Embolic and Ablative Therapy for Hepatocellular Carcinoma

Mian Khalid, MD[a], Alisa Likhitsup, MD, MS[b], Neehar D. Parikh, MD, MS[b,*]

KEYWORDS

• HCC • RFA • MWA • TACE • TARE • Y90 • BCLC

KEY POINTS

- Locoregional therapies encompassed by embolic and ablative approaches play an important role from very early to intermediate stages of hepatocellular carcinoma (HCC).
- Microwave ablation and radiofrequency ablation have replaced percutaneous ethanol injection as the major ablative therapies.
- Systemic therapy can be considered an alternative to transarterial chemoembolization for intermediate-stage HCC with a large tumor burden.
- Combination therapies are increasingly being explored to provide a more tailored approach to HCC patient care.

INTRODUCTION

Liver cancer is globally the sixth most common cancer and the third highest cause of cancer-related mortality.[1] The global incidence of liver cancer is projected to increase by 55% by 2040.[1] Hepatocellular carcinoma (HCC) comprises approximately 80% of liver cancers. Despite recent therapeutic advances, HCC has a poor prognosis with 5 year survival below 20%, primarily driven by late-stage diagnoses when curative therapies are often not possible.[2]

The Barcelona Clinic Liver Cancer (BCLC) is the most widely accepted HCC staging system that incorporates tumor size, number and location of tumors, liver function, and performance status.[2] The staging system also provides guidance for treatments at various stages of HCC.[2]

In early stages (BCLC 0/A), surgical resection is recommended for solitary HCC lesions or those with limited multifocal disease with preserved hepatic function with an

[a] Division of Gastroenterology, University of Maryland Medical Center, Baltimore, MD, USA;
[b] Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA
* Corresponding author. 1500 East Medical Center Drive, Ann Arbor, MI 48109.
E-mail address: ndparikh@med.umich.edu

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anatomically accessible tumor. Liver transplantation (LT) is the standard of care for HCC in early stages (typically restricted to Milan criteria in many Western countries) with clinically significant portal hypertension.[3] Locoregional therapies (LRTs) such as thermal ablation, chemoembolization, and radioembolization are treatment options that span the center of the BCLC staging spectrum, encompassing early and intermediate stage disease. LRTs are typically reserved for patients who are not candidates for resection, for bridging to resection or LT, or for downstaging to resection of LT.[4,5]

Herein, the authors review ablative and embolic therapies for the treatment of HCC with a focus on outcomes, safety, and multiple sequential treatment options.

ABLATIVE THERAPIES

Ablation relies on the principle of localized tumor tissue destruction, which limits the role to small tumors (typically HCC 3–4 cm or less). This therapeutic strategy can be leveraged especially for centrally located tumors that would otherwise require major hepatectomy and subsequent morbidity.[6] A recent multicenter, randomized controlled trial (RCT) demonstrated that for BCLC stage A tumors, radiofrequency ablation (RFA) offered a similar recurrence-free survival (RFS) 3.0 (95% confidence interval [CI], 2.4–5.6) years compared to surgery with RFS 3.5 (95% CI, 2.6–5.1) years (hazard ratio [HR], 0.92, CI, 0.67–1.25; P=.58).[7]

Local ablative therapies can be chemical-based or thermal-based therapies. Percutaneous ethanol injection (PEI) ablation was first demonstrated to be effective in 1987 by Shiina and colleagues[8] especially for small tumors (range 0.8–4.6 cm in the study). However, PEI use has fallen out of favor due to high risk of recurrence and tumor seeding of the abdominal wall by the needle track. RFA and microwave ablation (MWA) are 2 methods of thermal ablation that have largely replaced PEI in clinical practice. RFA is image guided, generally percutaneous (with the option for laparoscopic approach), and confers tumor necrosis by passing electric current directly through the tumor. As a principle, tumor necrosis is limited by tumor size with a negative inflection point beyond 3 cm. Thus, it is the therapy of choice for solitary tumors less than 2 cm according to the American Association for the Study of Liver Diseases (AASLD),[6] the European Association for the Study of the Liver (EASL),[9] and the Asian-Pacific Association for the Study of the Liver (APASL)[10] guidelines.

MWA utilizes electromagnetic energy leading to heat generation and coagulation necrosis in absence of current flow.[11] The principal benefit of MWA over RFA is being less affected by the heat sink effect when treatment is rendered for tumors near major vessels.[9] This allows for faster treatment times with less time needed for ablation compared to RFA and ability to treat multiple lesions simultaneously with multiple electrodes.[12]

The first clinical trial to evaluate MWA in the United States was published in 2007 on 87 patients with average tumor size 3.6 cm (range 0.5–9.0 cm), mean follow-up of 19 months, with 47% patients alive at the end of the study period with no evidence of disease, no procedure-related deaths, and overall mortality of 2.3%. The regional recurrence rate, however, was high at 43% with a mean follow-up of 19 months.[13] A meta-analysis including 774 patients found a nonsignificant trend toward higher complete response in patients treated with MWA compared to RFA (odds ratio [OR] 1.12, 95% CI 0.67–1.88, P=.67), but equivalent local recurrence rate (P=.98). MWA outperformed RFA in a subgroup analysis of studies enrolling patients with larger tumors up to 7 cm (OR 0.46, 95% CI 0.24–0.89, P=.02).[14] A head-to-head single-blinded phase II RCT comparing MWA versus RFA showed similar tumor progression at 2 years for both modalities (6% vs 12%, respectively, P=.27), infrequent

complications (7.1% and 14.4%, respectively), and no treatment-related deaths.[15] There have been several RCTs and meta-analyses with a trend toward MWA favored for treatment of larger tumors, long-term disease-free survival (DFS), and better safety profile than RFA (**Table 1**).

