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Indications and Best Practices for Intra-arterial Therapies to Treat Hepatocellular Carcinoma

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Abstract

Purpose of Review The purpose of this review is to re-evaluate the role of intra-arterial therapies for hepatocellular carcinoma (HCC) recommended by contemporary staging systems.

Recent Findings Currently, intra-arterial therapies are recommended by the Barcelona Clinic Liver Cancer (BCLC) staging system only for patients with BCLC B HCC in the form of trans-arterial chemoembolization. Recently, randomized controlled trials in patients with BCLC C HCC without metastatic disease have suggested a potential role for trans-arterial radioembolization (TARE) with fewer adverse events and better quality of life compared to sorafenib. Randomized controlled trials have also demonstrated the benefit of using combination therapy of trans-arterial chemoembolization (TACE) with ablation for patients with BCLC A HCC [single tumors (3–7 cm)] compared to ablation alone. Finally, promising results from single-center studies indicate that TARE using a radiation segmentectomy technique may be a potentially curative therapy for tumors less than 3 cm, supporting its use in patients with BCLC A HCC that are not amenable to surgical or ablative therapies.

Summary Recent randomized clinical trials have demonstrated the benefit of intra-arterial therapies in subpopulations of BCLC stages A, B, and C. These studies highlight the need for careful patient assessment, staging, and multidisciplinary discussion to consider treatments that are not currently included in guidelines but can improve patient outcomes for HCC.

Keywords Trans-arterial · Chemoembolization · Radioembolization · Hepatocellular carcinoma

Introduction

Liver cancer is the fourth leading cause of cancer death worldwide [1]. The most common type of primary liver cancer is hepatocellular carcinoma (HCC), followed by cholangiocarcinoma [2]. Treatment strategies for HCC are based upon staging criteria that take into account a patient's performance status, liver function, and tumor burden. Treatment guidelines vary by region; the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend the Barcelona Clinic Liver Cancer (BCLC) staging system and treatment recommendations due to its ability to accurately prognosticate patients with HCC (Fig. 1) [3•, 4, 5]. On the other hand, staging systems such as the Cancer of the Liver Italian Program (CLIP), Japan Integrated Staging (JIS), Chinese University Prognostic Index (CUPI), and the Hong Kong Liver Cancer (HKLC) staging systems are more frequently utilized in their eponymous regions [6]. However, it is worth noting that up to 40% of patients are treated outside of treatment guidelines in some centers [7]. In fact, some patients cannot be easily categorized into BCLC stages. For these patients, large studies in North American cohorts have shown that the receipt of multidisciplinary care (whether in the form of a multidisciplinary tumor board or clinic) and treatment at a high volume center are associated with improved survival [8, 9•, 10]. This review will use the BCLC staging system as a foundation for reviewing recent advances in the indications and best practices for intra-arterial therapies for HCC.

Intra-arterial therapies for HCC include hepatic artery chemoinfusion, bland trans-arterial embolization, trans-arterial chemoembolization (TACE), and trans-arterial radioembolization (TARE). Hepatic artery chemoinfusion

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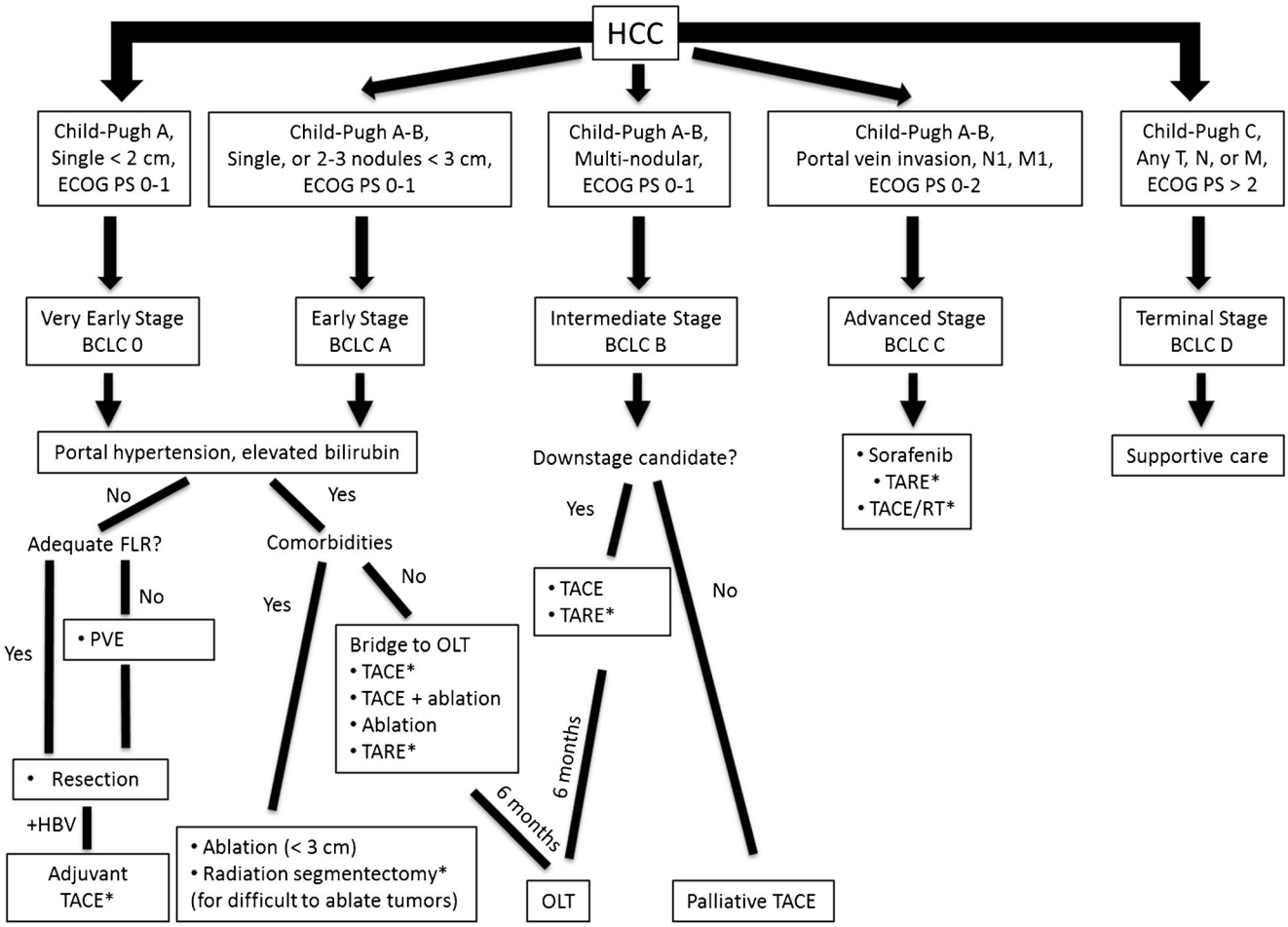

