Fu *et al. Hepatoma Res* 2024;10:42
DOI: 10.20517/2394-5079.2024.103

Hepatoma Research

Review

Open Access

Check for updates

Transarterial intervention therapy combined with systemic therapy for HCC: a review of recent five-year articles

Chao Fu[1,2,3#], Hongsen Chen[1,2,3#], Yifan Chen[1,2,3#], Wenbin Liu[1,2,3], Guangwen Cao[1,2,3]

[1]Department of Epidemiology, Key Laboratory of Biological Defense, Ministry of Education, Shanghai 200433, China.
[2]Department of Epidemiology, Shanghai Key Laboratory of Medical Bioprotection, Shanghai 200433, China.
[3]Department of Epidemiology, Navy Medical University, Shanghai 200433, China.
[#]Authors contributed equally.

Correspondence to: Prof. Guangwen Cao, Department of Epidemiology, Navy Medical University, 800 Xiangyin Rd., Shanghai 200433, China. E-mail: gcao@smmu.edu.cn

How to cite this article: Fu C, Chen H, Chen Y, Liu W, Cao G. Transarterial intervention therapy combined with systemic therapy for HCC: a review of recent five-year articles. *Hepatoma Res* 2024;10:42. https://dx.doi.org/10.20517/2394-5079.2024.103

Received: 31 Jul 2024 **First Decision:** 5 Sep 2024 **Revised:** 20 Sep 2024 **Accepted:** 29 Sep 2024 **Published:** 11 Oct 2024

Academic Editor: Guido Gerken **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Recently, the combination of interventional and systemic therapies has become an essential treatment modality for primary liver cancer (PLC). Interventional therapy might promote tumor necrosis and enhance immunogenicity, while the combination with systemic therapy further augments clinical efficacy. Clinical studies have demonstrated that, compared with interventional therapy alone, the combination of interventional therapy with either immunotherapy or targeted therapy can significantly improve tumor response rate and extend the survival period. Furthermore, the synergistic therapeutic approach may enable patients with initially unresectable hepatocellular carcinoma (HCC) to undergo surgery, thus enhancing the overall therapeutic outcome. The combined therapy not only maintains the occurrence and severity of adverse effects at a manageable level but also ensures that any associated adverse effects remain within a controllable scope. Most recent studies are retrospective analyses with small sample sizes. There is an imperative need for more large-scale, prospective, randomized controlled clinical trials to elucidate the optimal combination therapy modality and to identify the ideal patient group for treatment.

Keywords: TACE, HAIC, TAE, TARE, immunotherapy, targeted therapy

INTRODUCTION

hepatocellular carcinoma (HCC) constitutes 75%-85% of primary liver cancer (PLC) cases and ranks as the third leading cause of annual cancer-related deaths worldwide[1]. PLC remains the second leading cause of cancer-related mortality in China, accounting for approximately 44.4% of all cancer deaths in the population < 65 years[2]. HCC accounts for 93.0% of PLC cases, with serological positivity for HBV at 84.4% in Chinese HCC patients[3]. Surgical resection is currently the main modality for HCC. However, due to the occult onset and rapid progression of HCC, many patients are diagnosed at an advanced stage, missing the window for surgery[4]. Therefore, it is particularly important to investigate effective treatment methods for intermediate and advanced stages of HCC. In this context, transarterial interventions have emerged as prevalent and effective non-surgical therapeutic modalities for patients in these stages. Nevertheless, the efficacy of interventional therapy is not satisfactory for patients with extrahepatic metastases and those with type III and IV portal vein tumor thrombus (PVTT). For these patients, interventional therapy can exacerbate local tissue hypoxia, tumor progression, or recurrence. Additionally, the results of two Phase III trials (CheckMate 459 and KEYNOTE-240)[5,6] indicate that the effects of monotherapy are limited for patients with intermediate and advanced HCC who receive systemic therapy. Clinical trials that have evaluated combination strategies involving immune checkpoint inhibitors (ICIs) and other anticancer agents have produced more compelling results[7-9]. With the advancement of fundamental and clinical research, systemic therapy has become increasingly pivotal in the treatment of HCC[9-11]. However, most patients do not derive significant benefits from such treatments, and some may experience severe immune-related side effects, which can impact therapeutic efficacy. Thus, combination therapy modality based on interventional and systemic therapy has gained more and more attention. Previous studies have summarized the progress of the combination of interventional therapy and systemic therapy, but those articles are mainly based on past advancements[12]. This article summarized the latest developments in the efficacy analysis of transarterial intervention therapy combined with systemic therapy in the past five years.

TRANSARTERIAL INTERVENTION THERAPY

The liver is supplied by the portal vein and the hepatic artery. Contrary to normal liver tissue, where 75% of the blood supply comes from the portal vein, HCC lesions are predominantly supplied by the hepatic artery, with the remaining nourished by the portal vein[13]. This vascular disparity allows for the possibility of transarterial intervention and embolization of the hepatic artery that supplies the liver tumor, leading to tumor hypoxia and necrosis.

Transarterial Embolization (TAE) is an interventional therapeutic technique that employs endovascular embolic agents, such as gelatin sponge particles, polyvinyl alcohol (PVA) particles, and polyacrylamide microspheres, to selectively block the arterial vessels supplying blood to a tumor [Figure 1A]. This blockage induces local ischemia by depriving the tumor of its blood supply, thereby inhibiting its growth and preventing further spread. TAE is particularly indicated for the treatment of unresectable HCC, offering an effective treatment option for patients[14].

Transarterial Chemoembolization (TACE) not only obstructs tumor vasculature but also delivers high concentrations of chemotherapeutic agents directly to tumor cells, thereby reducing the toxicity of chemotherapy[14] [Figure 1B]. TACE is the most widely utilized form of interventional therapy and is considered the first-line treatment for patients with HCC who are not candidates for curative resection. Two techniques for performing TACE have been developed: (1) Conventional TACE: This method involves the infusion of cytotoxic chemotherapeutic agents mixed with lipiodol directly into the tumor, followed by the embolization of the arterial blood supply; (2) Drug-Eluting Beads Transarterial Chemoembolization (DEB-TACE): This advanced approach involves injecting doxorubicin-loaded microspheres into the hepatic

