanine aminotransferase, regardless of race and independent of HBV therapy.

The American Association for the Study of Liver Disease (AASLD) guidelines recommend HCC surveillance among HBV patients, based on the HCC incidence-rate thresholds of 0.2% or greater per year among those without cirrhosis and between 0.2% and 1.5% per year among patients with underlying cirrhosis.[17,18] The guidelines use family history of HCC, age, and race as additional criteria for HCC risk stratification in CHB. HCC surveillance is recommended for all patients with cirrhosis and, in the absence of cirrhosis, for Asian men older than 40 years and Asian women older than age 50 years. The guidelines also suggest that surveillance should start at a younger age for Africans and African Americans than for other races/ethnicities, without an exact specification of the age cutoff year, based on previous studies in South Africa, published in 1977 and 1988, which reported that African blacks with HBV might develop HCC at an age <40 years.[40,41] A recent study in multiple African countries confirmed the younger age of HBV-related HCC in these countries.[42]

Recent US-based studies confirmed that the age effect observed in the studies conducted in East Asia, the risk of HCC increased with age, and the inflection point for markedly increased risk of HCC was among those older than 40 years;[39,40] however, the VHA cohort data indicate an extremely low risk of HCC in all individuals younger than 40 years, including African American patients (annual incidence, 0.03%). Furthermore, irrespective of age, the risk of HCC among African Americans with chronic HBV was not significantly different from the risk among whites. These data show that, in the United States, African Americans with chronic HBV may not need surveillance at an earlier age than patients of other racial groups. This recommendation may still be relevant to Africans in whom aflatoxin exposure plays an additional role.

### *Nonalcoholic Fatty Liver Disease*

NAFLD has become the leading cause of chronic liver disease in most regions of the world, including the United States,[43] with up to 30% prevalence in the general population.[44] An estimated 20%–30% of patients with NAFLD develop progressive liver disease with necroinflammation and fibrosis that can result in cirrhosis in 10%–20% of cases.[45] The prevalence of NAFLD and risk of progression is higher among Hispanics than other racial and ethnic groups.[46] NAFLD is the fastest-growing cause of HCC-related transplantation in the United States,[47] although the exact magnitude, timing, and determinants of HCC in NAFLD patients are unclear. A systematic review of epidemiologic studies (published through 2011) examining the NAFLD-HCC link found mixed results, with HCC risk ranging from 0% to 38% over 5–10 years of follow-up[48]; subgroups with cirrhosis were at distinctly high HCC risk. Most published studies included small or modest-sized NAFLD cohorts and, thus, had few or no incident HCC cases. Furthermore, most studies evaluated patients in tertiary care settings. Thus, the generalizability of these findings to community-based clinical populations with NAFLD is unclear.

HCC occurring in the absence of cirrhosis is unusual and mainly occurs in up to 15% of HBV- related cases. Among new HCC cases without advanced fibrosis or cirrhosis in the United States, NAFLD constitutes the largest etiological proportion of cases.[49] This entity poses a challenge to clinical practice paradigms based on HCC risk mediated through cirrhosis. A lower proportion of patients with NAFLD-related HCC receive HCC surveillance before their HCC diagnosis or HCC-specific treatment than of patients with HCV-related HCC.[49] The available data on HCC risk support screening among patients with NAFLD-related cirrhosis, but it may be cost effective for patients with advanced fibrosis, especially those with multiple components of metabolic syndrome and Hispanics.

Irrespective of NAFLD, diabetes and obesity increase HCC risk. Type 2 diabetes was associated with a 2- to 3-fold increase in the risk of HCC,[50] including in cohort studies that reduce the likelihood of reverse association.[51] The use of metformin is associated with decreased risk, and the use of insulin or sulfonylureas may increase HCC risk.[52] Longer duration of diabetes may be associated with an incremental increase in risk.[53–55] A predictive model that was developed in patients with cirrhosis on the national liver transplantation waitlist database used diabetes in addition to age, race, etiology of cirrhosis, sex, and severity of liver

| Variable | Risk score |
|---|---|
| **Cirrhosis** | |
| No cirrhosis | 0 |
| Cirrhosis with age < 40 yr | 10 |
| Cirrhosis with age ≥ 40 yr | 6 |
| **Age** | |
| Age < 40 yr | 0 |
| Age 40–49 yr | 5 |
| Age 50–59 yr | 8 |
| Age 50 yr or older | 10 |
| **Gender** | |
| Female sex | 0 |
| Male sex | 2 |
| **Diabetes mellitus** | |
| Not diabetic | 0 |
| Diabetic | 1 |