Fig. 1 Modified BCLC staging system with new inclusion of intra-arterial therapies with strong evidence base in each category (marked by asterisk)

involves insertion of a catheter into the tumor-feeding vessel, which is connected to a subcutaneous port for delivery of chemotherapy (most commonly 5-Fluorouracil or cisplatin). However, all studies evaluating hepatic artery chemoinfusion are non-randomized with small study populations and are limited to advanced HCC or treatment-refractory HCC [11]. Although there is controversy on whether cytotoxic injury from intra-arterial chemotherapy is additive to the tumor necrosis induced by ischemia, a meta-analysis demonstrated survival benefit was observed with conventional TACE but not bland embolization, following sensitivity analysis [12]. Since that publication, three randomized control trials (RCT) have compared drug-eluting bead TACE to bland embolization. A more recent meta-analysis of all published six RCTs failed to show superiority of TACE over bland embolization, although the authors noted significant heterogeneity within the study populations [13]. Therefore, this review will primarily discuss the role of TACE and TARE for the treatment of HCC.

HCC is most commonly diagnosed at BCLC C (which is generally considered an incurable stage) in North America, Europe, China, and South Korea but at BCLC A (which is a potentially curative stage) in Taiwan and Japan [14]. The BCLC treatment algorithm currently recommends trans-arterial therapy only in the form of chemoembolization for the treatment of patients with BCLC B HCC [3•]. However, several recent randomized controlled trials have suggested benefit of newer trans-arterial therapies such as TARE and novel uses of TACE (e.g., combination therapy of TACE with ablation) in expanded populations. The purpose of this review is to discuss these new advances in intra-arterial therapies and demonstrate how they fit into existing clinical guidelines.

General Principles of Trans-arterial Therapies for Hepatocellular Carcinoma

Intra-arterial therapies are minimally invasive, image-guided procedures performed in an angiography suite, typically under moderate sedation. A trans-femoral or trans-radial approach is used to advance catheters and perform mesenteric angiography from the celiac and superior mesenteric artery to delineate hepatic arterial anatomy, extra-hepatic vascular anatomy, and assess portal vein patency. Typically, a microcatheter system (2.0–2.8 French) is then coaxially advanced to perform further

selective/super-selective arteriograms to define vascular supply to the tumor and determine a safe catheter position to administer treatment. The use of a microcatheter system minimizes occlusion of the inflow artery and ensures adequate arterial flow around the catheter to carry the treatment to the tumor, and permits very selective catheterization for drug-embolization agent delivery which has reported improved outcomes compared to non-selective approaches [15, 16].

Response to trans-arterial therapies can be evaluated by multiple imaging response assessment criteria including Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), and European Association for the Study of the Liver criteria (EASL). The main deficiency with RECIST criteria, which is based on tumor size, is that it encompasses viable and non-viable tumor, and interval tumor necrosis from chemoembolization may not create immediate decreases in tumor size [17]. EASL and mRECIST were then developed to overcome this deficiency by evaluating tumor enhancement as surrogate markers for viable tumor. Overall response to EASL and mRECIST within 2–3 months after TACE is associated with survival and these criteria are recommended over RECIST [18]. Similarly, EASL response to treatment of the primary index lesion (which may be the patient's only tumor, largest tumor, or tumor that was first treated) was shown to correlate with time to progression as well as overall survival [19].

