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Locoregional therapies for hepatocellular carcinoma: The current status and future perspectives

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers and a leading cause of cancer-related mortality. Locoregional therapies (LRTs) play a crucial role in HCC management and are selectively adopted in real-world practice across various stages. Choosing the best form of LRTs depends on technical aspects, patient clinical status and tumour characteristics. Previous studies have consistently highlighted the efficacy of combining LRTs with molecular targeted agents in HCC treatment. Recent studies propose that integrating LRTs with immune checkpoint inhibitors and molecular targeted agents could provide substantial therapeutic benefits, a notion underpinned by both basic and clinical evidence. This review summarised the current landscape of LRTs in HCC and discussed the anticipated outcomes of combinations with immunotherapy regimens.

KEYWORDS
combined modality therapy, hepatocellular carcinoma, immune checkpoint inhibitors, locoregional therapy, molecular targeted therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers and a leading cause of cancer-related death worldwide.[1] The Barcelona Clinic Liver Cancer (BCLC) staging system is the predominant model for HCC management.[2] According to the BCLC guidelines, locoregional therapies (LRTs) are primarily indicated for early- and intermediate-stage HCC. Reflecting regional clinical practices, alternative guidelines and consensus statements have been developed, such as the China Liver Cancer (CNLC) staging system and the Japan Society of Hepatology (JSH) consensus statements.[3–5] These guidelines exhibit notable differences in the indications for LRTs.[4–7] The therapeutic objectives of LRTs, as outlined in various guidelines, emphasise curative intent in the early stage, disease control in the intermediate stage and palliative care in the advanced stage.

LRTs, pivotal in HCC management, encompass tumour-targeted procedures under imaging guidance, generally categorised into the percutaneous approach and the intra-arterial approach.[8,9] The

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percutaneous approach mainly involves various ablations such as radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), cryoablation, and irreversible electroporation (IRE). Intra-arterial treatments for HCC mainly include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), transarterial embolisation, and hepatic arterial infusion chemotherapy (HAIC).

The landscape of LRTs for HCC has undergone a significant evolution in recent years. On one front, novel local procedures are emerging, potentially reshaping standard care practices.[10–12] For instance, the clinical efficacy of HAIC treatment is gaining increasing recognition. Its adoption in HCC treatment is notably expanding in Eastern countries, reflecting a shift in therapeutic strategies. On another front, the integration of LRTs with systemic therapies has been explored for over a decade, yet only a few studies have achieved successful outcomes. In the current era of cancer immunotherapy, emerging evidence suggests that integrating LRTs and immune checkpoint inhibitors (ICIs) could offer substantial therapeutic advantages.[9,13–15] Although numerous randomised controlled trials (RCTs) are ongoing to evaluate these combination therapies, their adoption in real-world clinical settings has already yielded promising results.[16,17] This review aims to encapsulate the advancements in LRTs for HCC and explores the prospective impact of integrating these therapies with immunotherapy. Additionally, it delineates the ideal candidates for various LRTs, providing a comprehensive perspective on their application in clinical practice.

OVERVIEW OF LOCOREGIONAL THERAPIES

Local ablation

The ablative techniques include two types: thermal and non-thermal. Thermal ablation includes heat-based technologies such as RFA and MWA, whereas cryoablation relies on the cooling principle. Non-thermal technologies include IRE and PEI. The recommended indications for locoregional ablation in HCC are listed in Table 1. The BCLC, CNLC, and National Comprehensive Cancer Network (NCCN) guidelines all recognise the use of RFA and MWA for early stage HCC treatment, with a preference for tumours of a smaller size. The tumour size, location, and liver function should be taken into full consideration, as well as the available local operator's expertise and experience. However, several specific recommendations vary in guidelines: the BCLC guideline recommends ablation for HCC patients who are not candidates for liver transplantation (LT), while CNLC advocates for unresectable HCC. The CNLC staging system recommends the MWA as an alternative to RFA. The NCCN recommends MWA for small or unresectable HCC, while the BCLC staging system suggests MWA as a potentially preferable option for HCC lesions ≤4 cm in size.[2,4,7]

The key studies regarding LRTs for HCC are summarised in Table 2. RFA remains the mainstay of locoregional ablation in early stage HCC.[4] An RCT observed comparable 1–4 years overall survival (OS) and recurrence-free survival (RFS) rates for RFA and surgical resection in treating small solitary HCC lesions (≤5 cm) (4-year OS: 67.9% vs. 64.0%; 4-year RFS: 46.4% vs. 51.6%).[18] In contrast, another RCT targeting small HCCs meeting the Milan criteria observed significantly lower OS and RFS rates for RFA compared to surgical resection over 1–5 years (5-year OS: 54.78% vs. 75.65%, $p = 0.001$; 5-year RFS: 28.69% vs. 51.30%, $p = 0.001$).[19] A long-term study and a systematic review suggested RFA as a first-line therapy for early stage HCC when surgery is not feasible.[20,21]

However, the 'heat-sink effect' associated with RFA may increase local recurrence (LR) risk, especially when lesions are proximal to the liver capsule or critical vascular structures.[22] Multibipolar RFA represents an advanced technique characterised using a complex approach that achieves larger ablation zones through the simultaneous use of probes.[9] The multibipolar mode increases the volume and predictability (margin) of ablation zones while exhibiting lower sensitivity to the heat sink effect.[23] Notably, multibipolar RFA demonstrates high efficacy in ablating larger tumours ranging from 3 to 5 cm in size.[24,25] A retrospective multicenter study reported that multibipolar RFA was associated with a lower rate of local tumour recurrence compared to monopolar RFA.[26]

