Locoregional Therapies for Hepatocellular Carcinoma

What Has Changed in the Past Ten Years?

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KEYWORDS

• HCC • Liver cancer • Locoregional therapy • Systemic therapy • TACE • TARE • Y90

KEY POINTS

- The evolution of locoregional therapies in the last decade has allowed for broader patient selection, individualized therapy with a refined, targeted approach, and less systemic toxicity and improved patient outcomes.
- With the rapidly changing landscape of systemic therapy, the role of locoregional therapies alone or in combination for downstaging and curative intent will continue to evolve as we await this coming decade.
- The timely transition from locoregioanl therapy to systemic therapy will need to be defined.

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the fastest growing cancers and is the fourth most common cause of cancer-related mortality worldwide.[1] In the last decade, treatment strategies and approaches for HCC have evolved dramatically, especially within the realm of locoregional therapies (LRT). These treatments have been shown to improve progression-free survival (PFS), disease-free survival, and overall survival (OS) in patients with HCC. LRTs can be used with curative intention, for downstaging or bridging to liver transplantation (LT) and as palliative therapy in inoperable, advanced HCCs. This review focuses on current trends in locoregional therapy as well as identifies the optimal time period to transition to systemic therapy (**Fig. 1**).[2]

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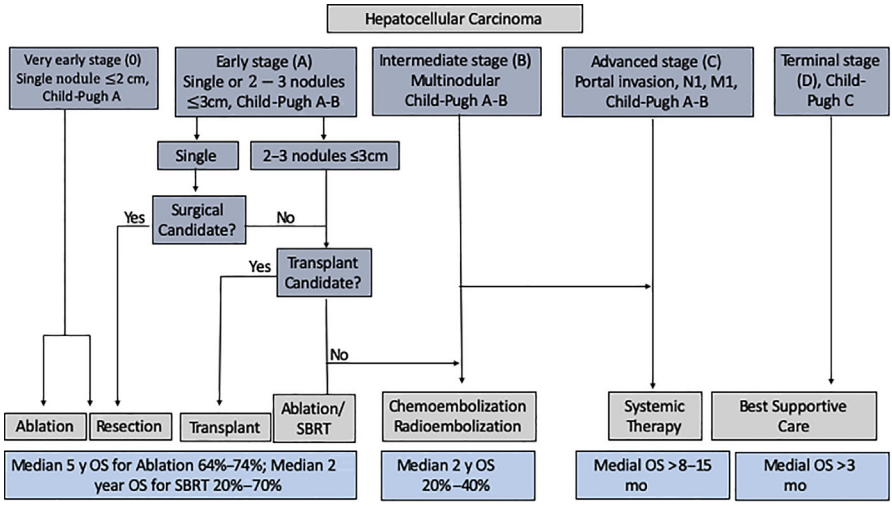

Fig. 1. Treatment algorithm and OS based on BCLC classification. (*Adapted from* Llovett J et al. Trial Design and Endpoints in HCC: AASLD consensus conference, Hepatology, 2020; with permission.)

Ablative Therapies

Image-guided tumor ablative therapies are a well-established form of local cancer treatment, with options evolving rapidly. Percutaneous ablative therapies focus on image-guided destruction of tumor tissue through direct application of either chemical- or energy-based treatment, with the benefit of offering curative intent for some patients. These treatments are typically indicated for patients with small HCCs, up to 3 lesions each $\leq$3 cm, Child-Pugh (CP) class A or B.[3]

Percutaneous ethanol injection

Ethanol-based ablative techniques were first described in the 1980s and previously served as the primary form of ablation. Complete tumor necrosis can be achieved in 90% of HCC nodules less than 2 cm[4]; however, for tumors greater than 2 cm, recurrence rates approached nearly 50%, likely because of incomplete necrosis achieved in larger tumors.[5] Although the technique offers low morbidity and mortality, ethanol ablation is typically no longer used as first-line treatment because of multiple randomized controlled trials (RCTs) and meta-analyses showing superiority with radiofrequency ablation (RFA) in terms of treatment response, local tumor cure rate, and OS.[3,6–12]

Radiofrequency ablation

RFA was first introduced in the treatment of HCC in the early 1990s and is the most commonly used ablative technique. This particular method uses high-frequency alternating current, converting radiofrequency energy into heat, thereby inducing damage to the tumor tissue. For early-stage HCC, RFA can be used as first-line therapy. In a recent study, RFA offered favorable long-term outcomes for patients with a single HCC lesion less than 3 cm when used as first-line therapy.[12] In this study, patients were followed for 10 years after treatment with an OS of 74.2% with prognostic factors for OS, including local tumor progression (LTP), CP class, platelet levels, intrahepatic distant recurrence, aggressive intrasegmental recurrence, and extrahepatic metastatic disease. In another study by Salmi and colleagues,[13] 5-year OS for HCC lesions

less than 3.5 cm approached 64%, with a local recurrence rate of 14%. Ablative margin by RFA affects development of LTP, although data are lacking regarding the ideal size of the tumor margin. Currently, a 0.5- to 1.0-cm margin is recommended.[14]

