

Review article

Advances in transarterial chemoembolization for hepatocellular carcinoma: Integration with systemic therapies and emerging treatment strategies



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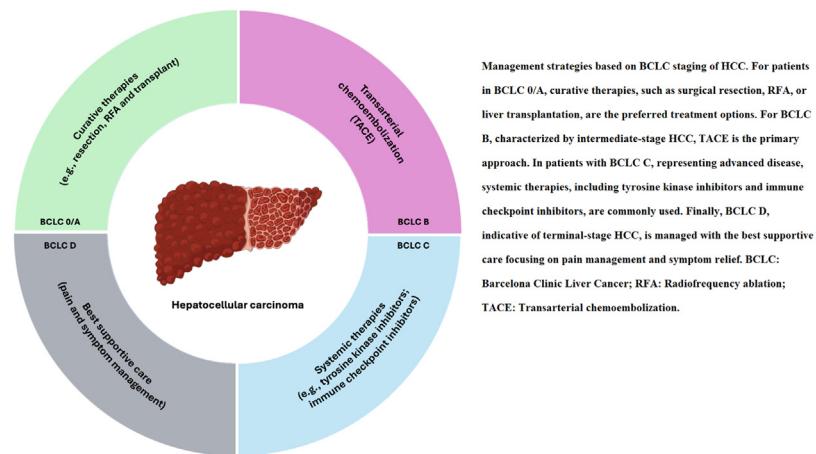
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HIGHLIGHTS

- Transarterial chemoembolization (TACE) is a key treatment for intermediate-stage hepatocellular carcinoma (HCC).
- Recent advancements include improved imaging, drug-eluting beads, and combination therapies with systemic treatments.
- Combining TACE with tyrosine kinase inhibitors and immune checkpoint inhibitors enhances efficacy and survival.

GRAPHICAL ABSTRACT



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ABSTRACT

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, posing considerable challenges due to its complex progression and limited curative options. Transarterial chemoembolization (TACE) is a cornerstone treatment for intermediate-stage HCC, as outlined in widely accepted clinical guidelines, including the Barcelona Clinic Liver Cancer (BCLC) framework. Over the years, TACE has evolved through technological innovations and novel therapeutic combinations designed to enhance efficacy and improve patient outcomes. Recent advancements include refined imaging techniques, innovative embolic materials, and the integration of systemic therapies such as tyrosine kinase inhibitors and immune checkpoint inhibitors. These developments have not only broadened the applicability of TACE but also enhanced its effectiveness in controlling tumor progression and extending survival in patients with unresectable disease. Despite these advancements, challenges persist, including the optimization of treatment protocols, the management of complications, and the need for personalized therapy tailored to diverse patient populations. This review highlights the latest progress

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and current understanding of TACE as a therapeutic modality for HCC. It also explores emerging trends, ongoing challenges, and the potential for novel combinations to redefine the therapeutic landscape. By synthesizing the latest evidence, this article aims to provide valuable insights for clinicians and researchers striving to improve HCC management and patient outcomes.

Introduction

Hepatocellular carcinoma (HCC), the most prevalent type of primary liver cancer, accounts for 90% of cases.¹ It represents a major global health challenge due to its high mortality rate and rising incidence. In 2020, HCC was the sixth most common cancer and the third leading cause of cancer-related deaths worldwide, with approximately 1 million new cases projected by 2025.^{1,2} Key risk factors include hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol consumption, and metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in Western countries.^{3,4} Despite advances in prevention, including HBV vaccination and antiviral therapies for HCV, the growing prevalence of non-alcoholic fatty liver disease (NAFLD) and obesity underscores the urgent need for improved management strategies.^{5,6} HCC is often asymptomatic in its early stages, leading to late diagnoses when curative options such as surgical resection and liver transplantation are no longer viable.⁷ Advanced cases are typically treated with systemic therapies, including tyrosine kinase inhibitors (TKIs), such as sorafenib (SOR), and immune checkpoint inhibitors (ICIs). However, these treatments extend survival by only a few months and are associated with significant side effects and resistance mechanisms.^{2,8} Furthermore, the genetic heterogeneity of HCC complicates the development of targeted therapies, as many actionable mutations remain unexplored.^{3,9}

Locoregional therapies, such as transarterial chemoembolization (TACE), are cornerstone treatments for HCC, particularly for intermediate-stage disease as defined by the Barcelona Clinic Liver Cancer (BCLC) staging system [Table 1; Figure. 1]. TACE is widely recognized as the standard of care for patients with BCLC stage B HCC, which accounts for approximately 20–30% of newly diagnosed cases.^{10–13} This minimally invasive procedure combines the localized delivery of chemotherapeutic agents with vascular embolization, enhancing tumor necrosis by reducing the tumor's blood supply and maximizing cytotoxic exposure. Several randomized controlled trials and meta-analyses have assessed the clinical efficacy of TACE demonstrating considerable survival benefits compared to best supportive care.¹⁴ The BCLC guidelines recommend TACE as the preferred treatment for patients with intermediate-stage HCC who have preserved liver function (Child-Pugh A or B), no vascular invasion, and no extrahepatic spread.^{12,15} These patients typically present with multinodular tumors, and TACE offers the best chance for disease control in this group. Despite its established role, TACE is a non-curative therapy designed to prolong survival and delay disease progression. The median survival for patients treated with TACE ranges from 16 to 20 months, compared to <12 months with supportive care alone.^{10,16} TACE is also employed in select off-label scenarios, such as bridging therapy for patients awaiting liver transplantation or as an adjunct to other modalities like radiofrequency ablation (RFA). However, the heterogeneity within the BCLC B stage highlights the need for more refined stratification to identify patients most likely to benefit from TACE.¹⁴ This review discusses the progress and current understanding of TACE as a therapeutic modality

for HCC. It also examines emerging trends, ongoing challenges, and the potential for innovative treatment combinations to transform the therapeutic landscape.

Basic mechanisms of transarterial chemoembolization

TACE is a minimally invasive procedure that combines targeted chemotherapy with vascular embolization to treat HCC. It leverages the liver's dual blood supply: the hepatic artery primarily supplies blood to tumors, while the portal vein predominantly perfuses the surrounding normal liver parenchyma.¹⁶ This anatomical feature allows for the selective embolization of the tumor-feeding arteries without substantially compromising healthy liver tissue. The procedure involves administering chemotherapy agents directly into the hepatic artery supplying the tumor, followed by embolic materials that block blood flow. This dual approach ensures a high local drug concentration while inducing ischemic necrosis in the tumor, thereby maximizing therapeutic efficacy.¹⁰ The foundation of TACE lies in the selective embolization of hepatic artery branches that supply the tumor. HCC tumors derive approximately 90% of their blood supply from the hepatic artery, making embolization an effective strategy to cut off their oxygen and nutrient supply while preserving portal vein perfusion to sustain healthy liver tissue.¹² Embolization is achieved using materials such as gelatin sponge particles, drug-eluting beads (DEBs), or lipiodol emulsions. These agents lodge within the arterioles, creating a localized ischemic environment that inhibits tumor growth and enhances the cytotoxic effects of the chemotherapy drugs.¹⁶ Ischemia also increases tumor hypoxia, which can induce apoptosis and necrosis, further reducing tumor viability. In TACE, chemotherapeutic agents – most commonly doxorubicin or cisplatin – are delivered directly to the tumor through the hepatic artery. This localized delivery achieves higher drug concentrations at the tumor compared to systemic chemotherapy while minimizing systemic toxicity. The chemotherapeutic agents are typically emulsified with lipiodol, which acts as a carrier to prolong drug retention within the tumor and enhance cytotoxic effects.¹⁰ Following drug administration, embolic agents are introduced to block arterial blood flow, inducing ischemia and further promoting tumor cell death through oxygen deprivation. This combined approach creates a two-pronged attack on the tumor: cytotoxic drugs directly destroy cancer cells, while ischemia induces tumor necrosis by starving cells of oxygen and nutrients. Over time, ischemia may also disrupt the tumor's microvascular structure, impairing its ability to grow and metastasize.¹²

Conventional TACE (cTACE) is the original form of TACE and remains a widely used modality for treating intermediate-stage HCC. The procedure involves injecting a chemotherapeutic agent – often emulsified with lipiodol – directly into the hepatic artery branches supplying the tumor, followed by embolization with particulate materials such as gelatin sponges or polyvinyl alcohol particles to occlude tumor blood flow. Lipiodol acts as a carrier, enhancing drug retention at the tumor

Table 1
BCLC criteria for hepatocellular carcinoma.