The advantages of MWA include high efficiency, short ablation time, and reduced the heat-sink effect when compared with RFA.[4] Similar efficacy was observed between RFA and MWA for small HCC in a RCT,[27] and between MWA and laparoscopic resection for solitary HCC (3–5 cm) in a large retrospective study.[28] IRE is a non-thermal ablation technique that utilises short, intense electric pulses to generate irreversible nanopores in cell membranes, subsequently inducing tumour cell death.[9] It offers the advantage of reducing the risk of injury to adjacent structures and situated at locations at risk, such as biliary structures.[9,23] Some studies have reported that IRE resulted in less liver failure than thermal ablation. Thus, IRE could be used for HCC not amenable to RFA or MWA due to the contradiction of tumour location or liver function.[23] PEI can be used to treat HCC in high-risk locations (close to the hepatic hilar region, gallbladder, and gastrointestinal tracts).[4] However, compared to RFA, PEI may result in inferior treatment outcomes while exhibiting similar complication rates in HCC within Milan criteria, as reported in a RCT.[29]

Transarterial chemoembolisation

TACE procedure consists of transcatheter administration of chemotherapeutic agents plus embolizing material to achieve strong cytotoxic and ischaemic effects, resulting in tumour necrosis. Two categories included conventional TACE (cTACE) using Lipiodol and TACE with drug-eluting beads (DEB-TACE). Selected intermediate patients without the option of LT but with well-defined tumour burden, preserved portal flow, and the feasibility of selective access to feeding tumour arteries are standard candidates for TACE.[2] According to the concept of treatment stage migration, TACE can be recommended for patients with early stage HCC in whom the

TABLE 1 Recommended indications for locoregional therapies of hepatocellular carcinoma.

Locoregional therapies	BCLC recommendations	CNLC recommendations	NCCN recommendations
Local ablation	• RFA is the first treatment approach for very early stage HCC (without vascular invasion or extrahepatic spread, with preserved liver function and PS 0) that is not feasible to LT • RFA is preferred over surgery for solitary HCC ≤3 cm without high-risk locations for ablation • RFA can be used for multifocal HCC within Milan criteria (≤3 nodules, each ≤3 cm) with contraindications to LT • MWA is potentially the best option for HCC <4 cm due to achieve more extensive tumour necrosis than RFA • PEI can be adopted in some patients with technical or safety concerns.	• Suitable for CNLC Ia and a proportion of Ib HCC (i.e., solitary tumours with a diameter of ≤5 cm or 2–3 tumours with a maximum diameter ≤3 cm) • First-line treatment for unresectable early stage HCC • TACE combined with ablation can be used for inoperable solitary or multiple tumours with a diameter of 3–7 cm • Selection of MWA or RFA based on the size and position of tumours, and the operator's experience due to similar efficacy	• Choice of ablative therapy for early stage HCC should be based on tumour size and location, underlying liver function, as well as available local radiologist expertise and experience • Ablative treatments are most effective for tumours <3 cm in an appropriate location away from other organs and major vessels/bile ducts, with the best outcomes in tumours <2 cm • MWA is an alternative to RFA for small or unresectable HCC
TACE	• First-line treatment option for the intermediate stage that defined as multifocal HCC (exceeding early stage) with preserved liver function, no cancer-related symptoms (PS 0), and no vascular invasion or extrahepatic spread • Disease with early stage not feasible or failure to curative therapy according to treatment stage migration • Selection of DEB-TACE and cTACE according to clinical preference due to the similar overall efficacy • Disease without the option of liver transplant but who have preserved portal flow and defined tumour burden	• IIb, IIIa, and a proportion of IIIb HCC, Child-Pugh A/B, and a PS score of 0–2 • Patients with resectable HCC (Ib/IIa stage) are unable or unwilling to receive surgery • Postoperative adjuvant TACE for patients at high recurrence risk • Downstaging/bridging therapy before curative surgery • DEB-TACE shared indications with cTACE; • TACE-based combinations are advocated for better outcomes	• Unresectable or inoperable tumours not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease • All tumours irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumour may be isolated without excessive non-target treatment • Evaluation of the arterial anatomy of the liver, patient's performance status, and liver function is necessary before the initiation of arterially directed therapy
HAIC	• Not specifically including HAIC on the list of treatment options for HCC	• Treatment option for TACE failure/refractoriness based on liver function • Disease with major portal vascular invasion, intrahepatic multinodular lesions, and Child-Pugh B liver function	• Not specifically including HAIC on the list of treatment options for HCC
TARE	• Could be considered in patients with unresectable single nodules <8 cm • Radiation lobectomy by TARE could be considered in selective patients to increase remnant liver volume as a bridge to resection	• Not been approved for clinical application until 2021 in Chinese mainland	• As part of arterially directed therapies, sharing major indications with TACE • Maybe appropriate in selective patients with advanced HCC, specifically segmental or lobar portal vein, rather than main portal vein thrombosis

