REVIEW ARTICLE

Classification and Current Treatment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive primary liver cancer that arises in a background of hepatic cirrhosis. In the United States, HCC has been increasing due to an increasing prevalence of the Hepatitis C virus which causes cirrhosis. Curative treatment of HCC is indicated when tumors are small and may include surgical resection, liver transplant, or radiofrequency ablation. Locoregional treatment includes transarterial chemoembolization and transarterial radioembolization which can be used as eithera an adjunct to surgical care or as primary therapy. This review article will examine the initial surveillance of patients at risk for HCC, the current guidelines related to diagnosis and staging of HCC, and will conclude with a review of best practices related to the treatment of HCC.

Keywords: Hepatocellular carcinoma, Locoregional therapy, Radiofrequency ablation, Transarterial chemoembolization, Transarterial radioembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the most common cause of death for individuals with cirrhosis.[1] The 1-year and 5-year survival rates for HCC are 50% and 20%, respectively, which rank among the worst survival rates for all cancers.[2] In the United States, the incidence of HCC has tripled since 1980, a finding that is largely driven by an increased prevalence of hepatitis C in the baby boomer population. In the future, the incidence of HCC is projected to remain elevated due to the increasing prevalence of cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD) in the United States.[3]

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For many patients diagnosed with HCC, transarterial chemoembolization (TACE), and transarterial radioembolization with yttrium-90 (Y90) will be indicated as part of a multimodal approach to either downstage disease (to a point where surgical resection or transplant may be indicated), prevent disease progression (particularly for patients on a liver transplant waitlist, so-called "bridge" therapy), or more generally with palliative intent aimed at prolonging survival for patients who are not candidates for surgery.

Below we review the current best practices related to initial surveillance for HCC, followed diagnosis, disease staging, and treatment.

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HCC SURVEILLANCE

While surgical indications are controversial, once tumors are multifocal, over 5 cm, or demonstrate vascular invasion, surgery is generally not performed because at that point occult extrahepatic spread is more likely which is associated with early disease recurrence. As a result, only 30–40% of patients who are diagnosed with advanced HCC are candidates for surgical intervention.[4] However, if patients are successfully integrated into a surveillance program, they have a 70% chance of being diagnosed at an early or very-early-stage. In these cases, early diagnosis is life-saving as curative interventions offer 5-year survival rates that uniformly surpass 60%.[5]

HCC surveillance is indicated for any individual with cirrhosis regardless of etiology per major US guidelines.[6,7] There may be a subset of individuals with Hepatitis B who do not yet have cirrhosis but are at high enough risk for developing HCC due to either high viral counts or an Asian or African heritage such that surveillance is cost-effective.[8] Similarly, surveillance for individuals who have F3 fibrosis diagnosed through liver biopsy may also represent a group where surveillance is cost-effective despite not yet having cirrhosis, although this is not definitely known.

HCC surveillance is performed through hepatic ultrasound every 4–8 months. The short interval surveillance is indicated because of the rapid median tumor doubling time of HCC which is 100 days.[9] The sensitivity of ultrasound surveillance ranges between 65% and 80%.[10] Patients with end-stage liver disease are not effectively screened with ultrasound and may require cross-sectional imaging to screen for HCC. This is based on a study of 27 individuals who had an ultrasound performed at an average of 90-days before liver transplant after which it was found that ultrasound was sensitive to HCC in only 20% of cases after correlation with pathologic evaluation of the liver explant.[11]

It is unknown if there a benefit to combining serum alpha-fetoprotein (AFP) measurement along with ultrasound surveillance. AFP alone is neither sensitive nor specific for disease detection. This is because many early HCC's do not secrete AFP, and moreover, the natural progression of liver cirrhosis is associated with increasing AFP levels.[12,13]

There is no indication to screen patients with NAFLD for HCC until a diagnosis of cirrhosis has been made. In fact, individuals with NAFLD-cirrhosis have a comparatively decreased incidence of HCC and overall fewer liver-related complications in comparison to virally mediated cirrhosis.[14]

HCC DIAGNOSIS

HCC can have a variable appearance on ultrasound. Three-quarters of HCC tumors <2 cm are hypoechoic and half of cases demonstrate increased vascularity.[15]

