A Review and Update of Treatment Options and Controversies in the Management of Hepatocellular Carcinoma

Mashaal Dhir, MBBS,[*] Alyson A. Melin, DO,† Jeffrey Douaiher, MD,† Chi Lin, MD, PhD,‡ Weining (Ken) Zhen, MD,‡ Shahid M. Hussain, MD, PhD,§ Jean-Francois H. Geschwind, MD,¶ Maria B. Majella Doyle, MD, MBA, FRCS,|| Ghassan K. Abou-Alfa, MD,[**] and Chandrakanth Are, MD, MBA, FRCS, FACS†

Objective: To review the current management, outline recent advances and address controversies in the management of hepatocellular carcinoma (HCC).

Summary of Background data: The treatment of HCC is multidisciplinary involving hepatologists, surgeons, medical oncologists, radiation oncologists, radiologists, interventional radiologists, and other disciplines. Each of these disciplines brings its unique perspective and differing opinions that add to controversies in the management of HCC.

Methods: A focused literature review was performed to identify recent studies on the management of HCC and thereby summarize relevant information on the various therapeutic modalities and controversies involved in the treatment of HCC.

Results: The main treatment algorithms continue to rely on hepatic resection or transplantation with controversies involving patients harboring early stage disease and borderline hepatic function. The other treatment strategies include locoregional therapies, radiation, and systemic therapy used alone or in combination with other treatment modalities. Recent advances in locoregional therapies, radiation, and systemic therapies have provided better therapeutic options with curative intent potential for some locoregional therapies. Further refinements in combination therapies such as algorithms consisting of locoregional therapies and systemic or radiation therapies are likely to add additional options and improve survival.

Conclusions: The management of HCC has witnessed significant strides with advances in existing options and introduction of several new treatment modalities of various combinations. Further refinements in these treatment options combined with enrollment in clinical trials are essential to improve the management and outcomes of patients with HCC.

Keywords: ablation, hepatocellular carcinoma, locoregional therapies, management, radiation, resection, systemic therapies, transplant

(*Ann Surg* 2016;xx:xxx–xxx)

From the [*]Department of Surgery, Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA; †Department of Surgery, Division of Surgical Oncology, University of Nebraska Medical Center, Omaha, NE; ‡Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE; §Department of Radiology, University of Nebraska Medical Center, Omaha; ¶Department of Radiology, Surgery and Oncology, Johns Hopkins School of Medicine, Baltimore, MD; ||Department of Surgery, Division of General Surgery, Abdominal Transplantation Section, Washington University School of Medicine, St. Louis, MO; and [**]Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY.

Disclosure: The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Chandrakanth Are, MD, MBA, FRCS, FACS, Jerald L and Carolynn J Varner Professor in Surgical Oncology and Global Health, Vice Chair of Education, Program Director General Surgery Residency, Department of Surgery/Genetics, Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha, NE 68198. E-mail: care@unmc.edu.

ISSN: 0003-4932/14/26105-0821
DOI: 10.1097/SLA.0000000000001556

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer and a leading cause of cancer-related mortality, with an estimated 782,000 new cases and 745,000 deaths in the year 2012.[1] HCC occurs more frequently in sub-Saharan Africa and Eastern Asia with over 50% of the cases in China alone.[1] The incidence of HCC continues to rise in the United States because of an increase in the prevalence of its major risk factors, mainly Hepatitis C virus (HCV)-induced cirrhosis and nonalcoholic steatohepatitis. Introduction of new curative drugs for the treatment of HCV including sofosbuvir has led to sustained viral responses with cure rates of 80% to 100% for various genotypes.[2] These high cure rates may significantly decrease the incidence of HCC in patients with chronic HCV in future. In 2014, there will be an estimated 33,190 new cases and 23,000 deaths due to liver and intrahepatic bile duct cancers in the United States, of which HCC will be the leading diagnosis.[3]

The management of HCC is rapidly evolving with the expansion of resection criteria, improved locoregional therapies, advent of novel targeted systemic therapies, newer techniques for internal and external radiation therapy, and the possibility of transplantation (Fig. 1). Because of the medical complexity of patients with HCC and the variability in the treatment modalities, patient selection and appropriate treatment allocation may be a challenge. Several staging systems have been made available to aid in patient selection (Table 1), yet the management of patients with HCC continues to be associated with numerous controversies.[4] The aim of the current article is to provide a review of the treatment options and the associated controversies in the management of HCC. A brief overview of imaging for HCC is provided before discussing the treatment options and controversies.

Recently, Liver Imaging Reporting and Data System (LIRADS) was proposed to standardize the reporting and data collection of computed tomography (CT) and magnetic resonance (MR) imaging for HCC.[5] This system of categorizing liver lesions in patients with cirrhosis or other risk factors for HCC allows radiologists to use consitent terminology, reduce the variability in imaging interpretation, enhance communication with referring physicians, and faciliate quality assurance and research. Current surveillance for HCC in high-risk patients is based on ultrasound (US) with or without alfa-fetoprotein (AFP).[6] US is operator dependent, and all focal lesions on US should be verified using a 4-phase contrast enhanced study (unenhanced, arterial, portal venous, delayed)—multidetector contrast enhanced CT (CECT) or a dynamic contrast enhanced MRI (DCE-MRI) with nonspecific or liver-specific contrast agents (Eovist).[6] Conventional FDG-PET has a low sensitivity for HCC, mainly because of the high glucose metabolic activity of the normal background liver. However, the newer 11C-Choline PET shows improved sensitivity and is promising especially for the detection of moderately differentiated HCC lesions.[7] For lesions >1 cm, a 4-phase CECT or DCE-MRI, with features of arterial hypervascularity and venous or delayed phase washout are sufficient to make a diagnosis of HCC.[5,6]

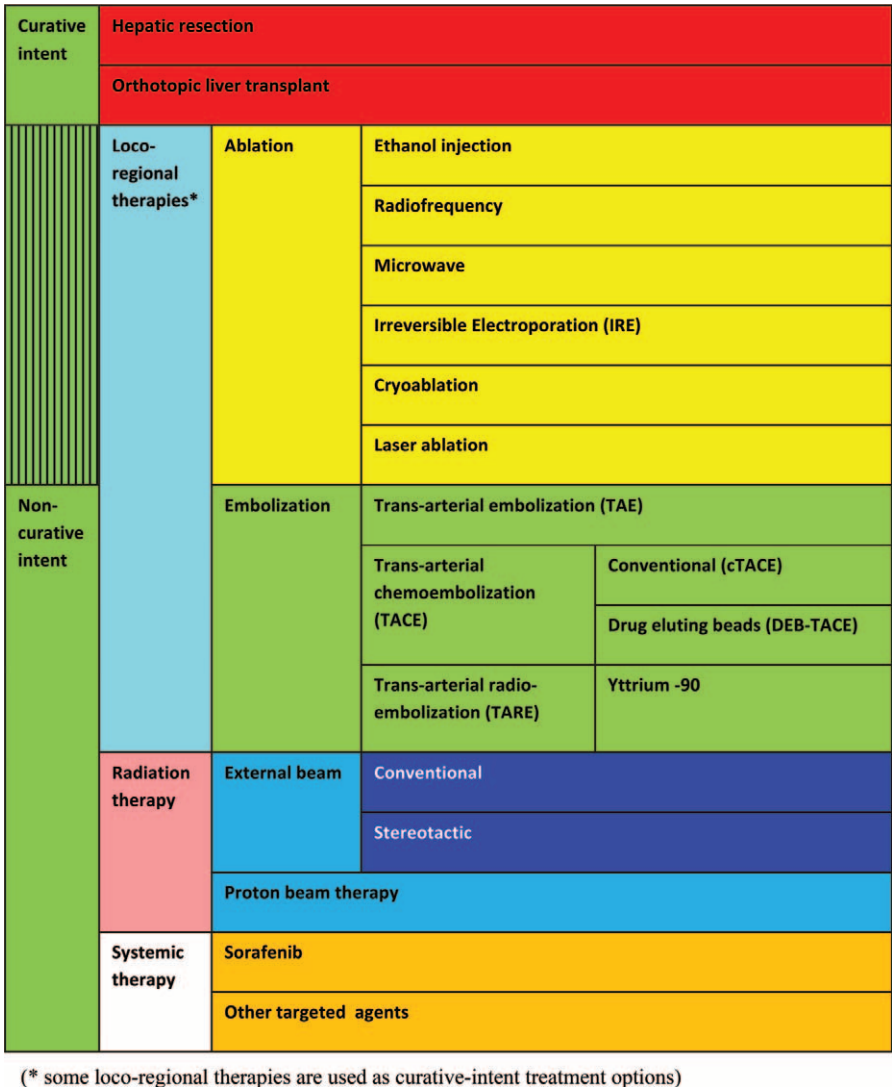


FIGURE 1. Major treatment options available to patients with HCC.