Abbreviations: BCLC, Barcelona clinic liver cancer; CNLC, China liver cancer; cTACE, conventional TACE; DEB-TACE, TACE with drug-eluting beads; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; LT, liver transplantation; MWA, microwave ablation; NCCN, national comprehensive cancer network; PEI, Percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

recommended treatments are not feasible or have failed.[2] There are discrepancies between the East and the West regarding the indications of TACE for HCC.[15,30] The CNLC staging system provided relatively broad indications for TACE from Ib to IIIb, equivalent to part of the BCLC A and C stages and the entire B stage.[4] When considering the candidates for TACE, all three recommendations highlight the comprehensive assessment of the individual performance status, tumour burden, and liver function.[22]

The selected trials regarding TACE for HCC are summarised in Table 2. Two milestone RCTs showed that cTACE resulted in better OS outcomes than best supportive care.[31,32] Thereafter, a systemic review that enrolled 10,108 patients treated with cTACE reported an objective response rate (ORR) of 52.5% (95% CI, 43.6%–61.5%), and a median OS of 19.4 months (95% CI, 16.2–22.6).[33] There is no evidence demonstrating the superiority of DEB-TACE over cTACE in terms of survival benefits, tumour response, and safety.[34–36]

TABLE 2 Selected randomised controlled trials identifying locoregional therapies in HCC.

Trial	BCLC stage	Region	Arms	Endpoints	Outcomes
Local ablation					
Lencioni et al., 2003	Early	Italy	RFA (n = 52) versus PEI (n = 50)	OS (2 years)	98% versus 88%; HR 0.2 (95% CI 0.02–1.69); p = 0.13
Lin et al., 2005	Early	Chinese Taiwan	RFA (n = 62) versus PEI (n = 62) versus PAI (n = 63)	LR (3 years)	LR 14% versus 34% versus 31%, all $p < 0.01$;
				OS (3 years)	OS 74% versus 51% versus 53%, all $p < 0.01$
Shiina et al., 2005	Early	Japan	RFA (n = 118) versus PEI (n = 114)	OS (4 years)	74% versus 57%; HR 0.54 (95% CI 0.33–0.89); p = 0.02
Chen et al., 2006	Early	China	RFA (n = 90) versus partial hepatectomy (n = 90)	OS (4 years)	OS 65.9% versus 51.6%; p = ns
Huang et al., 2010	Early	China	RFA (n = 115) versus surgical resection (n = 115)	OS (5 years)	OS 54% versus 75%; p = 0.001
				RFS (5 years)	RFS 28% versus 51%; p = 0.017
Feng et al., 2012	Early	China	RFA (n = 84) versus surgical resection (n = 84)	OS (3 years)	OS 67.2% versus 74.8%; p = 0.342
Peng et al., 2013	Early	China	RFA plus TACE (n = 94) versus RFA (n = 95)	OS (4 years)	OS 61.8 versus 45%; HR 0.52 (95% CI 0.33–0.88); p = 0.002
				RFS (4 years)	RFS 54.8% versus 38.9%; HR 0.57 (95% CI 0.37–0.89); p = 0.009
Chen et al., 2014	Early	China	RFA plus iodine-125 implantation (n = 68) versus RFA (n = 68)	TTR	TTR 93 versus 66.8 months; HR 0.50 (95% CI 0.31–0.81); p = 0.004
				OS	OS 95.8 versus 70.8 months; HR 0.50 (95% CI 0.31–0.80); p = 0.003
Wang et al., 2015	Early/intermediate	China	RFA versus (n = 180) versus cryoablation (n = 180)	LTP (3 years)	LTP 11% versus 7%; p = 0.043
				OS (5 years)	OS 38% versus 50%; p = 0.747
Ng et al., 2017	Early	China	Hepatic resection (n = 109) versus RFA (n = 109)	Recurrence	Overall recurrence 81.7% versus 71.3%; p = 0.09
Yu et al., 2017	Early	China	MWA (n = 203) versus RFA (n = 200)	LTP (5 years)	LTP 19.7% versus 11.4%; p = 0.11
Vietti Violi et al., 2018	Early	France, Switzerland	MWA (n = 76) versus RFA (n = 76)	LTP (2 years)	LTP 12% versus 6%; HR, 1.62 (95% CI 0.66–3.94); p = 0.27
Tak et al., 2018 (HEAT study)	Early/intermediate	Global	RFA plus LTLD (n = 354) versus RFA (n = 347)	PFS	PFS 13.9 versus 13.9 months, HR 0.96 (95% CI 0.79–1.18), p = 0.71
Xia et al., 2019	Early (recurrent HCC)	China	Repeat hepatectomy (n = 120) versus RFA (n = 120)	OS	37.5 versus 47.1 months; HR 1.26 (95% CI 0.91–1.76); p = 0.17
Takayama et al., 2021	Early	Japan	Surgery (n = 150) versus RFA (n = 151)	RFS	3.5 versus 3.0 years; HR 0.92 (95% CI 0.67–1.25); p = 0.58
TACE					
Llovet et al. (2002)	Intermediate/ advanced	Spain	TAE (n = 37)/cTACE (n = 40) versus symptomatic treatment (n = 35)	OS	25.3/28.7 versus 17.9 months; p = 0.009 (cTACE vs. control)

(Continues)

TABLE 2 (Continued)