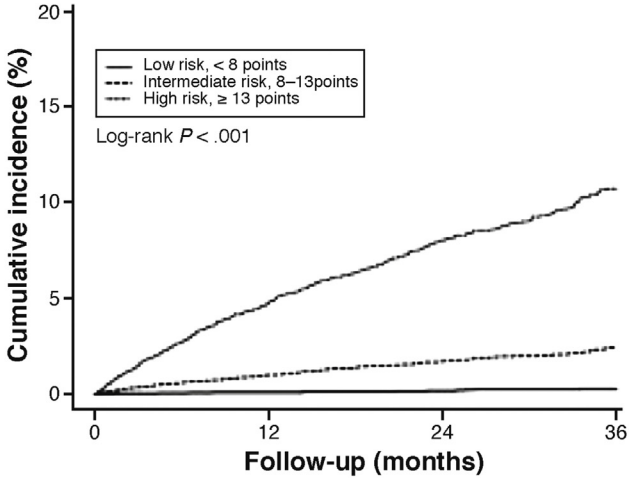


**Figure 3.** The risk of HCC among patients with hepatitis B receiving continuous antiviral treatment. Adapted from Hsu et al.[33] CAMD, Cirrhosis, Age, Male sex, and Diabetes mellitus.

dysfunction to predict the 1-year risk of HCC.[56] Most—but not all—studies are suggestive of a modest increase in the relative risk of HCC in obese persons. A systematic review of 10 cohort studies found a positive association between obesity, measured as body mass index, and risk of HCC in 7 studies (relative risks ranging from 1.4 to 4.1), no association in 2, and an inverse association in 1 study.[57] Moving beyond body mass index and into more proximal features in the association between body mass index and HCC, a cohort found that a high waist-to-hip ratio conferred a 3-fold higher HCC risk to participants in the upper tertile of waist/hip ratio than those in the lowest tertile.[58]

Population attributable fraction (PAF) is the proportion of cases of disease (i.e., HCC) that can be avoided by removing the underlying risk factor (i.e., NAFLD). PAF is calculated by using the prevalence (how common) and risk estimate (how strong). HCV and HBV are uncommon but are strong HCC risk factors in the general population; their PAFs are less than that of NAFLD, a highly prevalent but weak risk factor.[59] Nevertheless, population-based studies show that HCV remains the leading cause of HCC in the United States. In a national study among liver- transplant recipients, NAFLD was the most rapidly growing cause between 2002 and 2016 of HCC among US patients listed for liver transplantation, but HCV remained the leading HCC etiology.[60] In the US VHA hospital system, the annual proportion of NAFLD-related HCC patients remained stable during 2005–2010 (7.5%–12.0%), whereas that of HCV-related HCC increased from 61.0% to 74.9%.[4] The explanations for the divergence between high PAF for NAFLD-related HCC and studies showing a relatively low proportion of NAFLD among patients with newly diagnosed HCC is likely related to the fact that PAF does not consider temporal lag between risk-factor acquisition and HCC development; it may take several decades for cohorts affected with NAFLD to develop HCC in large numbers.[61]

## Diagnosis of HCC

The goal of surveillance is to detect HCC at an early stage, when curative options are feasible. The AASLD criteria for diagnosis of HCC in a patient with cirrhosis have been based on well-defined imaging characteristics (arterial enhancement with postarterial washout) without the need for a confirmatory biopsy.[62] In 2011, the American College of Radiology introduced the Liver Imaging Reporting and Data System (LI-RADS) to standardize the reporting of liver lesions. LI-RADS encompasses 5 categories, with LR-5 representing a definitive imaging diagnosis of HCC. More rigorous criteria were required for lesions of 1.0–1.9 cm than for lesions ≥2 cm. The most updated LI-RADS, version 2018 (available at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS) has amended the criteria for 1.0–1.9 cm LR-5 lesions to match[63] those of the updated 2018 ASSLD criteria: both state that a 1.0–1.9-cm lesion may be categorized as LR-5 if benign lesions and non-HCC malignancy have been excluded from consideration and there is a non-rim arterial phase hyperenhancement in combination with either washout or threshold growth, regardless of capsule appearance. The imaging feature of an enhancing capsule appearance is now required only in lesions ≥2 cm with neither washout appearance nor growth. For transplant prioritization, however, the Organ Procurement and Transplantation Network (OPTN) still requires washout plus capsule appearance if 50% growth within 6 months is not present in arterial enhancing lesions of 1–1.9 cm. A recent study found that LI-RADS did not outperform the AASLD criteria for HCC diagnosis in single lesions ≥3 cm.[64] Data are being collected to address unanswered questions and update LI-RADS every 3–5 years.[65]