Given the successes of RFA, head-to-head prospective RCTs have been conducted between RFA and surgical resection of localized HCC. In a study by Cucchetti and colleagues,[15] local resection of tumors was found to provide better survival outcomes in comparison to RFA for single nodules 3 to 4 cm in size; however, the treatment modalities were comparable in patients with tumors less than 2 cm and in patients with 2 to 3 small tumors $\leq$3 cm. Similar results were found by Fang and colleagues[16] for tumors less than 3 cm. This difference may be due to the limited ability of RFA to attain adequate tissue necrosis in larger tumors. When analyzed for cost efficacy, RFA was found to be superior for early-stage HCC and for multiple small HCCs. Given the notable survival benefit for single tumors 3 to 5 cm, surgery remained the more cost-effective option for these patients. In contrast, in a single-center RCT by Ng and colleagues[17] in 2017 comparing hepatic resection to RFA in patients with early-stage HCC, regardless of tumor size, RFA was not found to be superior to hepatectomy with regard to tumor recurrence rate and 10-year OS. RFA did allow for shorter treatment duration, less procedural blood loss, and decreased length of hospital stay. In a more recent study by Lee and colleagues,[18] local recurrence rate was higher in RFA (53% vs 26%), but OS was not significantly different between RFA and resection (86% vs 83%).

A limitation of RFA is the risk involved when lesions are too close in proximity to the liver capsule or critical structures, such as vasculature, because of what is referred to as the "heat-sink effect." Studies have shown that in these lesions, perivascular cells are not ablated effectively, increasing risk of local recurrence.[19] In addition, as previously mentioned, complete necrosis of lesions is less successful in larger lesions, increasing risk of local tumor recurrence.

In patients with very early-stage HCC, both RFA and resection are viable options. In patients who can undergo resection, this allows for pathologic examination of the tumor and subsequent risk stratification if the patient needs eventual LT.

Microwave ablation

Microwave ablation (MWA), first described in the 1970s, causes tumor destruction through hyperthermic injury via electromagnetic waves. Although prospective, randomized clinical data are limited regarding this technique, it offers certain advantages over RFA, such as shorter procedure time and less susceptibility to incomplete ablation. MWA is also less susceptible to the heat sink effect and is thus less limited by critical structures near the treatment field. Furthermore, the ability to use multiple probes during a single treatment allows for a larger treatment field, allowing for more effective treatment of larger lesions.[20] In a recent metaanalysis, similar efficacy was demonstrated by both RFA and MWA, and 1 study suggested potential superiority of MWA in larger HCCs.[21,22]

Survival probability for MWA has been shown to be greatest for lesions less than 4 cm.[23] Combination therapies for larger lesions, such as transarterial chemoembolization (TACE) followed by MWA, have shown favorable outcomes and are often used for lesions not amenable to treatment with a single modality alone.[24,25]

Cryoablation

The use of cryoablation, largely developed in the 1980s, involves the use of very low temperatures to kill tumor cells by producing intracellular and extracellular ice crystals, resulting in cell dehydration and rupture. In addition, this also induces

ischemic hypoxia to the tumor owing to vascular injury. This procedure is done with intraprocedural image-based monitoring, allowing for more control over the ablation field.[3] Long-term survival analysis data are limited for cryoablation, and most ablative treatments have transitioned to the newer modalities. It is, however, still sporadically used in conjunction with other locoregional therapies. An RCT involving 360 patients comparing RFA versus cryoablation in 1 to 2 HCC lesions $\leq$4 cm, cryoablation resulted in lower local tumor progression, although both treatment modalities had similar 5-year survival rates and were found to be equally effective.[26]

Irreversible electroporation

Irreversible electroporation (IRE) is a newer, nonthermal technique involving delivery of short electrical pulses into a given tumor, leading to cell death owing to apoptosis by producing irreversible pores in cellular membranes.[27,28] This technique offers the benefit of preserving connective tissue, vessels, and bile ducts, making it an option for treatment of those lesions in a position that makes surgery and thermal techniques high risk, such as central liver lesions.[29] These benefits were shown in a small study by Cheng and colleagues[30] when looking at posttransplant treatment fields. Bile ducts were preserved, and treatment fields showed complete pathologic necrosis. Interestingly, however, in another study looking at ablation zones, IRE was found to have the largest transition zone between living and necrotic tissue, potentially heightening risk of local recurrence.[31] IRE does require general anesthesia, multiple electrode insertions, and muscle blocks, introducing a risk that the aforementioned treatments do not.[3] In addition, the insertion channels cannot be cauterized, potentially increasing risk of bleeding complications.[28] In a German study, a retrospective analysis showed no difference in complication grade nor rates between thermal techniques and IRE.[28] This therapy is currently recommended for very early-stage HCC, although further, large-scale studies are needed to determine its efficacy and safety in comparison to the more commonly used thermal techniques.