The rate of major complications of RFA is generally similar to MWA (2.2%[16] vs 2.9%[17]) with minor complications at less than 5%[16] versus 7.3%[17], respectively. However, one retrospective propensity-matched analysis found more frequent major complications in MWA group than RFA (27 vs 7%, $P<.001$).[18] Complications for RFA include death (<1%), liver failure (1%–2%), hemorrhage (2%–4%), infection/abscess (<5%), intercostal nerve injury (<1%), bowel/biliary injury (1%), tumor lysis syndrome (1%–2%), and pneumothorax (<5%).[19] Complications for MWA include death (0%–0.18%), colon perforation (0%–1.11%), intraperitoneal bleeding (0%–0.92%), liver abscess (0%–2.78%), tumor seeding (0%–0.44%), bile duct injury (0%–2.78%), skin burn (0%–3.45%), and symptomatic pleural effusion (0%–3.67%).[20]

Factors that aid in the decision whether to pursue resection versus thermal ablation include tumor size, tumor location, and degree of hepatic dysfunction. In a decision analytic model, tumor size attenuated effectiveness of RFA to a greater degree than surgical resection, whereas hepatic dysfunction negatively affected prognosis post-surgical resection more compared to RFA.[21] The study concluded that patients with solitary tumors less than 2 cm and well-preserved liver function had equivalent outcomes for both surgical resection and RFA. As MELD increased (surrogate for liver function) above 10, the benefits of surgical resection became attenuated, tilting the benefit in RFA's favor. The alternating surgical resection versus RFA benefit was seen for solitary tumors 2 to 3 cm and oligo-nodular (2–3 tumors, <3 cm) with model of end stage liver disease (MELD) 10 as inflection point. Finally, surgical resection was preferred with tumors 3 to 5 cm, with depreciation in benefits with progression of hepatic dysfunction.

A systemic review of 18 meta-analyses revealed more favorable overall survival (OS; 7out of 18) and RFS (9 out of 18) outcomes for surgical resection over RFA.[22] In a meta-analysis of 6 RCTs and 30 propensity score matched studies, hepatic resection was found to have improved OS and RFS in early-stage HCC, whereas long-term outcomes on very-early stage HCC were similar between hepatic resection and RFA.[23] A subgroup analysis revealed RFA performed similarly to liver resection in OS when ablation margin was larger than 1 cm.[23] Therefore, tumor location in selecting the mode of therapy is important.

Stereotactic body radiation therapy (SBRT) is a form of ablative radiotherapy that is used for tumors not amenable to thermal ablation.[6] It is not limited by tumor size or location (dome or proximity to gallbladder).[24] A recent large, multinational retrospective study (n = 2064 patients) demonstrated SBRT significantly improves local tumor control for unresectable HCC, especially for tumors larger than 3 cm.[25] It is also a viable alternative to RFA and transarterial chemoembolization (TACE) as a bridging therapy to LT.[26]

There are other less commonly used LRTs with evidence for efficacy in the treatment of HCC, including irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), and histotripsy. IRE is a nonthermal ablation technique that uses electric pulses to induce cell death, preserving structural integrity of bile ducts and vessels.[27] It avoids the heat sink phenomenon of RFA. HIFU is a noninvasive ablation procedure that focuses ultrasound energy to induce tumor coagulative necrosis. Histotripsy is a noninvasive, nonthermal, image-guided ablation technique that uses short bursts of ultrasound waves to generate acoustic cavitation leading to mechanical destruction of tumor cells. A multicenter phase I feasibility trial (THERESA) on histotripsy was

Table 1
Highlights from selected articles on comparison between microwave ablation versus radiofrequency ablation with study type, number of patients, and outcomes identified

Treatment Modality	Study (Year)	Patients (n)	Type of Study	Outcomes	Effect Sizes
MWA vs RFA	Feng et al,[18] 2021	170	Multicenter, retrospective, propensity-score analysis	OS comparable, with PFS better in MWA	1 y OS 94% vs 96% (P = .249); 1 y PFS 73% vs 64% (P = .028)
MWA vs RFA	Violi et al,[15] 2018	152	Phase II RCT	Equivalent local tumor progression at 2 y for <4 cm lesions	6% vs 12% (P = .27)
	Chong et al,[60] 2020	93	RCT	Equivalent survival and safety	1-, 3-, and 5-y OS and DFS equivalent (P = .899 and P = .912)
	Radosevic et al,[61] 2022	82	Phase II RCT	Equivalent effectiveness, safety for 1.5–4 cm tumors	Technical success 98% vs 90% (P = .108) and LTP 21% vs 12% (P = .238)
MWA vs RFA	Facciorusso et al,[14] 2016	774	Meta-analysis	MWA favored with nonsignificant trend toward CR	CR for MWA > RFA with OR 1.12 (95% CI 0.67–1.88, P = .67)
	Facciorusso et al,[62] 2020	921	Meta-analysis	DFS favored MWA at 5 y	RR 3.66 (1.32–42.27)
	Dou et al,[63] 2022	4589	Meta-analysis	Equivalent OS; MWA with lower local tumor progression	OS at 5-y 0.79 (95% CI 0.51–1.21, P = .27)
	Zhang et al,[64] 2023	894	Meta-analysis	OS, RFS favored MWA at 5 y with better safety profile for <5 cm tumors	OS OR 0.48 (95% CI 0.34–0.68); RFS OR 0.44 (95% CI 0.30–0.65)

Abbreviations: CR, complete response; DFS, disease-free survival; LTP, local tumor progression; MWA, microwave ablation; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RFS, recurrence-free survival; RR, risk ratio.

published recently; however, the trial was not exclusive to HCC patients with only 1 out of 8 patients with HCC.[28] The primary endpoint (acute technical success) was achieved in all patients.