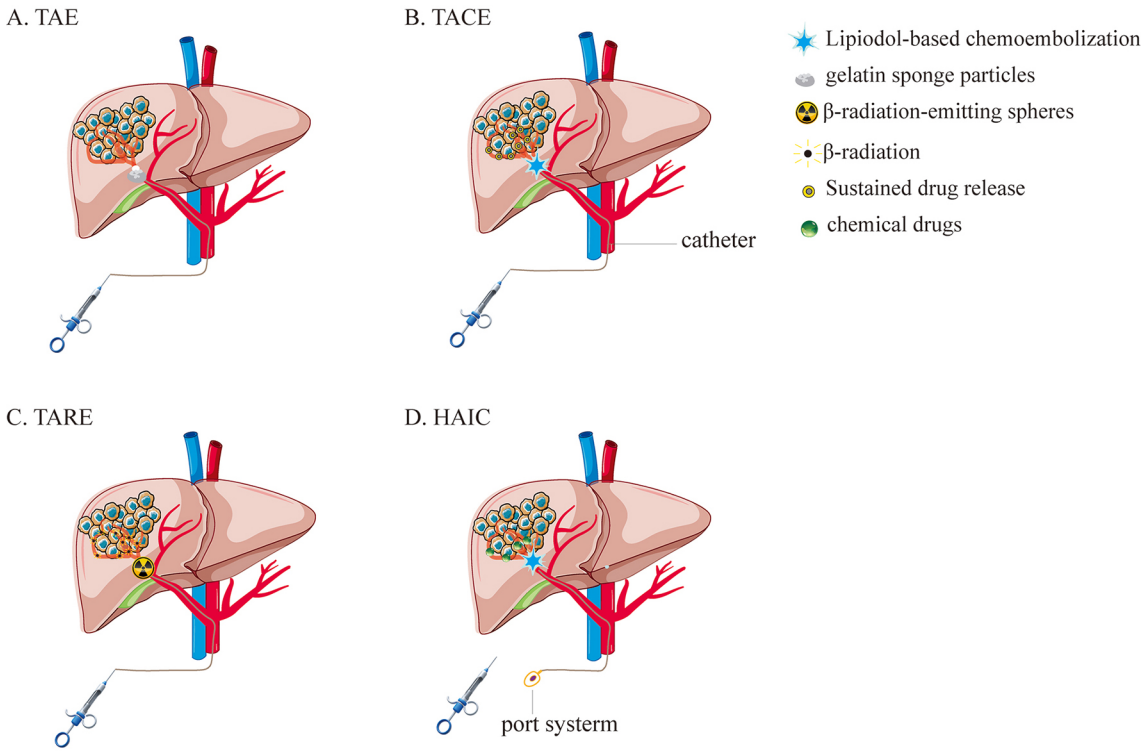

Figure 1. Four types of transarterial intervention therapy. A: TAE selectively obstructs the arterial vessels supplying the tumor using embolic agents, leading to ischemia and necrosis of the tumor tissue; B: TACE combines chemotherapeutic agents with embolic materials to selectively obstruct the blood supply to the tumor while delivering concentrated drugs directly to hepatocellular carcinoma cells; C: TARE involves the delivery of radioactive isotopes, such as Yttrium-90, to the liver via the hepatic artery, enabling selective destruction of tumor cells through beta radiation; D: HAIC involves the percutaneous infusion of chemotherapeutic agents directly into the hepatic artery, concentrating the treatment on the tumor while minimizing systemic toxicity. TAE: Transarterial embolization; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; HAIC: hepatic arterial infusion chemotherapy.

artery, where they effectively block the tumor's microvasculature while delivering a sustained release of the chemotherapeutic agent. The repetitive application of chemotherapeutic agents may lead to an accumulation of systemic toxicity, which not only increases damage to normal cells but also potentially induces drug resistance. Furthermore, arterial embolization exacerbates ischemia and hypoxia in the tumor, leading to a deterioration of the tumor microenvironment. This phenomenon allows the tumor not only to evade immune surveillance but also to augment its growth through enhanced glycolysis, ultimately precipitating recurrence and metastases.

Transarterial Radioembolization (TARE), also known as selective internal radiation therapy (SIRT), shares the same principle with TACE, except that it employs radioactive isotopes, such as Yttrium-90 (Y-90) or Lutetium-177 (Lu-177), in place of chemotherapeutic agents, with Y-90 being more commonly used in clinical practice. This radiation therapy involves the placement of microspheres loaded with radioactive isotopes into the liver via the hepatic artery, which emit beta rays at an average distance of 0.25 centimeters[15], thereby directly and selectively destroying tumor cells through close-range radiotherapy [Figure 1C]. Compared to conventional external radiation therapy, TARE demonstrates a reduced incidence of side effects, making it a milder treatment option for patients. The applicability of TARE is particularly suitable for patients with large tumor volumes who are not candidates for surgical resection, or who have exhibited an insufficient response to TACE and suboptimal outcomes from thermal ablation. However, despite its precision, TARE has certain limitations and potential risks. A primary concern is the off-target

distribution of Y-90 microspheres to non-tumoral tissues, which can lead to severe complications such as radiation-induced liver disease (RILD) or damage to adjacent organs[16]. Given its unique therapeutic approach, TARE has been widely applied in the treatment of HCC at all stages[15].

Hepatic arterial infusion chemotherapy (HAIC) has been widely applied in clinical practice in Asia, such as China, Japan, and South Korea, and has been incorporated into local guidelines for the treatment of HCC. However, in Western countries, the application of HAIC is relatively less common, and it has not been widely adopted in the treatment guidelines of major liver disease research organizations, such as the American Association for the Study of Liver Diseases (AASLD)[17], the European Association for the Study of the Liver (EASL)[18], and the Asian Pacific Association for the Study of the Liver (APASL). Furthermore, international medical oncology societies, such as the American Society of Clinical Oncology (ASCO)[19] or the European Society for Medical Oncology (ESMO)[20], also seldom mention HAIC in their treatment recommendations. HAIC is a well-established alternative strategy to systemic chemotherapy, characterized by the percutaneous placement of a catheter into the hepatic artery for the prolonged and continuous infusion of chemotherapeutic agents [Figure 1D]. This method enables the direct delivery of drugs to the blood vessels supplying the tumor, effectively increasing the local drug concentration while significantly reducing systemic toxic side effects. The chemotherapeutic agents exert their anticancer activity through the first-pass effect in the liver, further enhancing their therapeutic efficacy. HAIC was initially developed by Japanese researchers utilizing interferons, cisplatin, or a combination of fluorouracil and cisplatin, primarily for the treatment of patients with liver metastases from colorectal cancer. In China, significant advancements have been made in the application of this therapy, particularly with the integration of the FOLFOX (a combination of oxaliplatin, fluorouracil, and leucovorin) with HAIC for the treatment of advanced HCC. The efficacy of this combined therapeutic approach has been clinically validated among Chinese patients[21]. However, due to different understandings and practices regarding the indications, operational standards, and dosage selection for HAIC, the optimal protocol for HAIC treatment has not yet been standardized, and more high-quality clinical studies are still needed to enhance the evidence level for HAIC.

Based on the Barcelona clinic liver cancer (BCLC) staging system, the selection of therapeutic regimens for HCC has become widespread in Europe and the United States. Transarterial intervention therapy is suitable for early-stage, very early-stage, or intermediate-stage HCC, such as those classified as BCLC stages A and B, where TACE or SIRT are recommended by ESMO[20], while systemic therapy is more appropriate for advanced HCC[22]. The etiology of HCC in Western populations is often attributed to the hepatitis C virus as well as non-alcoholic and alcoholic liver diseases. In contrast, the predominant etiological factors for HCC in Chinese patients are chronic hepatitis B virus infection and exposure to aflatoxins. Chinese scholars possess much experience and unique insights in the management of HCC. Consequently, the Chinese guidelines are more inclined to formulate therapeutic strategies based on domestic clinical practices and research findings[21,23]. In China, the treatment of HCC is determined according to the China Liver Cancer Staging 2024 (CNLC 2024), where transarterial interventional therapy can be applied in the early, intermediate, and advanced stages. Surgical resection and ablation are performed in the very early, early, and intermediate stages. During the early and intermediate phases of HCC, one may opt for TACE alone or in combination with ablation therapy. Alternatively, systemic treatment can be considered, depending on the specific condition. For patients with advanced vascular invasion, TACE, systemic therapy, or surgical resection is recommended, while systemic therapy, TACE, or radiotherapy is recommended for patients with distant metastasis[21]. Due to the heterogeneity of HCC, patients exhibit varying responses to transarterial intervention therapy, resulting in different adverse effects.

SYSTEMIC THERAPY

Recently, the application of systemic therapy has opened up new horizons in the treatment of HCC. However, the majority of patients diagnosed with HCC are already at an advanced stage. Systemic therapy is customarily administered via a spectrum of pharmacological agents, including tyrosine kinase inhibitors (TKIs), ICIs, and anti-angiogenic monoclonal antibodies. Each of these medication classes is distinguished by its unique constellation of adverse effects. TKIs are frequently associated with palmar-plantar erythrodysesthesia syndrome, a dermatologic condition characterized by hand-foot skin reactions, as well as gastrointestinal manifestations such as diarrhea, and hemodynamic alterations, notably hypertension. Anti-angiogenic monoclonal antibodies are recognized for their potential to induce hypertension, proteinuria, and an increased propensity for bleeding episodes. Conversely, the adverse effects associated with ICIs are predominantly mediated through immunological mechanisms, resulting in conditions such as elevated serum transaminase levels, hepatic inflammation, and the emergence of autoimmune pathologies. These agents, therefore, require vigilant monitoring and management of their distinct side-effect profiles to ensure patient safety and therapeutic efficacy[24].

Guidelines from various Western countries, such as those from the National Comprehensive Cancer Network (NCCN), AASLD, and ASCO[14,17,19], indicate that systemic therapy is appropriate for patients with unresectable HCC who are not candidates for local treatment modalities. This includes patients with advanced HCC (BCLC stage C), some patients with intermediate-stage HCC (BCLC stage B), and patients with disease progression after local therapy.

In current clinical practice, TKIs play a significant role in first-line treatment, particularly sorafenib and lenvatinib. These drugs target tyrosine kinases within tumor cells, inhibiting tumor growth and angiogenesis, and have been widely applied in the treatment of various solid tumors.