Lesions <1 cm identified on screening ultrasound are typically not HCC but should be followed more frequently - every 3 months, until 2 years of sonographic stability have been demonstrated.[6] Cross-sectional imaging is generally not pursued until lesions are >1 cm as neither computerized tomography (CT) or magnetic resonansonace imaging (MRI) are likely to be helpful in further characterizing these small lesions (each have <50% sensitivity for detection of small HCC). MRI is more sensitive than CT for lesions >1 cm with respective sensitivity of 88% in comparison to 82% for CT. However, for lesions >2 cm, the comparative sensitivities are negligible (95% vs. 92%, respectively). Per lesion specificities are similar for each modality. MRI should be performed with a hepatobiliary contrast agent if possible such as gadoxetate disodium (Eovist®, Bayer Healthcare) as the demonstration of hepatobiliary phase hypointensity is associated with HCC and therefore increases sensitivity.[16]

HCC tumors display characteristic features which are reported in a standardized manner according to the LI-RADS guidelines.[17] LI-RADS 5 lesions are defined as any lesion >1 cm demonstrating arterial phase hyperenhancement which also displays at least two of the following three criteria: (1) Washout on portal venous or delayed phases, (2) an enhancing capsule, or (3) threshold growth (defined as a 50% increase in diameter in <6 months). LI-RADS 5 lesions are reported as "definitely HCC" with specificity >95%. Additional MRI features that can upstage the LI-RADS score (but never from LIRADS 4 to 5) include intermediate signal on fluid-sensitive sequences in comparison to background liver, restricted diffusion, or low-signal on delayed hepatobiliary phases. Importantly, for staging purposes, the size of each HCC lesion must be measured from outer edge to outer edge.

For individuals with indeterminate lesions on two separate modalities, the optimal next step, either liver biopsy or continued surveillance, is not known. What is known is that LI-RADS 3 and 4 lesions are associated with a respective 7% and 38% risk of HCC,[18] and second, while liver biopsy generally has 90% sensitivity for generating a HCC diagnosis it may be less sensitive for smaller lesions (one study finding a false negative rate in 40% of patients with lesions <3 cm).[19]

HCC STAGING

The staging of HCC is unique because mortality is determined not only by tumor characteristics (size, multifocality, and vascular invasion) but also by the degree of liver decompensation. In the United States, the National Comprehensive Cancer Network (NCCN) stages HCC based on three broad categories: (1) potentially resectable, (2) unresectable due to poor hepatic reserve (e.g. child-pugh C -- patient should be considered for transplant), and (3) unresectable due to comorbidities (patient should be considered for ablation or locoregional therapy).

Probably the most commonly used HCC staging system is the Barcelona Clinic Liver Criteria (BCLC) which has been adopted by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[20]

In 2014, the Hong Kong Liver Cancer (HKLC) staging system was published with one of the larger departures being a substratification of patients with portal venous invasion. Classically, under the BCLC, any patient with a tumor in the portal venous system was defined as Stage C and therefore considered to have advanced disease and treated with chemotherapy. In comparison, by HKLC criteria, patients with tumor in the portal venous system are substratified into populations with only branch portal vein invasion - a cohort which then is treated more aggressively; partial liver resection if the tumor is single, and the patient is Child-Pugh A, and all other cases of branch portal vein invasion receiving TACE. When treating this cohort of patients classically staged as BCLC-C 5-year overall survival (OS) was significantly improved when curative therapy was pursued as opposed to systemic chemotherapy (48.6% vs. 0.0%, respectively).[21] The HKLC has been validated in Western populations.[22]

CURATIVE TREATMENT FOR HCC

Partial surgical resection

Metastatic spread of HCC is initially through the portal vein causing multinodular intrahepatic metastases and then through the hepatic vein to cause extrahepatic metastases. For this reason, anatomic segmental resection along the portal blood supply is performed in an attempt to both resect the focus of HCC and to capture occult metastases along the portal vein.

