Advances and Future Directions in the Treatment of Hepatocellular Carcinoma

Ashil J. Gosalia, MD, Paul Martin, MD, and Patricia D. Jones, MD, MSCR

Dr Gosalia is a gastroenterology fellow in the Department of Medicine at the University of Miami Miller School of Medicine in Miami, Florida. Dr Martin is a professor and Dr Jones is an assistant professor in the Division of Hepatology at the University of Miami Miller School of Medicine. Dr Martin and Dr Jones are also affiliated with the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine.

Address correspondence to:
Dr Patricia D. Jones
University of Miami Miller School of Medicine
Department of Medicine
Division of Hepatology
1120 NW 14th Street
Miami, FL 33136
Tel: 305-243-1233
Fax: 305-243-3877
E-mail: pdjones@med.miami.edu

Abstract: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide. Liver transplant is considered the gold standard for curative therapy for HCC when patients are not candidates for surgical resection or ablation. Because a subset of patients with HCC have a survival rate with liver transplantation that is comparable to that of cirrhotic patients without tumors, the organ allocation system allows for increased priority for transplant in potential recipients within the Milan criteria. With the recent change in the Model for End-Stage Liver Disease exception point allocation, patients with HCC will now need to wait at least 6 months before being awarded extra points. This extension leads to increased time on the transplant waiting list and underscores the importance of locoregional therapy to contain the tumor burden. Fortunately, there has been significant progress in therapy for HCC in the past few decades, namely due to advances in interventional radiology, radiotherapy, and expanded surgical and transplant criteria. Recent advances in immunotherapy also provide promising options for patients who are not candidates for other therapies. This article highlights the major therapeutic options for HCC, including surgical resection, liver transplant, thermal and nonthermal ablation, chemoembolization, radiotherapy, and systemic chemotherapy, as well as discusses the evidence supporting these approaches.

Keywords
Hepatocellular carcinoma, treatment, interventional oncology, immunotherapy

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the second leading cause of cancer-related deaths globally, with more than 780,000 new cases of HCC reported in 2012.[1] The disease occurs most often in patients with cirrhosis due to chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus infection, or alcoholic liver disease. The incidence of HCC is rising in patients with nonalcoholic steatohepatitis.[2,3] Globally, the incidence of HCC varies. East Asia

and sub-Saharan Africa have higher rates of HCC compared to Europe and North America.[4] Chronic HBV infection is likely the driving force for this discrepancy, as the incidence of HCC closely mirrors HBV prevalence worldwide.

HCC usually has an insidious course and is often detected only when already advanced, with extensive tumor burden or portal vein thrombosis (PVT), and when curative options are no longer available. Patients can present with an acute decompensation of their liver disease, often due to PVT from tumor infiltration. Overall, the prognosis of patients with HCC is poor, although patients who are identified with small tumor burdens have curative options. An overview of the current therapies for HCC can be found in the Table. This article describes the staging of HCC and reviews the treatment options available for this disease, which broadly include curative therapies, locoregional therapies, and systemic therapies intended to control tumor growth.

Screening for Hepatocellular Carcinoma

According to guidelines issued by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), patients with increased risk of HCC should be screened with ultrasound on a semiannual basis.[5,6] Specifically, this includes all patients with cirrhosis, Asian men with HBV infection older than age 40 years, Asian women with HBV infection older than age 50 years, persons of African descent with HBV infection older than age 20 years, and persons with HBV infection with a family history of HCC.[5,6] In addition, EASL guidelines recommend HCC screening in persons with hepatitis C virus infection and stage 3 fibrosis.[5] Despite these recommendations, surveillance rates are surprisingly low, ranging from 2%[7] to 25%.[8] Because surveillance is significantly underutilized, it is unknown how regular application of surveillance would modify the landscape of treatments offered for HCC and would affect mortality.

A randomized, controlled trial (RCT) in China evaluating the impact of screening for HCC in HBV-infected patients demonstrated an increase in earlier-stage cancers in patients randomized to screening.[9] Another Chinese RCT, with 18,816 participants, found an increased proportion of early-stage cancers in patients randomized to screening and significantly improved 1-, 3-, and 5-year survival rates in patients receiving biannual screening compared with controls (65.9% vs 31.2%, 52.6% vs 7.2%, and 46.4% vs 0%, respectively).[10] Since the 1990s, Japan has implemented strategies for educating physicians and patients about the risk of HCC.[11] All patients at risk for HCC are eligible for government-supported screening; subsequently, only 6% of HCC patients in Japan are diagnosed with advanced-stage HCC.[11] Analysis of Japan's nationwide registry of all HCC patients demonstrates improvement in survival rates with the advent of regular surveillance; the median survival of HCC diagnosed from 1986 to 1990 was 22 months, compared with 50 months when the diagnosis was made from 2001 to 2005 (P<.001).[12] Therefore, if utilized appropriately, screening is expected to increase the proportion of cancers diagnosed at early stages, thus increasing the proportion of patients eligible for curative treatment options and extending survival. Currently, the majority of HCC cases are diagnosed at advanced stages.[13]

Diagnostic Workup of Nodules Found on Screening

Based on the AASLD guidelines, if a nodule larger than 10 mm is found on ultrasound, 4-phase computed tomography or contrast-enhanced magnetic resonance imaging is recommended for better characterization of the nodule.[6] If the nodule demonstrates arterial uptake of contrast and washout in the delayed venous phase on cross-sectional imaging, it is diagnostic of HCC. However, if the lesion does not enhance characteristically, liver biopsy or repeat imaging with another modality should be considered. Liver biopsy is useful when the diagnosis of HCC is uncertain, when imaging studies are inconclusive, when patients have a low pretest probability for HCC (ie, a noncirrhotic healthy patient), or when there is concern for possible metastatic disease or cholangiocarcinoma. Lesions smaller than 10 mm can be followed with a shorter interval, such as every 3 months, depending on the patient's individual risk and history.

Staging Models for Hepatocellular Carcinoma

Unique among other malignancies, HCC develops in a diffusely diseased organ; thus, its prognosis reflects not only the tumor characteristics but also the severity of the underlying liver disease. There are a variety of models used to stage HCC, including the Barcelona Clinic Liver Cancer (BCLC) staging system and the Cancer of the Liver Italian Program (CLIP) score. The BCLC staging system incorporates Child-Pugh class, performance status, tumor size, tumor number, and the presence of vascular invasion to guide therapy. The AASLD has adapted the BCLC staging system in its recommendations for the treatment of HCC.[6] The CLIP score utilizes Child-Pugh class, tumor morphology, α-fetoprotein levels, and presence of PVT to stratify patients, and has been externally validated.[14,15]