ICIs, as another class of important first-line therapeutic drugs, enhance the immune response against tumors by lifting the suppression that tumor cells exert on the immune system. Atezolizumab and durvalumab, as inhibitors of programmed death-ligand 1 (PD-L1), have been proven to be effective in various types of tumors. In addition, tremelimumab, as an inhibitor of cytotoxic T lymphocyte-associated protein 4 (CTLA-4), also shows its unique advantages in the treatment of specific tumors.

Anti-angiogenic monoclonal antibodies, such as bevacizumab, target vascular endothelial growth factor (VEGF) to block tumor angiogenesis, thereby inhibiting tumor growth and metastasis. This class of drugs also plays an important role in the first-line treatment of various tumors. The NCCN recommends prioritizing atezolizumab plus bevacizumab, tremelimumab plus durvalumab, sorafenib, lenvatinib, durvalumab, pembrolizumab, and nivolumab as first-line treatment drugs[14].

The AASLD 2023[17] considers systemic therapy suitable for patients with BCLC stages C and B. The strongly recommended first-line treatment drugs are atezolizumab plus bevacizumab or durvalumab plus tremelimumab. In the presence of specific contraindications, the guideline recommends TKIs such as sorafenib or lenvatinib as alternative treatment options. Furthermore, ICIs, including monoclonal antibodies against programmed death protein 1 (PD-1) or PD-L1, offer another therapeutic alternative for patients. According to the latest guidelines from the ASCO[19], the recommended first-line treatment drug combinations include atezolizumab plus bevacizumab and durvalumab plus tremelimumab. These treatment modalities are primarily indicated for patients with Child-Pugh Class A liver function. In cases where there are contraindications to these ICIs, TKIs, such as sorafenib or lenvatinib, may be considered alternative first-line treatment options.

The American Gastroenterological Association (AGA) and the ESMO both recommend atezolizumab plus bevacizumab, sorafenib, and lenvatinib as first-line therapeutic agents. They also propose cabozantinib, pembrolizumab, ramucirumab, regorafenib, and other agents such as bevacizumab, nivolumab, or nivolumab plus ipilimumab as second-line treatments[20,25]. The EASL[18] points out that the first-line treatment drug of choice is atezolizumab plus bevacizumab. If contraindications exist, sorafenib or lenvatinib is selected. Second-line treatment drugs include a variety of other TKIs and vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors, such as regorafenib, cabozantinib, and ramucirumab. The consensus among Chinese experts[21,26] suggests that systemic therapy is suitable for patients in the intermediate and advanced stages, such as those classified in the China Liver Cancer Staging (CNLC) IIb, IIIa, and IIIb stages. First-line treatment options include atezolizumab plus bevacizumab, suntilimab-bevacizumab analog, lenvatinib, sorafenib, donafenib, and FOLFOX chemotherapy. Second-line treatments comprise regorafenib, apatinib, camrelizumab, and tislelizumab.

A recent meta-analysis has evaluated the efficacy and safety of systemic treatments[27]. It was found that the combination of targeted therapy plus ICIs demonstrated superior therapeutic outcomes in terms of overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Notably, the combination of atezolizumab and bevacizumab was found to be superior to other treatments in multiple clinical outcomes within the context of targeted therapy plus ICIs. However, the combination of targeted therapy and ICIs increases treatment-related toxicity. The use of single-targeted drugs for the treatment of HCC has shown limited efficacy, constrained by the heterogeneity of HCC, necessitating the use of combination therapies to enhance therapeutic effects[28].

Sorafenib is often used as a control group to assess the efficacy of new drugs. The combination therapy of atezolizumab and bevacizumab has been proven to extend the median overall survival (mOS) in patients with HCC to 19.2 months, which is 5.8 months longer than that observed with sorafenib. Additionally, the PFS is also longer with this combination therapy than sorafenib alone[29]. The HIMALAYA study is a global, multicenter, open-label Phase III clinical trial that evaluated the efficacy of tremelimumab in combination with durvalumab for untreated, unresectable HCC patients who have not previously received systemic therapy. The results demonstrated an ORR of 20.1% according to Response evaluation criteria in solid tumors (RECIST) 1.1 criteria, the median PFS (mPFS) was achieved at 5.4 months, and the mOS reached 16.4 months. Therefore, compared with monotherapy using sorafenib, the combined treatment modality demonstrates a significantly enhanced therapeutic efficacy[30].

However, targeted therapies and ICIs have their limitations and side effects, particularly those related to treatment resistance and uncontrollable disease progression. Meanwhile, interventional therapies also have their constraints. There is an urgent need to integrate these three therapeutic modalities strategically to enhance synergistic effects. It deserves thorough investigation to realize more profound therapeutic benefits by integration.

IMMUNE MECHANISMS OF COMBINATION THERAPY

TACE is one of the most commonly used local therapeutic methods for HCC, primarily indicated for patients with HCC at CNLC stages IIb, IIIa, and some IIIb, with liver function classified as Child-Pugh A/B and Eastern Cooperative Oncology Group performance status (ECOG PS) scores ranging from 0 to 2. Some patients in the middle to advanced stages of HCC can achieve satisfactory outcomes from TACE treatment. However, for patients with extrahepatic metastasis and those with type III and IV PVTT, the efficacy of TACE is not satisfactory. Studies have demonstrated that TACE can cause local hypoxia in residual cancer tissue, enhance the expression of VEGF, and consequently increase the expression of EGFR, promoting

tumor angiogenesis and high expression of PD-L1 and leading to tumor recurrence and metastasis. TKIs such as sorafenib and regorafenib act on targets related to tumor angiogenesis, tumor cell proliferation/migration, and immune modulation, thereby exerting a comprehensive anti-angiogenic effect, inhibiting tumor cell proliferation and metastasis, and resisting immune suppression. The combination of TACE with molecular targeted therapy and/or immunotherapy can achieve a win-win situation. Theoretically, the combination of TACE with molecular targeted therapy and/or immunotherapy can effectively control tumor progression and extend the survival of patients. Currently, major guidelines recommend the use of TACE combined with targeted and/or immuno-integrative therapy for middle and advanced HCC to further improve the efficacy of TACE.

During the development of HCC, an immunosuppressive tumor microenvironment forms, enabling tumor cells to evade normal immune responses. In addition, the direct binding of PD-L1 expressed by tumor cells and PD-1 expressed by T lymphocytes in the tumor microenvironment can limit the activation and proliferation of T cells, weakening their cytotoxic effect on tumor cells. TACE and HAIC directly release chemotherapeutic agents into the lesion through the hepatic artery, achieving high local drug concentrations that are more efficient in killing tumor cells. In addition, the embolic agents used in TACE can obstruct the blood vessels that nourish the tumor, inducing ischemic necrosis of the tumor tissue. This leads to the release of a significant amount of tumor antigens, which enhances the recognition by antigen-presenting cells, stimulates the immune response, and recruits a greater number of cytotoxic $CD8^+$ T cells into the tumor microenvironment. This sequence of immunological events can alter the tumor microenvironment, transforming "cold" tumors, which are less receptive to immune therapies, into "hot" tumors with increased immune cell activity, thus potentially improving therapeutic outcomes. TACE can also reduce the number of Treg cells in peripheral blood, which is beneficial for enhancing the immune response. Immunotherapy (anti-PD-1/anti-PD-L1) mainly works by blocking the binding of PD-1/PD-L1 in the tumor microenvironment, relieving the inhibition of tumor cells on T cells, restoring T cell activity, and strengthening the immune system's recognition and cytotoxic effect on tumor cells. Therefore, the combination of TACE/HAIC with immunotherapy may have a synergistic effect, enhancing the immune response and improving antitumor effects. A liver cancer mouse model experiment demonstrated that the combination of TACE and immunotherapy can promote the apoptosis of liver cancer cells. The combined therapy can downregulate the expression of the TGFβR2 protein and upregulate the expression of SMAD7 and PTPN14 proteins, thereby inhibiting the proliferation, differentiation, and survival of tumor cells[31].