When contrast-enhanced imaging is not feasible or the findings are not characteristic of HCC, a targeted biopsy is warranted. Initial reports of complications such as needle track seeding varied from 3% to 9%. A meta-analysis of 8 studies reported a 2.7% risk of needle track seeding, pathologically confirmed, with a median time of diagnosis of 17 months from diagnostic biopsy.[66] This risk was 0% in a subsequent study, which used a coaxial cutting needle technique.[67] Multiple biopsies may be required to minimize sampling error with a false negative result, and with a negative biopsy result, close follow-up imaging is recommended in a suspicious lesion.[68]

## HCC Prognosis

HCC treatment options depend on tumor burden, degree of liver dysfunction, and performance status. The Barcelona Clinic for Liver Cancer (BCLC) staging system, which pairs these parameters with a recommended therapy, is the most widely used.[69] The median overall survival associated with therapy based on BCLC stage provides providers and patients with realistic expectations regarding anticipated average life expectancy. Overall survival is considerably shorter in patients with untreated HCC (Supplementary Table 1).[70,71]

The Hong Kong Liver Cancer staging system also takes into account prognostic factors and pairs each stage with a recommended therapy.[72] The Hong Kong Liver Cancer system consists of 9 stages and recommends more aggressive therapy among subsets of patients compared with the BCLC, including resection for those with multiple tumors and those with intrahepatic vascular invasion. This system will require prospective validation in Western patients to determine if the proposed therapies do indeed lead to improved overall survival.

## The Role of Tumor Biopsy in HCC

A tumor biopsy is used in some centers as a selection tool for orthotopic liver transplantation (OLT) to disqualify OLT in patients with poor prognostic features; however, it is not considered the standard of care. The Extended Toronto Criteria for liver transplantation has no limitation in tumor size or number, barring any systemic cancer-related symptoms (defined as weight loss exceeding 10 kg and performance status $>$ 0), extrahepatic spread, and vascular invasion. However, if the tumor burden exceeds the Milan criteria, a biopsy of the largest lesion is mandatory to rule out poorly differentiated HCC, which excludes OLT.[73] In a retrospective study, those exceeding the Milan criteria but meeting the Extended Toronto Criteria had a 5-year overall survival after OLT of 70%.

In a prospective study using the Extended Toronto Criteria in 243 patients with HCC listed for OLT, 43% exceeded the Milan criteria and had tumor biopsy before listing to exclude poorly differentiated HCC; 18% dropped out because of tumor progression.[74] The remaining 72 patients had OLT and had a 5-year post-OLT overall survival of 68%. There was a nonsignificant increase in HCC recurrence after OLT among those who exceeded vs those who me the Milan criteria (26% vs 16%, $P = .09$).

Tumor biopsy may also provide prognostic information on a molecular level. However, the use of gene signatures is limited by assessment to tumor tissue outside clinical studies and concern for heterogeneity within a tumor that could alter the predictive capability. Tumor biopsies would be expected to increase with development of targeted therapies against identified driver mutations. Furthermore, despite advancements in the molecular pathogenesis of HCC, systemic therapies with proven survival benefit have no known molecular signature to predict response.[75] In a biomarker study of the STORM trial, gene signatures failed to predict recurrence or prevention of HCC recurrence associated with adjuvant sorafenib use.[76] In HCV-induced HCC, examining tumor tissue identified genetic signatures enriched with immune cells in approximately 24% of cases, which were further subdivided based on the tumor microenvironment. An active immune response within the stroma was an independent predictor of overall survival in patients who had resection for HCC.[77] This may offer insight into predicting response to immune check-point inhibitors.

## Liver Transplantation

OLT offers the best chance for oncologic cure. However, access to OLT is based on the Milan criteria, which are dependent on tumor size and number (1 lesion $\leq$ 5 cm or 2–3 lesions with none exceeding 3 cm). Predictors of HCC recurrence after OLT, beyond tumor size and number, have emerged, including microvascular invasion (limited availability before OLT), serum $\alpha$-fetoprotein (AFP), and neutrophil-lymphocyte ratio (NLR).