Table. Currently Available Options for the Treatment of Hepatocellular Carcinoma

	Indications	Contraindications	Adverse Effects
Curative Treatments			
Surgical resection	• Solitary liver tumor • Unilobar disease	• Portal hypertension (hepatic venous pressure gradient ≥10 mm Hg) • Decompensated cirrhosis (Child-Pugh B/C) • Insufficient residual liver volume • Extrahepatic disease • Poor performance status	• Hepatic decompensation • Bleeding • Wound infection • Bile duct damage/biloma
Liver transplant	• Solitary liver tumor ≤5 cm in size • Up to 3 tumors, each ≤3 cm in size • Decompensated cirrhosis	• Macrovascular invasion of tumor • Extrahepatic disease • Severe comorbid disease (eg, severe cardiopulmonary disease) • Poor performance status	• Graft dysfunction/rejection • Bleeding • Wound infection • Bile duct damage/biloma
Locoregional Treatments			
Radiofrequency ablation/microwave ablation[a]	• Liver tumor ≤4 cm in size	• Macrovascular invasion of tumor • Main portal vein obstruction • Decompensated cirrhosis (Child-Pugh C) • Biliary obstruction • Proximity to vital structures (eg, bowel, diaphragm) not mitigated by open or laparoscopic technique	• Fever • Right upper quadrant pain • Portal vein thrombosis • Hepatic abscess • Bleeding (eg, subcapsular hematoma, hemoperitoneum)
Transarterial chemoembolization	• Lesions that are unresectable because of portal hypertension or lesion location • Patients awaiting liver transplant (downstaging tumors for transplant eligibility, preventing tumor progression while listed) • Decreasing tumor burden for resection	• Macrovascular invasion of tumor (main portal vein) • Main portal vein obstruction • Decompensated cirrhosis (Child-Pugh C) • Significant cardiac disease • Significant renal insufficiency • Biliary obstruction • Poor performance status	• Postembolization syndrome (fever, right upper quadrant pain, nausea, ileus, elevated liver enzymes) • Hepatic decompensation • Hepatic abscess • Gastroduodenal ulceration • Bile duct damage/biloma
Cryoablation	• Liver tumor ≤5 cm in size	• Decompensated cirrhosis (Child-Pugh B/C) • Macrovascular invasion of tumor (main portal vein) • Biliary obstruction • Proximity to vital structures (eg, bowel, diaphragm, gallbladder, blood vessel)	• Liver fracture • Hemorrhage • Coagulopathy • Biliary fistula • Hepatic abscess • Myoglobinuria • Cryoshock (multisystem organ failure)
Irreversible electroporation	• Liver tumor ≤4 cm in size (proximity to vascular structures is not a barrier)	• Pacemaker • Cardiac arrhythmia • Extensive extrahepatic metastases	• Bleeding • Fistula formation (eg, arteriovenous, biliary) • Cardiac arrhythmia

(Table continues on the next page.)

Table (continued). Currently Available Options for the Treatment of Hepatocellular Carcinoma

	Indications	Contraindications	Adverse Effects
Locoregional Treatments *(continued)*			
Transarterial radioembolization	• Lesions that are unresectable because of portal hypertension or lesion location • Patients awaiting liver transplant (downstaging tumors for transplant eligibility, preventing tumor progression while listed) • Patients with portal vein thrombosis • Decreasing tumor burden for resection	• Potential for >30 Gy radiation exposure to lung in a single session (99 mTc macroaggregated albumin scan with pulmonary shunt fraction >15%) • Prior hepatic radiation • Macrovascular invasion of tumor (main portal vein) • Decompensated cirrhosis (Child-Pugh C) • Significant cardiac disease • Significant renal insufficiency • Poor performance status • Biliary obstruction	• Hepatic decompensation • Hepatic abscess • Bile duct damage/biloma • Gastroduodenal ulceration • Postembolization syndrome (much milder than transarterial chemoembolization) • Radiation-induced liver disease • Radiation pneumonitis • Lymphopenia
Radiotherapy	• Unresectable lesions	• Decompensated cirrhosis (Child-Pugh B/C) • Inadequate liver volume outside of the treatment area • Prior hepatic radiation	• Gastroduodenal ulceration • Right upper quadrant pain • Radiation-induced liver disease • Hepatic abscess • Bile duct damage/biloma
Systemic Chemotherapies			
Sorafenib	• Unresectable lesions (Barcelona Clinic Liver Cancer stage C/D)	• Known severe hypersensitivity to sorafenib	• Diarrhea • Weight loss • Hand-foot-skin eruptions • Hypophosphatemia • Hypertension • Cardiac ischemia
Regorafenib	• Unresectable lesions (Barcelona Clinic Liver Cancer stage C/D) that have failed to respond to sorafenib	• Known severe hypersensitivity to regorafenib	• Same as sorafenib

[a]Ablative therapies are curative for small lesions; however, in larger lesions, they are considered bridge therapies.

The Italian Liver Cancer scoring system, or ITA.LI.CA, is a novel prognostic system that stratifies patients using Child-Pugh class, performance status, α-fetoprotein levels, and tumor characteristics (eg, size, presence of vascular invasion); it was recently validated and shown to have better prognostic ability than the BCLC staging system and CLIP score in Asian and European populations in an initial retrospective study.[16] Currently, the BCLC staging system is most commonly used to stage HCC. Tumor stage, presence of portal hypertension, severity of underlying liver disease, and performance status are easily incorporated into the BCLC staging algorithm, which is also used to guide selection of therapies ranging from surgical resection and liver transplantation to supportive care.

Curative Treatments

Surgical Resection

Surgical resection in carefully selected patients is a curative treatment option typically reserved for patients with single nodules and adequate hepatic function, such as patients with normal underlying liver function or Child-Pugh class A cirrhosis. Surgical resection is often not feasible due to a lack of adequate hepatic reserve, even when the lesion is technically resectable, owing to the high postoperative mortality risk. Hyperbilirubinemia or portal hypertension automatically precludes surgical resection. Traditionally, solitary tumors (BCLC stage A or B) in patients without evidence of portal hypertension were the only lesions thought to be amenable to surgery.

However, multiple recent studies challenge this notion In a retrospective analysis of 1259 patients with BCLC stage B or C HCC who underwent surgical resection compared to transarterial chemoembolization (TACE), surgical resection demonstrated superior survival at 1, 3, and 5 years.[17] The authors also analyzed more than 30 other studies that confirmed good long-term survival rates with surgical resection for intermediate or advanced HCC in the absence of portal hypertension, a condition that independently predicts poor prognosis. This study is limited by its retrospective nature, as there were likely individual patient differences that influenced the choice of resection vs TACE and, thus, influenced treatment results. However, surgical resection may be an effective modality of treatment for some intermediate HCCs; high-quality RCTs comparing surgical resection to interventional therapies are lacking. Although resection is not typically considered for any tumor with major vessel invasion, some centers offer surgery for advanced lesions not extending beyond a first-order branch of the portal vein and report adequate survival rates.[18] Prospective studies are needed to determine the safety and suitability of more aggressive surgical resection in patients with intermediate and advanced HCC. This treatment option may become important as the incidence of HCC increases while the availability of sufficient livers for transplant diminishes.