CURATIVE INTENT TREATMENT OPTIONS

Liver Resection

Liver resection may be considered the primary treatment modality in patients with HCC in the absence of cirrhosis. For cirrhotic patients, resection for HCC is considered if the cirrhosis is well compensated, that is, Child-Pugh A, no portal hypertension exists, and the Model for End stage Liver Disease (MELD) score is less than 10. However, resection is usually contraindicated in patients with advanced liver disease, that is, Child-Pugh C and the majority of patients with Child-Pugh B with portal hypertension. Unfortunately, recurrence rates tend to be high, because resection does not address the malignant potential of the future liver remnant (FLR). Salient issues and controversies related to hepatic resection for HCC are addressed below.

Preoperative Assessment of Liver Function

In the Western world, Child-Pugh scoring system has been traditionally used for the evaluation of liver function, despite the inconsistent predictive value. Furthermore, patients categorized as Child-Pugh class A may already have significant liver impairment because of latent or undiagnosed portal hypertension, this is, when clinical or radiologic criteria to diagnose portal hypertension assume importance.[6,8] Platelet count of less than 100,000/μL, splenomegaly, ascites requiring drug treatment or intervention, esophagogastric varices on upper endoscopy, and the presence of abdominal wall collaterals may point toward significant portal hypertension. In the absence of these criteria, some experts recommend hepatic venous catheterization to determine the wedge hepatic venous pressure (normal < 10 mm of Hg).[6,8] The MELD score is another valuable tool in the preoperative assessment of liver function in patients with cirrhosis.[9]

Evaluation of Future Liver Remnant (FLR) Volume

The size and volume of the FLR can be calculated using 3-dimensional (3D) CT volumetry. Total estimated liver volume (TELV) is calculated using body surface area (BSA) with the formula TELV (cm^3) $= -794 + 1267 \times$ BSA (m^2).[10] The ratio of CT-guided FLR volume measurement and TELV is called standardized FLR (sFLR). sFLR provides a determination of the percentage of TELV remaining after resection. For patients with HCC and cirrhosis undergoing resection, sFLR of at least 40% is recommended.[10]

TABLE 1. Summary of Various Staging Systems Used for HCC

Classification	Type	Number of Subtypes	Subtypes	Tumor Staging Criteria	Liver Function	Health Status
Okuda stage	System	3	Stage I, II, III	Tumor size (<50% vs >50% liver involvement)	Bilirubin Albumin Ascites	—
French	Score	3	A: 0 points B: 1–5 points C: ≥ points	Portal invasion AFP	Bilirubin Alkaline phosphatase	Karnofsky
CLIP	Score	7	0, 1, 2, 3, 4, 5, 6	Tumor morphology (</>50% liver involvement) Portal vein thrombosis AFP	Child-Pugh stage	—
BCLC	Staging	5	0: very early A: early B: intermediate C: advanced D: end stage	Portal invasion Metastases Morphology Okuda	Child-Pugh stage Portal hypertension Bilirubin	Performance status test
CUPI	Score	3	Low risk: score ≤1 Intermediate: 2–7 High: ≥8	TNM AFP	Ascites Bilirubin Alkaline phosphatase	Symptoms
TNM	System	4	Stage I, II, III, IV	Number of tumors Vascular invasion Metastases	Fibrosis	—
JIS	Score	6	0,1,2,3,4,5	TNM stage by LCSGJ	Child-Pugh stage	—
ER	System	2	ER wild-type ER variant	Estrogen receptor	—	—

BCLC indicates Barcelona-Clinic Liver Cancer staging; CLIP, cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; ER, estrogen receptor; JIS, Japanese Integrated Staging; LCSGJ, liver cancer study group of Japan. Adapted from Pons et al HPB 2005.[4]

Portal Vein Embolization in HCC for a Small sFLR

Portal vein embolization (PVE) induces hypertrophy by blood flow redistribution and release of cytokines such as hepatocyte growth factor and transforming growth factor α and β.[11] In patients with HCC and impaired liver function who are being considered for resection, PVE is offered to patients with sFLR of 35% to 40% or less.[11,12] In a recent meta-analysis by van Lienden et al[11] (n = 1791 with 365 HCC patients) PVE had a 96.1% clinical success rate (ie, surgery was not performed in 3.9% of patients, because of failure of PVE treatment). PVE had a mortality of 0.1%, major morbidity of 0.3% to 0.8%, and minor morbidity of 1.2% to 36.9%. Only 80% of the originally planned liver resections were eventually performed because of other factors such as insufficient hypertrophy or local tumor progression.[11] Another meta-analysis by Abulkhir et al[12] (n = 1088 with 265 HCC patients) reported a resection rate of 85% post PVE, zero mortality, and major complication rate of less than 1%. Shindoh et al[13] recommended at least a 5% but preferably a 10% increase in sFLR post PVE to optimize outcomes. In addition, sequential use of transarterial chemoembolization (TACE) and PVE is being employed to avoid tumor hypertrophy during the wait period while liver remnant is undergoing hypertrophy.[13] Kinetic growth rate of at least 2% per week of the sFLR is being utilized by some experts for liver resection in patients with colorectal liver metastases; however, its use in patients with HCC is being explored.[14] Some European and South American centers have recently explored the use of associated liver partition and portal vein ligation for staged hepatectomy to achieve rapid FLR hypertrophy. However, its use in US remains limited.

Anatomic Resection Versus Nonanatomic Resection in HCC

Several meta-analyses have shown that anatomic resection (AR) is associated with better overall survival (OS) and 5-year disease-free survival (DFS) compared with nonanatomic resection (NAR) with similar posthepatectomy morbidity and mortality in patients with HCC.[15] It is likely that NAR patients are more likely to have advanced cirrhosis therefore precluding AR. Current data supports that AR may be performed wherever feasible especially in patients with HCC 2 to 5 cm in size but NAR with negative margins may be acceptable strategy in patients who are unable to tolerate AR.

Regional Lymphadenectomy in HCC

The incidence of lymph node metastasis (LNM) in patients with HCC is approximately 5% (range 0–10%) although autopsy studies show a much higher rate, ranging from 25% (with cirrhosis) to 43.9% (without cirrhosis).[16,17] The treatment of LNM in patients with HCC remains controversial. Regional lymphadenectomy may not affect survival, but provides additional prognostic information.[16] Patients with LNM are more likely to develop recurrence and have poor long-term outcomes compared with those without LNM.[16] Ercolani et al[16] recommended regional lymphadenectomy in non-cirrhotic patients with HCC undergoing resection and sampling of at least 4 LNs in cirrhotic patients with HCC undergoing liver transplantation to provide adequate prognostic information. In the United States, experts support selective sampling of LNs based on preoperative imaging and enlargement of LNs at the time of operation.[17]

Large HCC (>10 cm in Size)

Large HCCs that constitute 10% to 20% of all HCCs are seen in younger patients and pose a major challenge.[18] The overall 5-year survival for such tumors ranges from 25% to 45%, and 5-year DFS in most studies varies from 15% to 35%.[18] Presence of gross vascular invasion, cirrhosis, multiple lesions/satellite nodules, poor histologic grade, elevated liver function tests, and high AFP levels contribute to its poor prognosis.[18] Several techniques such as PVE, downsizing with TACE, anterior approach, total vascular exclusion, and infusional chemotherapy may be required to resect these large lesions.

However, even when resection is possible in some patients, these tumors still remain a therapeutic challenge with poor prognosis.

Laparoscopic Liver Resections in HCC

Laparoscopic liver resections are increasing in popularity since the first laparoscopic liver resection in 1992.[19] In the absence of level 1 data, laparoscopic liver resection seems to be comparable to open liver resections in terms of morbidity, mortality, and short- and long-term oncologic outcomes.[20–22] In a review of 2804 laparoscopic liver resections (50% for malignancies of which 52% were for HCC), Nguyen et al[20] reported a 5-year OS and DFS of 50% to 75% and 31% to 38.5%, respectively. A meta-analysis of long-term outcomes comparing laparoscopic (n = 308) and open liver resections (n = 404) revealed similar 1-, 3-, and 5-year OS between the 2 groups (laparoscopic = 92%, 77.7%, and 61.95% and open = 91.3%, 76.5%, and 56.5%, respectively).[22] Laparoscopy is now an accepted strategy for resection of HCC, and further expansion will be based on the availability of more robust evidence, improving expertise and demonstration of cost-effectiveness.[19]

Outcomes

A meta-analysis (n = over 35,000 liver resections of which HCC = 13,497) documented a perioperative mortality and morbidity rate of 4.01% and 28.1%, respectively, for HCC patients.[23] Population based database studies also reported similar, though slightly higher mortality rates ranging from 4.6 to 7.3%. [24] Although mortality is low, morbidity continues to remain high with posthepatectomy liver failure (reported rates of 5%–15%) manifesting as one of the serious complications.[25,26] Therefore, careful patient selection and limiting resection to patients with well-compensated cirrhosis is essential. Recently, many groups have devised risk scores and nomograms to predict perioperative mortality after liver resections to improve patient selection.[25–27]

The 5-year OS after hepatic resection is approximately 25% to 50%.[21,28] Multifocal HCC and major vascular invasion are associated with poor survival.[21,28] In patients with small solitary HCC and well-preserved liver function, the 5-year OS may exceed 50%. Table 2 summarizes the outcomes after liver resection for HCC in selective series since 2000 (see supplementary reference file for the studies cited in Table 2, http://links.lww.com/SLA/A926).