Serum AFP has established its role as an important prognostic marker in HCC. AFP $>$ 1000 ng/mL has been reported in several studies to be an independent predictor of inferior post-OLT outcomes,[78–80] with recurrence rates approaching 50%. An AFP increase $>$7.5 ng/mL per month using several AFP datapoints was significantly associated with microvascular invasion and HCC recurrence after transplantation.[81] These data support the recent inclusion of an AFP threshold in the United Network for Organ Sharing eligibility criteria for an HCC Model for End Stage Liver Disease (MELD) upgrade. If the AFP level is $>$ 1000 ng/mL, an HCC MELD upgrade is not automatic in T2 lesions. To qualify for a standard MELD upgrade, the AFP level must decline to $<$ 500 ng/mL after locoregional therapy (LRT), and those with an AFP level $\geq$ 500 ng/mL anytime after LRT are referred to the review board as special cases. The AFP level closest to OLT is the most informative value in predicting post-OLT outcomes. A rising AFP is associated with increased post-OLT mortality, independent of tumor burden.[82]

Approximately one third of HCC tumors are non-AFP producers. It is unknown whether non-AFP tumors are biologically similar to those with an elevated AFP that declines with LRT. An analysis of patients with an AFP persistently less than 10 ng/mg while awaiting OLT showed a significantly lower proportion of microvascular invasion and poorly differentiated tumor on explant, both risk factors for HCC recurrence. Overall and recurrence-free survival were superior in tumors with AFP $<$ 10 ng/mL compared to AFP-producing tumors after stratifying for radiographic Milan status. Five-year overall survival was 71% in non-AFP producers within Milan criteria on imaging, and recurrence rate was only 6%. These data suggest that persistently normal AFP tumors have a less aggressive biological behavior than AFP-producing tumors. However, this conclusion is tempered by the AFP $<$ 10 ng/mL group's having received a greater number of LRTs before OLT.

Blood and tissue markers of chronic inflammation carry some prognostic value in various malignancies, including HCC. The blood NLR may predict HCC recurrence after OLT.

In a meta-analysis of 13 studies (1936 liver transplantations), the pretransplantation NLR (cutoff, 2.3–6.0) was associated with an inferior overall survival (HR, 2.22; 95% CI, 1.34–3.68), recurrence-free survival (HR, 3.77; 95% CI, 2.01–7.06), explant characteristic including microvascular invasion (odds ratio, 2.39; 95% CI, 1.20–4.77), and lower likelihood of meeting the Milan criteria (odds ratio, 0.26; 95% CI, 0.17–0.40).[83] A subgroup analysis suggested a pretransplantation NLR cut off of ≥4.0 has optimum prognostic performance. Further research is needed to verify whether age, LRT, HCV therapy, and time elapsed from NLR measurement to OLT influence the prognostic capability of NLR.

Proponents of expanding the Milan criteria have been unsuccessful in devising and testing a widely accepted alternative. Combining various biological parameters into scoring systems that include radiographic response to LRT, tumor markers (AFP or DCP/PIVKA levels), NLR, and waiting time has been proposed[84–86]; recurrence free survival after OLT is significantly lower in those exceeding the determined cutoffs in these scoring systems for tumors both within and exceeding the Milan Criteria (Table 1).

### *Prognosis in Intermediate and Advanced HCC*

The BCLC B stage represents a heterogeneous group of patients. Chemoembolization is the standard of care, based on several RCTs, which showed improved overall survival compared with best supportive care.[87,88] A subclassification consisting of 4 subgroups (B1–B4) has been proposed.[89] Those characterized as B1 (Child-Pugh [CP] 5–7, normal performance status, and up-to-7 tumor burden) had a median overall survival of 41 months. Similar overall survival (47.7 months) has been reported in highly selected patients treated with transarterial chemoembolization and drug-eluding beads.[90]

### *BCLC C Stage*

Advanced HCC carries a poor prognosis; however, the BCLC C stage is also quite heterogeneous. In a retrospective study of 835 patients with BCLC C HCC, differences in median overall survival were noted based on the criteria that led to advanced HCC assignment.[91] Median overall survival was significantly different, based on performance status (grade 1, 38.6 months; grade 2, 22.3 months) and presence of extrahepatic spread (11.2 months) or macrovascular invasion (MVI) (peripheral portal vein thrombosis, 11.2 months; main portal vein thrombosis, 7.1 months). Receipt of therapy also varied based on these components of the BCLC C stage, with curative options highest among those with performance status 1. This suggests that performance status 1 alone should not result in classification of advanced HCC.