TACE COMBINED SYSTEMIC THERAPY

Over the past five years, numerous studies have delved into the exploration of TACE in combination with systemic therapy. During this process, a significant number of Chinese scholars conducted a variety of innovative attempts in this field. Following the embolization of the hepatic artery through TACE, hypoxia frequently ensues. This state of reduced oxygen availability leads to an upregulation of Hypoxia-inducible factor-1 alpha (HIF-1α). The consequent increase in HIF-1α levels stimulates the synthesis of VEGF and Platelet-derived growth factor (PDGF), key regulators of angiogenesis. The resultant angiogenic activity can facilitate tumor regrowth and is often implicated in the recurrence of tumors after TACE[32]. Sorafenib can block the VEGF receptor. Therefore, combining sorafenib with TACE may yield new findings compared to TACE alone. In one study, because only 73.6% of OS events were reached, time to TACE treatment failure (TTUP) was used as an alternative indicator to OS. The study found that the TTUP in the TACE combination therapy group was significantly higher than in the TACE-only group [26.7 months *vs.* 20.6 months, HR 0.57 (95%CI:0.36-0.92), $P = 0.02$]; both PFS and ORR were also significantly higher than in the TACE-only group[33] [Table 1]. In addition to demonstrating significant effects compared to TACE, when comparing the combination of conventional Transarterial Chemoembolization (cTACE) and sorafenib with

Table 1. TACE alone or combined with systemic therapy

Group	Country or region	Ref.	Study design	
TACE plus sorafenib (*n* = 80) *vs.* TACE (*n* = 76)	Japan	Kudo *et al.* 2020[33]	RCT	
	TTUP	PFS	ORR, RECICL	
	26.7 months *vs.* 20.6 months, HR 0.57 (95%CI: 0.36-0.92), *P* = 0.02	25.2 months *vs.* 13.5 months, HR 0.59 (95%CI: 0.41-0.87), *P* = 0.006	57% *vs.* 47%, *P* = 0.23	
Sorafenib (*n* = 169) *vs.* sorafenib with cTACE (*n* = 170)	South Korea	Park *et al.* 2019[34]	RCT	
	OS	PFS		
	12.8 months *vs.* 10.8 months, HR 0.91 (90%CI 0.69-1.21), *P* = 0.290	5.2 months *vs.* 3.6 months, HR 0.73 (90%CI 0.59-0.91), *P* = 0.01		
Lenvatinib with TACE (*n* = 170) *vs.* lenvatinib (168)	China	Peng *et al.* 2023[36]	RCT	
	OS	PFS	ORR, RECIST 1.1	ORR, mRECIST
	17.8 months *vs.* 11.5 months, HR 0.45 (95%CI: 0.33-0.61), *P* < 0.001	10.6 months *vs.* 6.4 months HR 0.43 (95%CI: 0.34-0.55), *P* < 0.001	45.9% *vs.* 20.8%, *P* < 0.001	54.1% *vs.* 25.0%, *P* < 0.001
TACE plus PD-L1 and MTT (*n* = 376) *vs.* TACE (*n* = 450)	China	Zhu *et al.* 2023[39]	Cohort study	
	OS	PFS	ORR, mRECIST	
	19.2 months *vs.* 15.7 months, aHR 0.63, (95%CI: 0.47-0.83), *P* = 0.001	9.5 months *vs.* 8.0 months, aHR 0.70 (95%CI: 0.56-0.88), *P* = 0.002	60.1% *vs.* 32.0%, *P* < 0.001	
TACE plus camrelizumab and apatinib (*n* = 107) *vs.* TACE (*n* = 479)	China	Jin *et al.* 2023[40]	Cohort study	
	OS	PFS	ORR, mRECIST	
	24.1 months *vs.* 15.7 months, aHR 0.41 (95%CI: 0.26-0.64), *P* = 0.008	13.5 months *vs.* 7.7 months, aHR 0.52 (95%CI: 0.37-0.74), *P* = 0.003	59.5% *vs.* 37.4%, *P* = 0.002	
TACE-ICI-VEGF (*n* = 802) *vs.* ICI- VEGF (*n* = 442)	China	Jin *et al.* 2024[41]	Cohort study	
	OS, sIPTW	PFS	ORR, RECIST 1.1	ORR, mRECIST
	22.6 months *vs.* 15.9 months, aHR 0.63 (95%CI: 0.53-0.75), *P* < 0.0001	9.90 months *vs.* 7.40 months, aHR 0.74 (95%CI: 0.65-0.85), *P* < 0.0001	41.2% *vs.* 22.9%, *P* < 0.0001	47.3% *vs.* 29.7%, *P* < 0.0001
PA-TACE plus ICIs (*n* = 48) *vs.* PA-TACE (*n* = 42)	China	Yuan *et al.* 2023[42]	Cohort study	
	OS	RFS		
	24.5 months *vs.* 19.1 months, HR 0.47, (95%CI: 0.26-0.86), *P* = 0.014	12.76 months *vs.* 8.11 months, *P* = 0.038, HR 0.54, (95%CI: 0.32-0.9), *P* = 0.019		
TACE with HAIC plus TKIs and PD-1 inhibitors (*n* = 139) *vs.* TACE (*n* = 604)	China	Yuan *et al.* 2023[43]	Cohort study	
	OS	PFS	ORR, RECIST 1.1	ORR, mRECIST
	Not reached *vs.* 10.4 months, HR 0.22(95%CI: 0.16-0.30), *P* < 0.001	14.8 months *vs.* 2.3 months, HR 0.20 (95%CI: 0.15-0.26), *P* < 0.001	42.1% *vs.* 5.0%, *P* < 0.001	53.7% *vs.* 7.8%, *P* < 0.001
Durvalumab plus bevacizumab plus TACE (*n* = 204) *vs.* durvalumab plus TACE (*n* = 207) *vs.* TACE (*n* = 205)	Global	Lencioni *et al.* 2024[44]	RCT	
		PFS	ORR, mRECIST	
		15 months *vs.* 8.2 months, HR 0.77 (95%CI: 0.61-0.98), *P* = 0.032 10 months *vs.* 8.2 months, HR	43.6% *vs.* 41.0% *vs.* 29.6%	

					0.94 (95%CI: 0.75-1.19), P = 0.638	

TACE: Transarterial chemoembolization; cTACE: conventional transarterial chemoembolization; PD-1: programmed death protein 1; PD-L1: programmed death-(ligand)1; MTT: molecular targeted treatments; TACE-ICI-VEGF: TACE with ICIs plus anti-VEGF antibody/TKIs; ICI-VEGF: ICIs plus anti-VEGF antibody/TKIs; ICIs: immune checkpoint inhibitors; VEGF: vascular endothelial growth factor; TKIs: tyrosine kinase inhibitors; TTUP: time to TACE treatment failure; RECICL: response evaluation criteria in Cancer of the Liver; PA-TACE: postoperative adjuvant transarterial chemoembolization; sIPTW: stabilized inverse probability of treatment weighting; mRECIST: modified response evaluation criteria in solid tumors; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival; aHR: adjusted hazard ratio; ORR: objective response rate; RCT: randomized controlled trial.

sorafenib alone[34] [Table 1], the combination therapy group did not improve OS in advanced HCC [12.8 months *vs.* 10.8 months, HR 0.91, (90%CI 0.69-1.21), P = 0.290]. However, PFS was significantly shorter in the sorafenib group compared to the combination therapy group [5.2 months *vs.* 3.6 months, HR 0.73 (90%CI 0.59-0.91), P = 0.01]. Other secondary survival outcomes were also found to be better with the combination of cTACE and sorafenib. Subgroup analysis indicated that some patients with severe vascular invasion might benefit from the combination therapy.

Since its introduction in 2018, lenvatinib has emerged as a promising alternative to sorafenib, commonly used for the treatment of HCC. Compared to sorafenib, lenvatinib has shown an improvement in patient prognosis, although its efficacy has not been entirely satisfactory[35]. A multicenter, randomized, controlled phase III clinical trial compared the combination of lenvatinib with TACE to lenvatinib monotherapy for the treatment of advanced HCC. The results revealed that the ORR was higher in the combination therapy group [54.1% *vs.* 25.0%, P < 0.001, as assessed by modified response evaluation criteria in solid tumors (mRECIST)], both mOS [17.8 months *vs.* 11.5 months, HR 0.45 (95%CI: 0.33-0.61), P < 0.001] and PFS [10.6 months *vs.* 6.4 months HR 0.43 (95%CI: 0.34-0.55), P < 0.001] were significantly prolonged [Table 1]. Arterial interventional therapy combined with targeted drugs was found to be more significantly effective in terms of prognosis than targeted drug monotherapy. Although grade 3-4 adverse effects such as elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia were more common, they remained manageable[36]. The combination therapy group showed a reduction in PVTT, AFP levels, and tumor size, indicating that the combination of TACE and lenvatinib could exert a synergistic effect. However, these findings still require validation through large-scale clinical trials.