Trial	BCLC stage	Region	Arms	Endpoints	Outcomes
Lo et al. (2002)	Early/ intermediate/ advanced	Asian	cTACE (n = 40) versus symptomatic treatment (n = 39)	OS (3 years)	26% versus 3%; HR 0.50 (95% CI 0.31–0.81), p = 0.005
Okusaka et al., 2009	Intermediate	Japan	TAI (n = 82) versus cTACE (n = 79)	OS	22.6 versus 21.5 months; p = 0.383
Lammer et al., 2010 (PRECISION V trial)	Early/ intermediate/	Europe	DEB-TACE (n = 93) versus cTACE (n = 108)	6-month ORR	51.6% versus 43.5%; p = 0.11
Yu et al., 2014	Early/intermediate	China	TEA (n = 49) versus cTACE (n = 49)	OS	24.3 versus 20.1 months; p = 0.513
Golfieri et al., 2014 (PRECISION ITALIA trial)	Early/ intermediate/ advanced	Italy	DEB-TACE (n = 89) versus cTACE (n = 88)	2-year OS	56.8% versus 55.4%; p = 0.949
Ikeda et al., 2018	Intermediate/ advanced	Japan	cTACE with miriplatin (n = 129) versus cTACE with epirubicin (n = 128)	OS	36.5 versus 37.1 months; HR 1.01 (95% CI 0.73–1.40); p = 0.946
Ikeda et al. (2020) (JIVROSG-1302 PRESIDENT trial)	Early/ intermediate/ advanced	Japan	DEB-TACE (n = 99) versus cTACE (n = 101)	3-month CR rate	27.6% versus 75.2%; p < 0.0001
Zhu et al., 2022	Early/intermediate	China	cTACE with dicycloplatin (n = 22, A1) versus cTACE with dicycloplatin plus epirubicin (n = 25, A2) versus cTACE with epirubicin (n = 24, B)	ORR	50.0% versus 44.0% versus 29.17%; p = 0.093 (A1 vs. B); p = 0.338 (A2 vs. B)
HAIC					
Lyu et al., 2021 (FOHAIC-1)	Advanced	China	HAIC (n = 130) versus sorafenib (n = 132)	OS	13.9 versus 8.2 months; HR 0.408 (95% CI 0.301–0.552; p < 0.001)
Li et al., 2021	Early/intermediate	China	HAIC (n = 159) versus TACE (n = 156)	OS	23.1 versus 16.1 months; HR 0.58 (95% CI 0.4–0.75; p < 0.001)
Li et al., 2022	Early/intermediate	China	Postoperative adjuvant HAIC (n = 157) versus routine follow-up (n = 158)	DFS	20.3 versus 10.0 months; HR 0.59 (95% CI 0.43–0.81); p = 0.001)
TARE					
Salem et al., 2016	Early/intermediate	USA	TARE (n = 24) versus cTACE (n = 21)	TTP	>26 versus 6.8 months; HR 0.12 (95% CI 0.027–0.55); p = 0.001
Vilgrain et al., 2017 (SARAH trial)	Advanced	France	TARE (n = 237) versus sorafenib (n = 222)	OS	8 versus 9.9 months; HR 1.15 (95% CI 0.94–1.41); p = 0.18
Chow et al., 2018 (SIRveNIB trial)	Advanced	Asia-Pacific	TARE (n = 182) versus sorafenib (n = 178)	OS	8.8 versus 10.0 months; HR 1.12 (95% CI 0.9–1.4); p = 0.36)

Abbreviations: BCLC, Barcelona clinic liver cancer; CR, complete response; cTACE, conventional transarterial chemoembolization; DEB-TACE, TACE with drug-eluting beads; DFS, disease-free survival; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; LR, local recurrence; LTLD, lyso-thermosensitive liposomal doxorubicin; LTP, local tumour progression; MWA, microwave ablation; ORR, objective response rate; OS, overall survival; PAI, percutaneous acetic acid injection; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; RFS, recurrence-free survival; TAE, transarterial embolisation; TAI, transarterial infusion chemotherapy; TARE, transarterial radioembolization; TEA, transarterial Ethanol Ablation; TTP, time to tumour progression; TTR, time to recurrence.

Patients with earlier-stage HCC who are not candidates for curative options, including LT, surgical resection, and percutaneous ablation, can receive TACE procedures and experience long-term survival benefits.[2,37–40] Several observational studies have demonstrated that TACE can serve as a bridge therapy before LT for patients on the waiting list and is associated with lower waitlist dropout rates.[41–43] Additionally, TACE is associated with decreased HCC recurrence and improved OS post-LT, especially when the

expected waiting time exceeds 6–12 months.[44] Furthermore, TACE can function as a downstaging strategy for LT, aiming to reduce tumour burden and enable patients to meet acceptable transplantation criteria.[42,45]

Hepatic arterial infusion chemotherapy

By injecting highly concentrated chemotherapeutic drugs into the liver via the hepatic artery, HAIC was once commonly used to treat advanced HCC in Asian countries, especially Japan.[5,46] The consequent concentration of the regimens within the tumour would be expected to increase anti-tumour effects. However, the different chemotherapeutic drug regimens could be a critical factor influencing treatment efficacy.

