Comprehensive treatment of intermediate and advanced primary hepatocellular carcinoma based on transcatheter arterial chemoembolization (Review)

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Abstract. Primary hepatocellular carcinoma (HCC) represents a malignancy of notable clinical concern, marked by elevated global incidence and mortality rates. Despite advancements in therapeutic modalities, HCC management remains challenged by the insidious onset of early-stage disease and the limited efficacy of late-stage surgical interventions. Transcatheter arterial chemoembolization (TACE) has evolved as a pivotal intervention for HCC, with recent innovations fostering synergistic combination strategies to augment therapeutic outcomes. Synthesizing contemporary clinical evidence and anticipating future advancements in TACE-based multimodal approaches is imperative to refine therapeutic paradigms and optimize patient prognoses. The present review critically evaluates the current landscape of TACE-centered multimodal therapies and explores emerging innovations poised to redefine therapeutic frontiers in HCC management.

Contents

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1. Introduction

Hepatocellular carcinoma (HCC) is a global health burden, characterized by disproportionately high incidence and mortality rates across diverse populations. This malignancy arises from hepatocytes or intrahepatic biliary epithelial cells, underscoring its complex cellular origins. Epidemiological data estimate 905,700 cases and 830,200 associated deaths globally each year, positioning HCC as the third-leading cause of cancer-related mortality (1). Projections suggest a surge in incidence, with cases surpassing 1 million by 2025, further exacerbating its public health impact. In China, HCC ranks as the fourth most prevalent malignancy and the second-leading cause of cancer-related mortality (2), constituting a substantial public health burden. Curative modalities such as hepatectomy, liver transplantation and local ablation are associated with prolonged survival in patients with HCC (3), among which hepatectomy remains the gold standard for achieving durable remission. However, the unique immunological milieu of the liver and profound molecular heterogeneity of HCC contribute to its insidious progression, with a high proportion of patients presenting at intermediate to advanced stages (Barcelona Clinic Liver Cancer stages B-D) (4) at initial diagnosis, thereby precluding their eligibility for curative surgical intervention (5). Consequently, the prognosis remains dismal, with a median overall survival (OS) time of ~24 months (6). Even in carefully selected advanced HCC cases amenable to surgery, a biological cure remains elusive, characterized by high recurrence rates and dismal prognoses (7). Current therapeutic paradigms for advanced HCC predominantly depend on systemic and locoregional therapies; however, monotherapy frequently yields suboptimal efficacy, with unsatisfactory objective response rates (ORRs) and survival outcomes (8). By contrast, multimodal therapeutic strategies demonstrate marked improvements in tumor control and survival outcomes (9).

Recent technological innovations and evolving oncological paradigms have positioned comprehensive liver cancer therapy as a cornerstone for advanced HCC, heralding transformative potential for prognostic enhancement. The present review synthesizes contemporary evidence and clinical advancements

in transcatheter arterial chemoembolization (TACE)-based multimodal regimens for advanced HCC, delineating their translational implications.

2. TACE

In contrast to normal hepatic parenchyma, predominantly perfused by the portal vein (75%) and hepatic artery (25%), HCC exhibits a unique vascular dependency, with 85-90% of its blood supply originating from the hepatic arterial system. TACE capitalizes on this vascular disparity by selectively occluding tumor-feeding arteries, thereby inducing ischemic necrosis and exerting potent anti-neoplastic effects (10). First-line therapeutic modalities for advanced HCC encompass hepatic artery chemoembolization, transarterial radioembolization and systemic pharmacological interventions. In unresectable HCC, TACE represents the first-line intervention of choice (11), conferring dual benefits of tumor burden reduction and palliative symptom mitigation. Depending on the drug delivery platform, TACE is classified into conventional TACE, utilizing lipiodol-based emulsions, and drug-eluting bead TACE, employing microspheres for sustained chemotherapeutic release (12).

Despite its widespread adoption and demonstrated efficacy in advanced HCC cohorts (13), TACE is constrained by several limitations. Suboptimal rates of complete necrosis [<20% in some studies (14)] persist, attributable to tumor biological aggressiveness, anatomical complexity and technical challenges in achieving complete embolization. Additionally, monotherapeutic approaches frequently prove inadequate. The expanding clinical utilization of TACE has catalyzed the development of multimodal regimens integrating locoregional and systemic therapies, with TACE-based combinations emerging as the most validated strategy to potentiate antitumor efficacy.