There are multiple relative contraindications to liver resection (Table 1). In many cases, the volume of the future liver remnant (FLR) post-resection will be a limiting factor precluding hepatic resection. For patients with cirrhosis, the FLR must be at least 40% of the pre-resection liver volume. Before performing resection, many patients with anticipated small FLR will undergo portal vein embolization which causes ischemia of the embolized lobe and concomitant regenerative hypertrophy of the contralateral lobe (the FLR).[23] In some cases, partial resection is unable to be performed after portal vein embolization due to iatrogenic tumor progression in the non-treated lobe because of rapid shunting of blood flow. Although this is less common with HCC than with metastatic disease, it remains a potential adverse outcome.[24] For this reason, Y90 may offer better outcomes for patients with small FLR as it can be used to both treat ipsilateral HCC and additionally will cause hypertrophy of the FLR.[25]

Survival after hepatic resection is high with survival ranging from between 87% and 97% after 1 year and between 35% and 74% after 5 years.[30,33-35] Tumor size itself is not a limiting factor for hepatic resection as 5-year survival for tumors >10 cm is between 27% and 40%, which is superior to alternative therapies.[36] There may be a benefit to performing partial resection in patients with bilobar HCC or portal hypertension which classically are exclusion criteria.[37]

Liver transplant

In 1996, Mazzaferro *et al*. demonstrated that a 5-year OS of 75% could be obtained when liver transplant was performed for patients with HCC using relatively strict criteria before performing transplantation. This was a landmark study because prior to their publication, HCC was essentially seen as a contraindication to performing liver transplantation with early disease recurrence representing a frequent complication. These findings by Mazzaferro *et al*. gained wide acceptance and became known as the Milan Criteria.[38] In 2009, the same group expanded on the Milan Criteria with the so-called "Up-to-Seven" criteria that were found to confer a 5-year median OS of 71%.[39] Alternative and more liberal transplant criteria are represented by the expanded UCSF criteria, published in 2001 (Table 2). The reported 5-year median OS after transplantation by the UCSF group has been reported to be approximately 75%.[40]

In the United States, the Organ Procurement and Transplantation Network is operated by the United Network for Organ Sharing (UNOS), a group which is responsible for managing the transplant waitlists. Priority for receiving a liver transplant is based on the model for end-stage liver disease (MELD) score. While transplant rates vary by region, generally, an allocation MELD score between 15 and 24 confers a 1.9% chance to receive a transplant in 90 days, a MELD score between 25 and 29 confers a 6.6% chance of receiving a transplant in 90 days, and a MELD score between 30 and 34 confers a 23.7% chance of receiving a transplant in 90 days.[41] Importantly, for patients diagnosed with HCC, the MELD score does not accurately reflect their increased risk of mortality, so an exemption system is in place to add points to their baseline MELD score. To qualify for exemption points, a patient must satisfy the Milan criteria (stage T2 tumor by UNOS criteria) and have an AFP that is <1000 ng/mL. After an initial 6 months of waitlist time, these patients will then receive MELD-score exemption points totaling a MELD-score equivalent of 28 which then increases by 2 points every 3 months up to a maximum of 34 points.[42]

Many patients with HCC who are placed on the transplant waitlist will undergo locoregional treatments to prevent waitlist dropout due to disease progression (if their tumors grow >5 cm) they will be outside of the Milan Criteria and will no longer be transplant candidates. For these patients, RFA is generally indicated for tumors <3 cm, and TACE

Table 1: Relative contraindications to partial hepatic resection

Relative contraindications to partial hepatic resection	Supporting evidence
FLR <40%	6-month mortality of 38%[26]
Child-Pugh B or C	12-month mortality of 30% (Child-Pugh B) and 82% (Child-Pugh C)[27]
HVPG >10 mmHg	Grade 3–5 adverse events in 7% of patients with average HVPG of 7 mmHg.[28]
Main portal vein invasion	Median survival after partial resection is only 1-year.[29]
Total bilirubin >2 mg/dL	Median survival is 91 months if total bilirubin is <1 mg/dL; median survival is 30 months if the total bilirubin is >1 mg/dL.[30]
Bilobar tumors	Multi-site resection (e.g., requiring more than one *en bloc* resections) confers 3-year and 5-year OS of 35% and 16%, respectively, not significantly greater than locoregional therapy.[31]
Active hepatitis with AST or ALT twice the upper limit of normal	Post-operative death due to liver failure increases from 1.5% to 8.7%.[32]

FLR: Future liver remnant, HVPG: Hepatic vein-to-portal venous gradient, AST: Aspartate transaminase, ALT: Alanine transaminase, OS: Overall survival

Table 2: The Milan criteria, the New Milan criteria, and the UCSF criteria for liver transplantation. Evidence of portal venous invasion or extrahepatic metastases are excluding factors for each criteria