Patterns of HCC progression with sorafenib significantly affect postprogression survival.[92] Three patterns of progression include increase in intrahepatic/extrahepatic tumor size, new intrahepatic lesion, and new extrahepatic lesion. Development of a new extrahepatic lesion and/or new vascular invasion is an independent predictor of postprogression survival.[93]

## Therapeutic Advances

### *Very Early HCC*

Radiofrequency ablation (RFA) or resection are the main treatment options, and the choice depends on age; tumor location; comorbidities; and absence of clinically significant portal hypertension (CSPH), defined as hepatic venous

**Table 1.** Prognostic Models for Patients HCC Treated With Liver Transplantation

| Scoring system | Included parameters and cutoff (points) | Recurrence risk stratification | 5-y RFS (%) or recurrence (%) |
|---|---|---|---|
| MoRAL (United States)<br>N = 339<br>DDLT, 91%<br>LDLT, 9% | AFP > 200 ng/mL (6)<br>NLR > 5 (4)<br>Largest tumor > 3 cm (3) | 0–2 points: low<br>3–6 points: medium<br>7–10 points: high<br>>10 points: very high | RFS<br>MoRAL ≤ 10<br>- Within Milan: 90<br>- Outside Milan: 80<br>MoRAL > 10<br>- Within Milan: 45<br>- Outside Milan: 40 |
| MoRAL (Korea)<br>N = 566<br>LDLT, 100% | AFP<br>PIVKA<br>Formula = 11 × square root PIVKA + 2 × square root AFP | Low < 314.8<br>High > 314.8 | RFS<br>MoRAL ≤ 314.8<br>- Within Milan: 85<br>- Outside Milan: 70<br>MoRAL > 314.8<br>- Within Milan: 50<br>- Outside Milan: 18 |
| TRAIN (Time-Radiological-response-Alpha-fetoprotein-INflammation) (Brussels)<br>N = 289 | Radiographic response<br>AFP slope ≥ 15 ng/mL/mo<br>NLR > 5<br>Waiting time ≤ 120 d<br>Formula: 0.988 (if mRECIST-PD) + 0.838 (if AFP slope ≥ 15.0 ng/mL/mo + 0.452 (if NLR ≥ 5 ) – 0.03 WT (× months) | Low risk < 1.0<br>High risk ≥ 1.0 | Recurrence<br>TRAIN < 1<br>- Within Milan: 8.4<br>- Outside Milan: 26<br>Train ≥ 1<br>- Within Milan: 35<br>- Outside Milan: 100 |

pressure gradient < 10 mm Hg and bilirubin level < 1.0 mg/dL. There is no clear data-driven approach, with no randomized controlled trials (RCTs) in very early HCC comparing resection to ablation in candidates for either therapy. Response rates to ablation are excellent, with 5-year overall survival of up to 68%.[94] The BRIDGE Study, a multinational cohort etc, reported a significantly lower overall survival associated with ablation in nonideal candidates for resection compared with resection.[95] Therefore, a common approach is to "wait and not ablate" until a lesion reaches 2 cm; this has a <10% chance of progression beyond the Milan criteria.[96] and is endorsed by the AASLD for patients with a T1 lesion listed for OLT.[97] An alternative approach in CP A patients with early HCC is resection or ablation as first-line therapy, with OLT reserved only for tumor recurrence or hepatic decompensation.[98] The third approach is surgical resection in otherwise suitable candidates for OLT to determine the presence of high-risk features (vascular invasion, satellite lesions, poorly differentiated tumor) and early transplantation before HCC recurrence.[99] The recent AASLD guidelines recommend resection over RFA in compensated T1 and T2 disease. A subsequent Cochran review that included 4 RCTs of resectable T1/T2 HCC comparing resection to RFA found no significant difference in overall survival between the 2 approaches.