One of the major difficulties with predicting survival of HCC patients is the shared contribution of several factors including tumor stage, tumor biology, degree of liver dysfunction, and performance status. The Child-Pugh score (CP) may not appropriately stratify HCC patients, some of whom do not have cirrhosis, and furthermore, some of the CP variables are correlated (ascites and albumin) as well as graded on a subjective scale (ascites and encephalopathy) [20•]. Johnson et al. introduced the albumin-bilirubin (ALBI) grade and showed that it effectively distinguished survival among CP-A HCC patients from Asia, Europe, and the USA [20•]. Hickey et al. reported on the validity of ALBI grade in 765 HCC patients who underwent conventional trans-arterial chemoembolization (cTACE) or radioembolization with glass microspheres to predict survival. For the 337 patients who underwent cTACE, ALBI grade yielded distinct survival curves for subgroups of patients with CP-B cirrhosis, BCLC B HCC, and BCLC C HCC. The authors concluded that ALBI outperforms CP in discriminating survival and ALBI is most valuable in patients with CP-B and BCLC B disease [21]. However, the ALBI grade fails to account for portal hypertension and the PALBI grade is proposed to include portal hypertension by adding platelet count [22]. Liu et al. evaluated the ALBI and PALBI grade in 3182 Asian HCC patients with predominantly CP-A liver disease (73%). Overall, both ALBI and PALBI were able to differentiate each BCLC stage into three survival groups. The PALBI grade outperformed ALBI in providing higher discriminatory power [23]. Assessment of a patient's Eastern Cooperative Oncology Group performance status (ECOG PS) is an essential component of the pre-procedural evaluation, with intra-arterial therapies typically reserved for patients with ECOG PS < 2 [24].

Trans-arterial Chemoembolization

Chemoembolization is an image-guided trans-catheter therapy that delivers a cytotoxic agent (chemotherapy) followed by mechanical-occlusion-induced ischemia (embolization) to result in tumor necrosis [25]. Conventional TACE delivers an emulsion of aqueous chemotherapy and lipiodol to the tumor followed by particulate embolization. In 2002, two randomized controlled trials demonstrated survival benefit of conventional chemoembolization (cTACE) over best supportive care [26, 27]. In 2007, TACE with embolic microspheres (drug-eluting bead [DEB]-TACE) were introduced, which absorb chemotherapy from solution and release it in a controlled and sustained fashion, resulting in reduced drug delivery to the systemic circulation and increased local drug concentration compared to cTACE [28].

With the global adoption of cTACE in intermediate-stage HCC, one of the major limitations has been the wide variation in technique, including preparation of chemoembolic emulsion, choice of embolic material, size of microparticles, and type/combination of chemotherapy administered. Typically, a chemoembolic emulsion is created with an aqueous phase composed of non-ionic contrast and chemotherapy and an oil phase of lipiodol. The emulsion is administered until opacification of small peripheral portal venous radicles. Particulate embolization is then performed, typically with gelatin sponge or calibrated microparticles (usually 100–300 μm), to stop continued hepatic arterial inflow to the tumor-feeding vessels and increase retention of the chemoembolic emulsion within the tumor bed [15]. DEB-TACE theoretically provides a more standardized delivery platform to increase procedural uniformity with slow elution of drug to enhance intra-tumoral drug delivery. For typical DEB-TACE, the chemotherapy-loaded beads are mixed with at least 5–10 mL of non-ionic contrast per 1 mL of DC Bead prior to administration. The embolization endpoint is vascular stasis of the tumor-feeding artery (clearance in 2–5 heartbeats) and no additional embolization is typically necessary, although additional embolization with unloaded microspheres can be performed [29].

Two randomized controlled trials in Europe compared cTACE with DEB-TACE in BCLC A/B patients. The PRECISION V trial found no statistically significant improvement in response rates or disease control rate but DEB-TACE was associated with significant decreases in serious liver toxicity and doxorubicin-related side effects despite a higher

mean total dose of administered doxorubicin. In subgroup analysis, a significant benefit in objective response was found in Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease with DEB-TACE [30•]. The PRECISION ITALIA trial showed no difference in median time to progression (TTP) or 2-year overall survival (OS) between cTACE and DEB-TACE, but DEB-TACE patients experienced less post-procedural abdominal pain [31]. Non-superiority of DEB-TACE over cTACE was similarly concluded from a recent meta-analysis [32]. Due to these findings, at our institution, cTACE is more frequently used for BCLC B HCC and DEB-TACE is reserved for patients with worse liver function or performance status.

While these randomized trials used DC Beads ranging in size from 100 to 700 μm, prior studies concluded that particle sizes 100–300 μm are needed to reach tumor microvasculature and 70–150 μm particles are associated with greater tumor coverage, higher intra-tumoral doxorubicin concentration, and more uniform particle/drug distribution [33, 34]. This concept is reflected in technical recommendations to perform DEB-TACE with particle sizes of 100–300 μm but continued research to improve efficacy of DEB-TACE has focused on developing smaller caliber microspheres to prevent premature proximal embolization and facilitate distal embolization to maximize intra-tumoral chemotherapeutic delivery [29, 35, 36]. Consequently, multiple drug-eluting bead platforms with various sizes and compositions are available (Table 1). Each of these platforms was separately evaluated and demonstrated acceptable efficacy and toxicity [35–41]. No randomized data are available to identify the single best DEB-TACE platform.