Liver Transplant

Liver transplant is another curative option and is recommended in patients with HCC who have decompensated cirrhosis. To qualify for liver transplant, patients must have tumors that fall within the Milan criteria (ie, a solitary tumor up to 5 cm in size or 3 tumors up to 3 cm in size).[19] Macroscopic vascular invasion, regional nodal involvement, or distant metastases preclude liver transplantation. With the application of the Milan criteria, recurrence-free survival rates were greater than 90%.[19] However, there is concern that the Milan criteria are too restrictive, and patients with greater tumor burden might also have acceptable posttransplant survival. Yao and colleagues demonstrated that expanded criteria for liver transplant in patients with HCC did not adversely impact survival rates when compared to the rates associated with the Milan criteria.[20] The University of California San Francisco (UCSF) criteria permit transplant for solitary tumors that are 6.5 cm or smaller or when there are 3 or fewer nodules 4.5 cm or smaller each with a total tumor diameter of 8 cm or less. One-year survival for patients meeting UCSF criteria was 90%, whereas patients exceeding these criteria had a 1-year survival of only 50%.[20] A case series of 467 patients who underwent liver transplantation at the University of California Los Angeles demonstrated similar findings; lymphovascular invasion, tumor number, and poorly differentiated tumors all independently predicted poorer survival.[21]

Other studies have shown that UCSF criteria predict similar survival rates as the Milan criteria, which may help expand the role of liver transplant for HCC.[22,23] However, the impact of this expansion on current allocation policies is not clear, and exception points are presently only granted to patients whose cancer falls within the Milan criteria. Persons with tumors that exceed the Milan criteria can be treated with locoregional therapies with the goal of downstaging HCC to within the Milan criteria. Downstaging can also be used as a bridge to liver transplant with the goal of decreasing the risk of tumor progression and subsequent waiting list dropout. Although this concept has been adopted almost universally by transplant centers, there is conflicting evidence on its role in survival and cost-effectiveness. Due to the heterogeneity of survival data, treatment protocols, and regional variation in wait times for liver transplant, it is difficult to reach a definitive conclusion on the role of downstaging. A 2015 systematic review demonstrated that downstaging to within the Milan criteria was successful in approximately 40% of patients, although the HCC recurrence rate posttransplant was as high as 16%.[24] Another systematic review reported similar survival data for patients who underwent liver transplant within the Milan criteria, and for patients who were downstaged to within the Milan criteria who underwent liver transplant.[25] Large-scale studies are needed, as it remains unclear how long-term outcomes in downstaged patients compare to outcomes in patients whose HCC was always within the Milan criteria.

In recent years, there has been increased controversy surrounding the use of liver transplantation for HCC out of concern that HCC patients have an unfair survival advantage over non-HCC patients owing to receipt of Model for End-Stage Liver Disease (MELD) exception points for HCC. In an analysis of liver transplant rates, patients with HCC who were awarded 22 MELD exception points at the time of listing (along with subsequent exception points every 3 months) were transplanted at rates higher than their non-HCC counterparts in the first 6 months.[24] After 6 months, the rates were similar.[26] In an effort to diminish this disparity, the Organ Procurement and Transplantation Network and the United Network for Organ Sharing changed the MELD exception policy in 2015.[27] Prior to 2015, patients with HCC were listed with 22 MELD exception points for T2 lesions, and points were added every 3 months until the patient underwent or was no longer suitable for liver transplantation. Since October 2015, patients with T2 lesions are listed at their biological MELD score and after 6 months are awarded a MELD score of 28. Patients are then awarded exception points every 3 months to a maximum of 34 points.[27] This

change allows time to observe tumor behavior in the first 6 months of listing. Also, some studies suggest that a shorter wait to transplant portends a higher risk of posttransplant HCC recurrence and mortality.[28,29] Patients who drop out of the waiting list due to either progression or complication of their HCC may have aggressive tumor biology. In these cases, the longer interval to gain MELD exception points may identify those patients with aggressive disease and increased risk of recurrence, thereby avoiding futile liver transplantation. Living-donor liver transplant may obviate some of the controversy related to organ availability and allocation because the MELD exception policy does not apply. Living-donor liver transplant may also reduce geographic disparity by providing an option for liver transplant in regions in which donor organs are limited and, thereby, reducing waiting list dropout.

Locoregional Treatments

Treatment of HCC has rapidly evolved with interventional radiology. Percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and TACE are the major modalities utilized to control growth of HCC lesions.

Percutaneous Ethanol Injection

PEI, one of the oldest image-guided modalities,[30,31] involves direct injection of ethanol into the lesion, which induces tumor necrosis. Prior to RFA, PEI was considered first-line therapy for small HCC lesions. With the advent of RFA and improved imaging technology, PEI is typically not first-line therapy, as it has significant adverse effects. The procedure may cause significant postprocedural pain and typically requires multiple sessions to achieve complete treatment effect; additionally, there is a high risk of recurrence. Currently, PEI is most commonly used in combination with other interventional treatments such as TACE.[32,33] There have been reports of successful PEIs for adrenal, bone, and lymphatic metastases from HCC.[34-36]

Radiofrequency Ablation

In RFA, a probe is inserted percutaneously or laparoscopically under ultrasound guidance, and alternating current is applied to the tumor. The radiofrequency waves generate thermal energy leading to tumor necrosis. Multiple reports have demonstrated the efficacy of RFA. Patients within the Milan criteria have 1-year survival rates approaching 97%, 3-year survival rates between 60% and 87%, and 5-year survival rates between 40% and 75%.[37,38] The Child-Pugh score, initial response, and number and size of nodules all play a role in predicting survival.[37,38] Solitary lesions smaller than 3 cm are most appropriate for RFA. Lesions larger than 5 cm have a less robust treatment response, with one study citing a complete response of approximately 63%, compared to 93% in patients with lesions between 3 and 5 cm and 100% in lesions smaller than 3 cm.[39] Treatment success may increase when multiple probes are used for larger tumors, but these studies are limited by small sample sizes.[40,41] Exophytic lesions along the inferior edge of the liver or those in proximity to the hepatic dome are typically not treated with RFA due to the risk of bowel or diaphragmatic injury. In addition to percutaneous RFA, a laparoscopic approach can be considered to reduce the risk of injury to adjacent organs.[42] As with all modalities, postablation imaging and surveillance are used to confirm sustained treatment effect and to plan additional therapy as appropriate.

Microwave Ablation

Another modality useful for the treatment of HCC lesions less than 3 cm in size is MWA. In MWA, a needle electrode is typically advanced percutaneously under ultrasound guidance.[43] High-frequency microwaves are then delivered to the lesion to induce thermal destruction. This technique has been in use since the late 1980s, most frequently in Japan and China. When compared to RFA, MWA shows no statistically significant difference between complete response rates or 2-year local recurrence rates.[44,45] In another study, laparoscopic MWA showed superiority in reducing long-term local progression compared with laparoscopic RFA; however, there were no significant differences between 5-year survival rates and treatment response rates.[46] Whether these results can be extrapolated to percutaneous approaches remains to be studied. Although larger RCTs are needed to further compare the 2 technologies, MWA seems to be a suitable alternative to RFA.

Cryoablation

Cryoablation has been less utilized as more advanced ablative techniques have emerged, but still plays a role in select patients. The technique requires laparoscopy with direct application of a cryoprobe, with either liquid nitrogen or argon gas placed on the HCC lesion. Freezing induces irreversible damage to the tissue. Typically, 2 to 3 cycles are performed in a single session, and intraoperative ultrasound is used to monitor tumor destruction in real time. Cryoablation can be used as monotherapy or as part of a multimodal treatment approach. There are no RCTs evaluating the efficacy of cryoablation compared to other ablative modalities, although retrospective trials and case series have evaluated the efficacy of cryoablation. One large series of patients receiving cryotherapy demonstrated a 39.8% 5-year survival rate, and among the subset of patients with lesions less than 5 cm, survival was

55.4%.[47] The main disadvantage of cryoablation is that it is most often performed laparoscopically and may cause morbidity in patients with advanced cirrhosis. Complication rates have been reported to be upwards of 50% and include coagulopathy, cardiac arrhythmia, and liver fracture.[48] However, percutaneous application of cryoablation may mitigate these risks.[49,50] Cryoablation may have a role in special situations, such as treatment of residual disease at resection margins, but is rarely considered as a first-line therapy in the treatment of HCC.