3. TACE combined with local therapies

TACE combined with portal vein stenting and iodine-125 (I-125) brachytherapy. HCC complicated by portal vein tumor thrombus (PVTT) frequently exhibits concurrent hepatic arteriovenous shunting, which impedes effective embolization of the thrombus-associated vasculature during TACE. Consequently, TACE demonstrates suboptimal therapeutic efficacy in this subset of patients with HCC, representing a persistent clinical challenge in HCC management. A novel therapeutic paradigm integrating TACE with portal vein stenting and intra-luminal I-125 brachytherapy, pioneered through seminal contributions by Chinese researchers, has shown marked efficacy in patients with HCC and PVTT (15). In cases of PVTT involving the main portal vein or primary branches, the deployment of I-125-loaded stents or seed-releasing stents achieves dual objectives, namely, the alleviation of portal hypertension, the restoration of physiological hepatopetal flow, the optimization of hepatic functional reserve and the enablement of subsequent TACE by thrombus control (16). Evidence indicates that TACE combined with I-125-impregnated stents or radioactive seed-releasing stents enhances stent patency and extends OS time in patients with HCC and main portal vein thrombosis (17). A study (18) demonstrated that TACE-I-125 brachytherapy synergy achieves superior tumor response rates and survival outcomes compared with TACE monotherapy in complex HCC cases. Chen *et al* (19) demonstrated that the combination of I-125 brachytherapy with TACE resulted in a significant prolongation of median OS and progression-free survival (PFS) times, alongside a markedly higher ORR compared with TACE monotherapy. I-125 brachytherapy has been established as a safe and efficacious adjunct to minimally invasive locoregional therapies in HCC, with a favorable safety profile (20). Therefore, for patients with surgically unresectable primary liver cancer complicated by PVTT, if the tumor thrombus has not involved the main trunk and postoperative hepatic blood flow is expected to recover, this combination therapy can be adopted.

TACE combined with external beam radiotherapy (EBRT). External beam radiotherapy (EBRT), a non-invasive locoregional therapeutic modality, employs precisely calibrated ionizing radiation to selectively eradicate neoplastic cells. Ionizing radiation directly or indirectly damages macromolecules, impairing their function and triggering biological effects (21). A study (22) demonstrated that the combination of radiotherapy with TACE in patients with advanced HCC resulted in enhanced tumor control rates and superior survival outcomes relative to TACE monotherapy, with no statistically significant differences in adverse event rates observed between the two regimens. For unresectable PVTT, the combination of radiotherapy and TACE is now widely regarded as the preferred therapeutic regimen, with clinical studies (23-25) having established its superior efficacy in comparison to monotherapy with radiotherapy, TACE or sorafenib.

A comprehensive meta-analysis (26) demonstrated that the integration of TACE with radiotherapy in patients with advanced HCC and PVTT resulted in superior short-term clinical responses and enhanced OS outcomes [improved ORR: odds ratio, 4.22; 95% confidence interval (CI), 3.07-5.80; P<0.001; and OS: hazard ratio (HR), 0.69; 95% CI, 0.57-0.83; P=0.001], without a statistically significant increase in treatment-related adverse events, as systematically evaluated across diverse patient cohorts. Shui *et al* (27) studied 70 patients with HCC and PVTT and found that the combination of SBRT and TACE significantly prolonged OS time (12 vs. 3 months) compared with SBRT alone without subsequent TACE. Wu *et al* (28) showed that three-dimensional conformal radiation therapy combined with TACE may provide a better OS time than either technique alone in patients with HCC and PVTT. Radiotherapy has been shown to effectively downstage advanced HCC, particularly in managing thrombus formation. Even in cases involving thrombi localized to the main portal vein or its first-order branches, radiotherapy has been observed to induce complete thrombus necrosis, thereby promoting tumor downstaging. Consequently, the combination of TACE and radiotherapy enhances both tumor and thrombus control, thereby increasing the likelihood of successful downstaging (29). Collectively, the integration of TACE with radiotherapy has been shown to confer marked survival benefits and superior clinical efficacy in the treatment of HCC.

TACE combined with ablation therapy. Ablation therapy encompasses a diverse array of minimally invasive techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, high-intensity focused ultrasound, irreversible electroporation and percutaneous ethanol injection. The combination of TACE and ablation therapy demonstrates synergistic therapeutic advantages by collectively addressing the intrinsic limitations of each monotherapy (30). This multimodal approach significantly reduces tumor progression and recurrence rates, diminishes the necessity for repeated TACE sessions, mitigates chemotherapy-induced hepatic injury and resistance, enhances patient quality of life and prolongs OS time (31). This combined strategy demonstrates superior clinical outcomes compared with TACE or ablation monotherapy in patients with unresectable solitary or multifocal tumors (3-7 cm) classified as China Liver Cancer (CNLC) stages (12) Ib-IIa (32). In cases of CNLC stage Ia tumors located in anatomically challenging regions (e.g., adjacent to the diaphragmatic dome or critical intra-/extrahepatic vasculature), standalone ablation exhibits limited efficacy; however, adjunctive pre-ablation TACE enhances lesion demarcation, thereby facilitating precise targeting and comprehensive tumor eradication while minimizing procedural complications (32).