In addition to combining with TKIs, TACE can also be combined with ICIs for treatment. TACE also changes the tumor microenvironment. Animal experiments have found that after TAE, compared with the control group, the tumor group had a higher number of $CD3^+$, $CD4^+$, and $CD8^+$ tumor-infiltrating lymphocytes and increased PD-L1 expression[37]. These modifications are anticipated to augment the immune response against tumors, thereby providing a theoretical basis for the clinical investigation of combined treatment approaches using TACE or TAE with inhibitors of PD-1 or PD-L1. It has been shown that the cellular composition of the immune microenvironment in HCC is significantly altered subsequent to TACE therapy, with a pronounced increase in the Th17 cell population[38]. This observation provides a theoretical rationale for the combined therapeutic approach of TACE with ICIs, suggesting a potential synergistic effect in modulating the tumor immune response.

A retrospective cohort study has demonstrated that, when compared with solitary TACE therapy, the combination treatment of TACE with PD-L1 receptor inhibitors and various targeted drugs received superior OS, recurrence-free survival (RFS), and ORR after propensity score matching. Additionally, the combined regimen exhibited an acceptable safety profile[39] [Table 1]. The combination of TACE with camrelizumab and apatinib was found to improve prognosis significantly[40] [Table 1].

Another large-scale, multicenter cohort study showed that, after weight adjustment with stabilized inverse probability of treatment weights, TACE combined with ICIs and anti-VEGF antibody/TKIs[41] significantly improved mOS [22.6 months *vs.* 15.9 months, aHR 0.63 (95%CI: 0.53-0.75), $P < 0.0001$], and mPFS was also longer [9.90 months *vs.* 7.40 months, aHR 0.74 (95%CI: 0.65-0.85), $P < 0.0001$]. The ORR after TACE combined with ICIs and anti-VEGF antibody/TKIs was higher (47.3% *vs.* 29.7%, $P < 0.0001$, mRECIST) [Table 1]. However, the incidence of adverse events in the triple combination therapy group was higher, and severe adverse events (grade ≥ 3) in the TACE-ICI-VEGF group (178 patients, 22.2%) were greater than in the ICI-VEGF group (80 patients, 18.1%), but adverse events were still controllable. The aforementioned studies indicate that the combination of TACE with ICIs and anti-VEGF antibody/TKIs is not only feasible but also merits further investigation to elucidate its therapeutic potential and optimize its clinical application.

TACE uses chemotherapeutic agents and embolic agents to kill tumor cells, followed by the activation of the immune microenvironment by ICIs, while TKIs or anti-VEGF antibodies inhibit tumor angiogenesis. The combination of these three plays a synergistic antitumor effect. In addition to playing a positive role in patients with unresectable HCC, recent studies have found that TACE combined with systemic treatment also has a positive impact on the prognosis of patients after surgical resection of HCC. Among patients with PVTT, PVTT can adversely affect the prognosis of HCC patients after surgical resection and promote HCC recurrence. Postoperative adjuvant TACE (PA-TACE) treatment combined with ICIs compared to PA-TACE found that after R0 liver resection (complete resection of HCC), the efficacy of PA-TACE alone was not as significant as the combined treatment effect. TACE combined with immunotherapy can extend the survival of patients and prevent tumor recurrence[42] [Table 1].

Furthermore, among HCC patients with PVTT, retrospective research has shown that combining TACE with HAIC, along with the addition of targeted therapy and immunosuppressive agents, yields significant improvements in OS and PFS compared to TACE monotherapy. The ORR in the combined treatment group was substantially higher than that in the TACE-only group (53.7% *vs.* 7.8%, $P < 0.001$, mRECIST) [Table 1]. Additionally, the combined treatment group exhibited a higher rate of downstaging and pathological complete response (pCR)[43].

A recent global Phase III randomized controlled trial (EMERALD-1) has garnered widespread attention[44] [Table 1]. The D (durvalumab) + B (bevacizumab) + TACE regimen is the first ICIs-based strategy in a global Phase III trial, enrolling 616 patients with unresectable HCC categorized under BCLC Stage A (25.8%), Stage B (57.3%), and Stage C (16.1%). Compared to the TACE group, the D+B+TACE group exhibited a significant improvement in mPFS [15 months *vs.* 8.2 months, HR 0.77 (95%CI: 0.61-0.98), $P = 0.032$]. The secondary endpoint of mPFS for the D + TACE versus TACE did not reach statistical significance [10 months *vs.* 8.2 months, HR 0.94 (95%CI: 0.75-1.19), $P = 0.638$]. ORRs for D + B + TACE, D + TACE, and TACE were 43.6%, 41.0%, and 29.6%, respectively. The trial demonstrated that the safety profile of D + B + TACE is manageable and consistent with the safety characteristics of D, B, and TACE in the treatment of unresectable HCC. Although the data of OS are still under follow-up, based on the data published, the D + B + TACE regimen demonstrates the potential to establish a new standard of care for unresectable HCC.

HAIC COMBINED SYSTEMIC THERAPY

HAIC is another common form of arterial interventional therapy. Both TACE and HAIC are applicable for the treatment of large HCC with a diameter of 5 cm or greater, especially for advanced unresectable HCC patients with tumors ≥ 10 cm. A significant limitation of TACE is its potential inability to block the blood

supply completely to the tumor, which may not halt tumor growth in the short term. In contrast, HAIC can provide a sustained release of chemotherapeutic agents, serving as an alternative therapy to TACE[45]. For patients with insufficient liver reserve function, HAIC can serve as a means of downstaging treatment. The combination of HAIC with chemotherapeutic agents, such as fluorouracil, leucovorin, and oxaliplatin, has demonstrated high safety and efficacy. A retrospective study[46] analyzed patients with HCC who had a single tumor nodule larger than 10 cm in diameter, without vascular invasion or distant metastasis, to compare the efficacy of TACE with HAIC using the FOLFOX regimen. The study indicated that in the HAIC treatment group, the ORR and PFS were significantly better than those in the TACE treatment group, with an ORR of 44.3% *vs.* 10.4% (P = 0.001) and PFS of 8.9 months *vs.* 4.2 months (HR 0.67, 95%CI: 0.46-0.96, P = 0.030). However, in terms of OS, the OS in the HAIC treatment group was 21.3 months, which was not superior to the OS of 26.6 months in the TACE treatment group (HR 0.93, 95%CI: 0.59-1.46, P = 0.749) [Table 2]. Another comparative study enrolled patients aged 18 years or older who had been diagnosed with unresectable HCC classified as BCLC stage A-B (CNLC stage Ib-IIb). Patients who received HAIC with the FOLFOX regimen exhibited a superior mOS compared to those receiving TACE [23.1 months *vs.* 16.1 months, HR 0.58 (95%CI: 0.45-0.75), P < 0.001]. Additionally, PFS is also notably higher in the HAIC-FOLFOX treatment group [9.6 months *vs.* 5.4 months, HR 0.57 (95%CI: 0.45-0.72), P < 0.001][47] [Table 2].

As previously mentioned, sorafenib is often used as a control for evaluating the efficacy of treatment. Sorafenib, as a standard first-line treatment for HCC with PVTT or advanced HCC, has shown unsatisfactory effects[48]. When comparing HAIC-FOLFOX with sorafenib, the former showed significantly higher mOS [13.9 months *vs.* 8.2 months, HR 0.41 (95%CI: 0.30-0.55), P < 0.001], and the PFS was also better than using sorafenib alone [7.8 months *vs.* 4.3 months, HR 0.45 (95%CI: 0.34-0.60), P < 0.001][49] [Table 2]. The combination of HAIC with sorafenib can improve efficacy. A phase II clinical trial found[50] that the mOS in the combination therapy group was 16.3 months, compared to 6.5 months for sorafenib alone [HR 0.28, (95%CI: 0.15-0.53), P < 0.001], and the ORR in the combination therapy group was also higher than in the sorafenib group (41% *vs.* 3%, P < 0.001) [Table 2].