BCLC stage	Tumor characteristics	Liver function (Child-Pugh)	PS	Prognosis (median OS)
Stage 0 (very early)	Single tumor ≤2 cm, no vascular invasion, no extrahepatic spread	Child-Pugh A	PS 0	>5 years
Stage A (early)	1–3 nodules ≤3 cm each, no vascular invasion, no extrahepatic spread	Child-Pugh A-B	PS 0	>5 years
Stage B (intermediate)	Multinodular tumors (>3 nodules), no vascular invasion, no extrahepatic spread	Child-Pugh A-B	PS 0	>2.5 years
Stage C (advanced)	Tumors with major vascular invasion and/or extrahepatic metastasis	Child-Pugh A-B	PS 1–2	>2 years
Stage D (terminal)	Extensive tumor burden and/or severe liver dysfunction (decompensated cirrhosis)	Child-Pugh C	PS > 2	Approximately 3 months

BCLC: Barcelona Clinic Liver Cancer; OS: Overall survival; PS: Performance status.

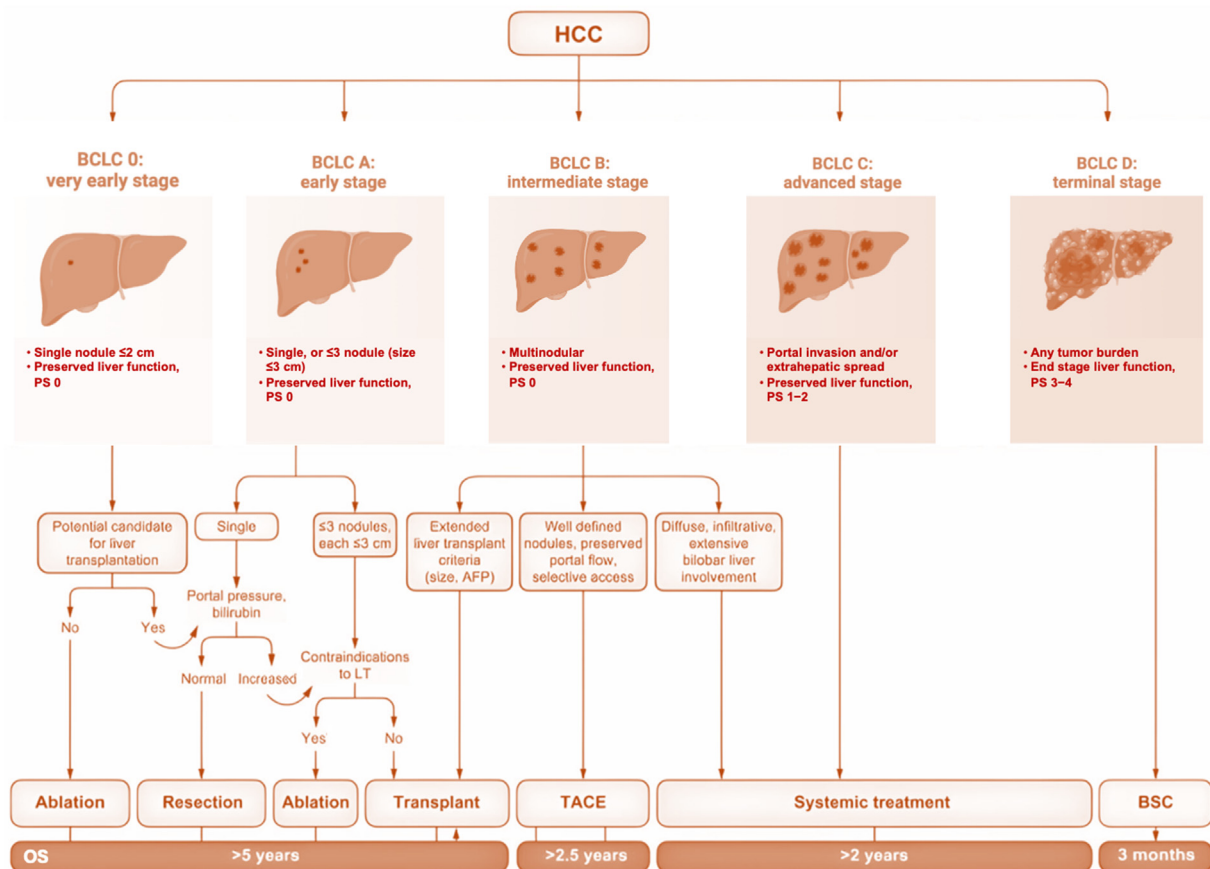


Figure 1. BCLC staging system for HCC. This figure outlines the different stages, ranging from very early (BCLC 0) to terminal (BCLC D). Each stage is characterized by tumor burden, liver function (as measured by PS), and recommended treatment strategies. Expected survival rates vary depending on the stage, with early stages having a better prognosis due to available curative treatments like surgical or ablative therapy, while advanced stages rely on systemic or supportive care with significantly reduced survival expectancy. AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; BSC: Best supportive care; HCC: Hepatocellular carcinoma; LT: Liver transplantation; OS: Overall survival; PS: Performance status; TACE: Transarterial chemoembolization.

site, while embolization induces ischemia, leading to tumor necrosis.^{10,16} Despite being effective in improving survival, cTACE has limitations, including variability in drug dosing, potential systemic drug leakage, and patient discomfort due to post-embolization syndrome (PES), a condition caused by ischemic injury. PES has been linked to worse survival outcomes.¹⁷ To enhance the efficacy and safety of TACE, emerging approaches are exploring novel technologies and combination therapies with other treatment modalities.

Recent advances in transarterial chemoembolization technology

Drug-eluting bead transarterial chemoembolization

Recent advancements in precision drug delivery have aimed to enhance the localized effects of TACE while minimizing systemic toxicity. One major innovation is the development of drug delivery systems, such as DEBs – including drug-covered (DC) beads, drug-eluting microspheres (DEMs) such as HepaSphere, LifePearl, TANDEM Beads, QuadraSphere, and nanoparticles – which allow controlled and sustained release of chemotherapeutic agents directly to the tumor site.^{18–24} Unlike cTACE, where chemotherapy and embolization occur in separate steps, DEBs combine both functions within a single agent, providing consistent drug delivery while maintaining embolization. This controlled, targeted release reduces systemic exposure to chemotherapy, thereby minimizing common cTACE-associated side effects such as PES and hepatotoxicity.¹⁰ In DEB-TACE, chemotherapeutic agents like doxorubicin are loaded into microspheres or beads that act as both a drug carrier and an embolic

material. These beads release the drug over days to weeks, ensuring a prolonged cytotoxic effect on the tumor while limiting systemic toxicity.¹⁶ DEB-TACE reportedly provides greater consistency in tumor response compared to cTACE, particularly in patients with preserved liver function.¹² DEBs have demonstrated superior tumor necrosis rates, especially in those with intermediate-stage HCC. A key advantage of using DEBs is that the therapy can be customized by selecting beads of specific sizes, which influences drug release kinetics and distribution within the tumor microenvironment. Smaller beads penetrate deeper into the tumor vasculature, allowing for more comprehensive tumor treatment.¹⁶ In addition, DEB-TACE is reportedly promising for high-risk patients with compromised liver function, offering better tolerability and safety profiles compared to cTACE.¹⁰