Transarterial Chemoembolization

TACE has become one of the most commonly used treatment modalities for HCC, both for primary therapy and for downstaging tumors and bridging to transplantation. TACE is typically considered in patients with multifocal HCC or with tumors that are not amenable to resection or ablative therapy without evidence of vascular invasion and relatively well-preserved hepatic reserve.[51] PVT is considered a contraindication to TACE due to the poor overall survival of patients with HCC and PVT and the increased risk of acute liver failure post-TACE. Other contraindications to TACE include macrovascular invasion of the tumor into the main portal vein, complete main portal vein obstruction, refractory hepatic encephalopathy, biliary obstruction, and Child-Pugh class C cirrhosis. Relative contraindications include a total bilirubin level greater than 2 mg/dL, greater than 50% of liver involvement with the tumor or tumor size at least 10 cm, cardiac or renal insufficiency, significant lung disease, or recent hepatic decompensation.[52] In select situations, patients with partial PVT not due to tumor infiltration may still be candidates depending on tumor location, thrombus extent and location, and operator expertise.

In TACE, percutaneous catheterization of the hepatic artery targets the feeding branches of the tumor.[53] The size, number, and distribution of lesions dictate the degree of selectivity required to achieve maximal therapeutic effect. Once the vessel has been selectively cannulated, a chemotherapeutic agent is infused. Typical agents used for infusion are doxorubicin, cisplatin, or mitomycin C. Some clinicians may utilize ethiodized oil (Lipiodol, Guerbet), a contrast material that theoretically promotes intratumoral chemotherapy retention while localizing the lesion radiographically.[54,55] Ethiodized oil enhances during posttreatment surveillance imaging and aids visualization of the previously treated site, but may also make it difficult to distinguish residual tumor from retained contrast. In addition, there have been reported cases of lipiodol emboli to the pulmonary and cerebral circulation.[6,56] Once the chemotherapeutic agent is infused, a procoagulant material (eg, Gelfoam, Pfizer) is usually injected to embolize the artery. Flow through the embolized vessel is usually re-established within 2 weeks, which allows for future access to the lesion for additional therapy. Tumor necrosis is induced by TACE via direct cytotoxicity from chemotherapy as well as ischemia.

There is a rising preference for the use of TACE with drug-eluting beads (DEB-TACE) over conventional TACE; however, data on long-term efficacy are mixed.[44] Individual studies have demonstrated that patients undergoing DEB-TACE for unresectable HCC have significantly improved overall survival compared with conventional TACE recipients.[57,58] The side-effect profile of DEB-TACE appears improved compared with that of conventional TACE, with diminished cardiac, hepatic, and gastrointestinal toxicity, theoretically because DEB-TACE allows for a slower release of the chemotherapeutic agent and less systemic exposure.[59] Either approach is reasonable, although given the possible lower side-effect profile of DEB-TACE, more centers are adopting this modality as a first-line treatment. Two or more sessions may be required depending on tumor response.

Although TACE has very low mortality (as low as 4% in patients with adequate hepatic reserve[60]), it is associated with significant posttreatment complications. Most commonly, patients develop postembolization syndrome and are often preemptively hospitalized for observation and symptom management. This syndrome, with varying severity, can be seen in up to 90% of patients after TACE and includes nausea, right upper quadrant pain, and ileus.[61] Typically, the aminotransferases and bilirubin become transiently elevated.[62] Patients undergoing TACE should receive adequate intravenous hydration and antiemetics to minimize symptoms. The role of prophylactic antibiotics is unclear; data suggest that routine use may not reduce postprocedure infection.[63] Other less common, but significant, complications include acute-on-chronic liver failure, liver abscess, and bile duct injury. Clinicians should be especially vigilant regarding acute hepatic decompensation in patients who receive TACE to a large vessel rather than subselective TACE, given the risk of collateral injury to functioning hepatocytes in the treatment zone, which further diminishes hepatic reserve. Long-term survival from HCC after conventional TACE is not significantly different than survival after bland embolization. Independent studies and a meta-analysis including a Cochrane review concluded that there is no compelling evidence to support or refute the use of TACE in unresectable HCC.[64,65]

Advances in Hepatocellular Carcinoma Therapy

Although the modalities previously explained are widely used for the treatment of HCC, newer therapies have

emerged and include transarterial radioembolization (TARE), irreversible electroporation (IRE), systemic radiotherapy, systemic chemotherapy, and immunotherapy. These modalities are still considered experimental, as there are no large-scale studies advocating their use over the current standard of care set down by the EASL and AASLD guidelines. Ongoing studies may provide more insight into the optimal use of these therapies.

Transarterial Radioembolization

TARE is a newer treatment modality for HCC, and involves selective catheterization of hepatic arteries with infusion of radioactive material into the feeding artery to induce tumor necrosis. Typically, resin or glass beads coated with yttrium-90 are used; however, lipiodol labeled with iodine-131 is used in adjuvant settings outside of the United States.[66] Unlike with TACE, TARE is not contraindicated in patients with PVT. There is no consensus regarding whether TARE is more efficacious than TACE. A recent meta-analysis comparing TARE to TACE demonstrated that 4-year survival rates were not significantly different and, therefore, TARE was noninferior to TACE.[67] It should be noted, however, that this analysis only included 5 studies out of a potential 172, signifying that these results may not be generalizable. Several retrospective, small-scale studies[68,69] show comparable or superior results of TARE compared to TACE, including longer time-to-progression and reduced toxicity, but there have been no large, randomized, prospective trials. The AASLD currently does not endorse TARE as standard therapy for HCC.[6] The National Comprehensive Cancer Network, along with other consensus groups, has adapted TARE as a reasonable therapeutic option for the treatment of HCC.[70] There are a few RCTs, including the PREMIERE trial[71,72] and the ongoing TRACE (Transarterial Radioembolization Versus Chemoembolization for the Treatment of Hepatocellular Carcinoma) trial,[73] that directly compare TARE with TACE. In the PREMIERE trial, patients who underwent TARE had longer time-to-progression and lower liver transplant dropout rates compared with patients who received conventional TACE. Overall survival, however, was not significantly different between both groups.[71,72]

The side-effect profile of TARE is better than that of TACE, requiring fewer hospital admissions and leading to less abdominal pain and lower elevation in transaminases.[74,75] To minimize the risk of extrahepatic radiation injury, candidates for TARE undergo hepatic angiography with cannulation of the tumor's feeding vessel and infusion of technetium-99m macroaggregated albumin. These molecules are similar in size to the spheres used for TARE and provide a pretreatment map. Additionally, this procedure estimates the degree of pulmonary and splanchnic shunting, therefore assessing the risk of pulmonary toxicity. A single photon emission computed tomography scan performed after administration assesses distribution of the tagged material. A pathologic pulmonary shunt fraction greater than 15% translates to a radiation dose greater than 30 Gy per treatment and increases the risk of pulmonary injury, thus limiting utilization in this scenario.[76] More common side effects include mildly elevated aminotransferase levels, abdominal pain, and nausea. Less common, but more significant, side effects include gastroduodenal ulcers, cholecystitis, and hepatic decompensation. In contrast to TACE, which typically requires a short hospital admission for symptom management, TARE is an outpatient procedure. TARE is an option for the treatment of HCC and offers therapy in situations in which TACE is contraindicated. Long-term outcome data are needed before it can be recommended over other therapies.