A retrospective cohort study involving 46 patients with large HCC (maximal diameter >5 cm) undergoing combined TACE-RFA therapy demonstrated favorable safety and clinical efficacy, with complete remission (CR) and partial remission (PR) rates of 82.6 and 17.4%, respectively, at 1-month follow-up. Cumulative local tumor progression rates at 1-, 2- and 3-year intervals were 4.3, 13.1 and 30.4%, respectively, while corresponding OS rates reached 89.1, 71.7 and 56.5% (33). A systematic meta-analysis evaluated the efficacy of TACE combined with MWA vs. TACE monotherapy in patients with early-to-intermediate-stage HCC (tumor diameter >5 cm). The combination therapy (TACE + MWA) demonstrated that, compared with TACE alone, TACE + MWA resulted in significantly higher 1-, 2- and 3-year OS rates [1-year OS: risk ratio (RR), 1.36; 95% CI, 1.28-1.44; P<0.001; 2-year OS: RR, 1.56; 95% CI, 1.40-1.74; P<0.001; and 3-year OS: RR, 2.07; 95% CI. 1.67-2.57; P<0.001] (34). Furthermore, combination therapy achieves enhanced local tumor control in anatomically critical zones (e.g., peribiliary or perivascular regions) among patients with CNLC stage IIb-IIIb, thereby reducing the likelihood of tumor invasion into adjacent vital structures (35).

TACE combined with hepatic arterial infusion chemotherapy (HAIC). The therapeutic efficacy of TACE is constrained by portal venous blood flow, resulting in incomplete tumor necrosis and acquired chemoresistance following repeated procedures. HAIC administers chemotherapeutic agents intra-arterially to target lesions, achieving sustained high-concentration drug exposure within tumor vasculature. This approach enhances tumoricidal efficacy, demonstrating significantly higher ORRs than systemic chemotherapy or sorafenib monotherapy (36).

In cases of multifocal HCC involving distinct hepatic segments or tumors with a dual arterial supply, neither HAIC nor TACE monotherapy may suffice. Combined therapy achieves synergistic antitumor effects through complementary mechanisms. Following TACE, adjunctive HAIC exposes viable residual tumor tissue to cytotoxic drug concentrations, thereby eradicating residual malignant cells, reducing embolization frequency and mitigating procedure-related complications (37). Li *et al* (37) reported that TACE-HAIC combination therapy significantly improved ORRs (14.6 vs. 2.4%; P=0.107) compared with TACE alone in unresectable HCC cohorts, with comparable incidence of grade ≥3 adverse events. The TACE-HAIC regimen confers enhanced clinical benefits in patients with HCC and bulky tumors (>5 cm diameter), particularly in terms of locoregional control and survival outcomes (38). In HCC with PVTT (particularly main trunk involvement), bulky tumors, high-flow arteriovenous shunts refractory to TACE or acquired TACE resistance, the integration of modified FOLFOX regimen-based HAIC potentiates TACE efficacy through chemosensitization (39).

4. TACE combined with systemic therapies

TACE combined with targeted therapy. TACE-induced ischemic and hypoxic microenvironments upregulate vascular endothelial growth factor receptor (VEGFR) expression, thereby promoting compensatory angiogenesis and facilitating residual tumor proliferation and metastatic dissemination (40). The combinatorial regimen of TACE and anti-angiogenic targeted agents exerts synergistic antitumor effects through dual modulation of tumor burden reduction and angiogenesis suppression. In advanced HCC, however, the extensive tumor burden compromises single-agent therapeutic efficacy, yielding an ORR of ~20% in monotherapy cohorts (41).