Biodegradable embolic agents

Biodegradable embolic materials represent an innovative advancement aimed at improving TACE outcomes. Unlike permanent embolic agents, biodegradable materials gradually degrade and are absorbed by the body after achieving their therapeutic role. This approach minimizes long-term complications, such as vascular damage, and eliminates the risk of permanent vessel occlusion, which can impair liver function and limit future treatment options.²⁵ Among the most commonly used biodegradable materials are polymers such as poly(lactic-co-glycolic acid) (PLGA) and starch-based microspheres. These agents can be loaded with chemotherapeutic drugs and tailored to degrade within specific time frames, aligning with the therapeutic window required for effective tumor

necrosis. Biodegradable embolic materials are particularly beneficial for patients undergoing repeated TACE sessions as they reduce the cumulative burden on the hepatic vasculature.¹⁰ A recent study introduced a novel biodegradable ion-exchange drug-eluting microembolic system designed to improve the efficacy of TACE for unresectable liver cancer. This platform, utilizing gelatin-based microembolics grafted with nano-sized poly (acrylic acid), enables high-efficiency electrostatic loading of doxorubicin with rapid encapsulation and sustained drug release for up to 2 months. In preclinical models, these microembolics demonstrated excellent deliverability, deep tumor drug retention, and superior tumor-killing effects, while promoting vessel remodeling and achieving sustained embolization with minimal inflammation.²⁶ Emerging biodegradable embolic technologies are also exploring the incorporation of bioactive compounds, such as anti-inflammatory agents or angiogenesis inhibitors, to enhance therapeutic outcomes. For instance, embolic agents that release both chemotherapy drugs and anti-vascular endothelial growth factor (VEGF) agents could simultaneously inhibit tumor growth and suppress angiogenesis, addressing the risk of recurrence and metastasis commonly observed after TACE.²⁷

Advances in imaging and targeting

The evolution of imaging technologies has considerably improved the precision and efficacy of TACE for HCC. One major advancement is the integration of cone-beam computed tomography (CBCT) into interventional radiology suites. CBCT provides real-time, high-resolution, three-dimensional imaging, enabling interventional radiologists to identify the arterial supply to HCC tumors with exceptional accuracy. This enhanced visualization enables the detection of tumor-feeding vessels that may not be visible in traditional angiography, resulting in more precise embolization. CBCT-guided TACE reportedly improves tumor coverage and treatment outcomes while minimizing damage to healthy liver tissue.^{16,25}

In addition to CBCT, other advanced imaging modalities, such as fusion imaging and fluoroscopy, are being employed to enhance targeting precision during TACE. Fluoroscopy ensures accurate catheter placement and optimal embolization of tumor-feeding arteries. As a real-time imaging technique, fluoroscopy enables interventional radiologists to navigate catheters through the hepatic vasculature, identify tumor-supplying vessels, and monitor the delivery of embolic agents. This level of precision is crucial for maximizing tumor response while minimizing damage to healthy liver tissue.²⁸ The integration of digital subtraction angiography (DSA) with fluoroscopy further enhances visualization, allowing for more selective embolization and improved treatment efficacy. Recent advancements have refined fluoroscopic techniques in TACE procedures. For example, biplane fluoroscopy, which provides two simultaneous imaging planes, improves catheter placement accuracy and reduces procedural complications.²⁹ In addition, real-time quantitative fluoroscopy has been developed to assess hepatic arterial blood flow changes during TACE, offering an objective measure of embolization endpoints.³⁰ This technique enables more precise embolization, reducing the risk of under- or over-treatment. Despite its benefits, fluoroscopy-based TACE procedures expose both medical staff and patients to ionizing radiation. A study assessing occupational radiation exposure during TACE found that interventional radiologists receive higher doses compared to assistants and technicians, emphasizing the need for radiation protection measures such as lead shielding and optimized procedural techniques.³¹ Meanwhile, fusion imaging, which combines real-time ultrasound or fluoroscopy with pre-procedural computed tomography (CT) or magnetic resonance imaging (MRI) scans, enhances tumor localization and guides catheter placement with greater accuracy. These innovations have expanded the ability to treat complex cases, including multi-nodular or poorly vascularized tumors. Additionally, advanced imaging enables dynamic tumor tracking during embolization, thereby enhancing the precision of therapeutic interventions.¹²

Integration with systemic therapies

The combination of TACE with ICIs has emerged as a promising strategy to enhance the therapeutic efficacy of HCC treatment. ICIs targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) have demonstrated considerable potential by reactivating the anti-tumor immune response. Integrating ICIs with TACE leverages the synergistic effects of localized tumor necrosis induced by TACE and systemic immune modulation by ICIs. Preclinical and early clinical studies suggest that combining TACE with ICIs, such as anti-PD-1/PD-L1 agents, may improve treatment outcomes. TACE-induced tumor necrosis leads to the release of neoantigens, enhancing immune recognition and response when paired with ICIs.^{32,33} This combination therapy can stimulate a more robust systemic anti-tumor immune response, potentially overcoming resistance mechanisms and improving outcomes for advanced HCC. The immunogenic effects of TACE are mediated by the induction of tumor necrosis, which releases tumor-associated antigens into the microenvironment. This antigen release primes the immune system, enabling ICIs to further activate cytotoxic T cells and enhance immune-mediated tumor destruction.³⁴ This synergistic interaction fosters a favorable environment for immune checkpoint blockade, enhancing the efficacy of treatments targeting the PD-1/PD-L1 axis. Additionally, TACE reduces tumor vascularity and hypoxia, potentially enhancing immune cell infiltration and the efficacy of ICIs.³⁵ SOR, a multikinase inhibitor, has been a cornerstone in the systemic treatment of HCC due to its ability to target key pathways involved in tumor growth and angiogenesis. It acts by inhibiting rapidly accelerated fibrosarcoma (RAF) serine/threonine kinases in the mitogen-activated protein kinase (MAPK) pathway, thereby reducing tumor proliferation while simultaneously blocking vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) to impair angiogenesis. Additionally, SOR also modulates immune responses by inducing macrophage pyroptosis, thereby triggering natural killer cell-mediated cytotoxicity against HCC.³⁶ Lenvatinib, another multikinase inhibitor, is also promising in systemic therapy in combination with TACE for HCC. It primarily acts by inhibiting angiogenesis by targeting VEGFR1–3 and fibroblast growth factor receptors (FGFRs) 1–4. This is particularly relevant in addressing the angiogenic rebound – a process in which hypoxia-induced VEGF upregulation occurs after TACE, promoting tumor regrowth.³⁷ This synergistic effect is achieved by targeting angiogenesis and enhancing the durability of TACE-induced tumor necrosis.^{37,38} By mitigating this rebound, lenvatinib enhances the therapeutic efficacy of TACE. Regorafenib, another multikinase inhibitor that targets VEGFR, FGFR, and PDGFR, has demonstrated efficacy as a second-line treatment following SOR failure. Its combination with TACE has been associated with improved overall survival (OS) and progression-free survival (PFS) in patients with intermediate and advanced HCC.^{39,40}

Cabozantinib, another TKI with activity against mesenchymal–epithelial transition (MET), VEGFR, and AXL, has been evaluated in combination with TACE in both first- and second-line settings. The CELESTIAL trial confirmed its efficacy as a second-line therapy and ongoing studies are exploring its role in combination regimens.^{41,42} Anlotinib, a novel TKI with anti-angiogenic properties, has been combined with TACE to enhance tumor necrosis while minimizing treatment-related toxicities.^{43,44} Monoclonal antibodies targeting the VEGF pathway, such as bevacizumab, have also been investigated in combination with TACE. Bevacizumab, when combined with ICIs like atezolizumab, has demonstrated superior OS compared to SOR in advanced HCC. The potential role of bevacizumab in combination with TACE is being explored.^{45,46}

Other emerging combined modalities

Another emerging approach involves radiotherapy-enhanced TACE, such as TACE combined with transarterial radioembolization (TARE) or

Table 2

Treatment modalities for hepatocellular carcinoma.