Chemotherapy Selection

The landmark studies that established the survival benefit of TACE in BCLC B patients used single-agent chemotherapy regimens of cisplatin and doxorubicin, which are the most commonly used agents [42]. Use of cisplatin has decreased due to shortages of cisplatin powder [15].

Of three randomized trials comparing a single-drug anthracycline versus platinum agent (cisplatin or miriplatin versus epirubicin), one study found improvement in median TTP, but none found a difference in tumor response rate or OS [43–45]. Variable results have been found when examining single versus multiple drug therapies. Two randomized trials demonstrated superior OS and tumor response rates with triple agent cTACE over single-agent cTACE regimens [46, 47]. Contrarily, two additional randomized controlled trials comparing a multidrug regimen versus single-drug regimen failed to show a significant difference in radiographic response or survival [48, 49]. Based on the available data, no specific chemotherapy regimen has demonstrated consistently superior outcomes.

Post-embolization Syndrome

Post-embolization syndrome is a known clinical sequelae of chemoembolization thought to arise from inflammatory response to local ischemia/necrosis and systemic effects of chemotherapy. Patients present with fever, anorexia, abdominal pain, and nausea/vomiting following the procedure, but are usually discharged in 24–48 h with adequate symptom control on oral medication. Transient rise in serum transaminases and, occasionally, serum bilirubin usually resolve within 10–14 days. In a recent systematic review, 48% of adverse events from cTACE were related to post-embolization syndrome [42]. With emphasis on post-procedural care of patients, management of this particular syndrome is paramount to improve quality of life and patient-reported outcomes. Two randomized controlled trials from 2017 have recently demonstrated the benefit of intravenous dexamethasone use to reduce post-embolization syndrome. Of note, two different regimens were utilized with one study administering a single pre-procedural dose, while the second study used a 3-day regimen with the first dose given before TACE and subsequent doses on post-procedure day 2 and 3 [50, 51]. Thus, the routine use of prophylactic steroids likely improves quality of life for patients after cTACE by reducing the incidence of post-embolization syndrome.

Trans-arterial Radioembolization

Trans-arterial radioembolization (TARE) is an image-guided trans-catheter therapy that delivers intra-arterial brachytherapy to hepatic malignancies. Current TARE isotopes include iodine-131 iodized oil and yttrium-90 microspheres [52]. Yttrium-90, a beta-emitter with a half-life of 64.2 h and mean energy of 0.94 MeV, is currently the most frequently used isotope for TARE. The primary mechanism for causing tumor necrosis with radioembolization is via beta particle radiation. The yttrium-90 isotope is commercially available in two formulations: impregnated within glass microspheres (TheraSphere, BTG International, London, UK) and bound to resin microspheres (Sirtex Medical, Sydney, Australia) [52]. The two products differ in size and activity per microsphere with resin spheres being slightly larger (20–60 μm, 50 Bq per microsphere) compared to glass (20–30 μm, 2500 Bq per microsphere) [53].

A typical yttrium-90 TARE consists of two outpatient procedures. The first "planning" procedure is a mesenteric angiogram for selection of a treatment position for yttrium-90 delivery and calculation of an appropriate radiation activity, which will maximize the radiation dose to the tumor and minimize the dose to normal liver and lungs. Extra-hepatic blood vessels arising in close proximity or distal to the selected

Table 1 DEB-TACE delivery platforms

Name of DEB	Vendor	Composition	Sizes (μm)	Comments
DC Bead® (not cleared by FDA for sale or distribution in the USA)	Biocompatibles UK	Polyvinyl alcohol (PVA) polymer modified with sulfonate groups	70–150 (DC Bead M1™) 100–300, 300–500, 500–700	Upon loading, beads undergo a 20–30% decrease in size and corresponding reduction in volume
LC Bead® (only available in the USA)	Biocompatibles UK	PVA polymer, Sulphonate-modified, N-fil hydrogel microspheres	70–150 (LC Bead M1™) 100–300, 300–500, 500–700, 700–900, 900–1200	
LC Bead LUMI™	Biocompatibles UK	PVA polymer with covalently bound iodine moiety (tri-iodobenzyl moiety)	70–150, 100–300	Inherent radiopacity, visible under CT, CBCT, and fluoroscopy, must be suspended soluble iodinated contrast (best with Visipaque)
HepaSphere™ (outside the USA only)	Merit Medical	Sodium acrylate alcohol copolymer	Dry size (hydrated size): 30–60 (120–240), 50–100 (200–400), 100–150 (400–600), 150–200 (600–800)	Expands to four times the dry-state diameter when in contact with blood, non-ionic contrast medium, or 0.9% NaCl
QuadraSphere® (USA only)	Merit Medical	Sodium acrylate alcohol copolymer	Dry size (hydrated size): QuadraSphere Q2™ 20–40 (80–160), 30–60 (120–240), 50–100 (200–400), 100–150 (400–600), 150–200 (600–800)	Expands to four times the dry-state diameter when in contact with blood, non-ionic contrast medium, or 0.9% NaCl
LifePearl®	Terumo Interventional Systems	Polyethylene glycol microspheres	100 ± 25, 200 ± 50, 400 ± 50	Tight size calibration, improved suspension time, higher loaded drug elution
Embozene TANDEM™ (not available in the USA)	Boston Scientific Corporation	Hydrogel microsphere with Polyzene-F coating (negatively charged hydrogel core and biocompatible perfluorinated polymer coating)	40 ± 10, 75 ± 15, 100 ± 25	Tight size calibration