The integration of sorafenib, a first-line multikinase inhibitor for HCC, with TACE significantly enhances OS and PFS times in patients with unresectable HCC (42). The phase II TACTICS trial demonstrated that TACE-sorafenib combination therapy markedly extended median PFS time (25.2 vs. 13.5 months; P=0.006), time to untreatable progression (26.7 vs. 20.6 months; P=0.02), and 1- and 2-year OS rates (96.2 vs. 82.7% and 77.2 vs. 64.6%) compared with TACE monotherapy (42). TACE potentiates intratumoral drug accumulation, thereby augmenting the antiproliferative and proapoptotic effects of sorafenib. The dual mechanism of sorafenib, namely direct tumor cytotoxicity and angiogenesis inhibition, effectively counteracts TACE-induced revascularization. The OPTIMIS real-world study demonstrated that the early integration of sorafenib into therapeutic regimens resulted in a significant prolongation of OS time relative to delayed or absent combination therapy (43). Consequently, the combination of sorafenib with TACE is recognized as a clinically recommended regimen, offering both efficacy and a favorable safety profile.

Regorafenib, a second-line multikinase inhibitor with enhanced VEGFR-2/3 inhibitory potency and broader anti-angiogenic activity compared with sorafenib, is indicated for sorafenib-refractory HCC. The phase III RESORCE trial established that sequential regorafenib therapy, administered subsequent to sorafenib treatment failure, achieved a median OS time of 10.6 months (95% CI, 9.1-12.1) and conferred a statistically significant survival benefit, with a HR of 0.63 (95% CI, 0.50-0.79; one-sided P<0.0001) (44). In second-line settings, regorafenib-TACE combination therapy exhibited a favorable ORR (42.3%) and disease control rate (DCR: 66.1%), with grade ≥3 adverse events limited to 15.3% of patients (45).

Lenvatinib, an oral multikinase inhibitor, exerts potent antitumor activity through the dual blockade of fibroblast growth factor receptor 1-4 and VEGFR1-3 signaling pathways (46). Preclinical HCC models further reveal its immunomodulatory properties via programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis suppression and tumor-associated macrophage polarization (47). However, monotherapy often leads to resistance, necessitating combination therapy. The multicenter LAUNCH trial demonstrated that lenvatinib-TACE combination therapy significantly improved median OS time (17.8 vs. 11.5 months; HR, 0.45; P<0.001), PFS time (10.6 vs. 6.4 months; HR, 0.43; P<0.001) and ORR (54.1 vs. 25.0%; P<0.001) vs. lenvatinib monotherapy (48). A retrospective study showed an 11.1% surgical conversion rate, a 5.5-month median PFS time and a 14.1-month median OS time for lenvatinib plus TACE in PD-L1-positive unresectable HCC (49). Japanese researchers suggest considering lenvatinib upfront followed by TACE as needed for patients with intermediate stage HCC beyond up-to-7 criteria (sum of the size of the largest HCC tumor in cm and the number of tumors) (50). Sequential lenvatinib and TACE show clinical advantages in advanced HCC (51).

Apatinib, a next-generation VEGFR-2 inhibitor exhibiting 10-fold greater binding affinity than sorafenib (52), has emerged as a promising adjunct to TACE regimens. A clinical study demonstrated that the combination of TACE and apatinib significantly prolonged median PFS time compared with TACE monotherapy (median PFS was 6.83 months with TACE + apatinib and 3.81 months with TACE alone), while maintaining a favorable tolerability profile (53).

Anti-VEGF monoclonal antibodies, including bevacizumab and biosimilars, bind to VEGF-A, inhibiting angiogenesis. A retrospective study of drug-eluting microsphere TACE plus bevacizumab in unresectable HCC cohorts demonstrated an ORR of 14.2%, a DCR of 100%, a median OS time of 13.0 months and absence of grade ≥3 toxicity (54). Excessive bevacizumab dosing may induce pathological tumor vessel normalization, paradoxically fostering hypoxia-mediated therapeutic resistance and compromising TACE-mediated ischemic cytotoxicity (55).

TACE combined with immunotherapy. HCC immunotherapy primarily utilizes immune checkpoint inhibitors (ICIs), which exhibit synergistic potential in combination with TACE to enhance clinical outcomes. TACE induces the release of tumor-associated antigens, thereby triggering immunogenic cell death and initiating antitumor immune responses. This process augments antigen-specific T lymphocyte infiltration, upregulates immunomodulatory factors and potentiates the efficacy of ICIs (56). A clinical study (57) demonstrated that TACE exerts immune-activating effects, providing robust support for the therapeutic rationale underlying TACE-ICI combination strategies. The phase II IMMUTACE trial (58) met its primary endpoint of ORR and demonstrated a favorable safety profile, thus corroborating the clinical efficacy of TACE-ICI combination therapy. Combination therapy of TACE with anti-PD-1 inhibitors demonstrated significant prolongation of both PFS and OS times in advanced HCC cohorts (59). One clinical trial demonstrated that TACE combined with pembrolizumab notably prolonged survival time among patients with sorafenib-refractory HCC (60).