Stereotactic body radiotherapy

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, presents an additional option for select patients with localized, unresectable HCC, used either individually or in conjunction with other treatment methods. Unlike traditional radiation therapy that involves multiple sessions of small-dose, daily radiation treatments, SBRT entails anywhere from 1 to 5 treatments at a higher biologically effective dose.[32] SBRT offers high rates of local tumor control, low toxicity, and PFS comparable to resection and RFA. In a study by Wahl and colleagues,[33] SBRT and RFA had similar success rates for tumors less than 2 cm; however, for those tumors greater than 2 cm, SBRT had improved control. Although there are no RCTs to date comparing SBRT to other accepted treatment modalities, SBRT shows promise in the management of HCC. Another arena where radiation has been examined is with the intent to bridge to transplant. The use if SBRT for bridging to transplant can be seen in centers were transarterial radioembolization (TARE) is not readily available. A single-center study from Toronto showed similar dropout rates and OS from listing/LT with external beam radiation compared with RFA or TACE,[34] suggesting that radiotherapy may offer an alternative therapy when TACE or RFA is not deemed feasible. Please refer to Chien Pong Chen's article, "Role of External Beam Radiotherapy in Hepatocellular Carcinoma," in this issue for a detailed discussion of the role for this therapy.

Catheter-Based Therapies

Both chemoembolization and radioembolization play a large role in the treatment paradigm of HCC. These 2 therapies have been refined over the last decade with broader applications and improved patient survival.

Chemoembolization

Because HCCs are uniquely supplied by the hepatic artery,[35,36] transarterial treatments have proven to be extremely effective in delivering targeted embolic therapy to the tumor while preserving and minimizing exposure to surrounding liver parenchyma, particularly when performed in a superselective manner. There are 3 types of embolization that are commonly used as intraarterial therapy for HCC: bland embolization, conventional transarterial chemoembolization (cTACE), and drug-eluting bead chemoembolization (DEB-TACE).[37]

Bland embolization or transcatheter arterial embolization (TAE) was the first generation of embolic agents used, first described in the late 1970s, and were divided into spherical and nonspherical subgroups with the goal of terminal vessel blockade.[37,38] Since its inception in the treatment of HCC, there have been conflicting data regarding its applicability compared with TACE, including results in RCTs.[39,40]

The most successful single-center data come from the Memorial Sloan Kettering group. In a retrospective analysis of 322 patients with advanced HCC treated with TAE, median OS was 21 months with a 1-year survival of 66%.[41] In patients without extrahepatic disease or vascular invasion, the OS at 1 and 3 years was 84% and 51%, respectively. A recent metaanalysis of 55 randomized controlled studies did not show any significant survival benefit with cTACE, DEB-TACE, or TARE when compared with TAE.[42]

cTACE was first performed in the 1980s as a method for targeted intraarterial delivery of chemotherapy to the tumor followed by an embolic agent.[43,44] There has been significant heterogeneity with TACE, including the chemotherapeutic agents used (cisplatin, doxorubicin, or mitomycin C either alone or in combination along with iodinated contrast and ethiodized oil),[45] as well as the embolic agent used (gelfoam, polyvinyl alcohol, or spherical embolic agents) to prevent drug washout and to increase intratumoral retention of the agents to induce cytotoxic cell death and ischemic necrosis. TACE evolved into the standard of care in patients with intermediate HCC as the result of 2 RCTs from Europe and Asia that met their primary endpoint of OS.[46,47] A systemic review of 101 studies of cTACE in 10,108 patients confirmed an objective response rate (ORR) of 52.5%, median OS of 19.4 months with 1-, 3-, and 5-year survival of 70.3%, 40.4%, and 32.4%.[48] The most common adverse event was postembolic syndrome, which was seen in almost 50% of patients, although procedure-related mortality remained low at 0.6%.

DEB-TACE or intraarterial injection of drug-eluting microspheres loaded with a chemotherapeutic agent (ie, doxorubicin) was developed in 2005.[49] DEB has allowed for predictable and sustained targeted drug delivery while minimizing plasma concentrations of chemotherapy, resulting in higher tumor retention of doxorubicin with minimal systemic absorption. In 2010, Lammer and colleagues[50] completed the first prospective, randomized controlled, multicenter study evaluating DEB-TACE versus cTACE in the treatment of advanced HCC, called the "PRECISION V study. In this study, 212 CP A/B patients were randomized to receive doxorubicin-eluting (DC) beads versus cTACE. Results were not statistically significant for primary aim of tumor response at 6 months with DC beads. Data showed complete response (CR) of 27% versus 22% and ORR of 52% versus 44% in the DC arm versus cTACE arm, respectively. However, there was a higher ORR in

patients with CP B disease and bilobar/recurrent disease with DC beads. Safety profiles of both treatment arms were similar (20.4% vs 19.4%), but there was significant less serious liver toxicity in the DC arm (16%) versus cTACE (25%). These results were validated in numerous subsequent studies[51–53] and various metaanalyses with similar tumor response rates.[54–59]