EMBOLIC THERAPIES

TACE is the primary embolic treatment strategy utilized for patients with intermediate-stage (BCLC stage B) HCC.[6] Patients undergoing TACE receive a concentrated dose of chemotherapy (with an infusion of lipiodol, an oily radio-opaque chemotherapeutic carrier agent) through selective catheterization of the arterial branch feeding the tumor, followed by embolization of tumor microcirculation to prolong target cytotoxic effect and minimize systemic toxicity (conventional TACE [cTACE]). The lipiodol is trapped in the HCC tumor up to a year, as opposed to only up to 4 weeks in non-tumor portions of the liver.[29] HCC tumors are primarily fed by the hepatic artery, rather than the dual blood supply (portal vein and hepatic artery) for the hepatic parenchyma, the latter is shielded by ischemia caused by embolization.[30]

TACE is recommended by the AASLD guidelines to be performed in a selective/segmental fashion rather than lobar approach to mitigate the risk of hepatic decompensation.[6] In a prospective study of 67 patients with multiple sub 5 cm HCC lesions not meeting Milan criteria treatment with selective versus lobar TACE resulted in significantly higher complete tumor necrosis (75.1% vs 52.8%, P=.002) with less frequent repeat sessions needed (31.5% vs 59.3%, P=.049).[31]

Although TACE is generally not curative, it can be used as a neoadjuvant therapy or downstaging prior to possible LT if eligible.[32] A systematic review and pooled meta-analysis of 13 studies (n = 950 patients) revealed successful downstaging within Milan criteria in 48% of patients (95% CI 39%–58%), however with relatively high post-LT HCC recurrence rates to 16% (95% CI 11%–23%).[5] TACE has been shown to prolong OS in patients with unresectable HCC in multiple RCTs and meta-analyses (**Table 2**). A recent major systematic review for TACE with more than 10,000 patients confirmed an objective response rate of 52.5% with OS of 70.3% at 1 year and 40.4% at 3 years.[33]

The use of TACE as the primary embolic option in intermediate HCC has evolved recently. There is an increasing recognition that intermediate-stage patients with significant intrahepatic disease burden may have limited responses to embolic LRTs.[34,35] The 2022 BCLC update stratifies intermediate-stage patients into 3 categories: (1) extended liver transplant group, which benefit from LT due to well-defined expanded criteria or downstaging; (2) well-defined nodules, preserved portal flow, and selective access are features ideally treated with TACE; and (3) diffuse, infiltrative, bilobular liver involvement are high-risk features in patients who benefit more from systemic therapy.[2] Therefore, patient selection is critical to ensure that TACE is offered only for patients in the second category to optimize outcomes.[36,37]

The concept of "TACE unsuitable" helps exclude patients who will not benefit from TACE despite having intermediate-stage HCC. The AASLD HCC guidelines propose TACE unsuitable factors based on tumor size (beyond United Network of Organ Sharing [UNOS]-downstaging criteria), tumor appearance (multinodular, bilobar, with >50% liver involvement, and infiltrative or nodular with poorly defined margins), biomarker levels (marked alpha-fetoprotein elevations), portal vein tumor thrombosis (large vessel invasion), and liver function (ALBI grade 2–3 or deteriorating liver function overtime).[6]

"TACE refractoriness" as a concept was proposed first in Japan in 2011,[38] but its definition has expanded to emphasize that repeating TACE beyond the criteria leads

Table 2
Highlights from selected studies on comparison between TACE and supportive care or arterial embolization with study type, number of patients, and outcomes identified

Comparison	Study (Year)	Patients (n)	Type of Study	Outcomes
TACE vs Arterial Embolization	Llovet et al,[65] 2002	112	RCT	Favoring TACE, survival benefit HR 0.47 (95% CI, 0.25–0.91, *P*=.025)
TACE (lipiodol) vs Symptomatic Treatment	Lo et al,[66] 2002	80	RCT	Favoring TACE, survival 26% vs 3% over 3 y, *P*=.002
TACE vs Arterial Embolization	Llovet and Bruix,[67] 2003	545	Meta-analysis	Favoring TACE, objective-treatment response in 35% (sensitivity analysis)
TACE vs Nonactive or Transarterial Chemotherapy	Camma et al,[68] 2002	2466	Meta-analysis	Favoring TACE vs non-active treatment, lower 2-y mortality (OR 0.54, *P*=.015). TACE not effective compared to TAE (*P*=.95)
TACE vs Best Supportive Care	Lencioni et al,[33] 2016	10,108	Systematic review	TACE objective response rate 52.5% with OS at 1 y 70.3%

Abbreviations: RCT, randomized controlled trial; TACE, transarterial chemoembolization; TAE, transarterial embolization.

to impaired liver function and resultant poor prognosis. It is defined broadly as increase in number or radiologic enhancement of treated nodules after 2 or more consecutive TACE sessions, no decrease in tumor marker immediately after TACE, and development of vascular invasion or extrahepatic spread.[39] Therefore, TACE is not offered more than 2 consecutive sessions if TACE refractoriness criteria are met. A proposed treatment paradigm for intermediate-stage HCC with respect to TACE is illustrated in **Fig. 1**.