HAIC with interferon, cisplatin, or fluorouracil plus cisplatin regimen was initially developed in Japanese patients. Two RCTs, SCOOP-2 and SILIUS trials, failed to demonstrate the therapeutic benefits of integration of HAIC and sorafenib compared to sorafenib alone in Japan.[47,48] The efficacy of HAIC of oxaliplatin, fluorouracil, and leucovorin (FOLFOX) regimens for advanced HCC has been confirmed in Chinese patients. A retrospective study reported that FOLFOX-HAIC was associated with longer median progression-free survival (PFS) and OS compared to sorafenib in advanced HCC.[49] FOHAIC-1 trial demonstrated the OS benefit of FOLFOX-HAIC over sorafenib in advanced HCC (median, 13.9 vs. 8.2 months; $p < 0.001$).[10] Another phase III trial indicated the survival advantage of FOLFOX-HAIC over TACE in patients with unresectable large HCC (largest diameter ≥7 cm) without macrovascular invasion or extrahepatic spread.[11] Notably, the differences in patient selection and efficacy between HAIC and TACE for HCC management warrant confirmation in future studies.[50]

HAIC can serve as a treatment option for TACE failure/refractoriness based on liver function and be used to treat HCC with major portal vascular invasion, and intrahepatic multinodular lesions according to CNLC guidelines and JSH consensus statements.[3,5,51] However, no RCT has yet demonstrated a clinical benefit from HAIC in a Western population with HCC. Moreover, HAIC has not been specifically included in the BCLC staging classification and treatment schedule.[2]

Transarterial radioembolization

TARE is performed by injecting microspheres coated with yttrium-90 (Y90, a ß-emitting isotope) into the hepatic tumour-feeding arteries. Y90 microspheres can selectively emit high-energy, low-penetration radiation to hepatic tumours.[52] The median OS after TARE ranges from 16.9 to 17.2 months for patients at the intermediate stage and 10–12 months for patients at the advanced stage with portal vein invasion.[53–56] The findings from a phase 2 trial (DOSISPHERE-01) revealed that the implementation of personalised dosimetry yielded a noteworthy enhancement in the ORR among patients with locally advanced HCC in comparison to standard dosimetry (71% vs. 36%, $p = 0.0074$).[57] These results imply that personalised dosimetry is poised to positively impact outcomes in clinical settings, underscoring its potential consideration in future trial designs. SARAH trial and SIRveNIB trials compared the efficacy and safety in patients with TARE versus sorafenib,[58,59] and found that the tumour response rate was significantly higher in the TARE group. TARE could be considered in patients with unresectable single nodules <8 cm and serve as a bridge to resection in selective patients using radiation lobectomy.

COMBINATION AMONG LOCOREGIONAL THERAPIES

Transarterial chemoembolisation with local ablation

TACE in combination with local ablation can potentially improve efficacy in unresectable HCC. TACE can reduce the cooling effect of tumour blood flow to enhance the effect of RFA thermal coagulation. An RCT showed that sequential TACE and RFA (first cTACE and then RFA) significantly improve OS and RFS than RFA monotherapy for solitary recurrent HCC lesions (≤5 cm).[60] While combined TACE and RFA therapy demonstrates improved OS and RFS than RFA alone in early stage HCC,[61,62] there are notable discrepancies in global guidelines. The CNLC guidelines advocate for the use of TACE in conjunction with RFA for stages Ib and IIa HCC, whereas the BCLC guidelines do not support this approach.[2,3] A retrospective study reported similar OS and RFS rates of MWA between patients with HCC after downstaging with TACE and those initially meeting the Milan criteria.[63] Although several retrospective studies also reported treatment benefits with TACE plus MWA over MWA alone,[64,65] no RCT was reported to identify treatment outcomes of TACE and local ablation with TACE alone.

Transarterial chemoembolisation with radiotherapy

TACE in combination with radiotherapy may provide therapeutic benefits. A systematic review indicated that TACE combined with radiotherapy was more therapeutically beneficial than TACE alone in unresectable HCC.[66] TACE in combination with external beam radiotherapy could significantly improve OS (55.0 vs. 43.0 weeks; $p = 0.04$) and time to disease progression (31.0 vs. 11.7 weeks; $p < 0.001$) when compared with sorafenib in HCC with macroscopic vascular invasion.[67] The CNLC guidelines advocate the combined use of TACE and external radiotherapy for treating patients with HCC at stages IIa, IIb, and IIIa. Conversely, this therapeutic approach is not endorsed by the BCLC guidelines.

In the field of brachytherapy, the implantation of iodine 125 seeds in the treatment of HCC has been reported in clinical practice in China and has not been widely adopted in most countries worldwide.[4,68]

Portal irradiation stent loaded with iodine 125 seeds placement plus TACE resulted in better OS than sorafenib plus TACE in patients with advanced HCC and portal vein tumour thrombosis.[69]

LOCOREGIONAL THERAPIES WITH MOLECULAR TARGETED AGENTS

Transarterial chemoembolization with molecular targeted agents

After embolizing tumour-feeding arteries, TACE induces hypoxia microenvironment and vascular endothelial growth factor (VEGF) upregulation, resulting in tumour angiogenesis and LR.[70,71] Tyrosine kinase inhibitors (TKIs) such as sorafenib can target VEGF and decrease angiogenesis induced by TACE. Thus, TACE, combined with TKIs, has a potential synergistic effect by inhibiting tumour angiogenesis and proliferation.