Inclusion criteria for liver transplant		
Milan criteria	**New Milan criteria,"Up-to-Seven"**	**UCSF criteria**
One tumor <5 cm or alternatively, Two or three tumors all <3 cm	The diameter of the largest tumor in centimeters plus The total number of discrete tumors Must be equal to or <7	One tumor <6.5 cm or alternatively, Two or three tumors each <4.5 cm so long as the sum of all diameters is not >8 cm

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or Y90 is used for multifocal or larger tumors. Using these modalities sequentially may provide the greatest decrease in waitlist dropout although evidence is mixed. One prospective review of 36 patients receiving TACE followed by RFA demonstrated waitlist dropout of 0%, 2.8%, and 5.5% at 3, 6, and 12 months, respectively, which was substantially better than standard waitlist dropout rates of 9%, 17%, and 32% at 3, 6, and 12 months.[43] Stereotactic body radiotherapy (SBRT) may be non-inferior with respect to waitlist dropout frequency in comparison to RFA, TACE, and Y90 but this is not certain.[44] SBRT is associated with less complete pathologic response of treated tumors on *ex vivo* analysis (28.5%) when compared to TACE (41%), RFA (60%), and Y90 (75%).[45] Notably, patients continue to remain listed based on their initial tumor criteria such that even if they were to have a complete response with bridging therapy, they remain eligible for liver transplantation.

Patients who do not meet criteria for liver transplant may be eligible to receive treatment aimed at downstaging disease such that they will become eligible for transplant. For patients who are successfully downstaged, transplant outcomes are not significantly different in comparison to patients who never required downstaging (5-year survival 77.8% for treated patients and 81% for patients not requiring downstaging).[46] TACE and Y90 are not associated with increased post-transplant complications when performed before transplantation.[47] The AASLD recommends that if a patient is able to be brought into the Milan criteria with any form of downstaging therapy, then they should be eligible for transplant or resection.[6] The EASL recommends resection or transplant after successful downstaging if the patient is involved in a clinical trial.[8]

With respect to specific treatments TACE is the most studied, but optimal treatment is not known. The largest retrospective review comparing TACE and Y90 found that for UNOS T3 lesions averaging 5.7 cm, 31% were able to be downstaged to T2 or better (<5 cm) with TACE whereas 58% were downstaged using Y90.[48] The study may have overestimated the effectiveness of Y90 for downstaging as a subsequent systematic review and pooled analysis (which included the previously referenced study) compared TACE and Y90 with findings of demonstrated downstaging success at 48% and 54%, respectively.[49]

Percutaneous RFA

RFA is an outpatient procedure that utilizes thermal energy to induce cellular death. RFA is recommended for individuals

who typically would receive surgical resection but are not felt to be surgical candidates either due to decompensated liver disease (total bilirubin over 2 mg/dL or hepatic venous pressure gradien over 10 mmHg) or due to other comorbidities.

3-year OS after RFA ranges from 65% to 90% which is associated with a non-significant trend toward slightly decreased survival in comparison to hepatic resection with a respective 3-year OS of 75% to 95%.[50-53] With respect to all-cause mortality, RFA is non-inferior to surgical resection with a (hazard ratio for partial resection of 0.80; 95% confidence interval 0.6–1.08).[54] RFA is likely superior to SBRT for HCC <5cm with a recent retrospective analysis demonstrating 5-year survival of 29.8% for RFA and 19.3% for SBRT.[55]

Performing TACE before RFA may be superior to either RFA or TACE alone in individuals with tumors >3 cm.[56,57] This may be due to a decrease in blood tumor vascularity after TACE which serves to decrease the degree of the vascular heat sink and improve the effectiveness of RFA. There is no definite evidence for when to perform RFA after TACE, although 3–5 weeks have been proposed.[58]

There are few contraindications to RFA. High risk areas to ablate are generally considered to be <5 mm from major structures such as the diaphragm, gallbladder, stomach, bowel, kidney, and hepatic or portal veins. Adverse events can be minimized by performing various techniques, including artificial induction of either abdominal ascites or pleural effusion, or introducing chilled saline into the biliary system to protect from thermal injury.[59-61]