### Hepatic Resection

Advancements in surgical technique, patient selection, and perioperative care have significantly reduced surgical mortality to 1%–3% at experienced centers.[100] The BCLC recommends resection in CP A patients with a single lesion (no size limit) without CSPH . In a study of more than 8000 patients in a multiregional cohort that assessed surgical management of newly diagnosed HCC, only 10% were considered ideal candidates for resection.[95] Even in patients with no CSPH and bilirubin level < 1.0 mg/dL, the future liver remnant may not be ≥ 40% to sustain adequate liver function after resection. In such cases, growth of the functional liver residual may be induced via portal vein embolization.[101] However, a concern is tumor growth while awaiting hypertrophy. Radioembolization has been used as a bridge to resection by treating the tumor and simultaneously inducing contateral hypertrophy, thereby increasing the functional liver residual by 26%–47% over 44 days to 9 months.[102,103]

Five-year recurrence rates approach 70% after resection, with two thirds of recurences occuring within 2 years related to intrahepatic spread. To date, no effective adjuvant therapy has been reported, including sorafenib.[104] The potential for early HCC recurrence after resection associated with DAAs has been hypothesized to be related to a dampening of tumor immune surviellence with rapid virologic clearance.[9] However, subsequent analysis has offered the alternative explantion of a selection bias related to the proximity of initiation of DAA therapy after resection.[105]

Resection in a subset of patients with preserved synthetic function and MVI of first-order (V1) or peripheral branches (V2) has been reported to achieve significantly improved overall survival compared with nonsurgical therapy in a Japanese cohort.[106] Further research is required before advocating this approach.

### Bridging to Transplantation

Patients awaiting OLT for HCC are at risk of tumor progression beyond the Milan criteria (T2) and, hence, waitlist dropout. Therefore, LRT is often used to delay tumor growth and maintain priority for transplantation. A meta-analysis of 2 studies reported that receipt of any form of LRT was associated with a nonsignificant decrease in dropout related to HCC progression and dropout from all causes compared with no LRT before OLT.[107] Furthermore, there was no significant difference in overall survival and recurrence after liver transplantation found to be associated with LRT. There was a high risk of selection bias and no RCTs. The updated AASLD guidelines recommend LRT in patients with T2 HCC listed for OLT but do not endorse a specific therapy.[95] A subsequent single-center study conducted over 6 years[108] in 45 BCLC A/B patients randomly assigned to receive TACE or yttrium 90 (Y90), with repeat therapy based on radiographic response. Time to tumor progression (TTP) was significantly longer in Y90: 6.8 months for cTACE and not reached for Y90 (>26 months; HR, 0.122; $P = .007$). Overall survival censored to liver transplantation was not significantly different between the 2 (TACE, 17.7 vs Y90, 18.6; $P = .99$).

### Downstaging to Transplantation

LRT to induce tumor necrosis and downstage to the Milan criteria has increased access to OLT in select patients. Successful downstaging has been reported in 24%–90% due to heterogeneity in radiographic assessment; downstaging protocols, including entry criteria and use of biological markers in addition to tumor size/number; and timeout period after response but before listing.[109] A meta-analysis reported a pooled success rate of 48%, with HCC recurrence of 16% after OLT.[110] Multimodal therapy was associated with higher rates of downstaging. In this analysis, downstaging was a radiographic endpoint; therefore, all patients included may not have been considered OLT candidates. A prospective downstaging study in OLT candidates reported no significant difference in 5-year post-OLT overall survival between those downstaged and T2 patients at listing: 90% vs 88%, respectively, with acceptable HCC recurrence of 7.5% among the downstaged cohort.[111] A subsequent multicenter retrospective study confirmed excellent post-transplantation outcomes.[112] AFP level > 1000 ng/mL before LRT and CP B/C predicted treatment failure. UNOS has recognized the role of downstaging, and it is now part of the policy for allocation. Patients who meet eligibility for downstaging (i.e., 1 lesion > 5 cm and ≤ 8 cm, or 2–3 lesions each < 5 cm and total diameter of all lesions ≤ 8 cm, or 4–5 lesions each < 3 cm and total diameter of all lesions ≤ 8 cm) and are successfully downstaged to the Milan criteria are eligible for the standard HCC MELD upgrade.

The most reported common downstaging modality is chemoembolization. External-beam radiation as a bridge to

OLT in a single-center study showed no significant difference in dropout rate, overall survival from listing, or OLT compared with RFA or TACE.[113] Radiotherapy may be an alternative therapeutic option when TACE or RFA are not feasible.