Orthotopic Liver Transplant

In 1996, Mazzaferro et al[29] published the Milan criteria (single HCC < 5 cm in size, 3 or fewer nodule each <3 cm in size and absence of extrahepatic spread or major vascular invasion) and documented that patients with HCC and tumors within the Milan criteria had similar outcomes after liver transplantation when compared with non-HCC patients. However, many studies do not take into account the mortality while awaiting liver transplantation or dropout from the waiting list, because many patients may experience disease progression. Several consensus statements have been issued recently that provide an insight into the role of orthotopic liver transplant (OLT) for HCC.[21,30,31] Salient issues and controversies related to transplantation for HCC are addressed below.

Organ Allocation and Exception Points

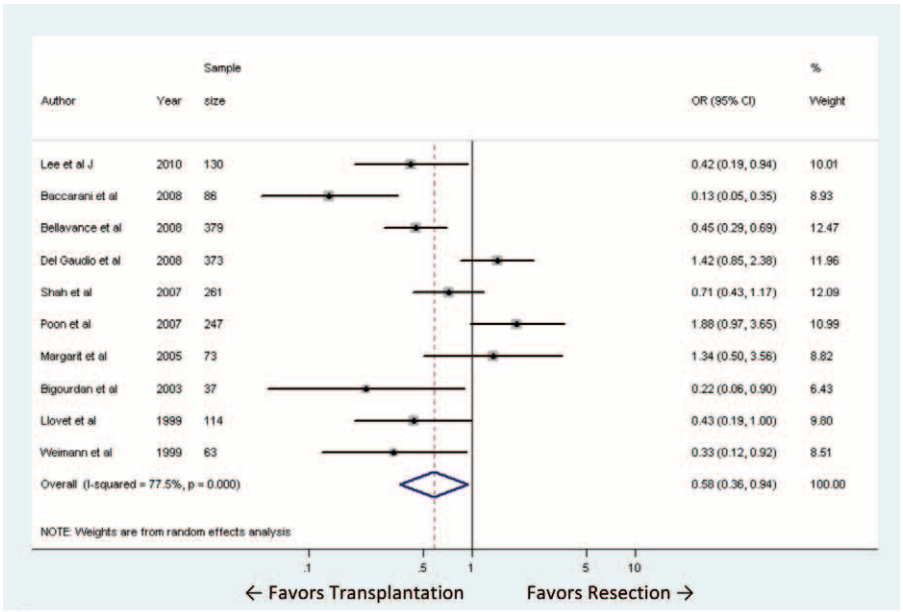
Organ allocation is based on MELD score. Patients meeting the American Liver Tumor Study Group-modified TNM stage II (1 tumor >2 cm but <5 cm or 2–3 tumors largest being <3 cm) receive a MELD score of 22, equivalent to a 3-month mortality of 15%. This helps limit the increased mortality and dropout associated with disease progression while on the waiting list. Transplant centers recertify this data every 3 months. Patients continuing to meet stage II definition receive additional 10% mortality risk points (3 MELD points every 3 months after review by the regional review board). However, some modifications were later proposed to this system because it was felt that patients with HCC seem to have significant advantage over non-HCC candidates under the current MELD system; the recently held national consensus conference proposed that patients with HCC within Milan criteria should stay within these criteria for 3 months before exception points can be granted, although this policy has not been implemented to date.[31]

HCC Within Milan Criteria in Patients With Child-Pugh A Cirrhosis: Resection Versus Transplantation

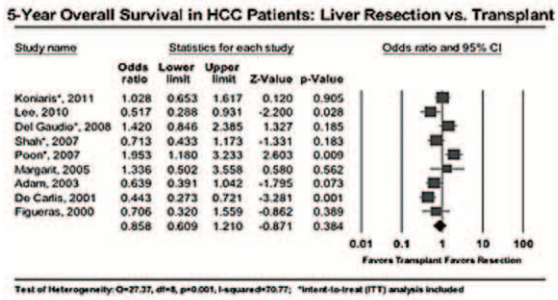
Child-Pugh class A cirrhotic patients with HCC who meet the Milan criteria are a subset of patients who can either be treated by resection or transplantation with comparable outcomes. There are proponents of each treatment type. Deciding between the 2 treatment modalities is influenced by surgeon specialty and local expertise. Recurrence may be higher after resection but transplantation is associated with longer waiting times due to organ shortage, disease progression while on waiting list, and cost implications secondary to immunosuppression. Several recent meta-analyses including Dhir et al,[32] Rahman et al,[33] and Proneth et al[34] (Fig. 2) have attempted to address this issue. These meta-analyses have noted that when resection and transplantation are compared in patients with early HCC, transplantation is associated with favorable 5-year OS and DFS. However, when an intention-to-treat analysis is performed taking into account the mortality associated with the waiting list, the 5-year OS between resection and transplant are comparable. Recurrence rates are significantly increased after resection compared with transplantation. Long-term outcomes may be worse after resection, with reported 10-year OS of 22% after resection versus 54% after transplantation.[35] Recently, a single single-center study (HCV-related early HCC $\leq$ 5 cm, Child A or B class, with 30% drop out rate) performed an intention-to-treat analysis and demonstrated better but statistically insignificant median survival for resection (61.8 vs 30.6 mo) although the transplant group had a lower recurrence rate (30% vs 71.5%, $P < 0.001$).[36] Resection and transplantation will continue to remain viable options until further evidence becomes available.

Extended Criteria HCC

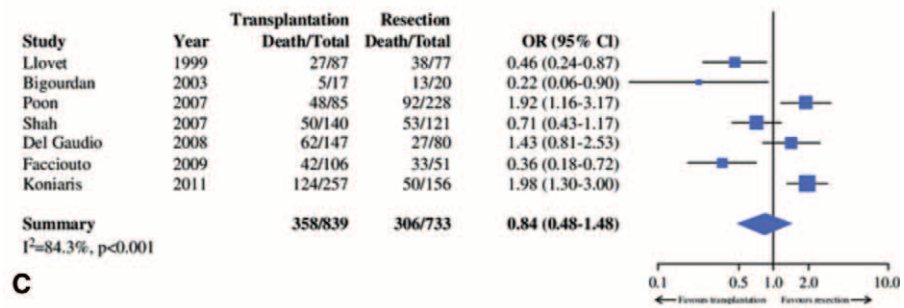
Several groups have proposed that Milan criteria are too restrictive and limit the transplant option to patients with very early disease. Researchers at the University of San Francisco (UCSF) observed that many times the explant tumors were bigger than the Milan criteria but this did not lead to poor outcomes. Based on these observations, they proposed the expanded UCSF criteria for HCC, which consist of (1) single tumor less than 6.5 cm, (2) maximum of 3 total tumors with none greater than 4.5 cm, and (3) multiple tumors with cumulative tumor size less than 8 cm.[37] The relevance of these criteria was supported by a subsequent study of 467 patients, which divided patients into 3 groups: Milan criteria (n = 173), UCSF criteria (n = 185), and Beyond UCSF criteria (n = 109).[37] The 1-, 3-, and 5-year survival were similar in the Milan and UCSF groups, which were superior to the Beyond UCSF group. Toso et al[38] reported a 3 institution study calculating the total tumor volume from pretransplant imaging that may be a useful tool for selection of patients with HCC for transplantation; they reported a total tumor volume cutoff of 115 cm^3, below which patients have similar outcomes to those within Milan and UCSF criteria. Several other new criteria that are less restrictive than the original Milan criteria have also been proposed such as ''Upto 7 criteria,'' ''Kyoto criteria,'' ''5–5 criteria,'' ''Asan criteria,'' and ''Hangzhou criteria.'' It is likely that as further evidence becomes available, indications for transplantation outside of the Milan criteria will continue to increase.



A



B



C

FIGURE 2. Representative figures from the published meta-analyses on resection versus transplant in patients with HCC. Adapted from Dhir et al (A),[32] Rahman et al (B),[33] and Proneth et al (C).[34]

Downstaging

Patients with confirmed downstaging to Milan criteria for a minimum period of 3 to 6 months after the initial therapy may be granted equivalent MELD exception points similar to patients who initially present with stage II HCC.[30,31] TACE and radiofrequency ablation (RFA) and more recently yttrium 90 are commonly utilized strategies for downstaging. In a recent systematic review (n = 720), Gordon-Weeks et al[39] documented a downstaging rate of 24% to 69% and transplantation rate of 9.6% to 57%. The 1-, 3-, and 5-year OS and DFS were similar to patients who were initially within the Milan criteria.