treatment position may need to be embolized to avoid non-target embolization to organs such as the duodenum, gall bladder, or stomach. After selection of a safe treatment position, technetium 99-m macroaggregated albumin is injected into the tumor. The patient then undergoes a nuclear medicine scan to quantify the relative accumulation of macroaggregated albumin particles within the liver and the lungs. This ratio, known as the lung shunt fraction, is used in radiation dose calculations. TARE can be safely performed if the target liver activity results in less than 30 Gy dose to the lungs for a single TARE treatment or less than 50 Gy cumulative dose to the lungs for all TARE treatments. Based on the planning arteriogram, radiation dosimetry is performed to calculate the activity to be administered.

The patient then returns for second procedure, a treatment angiography and implantation within 7–10 days. Treatment angiography confirms suitability of the treatment position and the yttrium-90 is then administered through the catheter. The patient receives another nuclear medicine scan to assess the area of implantation prior to discharge.

Although the techniques of catheter angiography and treatment delivery for TARE are similar to TACE, there is a high degree of variability in dosimetric considerations for therapy. A tumoricidal dose for HCC is considered to be > 120 Gy for resin microspheres and > 205 Gy for glass microspheres [54, 55]. The manufacturer instructions for use for resin microspheres recommend the use of the body surface area (BSA) model for dosimetry, whereas the Medical Internal Radiation Dosimetry (MIRD) model is used for glass microspheres. Two retrospective studies comparing outcomes for resin and glass TARE in patients with HCC have conflicting results, with one study showing no difference and the other showing better overall survival with glass [56, 57]. A systematic review evaluating differences in the safety profile of the two products found fewer gastrointestinal and pulmonary side effects with glass microspheres [58].

Indications

Early-Stage Disease

Early-stage HCC patients (BCLC 0/A) are candidates for curative therapies, which include resection, ablation, and liver transplantation [3•]. With optimal patient selection, greater than 70% 5-year overall survival can be achieved in patients with Child's A cirrhosis and early-stage HCC, although a more detailed discussion of curative options for early-stage HCC can be found elsewhere [59]. Herein, we discuss specific circumstances in which use of trans-arterial therapies (though not considered curative) may play a role in treatment of early-stage HCC.

TACE-Ablation Combination Therapy

A synergistic benefit of combination therapy with TACE and ablation is based on multiple mechanisms. Dual embolization of the hepatic arterial and portal venous blood flow following cTACE increases the ablation zone size by reducing the cooling effect of blood flow on thermal coagulation. The chemotherapeutic effect on cancer cells is also enhanced by hyperthermia. Finally, TACE prior to ablation can treat occult microlesions, which may ultimately contribute to recurrence [60••]. For solitary HCC measuring between 3 and 5 cm, performing TACE followed by thermal ablation has proven to be effective for local control with improved OS compared to thermal ablation alone in one RCT and improved progression-free survival (PFS) at 3 years in another [60••, 61]. One randomized controlled trial has also demonstrated improved OS in patients with HCC less than 7 cm by combining TACE with ablation compared to ablation alone [62••].

Adjuvant Trans-arterial Chemoembolization

While curative intent resection and ablation demonstrate good 5-year survival, these therapies are associated with rates of new tumor development at separate intra-hepatic sites of 70% at 5 years, highlighting a possible role for adjuvant therapies. The STORM trial failed to show a survival benefit for adjuvant sorafenib following resection or ablation [63]. The theory behind TACE in an adjuvant setting after resection or ablation is to treat occult microscopic tumor foci or intrahepatic metastases following resection when hepatocytes and tumor foci are stimulated into a regenerative state and are more susceptible to chemotherapy. A randomized controlled trial and meta-analysis of mostly hepatitis B-associated HCC patients following curative resection published within the last year demonstrated that adjuvant cTACE improved PFS and overall survival (OS) [64, 65]. It is worth noting that the majority of the studies were performed in Asia with a predominant hepatitis B patient population, which may not allow for extrapolation of the outcomes to patients with other etiologies of cirrhosis or fibrosis at the time of HCC treatment. At this time, the AASLD suggests against the use of adjuvant therapy after resection or ablation for early-stage HCC [4].