Cytokine-induced killer (CIK) cells exhibit potential for eradicating micrometastases, while dendritic cells (DCs) substantially augment CIK cell cytotoxicity through antigen-presentation mechanisms (61). The synergistic integration of DCs and CIK cells represents an emerging cell-based immunotherapeutic strategy for HCC. A comprehensive meta-analysis (62) demonstrated the superiority of TACE-DC-CIK combination therapy over TACE monotherapy in promoting an improved overall response, for half-year (RR, 1.16; 95% CI, 1.06-1.26; P=0.008), 1-year (RR, 1.22; 95% CI, 1.10-1.36; P=0.002) and 2-year (RR, 1.39; 95% CI, 1.16-1.66; P=0.004) OS, median OS (OR, 1.35; 95% CI, 1.04-1.66; P<0.00001) and PFS (RR, 1.9; 95% CI, 1.58-2.23; P<0.00001) in patients with HCC.

TACE combined with targeted therapy and immunotherapy. The integration of targeted therapy and immunotherapy synergistically potentiates the therapeutic efficacy of TACE. Targeted agents inhibit VEGF-mediated signaling pathways, thereby facilitating effector immune cell infiltration, counteracting tumor immune evasion, amplifying antitumor immunity and mitigating recurrence risks associated with post-TACE neoangiogenesis (63). The CHANCE001 trial (64), a multicenter real-world cohort study evaluating TACE combined with targeted-immunotherapy regimens in HCC, demonstrated that this multimodal approach significantly improved PFS time, OS time and ORR vs. TACE monotherapy in advanced HCC cohorts, while maintaining an acceptable safety profile.

Recent clinical evidence (65) indicates that TACE combined with sorafenib and ICIs confers prolonged PFS and OS times relative to TACE-sorafenib dual therapy. A retrospective cohort analysis (66) revealed that lenvatinib combined with TACE and PD-1 inhibitors demonstrated synergistic efficacy and safety in advanced HCC, with significantly superior PFS time, OS time, ORR and DCR compared with TACE-lenvatinib combination therapy.

In the context of conversion therapy for unresectable HCC, the combination of TACE with TKIs and PD-1 inhibitors achieved an ORR of 81.8% (18/22), a DCR of 90.9% (20/22) and a surgical conversion rate of 45.5% (10/22), including three cases attaining complete pathological remission post-resection (67). A retrospective investigation (68) of TACE combined with lenvatinib and PD-1 inhibitors in unresectable HCC revealed early tumor responses in 72.3% (68/94) of the cohort, accompanied by elevated surgical conversion rates and extended median PFS and OS times within this population.

TACE combined with traditional Chinese medicine (TCM). The integration of TCM with TACE exhibits synergistic therapeutic potential in the management of HCC. Accumulating clinical evidence (69,70) indicates that TACE combined with TCM adjunctive therapy enhances therapeutic outcomes, augments immune surveillance and mitigates adverse events associated with TACE monotherapy. Huaier Granule, a TCM formulation, has been shown to ameliorate clinical symptoms, potentiate immune function, suppress tumor recurrence and prolong OS time in patients with HCC who are undergoing TACE (71).

TACE combined with antiviral therapy. In patients with HCC and underlying hepatitis B virus or hepatitis C virus infections,

systematic integration of antiviral therapy with TACE is imperative to optimize therapeutic outcomes and long-term prognosis, as part of a pathophysiology-driven strategy (12,72). A clinical trial (72) demonstrated that chemo-lipiodolization was significantly correlated with a higher incidence of hepatitis attributed to HBV reactivation compared with other treatments (21.7 vs. 1.6%; P<0.001). Transarterial chemo-lipiodolization can reactivate patients with HBV and HBeAg-positive HCC; therefore, receiving chemo-lipiodolization should be closely monitored for HBV reactivation.

5. Conclusion

TACE is widely advocated in HCC therapeutics owing to its minimally invasive profile, broad clinical applicability, procedural repeatability and robust efficacy. Persistent challenges, including tumor recurrence and metastatic dissemination, continue to undermine therapeutic efficacy and long-term survival. Clinicians must integrate empirical insights with cutting-edge evidence on TACE-based multimodal regimens to tailor combination therapies that maximize survival benefits in advanced HCC. This opens new therapeutic pathways for addressing the complexities of advanced HCC, holding significant importance. Future investigations should prioritize optimizing therapeutic sequencing, refining temporal coordination of multimodal interventions, and devising strategies to enhance safety, tolerability and survival outcomes in HCC cohorts.

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Competing interests

The authors declare that they have no competing interests.

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