There are no clearly defined upper limits for size and number of lesions that preclude a patient from downstaging. However, presence of extrahepatic disease and major vascular invasion are often considered as contraindications for downstaging.[30] The recently held national consensus conference used the modified UCSF criteria to develop guidelines for selecting patients for downstaging.[31] This panel suggested the following inclusion criteria for downstaging: (1) single tumor greater than 5 cm and equal to or less than 8 cm in maximal diameter, (2) 2 or 3 tumors, each equals to or less than 5 cm in maximal diameter, with the sum of the maximal tumor diameter of all tumors 8 cm or less than 8 cm, and (3) no

evidence of vascular invasion on multiphase CT or MRI of abdomen.[31] As per the panel, successful downstaging is defined as tumor shrinking down to Milan criteria and drop in AFP levels below 500 ng/mL.[31] In patients who are successfully downstaged, a minimum waiting period of 3 months is recommended before transplantation. Several centers participating in these strategies have reported successful downstaging with good outcomes.

Bridging Therapies for HCC Before Liver Transplant

There are several roles of bridging therapies: (1) decrease the incidence of disease progression and dropout while on the waiting list, (2) downstage patients who are outside of the Milan criteria, (3) add neo-adjuvant therapy to improve the prognosis of patients undergoing OLT for HCC, (4) possibly avoid or delay the need for transplantation in patients who have a favorable response, and (5) as a selection tool for patients who have treatment responsive disease and may have a favorable prognosis overall.[21,31,37]

Current consensus guidelines recommend periodic (commonly 3 months) monitoring of listed patients using imaging and AFP measurements, to identify those who develop disease progression.[30] Bridging strategies with locoregional therapies may be used to decrease tumor-related dropout rates and are usually beneficial for patients with a waiting time of 6 months or more.[21,30,31] There is no evidence to suggest that bridging strategies are of any benefit in patients with United Network of Organ Sharing T1 tumors (<2 cm). Bridging strategies are most likely to benefit United Network of Organ Sharing T2 tumors (1 nodule 2–5 cm or 3 or fewer nodules each ≤3 cm) with likely waiting times of 6 months or longer, because these patients are at highest risk for dropout. [21,30,31]

Hepatic Resection and Salvage Liver Transplant

Resection may be used as a primary therapy for patients with preserved liver function, whereas OLT is reserved for patients who experience recurrence or liver failure, but there are conflicting results using this strategy. Some authors suggest similar outcomes using resection and salvage transplantation to primary liver transplantation, and others report worse outcomes. A recent systematic review by Hu et al[40] (n = 110) showed no difference in the 1-, 3-, and 5-year survival rates between salvage and primary liver transplants. This strategy may not be optimal for patients with HCV associated HCC, because these patients tend to have more aggressive recurrences compared with the patients with hepatitis B virus associated HCC.[41] However, choosing this strategy requires close patient follow-up, and patients who have T2 recurrences should be eligible for priority listing for HCC with the caveat that some patients will recur beyond T2 and will be ineligible for salvage transplantation.

One potential benefit of this approach is that resection may permit pathologic evaluation to identify any adverse tumor biological features that can improve patient selection for OLT.[41] However, in the US patients who undergo resection lose their priority listing precluding its use as a bridge to transplantation.[21] This makes resection a less-attractive option for HCC patients who are listed for transplantation in US. Some experts suggest that prognostic information similar to resection may be gained from a core biopsy, with minimal risk for seeding.

Outcomes

Table 2 summarizes the outcomes after liver transplantation in selected series since 2000 (see supplementary reference file for references, http://links.lww.com/SLA/A926). Perioperative mortality reported by major institutions is 0 to 5%; however, morbidity remains high. The 5-year OS after OLT for HCC within the Milan criteria varies from 41% to 78% with most studies ranging between 50% and 70%. Five-year DFS for OLT ranges from 60% to 80% in most studies. High AFP levels have been associated with increased recurrence and reduced survival post liver transplant.[42] The model proposed by Duvox et al[42] included the usual tumor size and number with the addition of AFP and has demonstrated superiority over Milan criteria in predicting recurrence. Using this model, patients beyond Milan criteria with AFP less than 100 ng/mL were at low risk of recurrence and those with levels above 1000 ng/mL were at higher risk of recurrence and reduced survival. Even for those within Milan criteria, an AFP level of more than 1000 ng/mL is associated with increased recurrence and reduced survival. In addition to high AFP, other factors associated with poor prognosis include poor tumor biology (poor differentiation, satellite lesions, microinvasion) and host-related factors such as HIV and HCV co-infection etc.[43,44] In summary, resection and transplantations are the main curative-intent treatment options for HCC. These treatment options should be considered complementary in the management of HCC. In addition, some experts consider radiofrequency ablation (RFA) as curative treatment. However, this remains controversial. This modality is discussed in detail below.

NON-CURATIVE INTENT TREATMENT OPTIONS

Locoregional Therapies

Locoregional therapies can be broadly divided into 2 categories, that is, ablation and embolization. Figure 3 delineates the algorithm for the use of locoregional therapies in HCC. Salient issues and controversies related to locoregional therapies for HCC are addressed below.

Ablation

Percutaneous ethanol injection (PEI) and RFA are the 2 most commonly used ablative treatments for HCC in addition to other modalities listed below.

Percutaneous Ethanol Injection (PEI)

Ethanol injection causes coagulative necrosis although its distribution may be blocked by intratumoral septa and/or tumor capsule resulting in heterogeneous distribution.[45] As a result, curative capacity of PEI is limited, particularly in tumors larger than 2 cm in size, and it requires multiple injections over multiple sessions. Lin et al[46] demonstrated a recurrence rate of 42% and 51% at 2 and 3 years, respectively, in patients with lesions approaching 3 cm in size. To overcome these limitations, some authors have reported high dose injections or use of multipronged needles.

Radiofrequency Ablation (RFA)

RFA is most suitable for tumors smaller than 3 cm in size and is considered less effective for tumors more than 4 cm in size. In a review of over 5000 tumors treated by RFA, recurrence at the tumor site increased with tumor size: 14% (≤3 cm), 25% (3–5 cm), and 58% (>5 cm).[47] However, these rates may change as new more sophisticated probes become available.

Radiofrequency Ablation vs Percutaneous Ethanol Injection

In a meta-analysis of 5 randomized controlled trials, RFA when compared with PEI demonstrated better outcomes.[48] RFA may be considered a first-line ablative treatment in patients with small HCC (<3 cm) and well-preserved liver functions. PEI may be reserved for lesions not suitable for RFA owing to the location. Supplementary Table 1, http://links.lww.com/SLA/A926, provides a summary of selected studies comparing RFA to PEI in patients with HCC.

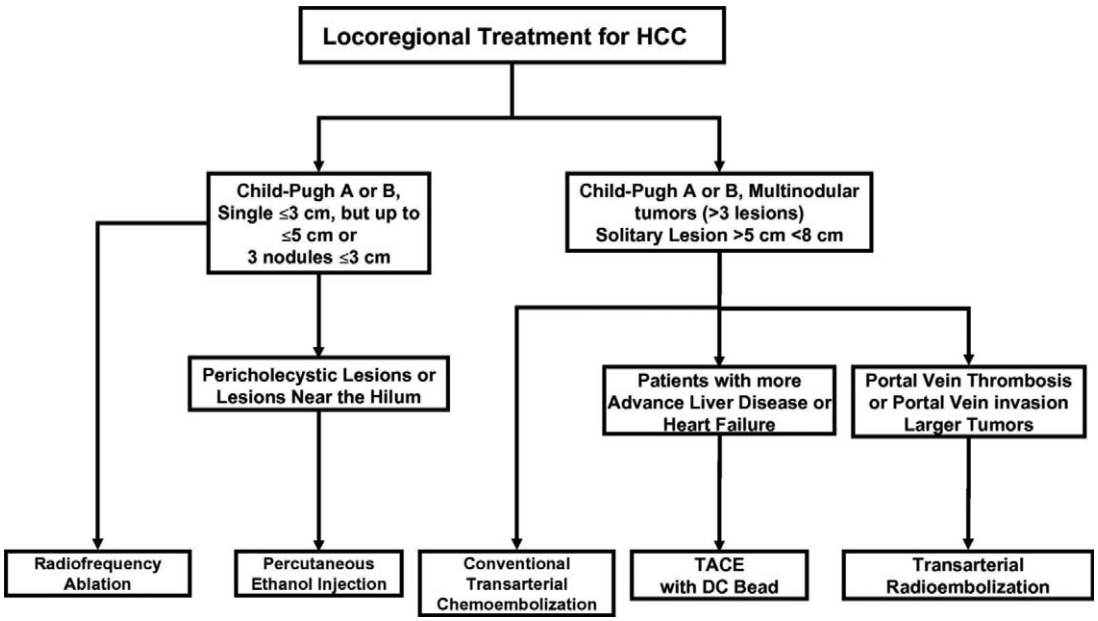


FIGURE 3. Algorithm for use of locoregional therapies in patients with HCC. Adapted from Meza-Junco et al.[54]

Radiofrequency Ablation Versus Liver Resection

The choice of RFA versus liver resection in some settings remains controversial. Most studies suggest that liver resection leads to higher overall and recurrence-free survival but outcomes may be comparable when tumors are less than 2 cm in size.[49] Therefore, RFA is considered a curative intent treatment option by some experts. Although overall mortality is low for both resection and RFA, the morbidity rates are shown to be consistently lower for RFA (Table 3, see supplementary reference file for references, http://links.lww.com/SLA/A926). Treatment options need to be tailored to the individual patient.