Irreversible Electroporation

IRE, commercially available as NanoKnife (AngioDynamics) in the United States, is a unique treatment that utilizes electrical pulses to create pores in the cellular membrane, leading to apoptosis and cell death. With this approach, there is minimal damage to surrounding parenchyma and vascular structures.[77,78] Furthermore, IRE may confer minimal risk in treating tumors in close proximity to vessels or encasing vessels, with only 4.4% of vessels demonstrating changes after treatment.[79] Studies have demonstrated excellent treatment response, with complete response in 97% of patients with lesions less than 3 cm in one study, and another study showing complete pathologic necrosis of the tumor on explant.[80,81] A 2014 systematic review also demonstrated treatment success rates ranging from 67% to 100%.[82] Lesions larger than 4 cm may be less responsive to treatment,[83] but more data and studies are needed to determine which characteristics favor treatment response. In a study comparing IRE to MWA, there was equivalent treatment response at 180 days, but less frequent transaminase level elevation, faster recovery, and lower readmission rates in the IRE group.[84] For HCC lesions in areas that are challenging to access, IRE remains a promising modality; however, more studies are needed to determine the factors predicting success of this treatment option.

Systemic Radiotherapy

The addition of systemic radiotherapy to the HCC armamentarium reflects advances in radiation oncology, including external beam radiation therapy (EBRT) and proton beam radiation therapy. Previously, standard EBRT was not considered for treatment of HCC due to hepatic radiosensitivity and concern for collateral damage

to healthy liver parenchyma. Even low-dose radiation (28-35 Gy) has a greater than 5% risk of radiation-induced liver injury, characterized by anicteric hepatitis, and can lead to liver failure, although rarely.[85] These doses are far lower than what is required to eradicate HCC lesions. With standard EBRT, there is an additional risk of radiation injury to adjacent organs, including the small intestine and kidneys.[86]

With the advent of stereotactic radiotherapy, EBRT has evolved and includes 3-dimensional conformal radiotherapy and intensity modulation radiation therapy (IMRT), which allow more precise localization, thereby sparing the surrounding parenchyma. With 3-dimensional conformal radiotherapy, doses of radiation greater than 90 Gy can be delivered to hepatic lesions without significant collateral radiation toxicity.[87] Complete treatment response from high-dose 3-dimensional conformal radiation therapy to HCC lesions is as high as 90%, with improved 2-year survival rates.[88] Factors limiting the radiation dose include Child-Pugh class B or C, prior TACE, PVT, and HBV infection.[89,90] By using computer-generated intensity modulation, IMRT allows for higher radiation doses than 3-dimensional conformal radiation therapy with a lower risk of radiation toxicity.[91] Furthermore, IMRT can be used with helical computed tomography and can be applied to multiple targets simultaneously. Likely, the higher radiation dose explains why IMRT has improved treatment response and overall survival compared to 3-dimensional conformal radiation therapy.[92-94]

Stereotactic radiotherapy is a relatively recent development and seems best suited for patients with small lesions and well-preserved hepatic function. Radiation toxicity varies due to tumor size and heterogeneity of tumor location.[95,96] In a trial comparing RFA to stereotactic radiotherapy for small, inoperable HCC, stereotactic radiotherapy showed delayed time-to-progression for tumors larger than 2 cm; overall survival and local response rates were similar for the 2 treatments.[97] Stereotactic radiotherapy has already been adapted as an alternative therapy by the National Comprehensive Cancer Network.[70]

Charged particle therapy, such as proton beam therapy, may have the greatest capacity to spare surrounding tissue from radiotoxicity, as proton beams lose very little energy until they reach their target.[98] Good local control rates have been demonstrated after proton beam therapy,[99] and 5-year control rates have been reported to be greater than 90%.[100] Overall survival rates vary due to differences in tumor size and underlying liver function.[100,101] A prospective RCT comparing TACE to proton beam therapy is ongoing; results of an interim analysis were recently published, and although no difference was found in overall survival, there was a trend toward improved 2-year local control and progression-free survival in the proton beam group that was not statistically significant.[102] Charged particle therapy is promising for select patients with HCC but requires further investigation.

Systemic Chemotherapy

Chemotherapy is reserved for patients with advanced HCC or BCLC stage C or D, and includes traditional agents such as doxorubicin, gemcitabine, and oxaliplatin. The EACH (Oxaliplatin [Eloxatin] Plus FOLFOX4 Compared With Single-Agent Doxorubicin [Adriamycin] as Palliative Chemotherapy in Advanced Hepatocellular Carcinoma Patients) trial compared a combination of fluorouracil, leucovorin, and oxaliplatin vs doxorubicin in a prospective, open-label trial; there was no significant difference in overall survival, but there was a trend toward increased overall survival in the combination chemotherapy group.[103] A recent meta-analysis evaluating oxaliplatin-based chemotherapy regimens demonstrated modest improvement in overall survival, although 1-year survival rates hovered just under 40%.[104]

Advanced HCC portends a poor prognosis, and there has been research attempting to find alternative systemic therapies. The first oral chemotherapeutic agent proven to have survival benefit in HCC is sorafenib (Nexavar, Bayer), an oral multikinase inhibitor, which is approved by the US Food and Drug Administration (FDA) as first-line therapy for advanced HCC. The SHARP (Sorafenib HCC Assessment Randomized Protocol) trial demonstrated median overall survival in the sorafenib arm of 10.7 months, compared with 7.9 months in the placebo arm.[105] Significant adverse reactions include diarrhea, weight loss, hand-foot-skin eruptions, and hypophosphatemia. Sorafenib is recommended for advanced-stage HCC per the AASLD and BCLC treatment guidelines.[6] Given the modest survival benefit, a recent analysis of the Surveillance, Epidemiology, and End Results–Medicare database was conducted to determine the survival rate and cost-effectiveness of sorafenib.[106] Although there was an overall survival benefit with sorafenib compared to controls, it was limited to only 31 days in those with decompensated liver disease. Thus, while sorafenib was deemed overall cost-effective for the entire cohort, it was not cost-effective in the subgroup of patients with hepatic decompensation.[106]

Multiple studies have combined sorafenib with interventional techniques, including TACE, to enhance response. Recent meta-analyses reviewing the combination of TACE and sorafenib have demonstrated longer time-to-progression, but results are conflicted as to whether this translates to increased overall survival.[107-109] In all analyses, combination treatment led to an increased rate of adverse reactions.[107-109] In the recent SPACE

(Sorafenib or Placebo in Combination With TACE) trial comparing DEB-TACE plus placebo to DEB-TACE plus sorafenib in patients with BCLC stage B HCC, there was no statistically significant difference in time-to-progression or overall survival.[110] Thus, combination therapy likely offers modest benefit without significantly improving overall survival and leads to more adverse events. Sorafenib and TARE have also been studied in combination; a small study showed improved overall survival and progression-free survival compared to historical experience with sorafenib monotherapy.[111] Combination therapy requires further investigation, especially given the advances in radiotherapy.