Several studies have been conducted comparing cTACE or DEB-TACE with TAE. Of the 5 RCTs, three showed similar OS between modalities,[47,60,61] one showed no difference in PFS or OS between the 2 treatments arms,[62] and one showed patients receiving DEB-TACE had longer time to progression (TTP) compared with TAE.[63] Combining LRT has also been studied with variable success. In a metaanalysis of 8 RCTs of 648 patients treated with combination of TACE + RFA RFA alone, combination therapy had a significant recurrence-free survival and OS especially in patients with intermediate and large (>3 cm) HCCs[64]; there was no benefit of combination therapy in patients with small tumors. Ginsburg and colleagues[65] performed a retrospective study examining the benefit of DEB-TACE + RFA or MWA in 89 patients with small HCCs and noted a 78% initial CR, median PFS of 9 months, and median OS of 39 months. There was no significant difference between the 2 modalities in efficacy or safety; there was a 3% adverse event rate, mainly related to prolonged hospitalization. Overall, these studies suggest that there may be a role of combination therapies in select patients.

Transarterial chemoembolization + sorafenib

Since the approval of Sorafenib for unresectable HCC, there have been several phase 3 RCTs that have aimed to demonstrate an improved OS and TTP with combination of TACE/DEB with tyrosine kinase inhibitors (TKIs) by blunting of the angiogenic flare after embolization compared with TACE alone. Several of these trials were negative; however, it did demonstrate that in highly selected candidates that the median OS for TACE is approximately 26 months.[66] Trial design may in part have led to negative results, including the timing of TKI relative to TACE/DEB, dosage and duration of TKI, and early termination of trials. Of note in the SPACE trial, those randomized to DEB + Sorafenib received only 1 DEB therapy because of conservative stopping rules of which several patients had subsequent additional DEB therapy once off the trial. A more recent phase 2 trial from Japan, Transcatheter Arterial Chemoembolization Therapy in Combination With Sorafenib, reported a significantly improved PFS in those receiving TACE + Sorafenib compared with TACE alone: 25.2 versus 13.5 months, respectively (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.41–0.87; $P = .006$).[67] The approach in this trial was unique in that the presence of new intrahepatic lesions did not lead to cessation of assigned therapy, leading to longer time on Sorafenib (median 38.7 weeks) relative to prior negative phase 3 trials (median range 17.0–24.0 weeks). Results of the coprimary endpoint of OS are awaited.

Transarterial chemoembolization + radiation therapy

A metaanalysis of 25 trials from Asia showed the pooled OS was significantly higher with TACE + radiation therapy compared with TACE alone (22.7 vs TACE 13.5 months; $P<.001$); however, there were higher adverse events because of gastric/duodenal ulceration and an increase in transaminases with the combination therapy.[68]

Transarterial radioembolization

Selective internal radiation therapy or TARE is a form of brachytherapy that allows intraarterial delivery of radioactive microspheres (loaded with Yttrium 90 or Y90) to the tumor bed.[69] TARE allows for higher targeted dose of radiation therapy internally to the tumor when compared with external beam radiation and SBRT. Although TACE

can cause occlusion of medium- and large-size arteries because of the size of particles used, Y90 microspheres are much smaller and target therapy within the capillary bed of the tumor delivering tumoricidal doses of radiation while sparing the surrounding liver tissue.[70] Two commercially available microspheres, glass/ceramic-based or resin-coated polystyrene, serve as delivery platforms and differ in particle size, activity, density, and composition.[71] TARE has traditionally been used in patients with intermediate or advanced disease, including those with bilobar disease or large tumors who are poor candidates for TACE, as well as those with tumors invading branch of the portal vein where TACE is contraindicated or those who progress on TACE. More recently, with a superselective approach, radiation segmentectomy has been used as potential curative therapy for smaller lesions.

Early prospective studies of TARE were mostly single-center reports (**Table 1**).[72–75] The most favorable results have been reported by the Milan group, which mostly comprised CP A patients, highlighting the competing risk of mortality related to tumor and liver failure.

Side effects include fatigue, abdominal discomfort, and nausea and vomiting. Expertise and proper angiography are imperative to avoid off-target delivery of radiation that can lead to complications.