Microwave Ablation

Microwave ablation (MWA) may have certain advantages over RFA such as higher temperature at the target tissue, less pronounced heat sink effect, shorter duration of therapy, less risk for skin burning, and effective treatment of cystic lesions.[45] Although earlier trials failed to show superiority over RFA, more recent studies have demonstrated equivalency to RFA in the treatment of HCC.[50] In a systematic review of 34 studies including 3 RCTs, Bertot et al[51] evaluated the mortality and complication rates associated with percutaneous ablative techniques including RFA, PEI, and MWA. The overall mortality rate (0.15%, 0.59%, and 0.23%) and morbidity (4.1%, 2.7%, and 4.6%) for RFA, PEI, and MWA, respectively, were comparable demonstrating the safety of MWA when compared with PEI and RFA.

Irreversible Electroporation

Irreversible electroporation (IRE) is a nonchemical nonthermal ablation technique that generates electrical pulses leading to cell death.[45] Safety and efficacy of IRE has been reported in clinical studies.[52] Currently, nonmetastatic unresectable HCC patients (underlying liver disease, portal hypertension) who are not candidates for transplantation or ablation with tumors located in proximity to blood vessels, bile ducts, diaphragm, or gastrointestinal tract may be candidates for IRE under controlled clinical settings.

Cryoablation

Some of the advantages of cryoablation over RFA include (1) less pain associated with the procedure, (2) ability to visualize the ice ball that allows for a precise evaluation of the treatment zone, and (3) less pronounced heat sink effect.[53] Another advantage of cryoablation is the ectopic antitumor effect, which indirectly suppresses nontargeted tumor nodules through release of tumor antigens and downregulation of regulatory T cells.[53] The more recent smaller probes have improved the complication profile (17% with older probes) and demonstrated favorable survival outcomes compared with RFA or surgical resection.

Other ablation therapies such as laser ablation therapy and high intensity focused ultrasound are being investigated.

Embolization

Embolization plays multiple roles in the management of HCC.[21,45,54]

The different types of arterial embolization employed in the treatment of HCC include (1) bland embolization with particles consisting of gelatin sponge or polyvinyl alcohol or polyacrylamide (transarterial embolization or TAE), (2) chemoembolization with doxorubicin or cisplatin (TACE, which can be of the conventional type [cTACE] or with drug-eluting beads [DEB TACE]), or (3) radioembolization with yttrium-90 (TARE) an emitter of beta radiation (discussed in the next section).

Transarterial Embolization (TAE) vs. conventional Transarterial Chemoembolization (cTACE) or Drug Eluting Beads (DEB) TACE

Although TACE has been shown to be superior to best supportive therapy, superiority of cTACE over TAE has not been established (Table 4).[55] Meta-analysis of RCTs conducted by Xie et al[55] noted that 6-, 9-, 12-, 24-, and 36-month OS of the cTACE group was not significantly higher than that of the TAE group (all $P > 0.05$). Further studies comparing cTACE to TAE are ongoing.

TABLE 3. Selected Studies Comparing Resection (RES) vs. Radiofrequency Ablation (RFA) in Patients with HCC

								Overall Survival, %						Recurrence Free Survival, %						Compli-cations			
Study	Type of Study	Country	Treatment	Patients	Size Criteria	Mean Tumor Size, cm	Follow-up	Median	1 yr	2 yrs	3 yrs	5 yrs	*P*	Median	1 yr	2 yrs	3 yrs	5 yrs	*P*	Rate, %	*P*	Mortality %	Comments
Eastern Studies																							
Chen et al, Ann Surg, 2006	RCT	China	RES	90	Solitary HCC ≤ 5 cm	—	Mean 29.2 mo		93.3	82.3	73.4		NS		86.6	76.8	69		NS	55	<0.05	1.1	Ablative therapy was equally effective but less invasive than resection in small solitary HCC
			RFA	71		—	Mean 27.9 mo		95.8	82.1	71.4				85.9	69.3	64.1			4.2		0	
Huang et al, Ann Surg, 2010	RCT	China	RES	115	Milan criteria	—	Median −3.87 yrs		98.3	96.5	92.2	75.7	0.001		85.2	73.9	60.9	51.3	0.017	27.8	<0.05	0	Surgical resection may provide better survival and lower recurrence for patients with HCC within Milan criteria
			RFA	115		—	Median −3.1 yrs		87	76.5	69.6	54.8			81.7	59.1	46	28.7		4.3		0	
Feng et al, J Hepatol, 2012	RCT	China	RES	84	Diameter upto 4 cm and upto 2 nodules	2.6 ± 0.8	3-year follow-up period		96	87.6	74.8		0.342		90.6	76.7	61.1		0.122	21.4	0.017	0	RFA may provide therapeutic effects similar to RES
			RFA	84		2.4 ± 0.6			93.1	83.1	67.2				86.2	66.6	49.6			9.5		0	
Western Studies																							
Lupo et al, HPB, 2007	Retrospective analysis	Italy	RES	42	Single HCC 3–5 cm without end-stage liver disease	4*	Mean 31 mo		91		57	43	0.824		74		35	14	0.283	16.6	0.242	2.3	Survival is determined by underlying liver disease rather than the treatment option
			RFA	60		3.65*	Mean 27 mo		96		53	32			68		18	0		10		0	
Abu-Hilal et al, J Gastrointest Surg, 2008	Retrospective analysis	UK	RES	34	Size 1–5 cm	3.8*	Median 43 mo	74 m	91	81		56	0.302	35 m	77	67		28	0.028	27	0.085	0	Surgical resection offers longer OS and DFS in small unifocal HCC
			RFA	34		3*	Median −30 mo	—	83	62		57		9 m	42	29		21		16		2.9	
Santambrogio et al, Ann Surg Oncol, 2009	Retrospective analysis	Italy	RES	78	Single HCC nodule and Child A Cirrhosis	2.87 ± 1.21	Mean 36.2 mo		93		85	54	0.163							33	0.015	0	
			RFA	74		2.63 ± 1.07	Mean 38.2 mo		88		66	41								16		0	
Li et al, J Am College Surgeons, 2014	ACS-NSQIP analysis	US	RES	Minor hepatectomy 837			30-d follow-up													21.3	<0.01	3.4	Higher complication rate of major hepatectomy over ablation
				Major hepatectomy 444																35.1		8.3	
			RFA	323																9.3		3.7	

ACS-NSQIP indicates American College of Surgeons National Surgical Quality Improvement Program; RES, resection; RCT, randomized controlled trial.
*Median.
For complete reference information, please see supplementary reference file.

Current practice is based on the preferences of treating physicians and other patient related factors.

DEB TACE Versus cTACE

Doxorubicin administered via drug-eluting beads in DEB TACE compared with cTACE may be associated with survival advantage, better local response, and a longer time to progression (TTP) in some studies (Table 5).[56] Supplementary reference file summarizes the references for the studies cited in Tables 4 and 5, http://links.lww.com/SLA/A926.

TACE is now becoming the standard of care for unresectable HCC and is mentioned in several guidelines including AASLD (American Association for the Study of Liver Diseases), NCCN (National Comprehensive Cancer Network), and EASL (European Association for the Study of Liver) because of the robust level 1 evidence.[6,8,57,58] Burrel et al[59] reported a median survival of 54 months for Barcelona clinic liver cancer (BCLC) stage A and 47 months median survival for BCLC stage B patients treated with DEB TACE, and this strategy is being employed by many centers. Use of TACE in treatment of HCC is contraindicated in cases of diffuse (>50%) involvement of the liver with tumor, hepatic insufficiency or failure (Child-Pugh class C), portal vein invasion, serum bilirubin of more than 3 to 5 mg/dL, or AFP level of more than 1000/ul.[45,54] Portal vein occlusion or thrombosis is no longer considered an absolute contraindication for TACE by some experts, because it can be performed with some modifications as long as there is good collateral portal venous circulation. Hypoxia induced by TACE is a limitation; TACE upregulates the hypoxia-inducing factor-1α, which in turn upregulates the vascular endothelial growth factor (VEGF), platelet-derived growth factor, and tumor angiogenesis. This has been implicated as a potential cause of high recurrence rates seen with TACE.[60–62] To overcome this phenomenon, TACE has been combined with other strategies such as ablation, radiation, and systemic therapy with sorafenib and VEGF inhibitors. TACE has also been combined with RFA for treatment of HCC and a recent meta-analysis demonstrated the benefits of this approach.[63] The combination of TACE with other strategies will continue to evolve.