Regorafenib (Stivarga, Bayer) is a new treatment recently approved by the FDA as a second-line therapy for advanced HCC in patients who failed treatment with sorafenib. Although structurally similar, regorafenib is more potent than sorafenib, with a similar side-effect profile. In the phase 3 clinical RESORCE (Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma) trial, patients with Child-Pugh class A cirrhosis and advanced HCC who progressed on sorafenib had a significantly longer overall median survival of 10.6 months in the regorafenib arm vs 7.8 months in the placebo arm (hazard ratio, 0.62; $P<.001$).[112] Progression-free survival and response to therapy were also significantly higher in patients treated with regorafenib.

Multiple other drugs, including lenvatinib (Lenvima, Eisai), cabozantinib (Cometriq, Exelixis), apatinib, and tivantinib, are under investigation for the treatment of advanced HCC and are in various stages of clinical trials. Additional data are needed before these treatments can be recommended.

Immunotherapy

Immunotherapy is promising for the treatment of HCC. Immune checkpoint inhibitors include antibodies targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1, and programmed cell death ligand-1 and -2.[113-115] Blocking these proteins restores T-cell function, allowing the immune system to more effectively detect and kill HCC cells. At the American Society of Clinical Oncology meeting in 2015, results of a phase 1/2 study with nivolumab (Opdivo, Bristol-Myers Squibb) in 47 patients with advanced liver cancer were presented; 68% of patients had drug-related adverse events, the complete response rate was 5%, and the partial response rate 14%.[116] Pembrolizumab (Keytruda, Merck) was associated with partial response and prolongation of survival in a patient with progressive metastatic HCC while being treated with sorafenib.[117] Tremelimumab (formerly ticilimumab, CP-675,206; Pfizer) is a monoclonal antibody targeting CTLA-4. In patients with advanced HCC, there was a partial response rate of 17.6% with time-to-progression of 6.5 months.[118] The use of tremelimumab plus RFA, cryoablation, or TACE in patients with BCLC B or C HCC was associated with a partial response rate of 26.3% in areas outside of the ablation zone, and median time to tumor progression was 7.4 months.[119] Ipilimumab (Yervoy, Bristol-Myers Squibb), a CTLA-4 inhibitor used in malignant melanoma[120] and renal cell carcinoma,[121] is currently being studied in combination with nivolumab for use in patients with advanced HCC.[122] At the time of this manuscript, there are 34 open clinical trials focused on immunologic manipulation for treatment of HCC.[123]

Conclusion

The incidence of HCC has been steadily increasing worldwide. Whereas other cancers have seen substantial decreases in mortality due to improvements in therapy over the past decade, the same cannot be said for HCC. Surgical resection, a curative treatment option, is often limited by patient characteristics. Although curative, liver transplantation is limited by the scarcity of donor organs. Much of the progress in the treatment of HCC is attributable to developments in the field of interventional oncology. Minimally invasive procedures such as RFA, MWA, TACE, TARE, and IRE are now used to cure small cancers and also as a bridge to liver transplantation. Sorafenib effectively prolongs survival in patients with advanced HCC, but its use in clinical practice is limited by side effects. Immunotherapy-based regimens and novel chemotherapeutic agents, including regorafenib, are expected to significantly improve the landscape for treatment of HCC. A multidisciplinary approach that is personalized for each patient is essential and will ensure dramatic improvement in outcomes for patients with HCC over the next decade. In the interim, increasing surveillance in patients at risk for HCC can identify tumors at an earlier stage, thus increasing chances for a curative therapy.

The authors have no relevant conflicts of interest to disclose.

References

1. Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. *Surg Oncol Clin N Am*. 2015;24(1):1-17.
2. Wong CR, Nguyen MH, Lim JK. Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. *World J Gastroenterol*. 2016;22(37):8294-8303.
3. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology*. 2010;51(6):1972-1978.
4. International Agency for Research on Cancer. Cancer fact sheets: liver cancer. http://gco.iarc.fr/today/fact-sheets-cancers?cancer=7&type=0&sex=0. Accessed June 13, 2017.
5. European Association for the Study of the Liver; European Organisation for

Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-943.
6. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022.
7. El-Serag HB, Kramer JR, Chen GJ, Duan Z, Richardson PA, Davila JA. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. *Gut*. 2011;60(7):992-997.
8. Palmer LB, Kappelman MD, Sandler RS, Hayashi PH. Surveillance for hepatocellular carcinoma in a Medicaid cirrhotic population. *J Clin Gastroenterol*. 2013;47(8):713-718.
9. Chen JG, Parkin DM, Chen QG, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen*. 2003;10(4):204-209.
10. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130(7):417-422.
11. Kudo M. Japan's successful model of nationwide hepatocellular carcinoma surveillance highlighting the urgent need for global surveillance. *Liver Cancer*. 2012;1(3-4):141-143.
12. Kudo M, Izumi N, Sakamoto M, et al; Liver Cancer Study Group of Japan. Survival analysis over 28 years of 173,378 patients with hepatocellular carcinoma in Japan. *Liver Cancer*. 2016;5(3):190-197.
13. Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology*. 2015;61(1):191-199.
14. Llovet JM, Bruix J. Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology*. 2000;32(3):679-680.
15. Ueno S, Tanabe G, Sako K, et al. Discrimination value of the new western prognostic system (CLIP score) for hepatocellular carcinoma in 662 Japanese patients. Cancer of the Liver Italian Program. *Hepatology*. 2001;34(3):529-534.
16. Farinati F, Vitale A, Spolverato G, et al; ITA.LI.CA study group. Development and validation of a new prognostic system for patients with hepatocellular carcinoma. *PLoS Med*. 2016;13(4):e1002006.
17. Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg*. 2014;260(2):329-340.
18. Kokudo T, Hasegawa K, Matsuyama Y, et al; Liver Cancer Study Group of Japan. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. *J Hepatol*. 2016;65(5):938-943.
19. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693-699.
20. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33(6):1394-1403.
21. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg*. 2007;246(3):502-509.
22. Patel SS, Arrington AK, McKenzie S, et al. Milan criteria and UCSF criteria: a preliminary comparative study of liver transplantation outcomes in the United States [published online August 22, 2012]. *Int J Hepatol*. doi:10.1155/2012/253517.
23. Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl*. 2002;8(9):765-774.
24. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. *Liver Transpl*. 2015;21(9):1142-1152.
25. Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Burls A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. *Br J Surg*. 2011;98(9):1201-1208.
26. Heimbach JK, Hirose R, Stock PG, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. *Hepatology*. 2015;61(5):1643-1650.
27. US Department of Health and Human Services. Organ Procurement and Transplantation Network. Revised liver policy regarding HCC exception scores. https://optn.transplant.hrsa.gov/news/revised-liver-policy-regarding-hcc-exception-scores. Accessed June 13, 2017.
28. Schlansky B, Chen Y, Scott DL, Austin D, Naugler WE. Waiting time predicts survival after liver transplantation for hepatocellular carcinoma: a cohort study using the United Network for Organ Sharing registry. *Liver Transpl*. 2014;20(9):1045-1056.
29. Roberts JP, Venook A, Kerlan R, Yao F. Hepatocellular carcinoma: ablate and wait versus rapid transplantation. *Liver Transpl*. 2010;16(8):925-929.
30. Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology*. 1986;161(2):309-312.
31. Shiina S, Yasuda H, Muto H, et al. Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR Am J Roentgenol*. 1987;149(5):949-952.
32. Chedid MF, Scaffaro LA, Chedid AD, et al. Transarterial embolization and percutaneous ethanol injection as an effective bridge therapy before liver transplantation for hepatitis C-related hepatocellular carcinoma. *Gastroenterol Res Pract*. 2016;2016:9420274.
33. Xu C, Lv PH, Huang XE, Wang SX, Sun L, Wang FA. Transarterial chemoembolization monotherapy in combination with radiofrequency ablation or percutaneous ethanol injection for hepatocellular carcinoma. *Asian Pac J Cancer Prev*. 2016;17(9):4349-4352.
34. Zuo CJ, Wang PJ, Shao CW, et al. CT-guided percutaneous ethanol injection with disposable curved needle for treatment of malignant liver neoplasms and their metastases in retroperitoneal lymph nodes. *World J Gastroenterol*. 2004;10(1):58-61.
35. Shibata T, Maetani Y, Ametani F, Itoh K, Konishi J. Percutaneous ethanol injection for treatment of adrenal metastasis from hepatocellular carcinoma. *AJR Am J Roentgenol*. 2000;174(2):333-335.
36. Kwon JH. Is percutaneous ethanol injection therapy still effective for hepatocellular carcinoma in the era of radiofrequency ablation? *Gut Liver*. 2010;4(suppl 1):S105-S112.
37. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology*. 2009;50(5):1475-1483.
38. Lee DH, Lee JM, Lee JY, et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology*. 2014;270(3):900-909.
39. Guglielmi A, Ruzzenente A, Battocchia A, Tonon A, Fracastoro G, Cordiano C. Radiofrequency ablation of hepatocellular carcinoma in cirrhotic patients. *Hepatogastroenterology*. 2003;50(50):480-484.
40. Seror O, N'Kontchou G, Ibraheem M, et al. Large (>or=5.0-cm) HCCs: multipolar RF ablation with three internally cooled bipolar electrodes—initial experience in 26 patients. *Radiology*. 2008;248(1):288-296.
41. Lin CC, Cheng YT, Chen M WT, Lin SM. The effectiveness of multiple electrode radiofrequency ablation in patients with hepatocellular carcinoma with lesions more than 3 cm in size and Barcelona Clinic Liver Cancer stage A to B2. *Liver Cancer*. 2016;5(1):8-20.
42. Kim KR, Thomas S. Complications of image-guided thermal ablation of liver and kidney neoplasms. *Semin Intervent Radiol*. 2014;31(2):138-148.
43. Sato M, Watanabe Y, Ueda S, et al. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology*. 1996;110(5):1507-1514.
44. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2016;31(3):645-653.
45. Chinnaratha MA, Chuang MY, Fraser RJ, Woodman RJ, Wigg AJ. Percutaneous thermal ablation for primary hepatocellular carcinoma: a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31(2):294-301.
46. Santambrogio R, Chiang J, Barabino M, et al. Comparison of laparoscopic microwave to radiofrequency ablation of small hepatocellular carcinoma (≤3 cm). *Ann Surg Oncol*. 2017;24(1):257-263.
47. Zhou XD, Tang ZY. Cryotherapy for primary liver cancer. *Semin Surg Oncol*. 1998;14(2):171-174.
48. Seifert JK, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. *J R Coll Surg Edinb*. 1998;43(3):141-154.
49. Niu LZ, Li JL, Xu KC. Percutaneous cryoablation for liver cancer. *J Clin Transl Hepatol*. 2014;2(3):182-188.
50. Wu B, Xiao YY, Zhang X, Zhang AL, Li HJ, Gao DF. Magnetic resonance imaging-guided percutaneous cryoablation of hepatocellular carcinoma in special regions. *Hepatobiliary Pancreat Dis Int*. 2010;9(4):384-392.
51. Crissien AM, Frenette C. Current management of hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)*. 2014;10(3):153-161.
52. Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. *Semin Intervent Radiol*. 2013;30(1):3-11.
53. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. *Dig Liver Dis*. 2016;48(6):571-577.
54. Idée JM, Guiu B. Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review. *Crit Rev Oncol Hematol*. 2013;88(3):530-549.