BCLC stage	Modality/agent	Mechanism of action	Advantages	Limitations	Common complications
BCLC 0–A (very early/early)	Surgical resection	Removal of the tumor and surrounding liver tissue	Potentially curative	High recurrence rates, invasive	Postoperative liver failure, infection
	Liver transplantation	Replaces liver, removing the tumor and cirrhotic liver	Curative; addresses the underlying liver disease	Limited donor availability, risk of rejection	Immunosuppression-related infections, recurrence
	RFA	Thermal destruction of the tumor via electrical currents	Minimally invasive, curative in early HCC	Ineffective for large/deep tumors	Thermal injury, incomplete ablation
	MWA	Thermal energy induces coagulative necrosis	Faster, effective for large tumors	Limited to localized tumors	Thermal injury to surrounding tissues
BCLC B (intermediate)	TACE	Chemotherapy + embolization of the tumor blood supply	Effective for local tumor control	Not curative, variable response rates	PES, liver dysfunction
	Radioembolization (Y90)	Radioactive Y90 microspheres induce tumor necrosis	Longer time to progression than TACE	Expensive, limited to specialized centers	Fatigue, abdominal pain, and radiation hepatitis
BCLC C (advanced)	Systemic therapy: Sorafenib	TKI	Prolongs survival in advanced cases	Modest survival benefit	Diarrhea, hand-foot syndrome, and hypertension
	Systemic therapy: Lenvatinib	TKI	Comparable efficacy to sorafenib	Not suitable for all patients	Hypertension, proteinuria
	Immune checkpoint inhibitors	PD-1/PD-L1 inhibitors enhance immune response	Promising response rates	Expensive, response variability	Immune-related adverse events (such as colitis)
Combination approaches	TACE + lenvatinib	TACE reduces blood flow; lenvatinib inhibits angiogenesis	Improved progression-free survival	Requires further clinical validation	Similar to TACE and lenvatinib complications
	TACE + immune checkpoint inhibitors	TACE induces immunogenic cell death, and ICIs boost the response	Synergistic effects, promising efficacy	Protocols are not yet standardized	Immune-related adverse events, PES

BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; ICI: Immune checkpoint inhibitor; MWA: Microwave ablation; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PES: Post-embolization syndrome; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; TKI: Tyrosine kinase inhibitor; Y90: Yttrium-90.

stereotactic body radiation therapy (SBRT). These approaches integrate the localized cytotoxic effects of TACE with the tumor-killing capabilities of radiation, offering a synergistic treatment strategy for large or advanced HCC tumors.¹² Yttrium-90 (Y90) radioembolization, also known as TARE, has gained recognition as a complementary or alternative therapy to TACE in patients with HCC [Table 2]. Y90 offers several advantages, including a longer time to progression (TTP) compared to TACE. For example, a randomized study comparing Y90 to TACE found a median TTP of >26 months for Y90 vs. 6.8 months for TACE.⁴⁷ Furthermore, Y90 radioembolization is associated with a lower incidence of post-procedural complications, such as hypoalbuminemia and diarrhea, enhancing its safety profile.⁴⁸ In addition, the use of Y90 as a bridge to liver transplantation has shown promising results, particularly in downstaging patients from higher to lower disease stages.⁴⁹

SBRT has emerged as an effective and noninvasive treatment modality for HCC, particularly for patients who are ineligible for surgery, ablation, or transarterial therapies. SBRT delivers highly conformal, high-dose, focused radiation in a few fractions, allowing precise tumor targeting while minimizing damage to surrounding liver tissue.⁵⁰ Studies have demonstrated local control rates as high as 90%, making SBRT a viable alternative to RFA or TACE for small to medium-sized tumors.⁵⁰ In addition, SBRT has shown promising outcomes in treating portal vein tumor thrombosis (PVTT), where it can not only induce tumor regression but also improve vascular patency.⁵¹ Compared to other local therapies, SBRT offers advantages in tumor control and flexibility. Unlike TACE, which requires arterial access and can be limited by poor tumor vascularization, SBRT is effective regardless of tumor blood supply. In addition, for patients with liver dysfunction (Child-Pugh B), SBRT may be preferable over TACE or RFA, as it results in lower hepatic decompensation rates.⁵² Several studies have explored the combination of SBRT and TACE for HCC, particularly in patients with advanced disease or macrovascular invasion. SBRT has been used as an adjunct to TACE to enhance local tumor control and improve survival outcomes. A meta-analysis comparing SBRT + TACE vs. SBRT alone found that the combination therapy improved OS, complete response rates, and disease control rates (DCRs) without considerably increasing adverse events.⁵³ Another study showed that for patients with HCC with macrovascular invasion, TACE + SBRT provided superior OS and PFS compared with TACE + SOR, suggesting that SBRT may be a viable alternative to

systemic therapy in select patients.⁵⁴ In addition, a retrospective analysis of liver transplant patients found that pre-transplant TACE + SBRT resulted in a higher rate of complete histopathological response compared to either treatment alone, indicating its potential as an effective bridging therapy.⁵⁵ Recently, a multi-institutional review of SBRT practice patterns in Australia demonstrated that SBRT is being increasingly used in clinical practice, particularly for patients for whom surgery or liver transplantation is not feasible.⁵⁶ SBRT is also being investigated as a bridge therapy for liver transplantation, with a study suggesting that it can effectively downstage tumors, making patients eligible for transplant while preserving liver function.⁵⁷ Moreover, combinations of SBRT with systemic therapies, such as ICIs, have shown potential synergistic effects in unresectable HCC.⁵⁸

Iodine-125 (¹²⁵I) brachytherapy has gained recognition as an effective localized treatment for HCC, particularly in patients with unresectable tumors or those who have experienced recurrence following other therapies. This treatment involves implanting radioactive ¹²⁵I seeds directly into the tumor, allowing continuous low-dose radiation exposure that effectively destroys malignant cells while minimizing damage to surrounding healthy tissue.⁵⁹ This form of interstitial brachytherapy has demonstrated promising results in controlling local tumor progression and delaying recurrence, making it a valuable option for patients with advanced-stage disease or those who are unsuitable for surgery. Recent studies have also highlighted the role of ¹²⁵I brachytherapy as an adjuvant therapy following RFA to improve local tumor control. Per a retrospective study, patients who underwent ¹²⁵I seed implantation after incomplete RFA had significantly longer PFS compared to those who received no additional treatment (18 vs. 9 months).⁶⁰ In addition, CT-guided ¹²⁵I brachytherapy has emerged as a safe and effective alternative for treating unresectable HCC, with studies reporting a median OS of 23.6 months and a local control rate of 88.8% at 2 years.⁵⁹ For patients with PVTT, ¹²⁵I brachytherapy has shown favorable outcomes. A study evaluating its efficacy in patients with HCC with PVTT found a 67.5% objective response rate (ORR), with substantial improvements in survival compared to historical controls.⁶¹ Furthermore, ¹²⁵I seed implantation combined with TACE has been explored as a combined strategy, yielding better tumor control and prolonged OS compared with TACE alone.⁶² The synergy between these treatments suggests that ¹²⁵I brachytherapy may enhance the therapeutic effect of other locoregional therapies.

Despite these advantages, challenges remain in standardizing¹²⁵ brachytherapy protocols, including dose optimization and patient selection criteria.