Several studies have been performed comparing efficacy of TACE versus TARE.[76–79] In a single-center retrospective analysis of 245 patients treated with transarterial locoregional therapy (122 with TACE and 123 with TARE), TTP was significantly

Table 1
Summary of patient characteristics and outcomes with transarterial radioembolization for the treatment of hepatocellular carcinoma

	Salem et al,[72] 2010 (n = 291) Single-Center Glass	Hilgard et al,[73] 2010 (n = 108) Single-Center Glass	Sangro et al,[74] 2010 (n = 325) Multicenter Resin	Mazzaferro et al,[75] 2012 (n = 52) Single-Center Glass
Patient characteristics				
CP A/B/C (%)	45/52/3	77/22 (≤7)/0	82/18/0	83/17 (≤7)/0
BCLC A/B/C/D (%)	17/28/52/3	2/47/51/0	16/27/56/1	0/33/67/0
Mean tumor size (cm)	7.0	—	—	5.6
Multifocal (%)	73	—	76	69
PVT (%)	43	31	23	67
Extrahepatic mets (%)	16	30	9	—
Outcome (excluded mets)				
Overall survival (mo)	CP A: 17.2 CP B: 7.7 BCLC A: 26.9 BCLC B: 17.2 BCLC C: 7.3	CP A: 17.2 CP B: 6.0 BCLC A: — BCLC B: 16.4 BCLC C: not reached	CP A: — CP B: — BCLC A: 24.4 BCLC B: 16.9 BCLC C: 10.0	CP A: — CP B: — BCLC A: — BCLC B: 18 BCLC C: 13
TTP (mo)	7.9 CP A: 10.8 CP B: 8.4	10.0	—	11

Abbreviations: mets, metastasis.

longer with TARE than TACE (13.3 vs 8.4 months) with no difference in OS between the 2 groups.[79] Early pilot RCTs comparing TACE and TARE found no significant difference in outcomes; however, TARE was given once and TACE was performed every 6 weeks until there was CR.[80] In 2016, PREMIERE, the largest RCT to date, randomized CP A/B patients with Barcelona Clinic Liver Cancer (BCLC) A/B HCC to cTACE versus Y90 and demonstrated significant longer median TTP (>26 months) with TARE than cTACE (6.8 months). Median OS and response to therapy were similar between both groups.[81] Lewandowski and colleagues[82] retrospectively compared the efficacy of TACE versus TARE for United Network for Organ Sharing (UNOS) downstaging criteria from T3 to T2 for potential LT. In this study, 43 patients in each arm received TACE or TARE, and median tumor size was similar in both arms (5.7 cm in TACE vs 5.6 cm in TARE). Downstaging to UNOS T2 occurred in 31% of patients with TACE and 58% of patients with TARE, whereas TTP was similar between both groups. OS survival was not significant between the 2 arms, although patients in the TARE arm had greater event-free survival. In most clinical scenarios, the safety and efficacy of TACE and TARE are equivalent, and use of one in favor of the other often depends on institutional bias and availability.

Another promising outcome of radioembolization therapy is the concept of radiation lobectomy and the unintentional volumetric hypertrophy that occurs on the contralateral side of the treated tumor secondary to radiation changes. Vouche and colleagues[83] demonstrated in a group of 83 patients with right unilobar malignancies (HCC, cholangiocarcinoma, and colorectal cancer) that Y90 radiation lobectomy was safe and effective to hypertrophy future liver remnant (FLR) with volumetric changes comparable to portal vein embolization (PVE). This finding was confirmed by Garlipp and colleagues[84] in 2 centers in Germany where patients with right-sided malignancies with limited or no left-sided tumor involvement were treated by right lobar PVE (n = 141) or TARE (n = 35). The investigators concluded that radioembolization resulted in substantial contralateral hypertrophy, albeit less than PVE with therapeutic (nonlobectomy) doses. The ability to synchronously treat the tumor while allowing for hypertrophy of FLR makes TARE an effective method of treatment as a bridge to resection.

In more recent years, segmental radioembolization has also increased in popularity. Radiation segmentectomy was defined as radioembolization of 2 or fewer hepatic segments with high-dose radiation.[85] In a study of 84 patients with advanced, inoperable HCC, radiation segmentectomy proved to be safe and efficacious with a significant response in size and necrosis (in 59% and 81% of patients, respectively).[85] Mean TTP was 13.6 months, and median OS was 26.9 months.

Studies comparing segmental radioembolization versus segmental chemoembolization showed the former to be a promising method of therapy for local tumor control with no significant increase in toxicity profile.[86] Padia and colleagues,[86] in a single-center retrospective study, examined 101 patients who underwent radiation segmentectomy with 77 patients who underwent segmental DEB-TACE or cTACE. In this cohort, patients receiving chemoembolization had worse performance status and CP class, whereas those receiving radioembolization had larger, infiltrative tumors with more vascular invasion. They reported index and overall CR of 92% and 84% for Y90 versus 74% and 58% for TACE, which was statistically significant. Index tumor progression at 1 and 2 years was 8% and 15% in the Y90 arm and 30% and 42% in the TACE arm. Median PFS and OS were also statistically significant, favoring radiation segmentectomy. Biederman and colleagues[87] examined radiation segmentectomy versus TACE in a single-center retrospective study of 112 patients with unresectable, solitary HCC $\leq$3 cm without evidence of metastasis or vascular invasion. In this study,