Trans-arterial Radioembolization

TARE may be used in several circumstances in the treatment of early-stage HCC. Although the BCLC guidelines recommend surgical resection for patients with early-stage disease, resection may not be feasible in patients with inadequate future liver remnants (< 40% in patients with cirrhosis/fibrosis) [66]. A single-center study demonstrated the use of a "radiation lobectomy" technique to be associated with a median 30% increase in the future liver remnant volume [67]. The theoretical advantage of this technique over portal vein embolization is the benefit of tumor control while awaiting future liver remnant hypertrophy. Published results on this technique are limited to single-center studies and no robust comparisons of radiation lobectomy to standard-of-care portal vein embolization (either alone or combined with TACE) are available.

Separately, two centers in the USA have also recently reported high local control rates with TARE using a technique known as radiation segmentectomy [68, 69]. In this technique, the activity required to achieve tumoricidal doses to HCC (120–150 Gy) assuming a lobar treatment volume is instead injected into a smaller volume of 1–2 segments resulting in very high target volume absorbed doses (173–369 Gy) [68, 70]. A more standard method for dosimetry has also been described whereby a target volume absorbed dose of > 190 Gy is recommended to calculate the required activity for administration [71•]. These centers have demonstrated high rates of complete pathologic necrosis (52%) and > 90% necrosis (48%) on explant for patients undergoing liver transplantation after radiation segmentectomy, high complete response rates by imaging criteria (59%), high PFS at 5 years (72%), and high OS at 5 years (75%) [70, 71•]. Despite these promising results, these studies should be viewed in the context of their design, i.e., all currently published studies on radiation segmentectomy are published from patients treated at two centers in the USA, with relatively small number of patients [40–97, 98••, 99••, 100], and with overlapping study periods that suggest overlapping patient populations. Intra-arterial radiation segmentectomy using yttrium-90 microspheres may be a good alternative for small HCC (< 3 cm) that cannot be safely ablated due to location (e.g., liver dome) or proximity to hepatic hilar structures, bile ducts, or adjacent organs (e.g., lung, gall bladder, colon) [72].

Intermediate-Stage Disease

The BCLC staging system recommends TACE for intermediate-stage disease [3•]. The AASLD recommends

locoregional therapy (LRT) over no therapy for BCLC B HCC patients. While no recommendation is made on a particular LRT to use, the AASLD recognizes that TACE has the best quality of evidence [73]. The initial acceptance of TACE as first-line therapy for intermediate-stage HCC occurred after two randomized controlled trials in 2002 demonstrated survival benefit of cTACE over best supportive care in unresectable HCC for up to 3 years [26, 27]. A more recent meta-analysis affirmed continued efficacy of cTACE based on survival rate data; however, no new RCTs were available since the landmark studies in 2002 [42]. The AASLD also notes that OS of patients treated with TACE in recent trials is superior to earlier TACE studies, suggesting that continued refinement in TACE technique has improved outcomes [73]. Recent studies demonstrate that combination therapy for selected patients with BCLC B HCC improves overall survival.

TACE-Ablation Combination Therapy

Combination therapy of TACE and ablation has also been compared to TACE in BCLC B patients. Yin et al. retrospectively compared RFA following cTACE with cTACE alone in 211 BCLC B patients (single tumor 5–8 cm or 2–5 tumors < 5 cm) and found significantly increased total tumor control rate as well as higher 1-, 3-, and 5-year survival with combination therapy [74]. In 2018, a retrospective, multicenter study stratified 230 BCLC B patients into B1–B4 substages according to the Bolondi classification: B1—Child-Pugh score 5–7, sum of diameter of largest tumor and tumor number is less than 7; B2—Child-Pugh score 5–6, sum of diameter of largest tumor and tumor number is greater than 7; B3—Child-Pugh score 7, sum of diameter of largest tumor and tumor number is greater than 7; B4—Child-Pugh score 8–9. The authors demonstrated superior survival in patients undergoing TACE/RFA compared with TACE; however, there were significant differences in Child-Pugh class, AFP level, DCP level, maximum tumor diameter, number of tumors, and BCLC B substages between the two groups. After propensity score matching, the 1-, 3-, and 5-year OS in substage B1 and B2 were superior for TACE/RFA compared to TACE alone [75].

Like thermal ablation, use of chemical ablation in combination with TACE has also been investigated. Fu et al. performed a meta-analysis that included 19 RCTs comparing combination therapy of TACE with percutaneous ethanol injection (PEI) versus monotherapy (TACE or PEI alone). The analysis included 1948 patients with T2 or T3 HCC with a majority of the studies from China. Combination TACE/PEI improved 1-, 2-, and 3-year survival, as well as reduced local tumor recurrence rate, AFP, and tumor size compared to monotherapy [76].

TACE-Sorafenib Combination Therapy

A combination of TACE and sorafenib has garnered particular interest due to the synergistic effect of the two therapies. Local tumor hypoxia induced by tumor necrosis following TACE stimulates tumor recurrence through induction of angiogenic growth factors, particularly vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). This process may be inhibited by sorafenib, a small molecule multikinase inhibitor with anti-angiogenic properties acting through the VEGFR-2, PDGFR, and Raf signaling pathway, as well as influence the pharmacokinetics of doxorubicin [77–79].