### Radioembolization

Radioembolization has been used across the BCLC.[114] Although no difference in overall survival has been shown between radioembolization and chemoembolization in BCLC A/B, Y90 has been shown to be feasible and safe in patients with MVI. Improvement in overall survival, particularly among patients with portal vein thrombosis (PVT), may be feasible by using a personalized approach with glass microspheres. A tumor threshold dose of $>$ 205 Gy has shown a significant improvement in overall survival and radiographic response rates compared with $<$ 205 Gy.[115] The tumor radiation dose and $^{99m}$Tc macroaggregated albumin quantification uptake into the tumor/PVT can stratify patients into good (PVT uptake on macroaggregated albumin $\geq$ 205 Gy) vs poor candidates.[116]

A prognostic model can identify patients with PVT (excluding main PVT) anticipated to derive a significant benefit with Y90 vs those to avoid because of futility.[117] Three variables consisting of bilirubin ($\leq$1.2 vs $>$1.2 mg/dL), extension of PVT (segmental, second order, first order), and tumor burden ($\leq$50% vs $>$50%) were used to construct prognostic categories. Patients with a favorable prognosis (0 points) had a median overall survival of 32.2 months. Median overall survival was significantly lower in those with intermediate prognosis (2–3 points) and dismal prognosis ($>$3 points) at 14.9 and 7.8 months, respectively.[118–120]

### Combination Therapy in Early or Intermediate HCC

**TACE Plus RFA.** TACE plus RFA is used to attempt to overcome the limited ablation in target lesions exceeding 3 cm. RCTs comparing TACE plus RFA vs RFA alone have been limited by insufficient power.[121] In a meta-analysis of 8 RCTs, patients with lesions $>$ 3 cm have shown higher overall survival associated with combination therapy, with no significant increase in major complications compared with TACE alone. No RCTs have compared the efficacy of TACE plus RFA with TACE. A small non-RCT trial comparing drug eluting beads plus RFA vs DEB reported significantly longer 2-year overall survival and lower recurrence rates in the combination arm.[122]

**TACE Plus Tyrosine-Kinase Inhibitors.** The intended synergy of combining sorafenib with TACE is to blunt the angiogenic surge associated with embolization-induced hypoxemia, thereby extending TTP and improving overall survival. Initial studies of this approach reported varied results. A meta-analysis of 6 trials concluded that the combination of sorafenib and TACE results in improved overall survival and TTP compared with TACE monotherapy.[123] However, subsequent large RCTs comparing TACE/DEB plus tyrosine-kinase inhibitors to TACE/DEB alone failed to show a clinical benefit with combination therapy. Tyrosine-kinase inhibitor initiation timing related to TACE/DEB, dosage, duration, and early terminations of trials may have affected the results.[124] In the SPACE trial, one third of patients in the combination arm received only 1 session of DEB because of conservative stopping rules.

A phase II trial in Japan of 156 patients, Transcatheter Arterial Chemoembolization Therapy in Combination With Sorafenib, reported a significantly longer progression-free survival in patients who received TACE plus sorafenib vs TACE alone, 25.2 vs 13.5 months, respectively (HR, 0.59; 95% CI, 0.41–0.87; $P = .006$).[125] The study design may explain the positive results. In contrast to prior trials, new intrahepatic lesions did not constitute progression that led to discontinuation of assigned therapy. The median duration of sorafenib in this trial was longer (38.7 weeks) compared with prior studies (TACE 2, SPACE, Post-TACE), ranging from 17.0 to 24.0 weeks. Most (89%) patients had no prior treatment with TACE. This, along with TACE administered on demand as opposed to scheduled, may have contributed to preservation of liver function to allow continuation of sorafenib. The co-primary endpoint of overall survival is not yet available.

### Therapy in Advanced HCC

Sorafenib is the standard treatment in patients with advanced HCC, based on improved overall survival in RCTs compared with placebo.[97,121,126,127] Predictive factors for sorafenib benefit in advanced HCC have been retrospectively identified.[128] Overall survival was significantly extended with sorafenib in those with HCV (HR, 0.47 vs 0.81), no extra hepatic spread (HR, 0.55 vs 0.84), and a low NLR (HR, 0.59 vs 0.81) compared with placebo. MVI, high AFP level ($>$ 200 ng/mL), and high NLR were poor prognostic factors for overall survival in the entire cohort First- and second-line agents have subsequently been positive in phase 3 RCTs in unresectable HCC (Table 2).