A common adverse effect of TACE is post-embolization syndrome, where fever and abdominal pain related to hepatic ischemia and tumor necrosis occur in about 50% of patients treated with TACE.[32] Treatment is supportive care with most patients improving within 48 hours. However, a double-blind RCT intravenous dexamethasone for 3 days peri-TACE was more effective than control (complete response rate 47.5% vs 10.2%, $P<.001$) to reduce post-embolization syndrome.[40] A systematic review compiled 21,461 adverse events post-TACE with liver enzymes abnormalities (18.1%), fever (17.2%), hematologic/bone marrow toxicity (13.5%), pain/abdominal pain (11.0%), and vomiting (6.0%), as top 5 adverse events. Overall mortality was 0.6%, most commonly due to liver insufficiency.[33]

An alternate method of TACE using drug-eluting beads (DEB), called DEB-TACE, uses embolic hydrogel microspheres loaded with a chemotherapeutic agent with the ability to slow and sustained drug release, to ensure high local drug concentrations and minimize adverse effects.[41] The first randomized phase II study (PRECISION V) compared TACE versus DEB-TACE in 212 patients with Child-Pugh A/B cirrhosis with large and/or multinodular, unresectable HCC (intermediate stage). DEB-TACE group had higher rates of complete response, objective response, and disease control but did not meet the threshold of superiority ($P=.11$). A subgroup of patients with bilobar and recurrent disease experienced a statistically significant improvement in objective response in DEB-TACE group ($P=.038$). DEB-TACE group also experienced

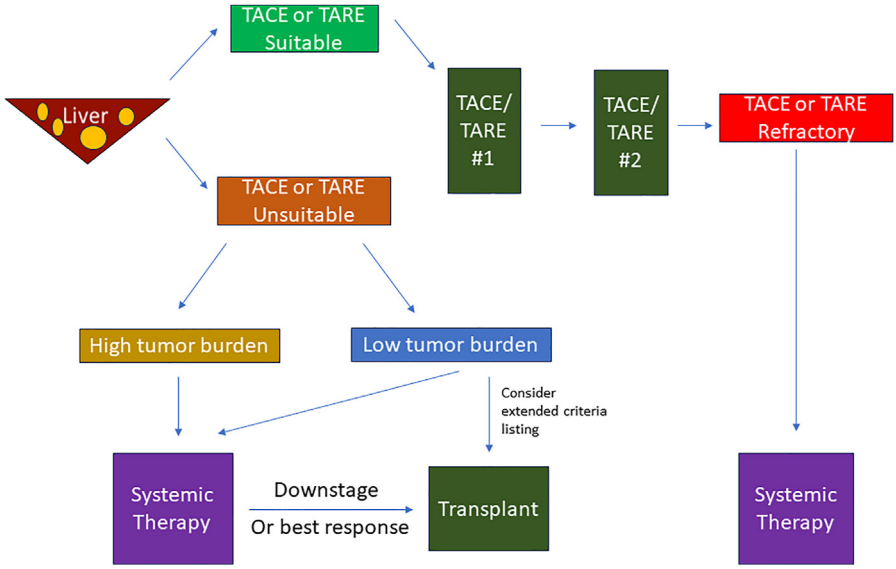

Fig. 1. Proposed treatment paradigm for management of Barcelona Clinic Liver Cancer (BCLC) B or intermediate stage hepatocellular carcinoma (HCC). TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

statistically significant reduction in serious liver toxicity ($P<.001$).[30] In a study of 104 patients treated with DEB-TACE, strictly selection (preserved liver function, absence of symptoms, extrahepatic spread, or vascular invasion) demonstrated a 50% survival at 4 years.[42] However, a meta-analysis of 7 studies (693 patients) comparing DEB-TACE and cTACE revealed essentially equivalent outcomes.[43] Therefore, AASLD,[6] EASL,[9] and APASL[10] guidelines do not recommend one method over another.

Transarterial radioembolization (TARE), also known as selective internal radiation therapy, involves the delivery of microspheres loaded with a radioisotope (eg, yttrium-90, ^{90}Y), a beta-emitter with a 2.67 day half-life. There is a greater diffusion of administered agents in tumors with TARE than TACE or other techniques.[44] A landmark multicenter retrospective study (Local radioEmbolization using Glass Microspheres for the Assessment of Tumor Control with Y-90 [LEGACY]) treated 162 consecutive patients with solitary unresectable HCC (<8 cm) with high-dose personalized dosimetry and found the best objective response rate at 88.3%, with 62.2% sustaining response longer than 6 months. Furthermore, the 3 year survival was 86.6%.[45] The benefits of high-dose personalized dosimetry were tested in DOSISPHERE-01, a multicenter randomized phase II trial, that evaluated personalized versus standard dosimetry approach for TARE in 60 patients with at least one HCC tumor larger than 7 cm. DOSISPHERE-01 found superior objective tumor response (71% vs 36%, $P=.0074$) and OS (HR 0.42, 95% CI 0.22–0.83) in the personalized treatment arm.[46] LEGACY subsequently resulted in the US Food and Drug Administration premarket approval for TARE.[47]