55 patients underwent Y90 segmentectomy compared with 57 patients who underwent segmental TACE. Y90 segmentectomy showed superior imaging response and longer time to secondary therapy when compared with segmental TACE. In a single-center retrospective study of 70 patients with unresectable, solitary HCC $\leq$5 cm, not amenable to percutaneous ablation or resection, the effectiveness of radiation segmentectomy (dose of >190 Gy) was assessed for curative intent.[88] Median TTP was 2.4 years, and OS was 6.7 years. In patients with tumors $\leq$3 cm (n = 45), OS was significantly longer than in patients with tumors greater than 3 cm with 1-, 3- and 5-year survival of 100%, 82%, and 75%, respectively. These studies confirm that radiation segmentectomy could be a viable curative option for early-stage HCC and similar in effectiveness to percutaneous ablation or resection.

Last, TARE has been shown to be safe and effective in portal vein thrombus (PVT). It has become clear that patient selection is paramount to obtaining clinically meaningful results and to avoid hepatic decompensation. Spreafico and colleagues[89] have developed a prognostic scoring system for patients with PVT intended for therapy with TACE. This prognostic scoring system consists of 3 identified factors that were independent predictors of OS. Points are given based on these 3 factors that included the degree of PVT extension V1 to V3 (mainly PVT, V4 was excluded), bilirubin level, and tumor burden. This scoring system can be used to identify the most ideal candidates with therapy with TARE who achieved median OS 32 months and those in which TARE should not be offered because of futility. Another technical aspect regarding TARE, which impacts OS, is boosted radiation dose into the tumor. Improvement in OS and response rates, particularly in those with PVT, has been demonstrated when greater than 205 Gy is delivered to the tumor.[90,91] This personalized approach is feasible with glass microspheres. The macroaggregated albumin (MAA) before Y90 administration is used to determine the distribution of the glass microspheres and quantify delivery of radiation to the tumor that can be boosted to achieve a dose greater than 205 Gy. It is important to recognize that not all patients will be candidates for boosted radiation because of risk of toxicity; this includes cases whereby greater than 120 Gy is estimated to be delivered to nontumorous tissue or when tumor volume exceeds 70% of the total liver volume. A phase 2 RCT, conducted at 4 centers in France, showed that the use of personalized dosimetry with a target of at least 205 Gy into the tumor led to a significant increase in OS (26.7 months) compared with standard dosimetry (10.7 months).[92]

As TARE becomes more widely accepted within the treatment paradigm of HCC, studies evaluating cost and convenience are also important. Currently, TARE requires a 2-step outpatient procedure; the first procedure is a diagnostic angiogram with an MAA scan to assess degree of lung shunting and potential for off-target delivery of radiation, which may require coil embolization to prevent. The patient returns on a separate day at which time the microspheres loaded with Y90 are delivered. The feasibility of same-day Y90 was reported by a single center in 78 patients using glass microspheres (77% with HCC).[92] More recently, the same institution reported that the lung shunt in T1/T2 lesions among 448 patients (excluding patients with transjugular intrahepatic portosystemic shunt) was negligible, and therefore, the lung shunt study could be eliminated. This finding supports the notion of streamlining patients to therapy with same-day Y90 and lowering cost.[93] Another single-center study evaluated the concept of same-day mapping and treatment with Y90 in a retrospective analysis of 26 patients with either HCC or liver metastases using resin microspheres.[93] Further studies will need to be conducted to evaluate the safety, efficacy, and reproducibility of this concept.

When Do You Transition from Locoregional Therapies to Systemic Therapy?

In the advent of impressive advances in systemic therapy, specifically combination therapies, it is imperative to be mindful of when LRT should cease and systemic therapies commence. This situation is however different than foregoing LRT at the initial presentation of HCC. These 2 scenarios will be addressed separately.

The approval of Sorafenib based on the results of the SHARP study in 2007 began the era of systemic therapy in HCC. Several agents tested in first-line trials failed to show noninferiority or superiority to Sorafenib over a 10-year period. However, in the last few years there have been several agents approved in both the first and the second line as a result of positive phase 3 RCTs demonstrating improved OS. The most recent positive trial was the IMbrave150 study, which showed a significant improvement in the coprimary endpoints of OS and PFS in patients treated with atezolizumab 1200 mg intravenously plus bevacizumab 15 mg/kg compared with Sorafenib 400 mg twice a day. No new safety signals were identified with this combination compared with monotherapy with each individual agent.

Phase 3 RCTs examining the safety and efficacy of systemic agents in unresectable HCC have been conducted in a population with preserved liver function, CP A, and largely comprise patients with BCLC C disease. However, there was a subset of patients with intermediate HCC, most deemed refractory to TACE. The 16% to 21% of BCLC B patients in first-line systemic trials showed a survival benefit with these agents.