Next, the combination of RFA and TACE has gained increasing recognition as an effective treatment strategy for HCC, particularly in patients with intermediate-stage disease or tumors unsuitable for monotherapy. TACE delivers chemotherapy directly to the tumor while inducing ischemic necrosis; however, it often leaves behind viable tumor cells, especially in larger lesions. Conversely, RFA uses thermal energy to destroy tumor cells but is limited by the tumor size and location. By combining these modalities, their synergistic effects can be leveraged to enhance tumor control.⁶³ Clinical studies have demonstrated that the combination of RFA and TACE yields superior outcomes compared to either treatment alone. A meta-analysis comparing combination therapy with RFA monotherapy found significantly improved OS and recurrence-free survival (RFS), along with higher complete response rates.⁶⁴ Another study reported that sequential TACE followed by early RFA led to better tumor control and prolonged OS compared to delayed combination therapy, highlighting the importance of optimal timing.⁶⁵ In addition, combination therapy appears particularly beneficial for patients with tumors between 3 and 5 cm, as these lesions are often sub-optimal candidates for RFA alone due to incomplete ablation and a high risk of recurrence. A study comparing TACE + RFA to either treatment alone found that the combined approach resulted in higher local tumor control rates and improved disease-free survival (DFS).⁶⁶ Moreover, for patients with early-stage HCC who are ineligible for curative resection, TACE + RFA has demonstrated survival outcomes comparable to those of surgical resection, reinforcing its potential as a curative alternative.⁶⁷ Despite its advantages, the combination of RFA and TACE also presents challenges, including increased procedural complexity, potential hepatotoxicity, and a higher incidence of post-treatment discomfort compared to monotherapy.

Microwave ablation (MWA) is an emerging treatment for HCC that is increasingly being used in combination with TACE. MWA employs high-frequency electromagnetic waves to induce coagulative necrosis of tumor tissues. Unlike traditional RFA, MWA offers faster ablation times and greater efficacy for larger tumors. When combined with TACE, MWA enhances local tumor control and has been associated with improved OS.⁶⁸ This synergistic effect is attributed to the complementary mechanisms of TACE reducing tumor vascularity, while MWA directly ablates cancer cells. Combining TACE with emerging modalities considerably improves clinical outcomes. For instance, a study comparing TACE and Y90 demonstrated higher tumor response rates with Y90 while maintaining the locoregional control benefits of TACE.⁶⁹ Similarly, TACE followed by MWA has been shown to provide enhanced local control, particularly for tumors >5 cm, where single-modality treatments may be insufficient.⁶⁸

Emerging technologies also help improve drug distribution within the tumor microenvironment. Smart embolic materials are being developed to respond to tumor-specific characteristics, such as pH or enzymatic activity, allowing for more targeted drug release. In addition, innovations in catheter technology, including microcatheters with steerable tips and pressure sensors, enable more precise delivery of embolic agents to tumor-feeding vessels while minimizing damage to surrounding healthy tissues.²⁷

Efficacy and outcomes of transarterial chemoembolization and its combination with systemic therapies

Clinical trials and evidence synthesis

TACE is a well-established cornerstone treatment for intermediate-stage HCC, as outlined in the BCLC guidelines. It is primarily used in patients with preserved liver function (Child-Pugh A or B) and no evidence of vascular invasion or extrahepatic spread. Clinical trials consistently show that TACE considerably improves OS in these patients, with

median OS ranging from 20 to 40 months in well-selected populations.^{37,38} The procedure achieves ORRs between 30 and 70% based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, with DCR often >80%. Adjuvant TACE has also been explored as a postoperative strategy to reduce recurrence and improve survival following curative resection. Per a study, it may be particularly beneficial for patients at high risk of recurrence, including those with large tumors, microvascular invasion (MVI), or multiple nodules.⁷⁰ A randomized clinical trial demonstrated that in patients with solitary tumors ≥5 cm and MVI, adjuvant TACE considerably prolonged DFS and OS compared to surgery alone.⁷¹ Meta-analyses further support the benefits of adjuvant TACE, showing improved OS and RFS, particularly in patients with high-risk features.⁷² However, not all studies confirm a clear advantage; some suggest that adjuvant TACE does not substantially reduce recurrence or improve survival, especially in low-risk patients.⁷³

Although TACE is effective for local tumor control, its long-term efficacy is often hindered by tumor recurrence and progression due to post-treatment angiogenic rebound. This challenge has led to increasing interest in combining TACE with systemic therapies to enhance outcomes. Emerging evidence indicates that combining TACE with ICIs or kinase inhibitors (such as SOR and lenvatinib) markedly improves OS and PFS compared to TACE alone. ICIs, such as anti-PD-1/PD-L1 agents, leverage TACE-induced tumor necrosis, which releases neoantigens and enhances immune activation. Preliminary data suggest that this combination strategy boosts tumor response rates and extends survival. For instance, a pilot study investigating TACE combined with anti-CTLA4 and PD-L1 inhibitors, such as tremelimumab and durvalumab, demonstrated tolerability, early efficacy, and enhanced immune activation in tumor biopsies.⁷⁴ Next, the pembrolizumab following TACE in HCC (PETAL) study assessed the safety and efficacy of TACE combined with the PD-1 inhibitor pembrolizumab in patients with liver-confined HCC. Among 15 patients, pembrolizumab was well-tolerated, with no dose-limiting toxicities reported after TACE, though treatment-related adverse events occurred in 93% of patients, most commonly skin rash, fatigue, and diarrhea. The ORR at 12 weeks post-TACE was 53%, with a 12-week PFS rate of 93% and a median PFS of 8.95 months. The median OS was 33.5 months.⁷⁵ Real-world studies have also demonstrated promising outcomes, with patients receiving TACE combined with PD-1 inhibitors and anti-angiogenic agents achieving a median OS of 14 months and a median PFS of 9.2 months.⁷⁶ The EMERALD-1 phase III trial evaluated the efficacy and safety of durvalumab + bevacizumab in combination with TACE (durvalumab + bevacizumab + TACE) vs. TACE alone in patients with embolization-eligible unresectable HCC.^{77,78} Among 616 randomized patients, the primary endpoint was met, as durvalumab + bevacizumab + TACE markedly improved PFS compared to TACE alone (median PFS: 15.0 vs. 8.2 months; hazard ratio [HR], 0.77). However, adding durvalumab alone to TACE (durvalumab + TACE) did not yield a statistically significant PFS benefit. The ORR was higher in the durvalumab + bevacizumab + TACE arm (43.6%) compared to TACE alone (29.6%), and the median TTP was longest in the durvalumab + bevacizumab + TACE group (22.0 vs. 10.0 months with TACE). Safety was manageable, with grade 3/4 treatment-related adverse events occurring in 32.5% of patients in the durvalumab + bevacizumab + TACE group vs. 13.5% in the TACE group.⁷⁷ In addition, a nationwide retrospective cohort study (CHANCE001) examined the real-world efficacy and safety of TACE combined with PD-L1 inhibitors and molecular targeted treatments in patients with HCC. Among 826 patients, 376 received combination therapy, while 450 underwent TACE monotherapy. After propensity score matching, 228 pairs were analyzed, demonstrating significantly improved median PFS in the combination group (9.5 vs. 8.0 months; HR, 0.70), along with longer OS (19.2 vs. 15.7 months; HR, 0.63) and a higher ORR (60.1% vs. 32.0%). Although grade 3/4 adverse events were more frequent in the combination group (15.8% vs. 7.5%), the safety profile remained acceptable.⁷⁹

Furthermore, a phase III randomized clinical trial evaluated the efficacy of SOR + TACE (SOR-TACE) vs. TACE alone in patients with

Table 3

Several clinical trials exploring TACE and its combination therapies.