TACE plus antiangiogenic drugs for HCC have been explored over 10 years (Table 3). Unfortunately, most studies failed to achieve the primary endpoint and demonstrate conclusive efficacy of combination therapy compared to TACE alone.[72–75] The TACTICS trial reported that PFS was significantly longer with TACE plus sorafenib than with TACE alone (median, 25.2 vs. 13.5 months; $p = 0.006$).[76] Recently, updated results of the TACTICS trial showed only little OS benefits without a significant difference between TACE plus sorafenib and TACE alone (median, 36.2 vs. 30.8 months; hazard ratio, 0.861; 95% CI, 0.607–1.223; $p = 0.40$).[77]

The TACTICS-L trial identified the efficacy (an ORR of 88.7%, and a complete response rate of 66.1%) and safety of TACE with lenvatinib in Japanese patients with unresectable HCC.[78] Similarly, the LAUNCH trial showed longer survival (median OS, 17.8 vs. 11.5 months; median PFS, 10.6 vs. 6.4 months, $p < 0.001$) and improved ORR (54.1% vs. 25.0; $p < 0.001$) with TACE plus lenvatinib than with lenvatinib alone in advanced HCC.[79]

Hepatic arterial infusion chemotherapy with molecular targeted agents

The SILIUS trial compared HAIC with low-dose cisplatin and fluorouracil plus sorafenib versus sorafenib alone in Japan, which did not meet its primary endpoint of OS superiority.[48] Another trial reported that FOLFOX-HAIC plus sorafenib improved OS, PFS, and tumour response with an acceptable safety profile compared with sorafenib in HCC patients with portal vein invasion.[12] The paradoxical results of the two studies regarding the effects of the first-line HAIC combination need further exploration. There were differences in several aspects, including HCC populations, aetiology, chemotherapeutic drug regimens, and procedure techniques, that may have an impact.[80]

Transarterial radioembolization with molecular targeted agents

The SORAMIC trial compared the efficacy of TARE plus sorafenib with sorafenib alone in advanced HCC.[81] The OS benefit of TARE plus sorafenib was not observed (12.1 vs. 11.4 months, $p = 0.95$). A subsequent analysis of the SORAMIC trial indicated that the addition of TARE to sorafenib therapy led to a significantly higher increase in the albumin-bilirubin score compared with sorafenib alone.[82] This finding implies that augmenting sorafenib with TARE may adversely affect liver function, potentially impairing prognosis post-treatment.

LOCOREGIONAL THERAPIES WITH IMMUNOTHERAPY-BASED REGIMENS

RFA with immunotherapy-based regimens

The potential immune stimulations of local ablation include increasing the exposure of tumour antigens, enhancing the immunogenicity of tumour antigens, activating antigen-presenting cells, and increasing tumour-specific T cells.[83,84] These potential mechanisms provide opportunities to combine local ablation with ICIs. An exploratory, proof-of-concept study indicated that combining tremelimumab (cytotoxic T-lymphocyte-associated protein four inhibitor) and local ablation therapy could result in significant accumulation of intra-tumoural $CD8^+$ T cells.[85]

Recently, a phase 1/2 trial showed that local ablation plus toripalimab (a programed death 1 [PD-1] inhibitor) was superior to toripalimab alone for second-line unresectable HCC in terms of OS (median, 18.4 vs. 13.2 months, $p = 0.005$) and PFS (median, 7.1 vs. 3.8 months, $p < 0.001$).[86] A similar OS (median, 19.3 months) outcome was also reported in a preliminary study that identified MWA combined with apatinib (a TKI) and camrelizumab (a PD-1 inhibitor) in advanced HCC.[87] Some trials identifying local ablation combined with ICIs in HCC, such as the adjuvant approach after ablation and the neoadjuvant approach before ablation, are still underway (Table 4). The phase 3 IMbrave050 trial, notable for being the first to show positive outcomes in adjuvant treatment for HCC, found that a combination of atezolizumab and bevacizumab significantly enhanced RFS in high-risk patients post-curative-intent resection or ablation compared to active surveillance.[88]

Transarterial chemoembolization with immunotherapy-based regimens

There are rationales for combining TACE with anti-PD-(Ligand [L])1 and molecular targeted therapies.[13,14,83] TACE results in necrosis of the tumour tissue and releases tumour antigens, which may promote

TABLE 3 Selected randomised controlled trials identifying locoregional therapies combined with systemic agents in HCC.