In the treatment of advanced HCC, a comparative analysis between the triple therapy comprising HAIC, lenvatinib, and a PD-1 inhibitor versus the dual therapy of lenvatinib combined with a PD-1 inhibitor, has demonstrated superior outcomes for the triple therapy in terms of mOS (26.3 months *vs.* 13.8 months, HR 0.43, P < 0.001) and PFS (11.5 months *vs.* 5.5 months, HR 0.43, P < 0.001)[51] [Table 2]. Another study reached the same conclusion[52] [Table 2].

TAE AND TARE COMBINED SYSTEMIC THERAPY

In the therapeutic management of HCC, TACE has not demonstrated a definitive advantage over TAE. A randomized controlled trial[53] divided untreated HCC patients into two groups, one receiving TAE with PVA particles and the other receiving sequential TACE (sTACE), where sTACE involved the arterial administration of cisplatin 50 mg 4 to 6 h before PVA embolization. In terms of ORR, sTACE was superior to TAE (47.3% *vs.* 67.4%, P = 0.068, mRECIST) [Table 3], yet the survival benefit of TACE over TAE remains unproven.

Invariant NKT cells (iNKT) are CD1d-restricted T cells with the capacity of antitumor immunity. A study reported that among patients who have failed to respond to TACE, the implementation of a therapeutic strategy combining TAE with the infusion of iNKT cells significantly improved clinical outcomes. Specifically, the PFS [5.7 months *vs.* 2.7 months, HR 0.32 (95%CI:0.16-0.63), P < 0.001] for patients receiving the combination therapy were considerably longer than those observed in patients undergoing TAE treatment. Additionally, the ORR (52% *vs.* 11%, P = 0.003, mRECIST) was higher in the group treated with

Table 2. HAIC alone or combined with systemic therapy

Group	Country or region	Ref.	Study design	
HAIC-FOLFOX (*n* = 70) *vs.* TACE (*n* = 77)	China	Deng *et al*. 2023[46]	Cohort study	
	OS	PFS	ORR, mRECIST	
	21.3 months *vs.* 26.6 months, HR 0.93 (95%CI: 0.59-1.46), *P* = 0.749	8.9 months *vs.* 4.2 months, HR 0.67 (95%CI: 0.46-0.96), *P* = 0.030	44.3% *vs.* 10.4%, *P* < 0.001	
HAIC-FOLFOX (*n* = 159) *vs.* TACE (*n* = 156)	China	Li *et al*. 2022[47]	RCT	
	OS	PFS	ORR, RECIST 1.1	ORR, mRECIST
	23.1 months *vs.* 16.1 months HR 0.58 (95%CI: 0.45-0.75), *P* < 0. 001	9.6 months *vs.* 5.4 months, HR 0.57 (95%CI: 0.45-0.72), *P* < 0.001	46% *vs.*18%, *P* < 0.001	48% *vs.* 33%, *P* = 0.004
HAIC-FOLFOX (*n* = 130) *vs.* sorafenib (*n* = 132)	China	Lyu *et al*. 2022[49]	RCT	
	OS	PFS	ORR, RECIST 1.1	ORR, mRECIST
	13.9 months *vs.* 8.2 months, HR 0.41 (95%CI: 0.30-0.55), *P* < 0.001	7.8 months *vs.* 4.3 months, HR 0.45 (95%CI: 0.34-0.60), *P* < 0.001	31.5% *vs.* 1.5%, *P* < 0.001	35.4% *vs.* 5.3%, *P* < 0.001
HAIC plus sorafenib (*n* = 32) *vs.* sorafenib (*n* = 32)	China	Zheng *et al*. 2022[50]	RCT	
	OS	PFS	ORR	
	16.3 months *vs.* 6.5 months, HR 0.28, (95%CI: 0.15-0.53), *P* < 0.001	9.0 months *vs.* 2.5 months; HR 0.26 (95%CI: 0.15-0.47), *P* < 0.001	41% *vs.* 3%, *P* < 0.001	
HAIC- lenvatinib -PD-1 (*n* = 89) *vs.* lenvatinib-PD1 (*n* = 53)	China	Fu *et al*. 2023[51]	Cohort study	
	OS	PFS	ORR, RECIST 1.1	ORR, mRECIST
	26.3 months *vs.* 13.8 months, HR 0.43, *P* < 0.001	11.5 months *vs.* 5.5 months, HR 0.43, *P* < 0.001	57.3% *vs.* 20.8%, *P* < 0.001	61.8% *vs.* 20.8%, *P* < 0.001
HAIC lenvatinib PD 1 (*n* = 58) *vs.* HAIC lenvatinib (*n* = 87)	China	An *et al*. 2023[52]	Cohort study	
	OS	PPS		
	43.6 months *vs.* 18.9 months, HR 0.47 (95%CI: 0.28-0.78), *P* = 0.003	35.6 months *vs.* 9.4 months, HR 0.35 (95%CI: 0.21-0.82), *P* < 0.001		

HAIC: Hepatic arterial infusion chemotherapy; HAIC-FOLFOX: HAIC using a combination of oxaliplatin, fluorouracil, and leucovorin; PD-1: programmed death protein 1; mRECIST: modified response evaluation criteria in solid tumors; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival; aHR: adjusted hazard ratio; ORR: objective response rate; RCT: randomized controlled trial; PPS: postprogression free survival.

Table 3. TAE alone or combined with systemic therapy

Group	Country or region	Ref.	Study design
TAE (*n* = 42) *vs.* sTACE (*n* = 44)	UK	Meyer *et al*. 2013[53]	RCT
	OS	PFS	ORR, mRECIST
	17.3 months *vs.* 16.3 months, HR 0.91, (95%CI: 0.51-1.62), *P* = 0.74	7.2 months *vs.* 7.5 months, HR 0.87, (95%CI: 0.52-1.450), *P* = 0.59	47.3% *vs.* 67.4%, *P* = 0.068
TAE with iNKT treatment (*n* = 27) *vs.* TAE (*n* = 27)	China	Guo *et al*. 2023[54]	RCT
	OS	PFS	ORR, mRECIST
	25.9 months *vs.* 17.3 months, HR 0.60 (95%CI: 0.32-1.13), *P* = 0.12	5.7 months *vs.* 2.7 months, HR 0.32 (95%CI: 0.16-0.63), *P* < 0.001	52% *vs.* 11%, *P* = 0.003

TAE: Transarterial embolization; TACE: transarterial chemoembolization; sTACE: sequential TACE; iNKT: Invariant NKT cells; mRECIST: modified response evaluation criteria in solid tumor; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival; aHR: adjusted hazard ratio; ORR: objective response rate; RCT: randomized controlled trial.

the combined approach compared to those receiving only TAE[54] [Table 3].

When comparing TARE with targeted therapy[55], TARE may offer longer OS for advanced HCC patients with segmental or lobar PVTT and good liver function compared to sorafenib or lenvatinib. TARE showed a longer mOS than TKIs (sorafenib and lenvatinib) [24.2 months *vs.* 8.4 months, HR 0.51 (95%CI: 0.32-0.81), $P = 0.004$], PFS was also longer for TARE [4.1 months *vs.* 3.2 months, HR 0.74 (95%CI: 0.48-1.14), $P = 0.17$], and ORR was better for TARE than for TKIs (53.0%-56.7% *vs.* 12.3%-15.0%) [Table 4].

In the comparative assessment of the therapeutic efficacy between TARE utilizing Y-90 resin microspheres and the combination immunotherapy of Atezolizumab plus Bevacizumab in patients with unresectable HCC[56], the mOS was observed to be 15.0 months for the TARE group and 14.9 months for another group [HR 0.98 (95%CI: 0.66-1.46), $P = 0.92$], mPFS was 4.4 months and 6.8 months [HR 0.75 (95%CI: 0.54-1.02), $P = 0.07$], and ORR were 19.8% *vs.* 25%. These findings revealed similar effectiveness outcomes for both treatment modalities [Table 4].

For patients who cannot be treated by surgery and for whom TACE is not feasible[57], the combination of TARE with sorafenib did not significantly improve OS compared to sorafenib alone [12.1 months *vs.* 11.4 months, HR 1.01 (0.81-1.25), $P = 0.95$] [Table 4], and the incidence of adverse events in the combined treatment group was higher than that in the group treated with sorafenib alone.