Trial name (NCT No.)	Population under study	Therapies under comparison	Primary endpoint(s)
EMERALD-1 (NCT03778957) ⁷⁷	Embolization-eligible uHCC, Child-Pugh A–B7, ECOG performance status 0–1, and no evidence of extrahepatic disease	TACE + durvalumab + bevacizumab vs. TACE + durvalumab vs. TACE + placebo	PFS for placebo vs. combination
CHECKMATE-74W (NCT04340193) ⁸³	Tumors that exceed the beyond Milan and up-to-7 criteria, eligible for TACE, with ECOG performance status 0–1	TACE + nivolumab + ipilimumab vs. TACE + nivolumab vs. TACE	OS and TTTP
LEAP-012 (NCT04246177) ⁸⁴	Confirmed HCC localized to the liver without portal vein thrombosis and not amenable to curative treatment, ≥ 1 measurable tumor per RECIST 1.1, ECOG performance status 0–1, Child-Pugh A, and no previous systemic treatment for HCC	TACE + pembrolizumab + lenvatinib vs. TACE + placebo	OS and PFS
TACE-3 (NCT04268888) ⁸⁵	Candidates for first TACE (intermediate HCC/BCLC B)	TACE + nivolumab vs. TACE	OS (TTTP for phase II)
REPLACE (NCT04777851) ⁸⁶	Intermediate-stage HCC with beyond up-to-7 criteria, not amenable to curative treatment but amenable to LRT with TACE or TARE, no prior systemic or LRT for HCC	Regorafenib + pembrolizumab vs. TACE	PFS
ABC-HCC (NCT04803994) ⁸⁷	Intermediate-stage HCC (multifocal, exceeding the Milan criteria, no extrahepatic spread, and no macrovascular invasion), with no curative treatment options, an ECOG performance status of 0, a Child-Pugh A classification, and ≥ 2 untreated lesions with a diameter > 10 mm and arterial hyperenhancement on cross-sectional imaging	Atezolizumab + bevacizumab vs. TACE	Time to treatment failure
NCT05319431 ⁸⁸	Documented HCC, CNLC IIa, IIb, or IIIa, the main portal vein was not completely obstructed, Child-Pugh A or B, at least one measurable lesion according to RECIST criteria, ECOG PS 0–1	Experimental: AK104 + lenvatinib + TACE	PFS
EMERALD-3 (NCT05301842) ⁸⁹	Confirmed HCC not amenable to curative therapy but eligible for embolization, Child-Pugh A, ECOG performance status of 0–1, measurable disease by mRECIST, and adequate organ and marrow function	Arm A (STRIDE + lenvatinib + TACE) vs. arm B (STRIDE + TACE) vs. arm C (TACE alone)	PFS
NCT05286320 ⁹⁰	EASL confirmed HCC, measurable mRECIST, ECOG 0, adequate organ function	Lenvatinib/pembrolizumab + SBRT combinations (single arm)	Safety rate and ORR
NCT05250843 ⁹¹	EASL confirmed HCC, conform to any of the following criteria: (1) multiple nodules > 3 ; (2) ≥ 2 nodules, any of which is > 3 cm; (3) invasion of the portal vein or hepatic vein, one-stage liver cancer resection is feasible, no previous anti-HCC treatment, ECOG < 2 , Child-Pugh A or B	TACE/HAIC combined with lenvatinib and sintilimab as neoadjuvant therapy before liver resection vs. surgery alone	RFS

ABC-HCC: Atezolizumab plus bevacizumab versus TACE in intermediate-stage hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; CNLC: China liver cancer staging; EASL: European Association for the Study of the Liver; ECOG: Eastern Cooperative Oncology Group; HAIC: Hepatic artery infusion chemotherapy; HCC: Hepatocellular carcinoma; LEAP-012: TACE combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic HCC; LRT: Locoregional therapy; mRECIST: Modified Response Evaluation Criteria in Solid Tumors Criteria; NCT: National Clinical Trial Number; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors Criteria; REPLACE: Regorafenib and pembrolizumab versus locoregional therapy with TACE or TARE, for the first-line treatment of intermediate-stage HCC with beyond up-to-7 criteria; RFS: Recurrence-free survival; SBRT: Stereotactic body radiation therapy; STRIDE: Single tremelimumab regular interval durvalumab; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TTTP: Time to transarterial chemoembolization progression; uHCC: Unresectable hepatocellular carcinoma.

recurrent intermediate-stage HCC and positive MVI after R0 hepatectomy. Conducted across five hospitals in China, the study enrolled 162 patients and found that SOR-TACE significantly improved OS (22.2 vs. 15.1 months; HR, 0.55) and PFS (16.2 vs. 11.8 months; HR, 0.54) compared to TACE alone. The ORR was also higher in the SOR-TACE group (80.2% vs. 58.0%). Although adverse events were more frequent with SOR-TACE, they remained manageable, with no unexpected toxicities or treatment-related deaths. These findings suggest that SOR-TACE provides superior clinical benefits and should be considered for patients with recurrent intermediate-stage HCC and positive MVI.⁸⁰ Similarly, clinical studies have consistently demonstrated improved outcomes when TACE is combined with lenvatinib compared to TACE alone. A retrospective study found that patients treated with TACE + lenvatinib had significantly longer median PFS (8.3 vs. 4.6 months) and OS (27.7 vs. 18.4 months) compared to those receiving TACE alone.³⁷ In addition, combination therapy achieved higher ORR and DCR, emphasizing its efficacy in tumor control. A separate multicenter study reinforced these findings, reporting a median PFS of 13.3 months and a median OS of 23.6 months in patients receiving TACE and lenvatinib. These results highlight the potential of this combination in managing unresectable HCC.⁸¹ Although promising, ongoing trials are being conducted to determine the optimal administration protocols for combining lenvatinib with TACE. Current approaches often involve preconditioning with lenvatinib to reduce tumor vascularity before TACE, followed by resumption of the drug post-embolization. Trials, such as the TACTICS-L study, have explored these strategies, demonstrating high response rates and

favorable safety profiles.³⁸ Recently, a phase III multicenter trial in China compared DEB-TACE combined with apatinib, a TKI that selectively inhibits the VEGFR-2, against DEB-TACE alone in patients with unresectable HCC. Among 243 randomized patients, those receiving DEB-TACE + apatinib exhibited significantly improved median PFS (7.1 vs. 5.2 months) and OS (23.3 vs. 18.9 months) compared to DEB-TACE alone. The combination therapy also resulted in higher ORRs (56.6% vs. 38.8%) and DCRs (89.3% vs. 80.2%). Although most treatment-related adverse events were mild and manageable, hepatic artery thinning and spasms were more frequently observed during the second DEB-TACE in the combination group. Apatinib-related side effects included hypertension, hand-foot syndrome, fatigue, and diarrhea.⁸² Several ongoing clinical trials investigating TACE and its combination strategies are summarized in Table 3.^{77,83–91}