RFA may be safe for individuals with Child-Pugh B cirrhosis with no change in total bilirubin, albumin, international normalized ratio (INR), ascites, or encephalopathy after treatment; however, for Child-Pugh C patients, the total bilirubin has been reported to significantly increase in more than half of patients. Moderate liver decompensation with respect to increased Child-Pugh score is expected after RFA with an expected increase from 6.4 (±1.4) to 6.9 (±2.0; $P < 0.05$).[62]

One large multicenter review of 3554 previous percutaneous RFA cases noted post-treatment mortality in six individuals (0.2% of cases), four of which were due to complications from bowel perforation or intra-abdominal sepsis. Major adverse effects occur in 2.2% of cases and include acute liver failure, hemorrhage, needle tract seeding, and liver abscess.[63] Biliary injury is uncommon (occurring in <1% of cases), which is important as post-RFA upstream biliary duct dilation will be often be incidentally noted on follow-up imaging and is considered a benign finding unless clinically significant cholestasis is present.

LOCOREGIONAL TREATMENT

TACE

TACE is performed through a transarterial femoral approach, taking advantage of the non-uniform arterial blood supply to HCC.While technique varies, TACE is typically performed by the administration of chemotherapeutics mixed with an oil-based vehicle (lipiodol), followed by bland embolization, typically with gelfoam. This technique is known as conventional, or cTACE. Alternatively, TACE may be administered with doxorubicin coated drug-eluting beads that slowly release chemotherapy over time and due to the size of the beads (between 100 and 500 µm) also cause embolization. Performing TACE with drug-eluting beads may confer a mortality benefit over cTACE, including better tumor response, fewer systemic adverse effects, and a decreased need for retreatment, although this has not been consistently demonstrated in the literature.[64]

In 2002, Llovet *et al*. demonstrated that for a cohort consisting of primarily early-stage HCC, survival was significantly improved with TACE; 28.7 months in the TACE treatment arm in comparison to 17.9 months for the control/no-treatment arm.[65] These findings were similar to a second group, Lo *et al*., who reported median survival of 30 months for patients with tumors <5 cm treated with TACE in comparison to 11.5 months for the supportive care cohort.[66] More recently, patients with HCC treated with TACE have had outcomes stratified by stage according to the BCLC with approximate outcomes as follows: BCLC A (median survival between 34 and 40 months), BCLC B (median survival between 16 and 17 months), and BCLC C (median survival between 4 and 7 months).[67,68] These findings can be weighed against the median survival for patients with BCLC Stage B and BCLC Stage C tumors without treatment, which are 6.1 and 3.7 months, respectively.[69]

TACE is often repeated based on the tumor response to treatment, however, the optimal number or timing of treatments is not known. One prospective study compared scheduled TACE (3 treatments sequentially performed at 2-month intervals) versus selective retreatment based on follow-up imaging (tumor enhancement or threshold growth). It was noted that there was a significant increase in survival in the group only given TACE when necessary, for example, in early-stage disease, a 3-year median OS of 39% was reported for the selective group versus 11% for the scheduled group.[70]

There are multiple clinical decision-making tools available to help identify patients who are unlikely to benefit from TACE however, none have consistently demonstrated an ability to predict patient survival with or without TACE.[71]

For individuals with BCLC stage C HCC, the standard of care is systemic chemotherapy with oral sorafenib (Nexavar,® Bayer) although in some cases TACE has been demonstrated to be non-inferior.[72-74] TACE may be safely performed on patients with portal venous tumor thrombus with survival ranging from 8 months to 13.1 months, with only 1% of cases in a pooled analysis having post-TACE liver decompensation.[75]

Data relative to combination therapy with TACE plus sorafenib (TACE+S) is mixed. A meta-analysis from 2017 concluded that 0.5-year and 1-year OS was improved with combination therapy.[76] In the past year, the TACE-2 trial, a large Phase III randomized controlled trial which assigned 157 advanced stage patients to receive either TACE+S or TACE+placebo found no significant difference in progression-free survival (238 days in the TACE+S group and 235 days in the TACE+placebo group).[77]

TACE is generally not performed for patients with Child-Pugh C liver disease but otherwise there are few limitations. The most common side effect after TACE is post-embolization syndrome (PES) which may include fever, abdominal pain, and nausea and occurs in over half of patients (Table 3). PES in itself is self-limiting; however, the occurrence of PES is not entirely benign as clinically significant PES after TACE is associated with increased mortality (25 months median OS vs. 16 months if Grade 3 or 4 PES).[78]