Trial	BCLC stage	Region	Arms	Endpoints	Outcomes
Local ablation combined with systemic agents					
Zhou et al., 2023	Intermediate/ advanced (second line)	China	Local ablation plus toripalimab (n = 65) versus toripalimab alone (n = 65)	PFS	7.1 versus 3.8 months, HR 0.57 (95% CI 0.40–0.82); $p < 0.001$
TACE combined with systemic agents					
Kudo et al., 2011 (POST-TACE trial)	Early/ intermediate	Japan, South Korea	cTACE (responders) plus sorafenib (n = 229) versus cTACE plus placebo (n = 229)	TTP	5.4 versus 3.7; HR 0.87 (95% CI 0.70–1.09); $p = 0.252$
Kudo et al., 2014 (BRISK-TA trial)	Early/ intermediate/ advanced	Global	cTACE or DEB-TACE plus brivanib (n = 249) versus cTACE plus placebo (n = 253)	OS	26.4 versus 26.1 months; HR 0.90 (95% CI 0.66–1.23); $p = 0.53$
Lencioni et al., 2016 (SPACE trial)	Intermediate	Global	DEB-TACE plus sorafenib (n = 154) versus DEB-TACE plus placebo (n = 153)	TTP	5.6 versus 5.5 months; HR 0.797 (95% CI 0.588–1.080); $p = 0.072$
Meyer et al., 2017 (TACE 2 trial)	Early/ intermediate	UK	DEB-TACE plus sorafenib (n = 157) versus DEB-TACE plus placebo (n = 156)	PFS	7.8 versus 7.7 months; HR 1.03 (95% CI 0.75–1.42); $p = 0.85$
Kudo et al., 2018 (ORIENTAL trial)	Early/ intermediate/ advanced	Japan, South Korea, Chinese Taiwan	cTACE plus orantinib (n = 445) versus cTACE plus placebo (n = 444)	OS	31.1 versus 32.3 months; HR 1.090 (95% CI 0.878–1.352); $p = 0.435$
Kudo et al., 2019 (TACTICS trial)	Early/ intermediate/ advanced	Japan	cTACE plus sorafenib (n = 80) versus cTACE (n = 76)	PFS	25.2 versus 13.5 months; HR 0.59 (95% CI 0.41–0.87); $p = 0.006$
Park et al., 2019 (STAH trial)	Advanced	South Korea	cTACE plus sorafenib (n = 170) versus sorafenib (n = 169)	OS	12.8 versus 10.8 months; HR 0.91 (CI 0.69–1.21); $p = 0.290$
Peng et al., 2022 (LAUNCH trial)	Advanced	China	TACE plus lenvatinib (n = 170) versus lenvatinib (n = 168)	OS	17.8 versus 11.5 months; hazard ratio, 0.45; $p < 0.001$
HAIC combined with systemic agents					
Kudo et al., 2018 (SILIUS trial)	Advanced	Japan	HAIC plus sorafenib (n = 102) versus sorafenib (n = 103)	OS	11.8 versus 11.5 months; HR 1.009 (95% CI 0.743–1.371); $p = 0.95$
Kondo et al., 2019 (SCOOP-2 trial)	Early/ intermediate/ advanced	Japan	HAIC plus sorafenib (n = 35) versus sorafenib (n = 33)	OS	10.0 versus 15.2 months, HR 1.08 (95% CI 0.63–0.86); $p = 0.78$
He et al., 2021	Advanced	China	HAIC plus sorafenib (n = 125) versus sorafenib (n = 122)	OS	13.37 versus 7.13 months; HR 0.35 (95% CI 0.26–0.48); $p < 0.001$
TARE combined with systemic agents					
Ricke et al., 2019 (SORAMIC trial)	Advanced	Europe, Turkey	TARE plus sorafenib (n = 216) versus sorafenib (n = 208)	OS	12.1 versus 11.4 months; HR 1.01 (95% CI 0.81–1.25); $p = 0.95$

Abbreviations: BCLC, Barcelona clinic liver cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TARE, yttrium-90 transarterial radioembolization; TTP, time to progression.

tumour-specific immune responses.[13,14] The liver contains immunosuppressive cell populations and has an intrinsic immune tolerance, which decreases the immune response to tumour.[89,90] TACE can be a locoregional inducer of immunogenic cell death in HCC and transform the immunosuppressive 'cold tumour' into a 'hot tumour' by restoring the immune microenvironment.[13,14,83,91]

TABLE 4 Summary of ongoing phase 3 trials of locoregional therapies combined with ICIs in HCC.

Trial (NCT number)	Population (BCLC stage)	Projected enrolment	Experimental arm	Control arm	Primary endpoint
RFA combined with ICIs					
RANT (NCT05277675)	Recurrent HCC after liver resection or RFA (early stage)	160	Neoadjuvant therapy (tislelizumab/ sintilimab + lenvatinib/ bevacizumab) plus RFA	RFA	1-year RFS and OS
TACE combined with ICIs					
EMERALD-1 (NCT03778957)	Not amenable to curative treatment but amenable to TACE (intermediate/advanced stage)	600	TACE in combination with durvalumab (arm A) TACE in combination with durvalumab and bevacizumab (arm B)	TACE in combination with placebos (arm C)	PFS (arm B vs. arm C)
LEAP-012 (NCT04246177)	Not amenable to curative treatment but amenable to TACE (intermediate stage)	950	cTACE plus pembrolizumab plus lenvatinib	cTACE	OS and PFS
TACE-3 (NCT04268888)	Not amenable to curative treatment but amenable to TACE (intermediate stage)	522	DEB-TACE plus nivolumab	DEB-TACE	OS
CheckMate 74W (NCT04340193)	Beyond Milan and up-to-7 criteria and eligible for TACE (intermediate stage)	765	TACE plus nivolumab plus ipilimumab TACE plus nivolumab	TACE	OS and TTTP (all arm A vs. arm C)
EMERALD-3 (NCT05301842)	Locoregional HCC not amenable to curative therapy (intermediate stage)	525	Tremelimumab, durvalumab, and lenvatinib in combination with TACE (arm A); Tremelimumab and durvalumab in combination with TACE (arm B)	TACE (arm C)	PFS (arm A vs. arm C)
NCT04559607	CNLC stage IIa-IIIa (intermediate/ advanced stage)	188	TACE plus camrelizumab plus apatinib	TACE	PFS
HAIC combined with ICIs					
NCT05233358	Low response or failure to TACE (intermediate and advanced stage)	176	HAIC combined with regorafenib and immune checkpoint inhibitors	TACE combined with regorafenib and immune checkpoint inhibitors	PFS
NCT05250843	High-risk recurrence after resection (intermediate and advanced stage)	90	Neoadjuvant therapy with TACE/ HAIC and lenvatinib and sintilimab before liver resection	Liver resection	RFS

Abbreviations: BCLC, Barcelona clinic liver cancer; CNLC, China liver cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, TACE with drug-eluting beads; HAIC, hepatic arterial infusion chemotherapy; ICIs, Immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival; RFA, Radiofrequency ablation; RFS, recurrence-Free survival; TACE, transarterial chemoembolization; TTTP, time to TACE progression.