Predictors of efficacy

The biology of HCC plays a crucial role in determining the efficacy of TACE. Key factors include tumor size, multiplicity, and differentiation. Poorly differentiated tumors and those with aggressive growth patterns tend to be less responsive to TACE due to their increased invasiveness and resistance to ischemia-induced necrosis.⁹² In addition, the presence of vascular invasion – often indicated by elevated serum alpha-fetoprotein (AFP) levels – is associated with lower response rates and shorter OS.⁹³ Tumor size is another critical determinant. Smaller tumors (≤ 3 cm in diameter) demonstrate higher complete response rates and longer survival

after TACE compared to larger tumors, which are more likely to contain hypoxic and necrotic regions that are resistant to embolization.⁹⁴ Tumor vascularity also considerably influences TACE efficacy. Hypervascular HCCs, characterized by a robust arterial blood supply, respond better to TACE, as embolization effectively deprives the tumor of oxygen and nutrients. Hypervascular tumors exhibit better radiologic responses and prolonged PFS compared to hypovascular or poorly perfused tumors.⁹⁵ However, TACE may also trigger an angiogenic rebound by upregulating VEGF and other pro-angiogenic factors in response to ischemia. High pretreatment VEGF levels have been linked to poorer outcomes, including reduced OS and PFS.⁹⁶ Anti-angiogenic therapies, such as lenvatinib, are being explored to counteract this effect and improve TACE efficacy.³⁷ Patient-related factors, including liver function, performance status, and comorbidities, critically impact TACE outcomes. Patients with preserved liver function, typically classified as Child-Pugh Class A or B, demonstrate better tolerance to TACE and improved survival rates. In contrast, those with decompensated liver cirrhosis face a higher risk of post-TACE hepatic failure and poorer outcomes.⁹⁷ Systemic inflammation markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have also been identified as predictors of TACE efficacy. Elevated NLR and PLR levels are associated with reduced OS and a higher likelihood of metastasis following TACE.⁹⁸

Circulating tumor cells (CTCs) and circulating cell-free DNA (cfDNA) have emerged as promising biomarkers for predicting TACE efficacy in HCC. These liquid biopsy techniques provide non-invasive methods for evaluating tumor burden, treatment response, and prognosis. Fluctuations in cfDNA levels before and after TACE reportedly correlate with treatment outcomes. One study found that patients with increased cfDNA and circulating tumor DNA (ctDNA) following TACE experienced substantially higher rates of disease progression and shorter PFS compared to those with stable or decreased levels.⁹⁹ Another study demonstrated that cfDNA profiling through copy number variations (CNVs) could predict TACE outcomes by identifying genomic instability associated with poor therapeutic response.¹⁰⁰ Similarly, CTC levels have been linked to TACE efficacy and long-term prognosis. Research indicates that patients with high pre-treatment CTC counts tend to have worse survival outcomes following TACE. Moreover, a post-TACE decline in CTC levels correlates with improved OS, whereas rising CTC counts suggest treatment resistance.¹⁰¹

Complications of transarterial chemoembolization

Studies have demonstrated that TACE induces considerable tumor necrosis, providing survival benefits across various cohorts. For instance, in a study of patients with cirrhosis with single HCC lesions, TACE

monotherapy achieved a complete tumor necrosis rate of 58%.¹⁰² In addition, combining TACE with agents such as lenvatinib or donafenib has shown improved disease control and prolonged PFS, particularly in advanced-stage cases.¹⁰³ However, TACE is associated with several complications, of which the most common is PES, characterized by fever, abdominal pain, and elevated liver enzymes. PES occurs in up to 25.7% of cases, as reported in a cohort study evaluating TACE with DEBs.¹⁰⁴ A retrospective cohort study examining patients with HCC treated with TACE at a tertiary referral center from 2008 to 2014 focused on PES, defined as fever with or without abdominal pain within 14 days post-TACE. Among 144 patients, 36.1% developed PES, which was linked to poorer survival outcomes. The median OS for the PES group was 16 months, with a 3-year OS rate of 18%, compared to 25 months and 41% in the non-PES group. A multivariate analysis further indicated that PES was associated with a two-fold increased risk of death.¹⁷ Although PES is typically self-limiting, it can delay subsequent treatments and impact patients' quality of life. Management strategies primarily involve supportive care, including analgesics and antipyretics. Liver dysfunction is another notable risk associated with TACE, particularly in patients with compromised hepatic reserve. The ischemic injury caused by embolization can further impair liver function, increasing the risk of hepatic decompensation.¹⁰⁵ In addition, TACE may stimulate tumor angiogenesis due to hypoxia-induced upregulation of VEGFs, which can contribute to treatment resistance and tumor progression.¹⁰⁶ This highlights the importance of careful patient selection and the potential role of adjunctive anti-angiogenic therapies to mitigate resistance mechanisms.

Transarterial chemoembolization vs. hepatic artery infusion chemotherapy

Hepatic artery infusion chemotherapy (HAIC) is an emerging locoregional treatment for advanced HCC, particularly in patients with unresectable tumors, PVTT, or a high intrahepatic tumor burden. Unlike systemic chemotherapy, HAIC delivers high concentrations of chemotherapeutic agents directly into the hepatic artery, maximizing tumor exposure while minimizing systemic toxicity.¹⁰⁷ Various HAIC regimens, including fluorouracil, leucovorin, oxaliplatin (FOLFOX), and cisplatin-based therapies, have shown promise in prolonging survival and enhancing tumor response.¹⁰⁸ HAIC is especially effective when combined with other therapies. The addition of ICIs, such as anti-PD-1 antibodies, and TKIs, like lenvatinib or SOR, has demonstrated synergistic anti-tumor effects.¹⁰⁹ A phase II study evaluating HAIC in combination with tislelizumab and lenvatinib for patients with PVTT reported a high ORR of 68.97%, suggesting HAIC may enable conversion therapy for previously unresectable cases.¹¹⁰ In addition, HAIC combined with

Table 4
Comparison of HAIC vs. TACE.

Feature	HAIC	TACE
Mechanism of action	Delivers high-dose chemotherapy continuously via the hepatic artery without embolization, maintaining blood supply to the liver	Injects chemotherapy and embolic agents into the hepatic artery, blocking tumor blood supply and causing ischemic necrosis
Best indications	Unresectable HCC with PVTT (including VP4) Large or multiple intrahepatic tumors HCC is unsuitable for TACE due to poor arterial enhancement	Intermediate-stage HCC (BCLC B) HCC with well-developed arterial blood supply Patients with preserved liver function
Suitability for VP4 PVTT	Recommended; maintains hepatic perfusion while treating the tumor	Not recommended; can worsen liver ischemia due to embolization
Suitability for tumors with poor arterial blood supply	Preferred: Continuous chemotherapy infusion allows drug penetration into hypovascular tumors	Less effective; requires a well-developed tumor arterial supply for embolization to work
Survival outcomes	Several studies report better PFS and OS in HAIC compared to TACE for advanced HCC	Standard of care for intermediate-stage HCC; survival outcomes vary based on liver function and tumor characteristics
ORR	Higher response rates compared to TACE in advanced-stage HCC	ORR varies; generally lower than HAIC in advanced cases
DCR	Higher DCR, particularly in combination with systemic therapy	Moderate DCR; often requires multiple sessions
Toxicity profile	Systemic chemotherapy toxicities (such as neutropenia, nausea, fatigue); less hepatic ischemia	Hepatic ischemia-related complications, such as post-embolization syndrome (fever, pain, nausea)
Procedure complexity	Requires catheter placement with continuous chemotherapy infusion; hospitalization may be needed	Outpatient or short-stay procedure; simpler than HAIC

BCLC: Barcelona Clinic Liver Cancer; DCR: Disease control rate; HAIC: Hepatic artery infusion chemotherapy; HCC: Hepatocellular carcinoma; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PVTT: Portal vein tumor thrombosis; TACE: Transarterial chemoembolization; VP4: Vascular invasion grade 4.

systemic treatments like anlotinib and penpulimab, a humanized anti-PD-1 immunoglobulin G1 (IgG1) antibody, has shown a significant DCR, reinforcing its potential as a first-line treatment strategy.¹¹¹