Several studies have compared TACE with TARE. A phase II RCT (PREMIERE) of 179 patients with BCLC stages A or B found TARE to significantly prolong time to progression (TTP) compared to cTACE (>26 months vs 6.8 months, $P=.0012$). Median survival time, censored to LT, was equivalent, however (18.6 months vs 17.7 months, respectively, $P=.99$).[48] A recent meta-analysis of 10 studies revealed similar results in objective response rate and safety profile, with 1 year progression-free survival (PFS) favoring TARE over TACE (OR 1.67, $P=.02$).[49] A clinical trial of 86 patients found TARE to require a lower number of treatment sessions per patient (average 1.4 ± 0.6) compared to TACE (2.2 ± 1.4), which translated to decreased hospitalization time and adverse events.[50]

TARE complications are largely a result of irradiation of nontarget tissues, leading to radioembolization-induced liver disease, a syndrome of jaundice, ascites, and elevated bilirubin.[51] The onset can delayed 4 to 8 weeks posttreatment, is more common in patients with impaired liver function prior to TARE, and can portend poor long-term survival outcomes even with good tumor response.[52,53] Other complications include post-radioembolization syndrome (a self-limited condition with fever, fatigue, nausea, and anorexia), biliary tract injury (biliary necrosis, biliary stricture), radiation gastritis, pneumonitis, and cholecystitis.[51]

COMBINATION THERAPIES

While ablative therapies are limited by the size of tumor size and proximity to major vessels, TACE is limited by incomplete embolization due to multiple possible arterial branches feeding the tumor.[53] Combination of ablative and embolic therapies has been explored in various studies to mitigate deficiencies that are intrinsic to each treatment strategy. Although some meta-analyses[54,55] have revealed improved OS and PFS for RFA + TACE compared to TACE, most recent studies have shown largely equivalent outcomes (**Table 3**). In a multi-way comparison between TACE combined with RFA or MWA or cryoablation compared to TACE alone, the TACE + MWA sub-

Table 3
Selected studies of the combination of locoregional therapies

Comparison	Study (Year)	Patients (n)	BCLC Stage	Type of Study	Outcomes
MWA after TAE vs MWA alone	Adwan et al,[69] 2023	112	Very-early to intermediate	Retrospective single center	TAE-MWA was significantly superior based on OS
LR vs RFA vs RFA + TACE	Zhang et al,[70] 2022	4249	Very-early and early	Meta-analysis	LR superior to RFA for OS and RFS. RFA + TACE > RFA based on 1 y RFS only (not for 3 or 5 y)
TACE+(RFA or MWA or cryoablation) vs TACE	Keshavarz & Raman,[71] 2022	5468	Intermediate	Meta-analysis	TACE + MWA sub-cohort with best efficacy and outcomes, especially age <60, tumor size <3 cm
TACE+(RFA or MWA) vs TACE	Yang et al,[72] 2022	1799	Intermediate	Meta-analysis	TACE+(RFA or MWA) better OS, PFS, and local tumor control rate without increase in complications
TARE post-TACE vs TARE	Vardar et al,[73] 2022	100	Intermediate or advanced	Retrospective single center	TARE + TACE longer OS, TTP, and fewer complications

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HIFU, high-intensity focused ultrasound; LR, liver resection; MWA, microwave ablation; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

Table 4
Ongoing clinical trials on combination of ablative or embolic therapies with systemic therapy

Treatment Regimen	Phase	Primary End Point(s)	Key Inclusion and Exclusion Criteria	Expected Reporting
Ongoing clinical trials of ablation with systemic therapy				
MWA with lenvatinib (NCT05444478)	NA	Tumor-free survival rate and OS at 36 mo	*Inclusion*: BCLC 0 B, CTP A or B (no more than 7), tumor number =<3 and size =<5 cm *Exclusion*: PVTT, extrahepatic disease, other LRT	2027
RFA or MWA with tirelizumab (NCT04652440)	Phase I Phase II	Safety and tolerability	*Inclusion*: CTP A, BCLC A or B, ECOG PS 0 or 1 *Exclusion*: prior systemic therapy	2024
RFA or MWA or brachytherapy or combined with TACE with pembrolizumab (NCT03753659)	Phase II	ORR by RECIST 1.1	*Inclusion*: CTP =<6, ECOG PS 0 or 1 *Exclusion*: extrahepatic disease, prior systemic therapy, prior radiotherapy within 4 wk	2024
Percutaneous ablation (RFA, MWA, or electroporation) with lenvatinib (NCT05113186)	Phase II	RFS at 1 y	*Inclusion*: CTP A, ECOG PS =<1, BCLC A, single tumor 3–5 cm or multiple tumors (max 3 =<3 cm) *Exclusion*: BCLC >A, prior systemic therapy, contraindications to ablation	2026
RFA with atezolizumab and bevacizumab (NCT04727307)	Phase II	RFS at 2 y	*Inclusion*: CTP A, ECOG PS =<1 *Exclusion*: PVTT, prior TACE or TARE, extrahepatic disease	2027
Ongoing clinical trials of TACE with systemic therapy				
TACE with tilelizumab and sorafenib	Phase II	1 y survival rate	*Inclusion*: CTP A, BCLC C stage *Exclusion*: Diffuse HCC, uncontrolled ascites, prior systemic therapy	Recruiting
DEB-TACE followed by durvalumab and tremelimumab (NCT03638141)	Phase II	ORR at 2 y defined by mRECIST	*Inclusion*: CTP A, ECOG PS 0 or 1 *Exclusion*: extrahepatic spread, PVTT, ascites, active HBV or HCV	2024