**Radioembolization With or Without Sorafenib.** The first large RCT, phase II, examining sorafenib vs Y90 (resin microspheres) plus sorafenib in inoperable, locally advanced HCC, SORAMIC (SORAfenib in combination with local MICrotherapy guided by gadolinium-EOB-DTPA-enhanced magnetic resonance imaging) showed no significant difference in primary endpoint, overall survival in the intended-to-treat analysis: 12.1 (sorafenib + Y90, n = 216)

**Table 2.** Systemic Therapy in HCC

| Therapy | Median overall survival (*mo*) | HR (95% CI) |
|---|---|---|
| First line | | |
| Lenvatinib vs sorafenib | 13.6 vs. 12.3 | 0.92 (0.79–1.06) |
| Second line | | |
| Regorafenib vs placebo | 10.6 vs. 7.8 | 0.63 (0.50–0.79) |
| Nivolumab[a] | 15.0/15.6 | NA |
| (Sor experienced: ESC/EXP) | | |
| Ramucirumab vs. placebo | 8.5 vs. 7.3 | 0.710 (0.531–0.949) |
| Cabozantinib vs. placebo | 10.2 vs. 8.0 | 0.76 (0.63–0.92) |

NA, not applicable.
[a]Phase I/II trial.

vs 11.5 months (sorafenib, n = 208) ($P$= 0.93).[129] Subgroup analyses of the patients treated per protocol identified improved overall survival in the Y90 plus sorafenib arm in patients younger than 65 years, with nonalcoholic etiology of liver disease and without cirrhosis. Increased adverse events, ≥grade 3, were noted in the combination group (73%) compared with sorafenib alone (65%).

Two other RCTs failed to show superiority of Y90 over sorafenib in advanced HCC.[130,131] In both trials, approximately one third of patients in the Y90 arm and 7%–9% in the sorafenib arm did not receive their planned therapy, and treatment-related adverse events were significantly lower in the Y90 group.

**TACE Plus External Beam Radiotherapy.** A meta-analysis of 25 Eastern trials (11 RCTs, n = 2577 patients) reported improved pooled overall survival (TACE + radiotherapy [RT], 22.7 mo vs TACE, 13.5 mo.; $P < .001$), but higher rates of gastric/duodenal ulcers and elevation in transaminases with TACE plus RT compared with TACE alone.[132] An RCT in 90 patients with HCC, CP A, with MVI without extrahepatic spread; 84% HBV; and no prior HCC treatment evaluated the safety and efficacy of TACE plus RT vs sorafenib alone (400 Gy twice daily, mean dose was 739 Gy/d).[133] Most patients with PVT had unilateral disease (58.9%). TACE was performed every 6 weeks, and RT was initiated 3 weeks after the initial TACE, with a planned total dose of 45 Gy to the targeted area. The primary endpoint of 12-week progression-free survival was significantly higher in the TACE-RT group than in sorafenib (86.7% vs 34.3%, $P < .001$). Independent of MVI extent, 24-week progression-free survival remained significantly higher in the TACE-RT group. Median TTP and overall survival were also significantly higher in the combination group (TTP, 31.0 vs 11.7 weeks; overall survival, 55 vs 43 weeks, respectively). Treatment crossover rate at 24 weeks was 90.7% in the sorafenib group to TACE/RT and 23% in the combination group to sorafenib because of tumor progression. Although adverse events were similar between the 2 groups, the safety and efficacy in a non-HBV population are not clear, and neither is the potential impact of not performing embolization out of concern of inducing liver dysfunction.

**LRT Plus Immune Oncology.** Immunotherapies are being combined with LRT with the hope of improving the expected median overall survival in those with advanced HCC.[134] The release of neoantigens induced by LRT- associated tumor necrosis may augment the response to immune checkpoint inhibitors. The first study used TACE or RFA in 32 patients (BCLC B/C with progressive disease at enrollment, 75% sorafenib experienced) followed by tremelimumab, an anti-CLLA-4 antibody, reported partial response in 26%, with TTP of 7.4 months and overall survival or 12.3 months.[135] Immune oncology in earlier-stage HCC is of concern because of risk of rejection in the post-transplantation setting.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2018.08.065.

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**Supplementary Table 1.** Prognosis of Untreated HCC

| Characteristics | Khalaf et al[70] (N = 518) | Giannini et al[71] (N = 600) |
|---|---|---|
| Cohort | United States, Veterans Affairs, 2004–2011 | 21 Italian centers, 1988–2008 |
| Median overall survival (*mo*) | 3.6 | 9.0 |
| Median overall survival by BCLC stage (*mo*) | 0/A: 13.6 | 0: 38 |
| | B: 9.5 | A: 25 |
| | C: 3.4 | B: 10 |
| | D: 1.6 | C: 7 |
| | — | D: 6 |