Radioembolization

Yttrium-90 (Y-90) is the most commonly used agent for selective internal radiation therapy or radioembolization.[64,65] The major indications for TARE include patients with nonmetastatic unresectable HCC who are not candidates for transplantation or ablation.[54,64,66] Because TARE does not cause ischemia, it can be used in patients with HCC who have portal vein thrombosis.[54,64,66] TARE can be used as a bridge to transplantation and for downstaging tumors outside the Milan criteria.[54,64,66] Patient selection is critical and has been previously described by Memon et al[64]; patients should have (1) good performance status (ECOG $\leq$ 2), (2) adequate pulmonary reserve, (3) creatinine less than 2 mg/dL, (4) adequate blood counts (platelet count $>50 \times 10^9$/L and granulocyte count $>1.5 \times 10^9$/L), and (5) acceptable liver function (Child-Pugh score $\leq$7). Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE) NCT01381211 (http://clinicaltrials.gov/show/NCT01381211) trial will likely clarify the efficacy of TARE versus TACE.

External Beam Radiation Therapy

3D Conformal Radiotherapy and Intensity-Modulated Radiotherapy

Historically, external beam radiation therapy (EBRT) had a limited role in the treatment of HCC because of the low whole-liver tolerance of radiation with a 5% risk of radiation-induced liver

TABLE 4. Selected Studies Comparing Transarterial Embolization (TAE) to Conventional Transarterial Chemoembolization (cTACE) or Drug Eluting Beads (DEB) TACE Since 2000 in Patients with HCC

Study Name	Study Type	Country	Treatment Type	Number of Patients	BCLC Stage, A/B/C	Mean tumor size ± SD, cm	Follow-up, mo	Response Rate			Time to Progression			Survival						Comments
								Comments	%	P	Median, mo	Mean, mo	P	Mean, (mo ± SD)	Median	6 mo, %	1 yr, %	2 yrs, %	3 yrs, %	P	
Llovet et al, Lancet, 2002	RCT	Spain	TAE	37	0/28/9	5.2	Mean 21.7	6 mo resonse (CR + PR)	43.2 (16/37)	TAE vs control = 0.001				25.3		75	50	29			cTACE better than control. No direct comparison of TAE vs cTACE but no difference in OS at 3 years.
			cTACE	40	0/35/5	4.9	Mean 21.2	WHO criteria	35.0 (14/40)	TACE vs control = 0.004				28.7		82	63	29	TACE vs control p = 0.009	
			Control	35	0/27/8	4.4	Mean 14.5							17.9		63	27	17		
Malagari et al, Cardiovasc Interven Radiol, 2010	RCT	Greece	TAE	43		8.1 ± 2.8		(CR + PR) at 12 mo	18.9	NS	9.05 ± 2.3		0.008			100	86			NS	No difference between TAE and DEB TACE
			DEB TACE	41		8.35 ± 2.75		EASL criteria	25.7		10.6 ± 2.7					100	85.3				
Meyer et al, Brit J Cancer, 2013	RCT	United Kingdom	TAE	42	9/16/15		Median follow-up 24 mo	Overall (CR + PR) at the end of treatment mRECIST criteria	47.3		7.2		0.59		17.3		68	39		0.74	No difference between TAE and cTACE
			cTACE	44	(2 unknown) 11/18/12 (3 unknown)				67.4		7.5				16.3		64	32			

For complete reference information, please see supplementary reference file.
CR indicates complete response; EASL, European Association for study of liver; mRECIST, modified response evaluation criteria in solid tumors; NS, not significant; PR, partial response; SD, standard deviation; WHO, World Health Organization.

TABLE 5. Selected Studies Comparing Conventional TACE to DEB TACE in Patients With HCC

								Response Rate			Time to Progression			Survival					
Study Name	Study Type	Country	Treatment Type	Number of Patients	BCLC Stage, A/B/C	Mean Tumor Size ± SD, cm	Follow-up, mo	Comments	%	*P*	Median, mo	Mean, mo	*P*	Mean (mo ± SD)	Median, mo	6 mo, %	1 yr, %	2 yrs, %	*P*	Comments
Song et al, J Hepatol, 2012	Retrospective comparative analysis	Korea	cTACE DEB TACE	69 60	A/B 28/41 A/B 27/33	5 ± 3.1 4.2 ± 2.8	Median follow-up 18 mo	Overall response	49.4 81.6	<0.001	7.6 11.7		0.018	24.7 ± 1.7 32.2 ± 1.9		80 93	67 88		0.005	Effect of DEB TACE was more pronounced in intermediate stage HCC
Golfieri et al, Br J Cancer, 2014	Randomized controlled trial	Italy	cTACE DEB TACE	88 89	A/B/C 41/23/24 A/B/C 41/26/22	2.8 (1–10)* 2.5 (0.9–9)*	At least 2 yrs or until death	CR at 12 mo	51.7 55.8	NS	9 9		0.776		28 29		83.5 86.2	55.4	0.949	DEB TACE and cTACE are equally effective and safe
Sacco et al, J Vasc Interven Radiol, 2011	Randomized controlled trial	Italy	cTACE DEB TACE	34 33	A/B 22/12 A/B 22/11	3.85 ± 1.89 4.47 ± 2.68	Mean follow-up, cTACE 27.2, DEB TACE 26.4	CR, PR at 1 mo	70.6, 29.4 51.5, 48.5	0.1	12.8 8.9		0.46					83.6 86.8	0.96	Comparable outcomes in patient with DEB TACE and cTACE
Lammer et al, Cardiovasc Interven Radiol, 2010	Randomized controlled trial	European Multicenter	cTACE DEB TACE	108 93	A/B 24/79 A/B 24/69	8.92 ± 5.93† 8.89 ± 5.21†	— —	CR, PR, stable disease	22.2, 21.3, 8.3 26.9, 24.7, 11.8	0.11										Although trial could not show superiority of efficacy of DEB TACE, patients with Child B, ECOG 1, bilobar disease, and recurrent disease had higher objetive response rate ($P < 0.038$)
Dhanasekaran et al, J Surg Oncol, 2010	Retrospective comparative analysis	US	cTACE DEB TACE	26 45	Okuda I/II/III 11/10/5 Okuda I/II/III 17/13/15	7.4 ± 4.91 5.49 ± 4.29	— —								9.4 (284 d) 20.3 (610 d)	58 72	46 67	19 40	0.031	DEB TACE offers a survival advantage over cTACE for patients with unresectable HCC

For complete reference information, please see supplementary reference file.
CR indicates complete response; ECOG, The Eastern Cooperative Oncology Group; NS, not significant; PR, partial response; SD, standard deviation.
*Median and range.
†mean +/− SD (standard deviation) of total sum of diameter of HCC lesions.

disease (RILD) after whole-liver doses of 30 to 35 Gy administered in 2 Gy fractions.[67] Several recent advancements have allowed the delivery of higher doses of radiation focally to the tumor, while decreasing exposure to surrounding healthy liver tissue, thereby reducing (although not eliminating) the toxic effects on the liver. This has expanded the role of EBRT in patients with HCC. In general, palliative-intent EBRT is used for symptom control, whereas definitive EBRT is used for local disease control. Definitive EBRT is reserved for patients with liver-confined HCC, who are not eligible for or have failed other therapies such as surgical resection and locoregional therapies.[66–68] Lastly, EBRT is often combined with other modalities to achieve a better response at tolerable doses and also to minimize the side effects.[66–68] Specific types of EBRT are discussed below.