Two randomized clinical trials that compared sequential cTACE followed by sorafenib with cTACE alone in BCLC B patients showed differing outcomes. Sansonno et al. demonstrated significantly longer TTP with combination therapy with no unexpected toxicity [80]. Contrarily, Kudo et al. found no benefit in median TTP or OS from combination therapy in HCC patients as well as more treatment-emergent adverse events compared to data from the SHARP and Asia-Pacific trials [81]. In the combination group, 41% of patients discontinued study treatment due to an adverse event and incidence of grade 3/4 hand-foot skin reaction was 35% [80, 81]. The SPACE trial compared concomitant DEB-TACE and sorafenib with DEB-TACE alone in BCLC B patients but failed to show a significant improvement in TTP [82]. Given the higher adverse event profile, it is premature to recommend combination TACE therapy with sorafenib to patients with BCLC B HCC.

Trans-arterial Radioembolization

Trans-arterial radioembolization is increasingly being used in clinical practice for treatment of intermediate and advanced stage HCC due to excellent tumor response rates and low clinical toxicity [83]. However, the latest guidelines from 2018 still support the use of TACE for BCLC stage B patients due to low quality of evidence for TARE for these patients [4, 73].

A randomized control trial of 24 patients with BCLC stage B disease underwent either DEB-TACE or resin TARE [84]. No differences in TTP, PFS, or OS were found. Death due to liver failure was more common in the resin TARE group but death due to tumor progression was more common the DEB-TACE group. Another randomized control trial between glass TARE and cTACE found that TARE was associated with longer TTP but similar OS but the majority of patients (> 75%) in each arm had BCLC stage A tumors [85].

There are numerous other retrospective cohort studies comparing TACE (cTACE and DEB-TACE) and TARE (glass and resin) for which at least two meta-analyses have been performed [86, 87]. These studies are heterogeneous with a mix of patients from each BCLC stage and therefore no firm

conclusions on the added value of TARE compared to TACE for BCLC stage B patients can be made at this time.

Advanced Stage Disease

Sorafenib is the first-line therapy recommended by guidelines for BCLC stage C patients as supported by survival benefit of approximately 3 months over best supportive care [88, 89]. Additional first- and second-line systemic therapies have shown promise in advanced HCC patients, including lenvatinib, regorafenib, cabozantinib, and nivolumab [4]. However, the BCLC stage C represents a heterogeneous patient cohort with median survival ranging from 2 to 12%, depending on extent of portal vein tumor thrombus and nodal versus distant metastases [90]. Therefore, intra-arterial therapies have been introduced to improve outcomes in patients with liver-only disease.

Trans-arterial Chemoembolization

TACE was traditionally contraindicated in BCLC stage C patients with vascular invasion due to risk of hepatic failure from ischemic liver damage. In the setting of compromised portal vein blood flow from macrovascular invasion, the liver parenchyma is more dependent on hepatic arterial blood supply putting patients at high risk of hepatic ischemia following chemoembolization in this clinical setting. However, prior research has shown that TACE can be performed safely in this patient population likely due to presence of periportal collateral circulation and use of superselective TACE, which minimizes parenchymal involvement [91]. Although regarded as safe, there are limited data demonstrating efficacy in BCLC stage C patients as they are excluded from most if not all TACE trials.

TACE-Sorafenib Combination Therapy

The clinical benefit of TACE combined with sorafenib in BCLC C patients is not well established. Retrospective studies comparing combination therapy with sorafenib alone failed to show a survival benefit [92, 93]. However, the GIDEON observational registry of over 3200 patients investigating the combination of TACE with sorafenib use in clinical practice did show a survival benefit with combination therapy, noting that this was not a randomized trial and the data suffered from selection bias where patients with a better prognosis were more likely to undergo concomitant TACE and sorafenib. Patients with concomitant TACE and sorafenib therapy had median OS of 21.6 months compared to 9.7 months in non-concomitant TACE patients and 12.7 months in prior-TACE patients compared to 9.2 months in non-prior-TACE patients [94]. Randomized trials documenting benefit of combination therapy with TACE and sorafenib in BCLC C patients are lacking. A recent meta-analysis concluded that combination therapy other than sorafenib alone for BCLC C has not been supported with high-quality evidence and further randomized studies are warranted [95].

TACE-Radiation Combination Therapy

The advent of 3D radiation therapy (RT) and stereotactic RT has allowed for higher doses of radiation to be administered to the liver with decreased risk of radiation-induced liver disease. With these advances, the combination of TACE and RT may provide synergistic therapeutic benefit via multiple mechanisms, e.g., RT treatment of residual cancer cells after TACE fed by collateral/recanalized blood supply; TACE-induced cell damage causing stimulation of radiosensitive cell proliferation; retention of chemotherapeutic agents within tumor cells has a radiosensitizing effect; RT treatment of smaller tumor volume following TACE; RT treatment of hypovascular tumors; RT extends tumor retention of lipiodol and chemotherapeutic agents. Huo et al. performed a meta-analysis of this combination therapy that included 25 trials, 11 of which were RCTs, and 2577 patients with unresectable HCC [96]. The authors found a survival benefit that progressively increased each year extending up to 5 years with combination therapy over TACE alone. TACE plus RT had significantly better partial and complete response rates, and less stable disease and progressive disease compared to TACE alone. However, there was also an increased incidence of gastroduodenal ulcers, elevated alanine transaminase, and elevated total bilirubin with combination therapy. Unfortunately, subgroup analysis demonstrated a non-significant trend of increased survival at 1, 2, and 3 years for combination therapy in patients with portal vein tumor thrombosis (PVTT) compared with those without PVTT.