COMBINATION THERAPY AND CONVERSION THERAPY

Surgical curative therapy remains the most effective means for liver cancer patients to achieve long-term survival. For those unsuitable for surgical resection, conversion therapy can provide an opportunity to undergo surgical resection. Currently, there is a wide variety of methods for the conversion therapy of HCC, including single systemic therapy, interventional therapy, or a combination of both. Despite the multitude of clinical trial programs, selecting the optimal conversion therapy is challenging due to the significant variability among patients. Of course, some clinical trials have demonstrated that combination therapy may have a higher conversion success rate. For example, the LAUNCH study (NCT03905967) showed that 15.3% of patients in the lenvatinib combined with TACE treatment group achieved surgical resection, including 2 cases of pCR[36]. An additional RCT focusing on patients with HCC and PVTT revealed that the surgical conversion success rate for the group treated with HAIC in combination with sorafenib was markedly higher than that of the sorafenib monotherapy group (12.8% *vs.* 0.8%, $P < 0.001$)[58]. In addition, radiotherapy combined with ICIs is also used for conversion therapy. A prospective study conducted by the Queen Mary Hospital of the University of Hong Kong explored the outcome of unresectable HCC treated with TACE combined with stereotactic body radiotherapy (SBRT) and PD-L1 monoclonal antibody (avelumab) in sequence, and the results showed that 12% of patients received radical treatment after the triple therapy[59]. With more in-depth clinical trials, combination therapy will play an increasingly important role in the conversion therapy of patients with unresectable HCC.

CONCLUSION

Over the past five years, significant advancements have been made in the treatment of HCC through the integration of arterial interventional therapies (TACE, TAE, TARE, HAIC etc.) and systemic treatments, including targeted drugs and immunotherapy. Studies have demonstrated that this combined therapeutic strategy significantly enhances tumor response rates, extends survival periods, and transforms inoperable HCC into operable conditions. Furthermore, the adverse events associated with the combined treatment regimen are controllable in terms of safety and do not significantly increase the incidence and severity of adverse events. Interventional therapies, particularly TACE and TARE, which occlude tumor blood supply

Table 4. TARE (SIRT) alone or combined with systemic therapy

Group	Country or region	Ref.	Study design
TARE (*n* = 60) *vs.* TKIs (sorafenib or lenvatinib) (*n* = 60)	South Korea	Hur *et al.* 2023[55]	cohort study
	OS	PFS	ORR
	24.2 months *vs.* 8.4 months, HR 0.51 (95%CI: 0.32-0.81), *P* = 0.004	4.1 months *vs.* 3.2 months, HR 0.74(95%CI: 0.48-1.14), *P* = 0.17	53.0%-56.7% *vs.* 12.3%-15.0%
TARE (*n* = 140) *vs.* atezolizumab-bevacizumab (*n* = 202)	Global	Agirrezabal *et al.* 2024[56]	RCT
	OS	PFS	ORR
	15.0 months *vs.* 14.9 months, HR 0.98 (95%CI: 0.66-1.46), *P* = 0.92	4.4 months *vs.* 6.8 months, HR 0.75 (95%CI: 0.54-1.02), *P* = 0.07	19.8% *vs.* 25%, *P* = 0.31
TARE (SIRT) plus sorafenib (*n* = 216) *vs.* sorafenib (*n* = 208)	Germany	Ricke *et al.* 2019[57]	RCT
	OS		
	12.1 months *vs.* 11.4 months, HR 1.01 (95%CI: 0.81-1.25), *P* = 0.95		

TARE: Transarterial radioembolization; SIRT: selective internal radiation therapy; mRECIST: modified response evaluation criteria in solid tumors; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival; aHR: adjusted hazard ratio; ORR: objective response rate; RCT: randomized controlled trial.

and deliver chemotherapeutic agents or radioactive isotopes directly to the tumor cells, are crucial non-surgical treatment modalities for intermediate to advanced HCC.

The application of targeted therapy agents and ICIs has introduced novel therapeutic strategies and hope for the treatment of HCC. Drugs such as TKIs, ICIs, and anti-angiogenic monoclonal antibodies play a pivotal role in systemic therapy. The combination of interventional therapy with systemic therapies, such as TACE with TKIs (e.g. sorafenib, lenvatinib) and ICIs (e.g. atezolizumab, durvalumab), has shown improved efficacy and prolonged survival in numerous clinical trials or cohort studies. Comparative studies between TACE and TAE in terms of mOS and PFS indicate that TACE may have certain advantages in some cases, while TAE has also shown comparable efficacy in certain studies. TARE may offer better survival outcomes in specific patient populations. Currently, several eagerly anticipated trials include the Phase III HIMALAYA (NCT03298451), LEAP-012 (NCT04246177), and EMERALD-1 (NCT03778957), as well as the Phase II PLATIC (NCT04814043). As more clinical trials report their final outcomes, our understanding and exploration of various therapeutic strategies for HCC will become increasingly clear.

Despite existing research exploring the efficacy of various therapeutic modalities for HCC, there remains a significant knowledge gap regarding the development of personalized therapeutic strategies based on patients' tumor characteristics and immune status. Considering the heterogeneity of HCC, future research should focus more on individualized treatment strategies, integrating genomic and immunological data to provide more precise and individualized treatment plans for patients. Most current research is based on small retrospective studies, lacking large-scale prospective randomized controlled clinical trials, which limits the generalizability and reliability of the conclusion. While the safety profile of combined treatment regimens is generally[30]manageable and well-tolerated, certain combinations, such as the use of lenvatinib in conjunction with TACE, have shown a higher incidence of grade 3 and 4 adverse events. Targeted therapy agents and ICIs may encounter therapeutic resistance and disease progression in specific patient populations. Therefore, there is an urgent need for additional large-scale, prospective, multicenter, randomized controlled clinical trials. Along with long-term follow-up and monitoring, these trials should assess the efficacy and safety of different treatment combinations and explore their underlying biological mechanisms. In the future, with the advancement of big data and artificial intelligence in the diagnosis and

treatment of HCC, personalized treatment based on combined therapeutic modalities is expected to make significant progress.

DECLARATIONS

Authors' contributions

Contributed to the conception and the design of the study, data search, and manuscript writing: Fu C
Made contributions to conception, manuscript writing, and table design: Chen H
Performed data search and manuscript writing: Chen Y
Made contributions to conception: Liu W
Supervised the article concept and revised manuscript: Cao G

Availability of data and materials

Not applicable.

Financial support and sponsorship

This research was funded by the Shanghai Municipal Health Commission (GWVI-11.1-10).

Conflicts of interest

Guangwen Cao is the Editor-in-Chief of the journal *Hepatoma Research*. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229-63. DOI PubMed
2. Jiang D, Zhang L, Liu W, et al. Trends in cancer mortality in China from 2004 to 2018: a nationwide longitudinal study. *Cancer Commun (Lond)* 2021;41:1024-36. DOI PubMed PMC
3. Lin J, Zhang H, Yu H, et al. Epidemiological characteristics of primary liver cancer in mainland China from 2003 to 2020: a representative multicenter study. *Front Oncol* 2022;12:906778. DOI PubMed PMC
4. Villanueva A. Hepatocellular carcinoma. *N Engl J Med* 2019;380:1450-62. DOI PubMed
5. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2022;23:77-90. DOI PubMed
6. Finn RS, Ryoo BY, Merle P, et al; KEYNOTE-240 investigators. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol* 2020;38:193-202. DOI PubMed
7. Ouyang T, Kan X, Zheng C. Immune checkpoint inhibitors for advanced hepatocellular carcinoma: monotherapies and combined therapies. *Front Oncol* 2022;12:898964. DOI PubMed PMC
8. Wen W, Zhang Y, Zhang H, Chen Y. Clinical outcomes of PD-1/PD-L1 inhibitors in patients with advanced hepatocellular carcinoma: a systematic review and meta-analysis. *J Cancer Res Clin Oncol* 2023;149:969-78. DOI PubMed
9. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7:6. DOI PubMed
10. Rizzo A, Ricci AD. Challenges and future trends of hepatocellular carcinoma immunotherapy. *Int J Mol Sci* 2022;23:11363. DOI PubMed PMC
11. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol* 2023;20:864-84. DOI PubMed