Three-Dimensional conformal radiation therapy (CRT) allows profile shaping of the beam of radiation to match the profile of the tumor. Mathematical models that quantitatively predict dose and volume relationship and the probability of developing RILD have facilitated the treatment planning of CRT.[69] Several studies have shown the effectiveness of CRT.[67] A more recent modification of CRT, intensity-modulated radiation therapy produces highly conformal dose distributions in the target volumes and minimizes the dose received by adjacent dose-limiting structures and has further improved the outcomes compared with CRT.[67,70] Technological advances such as image guidance and breathing motion management have made possible to deliver ablative doses to focal unresectable HCC. Total radiation dose seems to be one of the most important predictors of survival. Potential side effects including nausea/vomiting, fatigue, delayed liver toxicity, gastrointestinal bleeding, edematous-ascitic hepatic decompensation, and RILD have been described. Grade 3 or higher toxicities can occur in 15% to 30% of the patients.[67,69] The efficacy of CRT in treating HCC with portal venous thrombosis has been reported. The median OS of this cohort ranges from 4 to 13 mo in recent reports. Response of portal venous tumor thrombosis to RT tends to be slow, but eventual recanalization has been reported.[67]

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) involves the use of multiple radiation beam angles, delivered to the tumor with high precision and rapid fall-off doses away from the target. The reported objective responses rates of SBRT are 37% to 90% and 2-year survival ranges from 43% to 82%.[69] Complete pathologic responses have also been reported in 14% to 27% of patients. SBRT may be associated with the potential risk of RILD, progression of Child-Pugh class, chest wall toxicity (peripherally located lesions), and biliary toxicity, etc.[67] Grade 3 or higher toxicity with SBRT has been reported to be 0 to 40%. The risk of RILD is associated with treatment volume and liver functional status. As previously discussed, the mean liver doses associated with a 5% risk of classic RILD for HCC range from 28 to 35 Gy in 2 Gy per fraction depending on whether cirrhosis exists or not; however, if the effective liver volume irradiated is less than 25%, a dose above 100 Gy can be given with little risk of RILD. Therefore, keeping treatment target volume low is critical, to ensure sparing of enough residual liver from radiation toxicity. In addition, lower fractional and total doses are recommended for Child-Pugh B when compared with Child-Pugh A to minimize the side effects related to reduced tolerance.[69] In recent years, SBRT has been successfully used as a bridge therapy to halt the progression of HCC in patients on liver transplant waiting lists.[69] No intraoperative or long-term complications associated with this bridge therapy have been reported. A randomized phase III study of sorafenib versus SBRT followed by sorafenib in hepatocellular carcinoma is currently recruiting (Clinicaltrials.gov NCT01730937).

Proton Beam Radiation Therapy

Charged particle therapy, such as proton therapy, has distinct dosimetric advantages over therapy that utilizes photons, such as CRT, intensity-modulated radiation therapy, and SBRT.[66,68,71] Protons release their energy once they slow down after traveling a particular distance, that is, at a specified depth in each tissue; the energy is rapidly delivered over a short distance. This allows the release of high dose energy to the tumor with minimal surrounding tissue toxicity.[66–68,71] Recent prospective studies using proton beam radiotherapy in HCC have reported 5-year in-field local control rates of more than 70% and grade 3 or higher toxicity of 0 to 4%.[71] Indications for proton beam therapy are evolving. Some experts suggest that patients with nonmetastatic HCC with portal vein invasion, centrally located tumors, tumors not suitable for RFA such as those close to diaphragm or major blood vessels, and locally advanced tumors in Child-Pugh class B and C patients may be suitable for proton beam therapy.[71]

Systemic Therapy

Patients with metastatic disease or advanced HCC, not suitable for resection, transplantation, or locoregional therapies may be the candidates for systemic treatment. However, the use of such a treatment modality has been limited by the refractory nature of HCC tumors, possible hepatic dysfunction as a treatment complication, and the diversity of patient population. Many recently approved and currently tested systemic therapies, target one or few molecular pathways involved in HCC.[62,72]

HCC arises from complex molecular processes involving aberrations in multiple signaling pathways, which have been extensively reviewed elsewhere (supplementary Fig. 1, http://links.lww.com/SLA/A926). Sorafenib is an oral multikinase inhibitor, which suppresses tumor cell proliferation and angiogenesis. Sorafenib targets VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor β, receptor activation factor kinase, and B-Raf. Two double-blinded, randomized placebo controlled phase III trials have shown prolongation of median overall survival in patients treated with sorafenib when compared with the placebo arm.[73,74] Sorafenib HCC Assessment Randomized Protocol (SHARP) trial randomized 602 patients with the primary endpoint of overall survival. Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (Hazard ratio [HR] 0.69, 95% confidence interval [CI], 0.55–0.87, $P < 0.001$). Median time to radiologic progression was prolonged (sorafenib 5.5 months, placebo 2.8 mo, HR 0.58 [0.45–0.74], $P < 0.001$), but there was no difference in the median time to symptomatic progression (sorafenib 4.1 mo, placebo 4.9 mo, HR 1.08 [0.88–1.31], $P = 0.77$). The most common side effects of sorafenib include hand-foot skin reaction, diarrhea, and fatigue. The Asia pacific study was a mirror image trial performed on patients with advanced HCC, who had not received previous systemic therapy and had Child-Pugh class A cirrhosis. The median overall survival in this study was 6.5 months in the sorafenib arm compared with 4.2 months in the placebo arm (HR 0.68 [0.50–0.93], $P = 0.014$). Although the difference in median survival was small, HR was comparable between the SHARP and Asia-pacific trials (0.69 and 0.68, respectively). The investigators hypothesized that the more advanced disease may be responsible for a poorer median survival in the Asia Pacific trial. In the Asia pacific study, at baseline, more patients had extrahepatic disease, a greater number of hepatic tumors, poorer performance status, hepatitis B virus-associated HCC, and increased levels of AFP compared with the SHARP trial.[73] Another hypothesis argues that the etiologic factors of HCC might affect prognosis and influence the responsiveness of HCC to sorafenib.[62] These landmark trials serve as the

basis for using sorafenib as the standard of care for patients with advanced HCC.

Most patients in the above-stated trials had Child-Pugh class A disease and had bilirubin levels equal to or less than 3 mg/dL given the potential for hepatotoxicity associated with sorafenib. Management of sorafenib in patients with cirrhosis and liver dysfunction requires special attention to bilirubin levels and dose adjustments according to published guidelines. Sorafenib has been combined with TACE in patients with unresectable HCC. A randomized phase II study evaluated DEB TACE in combination with sorafenib or placebo [Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEB-DOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial]. The primary end point, median TTP determined by independent reviewers, was identical in the 2 arms: 169 days with sorafenib versus 166 days with placebo. Although the study was formally positive, given the predefined exploratory α of 0.15 (HR for TTP, 0.797; 95% CI, 0.588–1.080; $P = 0.072$), there was no difference in OS (HR, 0.898; 95% CI, 0.606–1.33; $P = 0.295$).[75]

In the first line setting, several other investigational agents are being tested in clinical studies (supplementary Table 2, http://links.lww.com/SLA/A926). Disappointingly, all of the referenced antiangiogenic phase III trials in the above-mentioned table are negative studies. One last effort in using antiangiogenic therapy for HCC treatment is dependent on combining sorafenib plus doxorubicin. A randomized phase III study of sorafenib plus doxorubicin versus sorafenib (www.clinicaltrials.gov NCT01015833) was recently closed to new patient accrual, as it was found to be unlikely that difference in OS and progression-free survival will be shown between the treatment arms. One more phase III study evaluating levantinib versus sorafenib in the first line setting is underway (www.clinicaltrials.gov NCT01761266).

In the second line setting, that is, after sorafenib failure or intolerance, efforts have been multivaried with focus on approaches other than antiangiogenesis. The one with the most clinical trials underway is c-met inhibition, with 2 phase III trials evaluating cabozatinib (www.clinicaltrials.gov NCT01908426) and tivantinib (www.clinicaltrials.gov NCT01755767) in the second line setting versus placebo. Several other clinical trials in the second line setting include placebo versus ADI-PEG 20, a pegylated arginine deiminase, an arginine degrading enzyme, isolated from *Mycoplasma* and formulated with polyethylene glycol (www.clinicaltrials.gov NCT01287585), or placebo versus another multikinase inhibitor, regorafenib (www.clinicaltrials.gov NCT01774344).