Without a potential curative therapy, the natural history of progression from intermediate to advanced disease is generally accepted to be inevitable. The increase in the availability of effective systemic options has led to a debate of the most appropriate timing to initiate in lieu of continued LRT in order to maximize exposure to and improved OS with sequential systemic therapies.[94] TACE is the most commonly used form of LRT in intermediate HCC. Overuse of TACE/Y90 can culminate in hepatic decompensation leading to a lost opportunity of meaningful benefit of tumor control with systemic agents owing to the competing risk of mortality from worsening liver disease. In addition, tumor progression with development of PVT, particularly main PVT or infiltrative tumor, can lead to rapid decline in hepatic function, making initiation of a systemic agent a safety, tolerability, and efficacy concern because of limited data in this patient population. Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with SorafeNib (GIDEON), a prospective observation study that collected data on the real-life experience with Sorafenib, found a significant decline in median OS per decrement in CP class (CP A: 13.6, CP B: 5.2, CP C: 2.6 months) despite no observed difference in TTP based on CP class.[95] Small studies have reported safety of Nivolumab in CP B with a median OS of 5.9 and 7.6 months in 2 separate cohorts.[96,97]

Although TACE is the recommended therapy for BCLC B patients, this group constitutes one that is quite heterogeneous, and not all in aggregate are suitable for TACE. Systemic therapy should ideally be started at time of TACE refractoriness or in BCLC B patients in whom TACE is unlikely to benefit, while liver function remains preserved. The Japan Society of Hepatology has defined TACE refractoriness as the inability to control a treated lesion or lesions (>50% viable lesion) and/or development of new tumors after $\geq$2 consecutive sessions of chemoembolization, continuous elevation in tumor markers, or appearance of extrahepatic spread or vascular invasion.[98] OPTIMIS was a global observational prospective trial that aimed to characterize TACE utilization and outcomes in a real-world setting of patients with BCLC stage B HCC or higher.[99] A total of 1650 patients were treated

with TACE of whom 32% were BCLC C, 7% had extrahepatic spread, and 7% had portal vein invasion. Response rates declined with each subsequent TACE, whereas progressive disease increased. At inclusion, 39% met TACE ineligibility criteria, and during the course of the study, 31% became TACE ineligible with less than 10% receiving Sorafenib at that time. Improved OS has been demonstrated in patients who were started on Sorafenib at the time of TACE refractoriness compared with those who continued to receive TACE.[100,101] This real-world study highlights the crucial need for defining consensus on when LRT no longer provides benefit and allows a timely transition to systemic therapy.

However, despite an accepted consensus on transitioning to systemic therapy once TACE refractoriness develops, approximately one-quarter of patients have already declined to CP B/C, thereby jeopardizing initiation and potential benefit of systemic agents.[99,101,102] The GIDEON trial found that the proportion of patients who were CP B at the time of starting Sorafenib was higher in those who received $\geq$6 TACE sessions.[103]

A nationwide database in Japan used α-fetoprotein (AFP), AFP-L3, and Des-gamma-carboxy prothrombin (DCP) levels before TACE in 1306 treatment-naïve patients with intermediate-stage HCC and preserved liver function.[104] A point was given for each marker if $\geq$100 ng/mL (AFP), greater than 10% (AFP-L3), and greater than 100 mAU/mL (DCP) to determine a tumor marker score. As the score increased, median OS diminished: 0, 1, $\geq$2 = 4.8, 3.8, 3.2 years, respectively; P<.01. A score $\geq$2 was an independent predictor of mortality; as such, the investigators concluded the tumor marker score could be used to prognosticate which patients with intermediate HCC will have a suboptimal response to TACE and predict TACE refractoriness.

A newer proposed term, TACE unsuitability, encompasses circumstances that predispose to one of the 3 scenarios associated with TACE: becoming TACE refractory, decline to CP B, or unlikely chance of tumor response.[105] Tumor burden beyond up-to-7 criteria is a predictor of TACE refractoriness as well as TACE leading to decline in liver function.[100] Initiation of TACE in those with albumin-bilirubin grade 2 is another group at high risk for reduction in hepatic reserve after TACE.[106] There are several identified situations that predict to TACE resistance, such as massive tumors, poorly differentiated HCC, multifocal intrahepatic metastasis, and sarcomatous changes induced by TACE. Such morphologic changes in HCC can occur when residual viable tumor is influenced by the hypoxia-induced angiogenic surge associated with TACE.[107]