Recently, a retrospective, multicenter study reported that TACE combined with nivolumab significantly extended median PFS in advanced HCC compared to nivolumab monotherapy (median, 8.8 vs. 3.7 months, $p < 0.01$).[17] A nationwide, retrospective cohort study (CHANCE001) included 800 HCC patients from 59 academic hospitals in China and suggested that TACE plus anti-PD-(L)1 and molecular targeted drugs resulted in longer OS (median, 19.2 vs. 15.7 months, $p = 0.001$) and PFS (median, 9.5 vs. 8.0 months, $p = 0.002$) than TACE monotherapy in intermediate and advanced HCC.[16] Subsequently, another retrospective study (CHANCE2211) reported a significant improvement in OS with TACE plus camrelizumab and apatinib over TACE alone (Median, 24.1 vs. 15.7 months, $p = 0.008$).[92] Moreover, the START-FIT trial indicated that sequential TACE and stereotactic body radiotherapy followed by PD-L1 inhibitor have promising outcomes for conversion therapy in locally advanced unresectable HCC with a theoretical conversion rate of 55%.[93]

Several RCTs are currently investigating the outcomes of combining TACE with immunotherapy-based regimens for

unresectable HCC, as outlined in Table 4. These trials encompass various combinations, including TACE with durvalumab plus bevacizumab (EMERALD-1), TACE with pembrolizumab plus lenvatinib (LEAP-012), TACE with nivolumab (TACE-3), TACE with nivolumab plus ipilimumab (CheckMate 74W), and TACE with tremelimumab plus durvalumab plus lenvatinib (EMERALD-3), among others. Notably, EMERALD-1 met its primary endpoint for PFS, marking it as the first global phase 3 trial to report positive outcomes in systemic therapy combined with TACE for locoregional HCC.

Beyond ICI combinations, other types of immunotherapies are being explored in combination with TACE for HCC treatment. Cao et al. reported the promising outcomes of transarterial viroembolization, a technique that integrates transarterial embolisation with oncolytic virus infusion, in rabbit VX2 tumour models.[94] The phase 2 ImmunoTACE trial revealed that adding tumour lysate-pulsed dendritic cell infusions to TACE and low-dose cyclophosphamide notably enhanced PFS (18.6 vs. 10.4 months, $p = 0.02$) in patients with intermediate-stage HCC.[95]

Hepatic arterial infusion chemotherapy with immunotherapy-based regimens

The therapeutic efficacy of chemotherapeutic drugs involves a considerable immunological component.[96] Chemotherapeutic agents can mediate immunostimulatory effects by targeting immune cells or cancer cells as well as altering whole-body physiology.[96] In the FOLFOX regimen, oxaliplatin and fluorouracil may serve as confirmed or potential inducers of immunogenic cell death, respectively.[96]

A real-world study included 135 patients with unresectable HCC and evaluated clinical outcomes of HAIC plus PD-(L)1 and molecular targeted drugs. The median OS was 30 months after successful conversion resection.[97] A phase II trial reported that HAIC in combination with lenvatinib and toripalimab had promising antitumour outcomes in patients with advanced HCC at high risk.[98] The median OS and PFS were 17.9 and 10.4 months, respectively. Relevant phase III studies have been underway (Table 4).

Transarterial radioembolization with immunotherapy-based regimens

Y90-TRAE can induce local and systemic immune activation of the HCC microenvironment, as shown by the high-dimensional analysis of tumour and systemic immune landscapes.[99] Granzyme B high expression and infiltration of $CD8^+$ T cells, $CD56^+$ NK cells, and $CD8^+$ $CD56^+$ NKT cells exhibited signs of local immune activation, and the upregulation of genes involved in innate and adaptive immune activation in Y90-TRAE-treated tumours.[99] The increase in tumour necrosis factor-α on both the $CD8^+$ and $CD4^+$ T cells as well as in antigen-presenting cells was observed after Y90-TARE in peripheral blood mononuclear cells.[99]

The CA 209–678 trial enrolled 40 advanced HCC patients treated with Y90-TARE followed by intravenous nivolumab 240 mg with an ORR of 30.6% (95% CI 16.4–48.1), which did not meet the study endpoint.[100] However, the NASIR-HCC trial showed promising anti-tumour activity with an ORR of 41.5% and a median OS of 20.9 months. The therapeutic outcome of TARE integrated with ICIs requires further investigation.

CONCLUSION

Over the past decade, LRTs for HCC have significantly evolved towards individualised treatment, characterised by precision, targeted approaches and reduced systemic toxicity, thereby enhancing patient OS. The criteria for patient selection for LRTs vary widely, reflecting the diversity of regional guidelines. Emerging procedures such as IRE have shown promising clinical benefits in HCC treatment, underscoring the need for future phase 3 trials. While the efficacy of HAIC has been established in Eastern populations, its therapeutic outcomes in Western patients warrant further exploration. Amidst the rapid advancements in targeted therapy and immunotherapy, the integration of LRTs with systemic therapy is undergoing a rigorous investigation. This approach has the potential to revolutionise HCC treatment and could significantly alter the treatment paradigm in the future. However, the optimal timing for such combination therapy remains undetermined. Lastly, given the relatively limited treatment response and survival benefits currently observed, the development of precise biomarkers and prognostic models is imperative to select the most suitable patients for these therapies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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