Some benefit of this combination treatment regimen for the BCLC C population has been seen in more recent studies. A randomized controlled trial compared cTACE plus external beam radiation therapy (EBRT) with sorafenib in treatment-naïve BCLC C patients. In the combination therapy group, cTACE was repeated every 6 weeks for the first 6 months and then every 6–8 weeks thereafter. EBRT began within 3 weeks after the first TACE with a planned total dose to the planning target volume of 45 Gy with fraction size of 2.5–3 Gy. This trial demonstrated significant improvements in 3-month PFS, radiologic response rate at 6 months, median TTP, and OS with no hepatic decompensation for patients undergoing combination therapy. Additionally, 11% of patients who underwent cTACE plus EBRT were successfully downstaged and underwent curative resection [97].

Trans-arterial Radioembolization

Two randomized control trials have compared the use of TARE to sorafenib for BCLC stage C HCC. The SARAH trial

was a multicenter open-label RCT at 25 centers of 467 BCLC stage C patients that found no difference in overall survival between the two treatments; however, there was better quality of life and safety profile of resin TARE compared to sorafenib [98••]. More recently, the SIRveNIB study of 360 advanced stage HCC patients also demonstrated similar OS but better safety for resin TARE [99••]. Both of these trials were designed to demonstrate superiority/detriment with overall survival as the primary outcome, which was not reached and the primary analysis was intention-to-treat. However, both trials demonstrated a significantly higher tumor response rate for the TARE arm compared to the sorafenib arm. This discrepancy between overall survival and the tumor response rate may be explained by the failure of approximately 1/4th of the patients in the TARE arm (23–28%) to complete treatment. A recent subgroup analysis of the SARAH trial has demonstrated that both overall survival and tumor response rates were significantly higher in patients who received greater than 100 Gy tumor-absorbed doses [100]. Studies have also demonstrated that the prescribed activity for resin microspheres is higher when using the MIRD dosimetry model compared to the BSA model, which was used in both trials [101]. Thus, despite the results of these large RCTs, treatment decisions with optimal patient selection and personalized dosimetry may improve outcomes for BCLC C patients treated with TARE. Although more data is needed comparing TARE with systemic therapy for BCLC C patients, TARE is currently the main treatment for BCLC C patients with vascular invasion recommended by the liver tumor board at our institution.

Patients Awaiting Liver Transplantation

Downstaging Trans-arterial Therapies

For patients beyond Milan criteria who are successfully downstaged with LRT, the AASLD suggests that these patients be considered for liver transplantation. The AASLD does not recommend one form of LRT over another [73]. A meta-analysis of three comparative studies showed significant increases in 1-year and 5-year post-transplant survival for downstaged patients compared to patients transplanted with T2 disease but did not find any differences based on the type of LRT used [102]. An additional meta-analysis that included 13 studies of 950 patients had a pooled downstaging success rate of 48% and a post-transplant recurrence rate of 16%. Subgroup analysis by treatment modality found no significant difference between TACE and TARE in downstaging success or post-transplant recurrence rates [103].

Bridging Trans-arterial Therapies

Due to increasing transplant wait times, the AASLD suggests bridging to transplant in patients listed for liver transplantation within Milan criteria to prevent tumor progression and waitlist dropout; however, a particular form of liver-directed therapy is not recommended [73]. In a meta-analysis evaluating LRT while on transplant waiting, non-inferior outcomes of bridging LRT compared with no therapy provides support for the use of bridging therapy, particularly because patients treated with LRT were more likely to have advanced tumors [102]. Furthermore, response to LRT may allow biological selection of patients by identifying aggressive tumor biology, predicting post-transplant survival/recurrence, and avoiding futile transplantation of scarce liver donors. Otto et al. studied 50 HCC patients who underwent liver transplant following bridging or downstaging cTACE. Freedom from recurrence after 5 years was significantly higher in patients with progression-free TACE during the waiting period compared to those who progressed following TACE (94.5% versus 35.4%). Multivariate analysis showed that progression-free course of TACE during waiting period and limited number of tumor nodules on explant was a significant predictor for freedom from recurrence [104].

Conclusions

In conclusion, several recent randomized clinical trials have demonstrated the benefit (both in OS as well as adverse events) for increasing patient populations, including TACE combined with ablation for BCLC A HCC and TARE for BCLC C patients. These studies highlight the need for a careful patient assessment, staging, and multidisciplinary discussion to identify optimal treatments that may not currently be included in guidelines but can improve patient outcomes for HCC.

Compliance with Ethical Standards

Conflict of Interest Michael Hsu, Muneeb Ahmed, and Ammar Sarwar each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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