TACE with atezolizumab and bevacizumab, concurrent vs on-demand treatment (NCT04224636)	Phase II	Survival rate at 24 mo	*Inclusion*: CTP A-B7, ECOG PS 0 or 1 *Exclusion*: extrahepatic disease, >7 tumors, 1 tumor $\geq$ 7 cm, prior TACE, major GIB	Currently recruiting; 2025
TACE with cabozantinib, ipilimumab, nivolumab (NCT04472767)	Phase II	PFS at 6 mo, complete response rate	*Inclusion*: CTP A-B7, ECOG PS 0–2 *Exclusion*: LRT in prior 3 mo, VP3/4 PVTT, extrahepatic disease	Currently recruiting; 2027
TACE/TAE with nivolumab (NCT04268888)	Phase II Phase III	OS, Time to TACE progression (TTTP)	*Inclusion*: CTP A, ECOG PS 0–1 *Exclusion*: Extrahepatic disease, history of variceal bleeding in past 4 wk, prior embolization, systemic, or radiation therapy	2026
TACE with durvalumab and bevacizumab (NCT03778957)	Phase III	PFS	*Inclusion*: CTP A-B7, ECOG PS 0–1 *Exclusion*: VP3/VP4 PVTT, extrahepatic disease	Initial data presented (EMERALD-1),[59] study completion year 2026
TACE with lenvatinib and pembrolizumab (NCT04246177)	Phase III	PFS per RECIST 1.1 and OS	*Inclusion*: CTP A, ECOG PS 0–1 *Exclusion*: uncontrolled ascites, recent GIB, heart failure, prior LRT	2029
Ongoing clinical trials of TARE with systemic therapy				
TARE with pembrolizumab (NCT03099564)	Early phase I	PFS at 6 mo defined by RECIST 1.1	*Inclusion*: CTP A-B7, ECOG PS 0–1, VP 1–2 PVTT, multifocal disease *Exclusion*: VP 3–4 PVTT	Results submitted 2023, pending as of 2024
TARE with nivolumab (NCT03033446)	Phase II	Response rate at 8 wk	*Inclusion*: CTP A, ECOG PS =<2 *Exclusion*: prior TARE	2024
TARE with durvalumab and bevacizumab (NCT06040099)	Phase II	PFS at 3 y	*Inclusion*: CTP A, ECOG PS 0 or 1 *Exclusion*: no extrahepatic disease, coinfection with HBV and HDV, history of >1 TACE or TARE procedure; prior systemic therapy	Recruiting; 2026

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; CTP, Child-Turcotte-Pugh; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GIB, gastrointestinal bleeding; LRT, locoregional therapy; mRECIST, modified response evaluation criteria in solid tumors; MWA, microwave ablation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PVTT, portal vein tumor thrombus; RFA, radiofrequency ablation; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; VP, portal vein invasion classification.

cohort was found to be most efficacious according to one large meta-analysis. The heterogeneity in results from many permutations of therapies speaks to the need to tailor therapy timing and combination to each patient's individual needs. As a principle, TACE pre-ablation can reduce tumor vascularity and heat sink effect, while post-ablation can treat residual positive margins.[53]

TACE is postulated to increase tumor hypoxia, increased hypoxia factor-1α, which in turn increases vascular endothelial growth factor and platelet-derived growth factor, leading to increased tumor angiogenesis.[9,56] Blocking these targets via a multi-kinase inhibiting agent such as sorafenib was the impetus for the randomized, prospective TACTICS trial in intermediate-stage HCC.[56] Final results of TACTICS highlighted a nonsignificant increase in median OS of 36.2 months with TACE plus sorafenib against 30.8 months with TACE alone (P=.40). There was, however, a statistically significant PFS favoring the combination therapy group (22.8 months vs 13.5 months, HR 0.661, 95% CI 0.466–0.938, P = .02).[57] A similar corollary involving ^{90}Y TARE plus sorafenib versus sorafenib alone phase III RCT (STOP-HCC) has completed data collection with final results pending publication.[58]

The advent of immune checkpoint inhibitors (ICIs) has spurred a pronounced interest in combining systemic immune therapies and LRTs. Given TACE has a propensity to release neoantigens, ICIs could synergistically augment therapy in HCC.[35] The most recent study in this arena is the global, randomized, double-blind phase III EMERALD-1 study that was recently presented in abstract form.[59] Durvalumab/bevacizumab plus TACE experienced higher PFS compared to TACE (median 15.0 vs 8.2 months, P=.032). Although the combination group had higher grade 3 or 4 adverse events (32.5% vs 13.5%), there were no treatment-related deaths in the combination group. Patients are being followed for OS outcomes; however, OS was not significantly different between groups at this interim analysis.[59] This represents the first global phase III trial to demonstrate a positive outcome in a combination systemic therapy plus TACE group; however, we await further data on overall efficacy and safety of this approach. **Table 4** highlights ongoing trials of LRTs with systemic therapy.

SUMMARY

HCC therapeutics is a multidisciplinary venture, with multiple treatment strategies that are established and several on the horizon as investigational agents. Both embolic and ablative therapies form a backbone for treatment of BCLC stages 0 to B/C tumors. Both locoregional approaches have unique mechanistic advantages, deficits, and adverse effect profiles, which need to be accounted prior to offering treatment. Combination therapy especially in high-risk multifocal unresectable HCC is a means to synergistically enhance treatment effect by minimizing the risk of hepatic decompensation and subsequent mortality. Combination of ICIs and TACE because of recent breakthroughs is especially promising for patients with high-risk multifocal HCC.