12. Wu Y, Wakil A, Salomon F, Pyrsopoulos N. Issue on combined locoregional and systemic treatment for hepatocellular carcinoma. *Hepatoma Res* 2023;9:6. DOI
13. Sutphin PD, Lamus D, Kalva SP, Li J, Corbin IR. Interventional radiologic therapies for hepatocellular carcinoma: from where we began to where we are going. In: Hoshida Y, editor. Hepatocellular Carcinoma. Molecular and Translational Medicine; 2019. pp. 169-94. DOI
14. National Comprehensive Cancer Network. NCCN Guidelines version 1. 2024: hepatocellular carcinoma. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1514. [Last accessed on 9 Oct 2024].
15. Sangro B, Carpanese L, Cianni R, et al; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011;54:868-78. DOI PubMed
16. Sangro B, Martínez-Urbistondo D, Bester L, et al. Prevention and treatment of complications of selective internal radiation therapy: expert guidance and systematic review. *Hepatology* 2017;66:969-82. DOI PubMed
17. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023;78:1922-65. DOI PubMed PMC
18. Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. *J Hepatol* 2021;75:960-74. DOI PubMed
19. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *J Clin Oncol* 2024;42:1830-50. DOI PubMed
20. Vogel A, Martinelli E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org; ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO clinical practice guidelines. *Ann Oncol* 2021;32:801-5. DOI PubMed
21. Sun HC, Zhou J, Wang Z, et al; Alliance of Liver Cancer Conversion Therapy; Committee of Liver Cancer of the Chinese Anti-Cancer Association. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). *Hepatobiliary Surg Nutr* 2022;11:227-52. DOI PubMed PMC
22. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;76:681-93. DOI PubMed PMC
23. Wen N, Cai Y, Li F, et al. The clinical management of hepatocellular carcinoma worldwide: a concise review and comparison of current guidelines: 2022 update. *Biosci Trends* 2022;16:20-30. DOI PubMed
24. Sangro B, Chan SL, Meyer T, Reig M, El-Khoueiry A, Galle PR. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. *J Hepatol* 2020;72:320-41. DOI PubMed PMC
25. Su GL, Altayar O, O'Shea R, et al. AGA clinical practice guideline on systemic therapy for hepatocellular carcinoma. *Gastroenterology* 2022;162:920-34. DOI PubMed
26. Xie DY, Zhu K, Ren ZG, Zhou J, Fan J, Gao Q. A review of 2022 Chinese clinical guidelines on the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr* 2023;12:216-28. DOI PubMed PMC
27. Li P, Hu M, Liu M, et al. The efficacy and safety of different systemic combination therapies on advanced hepatocellular carcinoma: a systematic review and meta-analysis. *Front Oncol* 2023;13:1197782. DOI PubMed PMC
28. Jin H, Shi Y, Lv Y, et al. EGFR activation limits the response of liver cancer to lenvatinib. *Nature* 2021;595:730-4. DOI PubMed
29. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;76:862-73. DOI PubMed PMC
30. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid* 2022;1:EVIDoa2100070. DOI PubMed
31. Li J, Zhang L, Tao Y, Sun Z, Ge Y, Hu S. Combination of transcatheter arterial chemoembolization and anti-PD-L1 liposomes therapy suppressed hepatocellular carcinoma progression in mice. *Eur J Pharm Sci* 2023;189:106549. DOI
32. Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. *Acta Radiol* 2008;49:523-9. DOI PubMed
33. Kudo M, Ueshima K, Ikeda M, et al; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020;69:1492-501. DOI PubMed PMC
34. Park JW, Kim YJ, Kim DY, et al. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: the phase III STAH trial. *J Hepatol* 2019;70:684-91. DOI PubMed
35. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-73. DOI PubMed
36. Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). *J Clin Oncol* 2023;41:117-27. DOI PubMed
37. Tischfield DJ, Gurevich A, Johnson O, et al. Transarterial embolization modulates the immune response within target and nontarget hepatocellular carcinomas in a rat model. *Radiology* 2022;303:215-25. DOI PubMed PMC
38. Liao Y, Wang B, Huang ZL, et al. Increased circulating Th17 cells after transarterial chemoembolization correlate with improved survival in stage III hepatocellular carcinoma: a prospective study. *PLoS One* 2013;8:e60444. DOI PubMed PMC
39. Zhu HD, Li HL, Huang MS, et al; CHANCE001 Investigators. Transarterial chemoembolization with PD-(L)1 inhibitors plus

molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther* 2023;8:58. DOI PubMed PMC

40. Jin ZC, Zhong BY, Chen JJ, et al; CHANCE Investigators. Real-world efficacy and safety of TACE plus camrelizumab and apatinib in patients with HCC (CHANCE2211): a propensity score matching study. *Eur Radiol* 2023;33:8669-81. DOI PubMed PMC
41. Jin ZC, Chen JJ, Zhu XL, et al; CHANCE2201 Investigators. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. *EClinicalMedicine* 2024;72:102622. DOI PubMed PMC
42. Yuan L, Feng J, Zhang Y, et al. Transarterial chemoembolization plus immune checkpoint inhibitor as postoperative adjuvant therapy for hepatocellular carcinoma with portal vein tumor thrombus: a multicenter cohort study. *Eur J Surg Oncol* 2023;49:1226-33. DOI PubMed
43. Yuan Y, He W, Yang Z, et al. TACE-HAIC combined with targeted therapy and immunotherapy versus TACE alone for hepatocellular carcinoma with portal vein tumour thrombus: a propensity score matching study. *Int J Surg* 2023;109:1222-30. DOI PubMed PMC
44. 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. *JCO* 2024;42:LBA432. DOI
45. Miyayama S, Matsui O, Zen Y, et al. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: observation on CT during arterial portography. *Hepatol Res* 2011;41:853-66. DOI PubMed
46. Deng M, Cai H, He B, Guan R, Lee C, Guo R. Hepatic arterial infusion chemotherapy versus transarterial chemoembolization, potential conversion therapies for single huge hepatocellular carcinoma: a retrospective comparison study. *Int J Surg* 2023;109:3303-11. DOI PubMed PMC
47. Li QJ, He MK, Chen HW, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus transarterial chemoembolization for large hepatocellular carcinoma: a randomized phase III trial. *J Clin Oncol* 2022;40:150-60. DOI PubMed
48. Nakazawa T, Hidaka H, Shibuya A, et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. *BMC Gastroenterol* 2014;14:84. DOI PubMed PMC
49. Lyu N, Wang X, Li JB, et al. Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: a biomolecular exploratory, randomized, phase III trial (FOHAIC-1). *J Clin Oncol* 2022;40:468-80. DOI PubMed
50. Zheng K, Zhu X, Fu S, et al. Sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib for hepatocellular carcinoma with major portal vein tumor thrombosis: a randomized trial. *Radiology* 2022;303:455-64. DOI PubMed
51. Fu Y, Peng W, Zhang W, et al. Induction therapy with hepatic arterial infusion chemotherapy enhances the efficacy of lenvatinib and pd1 inhibitors in treating hepatocellular carcinoma patients with portal vein tumor thrombosis. *J Gastroenterol* 2023;58:413-24. DOI PubMed
52. An C, Fu Y, Li W, Zuo M, Wu P. Postprogression treatment of lenvatinib plus PD-1 inhibitor in advanced hepatocellular carcinoma refractory to hepatic arterial infusion chemotherapy. *Cancer* 2023;129:2235-44. DOI PubMed
53. Meyer T, Kirkwood A, Roughton M, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. *Br J Cancer* 2013;108:1252-9. DOI PubMed PMC
54. Guo J, Bao X, Liu F, et al. Efficacy of invariant natural killer T cell infusion plus transarterial embolization vs transarterial embolization alone for hepatocellular carcinoma patients: a phase 2 randomized clinical trial. *J Hepatocell Carcinoma* 2023;10:1379-88. DOI PubMed PMC
55. Hur MH, Cho Y, Kim DY, et al. Transarterial radioembolization versus tyrosine kinase inhibitor in hepatocellular carcinoma with portal vein thrombosis. *Clin Mol Hepatol* 2023;29:763-78. DOI PubMed PMC
56. Agirrezabal I, Bouattour M, Pinato DJ, et al. Efficacy of transarterial radioembolization using Y-90 resin microspheres versus atezolizumab-bevacizumab in unresectable hepatocellular carcinoma: a matching-adjusted indirect comparison. *Eur J Cancer* 2024;196:113427. DOI PubMed
57. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 2019;71:1164-74. DOI PubMed
58. He M, Li Q, Zou R, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. *JAMA Oncol* 2019;5:953-60. DOI PubMed PMC
59. Chiang CL, Chiu KWH, Chan KSK, et al. Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): a single-arm, phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;8:169-78. DOI PubMed