The most serious adverse effect after TACE is acute liver failure (defined as bilirubin over 3 mg/dL, new ascites, INR over 2.2, or new encephalopathy within 2 weeks of TACE) which occurs in approximately 7.5% of patients. Other post-treatment adverse effects of TACE include a minimal increase in the Child-Pugh score, increasing from an average baseline of 5.6 up to 5.8 at 4 months after treatment (a finding which is primarily driven by a post-TACE increase in ascites occurring in approximately 10% of patients).[79] Additional adverse effects occurring in <2% of patients include renal failure, hepatic or splenic abscess, upper gastrointestinal (GI) bleeding, and/or gastroduodenal ulcer.

Y90 TRANSARTERIAL RADIOEMBOLIZATION

Y90 is a form of brachytherapy where the beta emitter Y90 is loaded onto either glass or resin microspheres and preferentially delivered to HCC through the hepatic artery thereby inducing radiation necrosis. Prospective evidence in support of Y90 has been growing over the previous decade. For BCLC Stage B patients (typically treated with TACE) median survival ranges from 15 to 25 months; for BCLC Stage C patients (typically treated with sorafenib) survival has been reported to range between 7.3 and 15 months.[84-87] In general, the upper limits of survival have been associated with Child-Pugh A disease and the lower limits represent treated individuals with Child-Pugh B disease. Y90 is usually not performed for patients with Child-Pugh C HCC due to the terminal nature of the disease (3-month predicted survival which increases to 4 or 5 months with treatment); however, if these patients are listed for transplant, segmental Y90 should be considered and can be performed as bridge therapy without a significant increase in adverse effects as compared to Child-Pugh A or B treated patients.[87]

Randomized head-to-head trials have been performed to better determine the role of Y90 in HCC. The PREMIERE trial, which was published in 2015, randomized 45 patients to receive either Y90 or TACE with a primary end-point of time to progression. Time to progression in the Y90 cohort was found to significantly outperform TACE (>26 months vs. 6.8 months; $P = 0.0012$); however, no significant survival benefit was demonstrated.[88] In SIRTACE, published in 2016, 28 patients were randomized to receive either Y90 or TACE. Y90 was found to have similar disease control rate and OS compared to TACE, a finding which was achieved despite patients requiring fewer Y90 treatments (3.4 average TACE treatments and 1 average Y90 treatment).[89]

With respect to Y90 for patients with advanced disease, two Phase III randomized controlled trials were published in 2017 comparing Y90 to sorafenib, the SARAH trial and SIRveNIB trial. SARAH randomized 467 patients to receive either Y90 or sorafenib, while SIRveNIB randomized 360 patients. The

Table 3: Common adverse effects after TACE[80-83]

Common adverse effects associated with TACE	Frequency (%)
PES	
Fever	58
Abdominal pain	43–48
Nausea or vomiting	33–34
PES requiring hospitalization	6–31
Liver decompensation	
Hyperbilirubinemia	10–23
Hypoalbuminemia	10
New ascites	6–25
New encephalopathy	2–9
Hematologic suppression (Grade 3 or 4 anemia or leukopenia)	7–29
Alopecia	13–18
Hepatic abscess (increased likelihood if there is a history of biliary anastomosis)	0–3
Procedural complication (puncture site hematoma, non-target embolization, and pulmonary embolism)	2–4

TACE: Transarterial chemoembolization, PES: Post-embolization syndrome

primary end-point in each trial was median OS; reported survival for Y90 was 8.8 months–8.0 months, respectively, and survival for sorafenib was 10.2 months–9.9 months. In each study, Y90 did not demonstrate non-inferiority (hazard ratio of 1.12 and 1.15 in SARAH and SIRveNIB, respectively, - a hazard ratio <1.08 typically the non-inferiority threshold); however, Y90 scored significantly higher on quality of life metrics and was noted to have fewer serious adverse events (an average of 5 in the Y90 group vs. 10 in the sorafenib group in the SARAH study).[90,91] The STOP-HCC and SORAMIC trials, scheduled to complete in 2019, are ongoing and will compare Y90 and sorafenib given in combination the initial safety analysis for the SORAMIC trial was published in 2015 which demonstrated no additional risk to performing Y90 followed by sorafenib.[92]