CLINICS CARE POINTS

- The treatment effect of ablative therapies is most limited by tumor size greater than 3 cm and proximity to large vasculature structures.
- Tumor hypoxia secondary to TACE leads to neoantigen release, which are promising potential targets for systemic therapies such as multi-kinase agents and ICIs.

- BCLC stage B patients with extensive, bilobar, liver-localized tumors should be offered systemic therapy rather than TACE alone to prolong DFS.

DISCLOSURE

N.D. Parikh has provided consultation services for Exelixis and Exact Sciences and served on advisory boards for Genentech, Eisai, Gilead, Sirtex, Fujifilm Medical, and AstraZeneca. The other authors have no disclosures.

REFERENCES

1. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol 2022;77(6):1598–606.
2. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76(3):681–93.
3. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334(11):693–9.
4. Agopian VG, Harlander-Locke MP, Ruiz RM, et al. Impact of pretransplant bridging locoregional therapy for patients with hepatocellular carcinoma within milan criteria undergoing liver transplantation: analysis of 3601 Patients from the US Multicenter HCC Transplant Consortium. Ann Surg 2017;266(3):525–35.
5. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transpl 2015;21(9):1142–52.
6. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023.
7. Takayama T, Hasegawa K, Izumi N, et al. Surgery versus radiofrequency ablation for small hepatocellular carcinoma: a randomized controlled trial (SURF Trial). Liver Cancer 2021;11(3):209–18.
8. Shiina S, Yasuda H, Muto H, et al. Percutaneous ethanol injection in the treatment of liver neoplasms. AJR Am J Roentgenol 1987;149(5):949–52.
9. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182–236.
10. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11(4):317–70.
11. Niemeyer DJ, Simo KA, Iannitti DA, et al. Ablation therapy for hepatocellular carcinoma: past, present and future perspectives. Hepat Oncol 2014;1(1):67–79.
12. Poulou LS, Botsa E, Thanou I, et al. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol 2015;7(8):1054–63.
13. Iannitti DA, Martin RC, Simon CJ, et al. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. HPB (Oxford) 2007;9(2):120–4.
14. Facciorusso A, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. Int J Hyperthermia 2016;32(3):339–44.
15. Vietti Violi N, Duran R, Guiu B, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol 2018;3(5):317–25.

16. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226(2):441–51.
17. Livraghi T, Meloni F, Solbiati L, et al. Complications of microwave ablation for liver tumors: results of a multicenter study. Cardiovasc Intervent Radiol 2012;35(4):868–74.
18. Feng Y, Wang L, Lv H, et al. Microwave ablation versus radiofrequency ablation for perivascular hepatocellular carcinoma: a propensity score analysis. HPB 2021;23(4):512–9.
19. Georgiades CS, Hong K, Geschwind JF. Radiofrequency ablation and chemoembolization for hepatocellular carcinoma. Cancer J 2008;14(2):117–22.
20. Liang P, Yu J, Lu MD, et al. Practice guidelines for ultrasound-guided percutaneous microwave ablation for hepatic malignancy. World J Gastroenterol 2013;19(33):5430–8.
21. Cucchetti A, Piscaglia F, Cescon M, et al. An explorative data-analysis to support the choice between hepatic resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. Dig Liver Dis 2014;46(3):257–63.
22. Qi X, Zhao Y, Li H, et al. Management of hepatocellular carcinoma: an overview of major findings from meta-analyses. Oncotarget 2016;7(23).
23. Hu L, Lin J, Wang A, et al. Comparison of liver resection and radiofrequency ablation in long-term survival among patients with early-stage hepatocellular carcinoma: a meta-analysis of randomized trials and high-quality propensity score-matched studies. World J Surg Oncol 2024;22(1):56.
24. Bae SH, Chun SJ, Chung JH, et al. Stereotactic body radiation therapy for hepatocellular carcinoma: meta-analysis and international stereotactic radiosurgery society practice guidelines. Int J Radiat Oncol Biol Phys 2024;118(2):337–51.
25. Kim N, Cheng J, Jung I, et al. Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma. J Hepatol 2020;73(1):121–9.
26. Sapisochin G, Barry A, Doherty M, et al. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol 2017;67(1):92–9.
27. Scheffer HJ, Nielsen K, de Jong MC, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol 2014;25(7):997–1011 [quiz 1011].
28. Vidal-Jove J, Serres X, Vlaisavljevich E, et al. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. Int J Hyperthermia 2022;39(1):1115–23.
29. Song JE, Kim DY. Conventional vs drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma. World J Hepatol 2017;9(18):808–14.
30. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of Doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33(1):41–52.
31. Golfieri R, Cappelli A, Cucchetti A, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Comparative Study. Hepatology 2011;53(5):1580–9.
32. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365(12):1118–27.
33. Lencioni R, de Baere T, Soulen MC, et al. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016;64(1):106–16.