A study of CP A patients beyond up-to-7 criteria reported improved OS in a propensity-matched TACE-naïve cohort treated with Lenvatinib (LEN) followed by on demand selective TACE (70%) compared with patients who received TACE (37.9 vs 21 months, respectively; HR 0.48; 95% CI 0.16–0.79).[105] The improved OS in the LEN-TACE group was ascribed to preservation of liver function allowing a longer treatment period with full-dose LEN and high tumor response rates associated with LEN. LEN has been reported to demonstrate high response rates in poorly differentiated HCC, a subgroup that historically had the worse prognosis. LEN-TACE sequential therapy in patients with TACE unsuitability is a shift in the paradigm of HCC therapy, and although reports of its efficacy are promising, additional studies are required to validate this approach as a standard of care. Another study from Japan reported real-life experience with LEN.[108] A total of 116 patients with BCLC B tumor, the vast majority CP A, were treated with systemic therapy as first-line therapy with 61% treated with LEN as initial therapy and the remainder treated with LEN as second- or third-line systemic therapy. Median OS was not reached, whereas median PFS was 14 months.

Earlier use of systemic therapy in patients with intermediate HCC guided by prognostic models with data supporting improved OS may lead to a paradigm shift in treatment in a subset of the BCLC B group. Consideration for an earlier initiation of systemic therapy needs to be balanced against the use of LRT for the intended purpose of downstaging to Milan criteria (MC). Some patients may not meet acceptable criteria for LRT because of the presence of ascites, performance status, or CP B; however, successful downstaging could allow access to transplantation, which offers the best chance for long-term OS in HCC. In addition, the ceiling of tumor burden for the accepted downstaging protocol adopted by UNOS includes tumor burden (1 lesion >5 cm and ≤8 cm, 2 or 3 lesions each less than 5 cm and total diameter of all lesions ≤8 cm, or 4 or 5 lesions each less than 3 cm and total diameter of all lesions ≤8 cm) that exceeds the up-to-7 criteria. Although guidelines have advocated for restriction in eligibility criteria for candidates for downstaging based on initial tumor burden in order to optimize chance of successful downstaging to MC, other single-center studies reported a 30% success rate in downstaging to the MC followed by LT with no limit on initial tumor size and number, including the presence of non–main PVT.[109] OS and recurrence rates were similar to those downstaged and those who met MC. The investigators concluded that patients exceeding the MC who are otherwise candidates for LT should undergo aggressive attempts at downstaging without an a priori exclusion. During the time period that this study was conducted, Sorafenib was the only systemic therapy approved for advanced HCC.

Combination therapy with TACE + radiation therapy has been compared with Sorafenib in an RCT in patients with CP A HCC with PVT (58.9% had unilateral disease) without metastatic disease.[110] TACE occurred every 6 weeks, and radiotherapy (RT; planned total dose of 45 Gy) was started after the first TACE. The combination group demonstrated a significantly longer 12-week PFS compared with Sorafenib 86.7% versus 34.3% retrospectively (P<.001). Independent of macroscopic vascular invasion extent, 24-week PFS remained significantly higher in the TACE-RT group. In addition, median TTP and OS were superior in the combination group (TTP: 31.0 vs 11.7 weeks; OS: 55 vs 43 weeks, respectively). Crossover owing to tumor progression was higher at 24 weeks in the Sorafenib group, 90.7%, compared with 23% in TACE/RT group. Of note, this study was conducted in a primarily hepatitis B virus population and therefore its applicability to other populations is not known.

With a decrease in priority for LT in HCC, it is expected that the use of living donor liver transplantation (LDLT) will continue to expand in HCC. A multicenter trial of LDLT in HCC exceeding the MC reported that the only independent predictor of OS was meeting the MC at time of LT.[111] The response to LRT to downstage both tumor burden and AFP levels has been shown to portend favorable long-term results and highlights that LRT can be used to gain insight into the biological aggressiveness of a tumor and serve as an important selection tool. Therefore, desertion of LRT in an otherwise appropriate LT candidate other than tumor burden and AFP could result in a potential lost chance for LT. Additional research is required to know if use of systemic therapy, specifically LEN with higher response rates, can lead to successful downstaging alone or in combination with LRT resulting in LT. Of note, an RCT of TACE + Sorafenib versus TACE in patients awaiting LT reported no significant difference in the primary endpoint of TTP; however, all patients within this trial met MC.[112]

Locoregional therapies + immune oncology

Immunotherapy is being studied in combination with LRT. The hope is to augment the immune response by causing release of neoantigens induced by LRT-associated

tumor necrosis and hence improve OS. The first proof-of-concept study used TACE or RFA in 32 patients (BCLC B/C with progressive disease at enrollment, 75% Sorafenib experienced) followed by tremelimumab, an anti-CLLA-4 antibody, resulting in a partial response in 26%, TTP of 7.4 months, and OS of 12.3 months.[113]

SUMMARY

The evolution of LRT in the last decade has allowed for broader patient selection, individualized therapy with a refined, targeted approach and less systemic toxicity, and improved patient outcomes. With the rapidly changing landscape of systemic therapy, the role of LRT alone or in combination for downstaging and curative intent will continue to evolve as we await this coming decade.

DISCLOSURE

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