Y90 generally is well tolerated (Table 4). The most common adverse effect is post-radioembolization syndrome which includes fatigue, nausea, abdominal pain, and/or cachexia and should be expected to occur in most cases. Grade 3 or 4 post-treatment liver decompensation may occur in as many as 21% of patients but is transient, with liver function typically returning to baseline after 20–29 days (Child-Pugh B or C and T4 tumors are the covariates independently associated with increased likelihood of liver decompensation).[87,93] GI ulceration is uncommon; however, if present can lead to edema and gastric outlet obstruction.[94] Radiation cholecystitis may be associated with biliary dyskinesia and requires cholecystectomy in <1% of cases.[95] Radiation pneumonitis has been reported to occur in 6.3% of cases when a median lung shunt fraction of 23.7% is present, highlighting the importance of pre-procedural Tc-MAA scintigraphy.[96,97]

Radioembolization induced liver disease (REILD) is somewhat nebulous to define but, in patients with cirrhosis, REILD may present with aspartate transaminase or alanine transaminase elevations over 5 times the upper limit of normal, bilirubin over 2 mg/dL, Child-Pugh score increase of more than 2, painful hepatomegaly, or new weight gain/ascites. REILD occurs in approximately 9% of patients with cirrhosis and may lead to death in 0.5–5.3% of cases. The incidence of REILD may be decreased with post-treatment steroid or ursodeoxycholic acid treatment.[98]

Table 4: Common adverse effects after Y90[93,99-101]

Common adverse effects association with Y90	Frequency (%)
PRS	
Nausea and/or vomiting	9–59
Fatigue	37–53
Abdominal pain	29
Cachexia	3–19
PRS (Grade 3 or 4)	<2
Liver decompensation	
Hypoalbuminemia (Grade 3 or 4)	5
Hyperbilirubinemia (Grade 3 or 4)	3–21
New ascites segmental (Grade 3 or 4)	0–19
Radiation-induced liver disease	1–9
Lymphopenia (any at 90 days)	88–100
Non-target embolization	
GI (gastrointestinal) ulceration	0–12.5
Radiation-induced cholecystitis	<2
Pulmonary pleural/parenchymal adverse effects	
Pleural effusion	<10
Radiation pneumonitis	0–6.3

PRS: Post-radioembolization syndrome, GI: Gastrointestinal, Y90: Yttrium-90

CONCLUSIONS

When able to be performed, treatment of HCC with curative intent including liver transplant, partial liver resection, or percutaneous RFA offer substantial increase in patient survival. Locoregional therapy, including TACE and Y90, is largely safe and can be used alongside surgical treatments in many cases. Y90 can be used before liver resection to provide both ipsilateral tumor control and contralateral liver remnant hypertrophy; however, it is not known if there is mortality benefit in these cases in comparison to portal vein embolization with or without TACE. Locoregional therapy can also be used to both downstage HCC such that more individuals will meet transplant inclusion criteria, as well as to prevent disease progression while patients await liver transplantation. With respect to both downstaging and bridge therapy, Y90 may have some advantage, but there remains an overall paucity of evidence relative to which locoregional therapy (or which combination) is superior among Y90, RFA, TACE, and SBRT.

Patients with intermediate, BCLC stage B, HCC have classically been treated with TACE; however, Y90 is an emerging alternative. Direct comparisons of TACE and Y90 are limited, and the superior treatment is not known. High quality single-center prospective studies such as the PREMIERE trial have demonstrated significant increase in progression-free survival for patients treated with Y90 while alternatively, the SIRTACE trial showed no significant mortality difference between the two modalities. With respect to TACE, it is not definitely known the ideal timing of sequential TACE treatments, which infusion composite is optimal, and the ideal way to identify patients who may no longer derive benefit from TACE due to advanced disease.

For patients with advanced, BCLC stage C, HCC the current standard of care is sorafenib; however, Y90 may be a

reasonable alternative for many patients. The SARAH and SIRveNIB trials demonstrated inferiority of Y90 with respect to sorafenib; however, adverse effects were nearly double in the sorafenib arm.

Future challenges will include better delineating the role of either TACE or Y90 used in combination with sorafenib for advanced disease. The ongoing SORAMIC and STOP-HCC trials represent eagerly awaited comparisons of HCC treated only with sorafenib or dual-treatment with sorafenib and Y90.

Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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