55. Giunchedi P, Maestri M, Gavini E, Dionigi P, Rassu G. Transarterial chemoembolization of hepatocellular carcinoma. Agents and drugs: an overview. Part 1. *Expert Opin Drug Deliv*. 2013;10(5):679-690.
56. Naorungroj T, Naksanguan T, Chinthammitr Y. Pulmonary lipiodol embolism after transcatheter arterial chemoembolization for hepatocellular carcinoma: a case report and literature review. *J Med Assoc Thai*. 2013;96(suppl 2):S270-S275.
57. Rahman FA, Naidu J, Ngiu CS, et al. Conventional versus doxorubicin-eluting beads transarterial chemoembolization for unresectable hepatocellular carcinoma: a tertiary medical centre experience in Malaysia. *Asian Pac J Cancer Prev*. 2016;17(8):4037-4041.
58. Chen P, Yuan P, Chen B, Sun J, Shen H, Qian Y. Evaluation of drug-eluting beads versus conventional transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41(1):75-85.
59. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR Am J Roentgenol*. 2011;197(4):W562-W570.
60. Garwood ER, Fidelman N, Hoch SE, Kerlan RK Jr, Yao FY. Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and synthetic hepatic dysfunction. *Liver Transpl*. 2013;19(2):164-173.
61. Dhand S, Gupta R. Hepatic transcatheter arterial chemoembolization complicated by postembolization syndrome. *Semin Intervent Radiol*. 2011;28(2):207-211.
62. Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. *Korean J Radiol*. 2009;10(5):425-434.
63. Wang J, He XD, Zhang YC. Antibiotic prophylaxis in transarterial therapy of hepatocellular carcinoma: a meta-analysis. *Can J Gastroenterol*. 2012;26(2):85-91.
64. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2011;(3):CD004787.
65. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology*. 1998;27(6):1578-1583.
66. Furtado R, Crawford M, Sandroussi C. Systematic review and meta-analysis of adjuvant i(131) lipiodol after excision of hepatocellular carcinoma. *Ann Surg Oncol*. 2014;21(8):2700-2707.
67. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol*. 2016;39(11):1580-1588.
68. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2011;140(2):497-507.e2.
69. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer*. 2010;116(5):1305-1314.
70. Benson AB III, Abrams TA, Ben-Josef E, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw*. 2009;7(4):350-391.
71. Gordon A, Lewandowski R, Hickey R, et al. Prospective randomized phase 2 study of chemoembolization versus radioembolization in hepatocellular carcinoma: results from the PREMIERE trial. *J Vasc Interv Radiol*. 2016;27(3)(suppl):S61-S62.
72. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2016;151(6):1155-1163.e2.
73. Seinstra BA, Defreyne L, Lambert B, et al. Transarterial radioembolization versus chemoembolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial. *Trials*. 2012;13:144.
74. Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: a meta-analysis. *Biosci Trends*. 2015;9(5):289-298.
75. Lance C, McLennan G, Obuchowski N, et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol*. 2011;22(12):1697-1705.
76. Kallini JR, Gabr A, Kulik L, Salem R, Lewandowski RJ. The utility of unilobar technetium-99m macroaggregated albumin to predict pulmonary toxicity in bilobar hepatocellular carcinoma prior to yttrium-90 radioembolization. *J Vasc Interv Radiol*. 2016;27(9):1453-1456.
77. Cannon R, Ellis S, Hayes D, Narayanan G, Martin RC II. Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. *J Surg Oncol*. 2013;107(5):544-549.
78. Narayanan G, Froud T, Suthar R, Barbery K. Irreversible electroporation of hepatic malignancy. *Semin Intervent Radiol*. 2013;30(1):67-73.
79. Narayanan G, Bhatia S, Echenique A, Suthar R, Barbery K, Yrizarry J. Vessel patency post irreversible electroporation. *Cardiovasc Intervent Radiol*. 2014;37(6):1523-1529.
80. Cheng RG, Bhattacharya R, Yeh MM, Padia SA. Irreversible electroporation can effectively ablate hepatocellular carcinoma to complete pathologic necrosis. *J Vasc Interv Radiol*. 2015;26(8):1184-1188.
81. Cheung W, Kavnoudias H, Roberts S, Szkandera B, Kemp W, Thomson KR. Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience and review of safety and outcomes. *Technol Cancer Res Treat*. 2013;12(3):233-241.
82. Scheffer HJ, Nielsen K, de Jong MC, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. *J Vasc Interv Radiol*. 2014;25(7):997-1011; quiz 1011.
83. Lencioni R, Crocetti L, Narayanan G. Irreversible electroporation in the treatment of hepatocellular carcinoma. *Tech Vasc Interv Radiol*. 2015;18(3):135-139.
84. Bhutiani N, Philips P, Scoggins CR, McMasters KM, Potts MH, Martin RC. Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC). *HPB (Oxford)*. 2016;18(7):593-599.
85. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1237-1248.
86. Chon YE, Seong J, Kim BK, et al. Gastroduodenal complications after concurrent chemoradiation therapy in patients with hepatocellular carcinoma: endoscopic findings and risk factors. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1343-1351.
87. Balter JM, Brock KK, Litzenberg DW, et al. Daily targeting of intrahepatic tumors for radiotherapy. *Int J Radiat Oncol Biol Phys*. 2002;52(1):266-271.
88. Mornex F, Girard N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies—mature results of the French phase II RTF-1 trial. *Int J Radiat Oncol Biol Phys*. 2006;66(4):1152-1158.
89. Seong J. Challenge and hope in radiotherapy of hepatocellular carcinoma. *Yonsei Med J*. 2009;50(5):601-612.
90. Cheng JC, Chuang VP, Cheng SH, et al. Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2000;47(2):435-442.
91. Kim TH, Park JW, Kim YJ, et al. Simultaneous integrated boost-intensity modulated radiation therapy for inoperable hepatocellular carcinoma. *Strahlenther Onkol*. 2014;190(10):882-890.
92. Yoon HI, Lee IJ, Han KH, Seong J. Improved oncologic outcomes with image-guided intensity-modulated radiation therapy using helical tomotherapy in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2014;140(9):1595-1605.
93. Hou JZ, Zeng ZC, Wang BL, Yang P, Zhang JY, Mo HF. High dose radiotherapy with image-guided hypo-IMRT for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombi is more feasible and efficacious than conventional 3D-CRT. *Jpn J Clin Oncol*. 2016;46(4):357-362.
94. Wang PM, Hsu WC, Chung NN, Chang FL, Fogliata A, Cozzi L. Radiotherapy with volumetric modulated arc therapy for hepatocellular carcinoma patients ineligible for surgery or ablative treatments. *Strahlenther Onkol*. 2013;189(4):301-307.
95. Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer*. 2012;118(21):5424-5431.
96. Kimura T, Aikata H, Takahashi S, et al. Stereotactic body radiotherapy for patients with small hepatocellular carcinoma ineligible for resection or ablation therapies. *Hepatol Res*. 2015;45(4):378-386.
97. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol*. 2016;34(5):452-459.
98. Petersen JB, Lassen Y, Hansen AT, Muren LP, Grau C, Høyer M. Normal liver tissue sparing by intensity-modulated proton stereotactic body radiotherapy for solitary liver tumours. *Acta Oncol*. 2011;50(6):823-828.
99. Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res*. 2005;11(10):3799-3805.
100. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer*.

2011;117(21):4890-4904.
101. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. *Cancer*. 2009;115(23):5499-5506.
102. Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: results of an interim analysis. *Int J Radiat Oncol Biol Phys*. 2016;95(1):477-482.
103. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol*. 2013;31(28):3501-3508.
104. Petrelli F, Coinu A, Borgonovo K, et al. Oxaliplatin-based chemotherapy: a new option in advanced hepatocellular carcinoma. a systematic review and pooled analysis. *Clin Oncol (R Coll Radiol)*. 2014;26(8):488-496.
105. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.
106. Parikh ND, Marshall VD, Singal AG, et al. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: an analysis of the SEER-Medicare database. *Hepatology*. 2017;65(1):122-133.
107. Zeng J, Lv L, Mei ZC. Efficacy and safety of transarterial chemoembolization plus sorafenib for early or intermediate stage hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. *Clin Res Hepatol Gastroenterol*. 2016;40(6):688-697.
108. Wang G, Liu Y, Zhou SF, et al. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. *Hepatol Int*. 2016;10(3):501-510.
109. Zhang L, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One*. 2014;9(6):e100305.
110. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol*. 2016;64(5):1090-1098.
111. Mahvash A, Murthy R, Odisio BC, et al. Yttrium-90 resin microspheres as an adjunct to sorafenib in patients with unresectable hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2016;3:1-7.
112. Trojan J, Waidmann O. Role of regorafenib as second-line therapy and landscape of investigational treatment options in advanced hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2016;3:31-36.
113. Wu P, Wu D, Li L, Chai Y, Huang J. PD-L1 and survival in solid tumors: a meta-analysis. *PLoS One*. 2015;10(6):e0131403.
114. He G, Zhang H, Zhou J, et al. Peritumoural neutrophils negatively regulate adaptive immunity via the PD-L1/PD-1 signalling pathway in hepatocellular carcinoma. *J Experim Clin Cancer Res*. 2015;34:141.
115. Xiao X, Lao XM, Chen MM, et al. PD-1hi identifies a novel regulatory B-cell population in human hepatoma that promotes disease progression. *Cancer Discov*. 2016;6(5):546-559.
116. Kuznar W. Nivolumab makes headwinds into liver cancer. *Am Health Drug Benefits*. 2015;8(spec issue):19.
117. Truong P, Rahal A, Kallail KJ. Metastatic hepatocellular carcinoma responsive to pembrolizumab. *Cureus*. 2016;8(6):e631.
118. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol*. 2013;59(1):81-88.
119. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66(3):545-551.
120. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
121. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J Immunother*. 2007;30(8):825-830.
122. ClinicalTrials.gov. A study to evaluate the effectiveness, safety and tolerability of nivolumab and the combination civolumab plus ipilimumab in patients with advanced liver cancer (CheckMate040). https://clinicaltrials.gov/ct2/show/NCT01658878. Identifier: NCT01658878. Accessed June 13, 2017.
123. ClinicalTrials.gov. Accessed June 13, 2017.