Although both TACE and HAIC deliver chemotherapy directly to the liver, they differ significantly in their mechanisms, efficacy, and patient suitability [Table 4]. TACE involves injecting chemotherapeutic agents mixed with embolic materials into the hepatic artery, causing ischemic necrosis by obstructing the tumor's blood supply.¹¹² In contrast, HAIC continuously infuses chemotherapy via a catheter placed in the hepatic artery without embolization, allowing for higher drug concentrations while maintaining blood flow.¹¹³ Several studies suggest that HAIC may offer superior therapeutic benefits in certain patient populations compared to TACE. A systematic review and meta-analysis found that HAIC achieved a significantly higher ORR and DCR than TACE, with fewer adverse events.¹¹³ In addition, a study comparing HAIC with modified FOLFOX (mFOLFOX) to TACE in patients with large, unresectable HCC reported a higher treatment response rate (46% vs. 18%) and improved OS (23.1 vs. 16.1 months) with HAIC.¹¹⁴ Furthermore, HAIC appears to be a better option for patients with PVTT, as it preserves hepatic perfusion while delivering high-dose chemotherapy.¹¹⁵ Despite these advantages, TACE remains the preferred standard of care for intermediate-stage HCC (BCLC stage B) due to its widespread availability and effectiveness in controlling localized tumors.¹¹² However, HAIC is gaining traction, particularly in East Asia, as a first-line therapy for advanced HCC and for patients who are refractory to TACE.¹¹⁶ Although both treatments offer distinct advantages, patient selection remains critical. Ongoing trials are currently exploring optimal combination strategies, including the integration of targeted therapies and immunotherapy, to further enhance outcomes.¹¹⁷

Current challenges and future directions of transarterial chemoembolization

Limitations in current transarterial chemoembolization protocols

One of the key challenges in TACE for HCC is the lack of standardized protocols, particularly in drug dosing and embolization techniques. cTACE employs an emulsion of chemotherapeutic agents mixed with lipiodol, followed by embolic agents, but optimal drug types and dosages vary widely across institutions. In addition, DEB-TACE further adds to this variability by using beads that slowly release chemotherapy over time. This inconsistency in treatment approaches results in heterogeneous outcomes and complicates direct comparisons across clinical trials.¹¹⁸ In addition, while super-selective embolization has demonstrated improved local tumor control and reduced complications, its widespread adoption is limited by technical complexity and the need for highly skilled operators.¹⁰⁵ Efforts to create standardized protocols have been hindered by the diversity of available agents, embolization techniques, and variations in tumor burden and liver function among patients. A pressing need remains for evidence-based guidelines that define best practices for drug selection, dosage optimization, and embolization strategies to enhance both safety and efficacy.

The efficacy of TACE also varies considerably based on tumor stage and patient health status. Patients with intermediate-stage HCC who have well-preserved liver function and localized disease generally respond better to TACE, showing improved OS and DCR.¹¹⁹ However, in advanced-stage HCC or cases with vascular invasion, the benefits are limited, and the risk of complications, such as post-embolization liver failure, increases.¹⁰⁶ In addition, patients with comorbidities like cirrhosis, portal vein thrombosis, or poor performance status often have lower tolerance for TACE, leading to highly variable treatment outcomes. This underscores the importance of patient selection and stratification. Researchers are investigating biomarkers, such as AFP levels or imaging-based assessments of tumor vascularity, to better predict treatment response and inform clinical decision-making.¹²⁰ Future studies should focus on developing predictive tools and refining selection criteria to ensure that TACE is utilized in patients who are most likely to benefit.

Challenges in combining therapies

Combining TACE with ICIs has shown promising preliminary results by leveraging the anti-tumor immune response triggered by TACE and enhancing it with immunotherapy. A pilot study investigating the combination of TACE with tremelimumab and durvalumab demonstrated safety and feasibility, with partial responses observed in 20% of patients and stable disease in 70%.^{74,121} Similarly, a regimen combining donafenib, anti-PD-1 antibodies, and TACE achieved an ORR of 62.1%, suggesting its potential as a first-line treatment for advanced HCC.¹²² However, differences in study protocols and patient populations make direct comparisons challenging, emphasizing the need for larger-scale trials to establish standardized protocols and validate long-term benefits. The integration of TACE with TKIs, such as lenvatinib, has also emerged as a promising strategy for improving outcomes. Preclinical studies suggest that lenvatinib counteracts TACE-induced angiogenesis, enhancing tumor response and reducing recurrence. A recent phase II study evaluating the combination of TACE, lenvatinib, and the PD-L1 inhibitor envafolimab in patients with advanced HCC reported an ORR of 36.1% based on RECIST criteria, with no treatment-related deaths.¹²³ This triple therapy achieved a DCR of 83.3%, highlighting its potential to markedly extend PFS and OS. Despite these promising findings, further clinical validation and integration into the BCLC guidelines are needed to establish its role in standard practice.

Future directions: potential for personalized transarterial chemoembolization

The development of biomarkers to predict the response to TACE has become a pivotal area of research, offering the potential for more personalized treatment strategies.¹⁰⁰ Genetic signatures, such as a six-gene panel (CXCL8, AFP, CYP1A1, MMP9, CYP3A4, and SERPINC1) have shown promise in distinguishing responders from non-responders.¹²⁴ Proteomics-based approaches have also identified proteins such as LRG1 and BCHE, which, when combined with clinical parameters, help predict sustained complete responses.¹²⁵ Furthermore, inflammatory markers like the NLR and PLR have demonstrated value in predicting TACE outcomes.¹²⁶ These biomarkers offer a means to stratify patients, optimize therapeutic strategies, improve survival, and reduce unnecessary interventions. Advancements in computational modeling and artificial intelligence (AI) are also being explored to enhance TACE efficacy. AI and machine learning (ML) have the potential to develop predictive models that assist clinicians in decision-making. For instance, an ML-derived 10-gene signature has been validated to accurately predict patient responses to TACE with high sensitivity and specificity.¹²⁷ Similarly, ML algorithms can analyze pre-procedural imaging to optimize catheter positioning and embolization strategies, improving drug distribution and treatment efficacy. A retrospective study of 108 patients with HCC who underwent their first DEB-TACE between 2017 and 2022 further reinforced the potential of AI-driven predictive models in enhancing treatment outcomes. Using logistic regression in ML, radiomics, clinical-radiological, and integrated models were developed and compared. The integrated model, which combined CT radiomics with clinical-radiological signatures, demonstrated the highest predictive accuracy, achieving an area under the curve (AUC) of 0.860 in the training group and 0.927 in the validation group. It also outperformed other models in sensitivity and specificity.¹²⁸ Furthermore, AI-driven imaging analysis has shown the potential to predict tumor characteristics, treatment responses, and survival outcomes, facilitating the selection of appropriate candidates for TACE.¹²⁹ These advancements enable precise tailoring of treatment protocols to each patient's unique tumor biology and clinical profile.

Conclusions

TACE remains a cornerstone treatment for intermediate-stage HCC, with ongoing advancements improving its efficacy and safety.

Innovations in imaging techniques, embolic agents, and the integration of systemic therapies, such as ICIs and TKIs like lenvatinib, are expanding the therapeutic potential of TACE. These developments offer promising avenues for enhancing survival and quality of life in patients with unresectable HCC. However, challenges remain in standardizing treatment protocols, managing complications, and tailoring therapies to individual patient profiles. Future research should focus on optimizing combination strategies and incorporating emerging technologies to refine treatment approaches. By embracing a multidisciplinary framework, the evolving role of TACE will continue to shape HCC management and drive advancements in patient care.

Authors contribution

Henry Sutanto: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review & editing; Galih Januar Adytia: data curation, formal analysis, investigation, writing – original draft, writing – review & editing; Elisa: data curation, formal analysis, investigation, writing – original draft, writing – review & editing; Ummi Maimunah: supervision, writing – original draft, writing – review & editing. All the authors have read and approved the final paper.

Ethics statement

None.

Declaration of generative AI and AI-assisted technologies in the writing process

In the preparation of this work, the author used ChatGPT to enhance readability and language. Following the use of this tool/service, the author reviewed and edited the content as necessary, taking full responsibility for the content of the publication.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The datasets used in the current study are available from the corresponding author on reasonable request.

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