34. Singal AG, Pillai A, Parikh ND. INASL consensus on management of HCC: navigating an evolving field. J Clin Exp Hepatol 2024;14(1):101292.
35. Singal AG, Kudo M, Bruix J. Breakthroughs in hepatocellular carcinoma therapies. Clin Gastroenterol Hepatol 2023;21(8):2135–49.
36. Coffman-D'Annibale K, Xie C, Hrones DM, et al. The current landscape of therapies for hepatocellular carcinoma. Carcinogenesis 2023;44(7):537–48.
37. Kotsifa E, Vergadis C, Vailas M, et al. Transarterial chemoembolization for hepatocellular carcinoma: why, when, how? J Pers Med 2022;12(3).
38. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice guidelines proposed by the Japan society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29(3):339–64.
39. Kudo M, Kawamura Y, Hasegawa K, et al. Management of hepatocellular carcinoma in Japan: JSH consensus Statements and Recommendations 2021 update. Liver Cancer 2021;10(3):181–223.
40. Ogasawara S, Chiba T, Ooka Y, et al. A randomized placebo-controlled trial of prophylactic dexamethasone for transcatheter arterial chemoembolization. Hepatology 2018;67(2):575–85.
41. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol 2015;62(5):1187–95.
42. 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(6):1330–5.
43. Gao S, Yang Z, Zheng Z, et al. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: a meta-analysis. Hepato-Gastroenterology 2013;60(124):813–20.
44. Salem R, Lewandowski RJ. Chemoembolization and radioembolization for hepatocellular carcinoma. Clin Gastroenterol Hepatol 2013;11(6):604–11 [quiz e43-4].
45. Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. Hepatology 2021;74(5):2342–52.
46. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol 2021;6(1):17–29.
47. Parikh ND, Pillai A. Recent advances in hepatocellular carcinoma treatment. Clin Gastroenterol Hepatol 2021;19(10):2020–4.
48. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151(6):1155–63.e2.
49. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: a systematic review and meta-analysis. World J Hepatol 2016;8(18):770–8.
50. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int 2015;35(2):627–35.
51. Jiang Z, Yang F, Wang W. Applications of yttrium-90 ((90)Y) in hepatocellular carcinoma. OncoTargets Ther 2024;17:149–57.
52. Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 2013;57(3):1078–87.

53. Narayanan A, Garza-Berlanga A, Lopera J. Multifocal hepatocellular carcinoma: a narrative review assessing treatment options from the interventional radiologist's perspective. Ann Palliat Med 2023;12(6):1244–59.
54. Ren Y, Cao Y, Ma H, et al. Improved clinical outcome using transarterial chemoembolization combined with radiofrequency ablation for patients in Barcelona clinic liver cancer stage A or B hepatocellular carcinoma regardless of tumor size: results of a single-center retrospective case control study. BMC Cancer 2019;19(1):983.
55. Wang X, Hu Y, Ren M, et al. Efficacy and safety of radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinomas compared with radiofrequency ablation alone: a time-to-event meta-analysis. Korean J Radiol 2016;17(1):93–102.
56. Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2020;69(8):1492–501.
57. Kudo M, Ueshima K, Ikeda M, et al. Final Results of TACTICS: a randomized, prospective trial comparing transarterial chemoembolization plus sorafenib to transarterial chemoembolization alone in patients with unresectable hepatocellular carcinoma. Liver Cancer 2022;11(4):354–67.
58. Chauhan N, Bukovcan J, Boucher E, et al. Intra-arterial therasphere yttrium-90 glass microspheres in the treatment of patients with unresectable hepatocellular carcinoma: protocol for the STOP-HCC phase 3 randomized controlled trial. JMIR Res Protoc 2018;7(8):e11234.
59. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. J Clin Oncol 2024;42(3_suppl):LBA432.
60. Chong CCN, Lee KF, Cheung SYS, et al. Prospective double-blinded randomized controlled trial of Microwave versus RadioFrequency Ablation for hepatocellular carcinoma (McRFA trial). HPB 2020;22(8):1121–7.
61. Radosevic A, Quesada R, Serlavos C, et al. Microwave versus radiofrequency ablation for the treatment of liver malignancies: a randomized controlled phase 2 trial. Sci Rep 2022;12(1):316.
62. Facciorusso A, Abd El Aziz MA, Tartaglia N, et al. Microwave ablation versus radiofrequency ablation for treatment of hepatocellular carcinoma: a meta-analysis of randomized controlled trials. Cancers 2020;12(12).
63. Dou Z, Lu F, Ren L, et al. Efficacy and safety of microwave ablation and radiofrequency ablation in the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. Medicine (Baltim) 2022;101(30):e29321.
64. Zhang L, Du F, Zhang Y, et al. Microwave ablation is superior to radiofrequency ablation in the treatment of hepatocellular carcinoma below 5 cm - a systematic review and meta-analysis. J Minimal Access Surg 2023;19(4).
65. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–9.
66. Lo C-M, Ngan H, Tso W-K, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(5):1164–71.

67. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37(2):429–42.
68. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002;224(1):47–54.
69. Adwan H, Adwan M, Vogl TJ. Combination therapy of bland transarterial embolization and microwave ablation for hepatocellular carcinoma within the milan criteria leads to significantly higher overall survival. Cancers 2023;15(20).
70. Zhang Y, Qin Y, Dong P, et al. Liver resection, radiofrequency ablation, and radiofrequency ablation combined with transcatheter arterial chemoembolization for very-early- and early-stage hepatocellular carcinoma: a systematic review and Bayesian network meta-analysis for comparison of efficacy. Front Oncol 2022; 12:991944.
71. Keshavarz P, Raman SS. Comparison of combined transarterial chemoembolization and ablations in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Abdom Radiol (NY) 2022;47(3):1009–23.
72. Yang Y, Yu H, Qi L, et al. Combined radiofrequency ablation or microwave ablation with transarterial chemoembolization can increase efficiency in intermediate-stage hepatocellular carcinoma without more complication: a systematic review and meta-analysis. Int J Hyperthermia 2022;39(1):455–65.
73. Vardar BU, Meram E, Karaoglu K, et al. Radioembolization followed by transarterial chemoembolization in hepatocellular carcinoma. Cureus 2022;14(4):e23783.