SUMMARY

The management of HCC continues to evolve. Resection and transplantation remain the cornerstones of complementary curative intent treatment options. Significant advances have been made in the locoregional therapies of HCC, which have become the primary treatment modality for patients not suitable for resection or transplantation. Systemic chemotherapy and radiation therapy play supporting roles with newer drugs and modalities on the horizon. Despite these advances, HCC remains a major cause of cancer-related mortality. Further research is essential to better understand the biology of HCC and enable the development of targeted novel therapies that tackle this lethal cancer and improve patient care.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136:E359–E386.
2. AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/. Accessed April 24, 2014.
3. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9–29.
4. Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. *HPB (Oxford)*. 2005;7:35–41.
5. American College of Radiology. Liver Imaging Reporting and Data System version 2014. http://www.acr.org/Quality-Safety/Resources/LIRADS. Accessed August 2015
6. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53:1020–1022.
7. Yamamoto Y, Nishiyama Y, Kameyama R, et al. Detection of hepatocellular carcinoma using 11C-choline PET: comparison with 18F-FDG PET. *J Nucl Med*. 2008;49:1245–1248.
8. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology.* 2005;42:1208–1236.
9. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). *Hepatology.* 2007;45:797–805.
10. Ribero D, Chun YS, Vauthey JN. Standardized liver volumetry for portal vein embolization. *Semin Intervent Radiol*. 2008;25:104–109.
11. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol*. 2013;36:25–34.
12. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg*. 2008;247:49–57.
13. Shindoh J, CW DT, Vauthey JN. Portal vein embolization for hepatocellular carcinoma. *Liver Cancer.* 2012;1:159–167.
14. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg*. 2013;216:201–209.
15. Cucchetti A, Cescon M, Ercolani G, et al. A comprehensive meta-regression analysis on outcome of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. *Ann Surg Oncol*. 2012;19:3697–3705.
16. Ercolani G, Grazi GL, Ravaioli M, et al. The role of lymphadenectomy for liver tumors: further considerations on the appropriateness of treatment strategy. *Ann Surg*. 2004;239:202–209.
17. Grobmyer SR, Wang L, Gonen M, et al. Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. *Ann Surg*. 2006;244:260–264.
18. Tsoulfas G, Mekras A, Agorastou P, et al. Surgical treatment for large hepatocellular carcinoma: does size matter? *ANZ J Surg*. 2012;82:510–517.
19. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg*. 2015;261:619–629.
20. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg*. 2009;250:831–841.
21. Jarnagin W, Chapman WC, Curley S, et al. Surgical treatment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford)*. 2010;12:302–310.
22. Parks KR, Kuo YH, Davis JM, et al. Laparoscopic versus open liver resection: a meta-analysis of long-term outcome. *HPB (Oxford)*. 2013;16:109–118.
23. Ramacciato G, D'Angelo F, Baldini R, et al. Hepatocellular carcinomas and primary liver tumors as predictive factors for postoperative mortality after liver resection: a meta-analysis of more than 35,000 hepatic resections. *Am Surg*. 2012;78:456–467.
24. Nathan H, Segev DL, Mayo SC, et al. National trends in surgical procedures for hepatocellular carcinoma: 1998–2008. *Cancer.* 2012;118:1838–1844.
25. Paugam-Burtz C, Janny S, Delefosse D, et al. Prospective validation of the ''fifty-fifty'' criteria as an early and accurate predictor of death after liver resection in intensive care unit patients. *Ann Surg*. 2009;249:124–128.
26. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery.* 2011;149:713–724.
27. Dhir M, Reddy SK, Smith LM, et al. External validation of a pre-operative nomogram predicting peri-operative mortality risk after liver resections for malignancy. *HPB (Oxford)*. 2011;13:817–822.
28. Nathan H, Schulick RD, Choti MA, et al. Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg*. 2009;249:799–805.
29. 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;334:693–699.

30. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*. 2012;13:e11–22.
31. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl*. 2012;16:262–278.
32. Dhir M, Lyden ER, Smith LM, et al. Comparison of outcomes of transplantation and resection in patients with early hepatocellular carcinoma: a meta-analysis. *HPB (Oxford)*. 2012;14:635–645.
33. Rahman A, Assifi MM, Pedroso FE, et al. Is resection equivalent to transplantation for early cirrhotic patients with hepatocellular carcinoma? A meta-analysis. *J Gastrointest Surg*. 2012;16:1897–1909.
34. Proneth A, Zeman F, Schlitt HJ, et al. Is resection or transplantation the ideal treatment in patients with hepatocellular carcinoma in cirrhosis if both are possible? A systematic review and metaanalysis. *Ann Surg Oncol*. 2014;21:3096–3107.
35. Chapman WC, Klintmalm G, Hemming A, et al. Surgical treatment of hepatocellular carcinoma in north america: can hepatic resection still be justified? *J Am Coll Surg*. 2015;220:628–637.
36. Sogawa H, Shrager B, Jibara G, et al. Resection or transplant-listing for solitary hepatitis C-associated hepatocellular carcinoma: an intention-to-treat analysis. *HPB (Oxford)*. 2013;15:134–141.
37. Earl TM, Chapman WC. Transplantation for hepatocellular carcinoma: the North American experience. *Recent Results Cancer Res*. 2013;190:145–164.
38. Toso C, Trotter J, Wei A, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl*. 2008;14:1107–1115.
39. Gordon-Weeks AN, Snaith A, Petrinic T, et al. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. *Br J Surg*. 2011;98:1201–1208.
40. Hu Z, Wang W, Li Z, et al. Recipient outcomes of salvage liver transplantation versus primary liver transplantation: a systematic review and meta-analysis. *Liver Transpl*. 2012;18:1316–1323.
41. Belghiti J, Carr BI, Greig PD, et al. Treatment before liver transplantation for HCC. *Ann Surg Oncol*. 2008;15:993–1000.
42. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012;143:986–994. e3 quiz e14–15.
43. Kluger MD, Salceda JA, Laurent A, et al. Liver resection for hepatocellular carcinoma in 313 Western patients: tumor biology and underlying liver rather than tumor size drive prognosis. *J Hepatol*. 2015;62:1131–1140.
44. Lewin M, Gelu-Simeon M, Ostos M, et al. Imaging features and prognosis of hepatocellular carcinoma in patients with cirrhosis who are coinfected with human immunodeficiency virus and hepatitis C virus. *Radiology*. 2015;277:443–453.
45. Lencioni R, Crocetti L. Local-regional treatment of hepatocellular carcinoma. *Radiology*. 2012;262:43–58.
46. Lin SM, Lin CJ, Lin CC, et al. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or=4 cm. *Gastroenterology*. 2004;127:1714–1723.
47. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg*. 2005;242:158–171.
48. Orlando A, Leandro G, Olivo M, et al. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2009;104:514–524.
49. Li L, Zhang J, Liu X, et al. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. *J Gastroenterol Hepatol*. 2012;27:51–58.
50. Ding J, Jing X, Liu J, et al. Comparison of two different thermal techniques for the treatment of hepatocellular carcinoma. *Eur J Radiol*. 2013;82:1379–1384.
51. Bertot LC, Sato M, Tateishi R, et al. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol*. 2011;21:2584–2596.
52. Kingham TP, Karkar AM, D'Angelica MI, et al. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. *J Am Coll Surg*. 2012;215:379–387.
53. Hu KQ. Advances in clinical application of cryoablation therapy for hepatocellular carcinoma and metastatic liver tumor. *J Clin Gastroenterol*. 2014;48:830–836.
54. Meza-Junco J, Montano-Loza AJ, Liu DM, et al. Locoregional radiological treatment for hepatocellular carcinoma; which, when and how? *Cancer Treat Rev*. 2012;38:54–62.
55. Xie ZB, Ma L, Wang XB, et al. Transarterial embolization with or without chemotherapy for advanced hepatocellular carcinoma: a systematic review. *Tumour Biol*. 2014;35:8451–8459.
56. 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:W562–570.
57. 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;56:908–943.
58. Benson AB 3rd, D'Angelica MI, Abrams TA, et al. Hepatobiliary cancers, version 2.2014. *J Natl Compr Canc Netw*. 2014;12:1152–1182.
59. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. *J Hepatol*. 2012;56:1330–1335.
60. Abou-Alfa GK. TACE and sorafenib: a good marriage? *J Clin Oncol*. 2000;29:3949–3952.
61. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. *J Clin Oncol*. 2011;29:3960–3967.
62. Abou-Alfa GK, Venook AP. The antiangiogenic ceiling in hepatocellular carcinoma: does it exist and has it been reached? *Lancet Oncol*. 2013;14:e283–288.
63. Liu Z, Gao F, Yang G, et al. Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: an up-to-date meta-analysis. *Tumour Biol*. 2014;35:7407–7413.
64. Memon K, Lewandowski RJ, Kulik L, et al. Radioembolization for primary and metastatic liver cancer. *Semin Radiat Oncol*. 2011;21:294–302.
65. Lee EW, Thakor AS, Tafti BA, et al. Y90 selective internal radiation therapy. *Surg Oncol Clin N Am*. 2015;24:167–185.
66. Schwarz RE, Abou-Alfa GK, Geschwind JF, et al. Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. *HPB (Oxford)*. 2010;12:313–320.
67. Feng M, Ben-Josef E. Radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol*. 2011;21:271–277.
68. Lee IJ, Seong J. The optimal selection of radiotherapy treatment for hepatocellular carcinoma. *Gut Liver*. 2012;6:139–148.
69. Tanguturi SK, Wo JY, Zhu AX, et al. Radiation therapy for liver tumors: ready for inclusion in guidelines? *Oncologist*. 2014;19:868–879.
70. Yoon HI, Lee IJ, Han KH, et al. Improved oncologic outcomes with image-guided intensity-modulated radiation therapy using helical tomotherapy in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2014;140:1595–1605.
71. Skinner HD, Hong TS, Krishnan S. Charged-particle therapy for hepatocellular carcinoma. *Semin Radiat Oncol*. 2011;21:278–286.
72. Siegel AB, Olsen SK, Magun A, et al. Sorafenib: where do we go from here? *Hepatology*. 2010;52:360–369.
73. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25–34.
74. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378–390.
75. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial. *J Clin Oncol*. 2012;30(suppl 4). abstr LBA154.